Food and Drug Administration
Center for Drug Evaluation and Research

Meeting: The Gastrointestinal Drugs Advisory Committee (GIDAC) will evaluate Sanvar (vapreotide acetate) for the proposed indication as an adjunctive therapy to endoscopic intervention for the control of acute esophageal bleeding as a result of portal hypertension.

May 19, 2009

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EXECUTIVE SUMMARY

DIVISION OF GASTROENTEROLOGY PRODUCTS

Application Type	NDA
Submission Number	21-761
Letter Date	October 1, 2008
Stamp Date	October 1, 2008
PDUFA Goal Date	July 1, 2009
Reviewer Name	Anil Rajpal, M.D., Acting Medical Team Leader
Review Completion Date	April 22, 2009
Established Name	Vapreotide acetate
Trade Name	Sanvar™ Injection
Therapeutic Class	Somatostatin Analogue
Applicant	Debiovision Inc.
Indication	Treatment of acute variceal bleeding due to portal hypertension, in association with endoscopic treatment

1 Executive Summary

1.1 Statement of Purpose

The purpose of the Advisory Committee meeting is to obtain advice from the Committee regarding the efficacy, safety, indication, and use of Sanvar (vapretotide) based on data from four randomized, double-blind, placebo-controlled trials and one single-arm, open-label trial. The Applicant, Debiovision Incorporated, proposes the following indication:

> "SANVAR® (vapreotide acetate) Injection is indicated as adjunctive therapy to endoscopic intervention for the control of acute esophageal bleeding as a result of portal hypertension."

The proposed dose (to be given prior to endoscopy) is an initial intravenous (I.V.) bolus injection of 50 µg followed by a continuous I.V. infusion of 50 µg/hr (1.2 mg/day) for up to five days; as proposed, dosing should be initiated within 24 hours after onset of hemorrhage, and should not continue for more than 24 hours without a confirmed diagnosis of variceal bleeding.

1.2 Background

This resubmission, received October 1, 2008, is a complete response to the Approvable Letter sent by the Division on December 21, 2004, and represents the second review cycle for this product.

1.2.1 Sanvar (vapreotide)

Vapreotide acetate is a cyclic octapeptide analogue of somatostatin. Although the mechanism of action of somatostatin and its analogs has not been clearly defined, this class of agents appears to decrease splanchnic blood flow by inhibiting the release of vasodilatory peptides such as glucagon, substance P, and vasoactive intestinal polypeptide.

Neither somatostatin nor its analogue octreotide are approved for the treatment of variceal bleeding in the United States. However, octreotide is currently being used off label for the treatment of acute variceal bleeding. (Octreotide is approved by the Agency for the treatment of acromegaly and diarrhea associated with carcinoid tumors.)

1.2.2 Esophageal Varices

Cirrhosis leads to clinically significant complications of portal hypertension (PHT), one of which is esophageal varices; in the presence of PHT, collateral routes of venous hepatic return develop with dilation of esophageal veins. When cirrhosis is diagnosed,

varices are present in about 50% of patients; despite the high prevalence of varices in patients with cirrhosis, variceal bleeding occurs in only about one-third of patients. Predictors of bleeding include: (1) variceal size; (2) Child-Pugh score; and (3) presence of red wale marks on endoscopy.

Current guidelines support vasoactive therapy having a role as an adjunct to endoscopic therapy (AASLD Practice Guidelines, 2007); however, supportive evidence is limited to a meta-analysis of eight studies (Banares et al., 2002).

1.3 Clinical Summary

The overall clinical database for this review includes the three randomized, placebo-controlled studies (VAP-14, VAP-07, and VAP-02) from the original NDA submission and two studies (VAP-301 and VAP-06) submitted for review in this complete response – one randomized placebo-controlled study and one open-label single arm study. The studies are summarized in the table below.

Table 1. Variceal Bleeding Studies

Study	Design	N*	Cause of Liver Cirrhosis
Original Submission			
VAP-14 (France; 1997-1998)	Multi-center, R, DB, PC	196	Alcoholism (85%)
VAP-07 (Egypt; 2002)	Single center, R, DB, PC	58	Viral hepatitis with schistosomiasis (83%)
VAP-02 (Hong Kong; 1997-2001)	Multi-center, R, DB, PC	102	Alcoholism (38%); Viral hepatitis (45%)
Current Submission			
VAP-06 (Eastern Europe; 2003-2004)	Multi-center, R, DB, PC	267	Alcoholism (62%); Viral hepatitis (38%)
VAP-301 (United States; 2006-2008)	Multi-center, Open-label, Single-arm	70	Alcoholism with Viral hepatitis (29%); Alcoholism (31%); Viral hepatitis (14%)

*ITT; R: Randomized; DB: Double-blind; PC: Placebo-controlled; Table modified from Clinical Efficacy Review

Each of the studies used the same dose of vapreotide and had a similar primary efficacy endpoint.

- Dose: Vapreotide was administered as an initial intravenous (IV) bolus injection of 50 µg followed by a continuous IV infusion at a rate of 50 µg/hour (1.2 mg/day) for five days with a follow-up period of 6 weeks. Vapreotide was started within 6 hours from admission and within 24 hours after hemorrhage onset; diagnostic and therapeutic endoscopy was performed no more than 12 hours from admission.
- Primary Endpoint: Hemostasis at the end of 5 days after endoscopic treatment; defined as hemostasis during the first two days (as assessed at 6 hours, and between 6 and 48 hours after endoscopy) followed by no re-bleeding from Day 3 to Day 5. Components of the endpoint were identical in all studies except VAP-06; the main difference was that VAP-06 had an additional criterion for a target hematocrit for the first two days.

1.3.1 Efficacy

The results of the studies in the original submission are in the table below.

Table 2. Control of Bleeding at End of 5 Day Infusion (VAP-14, VAP-07, VAP-02)

Study	Response Rate		Sanvar-Placebo	p-value
	Sanvar	Placebo		
VAP-14 (France; 1997-1998)	66% (65/98)	50% (49/98)	16%	p=0.021
VAP-07 (Egypt; 2002)	71% (22/31)	59% (16/27)	12%	p=0.35
VAP-02 (Hong Kong; 1997-2001)	55% (28/51)	51% (26/51)	4%	p=0.69

(Table above taken from Clinical Efficacy Review)

The NDA was not approved after the review of studies VAP-14, VAP-07, and VAP-02 because of the three studies, only VAP-14 had shown superiority of vapreotide to placebo; thus, the Applicant had not established substantial evidence of efficacy based on the Evidence of Effectiveness Guidance (i.e., did not meet the level of evidence requirements for a single study). The Guidance states, in general terms, that a single study would be acceptable for approval if it provided strength of evidence equal to two adequate, well-controlled studies. Key considerations by the Division (also described in the Guidance) included: (1) whether the observed outcome of VAP-14 was statistically very persuasive (the statistical reviewer offered a $p < 0.00125$ as an example of very persuasive); and (2) whether a single center was largely responsible for the observed effect.

The Applicant discussed the studies that could adequately address the review issues from the original review in meetings with the FDA after the original Approvable action. The Applicant proposed that a randomized placebo-controlled study, VAP-06, would establish effectiveness; however, preliminary results provided by the Applicant showed that the study did not show superiority of vapreotide over placebo. Thus, the Agency recommended that the Applicant conduct another randomized controlled trial. The Applicant made a case that a placebo-controlled trial could no longer be conducted, and the Agency ultimately agreed with an open-label single arm study comparing efficacy to the placebo arm of the study VAP-14 from the original submission. The reluctance to accept the historical control approach is grounded in its limitations, as outlined in the FDA Evidence of Effectiveness Guidance and 21 CFR 314.126 regarding limitations of historical controls. These include the introduction of un-measurable biases due to the study not being concurrently controlled (e.g., changes in patient population and standard of care since the historical control study was conducted) and due to the study not being randomized (e.g., imbalances across demographic and baseline disease characteristics).

The Applicant has now submitted two studies; VAP-06 and VAP-301, to be considered as part of the total body of evidence to support Sanvar (vapreotide) as treatment for variceal bleeding. The design of the two studies is described in Table 1 above, and the results are summarized in the table below.

Table 3. Control of Bleeding at End of 5 Day Infusion (VAP-301 and VAP-06)

Study	Response Rate	
	Sanvar	Placebo
VAP-301 (United States; 2006-2008)	77% (54/70)	--*
VAP-06# (Eastern Europe; 2003-2004)	51% (69/136)	53% (70/131)

*historical comparison to placebo arm of VAP-14
#from combining Applicant's pre-and post-amendment results (without stratification pre- and post- amendment)
(Table modified from Clinical Efficacy Review.)

VAP-06 does not demonstrate superiority of vapreotide over placebo.

The interpretability of VAP-301 is limited by the historical control design; VAP-301 and VAP-14 differed in baseline characteristics of the study populations and in the adjunctive endoscopic treatment modality utilized. These differences make the validity of cross study comparison questionable.

Compared to VAP-14, VAP-301 appeared to have more severe disease by some measures (higher proportion of patients with large varices and higher proportion with a more complex disease etiology - alcoholism plus viral hepatitis), similar severity of disease by other measures (similar proportion of Child Class C) and less severe disease by other measures (lower proportion of patients with three or more previous bleeding episodes).

A considerably higher proportion of patients in VAP-301 underwent adjunctive band ligation (instead of sclerotherapy) than VAP-14 (86% vs. 31%). Based on the results of VAP-14, band ligation appeared to be associated with a higher response rate for the primary endpoint than sclerotherapy; this suggests that the observed response rate in VAP-301 may be due at least in part to the higher proportion of patients who were treated with band ligation. Because VAP-14 was conducted about 10 years before VAP-301, it is important to consider possible improvements in operator performance of band ligation since that time as well.

In summary, we ask the Committee to consider the strength of evidence that Sanvar is effective given the efficacy data from Tables 2 and 3 above, in light of the strengths and weaknesses of each study.

1.3.2 Safety

Safety is described in the reviews of the original and current NDA submission (both included in this Briefing Package). In the original NDA review, based on 222 patients in the variceal bleeding studies, the clinical reviewer found that the safety profile of vapreotide was comparable with that of placebo, suggesting that events recorded were a reflection of the patients' underlying medical condition. In the current NDA review, based on 469 patients in the variceal bleeding studies, the clinical reviewer identified the following safety concerns: thrombocytopenia, thromboembolic events, disseminated

intravascular coagulation (DIC) events, a severe systemic inflammatory syndrome (SIRS) event, and cardiogenic shock events.

2 Points for Consideration by the Advisory Committee

- Do the available data support the efficacy of Sanvar "… as adjunctive therapy to endoscopic intervention for the control of acute esophageal bleeding as a result of portal hypertension"?

- Are there risks associated with the use of Sanvar in acute variceal bleeding that have not been adequately evaluated? If so, please state the risks that require further evaluation.

- Considering the currently available data, are there additional efficacy studies that should be obtained prior to approving Sanvar for the proposed indication? If so, please describe the design of the studies (e.g., placebo-controlled, dose-ranging).

- Considering the currently available data, are there additional safety data or studies that should be obtained prior to approving Sanvar for the proposed indication? If so, please describe.

- Based on currently available efficacy and safety data, should Sanvar be approved for the treatment of acute variceal bleeding?

CLINICAL REVIEW

Application Type	NDA (Class II Resubmission; Complete Response to Approvable Letter)
Application Number(s)	21-761
Submit Date(s)	September 30, 2008
Received Date(s)	October 1, 2008
PDUFA Goal Date	July 1, 2009
Reviewer Name(s)	Zana Marks, M.D., M.P.H.
Review Completion Date	April 17,2009
Established Name	Vapreotide
(Proposed) Trade Name	Sanvar
Therapeutic Class	Somatostatin Analogue
Applicant	Debiovision Inc.
Formulation(s)	Lyophilized Powder for injection; 0.6 mg/vial
Dosing Regimen	50 µg I.V. bolus followed by a continuous I.V. infusion of 50 µg/hr (1.2 mg/day) for 5 days
Indication(s)	Treatment of acute variceal bleeding due to portal hypertension, in association with endoscopic treatment
Intended Population(s)	Adult cirrhotic patients with acute variceal hemorrhage

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1 Introduction and Regulatory Background

Cirrhosis leads to clinically significant complications of portal hypertension (PHT). These complications appear most frequently when portal pressure is higher than 12 mmHg. In the presence of portal hypertension, collateral routes of venous hepatic return develop, with dilation of esophageal veins. Gastroesophageal varices or portosystemic collaterals formed after pre-existing vascular channels have been dilated by PHT are present in 40% to 60% of patients with cirrhosis. Their presence and size are related to the underlying cause, duration, and severity of cirrhosis. Despite the high prevalence of varices in patients with cirrhosis, bleeding occurs in only about a third of patients. In the absence of specific treatment, the failure to control acute bleeding or the occurrence of early re-bleeding occurs in up to 50% of cases. The highest risk of rebleeding is in the first five days following the index hemorrhage, after which the risk remains increased until the second or third month.

Although historically, mortality after acute variceal bleeding was as high as 30% to 50%, advances in both resuscitation methods and endoscopic techniques have reduced mortality rates to approximately 15 to 20% per bleeding event. If the patient survives the acute episode, the liver injury induced by bleeding and infection may result in an acute decompensation of cirrhosis with subsequent secondary mortality.

The immediate priority of the clinical management of an episode of variceal bleeding is the control of hemorrhage during the acute phase and the following days. Management methods include emergency shunt surgery, endoscopic sclerotherapy (injection of a sclerosant solution into or next to a bleeding varix), endoscopic variceal band ligation (ligation and strangulation of varices with rubber bands), balloon tamponade in rare circumstances, and vasoactive drug therapy following endoscopy. Emergency shunt surgery to control acute variceal hemorrhage is used rarely because it is associated with high operative mortality and increased post-operative risk for encephalopathy, liver failure and shunt thrombosis. Balloon tamponade is used rarely because 50% of patients experience recurrent hemorrhage after deflation of the balloon and 15% to 20% experience devastating complications during placement such as broncho-pulmonary aspiration and esophageal perforation. Currently, the most commonly used methods for management of acute variceal bleeding are endoscopic therapy in combination with vasoactive drug therapy which results in splanchnic vasoconstriction subsequently decreasing the portal pressure.

The current American Association for the Study of Liver Diseases guidelines (AASLD Practice Guidelines, Hepatology 2007) recommend that vasoactive pharmacological therapy such as somatostatin and octreotide should be started early on at admission before the endoscopic variceal ligation. Although these guidelines are being practiced all over the world it is important to note that supportive evidence is based on a meta-analysis of 8 studies (Banares et al., 2002). However, the studies included in the meta-analysis have limitations and supportive evidence does not seem to be robust.

The reduction of active bleeding following splanchnic vasoconstriction is expected to create better local visual conditions to conduct endoscopic treatment, thereby enhancing its effectiveness by allowing for the use of band ligation and reducing iatrogenic side effects induced by the spill over of sclerotic agents during sclerotherapy; often a secondary cause of esophageal ulceration and delayed severe rebleeding. In practice pharmacologic treatment may be initiated immediately before formal identification of the source of bleeding endoscopically, while endoscopic evaluation and treatment are often delayed by an average of up to 12 hours, due in part to lack of availability of facilities and trained personnel or suitable patient conditions. Since the failure to control bleeding is highest during the first hours to days following the onset of hemorrhage, early pharmacologic treatment to fill the gap between the beginning of hemorrhage and the initiation of endoscopy ideally would result in significantly improved overall hemostasis.

1.1 Product Information

Although the mechanism of action of somatostatin and its analogues has not been clearly defined, this class of agent appears to decrease splanchnic blood flow by inhibiting the release of vasodilatory peptides such as glucagon, substance P, and vasoactive intestinal polypeptide.

Vapreotide acetate, the subject of the current submission, is a long-acting cyclic octapeptide with pharmacologic properties mimicking those of the natural human peptide somatostatin.

1.2 Currently Available Treatments for Proposed Indications

Somatostatin and its analog octreotide are not approved for the indication of variceal bleeding in the United States. Octreotide, however, is used off-label in combination with therapeutic endoscopy in upper GI bleeding potentially due to varices.

1.3 Availability of Proposed Active Ingredient in the United States

Sanvar (Vapreotide) is not currently marketed in the United States for any indication.

1.4 Important Safety Issues With Consideration to Related Drugs

For a review of safety issues, please refer to the review performed by Dr. Wen-Yi Gao in the Division of Gastroenterology Products (DGP) under the same NDA (NDA 21-761).

1.5 Summary of Presubmission Regulatory Activity Related to Submission

1.5.1 Original Submission

1.5.1.1 Overview

On February 27, 2004, the Applicant (H3 Pharma) submitted efficacy and safety data (NDA 21-761) for vapreotide injection for the proposed indication of the treatment of acute variceal bleeding related to portal hypertension (PHT), in association with endoscopic therapy. (The previous clinical review of the original NDA submission was conducted by Dr. Fathia Gibril and is included in this briefing document.)

Initially, the clinical database in the NDA consisted of three studies:

- one pivotal phase 3 study conducted in France (VAP-14),
- one supportive phase 2b study conducted in Egypt (VAP-07), and
- one phase 3 study initiated in Hong Kong (VAP-02) that was subsequently terminated due to low recruitment.

The table below summarizes the features of the three studies reviewed in the original submission.

Table 1. Table of Clinical trials presented in support of Original Submission

Study	Study Design	Patient No Total/ITT	Gender ITT patients	Cause of liver cirrhosis	Comment
VAP-14 (France) (1997-1998)	Phase 3, multicenter, double-blind, randomized, placebo-controlled	227/196	148 males 48 females	Alcoholism (85%)	Pivotal study
VAP-07 (Egypt) (2002)	Phase 2b, single center, double-blind, randomized, placebo-controlled	72/58	all males	Viral hepatitis associated with schistosomiasis (83%)	Supportive study
VAP-02 (Hong Kong) (1997-2001)	Phase 3, multicenter, double-blind randomized, placebo-controlled	136/102	79 males 23 females	Alcoholism (38%) Viral hepatitis (45%)	Efficacy data are not considered useful by the sponsor in view of major protocol violations

(Table above is modified from the Medical Officer Review of the Original Submission.)

The Applicant initially submitted the efficacy results from two placebo-controlled studies: VAP-14 as a pivotal study and VAP-07 as a supportive study. A third study VAP-02 that was initiated in Hong Kong concurrently with the pivotal study (VAP-14) in 1997 was terminated in June 2001 due to poor recruitment rate and poor protocol compliance. As a result, the study was not considered useful by the sponsor for assessment of efficacy in view of major protocol violations

and was evaluated only for safety in the original NDA submission. However, upon the Division's request, the efficacy data from VAP-02 were provided as an amendment on September 22, 2004.

All three studies had the same intervention and the same inclusion/exclusion criteria. Eligible subjects aged 18 to 75 years with liver cirrhosis presenting with hematemesis and/or melena were randomized as early as possible after admission and in almost all cases treatment with the study agent was initiated prior to endoscopic diagnosis and treatment. After endoscopy, those subjects found to present a source of hemorrhage unrelated to PHT had their infusion stopped and these subjects were excluded from the intention-to-treat (ITT) population.

VAP-14: The pivotal study (VAP-14) was a multicenter, phase 3 study, in which 227 eligible subjects were enrolled into the study. After the exclusion of 31 subjects that were found to present a source of hemorrhage unrelated to PHT, the ITT population included 196 subjects: 98 subjects in each treatment group.

VAP-07: The supportive study (VAP-07) was a single center phase 2b pilot study, in which 72 eligible subjects were enrolled into the study. After the exclusion of 14 subjects that were found to present a source of hemorrhage unrelated to PHT, the ITT population included 58 subjects: 31 in the vapreotide group and 27 in the placebo group.

VAP-02: Study VAP-02 was a multicenter phase 3 study that was initiated in Hong Kong concurrently with the pivotal study in 1997. Due to poor recruitment rate and poor protocol compliance, the study was terminated in June 2001. A total of 136 patients were enrolled over nearly 4 years in five centers. According to the protocol, the estimated sample size was 150. After the exclusion of 34 patients that were found to present a source of hemorrhage unrelated to PHT, the ITT population included 102 patients: 51 subjects in each treatment group.

The etiology of liver cirrhosis was predominantly alcoholism in the pivotal study (VAP-14) population and alcoholism or viral hepatitis in the Hong Kong (VAP-02) study population, which are consistent with causes of cirrhosis in the U.S. population. In contrast, the cause of liver cirrhosis in the supportive study (VAP-07) population was parasitic (bilharzia) infection in association with viral hepatitis, a condition that is uncommon in Western countries.

Based on Child-Pugh scores (Class A, B or C), subjects in the pivotal study (VAP-14) and Hong Kong (VAP-02) study had more severe liver disease (Class C in 40% of the patients) compared with those in the supportive study (Class C in 9% of the patients).

1.5.1.2 Primary Endpoint

Primary Endpoint Definition:

The primary endpoint was hemostasis during the 5-day period following completion of endoscopic treatment (abbreviated thereafter Tendo). Hemostasis was defined as achievement of both primary hemostasis (no bleeding from Tendo+6 hours to Tendo+48 hours) and secondary hemostasis (no rebleeding between Tendo+48h to Tendo + 5 days).

The components of the assessment of the composite primary endpoint were:

1. Primary hemostasis (Tendo to 48 hours after Tendo):

- Assessed up to 6 hours after endoscopy:
  - transfusion requirement ≤ 4 units from Tendo;
  - systolic pressure > 80 mm Hg;
  - heart rate < 100 bpm (excluding other causes of tachycardia)
- Assessed between 6 hours and 48 hours after endoscopic treatment
  - transfusion requirement ≤ 2 units from Tendo + 6 hours
  - heart rate < 100 bpm
  - Hematocrit: no decrease ≥ 10 points in comparison with value of Tendo + 6 hrs

2. Secondary hemostasis (48 to 120 hours after Tendo):

- Assessed between 48 hours to 120 hours after Tendo:
  - no rebleeding (hematemesis , melena). [Rebleeding was defined as occurrence of new hematemesis or a new melena after a period of ≥ 24 hour of hemodynamic stability (vital signs, Hct or Hgb). A rebleeding episode implies that an initial control of the first hemorrhage was obtained.]

Rationale for Selection of Primary Endpoint:

Since hemodynamic stability is the primary goal of treatment for acute variceal bleeding, all vapreotide studies used a composite primary efficacy criterion for control of bleeding at 5 days, based on endpoint definitions for successful control of acute bleeding adapted from International Baveno Consensus Conferences on PHT (de Franchis. J Hepatol 2000). These Recommendations were adapted by the American Association for the study of Liver Diseases (Grace ND et al, Hepatology 1998) and were incorporated in the UK guidelines on the management of variceal hemorrhage in cirrhotic patients (Jalan & Hayes, Gut 2000).

1.5.1.3 Secondary Endpoints

The sponsor defined multiple secondary endpoints which included:

(a) absence of active bleeding at the time of diagnostic endoscopy
(b) hemostasis at 6 hours after randomization;
(c) number of units of blood administered during the study period;
(d) number of days in hospital;
(e) in-and-out-hospital survival (7-day, 30-day and 42-day).

According to the sponsor, analyses of secondary endpoints were performed for exploratory purposes. Therefore, the significance level was not adjusted for multiple comparisons.

1.5.1.4 Study Drug Dose and Duration of Therapy

An initial intravenous (IV) bolus injection of 50 μg vapreotide was followed by a continuous IV infusion at a rate of 50 μg/hour (1.2mg/day) for five days with a follow-up period of 6 weeks.

Rationale for Dose Selection and Duration of Therapy: Dose-optimizing studies were not conducted with vapreotide. The regimen selected for the current studies is largely empirical and was based on the regimen used in similar studies of octreotide and somatostatin in cirrhotic

patients with variceal hemorrhage. The optimal duration of the infusion of somatostatin or its analog is not known; in several previous trials, the duration of infusion was five days, since this corresponds to the period during which the risk of recurrence of bleeding is the highest.

Rationale for Duration of Study Period: The 6 week study period has been defined by the Consensus Conference as the period under which all mortality is considered as directly related to the episode of acute hemorrhage.

1.5.1.5 Efficacy Results

VAP-14 (pivotal study)

In the ITT population, analysis of the primary endpoint at the end of the five day infusion after endoscopic treatment demonstrated that hemostasis was achieved in a higher proportion of patients receiving vapreotide compared with those receiving placebo (66% [65/98] vs. 50% [49/98]; p=0.021). However, using the ITT population, the Agency's by-center analysis for the primary endpoint indicated that the rate of hemostasis in the vapreotide group was significantly higher than that of the placebo group only for Center 18 which had 28 patients (14% [28/196]), while the results in most centers showed a trend in favor of vapreotide. Of note, when Center 18 was excluded from the analysis, the effectiveness of vapreotide was no longer superior to that of placebo for the primary endpoint (63.9% [53/83] vs. 51.8% [44/85]; p=0.11). Though vapreotide was no longer statistically significantly superior to placebo when subjects at Center18 were excluded from the analysis, there was a 12% (64% vs. 52%) therapeutic gain in vapreotide treated patients which is similar to the observed therapeutic gain when Center 18 is included in the analysis.

For multiple secondary endpoints analyzed by the sponsor, significant benefits for vapreotide were observed for three secondary endpoints in the ITT population:

- Absence of Active Bleeding at the Time of Diagnostic Endoscopy: At the time of initial endoscopic procedure, control of bleeding was observed in a greater proportion of patients in the vapreotide group than in the placebo group (64%, 63/98 vs. 51%, 50/98; p=0.031). This action may be attributed solely to vapreotide, as it was observed before initiation of endoscopic treatment.
- Hemostasis at 6 hours After Randomization: Control of bleeding also was observed in a greater proportion of patients in the vapreotide group than in the placebo group at both six hours after endoscopy (88%, 86/98 vs. 60%, 59/98; p=0.00l) and 48 hours after endoscopy (73%, 72/98 vs. 54% , 53/98 ; p=0.005).
- Number of Units of Blood Administered During the Study Period: During the 5-day treatment period, fewer units of blood were administered to patients in the vapreotide group than in the placebo group (mean, 2.0 vs. 2.8 units, p=0.04).

VAP-07 (Egypt study)

In this single-center study, analysis of the primary endpoint in the ITT population, at the end of the 5-day infusion after endoscopic treatment demonstrated that hemostasis was achieved in 71% (22/31) of patients receiving vapreotide compared with 59% (16/27) of patients receiving

placebo, a difference that was not statistically significant (p=0.349). Similar results were observed in the PP population (83% [20/24] vs. 66% [12/18]; p=0.281).

Of multiple secondary endpoints analyzed by the sponsor, trends in favor of vapreotide were observed for survival at 42 days (84% [26/31] vs. 74% [20/27]) and treatment success over 42 days (65% [20/31] vs. 44% [12/27]).

VAP-02 (Hong Kong study)

This study showed no difference between the arms. In the ITT population, analysis of the primary endpoint at the end of the 5-day infusion after endoscopic treatment demonstrated that hemostasis was achieved in 55% (28/51) of patients receiving vapreotide compared with 51% (26/51) of patients receiving placebo, a difference which is not significantly different (p=0.692). The sponsor's analysis revealed similar results for the PP populations (52% [22/42] vs. 50% [19/38]; p=0.832). As well, none of the multiple secondary endpoints analyzed by the sponsor showed any significant difference between treatments in both the ITT and PP populations.

1.5.1.6 Other Relevant Information

Another study (VAP-06) was ongoing in Eastern Europe at the time of the review of the original submission; it was a randomized double blind placebo-controlled study of vapreotide for acute variceal bleeding that included approximately 260 patients and was conducted from April 2003 to October 2004.

The sponsor submitted an amendment on July 12, 2004 indicating that VAP-06 was ongoing in Eastern Europe. However, efficacy results from VAP-06 were not available at the time of the review of the original submission.

1.5.1.7 Summary of Efficacy Data from Original Submission

Superiority of vapreotide to placebo was demonstrated in a single study. Study VAP-14 demonstrated superiority of vapreotide relative to placebo when assessed for the primary endpoint; however, the findings were not robust. When one center that contributed 14% of the study population was dropped from the analysis, the statistical significance was not maintained (the p-value shifted from 0.02 to 0.11). The other two studies, VAP-07 (single-center Egypt trial) and VAP-02 (Hong Kong), did not demonstrate a significant difference between the vapreotide and placebo groups for the primary endpoint.

The table below summarizes the response rates for the primary endpoint for each of the three studies in the original submission (VAP-14, VAP-07, and VAP-02).

Table 2. Summary of the Response Rates for the Primary Endpoint (VAP-14, VAP-07, VAP-02)

Study	Response Rate			p-value
	Sanvar	Placebo	Sanvar-Placebo	
VAP-14 (France; 1997-1998)	66% (65/98)	50% (49/98)	16%	p=0.021
VAP-07 (Egypt; 2002)	71% (22/31)	59% (16/27)	12%	p=0.35
VAP-02 (Hong Kong; 1997-2001)	55% (28/51)	51% (26/51)	4%	p=0.69

(The table above was compiled by this reviewer from the Medical Officer's review of the Original Submission and the Sponsor's current submission.)

Based on the efficacy data presented, the Agency concluded that the single VAP-14 study finding of efficacy that was unsupported by independent evidence from supportive studies did not constitute substantial evidence of clinical efficacy.

1.5.2 Approvable Action

An Approvable Letter was sent to the applicant on December 21, 2004, outlining the reason for the approvable action as follows (see also Clinical Review by Dr. Fathia Gibril and Statistics Review by Dr. Wen-Jen Chen):

> "There is lack of substantial evidence that demonstrates the efficacy of vapreotide for the use in treatment of acute variceal bleeding related to portal hypertension associated with endoscopic treatment."

In order to resolve this deficiency, the applicant was given the recommendation below in that Approvable Letter:

> "Provide additional efficacy data from a well-controlled clinical trial."

1.5.3 Regulatory Activity after Approvable Action

The table below summarizes the regulatory activity after the Approvable action of Sanvar for variceal bleeding.

Table 3. Regulatory History After Approvable Action for Sanvar (NDA 21-761)

Date	Action
June 2005	Meeting with Division: ➢ Preliminary VAP-06 Results: The Division stated that preliminary VAP-06 results did not show superiority of vapreotide over placebo. ➢ Proposed Re-Analysis of VAP-06 Results: The Division stated that the sponsor's proposal to re-analyze VAP-06 primary efficacy results (using criteria of VAP-14) in a pre-amendment* subset of the population (comprising approximately one-fourth of the total) was not acceptable. ➢ Dose-Ranging Study: The Division recommended a dose ranging study to help identify the optimal dose.
Nov. 2005	Meeting with Division: ➢ Proposed Post-Approval Dose-Ranging Study: The Division stated that the sponsor's proposal to submit a Complete Response to Approvable Letter consisting of: (1) post-approval dose-ranging study (increased dose of bolus and infusion, and second bolus 10 minutes before endoscopic treatment; multicenter, randomized, two arms), and (2) data from VAP-06 was not acceptable; the Division requested a pre-approval study. ➢ Dose-Ranging Study (Prior to Approval): The Division suggested that a dose-ranging study (at least two different doses) to provide evidence of efficacy could be conducted (prior to approval); robust results could obviate the need for controlled clinical pre-marketing or post-marketing studies.
Feb. 2006	Meeting with Division: ➢ Proposed Single-Arm Open Label Study with Historical Control of 3 Prior studies: The sponsor proposed an open-label, single arm study that will be considered positive if the point estimate is within 10% of the proportion estimated from VAP-14, VAP-07, and VAP-06 (pre-amend. pop.) ➢ Single-Arm Open Label Study with Historical Control of VAP-14 only: The Division recommended that the historical control be the results from the pivotal French study (VAP-14) rather than the three trials combined; an alternative approach to compare the results to a historical control consisting of the extensive available literature available for octreotide in this patient population was also stated.
April 2006	Special Protocol Assessment (SPA) ➢ Proposed Single-Arm Open Label Study (Additional IV Bolus Just Prior to Endoscopy) Division's Response to SPA: ➢ No Additional IV Bolus: The Division recommended that the additional IV bolus not be included so that the dosing would be identical to that of VAP-14, and thus allow for an adequate comparison. ➢ Single Arm Study Acceptable: The Division agreed to a single arm study with the understanding that given the current standard of care available, a placebo controlled study was no longer possible. The Division acknowledged that it may be difficult to show statistical significance with the proposed study design, but felt a "clinical efficacy signal" might be detected.

* pre-amendment: prior to a protocol amendment.
(Table above was compiled by this reviewer using Meeting Minutes and SPA Responses from the Division File System [DFS].)

1.5.4 Current Submission

The current submission was received on October 1, 2008. The results of Studies VAP-301 and VAP-06 are provided in the current submission.

2 Review of Efficacy

2.1 Indication

In the "Indications and Usage" section, the Applicant proposed the underlined wording below for the acute variceal bleeding related to portal hypertension indication:

> **SANVAR® (vapreotide acetate) Injection is indicated as an adjunctive therapy to endoscopic intervention for the control of acute esophageal bleeding as a result of portal hypertension.**

2.1.1 Methods

The clinical data from two studies (VAP-301 and VAP-06) were analyzed to determine whether a clinical benefit was seen for patients with acute variceal bleeding who received vapreotide in combination with endoscopic therapy. Each of the studies used the same dose and duration of therapy as the previous studies in acute variceal bleeding.

Overview

VAP-301

General Design: VAP-301 was a single arm open label study.

Primary and Secondary Endpoints: The primary and secondary endpoints were the same as those of VAP-14. (See General Discussion of Endpoints section.)

Comparator: The results were compared qualitatively to the results of the completed study VAP-14.

VAP-06

General Design: VAP-06 was a randomized double-blind placebo-controlled study.

Primary Endpoint: The primary endpoint of VAP-06 differed from that of VAP-301. (See General Discussion of Endpoints section.)

Major Protocol Amendment: After approximately one-third of patients were enrolled in VAP-06, there was a major protocol amendment that changed the primary endpoint definition. (See Appendix 3.1 VAP-06.)

Statistical Analysis Plan: Approximately one year after the end of the study, there was an amendment to the Statistical Analysis Plan (SAP). Major changes included the following:

(1) Analysis of the pre-and post-protocol amendment populations separately; and
(2) Re-analysis of the data using VAP-14 criteria.

(See Appendix 3.1 VAP-06.)

Medical Officer's Comment:
Because the Statistical Analysis Plan (SAP) was changed one year after the study was completed, this reviewer does not agree with the re-analysis of the efficacy results of VAP-06 using VAP-14 criteria. Originally, the study failed on its pre-specified analysis. Therefore, the favorable results from the analyses based on changes to the definition of the endpoint after the study ended need to be interpreted with caution.

In addition, this reviewer does not agree with separate analyses of the pre-and post-amendment populations. An information request is pending for a re-analysis of overall primary efficacy results of VAP-06 stratifying by pre- and post-amendment populations, and using the respective primary endpoint criteria.

Selection Criteria

VAP-301 and VAP-06 each had identical inclusion and exclusion criteria. The pertinent inclusion and exclusion criteria for each of the studies are summarized in the table below:

Table 4. Pertinent Inclusion Criteria

Female/male cirrhotic pts. aged 18-75 yrs
Cirrhosis documented by at least one of the classical signs i.e., abdominal collateral venous circulation., firm liver with sharp lower edge, spider nevi, and/or ascites
Hematemesis &and/or melena thought to be related to portal hypertension
Time interval ≤ 24 hrs between onset of initial hem and initiation of the study drug infusion

(Inclusion criteria above are summarized from Page 14 of the VAP-06 & page 9 of the VAP-301 Protocol.)

Table 5. Pertinent Exclusion Criteria

Pt. treated with vasoactive drug, i.e., octreotide or vasopressin for the current hemorrhage
Known EVB in the previous 6 weeks
Known Child-Pugh score ≥ 13
Known complete portal vein thrombosis
Cancer
Chronic renal failure (serum creatinine > 1.5mg/dl)

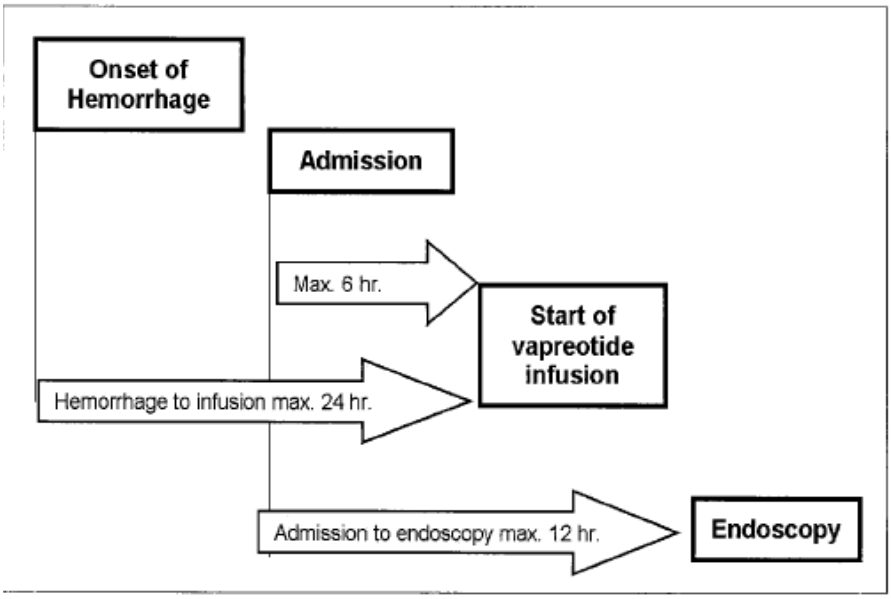
(Exclusion criteria above are summarized from Page 14of the VAP-06 & page 10 of the VAP-301 Protocol.)

Timing of Sanvar Infusion and Endoscopy

The timing of study agent infusion and of endoscopy were the same for both studies (see figure below). Sanvar was administered intravenously for five days in combination with endoscopy to patients with acute variceal bleeding due to portal hypertension.

Dose and Duration of Treatment: Cirrhotic patients with acute hematemesis and/or melena admitted to the emergency unit and meeting the eligibility criteria received, as soon as possible after admission (within a maximum of 24 hours following onset of hemorrhage and within the six hours following admission), Sanvar 50 µg I.V. bolus followed by an I.V. continuous infusion of 50 µg/h for five days. Diagnostic and therapeutic endoscopy was performed as soon as possible after the initiation of the study drug infusion, but no more than 12 hours after the patient's admission to the study center. A final follow up was performed on Day 42. Figure 1. below schematically depicts the study design.

Figure 1. Overview of Study Design (VAP-301 and VAP-06)



(The figure above is taken from Page 21 of the VAP-301 Study Report.)

General Discussion of Endpoints

VAP-301

Primary Endpoint

The primary efficacy criterion is the control of bleeding at 5 days after the end of endoscopic treatment (Tendo=120h) that is defined as primary control of bleeding + secondary control of bleeding + survival. Primary control of bleeding during the first 48 hours followed by no rebleeding from Day 3 to Day 5, and the patient being alive, will be considered as a successful treatment.

Primary control of bleeding *will be declared if the following criteria are met (successively* from Tendo to Tendo+6hr and from Tendo+6hr to Tendo+48hr periods):

Evaluation at Tendo + 6 hours:

- Transfusion requirements ≤4 units from Tendo
- Systolic blood pressure > 80 mmHg
- Heart rate < 100 bpm
- Alive

Evaluation between Tendo + 6 hours to Tendo + 48 hours:

- No new hematemesis
- Transfusion requirement ≤ 2 units from Tendo + 6hr
- Systolic blood pressure > 80 mmHg
- Heart rate < 100
- No decrease in hematocrit of > 10 points during the interval
- Alive

Secondary control of bleeding

Evaluation between Tendo + 48 hours to Tendo + 120 hours:

- Absence of re-bleeding (defined as a clinically significant re-bleeding* (hematemesis, melena**)
- Alive

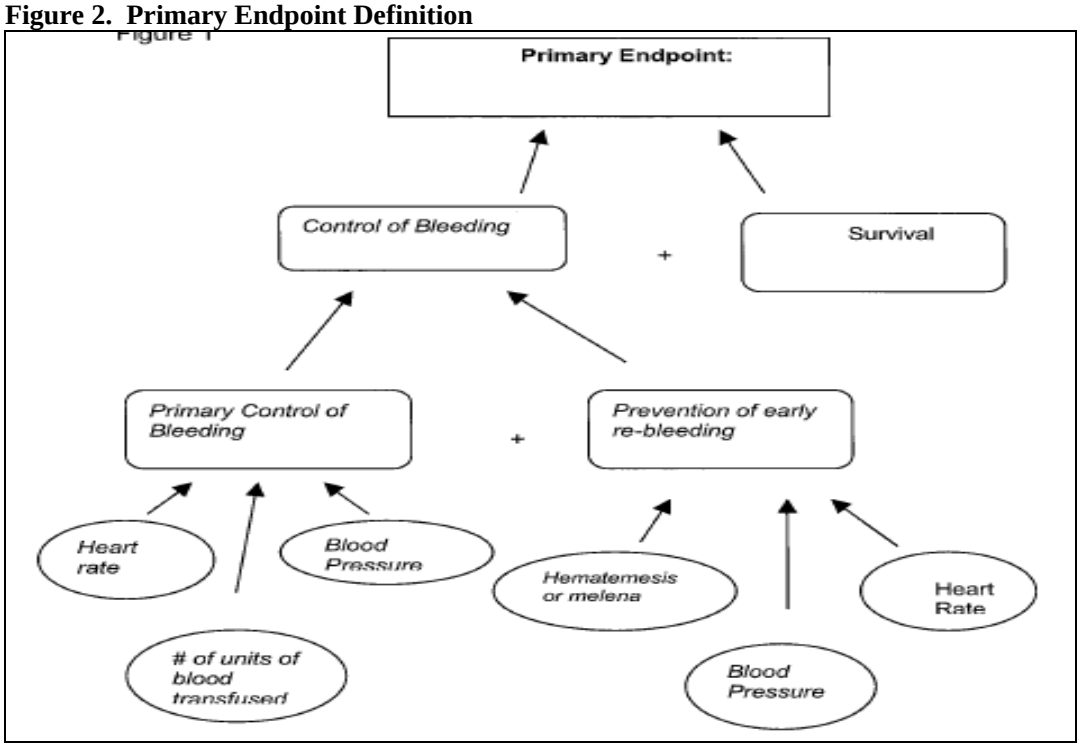
*An episode of clinically significant re-bleeding from Tendo + 48h to Tendo = 120h is defined as bleeding accompanied by at least one of the following of the Baveno criteria:

- A decrease in systolic blood pressure≥20 mmHg as compared with the average of the two preceding values
- An increase in heart rate≥ 20 bpm as compared with the average of the two preceding value
- A decrease in the hematocrit of at least 5 points as compared with the preceding value

** Melena will be considered as a rebleeding episode if it occurs after a period of 24 hours free of bleeding.

The primary endpoint definition is depicted in the figure below.

Figure 2. Primary Endpoint Definition



(Figure above is taken from Page 52 of the VAP-301 Study Protocol.)

Medical Officer Comment:
The primary goal of treatment for acute esophageal variceal bleeding is hemodynamic stability with early control of bleeding. All of the vapreotide studies used a composite primary efficacy criterion for the control of bleeding at 5 days, based on endpoint definitions for the successful control of acute bleeding adapted from the International Baveno Consensus Conference on portal hypertension (PHT) (de Franchis. J Hepatol., 2000). These Recommendations were adapted by the American Association for the Study of Liver Diseases (Grace ND et al, Hepatology 1998) and were incorporated in the UK guidelines on the management of variceal bleeding in cirrhotic patients (Jalen & Hayes, Gut, 2000). The sponsor's selection of endpoints was based on sound rationale. The Baveno Consensus Conference has sought to standardize the parameters to define control of bleeding and re-bleeding in cirrhotic patients whose upper gastrointestinal bleeding is related to (PHT). The results of the meeting produced guidelines for the management of patients as well as for the conduct of good clinical trials in the field of PHT.

<u>Secondary Endpoints</u>

The secondary efficacy endpoints are the following:

- Endoscopy facilitation: control of bleeding at first endoscopy after administration of vapreotide. This will be assessed by the presence of active bleeding (bleeding in jet or oozing) at endoscopy, and by the ability to identify the source of bleeding without being impeded by blood.

- Control of bleeding at Tinf + 6hrs: control of bleeding 6 hours after the initiation of study drug infusion (Tinf + 6hrs).
- Evaluation at Tinf + 6hrs (criteria to define success):
  - Transfusion requirement ≤4 units from Tinf
  - Systolic blood pressure > 80mmHg
  - Heart rate < 100bpm
  - Alive
- Control of bleeding by time periods (Tendo+6h, Tendo+48h and Tendo+120h) by Child Pugh class, carried out using the same criteria as described in the primary efficacy criteria.
- Blood transfusion units: Total number of blood units during the 5-day period of study drug infusion.
- Survival: In and out of hospital, 5-day and 42-day survival since admission will be recorded. Death will be related to bleeding or other causes when applicable (although it will be assumed, according to the Baveno definition, that death during the first 6weeks is related to the acute episode of bleeding).

VAP-06

Primary Endpoint

A protocol amendment was introduced after approximately one-third of the patients were enrolled. The amendment was implemented because of chronic blood shortages causing delays in transfusions. The delays in transfusions resulted in the following major change in the primary endpoint: decrease in the target Hct from 27 to 21. (See also Appendix 3.1 VAP-06.)

The primary endpoint of VAP-06 differed from that of the other studies. A key difference was that VAP-06 had an additional criterion for a target Hct for the first two days.

Original (Pre-Amendment) Primary Efficacy Endpoint:

The primary efficacy criterion is the control of bleeding over the 5 days after the end of endoscopic treatment (Tendo): primary control of bleeding and secondary control of bleeding with survival. Primary control of bleeding during the first 48 hours, followed by no bleeding from Day 3 to Day 5, and the patient being alive at Day 5 was considered a success.

Primary control of bleeding for the period beginning at the end of endoscopy and continuing for 6 hours after endoscopy, hemostasis was defined as:

- Transfusion requirement of <4 units of blood to produce a hematocrit of ≥ 27
- Systolic blood pressure of ≥70 mm Hg at the exact time Tendo+6; and
- Heart rate < 100 bpm at the exact time Tendo+6

Between 6 and 48 hours after endoscopy, hemostasis was defined by:

- Transfusion requirement <2 units of blood to maintain a hematocrit ≥ 27
- No new hematemesis
- Systolic blood pressure of ≥ 70 mm Hg
- Heart rate < 100bpm

Secondary Control of Bleeding
From 48 to 120 hours following endoscopy, secondary hemostasis was judged by the absence of a new episode of hematemesis or melena. During the 120-hour period after the end of endoscopy, tachycardia and hypotension were not taken into account if they could be clinically explained by a cause unrelated to hemorrhage (such as fever, anxiety, and delirium).

Revised (Post-Amendment) Primary Efficacy Endpoint

Same as above except:
- target hematocrit of ≥ 21 for both first 6 hours and for between 6 and 48 hours.

Medical Officer's Comments:
Study VAP-06 was conducted to provide supportive evidence of efficacy of the pivotal study, VAP-14. The protocol amendment resulted in a major alteration to the intended study design and subsequent analysis. The main difference in the two sets of criteria is that VAP-06 used the target hematocrit as a requirement for success, whereas in VAP-14, the target hematocrit was a guide for physicians to follow - not an endpoint. The hematocrit of 27% as a criterion made it difficult to achieve success especially at the time interval Tendo+6h. For patients arriving with an extremely low hematocrit (e.g. 17), it is difficult to transfuse enough blood in 6 hours to reach a hematocrit of 27%. The impact is further illustrated by examining the results in the post-amendment population, where the hematocrit of 21% was included as an absolute endpoint. In this group, the success rates are unusually high in both groups. With the threshold for success set so low, the sponsor states that it was impossible to discern a difference between the two groups using the criteria.

Secondary Endpoints

The secondary efficacy criteria were the same as those for studies VAP-14 and VAP-301. These included:
- Control of bleeding at first endoscopy as defined by rupture of varix with bleeding in jet or oozing.
- Control of bleeding 6 hours after the initiation of the study drug infusion (Tinf+6h)
- Total number of re-bleeding episodes per patient during the 42-day stud period
- Number of blood units used during the 5 day period of the study drug infusion
- The 5-and 42-day survival rate.

The sponsor presented results in the Pre-Amendment and Post-Amendment Populations separately for the secondary endpoints (See also Appendix 3.1 VAP-06.)

2.1.2 Demographic and Baseline Characteristics

2.1.2.1 VAP-301

Endoscopic Therapy Modality

The table below summarizes the endoscopic therapy modality for Study VAP-301; the table also includes the corresponding results of VAP-14.

Table 6. Endoscopic Therapy by Study and Treatment Group (ITT population)

	Statistic	VAP-301 (N=70)	VAP-14 (Sanvar) (N=98)	VAP-14 (Placebo) (N=98)
No diagnostic endoscopy	n (%)	0	2 (2.0%)	2 (2.0%)
Sclerotherapy only		3 (4.3%)	49 (50.0%)	55 (56.1%)
Band ligation only		60 (85.7%)	30 (30.6%)	30 (30.6%)
Sclerotherapy and band ligation		4 (5.7%)	1 (1.0%)	1 (1.0%)
Glue only		0	6 (6.1%)	1 (1.0%)
Band ligation and glue		0	0	1 (1.0%)
Other (1)		0	1 (1.0%)	1 (1.0%)
None		3 (4.3%)	9 (9.2%)	7 (7.1%)

(The table above was taken from page 31 of the Complete Response to Information Request Letter dated 2/16/2009.)

The distribution of endoscopic therapy modalities differed markedly between the VAP-14 and VAP-301 study groups. In the ITT population on the VAP-14 study, approximately 53% of received Sclerotherapy and approximately 31% received band ligation whereas in VAP-301 approximately 86% used band ligation only.

Medical Officer's Comments:
Subsequent to the completion of the VAP-14 study, endoscopic science has advanced and improved with more gastroenterologists becoming better skilled at band ligation. Band ligation has been accepted as having better outcomes than sclerotherapy and is now standard of care in the United States. There are limited data from head-to-head comparisons between the two endoscopic treatments in the setting of acute variceal bleeding.. This reviewer notes that the VAP-14 study was conducted more than 10 years ago and endoscopic band ligation combined with vasoactive therapy is the current standard of care for acute variceal bleeding. This is reflected in the treatment of the ITT population for study VAP-301. In this group 86% of patients received band ligation and only 4% received sclerotherapy.

Etiology of Cirrhosis

The table below summarizes the etiology of cirrhosis for Study VAP-301; the table also includes the corresponding results of VAP-14.

Table 7. Etiology of Cirrhosis by Study and Treatment Group (ITT population)

	Study DEBV-VAP/EVB-301	Study DEB-96-VAP-14	
Variable	vapreotide (N=70)	vapreotide (N=98)	placebo (N=98)
Causes of cirrhosis:			
Alcoholism only	31% (22)	84% (82)	86% (84)
Viral hepatitis only	14% (10)	3% (3)	3% (3)
Alcohol plus viral hepatitis	29% (20)	10% (10)	7% (7)
Other; Alcohol/Other; Biliary	26% (18)	3% (3)	4% (4)

(Table above is modified from table found on Page 113 of the VAP-301 Study Report.)

While the ITT population in study VAP-14 reported an etiology of cirrhosis that was predominantly pure alcoholic cirrhosis (84%) with only (10%) suffering from a combined etiology of alcoholism and viral hepatitis, only 31% of the patients in study VAP-301 had pure alcoholic cirrhosis. Twenty-nine percent (29%) of the patients in this study suffered a combined etiology of alcohol + viral hepatitis.

Medical Officer Comment:
The etiology of cirrhosis in VAP-301 is consistent with the findings of a study by Nguyen et al (2007) that reported a growing burden of hepatitis C-related disease among patients hospitalized in the US for portal hypertension complications. The prevalence of hepatitis C-related advanced liver disease among hospitalized patients increased from 12.9% in 1998 to 23.7% in 2003. The rate rose from 5.6% to 11.2% among those with combined HCV and alcohol related disease.

Variceal Size

The table below summarizes the size of varices for Study VAP-301; the table also includes the corresponding results of VAP-14.

Table 8. Size* of Varices by Study and Treatment Group Categories (ITT Population)

Variceal size	VAP-301	Vap-14 (Vapreotide)	Vap-14 (Placebo)
< 5 mm	10% (7/70)	31% (27/98)	28% (25/98)
≥ 5 mm	90% (63/70)	69% (59/98)	72% (65/98)

* Data on size was in VAP-301, and data on Grade was in VAP-14. To compare variceal size/grade across treatment and study groups, the sponsor categorized varices into two groups defined as Grade0-1/<5mm and Grade2-3/>5mm.This is in accordance with the current recommendations of the AASLD and the American College of Gastroenterology (Garcia-Tsao et al 2007). (Table above compiled by this reviewer using results from Pg 27 of Response to Information Request dated 2/16/09)

Based on variceal size/grade a much higher proportion of patients in the VAP-301 study had larger or more advanced stages of varices than those in the VAP-14 study.

Other Characteristics at Enrollment

The tables below summarize demographic and baseline characteristics for Study VAP-301; the tables also includes the corresponding results of VAP-14.

Table 9. Characteristics at Enrollment for ITT Population

	Study DEBV-VAP/EVB-301	Study DEB-96-VAP-14	
Variable	**vapreotide (N=70)**	**vapreotide (N=98)**	**placebo (N=98)**
Age (years)			
Mean	53	55	55
(range)	(28 – 72)	(32-73)	(29-75)
Gender distribution, males	76% (53)	68% (67)	81% (81)
Previous episodes of PHT bleeding:			
1 episode	23% (16)	19% (19)	18% (18)
2 episodes	7% (5)	9% (9)	7% (7)
3+ episodes	4% (3)	10% (10)	13% (13)
Previous treatment for portal hypertension:			
β-blockers	37% (26)	45% (44)	36% (35)
Nitrates	- (0)	3% (3)	2% (2)
Endoscopy	33% (23)	24% (24)	21% (21)

(Table above is taken from Page 113 of the VAP-301 Study Report.)

Table 10. Characteristics at Enrollment for ITT Population (cont.)

	Study DEBV-VAP/EVB-301	Study DEB-96-VAP-14	
Variable	**vapreotide (N=70)**	**vapreotide (N=98)**	**placebo (N=98)**
External signs of bleeding (hematemesis and/or melena)	70% (49)	73% (72)	84% (83)
Child-Pugh score, N (%)			
A-B	62% (43/69)	61% (56/92)	59% (55/94)
C	38% (26/69)	39% (36/92)	41% (39/94)
Albumin (g/dL) mean	2.57 ± 0.71	2.88 ± 0.64	2.75 ± 0.69
Prothrombin Level	19.86 ± 13.65	53.45 ± 14.9	48.2 ±16.5
Bilirubin (mg/dL) mean	3.62 ± 5.03	3.52 ± 4.70	3.47 ± 3.79
Hepatic Encephalopathy			
Absent	56 (80%)	84 (85.7%)	77 (79.4%)
Mild-moderate (I-II)	13 (18.6%)	9 (9.2%)	17 (17.5%)
Severe (III-IV)	1 (1.4%)	5 (5.1%)	3 (3.1%)
Ascites			
Absent	30 (42.9%)	62 (63.3%)	65 (67.0%)
Mild-moderate	34 (48.6%)	22 (22.5%)	22 (22.7%)
Severe	2 (8.6%)	14 (14.3%)	10 (10.3%)
Hemodynamics:			
Hematocrit, %	28.8	29.0	26.5
(range)	(15-42)	(12 – 47)	(9 – 42)
Hemoglobin, g/L	9.7	9.5	8.9
(range)	(5.2-14.1)	(3.5-13.9)	(2.9-14.3)

(Table above is taken from Page 113 of the VAP-301 Study Report.)

The severity of bleeding at admission in addition to the times between onset of hemorrhage, admission, infusion start and endoscopy are comparable between the two studies.

Proportions of Child Pugh Class C were similar between the two studies and both treatment groups of VAP-14.

The two study populations had similar baseline demographics and other laboratory parameters and sequelae of cirrhosis (hepatic encephalopathy and ascites).

Medical Officer's Comments:
The etiology of cirrhosis (higher proportion of patients with complex disease etiology - alcoholic liver disease and viral hepatitis), the size of varices (higher proportion of patients with large varices), and the lower prothrombin factor II levels suggest that the VAP-301 study population may have more severe disease. However, the proportion of Child Class C was similar between the two studies, and there was a higher proportion of patients that had three or more previous episodes of bleeding in VAP-14.

2.1.2.2 VAP-06

The table below summarizes the demographic characteristics for VAP-06.

Because a major protocol amendment occurred after 65 patients were enrolled (see Section Results are presented for the pre-amendment, post-amendment, and total populations.

Table 11. Demographic characteristics - ITT population

	Pre-Amendment		Post-Amendment		Total Population	
	Vapreotide	Placebo	Vapreotide	Placebo	Vapreotide	Placebo
N	32	33	104	98	136	131
Gender distribution, males	81% (26)	64% (21)	70% (73)	60% (59)	73% (99)	61% (80)
Age (years) Mean (range)	49 (28-72)	56 (35-80)	55 (18-78)	54 (18-79)	54 (18-78)	54 (18-80)
Weight (kg) (Median)	74	75	72	72	73	73
Height (cm) (Median)	172	170	171	170	171	170

(Table above is taken from Page 55 of the VAP-06 Study Report.)

Overall, the demographic characteristics appear similar between the pre- and post- amendment study groups with 81% males pre- and 70% males post-amendment. The mean age was 54 years. The mean age was 54.0 years, median height was 171cm and median weight was 70kg.

The table below, provides information regarding the etiology of cirrhosis and disease history for study participants in the pre and post amendment populations for study VAP-06.

Table 12. History of the disease - ITT population

	Pre-Amendment		Post-Amendment		Total Population	
	Vapreotide	Placebo	Vapreotide	Placebo	Vapreotide	Placebo
N	32	33	104	98	136	131
Etiology						
- Alcoholism	53% (17)	58% (19)	66% (69)	62% (61)	63% (86)	61% (80)
- Viral hepatitis	59% (19)	39% (13)	29% (30)	42% (41)	36% (49)	41% (54)
- Other	13% (4)	12% (4)	16% (17)	9% (9)	15% (21)	10% (13)
Median time from diagnosis of cirrhosis to inclusion (years)	2	3	2	2	2	2
Previous history of ascites	53% (17)	55% (18)	60% (62)	62% (61)	58% (79)	60% (79)
Previous history of hepatic encephalopathy	13% (4)	18% (6)	12% (12)	19% (19)	12% (16)	19% (25)
Known esophageal varices	94% (30)	83% (27)	68% (71)	65% (64)	74% (101)	69% (91)
Median time from diagnosis to inclusion (years)	1	2	2	1	2	2
Previous episode of hemorrhage related to portal hypertension:						
- 1 episode	19% (6)	12% (4)	17% (18)	16% (16)	18% (24)	15% (20)
- 2 episodes	31% (10)	15% (5)	12% (13)	5% (5)	17% (23)	18% (10)
– more than 2 episodes	19% (6)	15% (5)	12% (12)	11% (11)	13% (18)	12% (16)
Previous treatment for portal hypertension	56% (18)	42% (14)	34% (35)	31% (30)	39% (53)	34% (44)
β-blockers	47% (15)	30% (10)	23% (24)	28% (27)	29% (39)	28% (37)
Endoscopy	31% (10)	27% (9)	18% (19)	14% (14)	21% (29)	18% (23)
Nitrates	3% (1)	3% (1)	6% (6)	5% (5)	5% (7)	5% (6)

(Table above is taken from Page 58 of the VAP-06 Study Report.)(Alcoholism includes all patients with alcoholism, with or without any other etiology. "Other" includes all etiologies other than alcoholism or viral hepatitis.)

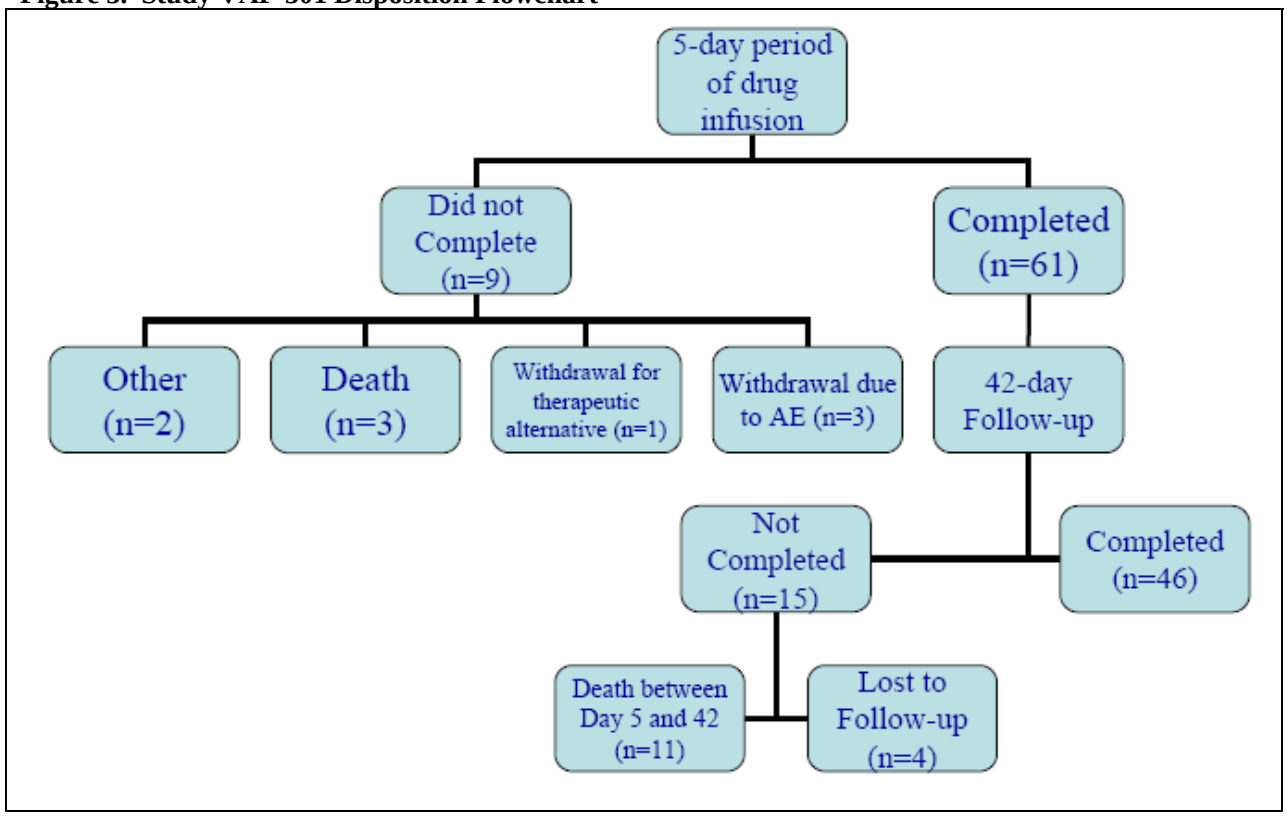
The etiology of cirrhosis was primarily alcoholism alone (63%) or in combination with other causes, viral hepatitis (36%), Previous history of ascites was reported in 58% of the patients and previous history of hepatic encephalopathy was reported in (12%) of the patients. 48% of the patients treated had already suffered from bleeding related to portal hypertension compared to 45% of placebo. There was no significant difference between treatment groups. Previous treatment for portal hypertension, whether pharmaceutical or endoscopic, was comparable between the treatment and placebo groups.

2.1.3 Subject Disposition

2.1.3.1. VAP-301

The disposition of the patients in Study VAP-301 is summarized in the flow chart below.

Figure 3. Study VAP-301 Disposition Flowchart



(The flowchart above was made by this reviewer using values in a chart found on Page 50 of the VAP-301 Study Report.)

Of the 70 ITT patients, 61 completed the 5-day treatment period. The reasons cited for premature discontinuation of the study drug were:

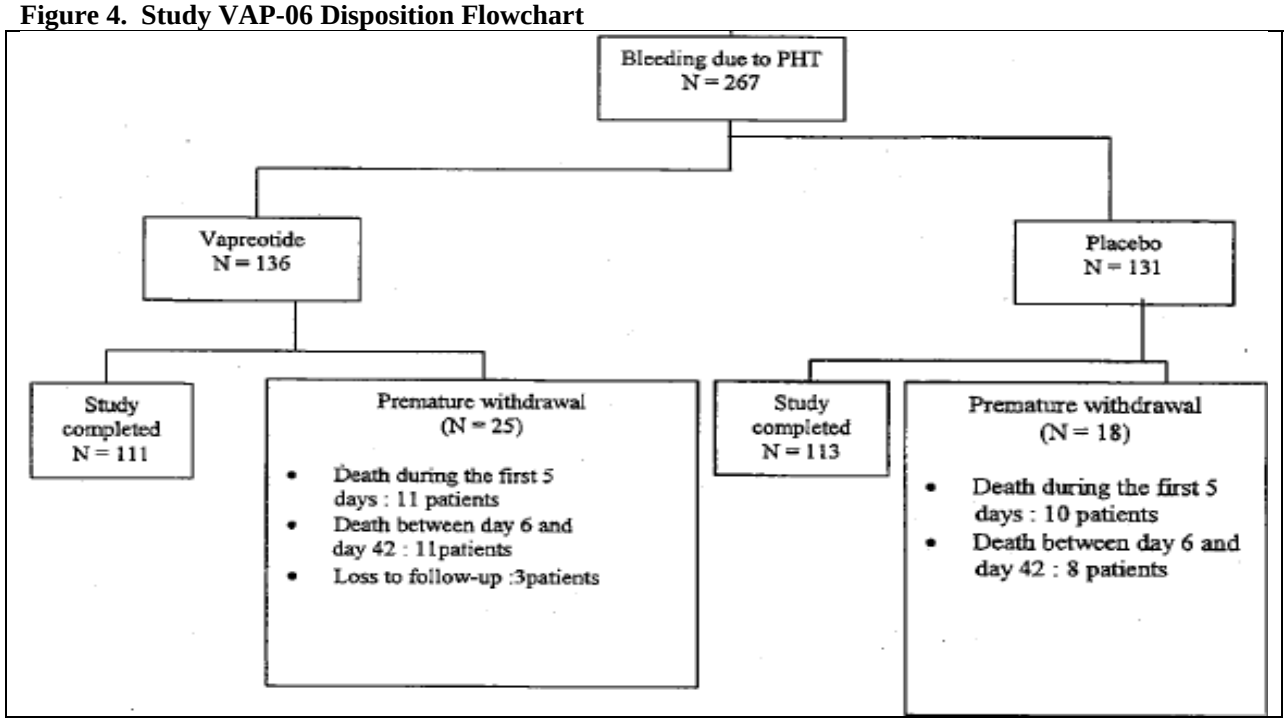
- Death (3)
- Uncontrolled bleeding requiring a therapeutic alternative (1)
- Other adverse experience or AE causing death (3)
- Other (2)

From the end of the 5 day treatment period to Day 42, 2 patients were lost to follow-up.

2.1.3.2 VAP-06

The disposition of the patients in Study VAP-06 is summarized in the flow chart below.

Figure 4. Study VAP-06 Disposition Flowchart



(The flowchart above is taken from Page 51 of the VAP-06 Study Report.)

Forty six patients did not complete the study. The following were listed as reasons for withdrawal:

- Death (n=40)
- Withdrawal of consent (n=2)
- Bleeding not related to portal hypertension (n=4)

2.1.4 Analysis of Primary Endpoint(s)

2.1.4.1 VAP-301

The primary efficacy results are shown in the table below for the ITT populations of VAP-301 and the qualitative comparator study VAP-14.

Table 13. Primary Efficacy Endpoint: Control of Bleeding at End of 5 day Infusion and Survival (ITT)

VAP-301	VAP-14	
Vapreotide	Vapreotide	Placebo
77% (54/70)	**66% (65/98)**	**50% (46/98)**

(Values in the table above were compiled by this reviewer from the VAP-301 Study Report and the Sponsor's Response to Information Request dated 2/16/09.)

Among the ITT population, 77% of patients in the VAP-301 study demonstrated treatment response as compared to 66% in the VAP-14 vapreotide-treated group and 50% of patients in the VAP-14 placebo group.

Response rates for individual components of the primary efficacy endpoint (i.e., control of bleeding by time period) are provided in the section on Secondary Endpoints (see Section 2.1.5.1).

Medical Officer's Comment:
While it is not clear why the VAP-301 response rate appears to be higher than that of the VAP-14 vapreotide group, the difference may in part be related to the endoscopic method used in combination with the study agent. VAP-14 was conducted over a decade ago and sclerotherapy was the treatment of choice (50% of patients received sclerotherapy while 31% of patients were treated with band ligation). Currently endoscopic variceal ligation or band ligation is the endoscopic treatment of choice for variceal hemorrhage and was used in 86% of the patients in VAP-301.

2.1.4.2 VAP-06

The tables below depict the efficacy results for the primary endpoint for the VAP-06 study.

The primary efficacy results are presented below by the Pre-Amendment and Post-Amendment Populations separately using the original and amended protocol specific criteria, respectively (see Appendix 3.1 VAP-06).

Table 14. Primary Efficacy Endpoint: Control of Bleeding at the End of the 5 day Infusion (Pre-Amendment*, Post-Amendment#, and Overall†; ITT)

Study	Sanvar	Placebo	Sanvar-Placebo
VAP-06 (Pre-amendment)	12.5% (4/32)	18.2% (6/33)	-6%
VAP-06 (Post-amendment)	62.5% (65/104)	65.3% (64/98)	-3%
VAP-06 (Overall)*	**50.7% (69/136)**	**53.4% (70/131)**	**-3%**

* Primary Efficacy Outcome in the Pre-Amendment ITT population using the original protocol specified criteria.
\# Primary Efficacy Outcome in the Post-Amendment ITT population using amended protocol specified criteria.
† Primary Efficacy Outcome in the Overall population based on combining Applicant's pre- and post-amendment results (without stratification pre- and post- amendment).
(Pre-amendment and post-amendment values in the table above were taken from Pages 64 and 115, respectively, of the VAP-06 Study Report.)

The following tables summarize the components of the primary endpoint for each of the pre- and post-amendment populations.

Table 15.Primary Efficacy Endpoint-ITT population (Pre-Amendment Population) VAP-06

Pre-Amendment Population			
	Vapreotide	Placebo	Odds Ratio
Primary Efficacy Endpoint	N=32	N=33	
Hemostasis at 5 days	12.5% (4/32)	18.2% (6/33)	0.64 (0.16-2.53)
Components of the Primary Efficacy Endpoint			
Hemostasis controlled at Tendo+6	34.4% (11/32)	27.3% (9/33)	1.40 (0.49-4.02)
Hemostasis between Tendo+6 and Tendo +48h	36.4% (4/11)	66.7% (6/9)	0.29 (0.04-1.82)
Hemostasis between Tendo +48h and Tendo+120h	100% (4/4)	100% (6/6)	N/A

*Primary Efficacy Outcome in the Pre-Amendment ITT population using original protocol specified criteria.
(Table above is taken from Page 64 of the VAP-06 Study Report.)

Table 16. Primary Efficacy Endpoint-ITT population (Post-Amendment Population*) VAP-06

Post-Amendment Population			
	Vapreotide	Placebo	Odds Ratio
Primary Efficacy Endpoint	N=104	N=98	
Hemostasis at 5 days	62.5% (65/104)	65.3% (64/98)	0.89 (0.50-1.57)
Components of the Primary Efficacy Endpoint			
Hemostasis controlled at Tendo+6	77.9% (81/104)	78.6% (77/98)	0.96 (0.49-1.87)
Hemostasis between Tendo+6 and Tendo +48h	84.0% (68/81)	84.4% (65/77)	0.97 (0.41-2.27)
Hemostasis between Tendo +48h and Tendo+120h	95.6% (65/68)	98.5% (64/65)	0.34 (0.03-3.34)

*Primary Efficacy Outcome in the Post-Amendment ITT population using amended protocol specified criteria.
(This table was taken from the VAP-06 study report; page 115.)

The VAP-06 results suggested a higher response rate in the placebo group than the vapreotide group. This was seen for each of the populations (i.e., the Pre-Amendment and Post-Amendment Populations).

2.1.5 Analysis of Secondary Endpoints(s)

2.1.5.1 VAP-301

Control of Bleeding by Time Period

The table below describes control of bleeding by time period in Studies VAP-301 and VAP-14.

Table 17. Control of Bleeding by Time Period Over Days 1-5 (VAP-301 and VAP-14)

Efficacy Criteria	Study VAP-301	Study VAP-14	
	vapreotide (N=70)	vapreotide (N=98)	placebo (N=98)
Primary efficacy criteria: survival and control of bleeding at day 5, % (n)	77% (54)	66% (65)	50% (49)
Subsets of primary efficacy criteria, % (n)			
• Control of bleeding at T endo+6h	94% (66)	88% (86)	60% (59)
• Success at Tendo+6h *and* control of bleeding from Tendo+6h to Tendo+48h	83% (58)	76% (74)	64% (63)
• Success in prior two categories *and* no re-bleeding from Tendo+48h to Tendo+120h	77% (54)	66% (65)	50% (49)

(Table above is taken from Page 7 of the Sponsor's Clinical Overview.)

As the time interval increased, the response rate for VAP-301 and for VAP-14 appeared to decrease across both studies and treatment groups. At each interval, patients in VAP-301 appeared to have a higher response rate at each specified time interval than then VAP-14 vapreotide group which in turn was higher than the VAP-14 placebo group.

Child-Pugh Class

The table below describes control of bleeding by time period and Child-Pugh Class in Study VAP-301.

Table 18. Control of Bleeding by Time Period and Child-Pugh Class – VAP-301 (ITT)

Control of bleeding at time period	CP Class A N=12	CP Class B N=31	CP Class C N=26	ITT Total N=69
Tendo+6h	100% (12)	93.5% (29)	92.3% (24)	94.2% (65)
Between Tendo and Tendo+48h	100% (12)	83.9% (26)	76.9% (20)	84.1% (58)
Between Tendo and Tendo+120h	100% (12)	80.6% (25)	65.4% (17)	78.3% (54)

(Table above taken from Page 7 of the Sponsor's Clinical Overview.)

The highest response rate was at Tendo + 6 h. At subsequent time intervals, the treatment response rate appeared to decrease; the greatest decrease was observed in the Class C group followed by the Class B group. Class A patients had control of bleeding at each of the time intervals.

Comparison across Child Classes, the response rates for Child Class C was lower than that of Child Class B which in turn was lower than that of Class A; this was observed for each of the time intervals assessed.

Blood Transfusions

The table below shows the number of blood units transfused over Days 1-5 in Studies VAP-301 and VAP-14.

Table 19. Number of Blood Units Transfused Over Days 1-5 (VAP-301 and VAP-14)

	Study DEBV-EVB/VAP-301	Study DEB-96-VAP-14	
	vapreotide (N=70)	vapreotide (N=98)	placebo (N=98)
Number of blood units per patient over Days 1-5	2.61 ±3.0	2.0 ± 2.2	2.8 ±2.8

Mean +/- SD is provided above.
(Table above is modified from table found on Page 116 of the VAP-301 Study Report.)

The number of blood units per patient over Days 1-5 in VAP-301 appeared to be higher than that in the VAP-14 vapreotide group.

In VAP-14, the vapreotide group appeared to require lower number of blood units per patient over Days 1-5 than the placebo group.

2.1.5.2 VAP-06

Secondary Efficacy Results

The tables below show secondary efficacy results for the Pre-Amendment and Post-Amendment ITT populations.

Table 20. VAP-06 Pre-Amendment ITT Population - Secondary Efficacy Results

	Vapreotide	Placebo	O.R.
N	32	33	
Endoscopy facilitation:			
Active bleeding	59.4% (19)	60.6% (20)	0.95 (0.35,2.56)
White nipple or no sign	43.8% (14)	36.4% (11)	1.36 (0.50,3.68)
Hemostasis at Tinf+6h (all the patients)	84.4% (27)	63.6% (21)	3.09 (0.94,10.13)
Re-bleeding episodes: – Between Tendo+48h and Tendo+120h	13.3% (4/30)	13.3% (4/30)	1.00 (0.23,4.33)
Total number of blood transfusion units: – During the first 5 days (mean (SD))	1.84 (2.23)	3.02 (3.39)	NA
Total duration of hospitalization (days) – All patients	7 (4,39)	8 (5,23)	NA
Number of patients surviving:			
– During the planned 42-day period of the study	87.5%(28)	81.8%(27)	1.56 (0.40,6.25)
– Between T_{inf} and $T_{endo+120h}$	93.7%(30)	90.9%(30)	1.49 (0.23,10.0)
– Between Day 6 and Day 42	93.3%(28)	90.0%(27)	1.56 (0.24,10.0)

(Table above is taken from Page 67 of the VAP-06 Study Report.)

Table 21. VAP-06 Post-Amendment ITT Population - Secondary Efficacy Results

	Vapreotide	Placebo	O.R.
N	104	98	
Endoscopy facilitation:			
Active bleeding	66.3% (69)	72.5% (71)	0.77 (0.42,1.41)
White nipple or no sign	30.8% (32)	31.6% (31)	0.97 (0.54-1.77)
Hemostasis at Tinf+6h (all the patients)	73.1% (76)	76.5% (75)	0.83 (0.44-1.57)
Re-bleeding episodes: – Between Tendo+48h and Tendo+120h	3.3% (3/91)	4.4% (4/90)	0.73 (0.16-3.37)
Total number of blood transfusion units: – During the first 5 days (mean (SD))	1.44 (1.96)	1.42 (2.08)	NA
Total duration of hospitalization (days) – All patients	8 (5,36)	8 (5,36)	NA
Number of patients surviving:			
– During the planned 42-day period of the study	82.7%(86)	87.8%(86)	0.67 (0.30,1.41)
– Between T_{inf} and $T_{endo+120h}$	91.3%(95)	92.9%(91)	0.81 (0.29,2.27)
– Between Day 6 and Day 42	90.5%(86)	94.5%(86)	0.56 (0.18,1.73)

(This table was taken from the VAP-06 study report; page 116.)

For the pre-amendment population, hemostasis at Tinf+6 h appeared to be higher in the vapreotide group than the placebo group although statistical significance was not achieved; total number of blood transfusion units during the first 5 days appeared to be slightly lower in the vapreotide group than the placebo group. Survival was similar between the two groups for the pre-amendment population.

For the post-amendment population, hemostasis at Tinf+6 h was similar in the vapreotide group and the placebo group; total number of blood transfusion units during the first 5 days was similar in the vapreotide group and the placebo group. Survival was similar between the two groups for the post-amendment population.

2.1.6 Subpopulations

2.1.6.1 VAP-301

Endoscopic Treatment Modality

The table below shows the proportion meeting the primary endpoint by endoscopic treatment modality in VAP-301 and in the qualitative comparator study VAP-14.

Table 22. Subgroup Analysis - Endoscopic Treatment (Control of Bleeding at Day 5 and Survival; ITT)

	Statistic	VAP-301 (N=70)	VAP-14 (Sanvar) (N=98)	VAP-14 (Placebo) (N=98)
Endoscopic Therapy Modality				
Band ligation		49/64(76.6%)	23/31(74.2%)	18/32(56.3%)
Sclerotherapy		5/7(71.4%)	31/50(62.0%)	26/56(46.4%)

Statistic is n/N (%)
(Table above is taken from Page 38 of the Response to Information Request dated 2/16/09.)

A higher percentage of vapreotide patients receiving band ligation met the primary endpoint in both studies and treatment groups compared to sclerotherapy although the number of patients receiving sclerotherapy in VAP-301 was small.

For both studies VAP-301 and VAP-14, the percentage of patients meeting the primary endpoint that received vapreotide and underwent band ligation was similar. However the number of patients treated with band ligation in VAP-301 is doubled that treated with band ligation in VAP-14 vapreotide groups. One of the cautionary rules of historical comparisons is to consider the potential for improvement of operator performance of an intervention over time. The conclusion that the treatment difference compared to placebo is due solely to vapreotide based on the apparent similar response rates between the vapreotide arms would rest on the premise that operator performance remained the same over the decade between VAP-14 and VAP-301.

In VAP-14 vapreotide treated patients had a higher response rate than placebo in both the band ligation and sclerotherapy subgroups. In VAP-14, comparison of the proportion of patients meeting the primary endpoint across the two endoscopic therapy modalities showed a higher response rate in the band ligation subgroups.

Variceal Size

The table below shows the proportion meeting the primary endpoint by variceal size in VAP-301 and in the qualitative comparator study VAP-14.

Table 23. Subgroup Analysis - Variceal Size (Control of Bleeding at Day 5 and Survival; ITT)

Variceal size	VAP-301	Vap-14 (Vapreotide)	Vap-14 (Placebo)
< 5 mm	57% (4/7)	78% (21/27)	72% (18/25)
≥ 5 mm	79% (50/63)	61% (36/59)	43% (28/65)

* Data on size was in VAP-301, and data on Grade was in VAP-14. To compare variceal size/grade across treatment and study groups, the sponsor categorized varices into two groups defined as Grade0-1/<5mm and Grade2-3/>5mm.This is in accordance with the current recommendations of the AASLD and the American College of Gastroenterology (Garcia-Tsao et al 2007). (Table above was compiled by this reviewer using results from Page 39 of the Complete Response to Information Request Letter dated 2/16/2009.)

For VAP-301, because there were so few patients with small varices (< 5 mm), the effect of variceal size on achievement of the primary endpoint was not easily discerned.

For VAP-14, the percentage of patients meeting the primary endpoint was lower for those with large varices (≥5 mm) compared with those with small varices (< 5mm).

Comparing VAP-301 to VAP-14 results, it appeared that for patients with large varices (≥ 5 mm), VAP-301 patients had a higher response rate.

Child-Pugh Class

Control of bleeding by time periods (Tendo+6h, Tendo+48h and Tendo+120h) and Child Pugh class was a secondary endpoint and is discussed in the Secondary Endpoints section.

Although response rates decreased with time for both Child Classes B and C, the greatest decrease was in the Child Class C group. Class A patients had control of bleeding at each of the time intervals.

(See also Section 2.1.5 Analysis of Secondary Endpoints.)

Etiology of Cirrhosis

The table below shows the proportion meeting the primary endpoint by underlying cause of cirrhosis in VAP-301 and in the qualitative comparator study VAP-14.

Table 24. Subgroup Analysis – Etiology of Cirrhosis (Control of Bleeding at Day 5 and Survival; ITT)

	Statistic	VAP-301 (N=70)	VAP-14 (Sanvar) (N=98)	VAP-14 (Placebo) (N=98)
Underlying cause of cirrhosis				
Alcoholism only		14/23 (60.9%)	55/83 (66.3%)	44/84(52.4%)
Viral hepatitis only		8/10 (80.0%)	2/3 (66.7%)	1/3(33.3%)
Alcoholism + viral hepatitis		17/20 (85.0%)	7/9 (77.8%)	2/7(28.6%)

Statistic is n/N (%)
* Other accounted for 17 patients in VAP-301 group, 2 in VAP-14 Sanvar group, and 4 in VAP-14 Placebo group. (See Section 2.1.2.)
(Table above is taken from Page 38 of the Sponsor's Response to the Information Request dated 2/16/09.)

In Study VAP-14, the number of patients in the categories of alcoholism + viral hepatitis and viral hepatitis only was very small; thus, it is difficult to discern the effect of the underlying cause of cirrhosis on achievement of the primary endpoint.

In Study VAP-301, it is also difficult to discern the effect of the underlying cause of cirrhosis primarily because of the very small number of patients in the viral hepatitis only category. Comparing the alcoholism only group to the alcoholism + viral hepatitis group suggested that the alcoholism + viral hepatitis group had a higher response rate; no conclusions can be drawn however because of the relatively small number of patients in each of the two groups.

2.1.6.2 VAP-06

No subgroup analyses were conducted.

2.1.7 Analysis of Clinical Information Relevant to Dosing Recommendations

No additional analysis of clinical information relevant to dosing recommendations was conducted.

2.1.8 Discussion of Persistence of Efficacy and/or Tolerance Effects

Survival

The table below shows survival at Day 5 and Day 42 in VAP-301 and in the qualitative comparator study VAP-14.

Table 25. Survival at Day 5 and Day 42 (VAP-301 and VAP-14)

	VAP-301	VAP-14	
	(Vapreotide)	(Vapreotide)	(Placebo)
Day 5	90% (63/70)	95% (93/98)	93% (91/98)
Day 42	74% (52/70)	86% (84/98)	79% (77/98)

(Values in the table above were compiled by this reviewer from Pages 70and 71 of the VAP-301 Study Report.)

For VAP-301, there appeared to be a greater decrease in survival from Day 5 to Day 42 than the vapreotide treated group of VAP-14; the survival rates for VAP-301 were similar to those of the placebo group for VAP-14.

Medical Officer's Comments:
It is possible that the lower survival rate in the VAP-301 group than the VAP-14 vapreotide group could be related to the more complex disease etiology (i.e., higher proportion with combination of alcoholic liver disease and viral hepatitis) and a higher proportion of patients with large varices (≥ 5 mm) in VAP-301 than in VAP-14. However, the proportions of patients with decompensated cirrhosis (Child C) were similar between the two groups.

3 Appendices

The review of individual study reports has been integrated into the Integrated Review of Efficacy (see Section 2). Pertinent information from individual study reports that is not integrated into the Integrated Review of Efficacy is summarized below.

3.1 VAP-06 Amendment History

Major Protocol Amendment:
A protocol amendment was introduced after approximately one-third of the patients were enrolled. The amendment was implemented because of chronic blood shortages causing delays in transfusions. The delays in transfusions resulted in the following major change in the primary endpoint: decrease in the target Hct from 27 to 21.

Amendment to the Statistical Analysis Plan:
There was also an amendment to the statistical analysis plan (SAP) approximately a year after the study ended; SAP is dated September 30, 2005. (The study was completed on October 13, 2004).
Major changes included the following:
(1) Analysis of the pre-and post-protocol amendment populations separately; and
(2) Re-analysis of the data using VAP-14 criteria.

Applicant's Presentation of Results of VAP-06:
The sponsor did not provide overall results; results were provided separately as pre-amendment/post-amendment population.
The sponsor presented the primary efficacy results based on the following:
(1) Re-analysis of the data using VAP-14 criteria for the Pre-protocol amendment population;
(2) Analysis using the original VAP-06 criteria for the Pre-protocol amendment population; and
(3) Analysis using the amended VAP-06 criteria for the Post-protocol amendment population.

Pending Information Request for Analysis of Overall Results:
An information request is pending for a re-analysis of overall primary efficacy results and overall secondary efficacy results of VAP-06 stratifying by whether a study participant belongs to the pre-amendment or post-amendment population. For the primary endpoint, the respective primary endpoint criteria are used for the pre- and post-amendment populations. This information request is dated April 17, 2009.

Statistical Comments
NDA 21-761

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1. Overview

This document describes study design features of Study 301 and other clinical studies of vapreotide in order to help committee members interpret the evidence contained in the resubmission and determine if the evidence supports the effectiveness of vapreotide. Additionally, this document gives my statistical perspective on these issues.

2. Characteristics of an adequate and well-controlled study

From a statistical perspective, Study 301 is not an adequate and well-controlled study as defined by the Code of Federal Regulations (21 CFR 314.126). An important characteristic of an adequate and well-controlled study is "a design that permits a valid comparison with a control to provide a quantitative assessment of drug effect." The design of Study 301 does not permit a valid comparison with a control.

The CFR recognizes several types of controls that can be used in clinical studies. Among these are a dose-comparison control and a historical control. Although FDA recommended a dose-ranging study design, the applicant instead chose to use a historical control – the treatment arms from Study VAP-14.

The CFR recognizes historical controls as an acceptable control group under certain circumstances. In addition, the CFR cautions that historical controls are often a weak comparator and that historical control designs are reserved for special situations:

> "(v) Historical control. The results of treatment with the test drug are compared with experience historically derived from the adequately documented natural history of the disease or condition, or from the results of active treatment, in comparable patients or populations. Because historical control populations usually cannot be as well assessed with respect to pertinent variables as can concurrent control populations, historical control designs are usually reserved for special circumstances. Examples include studies of diseases with high and predictable mortality (for example, certain malignancies) and studies in which the effect of the drug is self-evident (general anesthetics, drug metabolism)."

The applicant draws upon similarities between participants enrolled in VAP-14 and Study 301 to argue the efficacy of vapreotide. Unfortunately, the participants enrolled in Study 301 differ from the participants enrolled in VAP-14. The most notable difference is the type of endoscopic treatment used to control variceal bleeding. When VAP-14 was conducted, sclerotherapy was

the preferred modality. When Study 301 was conducted ten years later, band ligation was the preferred choice. In addition to band ligation giving better control of rebleeding, the techniques used to perform the procedure have likely improved as well. Today, the medical community considers bind ligation superior to sclerotherapy. The compositions of the patient populations in Study 301 and VAP-14 reflect this change in medical practice. In Study 301, 90% of the participants received band ligation compared with 31% of the participants in VAP-14; most other participants received sclerotherapy. Therefore, any treatment-related improvements seen in Study 301 could be due to changes in endoscopic treatment modalities and not to drug therapy.

In addition to the type of control group used in a clinical study, the method of assigning patients to treatment groups and measures taken to minimize bias are important characteristics in determining whether a study is adequate and well-controlled. Section (b) of 21 CFR 314.126 states:

> "(4) The method of assigning patients to treatment and control groups minimizes bias and is intended to assure comparability of the groups with respect to pertinent variables such as age, sex, severity of disease, duration of disease, and use of drugs or therapy other than the test drug. The protocol for the study and the report of its results should describe how subjects were assigned to groups. Ordinarily, in a concurrently controlled study, assignment is by randomization, with or without stratification.
> (5) Adequate measures are taken to minimize bias on the part of the subjects, observers, and analysts of the data. The protocol and report of the study should describe the procedures used to accomplish this, such as blinding."

Study 301 was an open-label, single treatment arm, historic control study design. Because we cannot be assured that bias was minimized, we cannot be assured that any observed effects are due to study drug. For example, it is possible that subjects who were more likely to respond were invited to enroll in the study or that the knowledge that all subjects were receiving study drug could have unknowingly influenced the assessments of the patient-level outcomes.

3. Level of clinical evidence in the submission

In this section, I review why the collective evidence from the studies submitted by the applicant does not meet the level of statistical evidence needed to support the effectiveness of vapreotide. Specifically, VAP-14 did not meet the criteria needed for a single study; Study 301 is not an adequate and well-controlled study; and the results from the meta-analysis, even if a meta-analysis could be used to support drug approvals, are not persuasive.

In the following section, I discuss the level of evidence needed from a single study to support the effectiveness of a drug product and the characteristics of a single, adequate and well-controlled study that could make a single study sufficient to support an effectiveness claim.

3.1 Overview of level of evidence needed to support effectiveness

"Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products", discusses issues relevant both to the original submission for Sanvar and to its resubmission. I want to focus on the section that describes the level of evidence needed from a single study, which is particularly relevant to VAP-14 and Study 301.

According to the guidance document, the scientific basis for requiring "more than one adequate and well-controlled study reflects the need for independent substantiation of experimental results. A single clinical experimental finding of efficacy, unsupported by other independent evidence, has not usually been considered adequate scientific support for a conclusion of effectiveness." The guidance documents states four reasons: potential bias, chance finding of a positive study result, generalizable study results and, rarely, scientific fraud. These reasons, as stated in the guidance document, are reproduced here:

"

- Any clinical trial may be subject to unanticipated, undetected, systematic biases. These biases may operate despite the best intentions of sponsors and investigators, and may lead to flawed conclusions. In addition, some investigators may bring conscious biases to evaluations.

- The inherent variability in biological systems may produce a positive trial result by chance alone. This possibility is acknowledged, and quantified to some extent, in the statistical evaluation of the result of a single efficacy trial. It should be noted, however, that hundreds of randomized clinical efficacy trials are conducted each year with the intent of submitting favorable results to FDA. Even if all drugs tested in such trials were ineffective, one would expect one in forty of those trials to "demonstrate" efficacy by chance alone at conventional levels of statistical significance.[5] It is probable, therefore, that false positive findings (i.e., the chance appearance of efficacy with an ineffective drug) will occur and be submitted to FDA as evidence of effectiveness. Independent substantiation of a favorable result protects against the possibility that a chance occurrence in a single study will lead to an erroneous conclusion that a treatment is effective.

- Results obtained in a single center may be dependent on site or investigator specific factors (e.g., disease definition, concomitant treatment, diet). In such cases, the results, although correct, may not be generalizable to the intended population. This possibility is the primary basis for emphasizing the need for independence in substantiating studies.

- Rarely, favorable efficacy results are the product of scientific fraud. "

Moreover, the guidance states that any study relied on to support effectiveness must be adequate and well-controlled. Although a single study usually cannot address these potential problems, the guidance identifies five characteristics of an adequate and well-controlled study that could make the results from a study adequate to support an effectiveness claim:

1. Large multicenter study
2. Consistency across study subsets
3. Multiples studies in a single study
4. Multiple endpoints involving different events
5. Statistically very persuasive finding

3.2 Original submission

Study VAP-14 did not provide the level of evidence needed from a single study. Although the study was multicenter, the results across study subsets were inconsistent. In particular, the largest study site (Center 18), which accounted for 14% of the enrollment, was the only site with a statistically significant treatment effect. When that site was excluded from the analysis, the treatment effect among the remaining study participants was not significant.

An unequal distribution among the two treatment groups in small esophageal varices may have accounted for the effect observed at Center 18. Compared with the placebo treatment group, the vapreotide treatment group in Center 18 had a higher prevalence of small varices, which respond to treatment better than do large varices. At all other sites, the distributions between treatment groups of variceal size were about the same. Potentially, the treatment effect seen at Center 18 may be due to the higher frequency of small esophageal varices among the vapreotide-treated subjects.

The submission also contained two other studies, VAP-07 and VAP-02, which did not show a statistically significant treatment effect.

Taken together, the three studies did not provide sufficient evidence to support the effectiveness of vapreotide.

3.3 Current submission

From a statistical perspective, the level of evidence provided by the current submission is not sufficient to support the effectiveness of vapreotide. The submission contains results from Study 301, which the applicant conducted to support the effectiveness of vapreotide, and the results of a meta-analyis.

Study 301 is open-label and contains only a single treatment arm. From my perspective, Study 301 is not an adequate and well-controlled study and, therefore, cannot support the

effectiveness of vapreotide. Two key features of the study design – open-label and a single treatment arm – do not permit ruling out "unanticipated, undetected, systematic biases" as stated in the guidance on clinical evidence. Moreover, due to the increased use of band ligation, the review team could not identify a suitable historical control for Study 301. Sclerotherapy, which is not as effective as bind ligation, was the primary endoscopic treatment used in the completed studies of vapreotide.

The applicant also submitted a meta-analysis to support the efficacy of vapreotide. Meta-analyses are rarely, if ever, used as the primary evidence to support drug approvals. Even if we did rely on meta-analyses, the results from the meta-analysis contained in the submission are not persuasive. The meta-analysis contains three studies: VAP-14, VAP-07 and VAP-06. The statistically significant treatment effect appears to be dominated by VAP-14. The other two studies are much smaller and are not statistically significant. For reasons stated in the review of the original submission, which contained VAP-14 and VAP-07, the evidence is insufficient to support the efficacy of vapreotide.

4. Conclusisons

From a statistical perspective, the collective evidence does not support the efficacy of vapreotide for the treatment of acute variceal bleeding related to portal hypertension in association with endoscopic treatment. Study 301, which the applicant conducted to address the deficiencies in the approvable letter, is open-label and contains only one treatment arm. Any open-label study, especially one with a single treatment arm, can introduce unknown biases in the operation of the study and the evaluation of the results. For example, potentially, investigators may have enrolled subjects who were more likely to respond to treatment. However, these biases are unmeasurable and the degree to which they are present is unknown.

Moreover, due to changes over time in the type of endoscopic treatment used to control variceal bleeding, the review team could not identify a suitable historical control to assess the treatment effect of vapreotide. Therefore, any perceived treatment-related improvements seen in Study 301 could be due to improvements in endoscopic treatment and not due to drug therapy.

Tab 3 Statistical Comments and Review of Efficacy

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Science
Office of Biostatistics

Statistical Review and Evaluation

CLINICAL STUDIES

NDA:	NDA 21-761
Drug Name:	Sanvar (vapreotide) IV Injection, 0.6 mg
Indication(s):	Treatment of acute variceal bleeding related to portal hypertension in association with endoscopic treatment.
Applicant:	Debiovision, Inc.
Date(s):	Letter date: 9/30/08 Receipt date: 10/1/08 PDUFA: 7/1/09
Review Priority:	Standard
Biometrics Division:	DB3
Statistical Reviewer:	Lisa A. Kammerman, Ph.D.
Concurring Reviewers:	Michael Welch, Ph.D.
Medical Division:	Division of Gastroenterology Drug Products (HFD-180)
Clinical Team:	Zana Marks, MD Hugo Gallo Torres, MD, Ph.D. Anil Rajpal, MD
Project Manager:	Stacy Barley, LCDR, M.S.N., M.H.A.

Keywords: Clinical studies, NDA review, meta-analysis

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APPENDICES (SEE PART 2 SECTION 2 OF BRIEFING DOCUMENT)

Tab 3 Statistical Comments and Review of Efficacy

1. EXECUTIVE SUMMARY

1.1. Conclusions and Recommendations

The statistical evidence provided in the re-submission of the NDA does not support the efficacy of vapreotide for the treatment of acute variceal bleeding related to portal hypertension in association with endoscopic treatment.

To address deficiences identified in the approvable letter and to demonstrate the efficacy of vapreotide, the re-submission contains one new study, Study 301, which is open-label and contains only a single arm. Due to changes over time in the endoscopic treatment for variceal bleeding, the medical reviewers cannot identify an historical control appropriate for Study 301. Band ligation is now the favored endoscopic modality for treating variceal bleeding and was the predominant therapy in Study 301. By contrast, sclerotherapy was the primary treatment in potential candidates for historical controls. Bind ligation produces better outcomes than does sclerotherapy. Therefore, any treatment-related improvements seen in Study 301 could be due to improvements in endoscopic treatment and not to drug therapy.

Even if an appropriate historical control exists, the open-label design and the presence of a single treatment arm casts doubt on Study 301 being an adequate and well-controlled trial. Any open-label study, especially one with a single treatment arm, can introduce unknown biases in the operation of the study and the evaluation of the results. These biases are unmeasurable and the degree to which they are present is unknown.

1.2. Brief Overview of Clinical Studies

Study 301, “The Early Use of Sanvar with Endoscopic Treatment for the Control of Acute Variceal Bleeding Due to Portal Hypertension”, is open-label and contains only a single treatment arm. Vapreotide was administered for 5 days in subjects with acute variceal bleeding due to portal hypertension. After the administration of vapreotide, a diagnostic endoscopy was performed to allow confirmation of the original bleeding. Subjects bleeding from varices underwent band ligation, sclerotherapy, or both, according to the protocols of the individual sites.

The primary objective is the control of bleeding at 5 days after the end of endoscopic treatment. A successful treatment consists of primary control of bleeding during the first 48 hours followed by no rebleeding from Day 3 to Day 5, and survival at Day 5.

1.3. Statistical Issues and Findings

Because Study 301 is open-label and contains a single treatment arm, it is not an adequate and well-controlled study. The results from Study 301 do not establish the efficacy of vapreotide.

2. INTRODUCTION

2.1. Overview

This NDA re-submission is a complete response to deficiencies stated in an approvable letter dated 12/21/2004. In response to the letter, the applicant conducted an open-label, single arm study – Study 301 – to establish the efficacy of vapreotide for the treatment of acute variceal bleeding related to portal hypertension in association with endoscopic treatment.

The original submission contained a single randomized, double-blinded, placebo-controlled study (VAP-14) that demonstrated superiority over placebo at the nominal significance level of 0.05. However, the results did not meet the level of evidence required of a single study. The results depended on a single center (Center 18), which accounted for 14% of the sample and which appeared to have subjects who were somewhat healthier than subjects enrolled in other centers. When subjects from Center 18 were excluded from the analyses, the results were statistically non-significant. Two other studies (VAP-07 and VAP-02) of vapreotide did not show superiority over placebo. For further details, see Dr. Wen-Jen Chen's statistical review, dated 12/3/2004.

After receiving the approvable letter, the applicant proposed an open-label, single-arm study of vapreotide. In his statistical review dated, 4/21/2006, Dr. Chen stated the proposed study was not acceptable for establishing the efficacy of vapreotide. The proposed study was not well-controlled trial and cross-trial comparisons were inappropriate.

Despite the statistical and clinical trial design issues, the applicant conducted the open-label, single-arm study (Study 301). For the reasons cited by Dr. Chen and due to the lack of an appropriate historical control, the evidence contained in the re-submission does not support the efficacy of vapreotide.

2.2. Data Sources

- Complete Response to Deficiencies, NDA 21-761 (paper submission), dated 9/30/08
- Statistical Review of NDA 21-761, dated 12/3/2004 (DFS file)
- Addendum to Statistical Review of NDA 21-761, dated 2/17/2006 (DFS file)
- Statistical Comments on Special Protocol Assessment, dated 4/21/2006 (DFS file)

3. STATISTICAL EVALUATION

3.1. Evaluation of Efficacy

In this section, I review Study 301, the new study conducted by the applicant to address the deficiencies cited in the approvable letter. In addition, I dissuss the potential historical controls identified as candidates by the medical team.

3.1.1. Study 301

The goal of Study 301, "The Early Use of Sanvar with Endoscopic Treatment for the Control of Acute Variceal Bleeding Due to Portal Hypertension", is to address deficiencies listed in the approvable letter issued on December 22, 2004 by the medical division.

The study is open-label and contains only a single treatment arm. Vapreotide was administered for 5 days in subjects with acute variceal bleeding due to portal hypertension. After the administration of vapreotide, a diagnostic endoscopy was performed to allow confirmation of the original bleeding. Subjects bleeding from varices underwent band ligation, sclerotherapy, or both, according to the protocols of the individual sites.

The primary objective is the control of bleeding at 5 days after the end of endoscopic treatment. A successful treatment consists of primary control of bleeding during the first 48 hours followed by no rebleeding from Day 3 to Day 5, and survival at Day 5.

Seventy subjects enrolled in the study. The origin of hemorrhage for almost all subjects (94%) was esophageal varices. Most subjects were male (76%) and the average subject was 53 years of age. Alcoholism was the predominant cause of cirrhosis, either alone (31%) or with viral hepatitis (29%).

Almost all subjects received band ligation (90%). Sclerotherapy, by itself or in combination with band ligation, accounted for 10% of the endoscopic treatment procedures.

Overall, 77% of the subjects were treatment successes (i.e, control of bleeding during the first 48 hours, no rebleeding from Day 3 to Day 5 and alive at Day 5) with a 95% confidence interval of 65.6% to 86.3%.

Although the applicant draws upon similarities between subjects enrolled in Study VAP-14 and Study 301 to argue the efficacy of vapreotide, a key difference is the choice of endoscopic treatment. In Study VAP-14, conducted over 10 years ago, sclerotherapy was the primary treatment, whereas band ligation is now the treatment of choice. The medical community recognizes band ligation as a treatment that gives better outcomes than does sclerotharpy. Also, the skills and techniques involved with band ligation have likely improved as well, potentially leading to better outcomes with band ligation today as compared with band ligation done 10 years ago.

In Study 301, 90% of the subjects received band ligation compared with 31% subjects in VAP-14. Thus, the higher treatment success rate in Study 301 compared with VAP-14 could be due to the use of band ligation and not to the effect of vapreotide.

Moreover, Study 301 is not an adequate and well-controlled study. Therefore, the results from this study do not establish the efficacy of vapreotide.

3.1.2. Historical Controls

Because Study 301 does not contain a comparator, the medical review team explored the possibility of using historical controls to help establish the efficacy of Sanvar. From among the published studies summarized in the NDA, the medical team identified five published studies with placebo arms that, potentially, can serve as historical controls. Four studies are in peer-reviewed journals and the fifth is in an abstract. describes key features of Study 301 and the five published studies. Two of the five studies cannot be used as historical controls. Signorelli 1996 is only an abstract. Zuberi 2000 is essentially a single site study.

The placebo arms in the remaining three studies cannot be used as comparators to establish the efficacy of Sanvar. In these studies (Besson 1995, Avegerinos 1997 and Cales 2001), sclerotherapy is the predominant endoscopic treatment whereas band ligation is the predominant treatment in Study 301. Therefore, any apparent treatment advantage when comparing Sanvar in Study 301 with the placebos in these two studies could be due to the effect of band ligation.

VAP-14, whose results did not satisfy the level of evidence needed to approve vapreotide in the original submission, is the subject of the Cales 2001 article.

Tab 3 Statistical Comments and Review of Efficacy

Table 1: Summary of important features of Study 301 and randomized studies containing placebo treatment arms. Only the placebo treatments are summarized in this table.

		Author and Year of publication				
	Study 301	Besson 1995	Signorelli 1996 (Abstract)	Avgerinos 1997	Zuberi 2000	Cales 2001
Number of subjects	70	101	30	104	35	93
Number of sites	15	15	Unknown	9	1 or 2	22
Country	US	France	Italy	Belgium (6), Netherlands (1), Greece (2)	Pakistan	France
Age:	53 (28-72)		Unknown	58	39	55
Males:	76%		Unknown	70%	80%	83%
Causes of cirrhosis:			Unknown			
Alcoholism:	31%	92%		59%	9%	86%
Viral hepatitis only:	14%			24%		
Alcochol plus viral hepatitis:	29%					
Other:	26%			18%		
Previous history of PHT bleeding					**	
1 episode:	23%					
2 episodes:	7%					
3+ episodes:	4%					
Previous treatment for portal hypertension;						
Beta-blockers:	37%			2%		46%
Nitrates:	0%					
Endoscopy:	33%	23%			**	21%
Origin of bleeding:						
Esophageal varix:	89%		100%	72%	100%	97%
Gastric varix:	7%					2%
Portal hypertensive gastropathy:	1%					1%
Varices and portal hypertensive gastro:	3%					
Gastric fundal varices					54%	
Gastric junctional varices					51%	
Congestive gastropathy					69%	
Endoscopic treatment:						
Sclerotherapy:	5%	100%	100%	100%	100%	56%
Band ligation:	90%					31%
Other:	-					13%
Band ligation plus sclerotherapy:	6%					

**: Subjects who had a session of endoscopic variceal sclerotherapy (EVS) earlier were excluded from the study

Source: Table 2.5-1 of the Clinical Summary and Module 5.4 (Literature References)

3.1.3. Meta-analysis

The re-submission includes a meta-analysis, "Meta-analysis of vapreotide for treatment of bleeding due to portal hypertension," of three placebo-controlled studies of vapreotide. The applicant concludes the results "provide statistically significant evidence of a positive effect of vapreotide on control of bleeding due to portal hypertension."

Five vapreotide studies were considered for inclusion in the meta-analysis. One study, VAP-02, was excluded because of the large number and types of protocol violations. A major amendment affected a second study, VAP-06. For the purposes of the meta-analysis, VAP-06 was considered two studies: pre-amendment and post-amendment. The meta-analysis included the pre-amendment portion – the post-amendment phase was excluded.

The meta-analysis included the following three studies:

- VAP-14
- VAP-07
- VAP-06 (pre-amendment)

To the extent possible, outcomes were standardized to agree with the definition used in VAP-14.

The applicant performed meta-analysis of the odds ratio using the DerSimonian and Laird technique. Table 2 summarizes the response rates and odds ratios for each study and a forest plot. The summary odds ratio was 1.83 (95% CI: 1.16- 2.87, p=0.009).

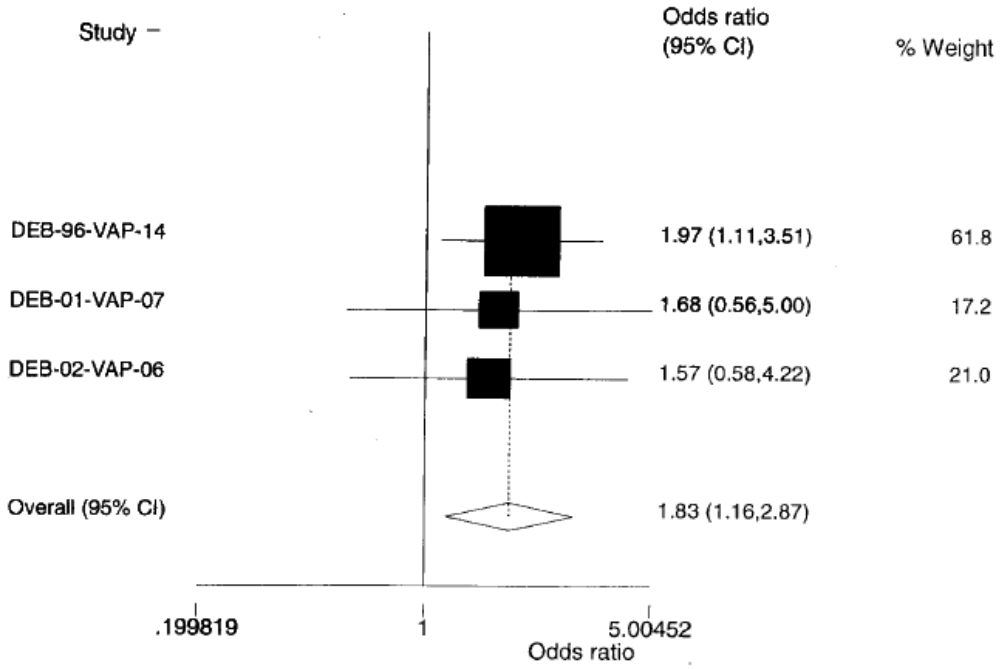
An unweighted, pooled estimate for the treatment success proportion was calculated, and exact binomial confidence limits were estimated. The proportion with control of bleeding in the combined studies is 66.5% (95% CI: 58.6% - 73.7%) for the vapreotide groups and 51.9% (95% CI: 43.8% - 59.9%) for the placebo groups.

Table 2: Summary of response rates and odds ratios from studies used in the meta-analysis, plus the results from Study 301

Study	Success	Vapreotide		Placebo		Odds Ratio [95% CI]
		N	%	N	%	
DEB-96-VAP-14 (pivotal)	Yes	65	66.3	49	50.0	1.97 [1.11, 3.51]
	No	33	33.7	49	50.0	
	Total	98		98		
DEB-01-VAP-07	Yes	22	71.0	16	59.3	1.681 [0.56, 5.00]
	No	9	29.0	11	40.7	
	Total	31		27		
DEB-02-VAP-06 Pre-amendment	Yes	20	62.5	17	51.5	1.569 [0.58, 4.22]
	No	12	37.5	16	48.5	
	Total	32		33		
DEBV-VAP/EVB-301	Yes	54	77.1	NA	NA	NA
	No	16	22.9	NA	NA	
	Total			NA		

Source: Table 1, "Meta-analysis of vapreotide for treatment of bleeding due to portal hypertension," Section 5.5.3.3, re-submission

Figure 1: Forest plot of meta-analysis results



Source: Figure 1, "Meta-analysis of vapreotide for treatment of bleeding due to portal hypertension," Section 5.5.3.3, re-submission

At best, results from a meta-analysis are only supportive evidence for efficacy. Moreover, the meta-analysis includes VAP-14, which is the largest of the three studies and the only one with a statistically significant odds ratio. This study appears to account for the statistically significant results of the meta-analysis. In other words, the results of the meta-analysis are essentially the results of VAP-14. As discussed by Dr. Chen in his review of VAP-14, VAP-14 is not sufficient for establishing the efficacy of vapreotide. By extension, the results of the meta-analysis, even if a meta-analysis could be used in a regulatory setting to establish efficacy, is not sufficient for supporting the efficacy of vapreotide.

3.2. Evaluation of Safety

Because Study 301 was conducted ten years after the other studies of vapreotide and because Study 301 does not contain a placebo treatment arm, pooled safety analyses should be conducted both with and without Study 301. The inclusion of Study 301, which does not have a concurrent placebo treatment arm, may introduce bias into the comparison of vapreotide with placebo.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

Not applicable.

5. SUMMARY AND CONCLUSIONS

5.1. Statistical Issues and Collective Evidence

Because Study 301 is open-label and contains a single treatment arm, it is not an adequate and well-controlled study. Due to changes over time in the endoscopic treatment for variceal bleeding, the medical reviewers could not identify an appropriate historical control for Study 301. Therefore, the results from this study cannot establish the efficacy of vapreotide.

5.2. Conclusions and Recommendations

The evidence provided in the re-submission of the NDA does not support the efficacy of vapreotide for the treatment of acute variceal bleeding related to portal hypertension in association with endoscopic treatment.

Study 301, submitted to support the efficacy of vapreotide, is open-label and contains only a single arm. Due to changes in medical practice, the medical reviewers could not identify an historical control appropriate for Study 301. Band ligation is now the favored endoscopic modality for treating variceal bleeding and was the predominant therapy in Study 301. By contrast, sclerotherapy was the primary treatment in studies that contained placebo treatments arms and were potential candidates for historical controls. Bind ligation yields better patient outcomes than does sclerotherapy. Therefore, any treatment-related improvements seen in Study 301 could be due to improvements in endoscopic treatment and not to drug therapy.

Even if an appropriate historical control existed, the open-label design and the presence of a single treatment arm casts doubt on Study 301 being an adequate and well-controlled trial. Any open-label study, especially one with a single treatment arm, can introduce unknown biases in the operation of the study and the evaluation of the results. These biases are unmeasurable and the degree to which they are present is unknown.

The results from the meta-analysis are not persuasive. Essentially, they reflect the findings from VAP-14, which was not sufficient to support approval of vapreotide.

CLINICAL REVIEW

DIVISION OF GASTROENTEROLOGY PRODUCTS

Application Type	NDA
Submission Number	21-761
Letter Date	October 1, 2008
Stamp Date	October 1, 2008
PDUFA Goal Date	July 1, 2009
Reviewer Name	Wen-Yi Gao, M.D., Ph.D.
Review Completion Date	April 22, 2009
Established Name	Vapreotide acetate
Trade Name	Sanvar™ Injection
Therapeutic Class	Somatostatin Analogue
Applicant	Debiovision Inc.
Formulation	Intravenous formulation
Dosing Regimen	50 µg I.V. bolus followed by a continuous I.V. infusion of 50 µg/hr (1.2 mg/day) for 5 days
Indication	Treatment of acute variceal bleeding due to portal hypertension, in association with endoscopic treatment
Intended Population	Adult cirrhotic patients with acute variceal hemorrhage

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1 BACKGROUND

1.1 Summary of Clinical Findings

1.1.1 Brief Overview of Clinical Program

The proposed indication is for the treatment of acute variceal bleeding due to portal hypertension in association with endoscopic treatment in adult cirrhotic patients.

Somatostatin and its analog octreotide are not approved for the variceal bleeding indication in the United States.

Summary of First Cycle Review

The clinical review of the original NDA submission was conducted by Dr. Fathia Gibril and is included in this briefing document.

In the first cycle review, the sponsor submitted three studies (Study VAP-14, Study VAP-07, and Study VAP-02) on February 27, 2004 to support the approval.

In Dr. Gibril's safety conclusions, she stated "The 5-day course of vapreotide for treatment of acute variceal bleeding due to portal hypertension is associated with no significant toxicity. The safety profile of vapreotide was comparable with that of placebo, suggesting that many events recorded were a reflection of the patient's underlying medical conditions."

Summary of Second Cycle (Current) Review

In the resubmission on October 1, 2008, the sponsor provided a single arm confirmative study (Study VAP-301) and a controlled efficacy and safety study (Study VAP-06):

- Study VAP-301 was an open label single arm study, in which 103 subjects were enrolled. After the protocol-pre-specified exclusion of 33 subjects, the ITT population included 70 subjects in one treatment arm. This study was comparable with the pivotal study in study population, Child-Pugh scores, methodology, safety and efficacy endpoints with the exception of single-arm open label design.

- The efficacy and safety study (Study VAP-06) was conducted in Romania and Bulgaria. The ITT population included 267 subjects. The original study design, population, methodology, safety and efficacy endpoints were comparable with the pivotal study. However, because of blood supply shortages, a major protocol amendment was made after enrollment of 70 patients. The amendment included revision to efficacy criteria.

In the updated safety profile (all vapreotide studies), there were nine clinical trials involving a total of 728 patients who received at least one dose of vapreotide.

Randomized, double-blind, placebo-controlled trials comprised 76% of patients in the safety database. The variceal bleeding studies comprised 64% of patients in the safety database. The daily dose of vapreotide was 1.2 mg/day in the majority (92%) of the studies, and 1.5 mg/day in the remainder. The route of administration was I.V. for the proposed variceal bleeding studies, and subcutaneous (S.C.) for the remainder of studies.

In the updated safety database (variceal bleeding studies), there were five clinical trials involving 469 patients who received at least one dose of vapreotide, and 347 patients in the placebo arms. Drs. Wen-Yi Gao and Zana Marks were responsible for the assessment of safety and efficacy, respectively.

Key findings of the pooled safety review were summarized as follows:
1) The 42-day mortality rates were similar between vapreotide and placebo arms: vapreotide 17.5% (82/469) vs. placebo 16.7% (58/347).

2) The 5-day mortality rates were similar between vapreotide and placebo arms: vapreotide 7.0% (33/469) vs. placebo 6.9% (24/347).

3) The causes of death that were found to be numerically higher (Days 1-5) in vapreotide arms than in placebo arms were as follows:

- Bradycardia / Cardiac Arrest 0.6% (3/469) vs. 0
- Septic shock 0.4% (2/469) vs. 0
- Disseminated intravascular coagulation (DIC) 0.2% (1/469) vs. 0;
  - Two additional deaths due to DIC on Days 11 and 12 vs. 0
- Respiratory failure / pulmonary embolism 0.2% (1/469) vs. 0
- Cerebrovascular accident 0.2% (1/469) vs. 0;
- Severe systemic inflammatory response syndrome (SIRS) 0.2% (1/469) vs. 0
- Thrombocytopenia / hypovolemic shock 0.2% (1/469) vs. 0

4) Death rate (Days 1-5) due to Hemorrhagic Shock was lower in vapreotide arms: 3.8% (18/469) vs. 5.5% (19/347)

5) Overall number of patients with SAEs in vapreotide arms (34%) was lower than in placebo arms (39%).

- Most frequently occurred SAEs were GI bleeding in both arms.

6) SAEs that were higher in vapreotide arms than placebo arms:

- Renal failure 3.2% vs. 1.4%
- Respiratory failure 1.7% vs. 0
- Thrombocytopenia 1.7% vs. 0.3%
- Bradycardia 1.1% vs. 0.3%

7) SAEs that were lower in vapreotide arms than in placebo arms:

- Melena 8.5% vs. 10.4%
- Hepatic encephalopathy 10.4% vs. 11.5%

- Upper GI hemorrhage 14.7% vs. 15.3%

8) Most common AE was GI bleeding:
- Vapreotide arms 23% vs. Placebo arms 26%

9) Most frequent cause of dropouts due to AEs was upper GI bleeding:
- Vapreotide arms 5% vs. Placebo arms 7%

Limitations of the available data include:
- No animal immunogenicity study
- Limited interim platelet count data from vapreotide trials. Vapreotide effects on the drop of platelet count are not clear.

In summary, it appears that higher death rates in vapreotide arms focus on the categories of intravascular coagulation, systemic inflammation, thrombocytopenia and bradycardia. Based on the available information, contributions of vapreotide exposure to the adverse reactions cannot be ruled out.

1.1.2 Safety

Exposure

The updated safety database (up to October 1, 2008) of vapreotide included nine clinical trials involving a total of 728 subjects who received at least one dose of vapreotide:
- Four randomized, double-blind, placebo-controlled studies and one open-label study involving a 5 day course of treatment for variceal bleeding (469 subjects);
- A randomized, double-blind, placebo-controlled trial involving a 7 day course of treatment for pancreatic surgery (Study DEB-98-VAP-06, 187 subjects); and
- Three small open-label efficacy studies involving prolonged treatment (21 to 180 days) for acromegaly (Study DEB-95-VAP-02, 15 subjects), carcinoid/neuroendocrine tumors (Study DEB-92-VAP-02, 35 subjects), and Crohn's disease (Study DEB-93-VAP-09, 22 subjects).

The daily dose of vapreotide was 1.2 mg in the majority (92%) of the studies, and 1.5 mg in the remainder. Randomized, double-blind, placebo-controlled trials comprised 75% of patients in the safety database. The variceal bleeding studies comprised 64% of patients in the safety database. Approximately 70% of the subjects in variceal bleeding studies (1.2 mg daily) completed the 5-day course of treatment.

Adverse Events (AEs)

Among patients receiving 1.2 mg/day vapreotide (or placebo), 79% of the 469 vapreotide-treated patients experienced at least one treatment-emergent adverse events (TEAEs), as compared with 83% of the 347 patients in the placebo group.

Comparison of adverse event rates by body system showed that hematopoietic and lymphoid system disorders in the vapreotide group were significantly higher than that of the placebo (4.9% [23/469] vs. 1.7% [6/347]; $p<0.05$) that includes a high incidence of thrombocytopenia (1.7% [8/469] vs. 0.3% [1/347]).

Common Adverse Events

The most common adverse events in variceal bleeding studies were gastrointestinal disorders: 262/469, 55.8% of vapreotide group versus 238/347, 68.5% of placebo control group (Safety Population).

TEAEs reported in ≥5% of vapreotide patients in variceal bleeding studies and overall studies in the safety databases include:

- Effects from the pharmacologic action of vapreotide, including abdominal pain, diarrhea, nausea, and vomiting due to imbalance of gastrointestinal hormonal secretory function; and hyperglycemia resulting from alterations in the balance between counter-regulatory hormones, insulin, glucagons, and growth hormone;
- Effects of underlying disease, but the drug effects can not be ruled out, including hepatic encephalopathy, melena, and gastrointestinal hemorrhage;
- Pyrexia;
- Headache.

There was no significant difference between vapreotide arms and placebo arms.

Serious Adverse Events (SAEs)

Among the 469 subjects who received at least one dose of vapreotide for the treatment of variceal bleeding, 34% (160/469) of the subjects experienced at least one SAE during the studies, while 38% (134/347) of the patients in the placebo groups experienced at least one SAE.

The SAEs included upper GI hemorrhage (hematemesis, melena), shock (hemorrhagic, hypovolemic), hepatic encephalopathy, hepatorenal syndrome, and hepatic failure. The sponsor concluded that these SAEs are solely disease-related.

Imbalanced SAE categories between vapreotide groups and control groups included disseminated intravascular coagulation (3 patients vs. 0), thrombocytopenia (9 patients vs. 1 patient), atrial fibrillation (4 patients vs. 0), bradycardia (5 patients vs. 0), gastrointestinal bleeding (101 patients vs. 87 patients), hematuria (4 patients vs. 1 patient), renal failure (13 patients vs. 4 patients), acute respiratory distress syndrome (4 patients vs. 1 patient), bronchial obstruction (2 patients vs. 0), bronchial spasm (2 patients vs. 0), pulmonary embolism (1 patient vs. 0), respiratory failure (8 patients vs. 0), cerebral vascular accident (2 patients vs. 0), shock (15 patients vs. 10). The contribution of drug effects to the imbalanced SAEs can not be ruled out.

Deaths

Eighty-two subjects (17.5%) of the 469 in vapreotide arms died during the 42-day studies, compared to 58 subjects (16.7%) of the 347 in placebo arms. The mortality rates were within the range of the reported hospital mortality of 15% to 20% of esophageal variceal bleeding due to cirrhosis in the United States (Dy SM 2003).

Thirty-three subjects (7.0%) of the 469 in vapreotide arms died during the 5-day treatment, compared to 24 subjects (6.9%) of the 347 in placebo arms.

Most common causes of deaths (Days 1-5) were uncontrolled initial hemorrhage and uncontrolled re-bleeding, followed by hemorrhagic shock. The vapreotide arms had lower rates compared with placebo arms:

- Initial hemorrhage: vapreotide 2.1% (10/469) vs. placebo 2.9% (10/347);
- Re-bleeding (upper GI hemorrhage, duodenal ulcer hemorrhage, melena): vapreotide 1.7% (8/469) vs. placebo 2.6% (9/347).

Less common causes of deaths (Days 1-5) had diversified disease categories. Events leading to death that occurred at a higher rate on vapreotide relative to placebo included:

- Bradycardia / Cardiac arrest: 0.6% (3/469)
- Septic shock: 0.4% (2/469)
- Severe systemic inflammatory response syndrome: 0.2% (1/469)
- Disseminated intravascular coagulation: 0.2% (1/469)
  - Two additional deaths due to DIC on Days 11 and 12 vs. 0
- Acute respiratory failure / pulmonary embolism: 0.2% (1/469)
- Cerebrovascular accident: 0.2% (1/469)
- Thrombocytopenia / hypovolemic shock: 0.2% (1/469)

Independent analysis of cause of death: On December 20, 2008, DGP requested that the sponsor provide individual clinical hematologic data and detailed narratives for analysis of cause-specific mortality. The sponsor provided the results of platelet count testing from four patients prior to deaths (Study VAP-301). The results revealed that three of the four patients experienced rapid drop of platelet counts after the initiation of vapreotide treatment.

Medical Reviewer's Safety Comments:
Because these deaths occurred after initiation of vapreotide treatment, and did not occur in controls, the contribution of vapreotide exposure to the deaths cannot be ruled out. This reviewer was concerned about two theoretical mechanisms that may have contributed to serious outcomes.
1) Could systemic activation of monocytes/macrophages (intravascular coagulation and systemic inflammation) have contributed to adverse outcomes, and 2) Could sympathetic inhibition and microvascular effects of somatostatin have contributed to adverse outcomes.

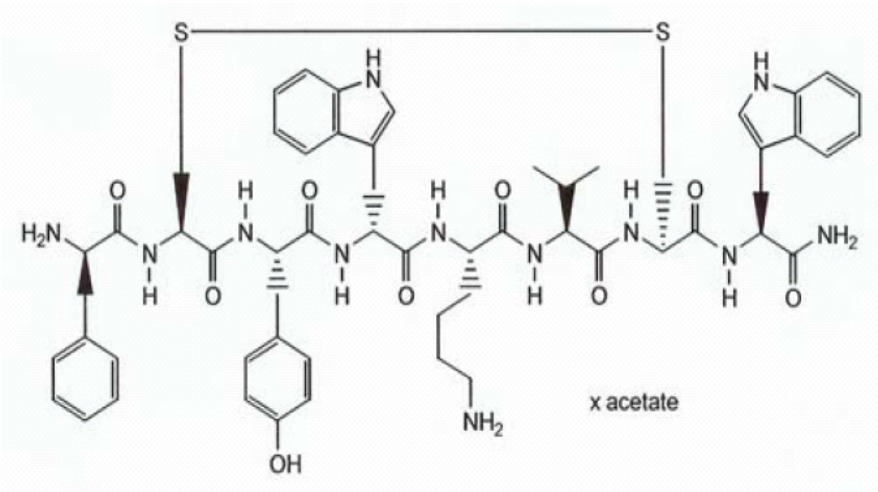
2 INTRODUCTION AND REGULATORY HISTORY

2.1 Product Information

The generic name of the product is vapreotide acetate and the trade name is Sanvar™. Vapreotide is a cyclic octapeptide analog of native somatostatin, mimics natural somatostatin pharmacologically, and has longer duration of action against somatostatin receptors (half life approximately 21 minutes, compared to 2 to 3 minutes for somatostatin).

Somatostatin (also known as growth hormone inhibiting hormone) is a peptide hormone that regulates the endocrine system and affects neurotransmission and cell proliferation. Specifically, it is an inhibitor of growth hormone, glucagon, and insulin. There are five known somatostatin receptors. The biological effects of somatostatin are probably mediated by a family of G protein-coupled receptors that are expressed in a tissue-specific manner.

Vapreotide Acetate Structure



Chemical Name: D-phenylalanyl-L-cysteinyl [2-7]-L-tyrosyl-D-tryptophyl-L-lysyl-L-valyl-L-cysteinyl [7-2]-L-tryptophanamide-disulfide.

Molecular Formula: $C_{57}H_{70}N_{12}O_9S_2$ (without acetate)

Molecular Weight: 1131.38

Drug Class: Somatostatin analog

Clinical Formulation: A single dose vial will contain a sterile, lyophilized powder containing 0.6 mg vapreotide acetate (0.012 mg/mL) and 11.42 mg of L-Glutamic acid (0.23 mg/mL or 0.023%) as a bulking and buffering agent.

Vapreotide acetate (Sanvar™), a new molecular entity, for intravenous (I.V.) injection is the product under review. Vapreotide is a long acting cyclic octapeptide with pharmacologic activities that mimic natural human peptide somatostatin. Somatostatin, also known as growth hormone inhibiting hormone, is a peptide hormone that regulates the neuroendocrine system and sympathetic cardiac activity, and affects acute phase proteins synthesis, systemic immune response, coagulation cascade, and cell proliferation via interaction with G-protein-coupled somatostatin receptors.

Somatostatin has vasoconstrictive activities. Although the mechanism of the vasoconstrictive action is not entirely clear at the present time, it appears to involve both direct and indirect actions: 1) Somatostatin directly increases calcium influx into smooth muscle cells in the artery and vein wall, which triggers vasoconstriction. 2) Somatostatin inhibits the release of vasodilatory peptides from entero-endocrine cells such as glucagon, vasoactive intestinal polypeptide and substance P. The inhibition brings about vasoconstriction. Vapreotide is more potent inhibitor of growth hormone, glucagon, and insulin release than somatostatin.

In addition, this reviewer had concerns based on the Somatostatin 2A receptor found to be expressed on presympathetic neurons in the rostral ventrolateral medulla (RVLM) that maintain blood pressure in rats, and concerns that somatostatin may activate the monocyte/macrophage system based on literature reports. (This is discussed in Section 9.2 Reviewer's Additional Discussion.)

2.2 Currently Available Treatment for Indications

Somatostatin, octreotide, and terlipressin are not approved for the variceal bleeding indication in the United States. However, octreotide has been used widely off label. Octreotide is approved by the Agency for the indication of acromegaly and diarrhea secondary to carcinoid tumors.

2.3 Important Issues with Pharmacologically Related Agents

Repeat-intravenous infusion of somatostatin leading to baboon's death
Study by Koerker et al. showed that of baboons (13/13) treated with repeat somatostatin I.V. infusion (at 0.8 mcg/ kg • min) died, whereas only one (1/6) in the placebo control died. Thrombocytopenia was observed in six of seven baboons repeatedly treated with somatostatin. Autopsy revealed microscopic pulmonary hemorrhage and increased hemosiderin in lung and liver (Koerker 1975).

Effects of somatostatin on activation of monocytes, leading to intravascular coagulation, systemic inflammation and thrombocytopenia
There are five subtypes of somatostatin receptors in humans. All of the five types of receptor are expressed on the surface of circulating CD14-positive monocytes. Binding of somatostatin to the receptors brings about activation of monocyte to synthesize monocytic tissue factor (CD142) in healthy adults (Boden 2007).

In patients with liver cirrhosis, increased expression of monocytic tissue factor may be associated with activation of monocytes and platelets, which may lead to thrombogenesis, inflammation, and uncontrolled immune toxicity (Panasiuk 2007; Tacke 2001).

In addition, this reviewer had concerns based on the Somatostatin 2A receptor found to be expressed on presympathetic neurons in the rostral ventrolateral medulla (RVLM) that maintain blood pressure in rats, and concerns that somatostatin may activate the monocyte/macrophage system based on literature reports. (This is discussed in Section 9.2 Reviewer's Additional Discussion.)

Case-report: Octreotide associated thrombocytopenia in a cirrhotic patient
A case report by Demirkan et al. described a 42-year-old female with a history of hepatitis C-induced cirrhosis, gastrointestinal bleeding, and alcohol abuse who presented to the hospital with hematemesis and melena. She was treated with octreotide I.V. at 50 mg/hr for 5 days. Her platelet count dropped immediately after the initiation of octreotide treatment from 122 $x10^9$ / L to 62 $x10^9$ / L. Subsequent esophagogastro-duodenoscopy revealed Grade II varices. Blood cultures grew Gram-positive cocci. After 9 months, a similar platelet drop occurred again after another octreotide treatment (Demirkan 2000).

Octreotide postmarketing experience
In the Sandostatin LAR® Depot (octreotide acetate for injectable suspension) labeling, the following is stated in "Section 6.2 Postmarketing Experience":

> The following adverse reactions have been identified during the postapproval use of Sandostatin. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.
>
> Myocardial infarction has been observed in the postmarketing setting, mainly in patients with cardiovascular risk factors. Hypoadrenalism has been reported in some reports in patients 18 months of age and under.

Additional events reported in the postmarketing setting include anaphylactoid reactions, including anaphylactic shock, cardiac arrest, renal failure, renal insufficiency, convulsions, atrial fibrillation, aneurysm, hepatitis, increased liver enzymes, gastrointestinal hemorrhage, pancreatitis, pancytopenia, thrombocytopenia, arterial thrombosis of the arm, retinal vein thrombosis, intracranial hemorrhage, hemiparesis, paresis, deafness, visual field defect, aphasia, scotoma, status asthmaticus, pulmonary hypertension, diabetes mellitus, intestinal obstruction, peptic/gastric ulcer, appendicitis, creatinine increased, CK increased, arthritis, joint effusion, pituitary apoplexy, breast carcinoma, suicide attempt, paranoia, migraines, urticaria, facial edema, generalized edema, hematuria, orthostatic hypotension, Raynaud's syndrome, glaucoma, pulmonary nodule, pneumothorax aggravated, cellulitis, Bell's palsy, diabetes insipidus, gynecomastia, galactorrhea, gallbladder polyp, fatty liver, abdomen enlarged, libido decrease, and petechiae.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 Animal Pharmacology/Toxicology

Pharmacology
In vitro receptor binding studies with vapreotide showed that vapreotide selectively binds to somatostatin receptors with high affinity, i.e. the dissociation constant of vapreotide to somatostatin type 2 is K_d = 5.4 nM, type 3 K_d = 30.9 nM, and type 5 K_d = 0.7 nM.

The selectivity of vasoconstrictive effect of vapreotide on portal blood flow in a five-day vapreotide infusion has not been studied.

Safety Pharmacology
Safety pharmacology studies explored the effects of vapreotide on the cardiovascular system, CNS system, gastrointestinal system, and pulmonary system at doses of at least 25-times the proposed daily dose in humans (about 20 mcg/kg based on 1.2 mg/day and 60 kg of body weight). Results showed no significant drug-related adverse effects and documented expected pharmacologic effects of vapreotide, including reduction in gastrointestinal motility in fasted mice.

Toxicology
The toxicology of vapreotide was studied in rats and dogs. Effects of vapreotide on peripheral platelet count in rats and dogs were unremarkable.

<u>Significant findings</u>

- In the 13-week subcutaneous study (Study 368-265-011) in dogs, hemoglobinuria was detected in approximately 60% of the treated animals. Fecal analysis revealed increased occult blood.
- In the 26-week subcutaneous toxicity study (Study T913) in dogs, the NOAEL could not be determined because the treatment related effects were observed at all

dose levels. Treatment-related histopathogical changes were observed in the gastrointestinal tract (diffuse subacute enteritis in the jejunum and ileum), submaxillary salivary gland (lobular sclerosis) and gallbladder (hypersecretion and fluid retention).

- In the 26-week study, significant treatment-related decreases in erythrocyte count, hemoglobin level, and hematocrit were observed in all treated males and females ($p \leq 0.01$).
- An immunogenicity study was not conducted.

QT prolongation analysis

The sponsor provided *in vitro* and *in vivo* animal studies, as well as clinical results to show that there is no evidence that vapreotide delays ventricular repolarization (QT prolongation). The results were reviewed by Drs. Monica Fiszman, Christine Garnett, and Norman Stockbridge (QT Interdisciplinary Review Team, Division of Cardiovascular and Renal Product). They provided the following comments to DGP:

"Per the ICH E14 guidelines, all NMEs with systemic bioavailability should undergo a TQT evaluation. Since there have been no reports of QT prolongation or AEs related to QT prolongation in clinical development, we defer to DGP regarding completing the TQT assessment as a post-marketing commitment based on risk-benefit considerations."

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

The sources of clinical data used in the review were from clinical trials conducted by the applicant or designees as described in Table 1.

Table 1: Clinical trials presented in supporting NDA 21-761*

Study (location)	Study Design	Patients No. Total/Vap	Gender (Vap Pts)	Cause of liver cirrhosis	Comment
VAP-301 (USA)	Phase 3, single center, open-label, uncontrolled	103/103	78 males 25 females	Alcoholism (31%); Viral hepatitis (14%); Alcohol plus viral hepatitis (29%)	Supportive single arm study
VAP-06 (Eastern Europe)	Phase 3, multicenter, double-blind, randomized, placebo-controlled	278/144	102 males 42 females	Alcoholism (62%); Viral hepatitis (36%)	Supportive study
VAP-14 (France)	Phase 3, multicenter, double-blind, randomized, placebo-	227/111	76 males 35 females	Alcoholism (85%)	Pivotal study

	controlled				
VAP-02 (Hong Kong)	Phase 3, multicenter, double-blind, randomized, placebo-controlled	136/70	62 males 8 females	Alcoholism (38%); Viral hepatitis (45%)	Supportive study
VAP-07 (Egypt)	Phase 2, multicenter, double-blind, randomized, placebo-controlled	72/41	41 males	Viral hepatitis associated with schistosomiasis (83%)	Supportive study

*From the reviewer's notes summarized based on the NDA submission

4.2 Review Strategy

The clinical efficacy and safety of the resubmission were assessed by a joint review: The safety was reviewed by Dr. Wen-Yi Gao, and the efficacy was reviewed by Dr. Zana Marks.

The safety review focused on the five variceal bleeding studies as listed in Table 1. All clinical trials were reviewed and were summarized in the safety analysis.

The method of analysis of mortality data is summarized as follows:
1) Compare proportions of deaths in vapreotide and placebo arms within each cause of death category
2) Request additional clinical laboratory data from the sponsor based on the comparison if necessary
3) Determine temporal relation with vapreotide administration
- For example, clinical deterioration shortly after initiation of vapreotide treatment
- Focus on the 33 deaths that occurred within 5 days of vapreotide treatment

4) Attempt to identify a common mechanism to explain particular causes of death that are more frequent in vapreotide arms than in placebo arms.

4.3 Data Quality and Integrity

Division of Scientific Investigations (DSI) audited the pivotal study (VAP-14). Since the study was conducted in 22 centers in France, three centers (Centers #1, #14 and #18) with relatively larger number of study subjects were chosen by Dr. Fathia Gibril for DSI inspection.

The overall assessment (December 20, 2004) by the DSI medical reviewer Dr. Khairy Malek stated that there were some protocol deviations and delay in SAE reporting noted. For the study sites that were inspected, there was sufficient documentation to assure that all audited subjects did exist, that all enrolled subjects received the assigned study

medication, and had their primary efficacy endpoint captured as specified in the protocol. No underreporting of adverse events was noted. Data from these centers that had been inspected appear acceptable for use in support of this NDA.

The overall quality of the resubmitted safety database was acceptable. For an independent review of causes of the 33 deaths during 5-day treatment, the reviewer requested additional clinical information, such as detailed clinical laboratory data from the sponsor. It appeared that Study VAP-301 provided more detailed information than the other four studies.

4.4 Compliance with Good Clinical Practices

According to the sponsor, **Studies VAP-14, VAP-02, VAP-07, VAP-06** and **VAP-301** were conducted based on Good Clinical Practice (GCP) guidelines, as documented in the International Conference on Harmonization (ICH) and the Food and Drug Administration (FDA).

4.5 Financial Disclosures

The sponsor Debiovision has submitted FDA Form 3454 certifying that no investigator of any of the covered clinical studies had any financial interests to disclose.

Medical Officer Comment:
The Applicant has adequately disclosed financial arrangements with clinical investigators in this application. The submitted financial disclosures do not bring up concerns which would possibly jeopardize the integrity of the data.

5 INTEGRATED REVIEW OF SAFETY

5.1 Methods and Findings

The safety and tolerability of vapreotide in treatment of variceal bleeding were assessed based on the updated safety database in the resubmission. It included five studies (VAP-14, VAP-02, VAP-07, VAP-301, and VAP-06). The safety variables were adverse events (AE), narratives, clinical laboratory results and physical examinations.

The updated safety database was different in two aspects from the original safety database:

1) Numerical changes of the safety reports from the first three studies (VAP-14, VAP-02, and VAP-07) due to the following: "Since the VAP-301 study was coded using MedDRA 9 and the previous studies were coded using MedDRA 6, safety information for all studies was trans-coded to MedDRA 10 in order to harmonize the terms in the safety database. Additionally, MedDRA Preferred Terms were consolidated to ensure that related events were reported consistently. As a result, some event rates differ from those reported in the original NDA." (From the sponsor's resubmission.)
2) Addition of two new studies (VAP-301 and VAP-06) with 247 patients in vapreotide arms and 134 patients in placebo arms.

Specifically, Study VAP-301 (conducted in the United States) provided detailed narratives of the deaths and their clinical laboratory values, which allowed independent review of the cause of death. However, because there was no placebo arm for VAP-301, it was difficult to discern causality.

According to the updated safety report, this review identified the following deaths in disease categories during the 5-day vapreotide treatment. The deaths were from Studies VAP-301 (6 deaths), VAP-14 (2 deaths), VAP-06 (1 death), and VAP-02 (1 death):

1) Bradycardia / asystolia (3 deaths vs. 0)
2) Septic shock (2 deaths vs. 0)
3) Severe systemic inflammatory response syndrome (1 death vs. 0)
4) Disseminated intravascular coagulation (1 death vs. 0)
   – Two additional deaths due to DIC on Days 11 and 12 vs. 0
5) Respiratory failure / pulmonary embolism (1 death vs. 0)
6) Cerebrovascular accident (1 death vs. 0)
7) Thrombocytopenia / hypovolemic shock (1 death vs. 0)

In addition, the review identified the following non-fatal SAEs from the variceal bleeding studies:

- Thrombocytopenia (8 patients vs. 1 patient)
- Bradycardia (5 patients vs. 1 patient)
- Respiratory failure (8 patients vs. 0)

Because of the imbalanced SAEs in vapreotide groups, the reviewer visited the postmarketing experience of octreotide (another somatostatin analog). A similar pattern of adverse events of octreotide was reported in treatment of non-variceal bleeding patients (see Section 2.3 octreotide postmarketing experience for details).

Then the reviewer focused on the 33 deaths during the 5-day treatment of variceal bleeding studies. DGP requested additional clinical laboratory results in order to investigate the temporal relationship of the clinical deterioration and vapreotide exposure. The sponsor provided four records of platelet counts prior to deaths (Study VAP-301, Patients ID #1201, #0305, #0604 and #0409). These data showed that in some patients the pre-existing low platelet counts further dropped upon initiation of vapreotide treatment.

Although many events recorded could have been a reflection of the patients' underlying medical conditions, this reviewer concluded that the contribution of vapreotide on the imbalanced disease categories cannot be ruled out.

There were 33 (33/469) deaths in the vapreotide arms during the 5-day treatment, and 24 (24/134) in the placebo arms. The 5-day mortality rates of vapreotide arms (7.0%) and of placebo arms (6.9%) were within the reported range of the overall hospital mortality rates in the United States (15% to 20%, Dy SM 2003).

Most of the deaths in both arms could be attributed to uncontrolled initial hemorrhage or re-bleeding, hemorrhagic shock, and hepatic failure. However, some SAEs, such as bradycardia / asystolia, systemic inflammation, and disseminated intravascular coagulation, occurred only in the vapreotide arms, suggesting the contribution of drug effects cannot be ruled out.

There were 273 SAEs that occurred in 160 (160/469) patients in the vapreotide groups, compared to 229 SAEs in 134 (134/347) patients in the placebo groups. SAEs occurring with higher incidences in vapreotide arms included disseminated intravascular coagulopathy, thrombocytopenia, bradycardia, atrial fibrillation, hepatorenal syndrome, hyperglycemia, acute respiratory distress syndrome, respiratory failure, pulmonary edema, and metabolic acidosis. SAEs occurring with lower incidences in vapreotide arms included melena, hepatic encephalopathy, and upper GI hemorrhage.

5.1.1 Deaths

Mortality rates during the 42-day studies

Eighty-two subjects (17.5%) of the 469 in vapreotide arms died during the 42-day studies, while 58 subjects (16.7%) of the 347 in placebo arms. The mortality rates were within the range of the reported hospital mortality 15% to 20% of esophageal variceal bleeding due to cirrhosis in the United States (Dy SM 2003). Tables 2 and 3 show the overall mortality rates in each of the variceal bleeding studies.

Table 2: Overall Mortality Rates of Variceal Bleeding Studies*

Time of Death	VAP-301	VAP-14		VAP-06		VAP-07		VAP-02	
	Vapre N=103	Vapre N=111	Placebo N=116	Vapre N=144	Placebo N=134	Vapre N=41	Placebo N=31	Vapre N=70	Placebo N=66
Days 1-5	9	6	8	11	10	2	4	5	2
Days 6-42	17	11	17	12	9	4	4	5	4
Total	26	17	25	23	19	6	8	10	6
Percentage	25.2% (26/103)	15.3% (17/111)	21.6% (25/116)	16.0% (23/144)	14.2% (19/134)	14.6% (6/41)	25.8% (8/31)	14.3% (10/70)	9.1% (6/66)
Overall mortality of vapreotide arms: 17.5% (82/469); Placebo arms: 16.7% (58/347); Overall mortality of vapreotide arms not including Study VAP-301: 15.3% (56/366); Placebo arms: 16.7% (58/347).									

*From the reviewer's notes based on clinical narratives in Module 5.

Table 3: Overall Mortality Rates (Days 1-42) of Individual Studies*

	Vapreotide	Placebo
VAP-301	25% (26/103)	N/A
VAP-14	15% (17/111)	22% (25/116)
VAP-06	16% (23/144)	14% (19/134)
VAP-07	15% (6/41)	26% (8/31)
VAP-02	14% (10/70)	9% (6/66)
Total	17.5% (82/469)	16.7% (58/347)

*From reviewer's notes based on Module 5.

Deaths occurring during the 5-day vapreotide treatment

Thirty-three subjects (7.0%) of the 469 in vapreotide arms died during the 5-day treatment, while 24 subjects (6.9%) of the 347 in placebo arms died.

Table 4: Mortality Rates (Days 1-5) of Individual Studies*

	Vapreotide	Placebo
VAP-301	8.7% (9/103)	N/A
VAP-14	5.4% (6/111)	6.9% (8/116)
VAP-06	7.6% (11/144)	7.4% (10/134)
VAP-07	4.9% (2/41)	13% (4/31)
VAP-02	7.1% (5/70)	3.0% (2/66)
Total	7.0% (33/469)	6.9% (24/347)

*From reviewer's notes based on Module 5.

The most common causes of deaths were uncontrolled initial hemorrhage that developed into hemorrhagic shock and uncontrolled re-bleeding. Approximately 54% (18/33) of the deaths in the vapreotide arms could be attributed to uncontrolled initial bleeding, re-bleeding, and hemorrhagic shock, compared to 79% (19/24) in the placebo arms (Table 6).

Vapreotide arms had lower death rates due to GI bleeding as compared with placebo arms:

- Initial bleeding: vapreotide 30% (10/33) vs. placebo 41% (10/24);
- Re-bleeding (upper GI hemorrhage, duodenal ulcer hemorrhage, melena): vapreotide 24% (8/33) vs. placebo 37% (9/24).

Causes of death for which rates were higher in vapreotide arms as compared with placebo arms included:
1) Bradycardia[1] / asystolia 0.6% (3/469) vs. 0
2) Septic shock 0.4% (2/469) vs. 0
3) Severe systemic inflammatory response syndrome 0.2% (1/469) vs. 0
4) Disseminated intravascular coagulation[2] 0.2% (1/469) vs. 0
5) Respiratory failure / pulmonary embolism 0.2% (1/469) vs. 0
6) Cerebrovascular accident 0.2% (1/469) vs. 0
7) Thrombocytopenia / hypovolemic shock 0.2% (1/469) vs. 0.

[1]Bradycardia followed by asystolia suggesting cardiogenic shock.
[2]Two additional deaths due to DIC in vapreotide arms on Days 11 and 12 (Patient IDs #0201 and #1036 in Studies VAP-301 and VAP-06, respectively).

Causes of death for which rates were lower in vapreotide arms as compared with placebo arms included hemorrhagic shock: 3.8% (18/469) vs. 5.4% (19/347)

According to the narratives, certain deaths in vapreotide arms, such as those due to hepatic encephalopathy, acute renal failure, and acute respiratory failure, tended to be sudden onset, whereas deaths in placebo arms tended to be gradual onset.

In summary, cause analysis showed eight types of death: 1) disseminated intravascular coagulation (DIC), 2) cerebrovascular accident (CVA), 3) pulmonary embolism, 4) systemic inflammatory response syndrome (SIRS), 5) bradycardia / cardiac arrest, 6) sudden onset of multi-organ failure, such as acute respiratory failure, acute renal failure, and acute encephalopathy, 7) severe thrombocytopenia leading to re-bleeding and hypovolemic shock, and 8) septic shock (Table 5). (Potential mechanism of death is discussed in Appendix 9.2.)

Table 5: Summary of Deaths (Days 1-5) During Vapreotide Treatment[1]

Cause of Death	Vapreotide (N=469)	Placebo (N=347)
	Deaths (N=33) (7.0%)	**Deaths (N=24) (6.9%)**
Initial bleeding / hemorrhagic shock	10 (2.1%)	10 (2.9%)
Re-bleeding / hemorrhagic shock	8 (1.7%)	9 (2.6%)
Hepatic encephalopathy	4 (0.8%)	3 (0.8%)
Bradycardia / asystolia	3 (0.6%)	0
Hepatorenal failure	2 (0.4%)	1 (0.3%)
Septic shock	2 (0.4%)	0
Respiratory failure / Pulmonary embolism[2]	1 (0.2%)	0
Severe Systemic Inflammatory Response Syndrome[3]	1 (0.2%)	0
Disseminated Intravascular Coagulation[4]	1 (0.2%)	0
Thrombocytopenia, hypovolemic shock	1 (0.2%)	0
Stroke, intracerebral hemorrhage	1 (0.2%)	0
Others[5]	0	1 (0.3%)

[1]From the reviewer's notes based on the narratives in Module 5, Clinical Reports.
[2]Based on the comments of the investigator (Study VAP/EVB-301), it was consistent with pulmonary embolism.
[3]Based on the diagnosis (patient #1201) described in the narrative (Study VAP/EVB-301).
[4]Based on the diagnosis (patient #0409) described in the narrative and the clinical laboratory data (Study VAP/EVB-301).
[5]Patient #144 (Study VAP-14) experienced respiratory distress and died 4 minutes after sclerotherapy. Concomitant medications included propranolol, diclofenac, and zolpidem. The investigator concluded as "possibly related to other drugs".

Table 6: Source of death (Days 1-5) from Variceal Bleeding Studies*

Cause of Death	VAP-301	VAP-14		VAP-06		VAP-07		VAP-02	
	Vapre N=103	Vapre N=111	Placebo N=116	Vapre N=144	Placebo N=134	Vapre N=41	Placebo N=31	Vapre N=70	Placebo N=66
Initial bleeding / hemorrhagic shock	3	2	4	3	4	1		1	2
Re-bleeding/ Hemorrhagic shock	1	1	3	3	4	1	2	2	
Hepatic encephalopathy		1		2	1		2	1	
Hepatorenal failure				2	1				
Bradycardia, asystolia	1	1		1					
Septic shock	1							1	
Respiratory failure / Pulmonary embolism	1								
Severe Systemic Inflammatory Response Syndrome	1								
Disseminated Intravascular Coagulation	1								
Severe thrombocytopenia hypovolemic shock	1								
Stroke, intracerebral hemorrhage		1							
Others			1						
Total Deaths	9	6	8	11	10	2	4	5	2
Total Deaths in Vap arms: 33; Placebo arms: 24									

*From the reviewer's notes based on clinical narratives in Module 5.

Narratives of Selected Deaths in the Vapreotide Arms

1) Severe systemic inflammation

- **Severe systemic inflammatory response syndrome (SIRS)**
  Patient #1201(Study VAP-301): 47 year-old male (Child Score 8, Class B, alcohol cirrhosis, hepatitis B, thrombocytopenia at baseline) developed severe systemic inflammatory response syndrome (SIRS) within a few hours after the initiation of vapreotide treatment. At the same time, his platelet count dropped rapidly from 127 to 99, then 75 x 10^9/L. He developed intractable hypotension with systolic blood pressure in the 60s and 50s, and did not respond to vasopressor (dopamine, norepinephrine) treatments. No re-bleeding was identified. He died of multi-organ failure twenty-two hours after the initiation of vapreotide treatment.

2) Severe thrombocytopenia

- **Intractable thrombocytopenia and hypovolemic shock**
  Patient #0604 (Study VAP-301): 51 year-old male with alcoholic cirrhosis, thrombocytopenia, Child Score 12, Class C at baseline experienced exacerbated platelet count drop from 100 to 44, then 22 after the initiation of vapreotide treatment. He received multiple transfusions (PRBC and platelets), but the counts were not being corrected. Endoscopy revealed Grade III esophageal varices. He experienced re-bleeding within 24 hours. Vasopressor treatments were not successful. On Day 5, he died of hypovolemic shock and multi-organ failure.

3) Fatal thromboembolism

- **Stroke**
  Patient #158 (Study VAP-14): 61 year-old male developed sudden onset of left hemiparesis after the initiation of vapreotide treatment. His clinical condition rapidly deteriorated to hemiplegia and coma. CT scan documented a deep intracerebral hemorrhage of the right hemisphere. He died on Day 2. The cause of death diagnosed by the investigator was cerebrovascular accident.

- **Pulmonary embolism**
  Patient #1701 (Study VAP-301): 50 year-old male with alcoholic cirrhosis, Child Score 7, Class B, and left pleural effusion was hemodynamically stable at baseline. He experienced two episodes of abrupt onset of dyspnea and O_2 desaturation, and died of respiratory failure on Day 5. EGD did not identify active bleeding. CXR showed no significant change of pleural effusion as compared with the control at baseline. The cause of death was consistent with pulmonary embolism as diagnosed by the investigator.

4) Coagulopathy

- **Disseminated intravascular coagulation (DIC)**
  Patient #0409 (Study VAP-301): 43 year-old female with alcoholic cirrhosis, elevated INR, hepatic failure, and Child score 11 at baseline experienced rapid drop of platelet count from 100 to 56 after the initiation of vapreotide treatment. She developed acute renal failure, severe metabolic acidosis, and DIC (D-dimer value greater than 10009 mg/mL). EGD examination did not identify recent bleeding. On Day 5, she died of acidosis, acute renal failure, hepatic failure and DIC.

5) Cardiac insufficiency

- **Bradycardia**
  Patient #1707 (Study VAP-301): 45 year-old male with a history of hepatitis C infection associated cirrhosis and HIV infection, Child Score 12, Class C had platelet count of 53 $x10^9$/L at baseline. He was alert, responding to commands with a blood pressure of 76/34. After the initiation of vapreotide infusion, he had generalized abdominal distention. Bleeding was noted during the unsuccessful attempt to place a central line. Pressure was applied along with other measures to stop bleeding. Two units of PRBC (packed red blood cells) were being transfused

for a decreased hematocrit and hemoglobin. The patient became unresponsive. He had bradycardia and died of cardiac arrest a few hours later.

Potential mechanism of death is discussed in Appendix 9.2.

5.1.2 Other Serious Adverse Events

Among patients with variceal bleeding assigned to vapreotide treatment, SAEs occurring in ≥1% of patients included thrombocytopenia (1.7%), bradycardia (1.1%), cardiac arrest (1.1%), cardio-respiratory arrest (1.3%), melena (8.5%), upper GI hemorrhage (12.6%), hepatic encephalopathy (10.4%), hepatorenal syndrome (1.9%), esophageal varices hemorrhage (2.1%), septic shock (1.1%), renal failure (3.2%), respiratory failure (1.7%), and hemorrhagic shock (2.3%); because the pro-coagulation and pro-inflammation effects of vapreotide overlapped with the profiles of underlying disease and disease-related complications, the causative relationship of vapreotide treatment can not be ruled out.

Table 7: Treatment-Emergent Adverse Events Occurring in ≥1% of Patients in Pooled Variceal Bleeding Studies (ITT)*

Body System	Vapreotide N=469	Placebo N=347
Blood & Lymphatic System Disorders		
Thrombocytopenia	8 (1.7%)	1 (0.3%)
Cardiac Disorders		
Bradycardia	5 (1.1%)	1 (0.3%)
Cardiac Arrest	5 (1.1%)	4 (1.2%)
Cardio-Respiratory Arrest	6 (1.3%)	4 (1.2%)
Gastrointestinal Disorder		
Melena	40 (8.5%)	36 (10.4%)
Upper Gastrointestinal Hemorrhage	59 (12.6%)	50 (14.4%)
Hepatobiliary Disorders		
Hepatic Encephalopathy	49 (10.4%)	40 (11.5%)
Hepatorenal Syndrome	9 (1.9%)	6 (1.7%)
Esophageal Varices Hemorrhage	10 (2.1%)	3 (0.9%)
Infections & Infestations		
Septic Shock	5 (1.1%)	3 (0.9%)
Renal & Urinary Disorders		
Renal Failure	15 (3.2%)	5 (1.4%)
Respiratory Disorders		
Respiratory Failure	8 (1.7%)	0
Vascular Disorders		
Hemorrhagic Shock	11 (2.3%)	8 (2.3%)

*From the sponsor's submission Table 7 in Summary of Safety Module 5, Section 5.3.5.3

Medical Officer's Comments:
Although this was a small size safety assessment, the results suggested that:

- ***The overall bleeding AEs in vapreotide arms (23%, 109/469) were slightly lower than that of placebo arms (26%, 89/347) as assessed by upper GI hemorrhage, melena, and esophageal varices hemorrhage.***
- ***Thrombocytopenia in vapreotide arms (1.7%, 8/469 vs. 0.3%, 1/347) was more frequent compared with placebo arms.***
- ***Respiratory failure in vapreotide arms (1.7%, 8/469 vs. 0) was more frequent than the placebo.***
- ***Bradycardia in vapreotide arms (1.1%, 5/469) was more frequent than the placebo (0.3%, 1/347).***
- ***Renal failure in vapreotide arms (3.2%, 15/469) was more frequent than the placebo (1.4%, 5/347).***

5.1.3 Dropouts Due to AEs and Other Significant Adverse Events

There was an 8.3% (39/469) dropout rate with vapreotide treatment in association with an adverse event, while there was an 8.6% (30/347) dropout rate in the placebo arms (Table 8). The most frequent dropouts were due to upper GI bleeding. The rate of vapreotide arms (5.1%, 24/469) was lower than that of placebo arms (7.2%, 25/347).

Other dropouts due to AEs higher than placebo included hepatic encephalopathy, multi-organ failure, cardiogenic shock, cerebrovascular accident, infection site phlebitis, hepatorenal syndrome, hypotension, septic shock, and leukopenia.

Table 8: Dropouts Due to Adverse Events[1]

Adverse Events	**Vapreotide N=469**	**Placebo N=347**
Upper GI Hemorrhage[2]	24 (5.1%)	25 (7.2%)
Hepatic Encephalopathy	4 (0.8%)	1 (0.3%)
Multi-organ Failure	2 (0.4%)	0
Infection	1 (0.2%)	1 (0.3%)
Accidental Overdose	1 (0.2%)	1 (0.3%)
Cardiogenic Shock	1 (0.2%)	0
CVA	1 (0.2%)	0
Infusion Site Phlebitis	1 (0.2%)	0
Hepatorenal Syndrome	1 (0.2%)	0
Hypotension	1 (0.2%)	0
Septic Shock	1 (0.2%)	0
Leukopenia	1 (0.2%)	0
Rectal Hemorrhage	0	1 (0.3%)
Others[3]	0	1 (0.3%)
Total Dropouts	**39 (8.3%)**	**30 (8.6%)**

[1] From reviewer's notes based on Module 5 of submission. [2]Includes Upper GI Hemorrhage and Melena
[3]Investigator note: Asthmatic attack due to concomitant administration of β-blocker (Study VAP-14).

No other significant adverse events were identified in this submission.

5.1.4 Common Adverse Events

The most common adverse events in variceal bleeding studies were gastrointestinal disorders. Vapreotide arms had lower rate of GI disorders (55.8%, 262/469 vs. 68.5%, 238/347) (Table 9).

Table 9: Most Common Adverse Events Occurring in ≥5% of Patients in Variceal Bleeding Studies

Body system	Vapreotide N=469	Placebo N=347
Gastrointestinal Disorders	262 (55.8%)	238 (68.5%)
Abdominal Pain	36 (7.7%)	29 (8.3%)
Melena	40 (8.5%)	36 (10.4%)
Upper Gastrointestinal Hemorrhage	59 (12.6%)	50 (14.4%)
General Disorders & Administer Site Conditions	149 (31.7%)	122 (35.1%)
Pyrexia	90 (19.2%)	74 (21.3%)
Hepatobiliary Disorders	82 (17.4%)	66 (19.0%)
Hepatic Encephalopathy	49 (10.4%)	40 (11.5%)
Nervous System Disorders	50 (10.6%)	54 (15.5%)
Headache	31 (6.6%)	34 (9.8%)

*From the sponsor's submission Table 7 in Summary of Safety, Module 5, Section 5.3.5.3

Treatment-emergent adverse events (relationship to drug not established, not excluding events related to underlying disease) reported by at least 2 patients receiving vapreotide were:

- Hematopoietic and Lymphoid System Disorders: coagulopathy (3 patients), disseminated intravascular coagulation (3 patients), leukopenia (2 patients), pancytopenia (3 patients), thrombocytopenia (8 patients);
- Cardiac Disorders: atrial fibrillation (4 patients), bradycardia (4 patients), cardiac arrest (5 patients), cardio-respiratory arrest (6 patients), tachycardia NOS (5 patients);
- Endocrine Disorders: diabetes mellitus (3 patients);
- Gastrointestinal Disorders: abdominal distension (4 patients), abdominal pain (36 patients), ascites (6 patients), dyspepsia (13 patients), constipation (4 patients), melena (40 patients), upper gastrointestinal hemorrhage (59 patients);
- General Disorders & Administration Site Conditions: chest pain (19 patients), pyrexia (90 patients);
- Hepatobiliary Disorders: hepatic encephalopathy (38 patients);
- Infections: pneumonia (10 patients), septic shock (5 patients);
- Metabolism & Nutrition Disorders: hyperglycemia (15 patients), hyperkalemia (3 patients), hypernatremia (4 patients), hypocalcemia (2 patients), hypokalemia (11 patients), hypomagnesaemia (4 patients);
- Nervous System Disorders: headache (31 patients), convulsions NOS (7 patients), encephalopathy (11 patients);
- Renal & Urinary Disorders: renal failure (13 patients), hematuria (4 patients), anuria (2 patients);

- Respiratory Disorders: acute respiratory distress syndrome (4 patients), bronchial obstruction (2 patients), bronchospasm (2 patients), dyspnea (3 patients), pleural effusion (5 patients), pulmonary edema (2 patients), respiratory failure (8 patients);
- Vascular Disorders: cerebrovascular accident (2 patients), hypertension (3 patients), hypotension (9 patients).

5.1.5 Eliciting adverse events data in the development program

Adverse event data from the variceal bleeding trials were obtained on a daily schedule during the studies (from Day 1 to Day 5) and a follow-up visit on Day 42. General AE assessment was made at the clinical visits throughout the 5-day study period. Laboratory assessment was conducted at screening period and during the study.

5.1.6 Identifying common and drug-related adverse events

Treatment-emergent adverse events (TEAEs) that occurred with higher incidence in the vapreotide arms included thrombocytopenia, DIC, bradycardia, septic shock, hyperglycemia, metabolic acidosis, renal failure, acute respiratory distress syndrome, respiratory failure, cerebrovascular accident, and hemorrhagic shock (Table 10).

Table 10: TEAEs Occurring with Higher Incidence in Vapreotide Arms than in Placebo Arms

Body System	Vapreotide N=469	Placebo N=347
Blood & Lymphatic System Disorders	23 (4.9%)	6 (1.7%)
Thrombocytopenia	8 (1.7%)	1 (0.3%)
Leukopenia	2 (0.4%)	0
Pancytopenia	3 (0.6%)	0
Disseminated Intravascular Coagulation	3 (0.6%)	0
Cardiac Disorders	33 (7.0%)	17 (4.9%)
Bradycardia	5 (1.0%)	1 (0.3%)
Atrial Fibrillation	4 (0.9%)	0
Cardiogenic Shock	1 (0.2%)	0
Cardio-Respiratory Arrest	6 (1.3%)	4 (1.2%)
Tachycardia	3 (0.6%)	1 (0.3%)
Endocrine Disorders	3 (0.6%)	1 (0.3%)
Diabetes Mellitus	3 (0.6%)	1 (0.3%)
Gastrointestinal Disorder	262 (55.8%)	238 (68.5%)
Ascites	6 (1.3%)	2 (0.6%)
Hepatobiliary Disorders	82 (17.4%)	66 (19.0%)
Hepatorenal Syndrome	9 (1.9%)	6 (1.7%)
Esophageal Varices Hemorrhage	10 (2.1%)	3 (0.9%)
Infections & Infestations	56 (11.9%)	28 (8.0%)
Septic Shock	5 (1.1%)	3 (0.9%)
Metabolism & Nutrition Disorders	47 (10.0%)	18 (5.1%)
Hyperglycemia	15 (3.2%)	9 (2.6%)
Hyperkalemia	3 (0.6%)	0
Hyper natremia	4 (0.9%)	0
Hypocalcemia	2 (0.4%)	0
Hypokalemia	11 (2.3%)	3 (0.9%)
Hypomagnesemia	4 (0.9%)	0
Metabolic Acidosis	4 (0.9%)	0
Nervous System disorders	50 (10.6%)	54 (15.5%)
Coma	3 (0.6%)	1
Insomnia	8 (1.7%)	3 (0.9%)
Psychomotor Hyperactivity	6 (1.3%)	1 (0.3%)
Renal & Urinary Disorders	24 (5.1%)	10 (2.8%)
Renal Failure	15 (3.2%)	5 (1.4%)
Hematuria	4 (0.9%)	1 (0.3%)
Respiratory Disorders	53 (11.3%)	39 (11.2%)
Acute Respiratory Distress Syndrome	4 (0.9%)	1 (0.3%)
Bronchial Obstruction	2 (0.4%)	0
Bronchospasm	2 (0.4%)	0
Pleural Effusion	5 (1.1%)	1 (0.3%)
Pulmonary Edema	2 (0.4%)	0
Respiratory Failure	8 (1.7%)	0
Vascular Disorders	40 (8.5%)	34 (9.8%)
Cerebrovascular Accident	2 (0.4%)	0
Hypotension	9 (1.9%)	5 (1.4%)
Hemorrhagic Shock	15 (3.2%)	10 (2.8%)

*From the sponsor's submission: Table 7 in Summary of Safety, Module 5, Section 5.3.5.3.

Medical Officer's Comments:
It is difficult to distinguish drug effects from known complications in decompensated cirrhotic patients. The following adverse reactions occurred more frequently in vapreotide arms compared with placebo arms:

- ***Thrombocytopenia***
- ***DIC***
- ***Bradycardia***
- ***Renal failure***
- ***Hematuria***
- ***Acute respiratory distress syndrome, bronchospasm, pulmonary edema, respiratory failure***
- ***Cerebrovascular accident***

Thus, the contributions of vapreotide on these conditions can not be ruled out.

5.1.7 Laboratory Findings

Laboratory tests consisted of hematology (hemoglobin, erythrocyte count, leukocyte count, platelet count) and serum chemistry (sodium, creatinine, glucose, AST, ALT) were measured at baseline and at the end of infusion. Platelet count was not measured in Studies VAP-07 and VAP-06. Total bilirubin and alkaline phosphatase were only tested in Study DEB-98-VAP-06. Assays were performed in the local or central laboratory usually used at each investigative site.

Laboratory parameters consistent with chronic liver disease included mean ALT and AST above normal range and mean glucose levels at the upper end of normal range in the four studies enrolling mainly patients with alcoholic cirrhosis and well above normal range in the third study enrolling patients with portal hypertension due to viral hepatitis and schistosomiasis. Mean erythrocyte levels were below the normal range, consistent with acute hemorrhage. Changes observed in laboratory parameters at the end of the vapreotide infusion generally supported that at the end of treatment, erythrocyte levels were stabilized, consistent with the control of hemorrhage, and mean glucose levels decreased markedly, consistent with expected pharmacological effects that may bring about decrease of serum levels of glucose. The decrease in mean leukocytes observed over the course of vapreotide treatment also is consistent with achieving control of bleeding.

There was a 22% decrease of the mean platelet count between baseline and the end of treatment (133.6 ±84.5% vs. 109.1 ±59.7%) in Study VAP-301. A large variation of these values indicated that remobilization of platelets from bone marrow to peripheral blood may occur. Patients who had pre-existing hypo-thrombocytopenia and did not have the reserved platelets may suffer profound thrombocytopenia and coagulopathy. The rest of the variceal studies did not provide consistent platelet data.

Table 11: Summary of Hematology Laboratory Parameters at Baseline and End of Treatment in Vapreotide Arms

Hematology Parameter	DEBV-VAP/ EVB-301		VAP-14		VAP-06		VAP-07		VAP-02	
	Baseline	End of Infusion (Day 5)	Baseline	End of Infusion (Day 5)	Baseline	End of Infusion (Day 5)	Baseline	End of Infusion (Day 5)	Baseline	End of Infusion (Day 5)
Hemoglobin g/dL Female	9.96 ±2.14 (n=26)	9.62 ±2.16 (n=22)	9.09 ±2.60 (n=33)	9.45 ±1.56 (n=32)	8.88 ±2.13 (n=42)	9.10 ±1.41 (n=38)	N/A	N/A	8.18 ±1.52 (n=62)	10.23 ±1.37 (n=8)
Hemoglobin g/dL Male	9.90 ±2.41 (n=77)	9.72 ±1.54 (n=69)	9.59 ±2.33 (n=74)	9.58 ±1.42 (n=66)	9.54 ±2.32 (n=102)	9.22 ±1.63 (n=86)	8.89 ±3.28 (n=41)	8.28 ±2.49 (n=31)	10.15 ±2.51 (n=62)	10.44 ±2.03 (n=61)
RBC 10^{12}/L	3.12 ±0.78 (n=90)	3.22 ±1.01 (n=54)	2.92 ±0.69 (n=111)	2.97 ±0.48 (n=92)	3.01 ±0.68 (n=131)	3.24 ±0.53 (n=119)	3.53 ±0.97 (n=41)	3.56 ±0.77 (n=30)	3.22 ±0.85 (n=68)	3.47 ±0.63 (n=61)
WBC 10^9/L	9.89 ±5.66 (n=103)	7.22 ±5.89 (n=63)	8.32 ±4.35 (n=111)	6.59 ±3.41 (n=92)	7.74 ±4.58 (n=142)	5.60 ±2.94 (n=126)	7.02 ±4.00 (n=41)	3.90 ±1.78 (n=30)	8.97 ±4.43 (n=70)	7.45 ±4.73 (n=62)
Platelet 10^9/L	133.6 ±84.5 (n=102)	109.1 ±59.7 (n=62)	110.9 ±78.0 (n=111)	102.6 ±72.2 (n=92)	Not tested	Not tested	Not tested	Not tested	102.1 ±59.2 (n=70)	99.3 ±63.0 (n=62)

*From the sponsor's submission Table 22 in Summary of Safety, Module 5 Section 5.3.5.3

Table 12: Summary of Blood Chemistry Laboratory Parameters at Baseline and End of Treatment in Vapreotide Arms

Blood Chemistry Parameter	DEBV-VAP/ EVB-301		VAP-14		VAP-06		VAP-07		VAP-02	
	Baseline	End of Infusion (Day 5)	Baseline	End of Infusion (Day 5)	Baseline	End of Infusion (Day 5)	Baseline	End of Infusion (Day 5)	Baseline	End of Infusion (Day 5)
Glucose mg/dL	150.5 ±70.1 (n=103)	125.5 ±39.1 (n=64)	163.5 ±87.1 (n=108)	131.0 ±62.9 (n=96)	125.2 ±53.9 (n=140)	120.9 ±46.3 (n=124)	185.7 ±131.0 (n=40)	132.5 ±69.3 (n=31)	174.7 ±132.7 (n=59)	163.1 ±85.0 (n=51)
Creatinine mcmol/L	90.8 ±49.3 (n=103)	82.7 ±45.3 (n=64)	92.2 ±107.2 (n=110)	90.6 ±100.1 (n=92)	93.1 ±55.5 (n=138)	90.5 ±49.1 (n=125)	82.4 ±38.8 (n=40)	83.8 ±21.5 (n=31)	106.2 ±56.9 (n=70)	97.7 ±45.3 (n=62)
Sodium mmol/L	Not tested	Not tested	138.0 ±4.8 (n=110)	135.2 ±4.5 (n=92)	Not tested	Not tested	130.6 ±7.1 (n=28)	126.6 ±6.2 (n=16)	137.6 ±5.1 (n=69)	137.2 ±4.7 (n=62)
Potassium mmol/L	Not tested	Not tested	Not tested	Not tested	Not tested	Not tested	5.2 ±1.6 (n=27)	4.9 ±1.5 (n=16)	Not tested	Not tested
Chloride mmol/L	Not tested	Not tested	Not tested	Not tested	Not tested	Not tested	Not tested	Not tested	Not tested	Not tested
AST U/L	111.4 ±154.7 (n=102)	108.8 ±260.2 (n=59)	166.8 ±900.4 (n=110)	73.7 ±56.5 (n=96)	115.5 ±210.7 (n=139)	71.5 ±43.2 (n=125)	45.3 ±24.8 (n=40)	42.7 ±27.7 (n=31)	253.8 ±653.8 (n=69)	77.2 ±94.4 (n=62)
ALT U/L	51.6 ±51.7 (n=98)	51.8 ±53.7 (n=59)	65.7 ±334.1 (n=110)	41.5 ±36.5 (n=95)	58.1 ±55.8 (n=140)	45.6 ±35.5 (n=125)	43.9 ±21.5 (n=41)	33.3 ±22.7 (n=31)	62.2 ±143.5 (n=69)	54.1 ±64.6 (n=62)
Alkaline Phosphatase U/L	Not tested	Not tested	Not tested	Not tested	Not tested	Not tested	Not tested	Not tested	Not tested	Not tested
Bilirubin mg/dL	Not tested	Not tested	Not tested	Not tested	Not tested	Not tested	Not tested	Not tested	Not tested	Not tested

*From the sponsor's submission Table 22 in Summary of Safety, Module 5 Section 5.3.5.3

Medical Officer's Comments:
There was a 22% decrease of the mean platelet count between baseline and the end of treatment (133.6 ±84.5 vs. 109.1 ±59.7) in Study VAP-301 (Table 11). As per protocol, no interim platelet counts during the study were systematically measured. The 22% decrease of platelet count could be dangerous in patients with decompensated liver function. Contribution of vapreotide to the platelet count decrease can not be ruled out. It should be noted that with blood transfusions, some level of platelet count decrease is expected.
The rest of the clinical laboratory profile appeared unremarkable.

5.1.8 Vital Signs

Vital sign parameters included systolic blood pressure, diastolic blood pressure, heart rate, and body temperature (see the sponsor's submission, Module 5, Section 5.3.5.3). There were no clinically important trends within or between treatment groups with respect to vital signs or physical examination findings.

5.2 Adequacy of Patient Exposure and Safety Assessments

Section 7.2 provides an assessment of the adequacy of drug exposure and the safety evaluations performed as part of the development program. The following four questions were assessed:

1) Whether or not all tests reasonably applicable were conducted to assess the safety of the new drug?

Medical Officer's Comments:
No. The platelet count was not measured after the initiation of vapreotide treatment. Upon the reviewer's request, the sponsor provided only four sets of platelet count from patients who died in the 5-day study (Study VAP-301).

2) Was there adequate experience with the drug in terms of overall numbers of patients and in appropriate demographic subsets of patients?

Medical Officer's Comments:
The total number of patients being studied was 469 subjects. It is acceptable though it is small in size. The demographic subsets of patients, i.e. the source of liver cirrhosis and Child-Pugh scores (Class A, B or C) are acceptable.

3) Were all potentially important findings adequately explored?

Medical Officer's Comments:
No. The potentially important findings included imbalanced SAEs (DIC, thrombocytopenia, severe systemic inflammatory response syndrome, and sudden onset of respiratory failure) could be further explored. This reviewer recommends that the Applicant evaluate the impact of vapreotide on peripheral platelet count, inflammatory cytokines, T-cell activation, and the coagulation cascade.

5.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

The primary safety data sources used in conducting the review were described in Section 4.

5.2.2 Demographics

Demographic characteristics of the pooled populations from the five variceal bleeding studies included:

- VAP-14 (vapreotide 111; placebo 116; France)
- VAP-02 (vapreotide 70; placebo 66; Hong Kong)
- VAP-07 (vapreotide 41; placebo 31; Egypt)
- VAP-06 (vapreotide 144; placebo 134; Eastern Europe)
- VAP-301 (vapreotide 103; placebo 0; USA)

Demographic characteristics of the pooled populations from other indications included:

- DEB-92-VAP-02 (vapreotide 35; placebo 0): neuroendocrine tumors/carcinoid
- DEB-93-VAP-09 (vapreotide 22; placebo 0): Crohn's disease
- DEB-95-VAP-02 (vapreotide 15; placebo 0): Acromegaly
- DEB-98-VAP-06 (vapreotide 187; Placebo 189): pancreatic surgery

These are summarized in Table 13 below:

Table 13: Demographic Characteristics of Safety Population

Demographic Characteristic	Variceal Bleeding Five Studies		Studies in Other Disease Populations	
	Vapreotide N=469	Placebo N=347	Vapreotide N=259	Placebo N=189
Age				
N	455	337	259	189
Mean ± SD	54.2 ± 10.5	55.1 ± 10.6	59.1 ± 16.1	61.5 ± 12.7
Range	18-78	18-81	17-89	19-86
18-40 years	43 (10%)	28 (8%)	37 (14%)	13 (7%)
41-64 years	329 (72%)	244 (72%)	115 (45%)	95 (50%)
65-75 years	78 (17%)	61 (18%)	63 (24%)	56 (30%)
>75 years	5 (1%)	4 (1%)	43 (17%)	25 (13%)
Gender				
Male	358 (76%)	256 (74%)	139 (54%)	100 (53%)
Female	111 (24%)	91 (26%)	120 (46%)	89 (47%)

*From the sponsor's submission, Table 3 in Summary of Safety, Module 5, Section 5.3.5.3.
Note: All of the variceal bleeding studies except Study VAP-301 were performed in foreign countries. Information on race was not collected.

In variceal bleeding studies, there were more male subjects than female subjects in both the vapreotide (76% vs. 24%) and placebo (74% vs. 26%) arms. The distribution of age and gender characteristics was similar in variceal bleeding studies across the vapreotide and placebo groups.

Table 14 shows the distribution of Child-Pugh score class in the five variceal bleeding studies. Studies VAP-301, VAP-14, and VAP-06 had comparable severe liver disease (Class C). Studies VAP-02 and VAP-07 had less severe liver disease than the above three studies, with Study VAP-07 having the least severe liver disease.

Table 14: Child-Pugh Class at Baseline (ITT Population)

Child-Pugh Class	VAP-301 (USA)	VAP-14 (France)		VAP-06 (Eastern Europe)		VAP-07 (Egypt)		VAP-02 (Hong Kong)	
	Vapre N=69	Vapre N=92	Placebo N=94	Vapre N=136	Placebo N=131	Vapre N=31	Placebo N=27	Vapre N=51	Placebo N=51
Class A	12 (17.4%)	14 (15.2%)	14 (14.9%)	N/A	N/A	10 (32.3%)	7 (25.0%)	8 (15.7%)	6 (11.7%)
Class B	31 (44.9%)	42 (45.7%)	41 (43.6%)	N/A	N/A	17 (54.8%)	15 (55.6%)	24 (47.1%)	25 (49.0%)
Class C	26 (37.7%)	36 (39.1%)	39 (41.5%)	55 (40.4%)	66 (50.4%)	2 (6.5%)	3 (9.7%)	15 (29.4%)	19 (37.2%)
Class A+B	43 (62.3%)	56 (60.9%)	55 (58.5%)	74 (54.4%)	61 (46.6%)	27 (87.1%)	22 (70.9%)	32 (62.7%)	31 (60.7%)

*From the reviewer's notes based on the submission of Module 5.

5.2.3 Extent of exposure (dose/duration)

Planned and actual mean drug exposures for the seven vapreotide studies are summarized in Table 13. The majority of the safety population (92%) was scheduled to received the proposed daily dose of 1.2 mg vapreotide for five days (64%), or more (28%). The actual exposure was less than planned, largely due to protocol-specified discontinuations of study drug.

Table 15: Extent of Exposure to Vapreotide in Safety Population

Study	Treatment Duration (days)			Number of Patients at Daily Dose		Mean exposure: Daily Dose x Actual Mean Duration
	Planned	Percent completed 5- or 7-day course	Actual mean ± SD	1.2 mg	1.5 mg	
Variceal Bleeding Studies						
VAP-14	5	76%	3.8 ± 1.9	111	0	4.6 mg
VAP-02	5	54%	2.5 ± 1.7	70	0	3.0 mg
VAP-07	5	69%	4.2 ± 1.8	41	0	5.0 mg
VAP-06	5	82%	4.6 ± 1.4	144	0	5.5 mg
VAP-301	5	59%	3.3 ± 2.3	103	0	4.0 mg
	Total	70%	3.8 ± 1.9	469	0	4.6 mg
Studies in Other Disease Populations						
DEB-92-VAP-02	90-180	N/A*	180 ± 234	0	35	270.9 mg
DEB-93-VAP-09	28	N/A	25.3 ± 4.9	0	22	38.0 mg
DEB-05-VAP-02	21	N/A	21.0 ± 0.0	15	0	25.2 mg
DEB-98-VAP-06	7	73%	4.4 ± 2.9	186	0	5.3 mg
			Total	201	37	N/A
Total Vapreotide Studies				670	57	N/A

From the sponsor's submission Table 4b in Summary of Safety, Module 5, Section 5.3.5.3
*N/A: Not available

In the variceal bleeding studies, 15.3% (59/385) of patients in vapreotide groups in the ITT population failed to complete the scheduled 5-day course of treatment because of death due to underlying disease (Drug effects can not be ruled out) (7.8%), use of alternative therapy (4.2%), adverse events not leading to death (1.3%), and other reasons (2.1%) (Table 16, ITT population). However, fewer patients (8.6%, 30/347) in placebo groups failed to complete the scheduled 5-day course of treatment.

Table 16 shows the disposition of 463 patients to vapreotide arms, whereas the number in the safety tables was 469 patients. The difference is due to that five patients randomized to placebo (Patient #10, #24, #36, #45, #49) in Study VAP-07 that were found to be treated with vapreotide. These patients were added to the vapreotide group for safety analyses.

Table 16: Patient Disposition in Variceal Bleeding Studies (Vapreotide Groups)

Disposition	VAP-14 France[a]	VAP-07 Egypt[b]	VAP-06 E Europe[c]	VAP-301 USA[d]	VAP-02 Hong Kong[e]
Patients enrolled/randomized	111	36	145	103	68
Randomized but not treated	0	0	1	0	0
No endoscopy performed (protocol violations)	1	0	2	2	0
Protocol-specified withdrawal at endoscopy:					
Bleeding not due to portal Hypertension	13	1	9	25	18
Cause of bleeding unknown	0	0	0	6	0
Other	0	4	0	0	0
ITT population	98	31	136	70	50
Withdrawal Days 1-5:					
Death	5	2	11	7	5
Adverse event	3	0	0	2	0
Therapeutic alternative required for uncontrolled bleeding	4	2	4	0	6
Other	2	2	2	0	2
ITT population completing 5-day treatment, n (%)	84 (86%)	25 (81%)	119 (88%)	61 (87%)	37 (74%)

*From the sponsor's submission Table 3, Module 1 Section 1.11.2

A: In the VAP-14 study, one patient (#96) did not have endoscopy but was included in the ITT population. From the ITT population, five patients (#41, #74, #158, #202, #223) died prior to completing study treatment; four patients (#53, #64, #93, #184) discontinued study treatment due to SAEs and to receive therapeutic alternatives; and two patients (#29, #68) discontinued study treatment at the sponsor's request.

B: In the VAP-07 study, four patients (#18, #32, #42, #51) were excluded from the ITT population for bleeding due to pure bilharzias etiology. From the ITT population, two patients (#22, #34) died prior to completing study treatment; two patients (#9, # 68) discontinued treatment due to SAEs and to receive alternative treatment for uncontrolled bleeding; and two patients (#6, #61) withdrew consent prior to completing study treatment.

C: In the VAP-06 study, one patient who was randomized but not treated (#5135) and two patients (#5081, 5181) who died prior to endoscopy were included in the ITT population. From the ITT population, 11 patients (#1923, #5018, #5031, #5044, #5064, #5080, #5081, #5090, #5123, #5181, #5909) died prior to completing study treatment, four patient (#1017, #1041, #5146, #5908) discontinued treatment to receive a therapeutic alternative for uncontrolled bleeding, one (#5044) discontinued for an adverse event, and one (#1013) withdrew consent prior to completing study treatment.

D: In the VAP-301 study, two patients were excluded from the ITT population for major protocol violations, one (#0813) who had been enrolled previously for an earlier bleeding event and one (#0807) with severe respiratory complications that precluding endoscopy. From the ITT population, seven patients (#0105, #1305) discontinued study treatment due to adverse events.

E: In the VAP-02 study, five patients (#025, #061, #9017, #9031, #9038) died prior to completing study treatment, six patients (#021, #072, #088, #101, #9007, #9030) discontinued to receive a therapeutic alternative for uncontrolled bleeding; and two patients (#202, #402) discontinued for other reasons.

5.2.4 Adequacy of Overall Clinical Experience

- Whether an adequate number of subjects were exposed to the drug, including adequate numbers of various demographic subjects and people with pertinent risk factors.

Medical Officer's Comments:
A total of 469 patients were exposed to vapreotide intravenous infusion in variceal bleeding studies. A total of 726 patients were exposed to vapreotide intravenous infusion in studies including other disease populations. The number of subjects seems acceptable, including the demographic subsets and people with pertinent risk factors.

- Whether doses and durations of exposure were adequate to assess safety for the intended use.

Medical Officer's Comments:
The dose and duration of vapreotide exposure was chosen from the octreotide treatment strategy. It was acceptable based on the available information at the present time.

- Whether the design of studies (open, active-control, placebo-control) was adequate to answer critical questions.

Medical Officer's Comments:
The placebo-controlled variceal bleeding studies were adequate to evaluate the general safety of vapreotide. This reviewer however has concerns that the studies were not designed to adequately answer questions regarding potential pro-coagulation and pro-inflammation toxicities of vapreotide.

- Whether patients excluded from the study (e.g., diabetics, people over 75, people with recent myocardial infarction, people with renal or hepatic functional impairment, or people on particular other therapy) limit the relevance of safety assessments. This may depend on the signals of toxicity that were observed in the patients who were studied.

Medical Officer's Comments:
The inclusion and exclusion criteria of the studies were appropriate.

5.2.5 Assessment of Quality and Completeness of Data

Medical Officer's Comments:
The overall quality and completeness of the data available for conducting the safety review seems acceptable. This assessment was based on the resubmission of reports of adverse events, narratives of serious adverse events, and laboratory results.
There were significant differences in data quality and completeness between the individual study conducted in the United States (VAP-301) and the other studies conducted outside the United States (VAP-14, VAP-02, VAP-06, VAP-07):
1) Quality of narratives of patients who died within the 5-day treatment: Study VAP-301 provided detailed clinical findings, whereas the other four studies only provided brief conclusions.
2) Quality of clinical laboratory data: Study VAP-301 provided platelet count of patients who died within the 5-day treatment, and D-dimer values to support the DIC diagnosis in some patients. The other four studies did not provide these data.
As a result, Study VAP-301 supports an independent review.

5.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

Medical Officer's Comments:
The selected serious adverse events and cases (possibility of being drug-related is not ruled out) are summarized below.

1) Severe thrombocytopenia combined with intractable bleeding

- Patient #0604 (Study VAP-301): 51 year-old male with alcoholic cirrhosis and thrombocytopenia (Child Score 12 at baseline) experienced exacerbated platelet count drop from 100 to 44, then 22 10^9/L after the initiation of vapreotide treatment. Endoscopy revealed severe Grade III varices. He experienced re-bleeding episodes in 24 hours. He was given multiple transfusions (PRBC and platelets) and vasopressor treatments with no success. On Day 5, he died of hypovolemic shock and multi-organ failure.
- Non-fatal serious adverse events: Thrombocytopenia: 8 patients in treated groups vs. 1 patient in placebo groups.

2) Severe systemic inflammatory response syndrome (SIRS)

- Patient #1201(Study VAP-301): 47 year-old male (alcoholic cirrhosis, hepatitis B, thrombocytopenia, and Child Score 8 at baseline) developed severe systemic inflammatory response syndrome a few hours after the initiation of vapreotide treatment. His platelet count dropped from 127 to 99, then 75 during the treatment. He experienced intractable hypotension with systolic blood pressure 60s and 50s, and did not respond to vasopressor (dopamine, norepinephrine) treatments. No re-bleeding was identified. He died of multi-organ failure twenty-two hours after the initiation of vapreotide treatment.

3) Thromboembolism

- **Stroke**
  Patient #158 (Study VAP-14): 61 year-old male (alcoholic cirrhosis) experienced sudden onset of left hemiparesia after the initiation of vapreotide treatment. His clinical condition rapidly deteriorated to hemiplegia and coma. CT scan documented a deep intracerebral hemorrhage of the right hemisphere. He died on Day 2. The cause of death diagnosed by the investigator was cerebrovascular accident.
- **SAEs:** Cerebrovascular accidents: 2 patients in treated groups vs. 0 in placebo groups.

- **Pulmonary embolism**
  Patient #1701 (Study VAP-301): 50 year-old male (alcoholic cirrhosis, Child Score 7) with left pleural effusion was hemodynamically stable at baseline. He experienced two episodes of abrupt onset of dyspnea and O_2 desaturation, and died of respiratory failure on Day 5. CXR showed no significant change of pleural effusion as compared with the control at baseline. The cause of death was consistent with pulmonary embolism as diagnosed by the investigator.
- **SAEs:** Respiratory failure: 8 patients in treated groups vs. 0 in placebo groups; Pulmonary embolism: 1 patient in treated groups vs. 0 in placebo groups; Pulmonary edema: 2 patients in treated groups vs. 0 in placebo groups.

4) Coagulopathy

- **Disseminated intravascular coagulation (DIC)**
  Patient #0409 (Study VAP-301): 43 year-old female (alcohol cirrhosis, hepatic failure, coagulopathy, and Child score 11 at baseline) experienced rapid drop of platelet count from 100 to 56 after the initiation of vapreotide treatment. She developed acute renal failure, severe metabolic acidosis, and DIC (D-dimer value greater than 10009 mg/mL). EGD examination did not identify recent bleeding. On Day 5, she died of acidosis, acute renal failure, hepatic failure and DIC.

5) Cardiac insufficiency

- **Bradycardia**
  Patient #1707 (Study VAP-301): 45 year-old male with a history of cirrhosis, hepatitis C and HIV infection had Child Score 12 and platelet count of 53 $x10^9$/L at baseline. He was alert, responding to commands with a blood pressure of 76/34. After the initiation of vapreotide infusion, his abdomen became distended. Bleeding was noted during the unsuccessful attempt to place a central line. Two units of PRBC (packed red blood cells) were being transfused for a decreased hematocrit and hemoglobin. The patient became unresponsive. He had bradycardia and died of cardiac arrest a few hours later.
- **SAEs:** Bradycardia: 5 patients in treated group vs. 1 patient in placebo.

6 ADDITIONAL CLINICAL ISSUES

6.1 Dosing Regimen and Administration

For the variceal bleeding indication, the study dose was an initial I.V. bolus injection of 50 mcg followed by a continuous I.V. infusion at the rate of 50 mcg/hr (1.2 mg/day) for 5 days. The dose selection was based on previous studies using somatostatin and its analog octreotide for the same indication.

Dose-optimizing studies of vapreotide were not performed.

6.2 Drug-Drug Interactions

Vapreotide is a cyclic peptide. Information on drug-drug interactions is not available.

6.3 Special Populations

No dose modification for race and gender is suggested by the sponsor's submission. Hepatic and renal impairment studies showed no effect on the pharmacokinetics of vapreotide in adult patients. For pediatric patients with hepatic or renal insufficiency, special dosing was not studied.

7 OVERALL ASSESSMENT

7.1 Conclusions

This safety review is based on the updated safety database from five variceal bleeding studies (VAP-14, VAP-02, VAP-07, VAP-301, and VAP-06) with 469 patients who received at least one dose of I.V. vapreotide during the 42-day study period. The safety findings are summarized as follows:

1) The 42-day mortality rate in the vapreotide group (17.5% [82/469]) was similar to that in the placebo group (16.7% [58/347]).

2) The 5-day mortality rate in the vapreotide group (7.0% [33/469]) was similar to that in the placebo group (6.9% [24/347]).

3) There were events for which deaths occurred at a higher rate on vapreotide relative to placebo during the 5 day treatment. The imbalanced adverse event categories appeared to be concentrated in disseminated intravascular coagulation, cerebrovascular accident, acute respiratory failure, severe systemic inflammation response syndrome, and thrombocytopenia; contribution of vapreotide effects on these deaths cannot be ruled out.

Based on the available safety information, this reviewer concludes that the safety of vapreotide treatment in the proposed population has not been established. This reviewer believes that the following risks may not have been adequately evaluated: thrombocytopenia, thromboembolism, systemic inflammation, DIC, and bradycardia.

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9 APPENDICES

9.1. INDIVIDUAL STUDY REVIEWS

Disclaimer: Tabular and graphical information is from sponsor's submission unless stated otherwise.

A. Study VAP-301 (New study in the United States)

BACKGROUND INFORMATION
Title: The Early Use of Sanvar with Endoscopic Treatment for the Control of Acute Variceal Bleeding Due to Portal Hypertension

Phase of Study: 3

Objective: To assess the clinical benefit of the early use of Sanvar in combination with endoscopic treatment for the control of acute variceal bleeding in order to provide confirmatory evidence of the efficacy demonstrated in VAP-14

Study design: Open label, historical control, and multicenter study in cirrhotic patients suffering from variceal bleeding. Patients received vapreotide (50 µg bolus in emergency followed by an I.V. infusion 50 µg/hr for 5 days). After the beginning of infusion, the patients underwent endoscopic treatment of their bleeding varices according to the anatomic origin of bleeding.

Table 1: Demographic Characteristics: Safety and ITT Populations (Study VAP-301)

Parameter (%)	**Safety Population N=103**	**ITT Population N=70**
Gender N(%)		
Male	77 (74.8%)	53 (75.7%)
Female	26 (25.2%)	17 (24.3%)
Age (years)		
N	103	70
Mean (SD)	53.1 ±8.5	53.3 ±8.4
Min-Max	27.9-71.8	27.9-71.8
Median	51.7	52.0
Weight (kg)		
N	100	69
Mean (SD)	84.4 ±21.1	84.1 ±21.9
Min-Max	41.4-146	41.4-146
Median	80.9	80.9
Height (cm)		

N	95	67
Mean (SD)	174 ±9.6	174 ±9.9
Min-Max	155-198	155-198
Median	173	175

From the sponsor's submission Module 5 Volume 4.6, Table 11.2

Table 2: History of Disease (Disease Factors)

	Safety Population (N=103) N(%)	**ITT Population (N=70) N(%)**
Known underlying cause	103	70
Alcoholism	38 (36.9%)	22 (31.4%)
Viral Hepatitis	14 (13.6%)	10 (14.3%)
Biliary	2 (1.9%)	2 (2.9%)
Other	12 (11.7%)	8 (11.4%)
Alcoholism/Viral Hepatitis	28 (27.2%)	20 (28.6%)
Alcoholism/Other	9 (8.7%)	8 (11.4%)
Age at diagnosis of cirrhosis (years)		
N	81	58
Mean (SD)	50.7 (±9.2)	50.7 (±9.0)
Median	50.2	50.2
Min-Max	26.3-70.4	26.3-70.4
Time from diagnosis of cirrhosis to admission (years)		
N	81	58
Mean (SD)	3.2 (±4.9)	2.9 (±4.9)
Median	2.0	1.5
Min-Max	0.0-28.0	0.0-28.0
Known previous history of:		
Ascites	47 (45.6%)	36 (51.4%)
Hepatic encephalopathy	24 (23.3%)	16 (22.9%)

From the sponsor's submission Module 5 Volume 4.6, Table 11.3;
Alcoholism: alcoholism as the only cause of cirrhosis;
Viral hepatitis: viral infection as the only cause of cirrhosis;
Other: all the other underlying causes.

SAFETY EVALUATION

Extent of exposure

Vapreotide was administered to 103 enrolled patients who presented at the emergency department with a history of cirrhosis and acute upper gastrointestinal hemorrhage. As per protocol, the administration of vapreotide was discontinued in 31 patients for whom the origin of the hemorrhage at endoscopy was found not to be related to portal hypertension. Treatment was discontinued early in an additional 12 patients.

The median daily dose for the safety population, including patients whose treatment was discontinued, was 1.2 mg and the median 5-day total dose was 5.94 mg, or 99% of the planned dose.

Table 3: Extent of Exposure Study VAP-301

Study	Daily Dose	Number of Patients	Exposure (Days)			
			Mean Duration	SD	Median	Range
VAP-301	1.2 mg	103	3.266	2.287	4.999	0.001 – 5.449

*From the sponsor's submission Study VAP-301 report

Adverse Events (AEs)

A total of 275 AEs were reported over the 42-day course of study. Overall, 72 (69.9%) of patients experienced at least one adverse event, and 34 (33.0%) patients at least one severe adverse event (SAE).

Common adverse events

The most frequently occurred treatment-emergent AEs (≥ 5%) included:

- Hypokalemia (11/103, 10.7%),
- Renal failure (10/103, 9.7%),
- Abdominal pain (7/103, 6.8%),
- Nausea (7/103, 6.8%),
- Nasophageal varices bleeding (7/103, 6.8%),
- Pneumonia (7/103, 6.8%), and
- Hypotension (6/103, 5.8%).

The intensity of these adverse events was primarily rated as moderate or severe. Most of them were classified as not related to the study drug by the investigator.

The treatment-emergent AEs reported at frequency of < 5%, but ≥ 1% included the follows:

Blood and Lymphatic System Disorders:

- Anemia (3, 2.9%), coagulopathy (3, 2.9%), DIC (2, 1.9%), leucopenia (2, 1.9%), and thrombocytopenia (2, 1.9%)

Cardiac Disorders:

- Bradycardia (3, 2.9%), atrial fibrillation (2, 1.9%), cardiac arrest (2, 1.9%), and tachycardia (3, 2.9%)

Gastrointestinal Disorders:

- Upper gastrointestinal hemorrhage (14, 13.6%), and melena (2, 1.9%)

General Disorders:

- Generalized edema (2, 1.9%), multi-organ failure (3, 2.9%), pain (5, 4.9%), and pyrexia (5, 4.9%)

Hepatobiliary Disorder:

- Ascites (4, 3.9%), hepatic encephalopathy (5, 4.9%), and hepatorenal syndrome (2, 1.9%)

Infections:

- Septic shock (5, 4.9%)

Metabolism:

- Hyperglycemia (4, 3.9%), hypernatremia4, 3.9%), and metabolic acidosis (4, 3.9%)

Nervous System Disorders:
- Headache (5, 4.9%)

Psychiatric Disorders:
- Psychomotor hyperactivity (3, 2.9%)

Renal and Urinary disorders:
- Hematuria (2, 1.9%)

Respiratory Disorders:
- Acute respiratory distress syndrome (3, 2.9%), pleural effusion (3, 2.9%), pulmonary edema (2, 1.9%), and respiratory failure (5, 4.9%)

The intensity of the less common adverse events was primarily rated as moderate or severe. Most of them were classified as not related to the study drug by the investigator. Only bradycardia and nauseas were considered by the investigator to have a reasonable causal relationship to the study drug.

Deaths

Nine patients died during the first five days of treatment. The sponsor stated that none of the deaths were due to the effects of vapreotide. According to the sponsor, the causes of death included uncontrolled initial hemorrhage (2 deaths) or its complications such as multi-organ failure (3 deaths), renal failure (1), respiratory failure (1), cardiac arrest (1), and septic shock (1).

Medical Officer's Comments:
Previous studies demonstrated that hemorrhage per se did not cause intravascular coagulation or thromboembolism (Hardaway, 2001). DGP requested additional clinical laboratory results of these patients. The results suggest that the drug effects cannot be ruled out (Table 4).

Table 4: Summary of Nine Deaths in 5-Day Treatment in Study VAP-301 (Review's Notes)*

Patient ID	Age (yrs)	Sex	Dose (mg)	Time of Death (Days)	Description
1707	45	M	1.2	1	• Non-esophageal re-bleeding • Bradycardia • Cardiac arrest
1201	47	F	1.2	1	• Severe systemic inflammatory response syndrome • Platelet count drop after initiation of infusion • Intractable hypotension • Subacute DIC, multi-organ failure
0305	60	M	1.2	2	• Initial bleeding leading to hemorrhagic shock • Platelet count drop after initiation of infusion • Anuric renal failure • Multi-organ failure
0604	51	M	1.2	5	• Intractable bleeding and hypotension • Rapid platelet count drop from 100 to 22 10^9/L after infusion • Acute renal failure • Multi-organ failure
1701	50	M	1.2	5	• Abrupt O_2 desaturation during infusion • Respiratory failure
0409	43	F	1.2	5	• Rapid platelet count drop after initiation of study • Acute renal failure • DIC
0805	60	M	1.2	2	• S/P TIPS placement • Infection by MRSA • Septic shock
0410	51	M	0	0	• Uncontrolled duodenal ulcer bleeding, withdrawn
0811	52	M	1.2	1	• Uncontrolled GI bleeding • Unsuccessful TIPS, withdrawn

*From the reviewer's notes based on the sponsor's submitted narratives and clinical laboratory results, Module 5, Volume 4.6.

The summary of selected narratives of patients who died in the 5-day vapreotide infusion is as follows:

1) Multi-organ failure:

- **Severe systemic inflammatory response syndrome (SIRS)**

  Patient #1201: 47 year-old male (alcohol cirrhosis, hepatitis B, Child Score 8, thrombocytopenia at baseline) experienced severe systemic inflammatory response syndrome and rapid platelet count drop from 127 to 99 to 75 10^9/L after the initiation of vapreotide treatment. He developed intractable hypotension with systolic blood pressure 60s and 50s, not responded to vasopressor (dopamine, norepinephrine) treatments. No re-bleeding was identified. The thrombocytopenia plus D-dimer > 20 mcg/mL indicated the on-going development of subacute DIC. He died of multi-organ failure twenty-two hours after the initiation of vapreotide treatment.

- **Acute renal failure and pulmonary edema**

Patient #0305: 60 year-old male (alcoholic cirrhosis, Child Score 7 at baseline) experienced rapid platelet count drops from 197 (on Day 1) to 144, then 85 10^9/L (on Day 2) after the initiation of infusion. He developed both acute renal failure and pulmonary edema in one day, and died on Day 2 of treatment.

- **Severe thrombocytopenia and hypovolemic shock**

Patient #0604: 51 year-old male (Child Score 12, alcoholic cirrhosis, thrombocytopenia at baseline) experienced exacerbated platelet count drops from 100 to 44, then 22 10^9/L after the initiation of vapreotide treatment. Endoscopy revealed Grade III varices, but was unable to stop all bleedings. He suffered from re-bleeding within 24 hours. He was given multiple transfusions (PRBC and platelets) and vasopressor treatments, but the platelet counts were not corrected. On Day 5, he died of hypovolemic shock and multi-organ failure.

2) Respiratory failure:

- **Pulmonary embolism**

Patient #1701: 50 year-old male (Child Score 7, alcoholic cirrhosis) with left pleural effusion was hemodynamically stable at baseline. He experienced two episodes of abruptly onset of dyspnea and O_2 desaturation, and died of respiratory failure on Day 5. CXR showed no significant change of pleural effusion as compared with the control at baseline. The cause of death was consistent to pulmonary embolism as diagnosed by the investigator.

3) Coagulopathy

- **Disseminated intravascular coagulation (DIC)**

Patient #0409: 43 year-old female (alcoholic cirrhosis, hepatic failure, coagulopathy, Child Score 11 at baseline) with elevated INR and hepatic failure experienced rapid drops of platelet count from 100 to 56 10^9/L after the initiation of vapreotide treatment. She developed acute renal failure, severe metabolic acidosis, and DIC (D-dimer value greater than 10009 mg/mL). EGD examination did not identify recent bleeding. No pathogen identified. On Day 5, she died of acidosis, acute renal failure, hepatic failure and DIC.

4) Cardiac insufficiency

- **Bradycardia**

Patient #1707: 45 year-old male (Child Score 12) with a history of hepatitis C infection associated cirrhosis and HIV infection had platelet count of 53 x10^9/L at baseline. He was alert, responding to commands with a blood pressure of 76/34. After the initiation of vapreotide infusion, his abdomen was distended with soft bowel sounds present. Bleed was noted during the unsuccessful attempt to place a central line. Two units of PRBC (packed red blood cells) were being transfused for a decreased hematocrit and hemoglobin. The patient became unresponsive. He had bradycardia, and died of cardiac arrest a few hours later.

Medical Officer's Comments:
There were two patients who died of DIC (#0409 on Day 5 and #0201 on Day 12). Because the study did not have a control, the drug effect on the DIC deaths cannot be ruled out.

There were seventeen patients died between Day 5 and Day 42. Table 5 summarized these deaths.

Table 5: Deaths Occurred After 5 Days Treatment in Study VAP-301 [1]

Patient ID	Age (yrs)	Sex	Dose (mg)	Time[2] (Days)	Description
0101	67	F	1.2	8	Sudden death
0106	54	F	1.2	18	Multi-organ failure 5-day after treatment
0201	64	M	1.2	12	Renal failure, DIC
0401	41	M	1.2	11	Acute respiratory distress syndrome, renal failure 6 day after treatment
0405	49	M	1.2	8	Sudden death
0406	51	M	1.2	>19	Hepatic malignancy
0412	37	M	1.2	9	Hepatorenal syndrome
0416	55	M	1.2	8	Pleural effusion and pneumonia 2 days after starting Sanvar; dead of pneumonia
0417	59	M	1.2	28	Hematemesis 4 days after Sanvar treatment; developed MRSA septic shock
1002	47	M	<1	41	Cause of death unknown
1003	51	M	<1	10	Fungemia, sepsis
1301	61	M	1.2	22	Bleeding of esophageal varices
1302	69	M	1.2	12	Massive variceal bleeding, renal failure
1308	61	M	1.2	24	Pneumonia
1601	65	M	1.2	6	Bleeding due to duodenal ulcer
1605	70	F	1.2	28	Respiratory distress 15 days after Sanvar treatment; renal failure; cardiac decompensation
1703	64	M	<1	28	Respiratory failure 1 day after treatment; pneumonia

[1]From the reviewer's notes based on the sponsor's submission Module 5, Volume 4.6 Narratives of Deaths.
[2]Time: Days after completion of vapreotide treatment

Non-fatal SAEs

During the 42-day study, 36 (35.0%) patients reported at least one serious adverse event. Among them, 15 (14.6%) patients experienced at least one SAE over the first 5-days of treatment.

Most of the SAEs (78.9%, 45/57) occurred after Day 5 of study treatment. Many of these SAEs were re-hospitalization due to complications of end-stage liver disease, such as ascites, hypotension, pleural effusion, peritonitis, infection and hematemesis or melena.

Clinical Laboratory Evaluation

Laboratory parameters (RBC, WBC, creatinine. Platelets, AST, ALT, and serum glucose) were evaluated at admission and at Day 5. The result showed that the mean serum glucose was decreased from 158 mg/dL (70 patients) at baseline to 126 mg/dL (62 patients). There was a mild decrease of white blood cells from 10.2 million/mm^3 at baseline (70 patients) to 7.2 million/mm^3 (61 patients). The change of red blood cell counts was unremarkable.

There was a 22% decrease of the mean platelet count between baseline and the end of treatment (133.6 ±84.5% vs. 109.1 ±59.7%). A large variation of these values indicated that platelet remobilization may occur.

Safety summary of Study VAP-301

The safety population included 103 patients. Forty-three (41.7%) of the subjects discontinued the study drug before completing the 5-day infusion period because they were found at endoscopy to have bleeding unrelated to portal hypertension (n=31, 30.1%), deviations from the protocol (n=2), therapeutic alternative (n=1), death (n=3), other adverse event (n=3), and other cause (n=3).

Overall, 59 (57.3%) of patients experienced at least one adverse event over the first 5 days of study treatment and 72 (69.9%) of patients experienced at least one adverse event over the 42-day course of the study. The most commonly reported adverse events were hypokalemia (10.7%), nausea (6.8%), renal failure (9.7%), pyrexia (4.9%), hypotension 5.8%), and headache (4.9%). Of the total 275 events, 69.5% were rated as mild or moderate and 30.5% were rated as severe. Three adverse events [bradycardia (1) and nausea (2)] reported in two patients were considered by the sponsor to have a "causal relationship to vapreotide". All three recovered without discontinuation of vapreotide.

A total of (14.6%) patients experienced at least one SAE over the first five days of study treatment and 36 (35.0%) of patients experienced at least one SAE over the 42-day course of the study. Nine (8.7%, 9/103) patients died during the first five days of the study and 17 (16.5%, 17/103)) died from days 6 to 42.

The reviewer requested additional clinical laboratory results of the deaths for independent review. The review found that vapreotide exposure appeared to associate with DIC, severe systemic inflammatory response syndrome, thromboembolism, bradycardia and aggravation of thrombocytopenia based on the comparison with placebo arms (four studies), and the temporal relation.

Medical Officer's Conclusions (Study VAP-301)
This is a single-arm open-label study which does not allow adequate comparative assessments.

B. Study VAP-06 (New study in Eastern Europe)

BACKGROUND INFORMATION

Title: The Early Association of Vapreotide to Endoscopic Treatment for the Control of Acute Variceal Bleeding, and Prevention of Early Re-bleeding in Cirrhotic Patients

Phase of Study: 3

Objective: To quantify the extent to which vapreotide in association with endoscopic treatment can improve control of bleeding at 5 days (control of bleeding means control of initial bleeding, prevention of early re-bleeding, and survival during the 5-day study period.)

Study design: Double blind, placebo-controlled, multicenter study in cirrhotic patients suffering from acute variceal bleeding, with a follow-up of 6 weeks. Patients were randomized at admission to receive either vapreotide (50 µg I.V. bolus in emergency followed by continuous I.V. infusion of 50 µg/hr for 5 days). After the randomization and beginning of infusion, the patients underwent endoscopic treatment of their bleeding varices according to the anatomic origin of bleeding.

Table 1: Demographic Characteristics: ITT Populations (Study DEB-02 VAP-06)*

	Pre-Amendment		Post-Amendment		Total Population	
	Vapreotide	Placebo	Vapreotide	Placebo	Vapreotide	Placebo
N	32	33	104	98	136	131
Gender% Males	81% (26)	64% (21)	70% (73)	60% (59)	73% (99)	61% (80)
Mean Age, yr (Range)	49 (28-72)	56 (35-80)	55 (18)	54 (18-79)	54 (18-78)	54 (18-80)
Weight, kg Median	74	75	72	72	73	73
Height, cm Median	172	170	171	170	171	170

*From the sponsor's submission Module 5 Volume 4.1

Table 2: History of the Disease (ITT Population)[1]

	Pre-Amendment		Post-Amendment		Total Population	
	Vapreotide	Placebo	Vapreotide	Placebo	Vapreotide	Placebo
N	32	33	104	98	136	131
Etiology						
-Alcoholism[2]	53% (17)	58% (19)	66% (69)	62% (61)	63% (86)	61% (80)
-Viral hepatitis[3]	59% (19)	39% (13)	29% (30)	42% (41)	36% (49)	41% (54)
-Other[4]	13% (4)	12% (4)	16% (17)	9% (9)	15% (21)	10% (13)

Median time from diagnosis of cirrhosis to infusion, yr	2	3	2	2	2	2
Previous history of ascites	53% (17)	55% (18)	60% (62)	62% (61)	58% (79)	60% (79)
Previous history of hepatic encephalopathy	13% (4)	18% (6)	12% (12)	19% (19)	12% (16)	19% (25)
Known esophageal varices	94% (30)	83% (27)	68% (71)	65% (64)	74% (101)	69% (91)
Median time from diagnosis to inclusion, yr	1	2	2	1	2	2

[1]From the sponsor's submission Module 5 Volume 4.1
[2]Alcoholism included all patients with alcoholism, with or without any other etiology.
[3]Viral hepatitis is similarly defined.
[4]"Other" includes all the other etiologies.

SAFETY EVALUATION

Extent of exposure

Vapreotide was administered at least one dose to 144 patients (vapreotide arm 144, placebo arm 134) who were randomized to the treatment arm at the emergency department. Approximately 77% (111/144) patients completed the 5-day treatment with 1.2 mg vapreotide infusion/day.

As per protocol, the infusion was discontinued in the patients who had hemorrhage unrelated to portal hypertension (N=5). In addition, the infusion was discontinued in 28 patients for the following reasons:

- Therapeutic alternative (7 patients in the vapreotide arm and 10 patients in the placebo arm)
- Death (6 patients in the vapreotide arm and 2 patients in the placebo arm)
- Consent withdrawn (1 patient in the vapreotide arm)
- Other reasons (1 patient in the vapreotide arm)
- Other adverse events (1 patient in the vapreotide arm)

The failure to control hemorrhage and/or re-bleeding was the main reason for switching to a therapeutic alternative. The nature of this alternative was either a drug alone (mainly somatostatin or octreotide) or in association to balloon tamponade.

The median time between start of product infusion and premature discontinuation of infusion was 18.2 hours (range 0 to 119 hours).

No significant difference was found between the two treatment arms regarding rate of withdrawal, discontinuation due to a therapeutic alternative, and median time to withdrawal.

Table 3: Cause of early interruption of Study VAP-06 (Safety Population)[1]

Cause of interruption	Vapreotide N=144	Placebo N=134
Bleeding not related to portal hypertension[2]	3	2
Therapeutic alternative[3]	7	10
Consent withdrawn[4]	1	0
Death[5]	6	2
Other adverse event[6]	1	0
Other cause[7]	1	0
Total	19	14

[1]From sponsor's submission: Final report of Study VAP-06, Module 5
[2]Including patients #5004, #5054, and #5063 in vapreotide arm; patients #5010 and #5041 in placebo arm
[3]Including patient #1017, #1041, #5018, #5080, #5090, 5146, and #5908 in vapreotide arm; patients #1004, #1043, #5016, #5019, #5045, #5050, #5056, #5141, #5182, and #5901 in placebo arm
[4]Including patient #1013 in vapreotide arm
[5]Including patient #1923, #5031, #5064, #5123, #5181, and #5909 in vapreotide arm; patients #1020, and #5132 in placebo arm
[6]Including patient #5044 in vapreotide arm
[7]Including patient #5081 in vapreotide arm

Adverse Events (AEs)
A total of 309 AEs were reported to vapreotide arm over the 42-day course of study. Overall, 117 (81%, 117/144) of patients in vapreotide arm experienced at least one adverse event, compared to 111 (82%, 111/134) of patients in placebo arm.

Common Adverse Events
The most frequently occurred vapreotide treatment-emergent AEs (≥ 5%) included esophageal varices hemorrhage (29.8% vs. 33.5%), flatulence (29.8% vs. 27.6%), headache (15.2% vs. 23.8), and pyrexia (11.8% vs. 19.0%).

Table 4: Adverse events occurring in more than 5% of patients (Study VAP-06)*

AE Category	Vapreotide (N=144)			Placebo (N=134)		
	N	%	AEs	N	%	AEs
Esophageal Varices hemorrhage	43	29.8	62	45	33.5	58
Flatulence	43	29.8	46	37	27.6	38
Headache	22	15.2	22	32	23.8	33
Pyrexia	17	11.8	18	19	14.1	21

Chest Pain	16	11.1	18	12	8.9	12
Hepatic Encephalopathy	13	9.0	13	10	7.4	11
Abdominal Pain Upper	11	7.6	14	10	7.4	10
Shock Hemorrhagic	8	5.5	8	8	5.9	8

*From sponsor's submission: Final report of Study VAP-06, Module 5

Deaths

Overall death rate during the 42-day study was 16% (23/144) in the vapreotide arm, and 14% (19/134) in the placebo arm. The 5-day death rate in the vapreotide arm was 7.6% (11/144), and 7.4% (10/134) in the placebo arm.

Table 5: Summary of Deaths During Vapreotide Treatment

	Vapreotide (N=144)	**Placebo (N=134)**
Cause of Death	**Deaths (N=11)**	**Deaths (N=10)**
Initial bleeding / hemorrhage shock	3	4
Re-bleeding / hemorrhage shock	3	4
Hepatic encephalopathy	2	1
Hepatorenal failure	2	1
Bradycardia / aystolia	1	0

Other Serious Adverse Events

There were 97 serious adverse events occurred in 49 (34%, 49/144) patients in the vapreotide arm, while 98 SAEs in 53 (39%, 53/134) patients in the placebo arms.

Table 6: Summary of Serious Adverse Events*

SAEs	Vapreotide (N=144)	Placebo (N=134)
Esophageal varices hemorrhage	43 (30.0%)	45 (33.4%)
Hepatic encephalopathy	18 (12.5%)	15 (11.1%)
Shock, hemorrhagic	8 (5.6%)	8 (6.0%)
Thrombocytopenia	6 (4.1%)	0
Cardio-respiratory arrest	5 (3.4%)	3 (2.2%)
Hepatorenal syndrome	4 (2.8%)	1 (0.8%)
Hepatic failure	1 (0.7%)	2 (1.5%)

*From sponsor's submission: Final Report of Study VAP-06

Dropouts Due to Adverse Events

There were 4 dropouts due to AEs in the vapreotide arm, and one dropout in the placebo arm.

Vapreotide dropouts:

- Hepatic coma (2 dropouts)
- Cardio-respiratory arrest (1 dropout)
- Hepatorenal syndrome (1 dropout)

Placebo dropout:

- Hepatic encephalopathy (1 dropout)

Clinical Laboratory Evaluation

Laboratory parameters (RBC, WBC, creatinine, AST, ALT, and serum glucose) were evaluated at admission and at Day 5. There were no clinically significant changes of hemoglobin, RBC, WBC, glucose, creatinine, AST, and ALT.

Platelet count was not measured.

Safety summary of Study VAP-06

Safe database included 144 patients who received at least one dose of vapreotide. There were approximate 77% (111/144) patients who completed the 5-day treatment with 1.2 mg vapreotide infusion/day.

The 5-day mortality of vapreotide arm was 7.6% (11/144), and placebo arm 7.4% (10/134). Whereas the 42-day mortality of vapreotide arm was 16.0% (23/144), and placebo arm 14.2% (19/134).

The most common cause of deaths was hemorrhage shock. There was no significant difference between the vapreotide arm 4.1% (6/144) and placebo arm 5.9% (8/134).

Comparison of adverse events, thrombocytopenia occurred more frequently in the vapreotide arm than placebo arm (0.4%, 6/144 vs. 0).

Medical Officer's Conclusions (Study VAP-06)

1) The overall mortality rate of the vapreotide arm was comparable with that of placebo arm (16% vs. 14%).

2) The vapreotide arm had more thrombocytopenia adverse events as compared with the placebo arm.

9.2. REVIEWER'S ADDITIONAL DISCUSSION

There were 10 deaths (30%, 10/33) in the imbalanced disease categories during the 5-day treatment of variceal bleeding studies. The imbalanced causes of deaths included multi-organ failure, DIC, cerebral vascular accident, intractable hypotension, severe inflammatory response syndrome, and bradycardia.

Based on the available information, the connection of the diverse causes of deaths with a common pathogenic pathway (i.e. shock toxin pathway) can not be ruled out. In the pathway, activated monocyte / macrophage (M/M) system is the central player.

1) Mechanisms of intravascular coagulation in variceal bleeding patients

Previous animal studies demonstrated that hemorrhagic shock per se does not cause intravascular coagulation (Hardaway, 2001). This may explain why the control arms were lacking in DIC or CVA. When hemorrhage combined with hemolyzed blood cells, it brings about sepsis. Sepsis triggers activation of intravascular coagulation cascade (Hardaway, 1964), leading to DIC and septic shock (Figure 1). The active component of hemolyzed blood cells is aminophospholipid (APL, also known as shock toxin). APL is released from the inner layer of cell wall, and is extremely thrombogenic.

At low levels, APL predominantly serves to activate monocytes and macrophages and complements to cause local cell wall lyses. The mononuclear phagocytes respond to APL action by producing TNFα, which in turn, induces IL-1 synthesis. TNFα and IL-1 act on endothelial cells to produce IL-6 and IL-8, as well as adhesion molecules. The adhesion molecules include MCP-1 (monocyte chemotactic protein-1), ICAM-1 (intercellular adhesion molecule-1), VCAM-1 (vascular cell adhesion molecule-1), and selectins (adhesion of platelets and leukocytes in inflammation).

With moderate to high levels of shock toxin, cytokine-induced secondary effectors (e.g., nitric oxide and platelet-activating factor) become significant. Nitric oxide may cause clinically intractable hypotension. PAF causes platelet aggregation, thrombocytopenia and intravascular coagulation (Figure 2).

At even higher levels of shock toxin, the syndrome of septic shock may become predominant. High levels of cytokines and secondary mediators may lead to:

- Systemic vasodilation (intractable hypotension)
- Diminished myocardial contractility (cardiac insufficiency)
- Widespread endothelial injury and activation, causing
    - systemic leukocyte adhesion (systemic inflammatory response syndrome) and
    - pulmonary alveolar capillary damage (acute respiratory distress syndrome)
- Activation of the coagulation system, causing disseminated intravascular coagulation (DIC and multi-organ failure)

Multi-organ failure may be caused by hypo-perfusion resulting from the combined effects of widespread vasodilation and myocardial pump failure. DIC may induce multi-organ system failure by affecting the liver and kidneys, as well as systemic inflammatory response syndrome (Parrillo, 1993; Ognibene, 1997).

Potential roles of somatostatin agonist in shock toxin pathway.
The role of somatostatin agonists in shock toxin pathway is not clear. However, it is known that the agonists activate monocyte/macrophage cells:

- Activated M/M cells release tissue factor to trigger coagulation cascade;
- Activated M/M cells produce TNFα and IL-1 to activate inflammatory cytokine cascade;
    - IL-8 is responsible for recruiting neutrophils
    - IL-1 for activating T-lymphocytes
- Activated M/M cells produce PAF (platelet-activating factor) to cause platelet aggregation (Figures 1 and 2).

Thus, possible explanations for the imbalanced DIC, CVA, PE, SIRS and septic shock occurred in vapreotide arms include:

- Monocytic tissue factor may be released into systemic circulation to trigger coagulation cascade.
- Uncontrolled inflammatory cytokines and leukocytes may expand localized bacterial infection into systemic circulation.
- Uncontrolled inflammation may increase hemolysis.

Figure 1: Destruction of cell wall generates shock toxin

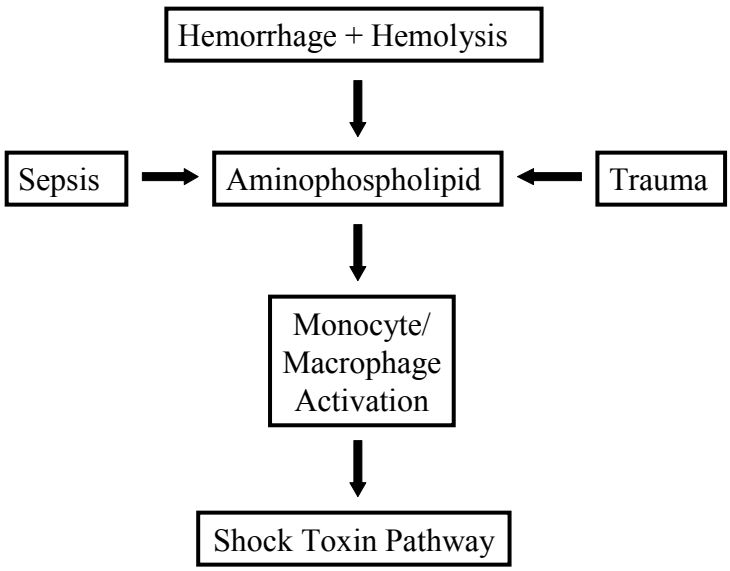
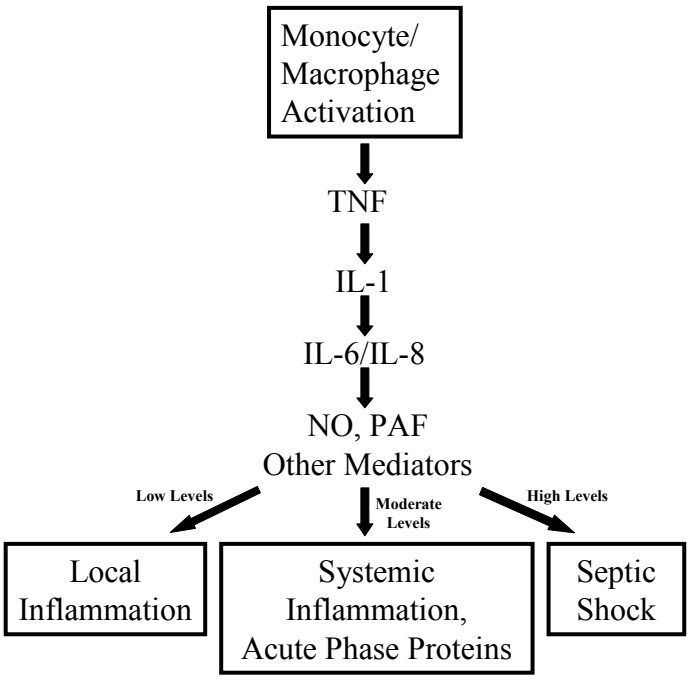


Figure 2: Aminophopholipids Induced Cytokine Cascade and Shock Pathway



Note: NO, nitric oxide; PAF, platelet-activating factor

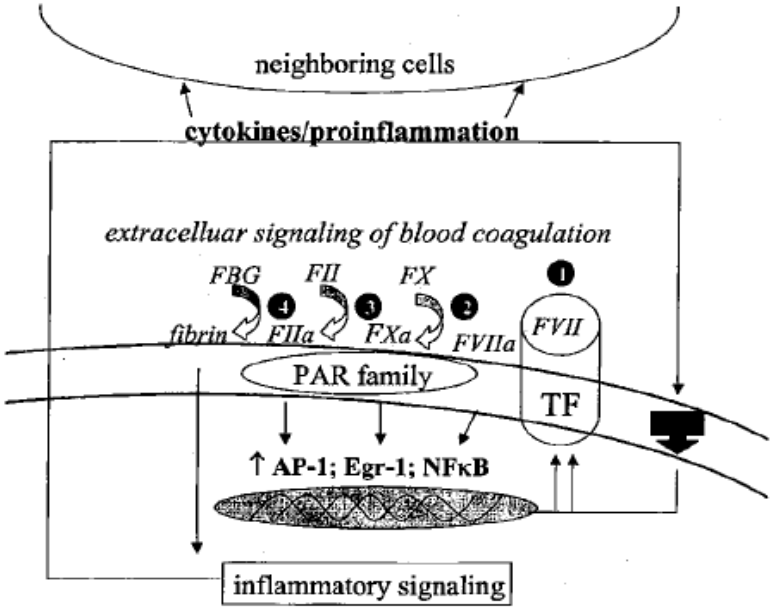
2) Potential mechanism of tissue factor associated coagulation and inflammation

The mechanism of somatostatin agonist induced systemic inflammation and thromboembolism is not entirely clear. It is known that somatostatin receptors are constantly expressed on the surface of monocytes (CD42 positive cells). Binding of somatostatin to the receptor bring about activation of monocyte to synthesize and to release tissue factor (TF). The activation of monocyte is also dependent on plasma levels of glucose and insulin (Boden 2007).

Tissue factor not only initiates extracellular signaling (the extrinsic blood coagulation), but also triggers intracellular signaling to produce inflammatory cytokines, adhesion molecules, and growth factors (Chu 2005, Figure 3). The mechanism of TF mediated inflammation involves PAR (protease-activated receptors) induced inflammatory cytokines [such as TNFα and interleukins (IL-1, IL-6, IL-8)], adhesion molecules (such as MCP-1, ICAM-1, VCAM-1), selectins (adhesion of platelets and leukocytes in inflammation), and growth factors (VEGF, PDGF, bFGF).

The anticipated clinical outcomes include wide spread fibrin thrombi, diffuse circulatory insufficiency (e.g., brain, lungs, heart, and kidneys) and multi-organ failure, thrombocytopenia, coagulopathy, severe cytokine release syndrome, and disseminated intravascular coagulation (DIC).

Figure 3: Mechanism of TF induced coagulation-inflammation cycle*



Legend to Figure 3: TF induced coagulation-inflammation cycle. TF initiates the extrinsic blood coagulation (italics) that is mediated by sequential serine protease (i.e. FVII, FX, and FII) activations; FVIIa, FXa, and FIIa are coagulant mediators fulfilling the clotting signaling in the extracellular compartment. Reaction 1 presents TF-dependent FVII activation. Reaction 2 activates FX to FXa, which is catalyzed by TF/FVIIa binary complex. In Reaction 3, FII undergoes proteolytic activation catalyzed by prothrombinase containing active FXa. FIIa then cleaves FBG (fibrinogen), and fibrin clot is formed following polymerization and stabilization/cross linking (Reaction 4). The coagulant signals including the mediators (FVIIa, FXa, and FIIa) and fibrin are proinflammatory. In general, PAR (protease activated receptors) superfamily transmits FVIIa, FXa, and FIIa signaling, which activates intracellular signaling pathways including transcription factors (AP-1: activator protein 1, a transcription regulator; Egr-1: a nuclear protein functions as a transcriptional regulator; NFκB: a protein complex functions as transcriptional regulator). As a result, inflammation cytokines, adhesion molecules, and growth factors are produced. Neighboring cells are also activated (Chu AJ, 2005).
*From the reference Chu AJ, 2005.

3) Inhibitory effects of somatostatin and lanreotide on cardiac rhythm

Bulbospinal neurons in the rostral ventrolateral medulla (RVLM) are critical for the maintenance of sympathetic vasomotor tone and normal cardiovascular reflex function. A study by Burke et al. showed that RVLM pre-sympathetic neurons express somatostatin 2A receptors that are essential for maintaining and generating sympathetic vasomotor tone (Burke, 2008). Bilateral microinjection into the RVLM of either somatostatin or the receptor agonist lanreotide evoked dramatic, dose-dependent sympathetic inhibition, hypotension, and bradycardia that were blocked by the sst2 (somatostatin type 2) receptor antagonist BIM-23627 in anesthetized rats. Bilateral RVLM microinjection of somatostatin also attenuated chemoreceptor and somatosympathetic reflect function.

DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS

Medical Officer's Review

Application Type	NDA
Submission Number	21-761
Serial Number	N/000
Letter Date	February 27, 2004
Stamp Date	March 03, 2004
PDUFA Goal Date	January 1, 2005
Reviewer Name	Fathia Gibril, M.D., M.H.Sc.
Review Completion Date	December 6, 2004
Established Name	Vapreotide acetate
(Proposed) Trade Name	Sanvar™ Injection
Therapeutic Class	Somatostatin Analogue
Applicant	H3 Pharma, Inc.
Priority Designation	Standard
Formulation	parenteral
Dosing Regimen	50 µg IV bolus followed by a continuous IV infusion of 50 µg/hr for 5 days
Indication	Treatment of acute varcieal bleeding due to portal hypertension, in association with endoscopic treatment
Intended Population	Adult cirrhotic patients with acute variceal hemorrhage

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Clinical Review for NDA 21-761

Executive Summary

I. Recommendations

A. Recommendation on Approvability

From a clinical standpoint, the reviewer recommends that vapreotide be considered approvable for the indication of acute variceal bleeding due to portal hypertension (PHT), in association with endoscopic treatment.

The issuance of an approval is dependent up on the completion and review of an additional controlled study that confirms the results from study DEB-96-VAP-14 (pivotal study).

B. Recommendation on Phase 4 Studies and/or Risk Management Steps

There are no recommendations for phase 4 studies.

II. Summary of Clinical Findings

A. Brief Overview of Clinical Program

The drug under review is vapreotide acetate (Sanvar™), a new molecular entity, for intravenous (IV) injection. Vapreotide acetate is a long acting cyclic octapeptide with pharmacologic properties mimicking those of the natural human peptide somatostatin. It is more potent inhibitor of growth hormone, glucagon, and insulin release than somatostatin. Although the mechanism of action of somatostatin and its analogs has not been defined clearly, this class of agents appears to decrease splanchnic blood flow by inhibiting the release of vasodilatory peptides such as glucagon, vasoactive intestinal polypeptide and substance P. In most European countries, somatostatin and its analogue octreotide are approved for the indication of variceal bleeding. None of these drugs or any other drugs are approved for variceal bleeding indication in the United States.

The proposed indication is for the treatment of acute variceal bleeding related to PHT, in association with endoscopic treatment. In support of the proposed indication, the sponsor, Pharma H3 Inc., submitted the efficacy results from two controlled studies: study DEB-96-VAP-14 as a pivotal study and study DEB-01-VAP-07 as supportive study.

A third study DEB-97-VAP-02 that was initiated in Hong Kong concurrently with the pivotal study (DEB-96-VAP-14) in 1997 was terminated in June 2001 due to poor recruitment rate and

poor protocol compliance. As a result, the study was not considered useful by the sponsor for assessment of efficacy in view of major protocol violations and was evaluated only for safety in the original NDA submission. Up on the Agency's request, the efficacy data were provided as an amendment on September 22, 2004.

All three studies were randomized, double-blind, placebo-controlled studies using identical study design, the same intervention and the same inclusion/exclusion criteria.

Eligible male or female aged 18 to 75 years with liver cirrhotic presenting with hematemesis and/or melena were randomized as early as possible after admission and in almost all cases treatment with a study drug was initiated prior to endoscopic diagnosis and treatment. After endoscopy, those subjects found to present a source of hemorrhage unrelated to PHT had their infusion stopped and these subjects were excluded from the intention-to-treat (ITT) population.

- The pivotal study (DEB-96-VAP-14) was a multicenter, phase III study, in which 227 eligible subjects were enrolled into the study. After the protocol-specified exclusion of 31 subjects, the ITT population included 196 subjects: 98 subjects in each treatment group.
- The supportive study (DEB-01-VAP-07) was a single center phase IIb pilot study, in which 72 eligible subjects were enrolled into the study. After the protocol-specified exclusion of 14 subjects, the ITT population included 58 subjects: 31 in the vapreotide group and 27 in the placebo group.
- Study (DEB-97-VAP-02) was a multicenter phase III study that was initiated in Hong Kong concurrently with the pivotal study in 1997. Due to poor recruitment rate and poor protocol compliance, the study was terminated in June 2001. A total of 136 patients were enrolled over nearly 4 years in five centers. According to the protocol, the estimated sample size was 150. After the protocol-specified exclusion of 34 patients, the ITT population included 102 patients: 51 subjects in each treatment group.

All studies were comparable in terms of study population, methodology, safety and efficacy endpoints with the following exceptions:

- The etiology of liver cirrhosis was alcoholism in the pivotal study population and alcoholism or viral hepatitis in the Hong Kong study population, which are consistent with causes of cirrhosis in the U.S. population. In contrast, the cause of liver cirrhosis in the supportive study population was parasitic (bilharzia) infection in association with viral hepatitis, a condition that is uncommon in Western countries.
- Based on Child-Pugh scores (class A, B or C), subjects in the pivotal study and Hong Kong study had more sever liver disease (class C in 40% of the patients) compared with those in the supportive study (class C in 9% of the patients). In other words, a great majority of patients (88%, 48/54) in the supportive study have class A and B.
- The ratio of male to female was comparable in both pivotal and Hong studies, while only male subjects were involved in the supportive study.

The safety profile of vapreotide was developed from seven clinical trials involving a total of 481 subjects who received at least one dose of vapreotide. Randomized, double-blind, placebo-controlled trials comprised 96% of patients in the safety data base. The variceal bleeding studies

comprised 52% of patients in the safety data base. The daily dose of vapreotide was 1.2 mg/day in the majority (88%) of the studies, and 1.5 mg in the reminder. The mode of administration was IV for the proposed indication, and subcutaneous (SC) for the reminder of studies. At the time of this NDA submission, vapreotide has not been approved for use in any country.

On July 12, 2004, the sponsor submitted an amendment indicating that another identical Phase III study of vapreotide for the proposed indication was initiated in April 2003 in Eastern Europe in response to questions raised during the EMEA review of vapreotide. As of June 1, 2004, 230 patients had been recruited. The study enrollment was completed in October 2004. The sponsor plans to provide a final study report as soon as it becomes available. This information was communicated during a teleconference held with the sponsor on October 17, 2004, when the sponsor was notified about the inadequacy the efficacy data submitted under the current NDA.

B. Efficacy

Primary Endpoint

The primary endpoint was hemostasis during the 5-day infusion period following completion of endoscopic treatment (Tendo). Hemostasis was defined as achievement of both primary hemostasis (no bleeding from Tendo+6 hours to Tendo+48 hours) and secondary hemostasis (no rebleeding between Tendo+48h to Tendo+ 5days).

Primary Efficacy Variables Assessment

To assess the primary endpoint, the sponsor used 3 types of criteria based on Recommendations from Consensus Conference: a) the acute bleeding time-frame during the first 48 hours with 2 different criteria to evaluate primary hemostasis, i.e. bleeding within 6 hour and after 6 hour following the end of endoscopic treatment **(Tendo)**, b) secondary hemostasis was evaluated between 48 hour to 120 hour (Day 3 to 5) for rebleeding.

Primary hemostasis:

1. Assessed up to 6 hours after endoscopy:
   - transfusion requirement ≤ 4 units from Tendo;
   - systolic pressure > 80 mm Hg;
   - heart rate < 100 bpm (excluding other causes of tachycardia)
2. Assessed between 6 hours and 48 hours after Tendo
   - transfusion requirement ≤ 2 units from Tendo + 6 hrs
   - heart rate < 100 bpm
   - Hematocrit: no decrease ≥ 10 points in comparison with value of Tendo + 6 hrs

Secondary hemostasis:
Assessed between Tendo + 48 hour to Tendo +120 hour: no rebleeding (hematemesis, melena). Rebleeding was defined as occurrence of a new hematemesis/melena after a period of ≥ 24 hour of hemodynamic stability (vital signs, Hct or Hgb). A rebleeding episode implies that an initial control of the first hemorrhage was obtained.

Secondary Endpoints

The sponsor defined multiple secondary endpoints which included: absence of active bleeding at the time of diagnostic endoscopy; hemostasis at 6 hour after randomization; number of units of blood administered during the study period; number of days in hospital; in-and-out-hospital survival (7-day, 30-day and 42-day). The sponsor states that the analyses of secondary endpoints were for exploratory purposes. Therefore, the significant level was not adjusted for multiple comparisons.

Study Drug Dose and Duration of Therapy

An initial IV bolus injection of 50 µg vapreotide followed by a continuous IV infusion at a rate of 50 µg/hour (1.2 mg/day) for five days with a follow-up period of 6 weeks.

The sponsor's rationale for selecting Endpoints:
Since hemodynamic stability is the primary goal of treatment for acute variceal bleeding, all vapreotide studies used a composite primary efficacy criterion for control of bleeding at 5 days, based on Recommendation from International Baveno Consensus Conferences for Definitions on Endpoints, Methodology and Therapeutic Strategies in Portal Hypertension (de Franchis R et al. J Hepatol 1992, 1996 and 2000). These Recommendations were adapted by the American Association for the study of Liver Diseases (Grace ND et al. Hepatology 1998) and were incorporated in the UK guidelines on the management of varcieal hemorrhage in cirrhotic patients (Jalan & Hayes, Gut 2000).

Although demonstration of a statistically significant effect on survival at 6 weeks is the most desirable study endpoint, such a trial would require a population size that is not feasible for a rare disease. According to the report in the document submitted, there are a total of about 23,000 cases annually of esophageal variceal bleeding in cirrhotic patients with PHT.

Rationale for dose selection, duration of therapy and duration of follow-up:
Dose-optimizing studies were not conducted with vapreotide. The regimen selected for the current studies is based on the regimen used in similar studies of octreotide and somatostatin in cirrhotic patients with variceal hemorrhage. The optimal duration of the infusion of somatostatin or its analog is not known. In several previous trials, the duration of infusion was 5 days, since this corresponds to the period during which the risk of recurrence of bleeding is the highest. The 6 week study period has been defined by consensus as the period under which all mortality is considered as directly related to the episode of acute hemorrhage.

MO comment: the sponsor's selection of endpoints, duration of therapy and follow-up period were based on sound rationale. The appropriateness of the sponsor's vapreotide dose selection in the current submission cannot be validated since available data indicate that the conventional dose of somatostatin used in clinical studies is largely empirical. A recent controlled study comparing different schedules of somatostatin in the treatment of acute variceal bleeding suggests that using a higher dose of somatostatin infusion achieves a higher rate of hemostasis than the conventional dose in patients with active variceal bleeding at endoscopy (Mointinoho E

et al: J Hepatol 2001). Whether a vapreotide dose that is higher than the dose used in the current submission would produce similar outcomes cannot be determined without conducting a clinical trial.

Efficacy Results

- Study DEB-96-VAP-14 (pivotal study)

In the ITT population, analysis of the primary endpoint at the end of the five-day infusion after endoscopic treatment demonstrated that hemostasis was achieved in 66% (65/98) of patients receiving vapreotide compared with 50% (49/98) of patients receiving placebo, a result that was statistically significant in favor of vapreotide (p=0.021). Similar results were observed in the per-protocol (PP) population 73%, 56/77 vs. 53%, 43/83; p=0.006.

However, using the ITT population, the Agency's by-center analysis for the primary endpoint indicates that the rate of hemostasis in vapreotide group is significantly higher than that of placebo group only for center 18 involving 28 subjects (28/196, 14%), while the results in most centers showed a trend in favor of vapreotide. On the other hand, when center 18 was excluded from the analysis, the effectiveness of vapreotide was no longer superior to that of placebo for the primary endpoint (63.9%, 53/83 vs. 51.8%, 44/85; p=0.11) indicating that the sponsor's reported result was mainly driven from subjects at a single center, i.e. center 18.

The significant findings observed in subjects at center 18 may be explained, at least partly, by the involvement of higher percentage of cirrhotic subjects with Child class A and B (81%, 22/27) compared with 56% (89/160) of subjects not at center 18 (Agency's analysis). This observation is supported by the sponsor's post hoc subgroup analysis of pooled results indicating that vapreotide was superior to placebo for the primary endpoint in subjects with Child class A and B (73%, 29/55 vs. 52%, 41/56), but not for subjects with Child class C (58%, 21/36 vs. 48%, 19/39). However, due to the small sample size the data for the latter subgroup are not sufficient to allow for a valid conclusion to be drawn.

MO comment: Although the Agency's by center analysis of primary endpoint in the ITT population indicate that the superiority of vapreotide to placebo was driven from subjects at center 18, results in most centers indicate trends in favor of vapreotide. Further, although vapreotide was no longer superior to placebo when subjects at center 18 were excluded from the analysis, there was a 12% (63% vs. 51%) therapeutic gain in vapreotide treated subjects which is clinically significant in light of the serious conditions being treated.

When comparison is made with published data, the rate of control of bleeding with vapreotide in this study appears low, compared with that in previous studies using drugs from the same pharmacologic class (Besson I et al. N Engl J Med 1995; Sung JJy et al. Lancet 1995). However, the overall rates of hemostasis observed are similar in recent trials that used comparable criteria set by the Consensus Conference [e.g. 65% with somatostatin in association with sclerotherapy (Avgerinos A et al. Lancet 1997)].

For multiple secondary endpoints analyzed by the sponsor, significant benefits for vapreotide were observed for three secondary endpoints in the ITT population:

- At the time of initial endoscopic procedure, control of bleeding was observed in a significantly greater proportion of patients in the vapreotide group than in the placebo group (64%, 63/98 vs. 51%, 50/98; p=0.031). This action can be attributed solely to vapreotide, as it was observed before initiation of endoscopic treatment.
- Control of bleeding also was observed in a significantly greater proportion of patients in the vapreotide group than in the placebo group at both six hours after endoscopy (88%, 86/98 vs. 60%, 59/98; p=0.00l) and 48 hours after endoscopy (73%, 72/98 vs. 54% , 53/98 ; p=0.005).
- During the 5-day treatment period, significantly fewer units of blood were administered to patients in the vapreotide group than in the placebo group (mean, 2.0 vs. 2.8 units, p=0.04).

MO comment: Although the results of secondary endpoint analysis support the primary endpoint, the reader is cautioned that the numerous p-values presented are not adjusted for multiple comparisons that have been performed.

- Study DEB-01-VAP-07 (supportive study)

In the ITT population, analysis of the primary endpoint at the end of the 5-day infusion after endoscopic treatment demonstrated that hemostasis was achieved in 70% (22/31) of patients receiving vapreotide compared with 59% (16/27) of patients receiving placebo, a difference that was not statistically significant (p=0.349). Similar results were observed by the sponsor's analysis in the PP populations (83%, 20/24 vs. 66%, 12/18; p=0.281).

Of multiple secondary endpoints analyzed by the sponsor, trends in favor of vapreotide were observed for survival at 42 days (84%, 26/31 vs. 74%, 20/27) and treatment success over 42 days (65%, 20/31 vs. 44%, 12/27). The clinical significance of these observations are questionable in light of the lack of efficacy of vapreotide for the primary endpoint and also the multiple comparisons performed without making adjustments for multiplicity.

MO comment: Despite the involvement of higher percentage of cirrhotic patients with Child class A and B (88%, 48/54*) in this study, the findings failed to confirm the results observed in the pivotal study. The difference may be explained by the small study size, and at least partly, by the schistosomiasis contribution to PHT. Available data suggest that variceal bleeding secondary to presinusoidal blockade as observed in schistosomiasis, but also during the physical obstruction of the portal vein by thrombus or a tumor, dose not respond to treatment with somatostatin.*

- Study DEB-97-VAP-02 (Hong Kong study)

In the ITT population, analysis of primary endpoint at the end of the 5-day infusion after endoscopic treatment demonstrated that hemostasis was achieved in 55% (28/51) of patients receiving vapreotide compared with 51% (26/51) of patients receiving placebo. A difference

which is not significantly different (p=0.692). The sponsor's analysis revealed similar results for the PP populations (52%, 22/42 vs. 50%, 19/38; p=0.832). As well, none of the multiple secondary endpoints analyzed by the sponsor showed any significant difference between treatments in both the ITT and PP populations.

MO comment: Despite the similarities regarding demographics, baseline characteristics or etiology of liver cirrhosis of the populations described in the pivotal study, the findings observed in the Hong Kong study are quite different from that of the pivotal study (DEB-97-VAP-14). Hemostasis rate at the end of 5 days (primary endpoint) was quite similar in the vapreotide and placebo groups in the Hong Kong study. In contrast, vapreotide was superior to placebo for the primary endpoint in the pivotal study. The reasons for such variability in the outcomes are unclear to this reviewer. Based on the reviewer's assessment, the findings observed in the Hong Kong study could not be explained by the protocol violations as suggested by the sponsor. This reviewer finds no obvious quantitative or qualitative differences in protocol violations in this study when compared with those described in the pivotal study.

Reviewer's Efficacy Conclusions

The reviewer's assessment of the efficacy data from three clinical studies, i.e. DEB-96-VAP-14, DEB-01-VAP-07 and DEB-97-VAP-02 showed that the latter two studies did not demonstrate a significant difference between vapreotide and placebo groups for the primary endpoint (hemostasis at the end of 5-day infusion) in both prespecified ITT and PP populations. The superiority of vapreotide to placebo was demonstrated in one study (DEB-96-VAP-14) when assessed for the primary endpoint, in both the ITT and PP populations.

However, the superiority of vapreotide to placebo in study DEB-96-VA-14 was driven by center 18 involving 28 patients (28/196; 14%) whose underlying liver disease was predominantly class A and B as determined by Child-Pugh score. However, the results from most centers showed trends in favor of vapreotide. In addition, although the effectiveness of vapreotide was no longer superior to that of placebo when subjects from center 18 were excluded from the analysis, there was a 12% therapeutic gain in vapreotide treated group which is clinically significant in light of the serious conditions being treated.

Based on the assessment of the efficacy data presented, this reviewer concluded that a single clinical study finding of efficacy, unsupported by an independent evidence is not adequate for a conclusion of a substantial evidence of effectiveness. An additional well controlled study is required that confirms the findings from the pivotal study (DEB-96-VAP-14).

C. Safety

The safety profile for vapreotide was developed from seven clinical trials involving a total of 481 subjects who received at least one dose of vapreotide acetate: three randomized, double-blind, placebo-controlled studies involving a 5 day course of treatment for variceal bleeding (proposed indication); a randomized, double-blind, placebo-controlled trial involving a 7 day course of treatment for pancreatic surgery (Study DEB- 98-VAP-06); and three small open

efficacy studies involving prolonged treatment (21 to 180 days) for acromegaly (Study DEB-95-VAP-02), carcinoid/neuroendocrine tumors (Study DEB- 92-VAP-02), and Crohn's disease (Study DEB-93-VAP-09). The daily dose of vapreotide was 1.2 mg in the majority (88%) of the studies, and 1.5 mg in the remainder. Randomized, double-blind, placebo-controlled trials comprised 96% of patients in the safety database. The variceal bleeding studies comprised 52% of patients in the safety database.

Adverse Events (AEs)

In general, the adverse event profile was comparable in both treatment groups. In controlled studies, AEs were reported by 81% of subjects receiving 1.2 mg/day vapreotide and 83% of subjects receiving placebo. Comparisons of AE rates by body system showed no significant difference between the treatment groups for most categories, with the exception of higher AEs rates for the placebo group for psychiatric disorders (anxiety, delirium tremens, insomnia); renal and urinary disorders (oliguria, urinary retention), respiratory disorder (dyspnea, pleural effusion). There were no body system categories in which AEs rates were higher for vapreotide than for placebo groups.

Adverse Events 5%-20%: Treatment-emergent adverse events (relationship to drug not established, excluding events related to underlying disease) occurring in 5%-20% of patients receiving vapreotide acetate were: Blood and Lymphatic System: anemia NOS (6.5%); Gastrointestinal Disorders: abdominal pain (6.6%), constipation (9.6%), diarrhea (7.9%), nausea (17.2%), vomiting (7.1%); General Disorders & Administration Site Conditions: pyrexia (18.9%); Metabolism and Nutrition Disorders: hyperglycemia NOS (7.5%); Psychiatric Disorders: insomnia (6.2%); Skin and Subcutaneous Tissue Disorders: pruritus (5.4%).

Treatment-emergent adverse events (relationship to drug not established, excluding events related to underlying disease) reported by at least 2 patients receiving vapreotide acetate were:

- Blood and Lymphatic System Disorders: coagulopathy (2 patients), leukocytosis (5);
- Cardiac Disorders: atrial fibrillation (8), cardiac arrest (2), tachycardia NOS (13);
- Gastrointestinal Disorders: abdominal distention (8), ascites (10), dyspepsia (14), impaired gastric emptying (23), esophageal ulcer (11);
- General Disorders & Administration Site Conditions: chest pain (8), fatigue (7), hyperpyrexia (4), infusion site phlebitis (4), injection site inflammation (6), injection site nodule (21), edema (15);
- Hepatobiliary Disorders: cholelithiasis (4);
- Metabolism and Nutrition Disorders: dehydration (4), diabetes mellitus NOS (5), , hypocalcemia (11), hypoglycemia (4), hypokalemia (20), hypomagnesemia (14);
- Nervous System Disorders: convulsions NOS (6), dizziness (6), encephalopathy (6), headache (13);
- Psychiatric Disorders: agitation (7), anxiety (8), confusional state (17);
- Renal and Urinary Disorders: dysuria (5), oliguria (11), urinary retention(3);

- Respiratory, Thoracic and Mediastinal Disorders: dyspnea (9), pleural effusion (18), pulmonary edema NOS (7);
- Vascular Disorders: hypertension (19), hypotension (14), orthostatic hypotension (3).

In the variceal bleeding studies, with the exception of gastrointestinal disorders attributable to pharmacologic effects and pyrexia reported in 28% of vapreotide treated subjects, the only adverse effects reported in ≥ 5% of subjects were expected disease-related events: hepatic encephalopathy (11.3%), esophageal variceal hemorrhage (8.6%), hematemesis (6.8%), and esophageal ulcer (5.0%). [The corresponding rates for placebo subjects were pyrexia in 23.5%, hepatic encephalopathy in 10.8%, esophageal variceal hemorrhage in 9.4%, hematemesis in 2.8% and esophageal ulcer in 8.5%].

Among the 222 subjects who received at least one dose of vapreotide for treatment of variceal bleeding 33% (74/222) experienced serious disease-related adverse events such as rebleeding (hematemesis, melena), shock (hemorrhagic, hypovolemic), hepatic encephalopathy, hepatorenal syndrome, hepatocarcinoma, and hepatic failure. Similarly, 38% (81/213) of patients in the placebo groups experienced SAEs.

In the variceal bleeding studies a total of 62 deaths occurred during the study that was comparable between treatment groups: 28 in the vapreotide group and 34 in the placebo group. Overall, the most common cause of death was hematemesis with or with organ failures (37%), followed by hepatic encephalopathy (22%) and hemorrhagic shock (16%) ad were comparable between the two treatment groups.

Reviewer's Safety Conclusions

The 5-day course of vapreotide for treatment of acute variceal bleeding due to portal hypertension is associated with no significant toxicity. The safety profile of vapreotide was comparable with that of placebo, suggesting that many events recorded were a reflection of the patients' underlying medical conditions.

The short-term course of vapreotide therapy was not associated with the biliary tract abnormalities and cardiac function abnormalities observed as a result pharmacologic activity with extended exposure.

D. Dosing

The recommended dose: An initial IV bolus injection of 50 µg vapreotide should be followed immediately by a continuous IV infusion at a rate of 50 µg/hour (1.2 mg/day) for five days. Vapreotide treatment should not be continued for more than 12 to 24 hours without confirmed diagnosis of variceal bleeding due to portal hypertension.

No dose-optimizing studies were performed with vapreotide. The dose selection was largely empirically as described above.

E. Special Populations

Pediatric

On August 5, 2003, a request to waive requirements to comply with the Pediatric Rule was submitted to the Agency (S/N 023 to IND 59,287). The request for waiver was on the basis that vapreotide has Orphan Drug Designation. On January 26, 2004, the Agency granted the waiver for pediatric studies for vapreotide for the proposed indication.

Analysis by Gender and Age

For the pivotal study, the Agency's subgroup analysis, for males, indicates that hemostasis rate was significantly higher in vapreotide group than placebo group (p=0.029). While, for females, the hemostasis rate was only numerically higher in vapreotide group than placebo group (p=0.43). The subgroup analysis for patients aged ≤ 65 years, hemostasis rate was significantly higher in the vapreotide group than the placebo group (p=0.014). Whereas for patients aged > 65 years, hemostasis rate was only numerically higher in the vapreotide group than the placebo group (p=0.72). It should be noted that the sample size is too small to allow for a meaningful observation difference in the efficacy rates with respect to gender and age.

Analysis by Race

All clinical studies were performed in foreign countries. Information on race was not collected.

Pregnancy use

Vapreotide is contraindicated in pregnancy. There is no experience with use of vapreotide in human pregnancy.

CLINICAL REVIEW

Clinical Review Section

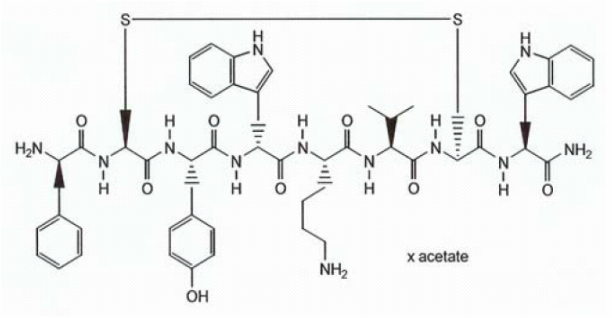
Clinical Review

I. Introduction and Background

A. Drug Established and Proposed Trade Name, Drug Class, Sponsor's Proposed Indication(s), Dose, Regimens, Age Groups

Non-propriety Name: Vapreotide acetate
Proposed Trade Name: Sanvar™
Drug Class: Somatostatin Analog

Chemical Structure



Chemical Name: D-phenylalanyl-L-cysteinyl[2-7]-L-tyrosyl-D-tryptophyl-L-lysyl- L-valyl-L-cysteinyl [7-2]-L-tryptophanamide- disulfide.

Molecular Formula: $C_{57}H_{70}N_{12}O_9S_2$ (without acetate)

Proposed Indication:
Treatment of acute variceal bleeding related to portal hypertension, in association with endoscopic treatment

Dose and Regimen:
Vapreotide treatment should be initiated within 24 hours after onset of hemorrhage and preferably before endoscopic treatment. An initial IV bolus injection of 50 µg should be followed immediately by a continuous IV infusion at a rate of 50 µg/hour (1.2 mg/day) for five days. Vapreotide treatment should not be continued for more than 12 to 24 hours without a confirmed diagnosis, or previous diagnosis of variceal bleeding due to portal hypertension.

B. State of Armamentarium for Indication(s)

(Literature Review)

Portal hypertension is the main complication of cirrhosis, because it is directly responsible for two of its most common and potentially lethal complications: variceal hemorrhage and ascites.

CLINICAL REVIEW

Clinical Review Section

Cirrhosis leads to both an increase in hepatic sinusoidal pressure and an increase in portal pressure gradient resulting in resistance to portal flow. An obstruction to portal flow is mostly caused by an architectural distortion of the liver secondary to fibrous tissue and regenerative nodules. A second and major contributing factor to portal hypertension is believed to be an increase in blood flow through the portal venous system due to splanchnic arteriole vasodilatation, which is caused by an excessive release of endogenous vasodilators. While a threshold portal pressure of 10-12 mm Hg is necessary for the development of varices, there appears no clear correlation between the degree of portal pressure and the risk of bleeding.

The prevalence of esophageal varices is very high: when cirrhosis is diagnosed, varices are present in about 50% of patients. Available data indicate that their presence and size are related with the severity of liver dysfunction expressed by Child-Pugh classification (class A, B or C): while about 40% of patients with compensated liver function (class A) have varices, they are present in about 60% of patients with poor liver function (class C). Once diagnosed, the overall incidence of variceal bleeding is about 25% at 2 years in non-selected patients. The most predictive factors related to the risk of bleeding are large variceal size, presence of red weal marks in the varices, and severity of the liver dysfunction (Child-Pugh score is driven from albumin, bilirubin, prothrombine time, hepatic encephalopathy and ascites).

Although bleeding from esophageal varices ceases spontaneously in up to 40% of the patients, the mortality of an episode of variceal hemorrhage is about 30% and occurs mostly in patients with Child class C and in those with early rebleeding. Early rebleeding occurs in about 40% of the patients within 6 weeks; however, the risk of rebleeding is the greatest the first 5 days following the index bleeding. Therefore, treatment of acute variceal bleeding encompasses two important aspects: control of acute bleeding and to prevent early recurrence. In addition, a general measure that is currently considered standard in the care of patients with variceal bleeding is the use of short-term antibiotic prophylaxis.

Management methods include: 1) emergency shunt surgery, transjugular intra-hepatic porto-systemic shunt (TIPS); 2) physical obliteration of varices by means of endoscopic sclerotherapy, endoscopic variceal band ligation or balloon tamponade; 3) vasoactive drug therapy followed by endoscopy.

In uncontrolled bleeding, both emergency TIPS and surgical shunts are reported to be extremely effective in the control of bleeding, but their invasiveness and post-procedure complications - mainly with surgical shunt- result in a high morbidity and mortality. Currently, Balloon tamponade is not used routinely, but rather as a temporal bridge until definitive treatment is undertaken in case of massive bleeding. About 50% of patients experience recurrent hemorrhage after deflation of the balloon and 15% to 20% experience devastating complications during placement (aspiration and esophageal perforation). Currently, the most commonly used methods for management of acute variceal hemorrhage are endoscopic therapy (sclerotherapy or band ligation) with or without vasoactive drug. Both methods of endoscopic therapy have comparable efficacy in controlling acute variceal bleeding.

Pharmacologic therapy aimed at correcting the increased portal venous inflow is based on the use of splanchnic vasoconstrictors, such as vasopressin and its analog (terlipressin) and somatostatin and its analogue (octreotide).

Vasopressin is the most potent splanchnic vasoconstrictor. It reduces blood flow to all splanchnic organs, thereby leading to a decrease in portal venous inflow and a decrease in portal pressure. However, the clinical usefulness of vasopressin is limited by its serious side effects that are related to splanchnic vasoconstriction (e.g. bowel ischemia) and to systemic vasoconstriction (e.g. hypertension and myocardial ischemia). Terlipressin is a synthetic analog of vasopressin that has a longer biological activity and significantly fewer side effects than vasopressin.

Somatostatin and its analogue octreotide also cause splanchnic vasoconstriction at pharmacologic doses. Although it has been considered that this effect is caused by an inhibition of the release of vasodilatory peptides (mainly glucagon), recent studies in humans suggest that it has a local vasoconstriction effect. It has been reported that another effect of this class of drug is a blunting of postprandial hyperemia, the abrupt increase in portal pressure that occurs after meals. The absence of side effects of these drugs represents a major advantage over other agents, allowing them to be administered for a longer period of time.

The current consensus recommendation of experts worldwide is to start treatment with a vasoactive drug from admission for acute variceal hemorrhage and to associate endoscopic therapy at time of diagnostic endoscopy. Since the failure to control bleeding is highest during the first hours to days following hemorrhage, early active pharmacologic treatment to fill the gap between the beginning of hemorrhage and initiation of endoscopy is believed to result in significantly improved overall hemostasis. However, a recent meta-analysis suggests that this approach improves the control of bleeding and reduces early rebleeding, but has no significant effect on mortality with the exception of terlipressin (vasopressin analog), the only vasoactive drug that has been shown to improve survival benefit.

In most European countries, somatostatin and its analog octreotide, and terlipressin are approved for the treatment of variceal bleeding. None of these drugs are approved for the variceal bleeding indication in the United States. However, octreotide has been used widely off label. Octreotide is approved by the Agency for the indication of acromegaly and diarrhea secondary to carcinoid tumors.

C. Important Milestones in Product Development

- On November 5, 1999, IND 59,287 was submitted by Debiopharm SA, to investigate vapreotide for the prevention of postoperative complications following pancreatic resection. The sponsorship of this IND was transferred to H3 Pharma, Inc. on January 26, 2004.
- The compound has been granted Orphan Drug designation for the treatment of variceal bleeding.
- On June 20, 2000, a pre-NDA meeting was held to discuss a proposed NDA for vapreotide for the treatment of acute variceal hemorrhage in cirrhotic patients. The

sponsor proposed a single pivotal study (DEB-96-VAP-14) to support the proposed indication. The sponsor was advised that the study was not sufficiently large or statistically convincing to demonstrate safety and efficacy. In response to the sponsor's comment, the Agency clarified that orphan status has no impact on the standard of evidence required for approval.

- On July 11, 2003, the Agency's response to the sponsor's question on the adequacy of a single pivotal study (DEB-960VAP-14) and a second phase IIb study (DEB-01-VAP-07) to support an NDA for vapreotide in the treatment of acute variceal bleeding was faxed to the sponsor. The sponsor was advised that the proposed second phase IIb study may not be adequate to support the proposed NDA.
- On January 26, 2004, the agency granted the waiver for pediatric studies for vapreotide for the proposed indication.

D. Other Relevant Information

On July 12, 2004, an amendment was submitted by the sponsor indicating that an additional larger clinical study (DEB-02-VAP-06) is being conducted in Eastern Europe that was initiated in response to questions raised during the EMEA review of vapreotide. This 260-patient study was initiated in April 2003 and as of June 1, 2004, 230 patients had been recruited. Study enrollment was complete in October 2004.

The sponsor is committed to provide a final study report as an amendment to the NDA 21-761 as soon as it becomes available. This information was communicated during a teleconference held with the sponsor on October 17, 2004, when the sponsor was notified about the inadequacy the efficacy data submitted under the current NDA.

E. Important Issues with Pharmacologically Related Agents

Somatostatin and its analogue octreotide are approved in many European countries for the treatment of acute variceal bleeding. Available data do not indicate a serous toxicity with these drugs. In the United States, octreotide is being used off label for the treatment of acute varcieal bleeding. Octreotide is approved by the Agency for the treatment of acromegaly and diarrhea associated with carcinoid tumors.

II. Clinically Relevant Findings From Chemistry, Animal Pharmacology and Toxicology, Microbiology, Biopharmaceutics, Statistics and/or Other Consultant Reviews

Note: The following information is directly excerpted from the sponsor's document. The reader may refer to the Division's individual discipline review for detailed information and recommendations.

Non-clinical Studies

Pharmacology

Vapreotide is a cyclic octapeptide analog of the human peptide somatostatin. The somatostatin peptides exert a diverse array of biological effects, including the inhibition of many different endocrine and exocrine secretions, behavior and autonomic effects and effects on intestinal motility, vascular contractility, intestinal absorption of nutrients and ions, and cell proliferation. In humans, somatostatin reduces splanchnic blood flow by inhibiting the release of vasodilatory gastrointestinal peptides such as glucagon, vasoactive intestinal polypeptide, calcitonin, gene-related peptide, and substance P. In stable cirrhotic patients not suffering from acute variceal bleeding, somatostatin induces modest reductions in hepatic blood flow, wedged venous pressure, and azygous blood flow, a measure of the collateral blood flow including variceal flow.

Effects on Portal Hypertension: Vapreotide has been shown to decrease hepatic and collateral blood flow in two experimental models of portal hypertension. The acute hemodynamic effects of vapreotide were investigated in a classic model of portal hypertension induced by partial ligation of the portal vein. Conscious male rats (8 per group) were given 30 minute intravenous infusions of vapreotide (0, 2, 4, and 8 µg/kg/h) two weeks after surgery. Portal and venous pressures were monitored via catheters inserted at the time of surgery and cardiac output and regional blood flow (in association with the splanchnic organs and renal, coronary, and bronchial blood flow) were measured by the radioactive microsphere method using microspheres labeled with Il3Sn. Measurements before and after vapreotide infusions showed that vapreotide caused significant dose independent decreases in portal pressure and portal system vascular resistance.

Safety Pharmacology

Safety pharmacology studies examined the effects of vapreotide on the cardiovascular system, CNS system, gastrointestinal system, and pulmonary system at doses at least 25-times the proposed daily dose in man of about 20 µg/kg (based on l.2 mg/day and 60 kg body weight). Results showed no significant drug-related adverse effects and documented expected pharmacologic effects of vapreotide, including reduction in gastrointestinal motility in fasted mice.

Toxicology

Single dose toxicity studies of vapreotide, using both subcutaneous and intravenous routes of administration, were conducted in rats and dogs. In both species, the minimum lethal dose was estimated at -4 mg/kg (IV) and >4 mg/kg (SC). Single dose intravenous toxicity studies of vapreotide in mice suggested a minimum lethal dose of approximately 30 to 40 mg/kg.

Repeated dose intravenous toxicity studies of vapreotide were conducted in Sprague-Dawley rats given up to 2.4 mg/kg/day for 4 weeks and in Beagle dogs given up to 1.2 mg/kg/day for 4 weeks. Both control and treated animals showed abscesses at infusion sites. With the exception of these infusion site reactions, rats showed no clinical signs of toxicity and no drug-related

findings on gross and microscopic examinations. Throughout treatment, treated dogs experienced frequent diarrhea and/or soft stools and reduced body weight gains, despite normal food consumption. The incidence of diarrhea and soft stool decreased and body weight gain increased during a two-week recovery period. This was interpreted as a pharmacologic effect of vapreotide on gastrointestinal hormonal-secretory function. At necrospy, slight to mild chronic inflammation in knee joints and lymphoid depletion in thymus were observed in some dogs; these signs had recovered fully at the end of a two-week recovery period.

Genotoxicity studies showed no mutagenic activity for vapreotide.

Carcinogenicity studies were not performed.

III. Human Pharmacokinetics and Pharmacodynamics

A. Pharmacokinetics

Pharmacokinetic assessments were not made following a 5-day continuous intravenous infusion of 1.2 mg/kg/day vapreotide (the recommended dosing in cirrhotic patients with acute variceal bleeding), available results suggest no risk of drug accumulation.

Pharmacokinetic studies of vapreotide acetate following a single intravenous administration were conducted in healthy volunteers as well as in patients with liver impairment. Results from the various studies showed that vapreotide was eliminated rapidly in both healthy subjects and subjects with liver impairment, reflected by a high clearance rate and short half-life (~10 min). The rapid elimination also was confirmed by a low mean residence time of vapreotide in the systemic circulation (~14 min). The sponsor stated that there were no significant differences in PK parameters between healthy subjects and subjects with liver impairment.

B. Pharmacodynamics

The sponsor stated that based on reported pharmacodynamic actions of somatostatin, the primary endpoint for assessment of pharmacodynamic effects of vapreotide was chosen to be an increase in pulmonary artery wedge pressure (In the case of splanchnic constriction, an increase in pulmonary artery wedge pressure is thought to reflect the redistribution of splanchnic blood flow into the vena cava). In patients with stable cirrhosis, a single intravenous injection of vapreotide caused a significant increase in mean pulmonary arterial and wedge pressures at 5 minutes (from 16.0±15.0 to 21.5±8.4 mmHg, $p<0.05$). No significant differences were observed for hepatic venous pressure or azygous blood flow.

No drug-drug interaction studies have been performed with vapreotide.

IV. Description of Clinical Data and Sources

A. Overall Data

Sources of data used in the review are from three clinical trial programs as described in Table 1.

B. Tables Listing the Clinical Trials

Table 1. Clinical trails presented in support of NDA 21-761

Study (location)	Study Design	Patient No Total/ITT	Gender ITT patients	Cause of liver cirrhosis	Comment
DEB-96-VAP-14 (France)	Phase III, multicenter, double-blind, randomized, placebo-controlled	227/196	148 males 48 females	Alcoholism (85%)	Pivotal study
DEB-97-VAP-02 (Hong Kong)	Phase III, multicenter, double-blind randomized, placebo-controlled	136/102	79 males 23 females	Alcoholism (38%) Viral hepatitis (45%)	Efficacy data are not considered useful by the sponsor in view of major protocol violations
DEB-01-VAP-07 (Egypt)	Phase IIb, single center, double-blind, randomized, placebo-controlled	72/58	all males	Viral hepatitis associated with schistosomiasis (83%)	Supportive study

MO comment: Study DEB-97-VAP-02 was initiated in Hong Kong concurrently with the pivotal study in France (DEB-96-VAP-14) in 1997. The sponsor indicated that, in view of the poor recruitment rate and poor protocol compliance, the study was terminated in June 2001. As a result, the study was not considered useful by the sponsor for assessment of efficacy in view of major protocol violations and was evaluated only for safety in the original NDA submission.

On June 25, 2004, the Agency requested the efficacy evaluation for the Hong Kong study. Subsequently, the efficacy results were provided as an amendment on September 22, 2004.

C. Postmarketing Experience

At the time of this NDA submission, vapreotide has not been approved for use in any country.

D. Literature Review

The sponsor summarized relevant literature and provided copies of publications to support the findings and study design of the studies. The reviewer performed additional literature search utilizing the Agency's on line database as well as resources and used them in describing various

portions of this review. Based on available literature, the Reviewer concurs with the sponsor in regard to the appropriateness of the study design as well as the definition of endpoints used in the clinical studies submitted under the current NDA.

V. Clinical Review Methods

A. How the Review was Conducted

The reviewer has approached this submission first by focusing upon what the sponsor has requested, and what evidence has been submitted in support of that request. The materials reviewed include all volumes pertinent to clinical trials with emphasis on the protocols and clinical study reports.

This review followed a stepwise fashion directed to determine the factual clinical evidence to support the sponsor's proposed use of vapreotide. The three clinical trials were examined in the following order: First study DEB-96-VAP-14 (pivotal study), followed by study DEB-01-VAP-07 (supportive study), and then study DEB-97-VAP-02 (prematurely terminated study). For each trial, the protocol was examined first, and then the reported data for each trial were assessed for efficacy and safety. The reviewer's final judgment on safety and efficacy for the proposed indication was based on the safety profile of the test drug and whether the stated primary objective endpoint was achieved.

B. Overview of Materials Consulted in Review

The sponsor submitted the current NDA in the Common Technical Document Format (CTD) as a paper version. Volumes summarizing preclinical findings, chemistry, pharmacokinetics and pharmacodynamic of vapreotide and all volumes pertinent to clinical section: The volumes follow:

- Module 1 (volume 1.1)
- Module 2 (volume 1.1-1.2)
- Module 5 (volume 1.1-1.59)

Other reviewed materials include:

- Pre-NDA meeting minutes, dated June 20, 2000
- Agency responses dated July 11, 2003 (facsimile) to sponsor's questions listed in pre-NDA background package submitted on June 13, 2003
- Amendment submitted July 12, 2004, in reference to additional clinical trial being conducted
- Amendment submitted October 7 2004, regarding responses to clinical questions submitted by this reviewer

- Amendment submitted on September 22, 2004. Efficacy evaluation results for study DEB-97-VAP-02
- Review of literature relevant to the NDA
- FDA "Guidance for Industry Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products", US department of HHS, FDA, CDER, CBER, May 1998
- The most current Physician Desk Reference (PDR) on line

C. Overview of Methods Used to Evaluate Data Quality and Integrity

Since the pivotal study was conducted in 22 centers in France, three centers (# 1, 14 and 18) with relatively larger number of study subjects were chosen by this reviewer for the Division of Scientific Investigation (DSI) inspection. In addition, DSI was notified the preliminary efficacy analysis results performed by the Division's statistician as per the medical review team request indicating that the superiority of vapreotide to placebo in the pivotal study was mainly driven from subjects at center 18. The audit report from DSI is pending at this time.

Furthermore, in the course of NDA review, this reviewer has requested clarifications on a number of clinical issues. The clinical issues/questions along with the sponsor's responses that appeared satisfactory can be found on the amendment submitted in October 7, 2004. The quality and results of the data were discussed and reanalyzed for verification purposes by the Agency's statistical reviewer.

D. Were Trials Conducted in Accordance with Accepted Ethical Standards

The sponsor states study protocols and informed consent were reviewed and approved by an appropriate Independent Ethics Review Committee or Institutional Review Board (IRB) that conforms to the Declaration of Helsinki and local laws prior to enrollment of participants into the study.

The study was conducted in accordance with the ethical principles of the Declaration of Helsinki (as amended in Tokyo, Venice and Hong Kong). Good Clinical Practice for trials on medical products in European Community was followed, as well as the regulations of the countries where the trial was conducted.

A signed informed consent was obtained and documented for each patient prior to entering the study. If the written informed consent was not possible because of emergency conditions, a verbal consent was obtained from the patient, and he/she was confused a written consent form was obtained from relatives.

E. Evaluation of Financial Disclosure

H3 Pharma, the sponsor of the NDA indicated that all clinical studies included in this submission were sponsored by Debiopharm SA. Consequently, the H3 Pharma has provided a completed form FDA 3454, based on attestations by the Debiopharm SA.

Debiopharm has attested to the following:

(i) Debiopharm did not enter into any financial arrangement with any clinical investigator in any of the covered clinical studies, whereby the value of the compensation to the clinical investigator for conducting the study could be influenced by the outcome of the study;

(ii) Debiopharm did not make significant payments of other sorts to any clinical investigator in any of the covered clinical studies, such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation, or honoraria;

(iii) No clinical investigator in any of the covered clinical studies held any proprietary interest in the tested product; and

(iv) No clinical investigator in any of the covered clinical studies had any significant equity interest in Debiopharm.

VI. Integrated Review of Efficacy

A. Brief Statement of Conclusions

The reviewer's assessment of the efficacy data from three clinical studies, i.e. DEB-96-VAP-14, DEB-01-VAP-07 and DEB-97-VAP-02 showed that the latter two studies did not demonstrate a significant difference between vapreotide and placebo groups for the primary endpoint (hemostasis at the end of 5-day infusion) in both prespecified ITT and PP populations. Whereas, the superiority of vapreotide to placebo was demonstrated in one study (DEB-96-VAP-14) when assessed for the primary endpoint, in both the ITT and PP populations.

However, the superiority of vapreotide to placebo , in study DEB-96-VAP-14 was driven by center 18 involving 28 patients (28/196; 14%) whose underlying liver disease was predominantly class A and B as determined by Child-Pugh score. However, the results from most centers show trends in favor of vapreotide. In addition, although the effectiveness of vapreotide was no loner superior to that of placebo when subjects from center 18 were excluded from the analysis, there was a 12% therapeutic gain in vapreotide treated group which is clinically significant in light of the serious conditions being treated.

Based on the assessment of the efficacy data presented, this reviewer concluded that a single clinical study finding of efficacy, unsupported by independent evidence is not adequate for a conclusion of a substantial evidence of effectiveness. An additional well controlled study is required that confirms the results from the pivotal study (DEB-96-VAP-14).

B. General Approach to Review of the Efficacy of the Drug

Utilizing sponsor's submitted data, the three studies were reviewed independently and compared to the sponsor's Integrated Summary of Efficacy. Demographics, baseline characteristics and efficacy results from each study were compared. In addition, the Agency's statistical reviewer performed efficacy analyses to verify the sponsor's claim of efficacy of vapreotide for the proposed indication.

C. Detailed Review of Trials by Indication

The sponsor conducted three randomized, double-blind, placebo-controlled studies (DEB-96-VAP-14, DEB-01-VAP-07 and DEB-97-VAP-02) to assess the efficacy of vapreotide for the treatment of acute variceal bleeding due to PHT, in association with endoscopic treatment. However, study DEB-97-VAP-02 that was initiated in Hong Kong concurrently with DEB-96-VAP-14 in 1997 was terminated in June 2001 due to poor recruitment rate and poor protocol compliance. As a result, the sponsor did not consider the efficacy assessment to be useful and was evaluated only for safety in the original NDA submission. Efficacy was evaluated up on the Agency's request and was provided on September 22, 2004.

The study design was identical in all studies using the same intervention, the same inclusion/exclusion criteria and efficacy endpoints. Vapreotide was administered as an IV bolus injection of 50 µg followed by a continuous IV infusion of 50 µg/hr (1.2 mg/day) for 5 days, with a follow-up period of 6 weeks (42 days).

The primary objective was to quantify to which extent vapreotide in association with endoscopic treatment can improve hemostasis at 5 days, i.e. control of initial bleeding and prevention of early rebleeding.

Eligible male or female subjects aged 18 to 75 years with liver cirrhosis presenting with hematemesis and/or melena were randomized as early as possible after admission (delay ≤ 6 hours between admission and randomization) and in all most all cases treatment with study drug was initiated prior to endoscopic diagnosis and treatment. After endoscopy, those patients found to present a source of hemorrhage unrelated to PHT had their infusion stopped and these patients were excluded from the ITT population. Relevant exclusion criteria include coma, which is a contraindication to endoscopy, end-stage liver disease and diffuse hepatocellular carcinoma, which are conditions that can cause mortality independent of the presence of variceal bleeding.

Study DEB-96-VAP-14 (pivotal study) was a multicenter, randomized, double-blind, placebo-controlled phase III study, in which 227 eligible patients with acute upper gastrointestinal bleeding were randomly assigned to receive vapreotide or placebo infusion within a mean (±SD) of 2.3 ±1.5 hours after admission. Study subjects received a diagnostic/therapeutic endoscopy at a mean (±SD) of 2.6±3.3 hours after initiation of study drug infusion. After the exclusion of 31 subjects (13 vapreotide, 18 placebo) whose bleeding was found at diagnostic endoscopy to be due to causes other than portal hypertension and who had their infusions stopped, there were 98 ITT patients in each group.

Study DEB-01-VAP-07 (supportive study) was a single-center, randomized, double-blind, placebo-controlled phase lIb study, in which 72 eligible patients with acute upper gastrointestinal bleeding were randomly assigned to receive vapreotide or placebo within six hours after admission. Study subjects received a diagnostic and therapeutic endoscopy after initiation of study drug infusion and within 12 hours of admission. After the protocol-specified exclusion of 14 subjects who had their infusions stopped after diagnostic endoscopy, the ITT population included 58 patients: 31 in the vapreotide group and 27 in the placebo group.

Study (DEB-97-VAP-02) was a multicenter, randomized, double blind, phase III study in which a total of 136 eligible patients were enrolled over nearly 4 years in five centers. The estimated sample size was 150. After the protocol-specified exclusion of 34 patients, the ITT population included 102 patients: 51 subjects in each treatment group.

Primary Endpoints

The primary endpoint was hemostasis during the 5-day period following completion of endoscopic treatment (abbreviated thereafter Tendo). Hemostasis was defined as achievement of both primary hemostasis (no bleeding from Tendo+6 hours to Tendo+48 hours) and secondary hemostasis (no rebleeding between Tendo+48h to Tendo + 5 days).

Primary Efficacy Variables Assessment

To assess the primary endpoint, the sponsor used 3 types of criteria based on Recommendations from Consensus Conference: a) the acute bleeding time-frame during the first 48 hours with 2 different criteria to evaluate primary hemostasis, i.e. bleeding within 6 hour and after 6 hour following endoscopy (Tendo), b) secondary hemostasis was evaluated between 48 hour to 120 hour (Day 3 to 5) for rebleeding.

Primary hemostasis:

1. Assessed up to 6 hours after endoscopy:
   - transfusion requirement ≤ 4 units from Tendo;
   - systolic pressure > 80 mm Hg;
   - heart rate < 100 bpm (excluding other causes of tachycardia)
2. Assessed between 6 hours and 48 hours after endoscopic treatment
   - transfusion requirement ≤ 2 units from Tendo + 6 hrs
   - heart rate < 100 bpm
   - Hematocrit: no decrease ≥ 10 points in comparison with value of Tendo + 6 hrs

Secondary hemostasis:
Assessed between Tendo + 48 hour to Tendo +120 hour: no rebleeding (hematemesis , melena). Rebleeding was defined as occurrence of new hematemesis or a new melena after a period of ≥ 24 hour of hemodynamic stability (vital signs, Hct or Hgb). A rebleeding episode implies that an initial control of the first hemorrhage was obtained.

Secondary Endpoints

The sponsor defined multiple secondary endpoints which included:

- absence of active bleeding at the time of diagnostic endoscopy
- hemostasis at 6h after randomization;
- number of units of blood administered during the study period;
- number of days in hospital;
- in-and-out-hospital survival (7-day, 30-day and 42-day).

According to the sponsor, analyses of secondary endpoints were performed for exploratory purposes. Therefore, the significant level was not adjusted for multiple comparisons.

Rational for Selection of Primary Endpoint: Since hemodynamic stability is the primary goal of treatment for acute variceal bleeding, all vapreotide studies used a composite primary efficacy criterion for control of bleeding at 5 days, based on endpoint definitions for successful control of acute bleeding adapted from International Baveno Consensus Conferences on PHT (de Franchis. J Hepatol 2000). These Recommendations were adapted by the American Association for the study of Liver Diseases (Grace ND et al, Hepatology 1998) and were incorporated in the UK guidelines on the management of varcieal hemorrhage in cirrhotic patients (Jalan & Hayes, Gut 2000).

Although demonstration of a statistically significant effect on survival at 6 weeks is the most desirable study endpoint, such a trial would require a population size that is not feasible for a rare disease. According to the report in the document submitted, there are a total of about 23,000 cases annually of esophageal variceal bleeding in cirrhotic patients with PHT.

Rationale for Dose Selection/Duration of therapy/Duration of Study period:
Dose-optimizing studies were not conducted with vapreotide. The regimen selected for the current studies is largely empirical and was based on the regimen used in similar studies of octreotide and somatostatin in cirrhotic patients with variceal hemorrhage.

The optimal duration of the infusion of somatostatin or its analog is not known. In several previous trials, the duration of infusion was 5 days, since this corresponds to the period during which the risk of recurrence of bleeding is the highest. The 6 week study period has been defined by consensus as the period under which all mortality is considered as directly related to the episode of acute hemorrhage

MO comment: the sponsor's selection of endpoints, duration of therapy and follow-up period were based on sound rationale. The appropriateness of the sponsor's vapreotide dose selection in the current submission cannot be validated since available data indicate that the conventional dose of somatostatin used by the sponsor to estimate the vapreotide dose is largely empirical. A recent controlled study comparing different schedules of somatostatin in the treatment of acute variceal bleeding suggests that using a higher dose of somatostatin infusion achieves a higher rate of hemostasis than the conventional dose in patients with active variceal bleeding at endoscopy (Mointinoho E et al: J Hepatol 2001). Whether a vapreotide dose that is higher than

the dose used in the current submission would produce similar outcomes cannot be determined without conducting a clinical trial.

Statistical and Analytical Plans

Efficacy analyses were conducted in two sets of patients: intent-to-treat (ITT) and per protocol (PP) populations. ITT analysis was conducted in all randomized patients, regardless of any protocol deviation and according to the randomized treatment. PP analysis was conducted in all randomized patients according to the treatment actually received, except for those who did not fulfill any of the following situations:

- The patient had non-permitted concurrent treatment;
- The patient had no assessment before going off-treatment due to loss to follow-up, withdrawn consent, or concurrent illness;
- Hemorrhage due to causes other than PHT.

Safety analysis was conducted in all patients who received any dose of vapreotide or placebo.

The null hypothesis (H_0) was that there was no difference between treatments on primary efficacy criterion and the alternative hypothesis was that there was a true difference. The α risk p-values reported were two-sided and the statistical significance nominal limit was set to 0.05. The test of the primary criterion was for *confirmatory* purposes; all other tests performed were for *exploratory* purposes. Therefore the significant level was not adjusted for the latter analyses.

The primary endpoint was analyzed in contingency table by the chi-square test. Rate of hemostasis and two-sided 95% confidence interval (CI) were constructed per treatment arm, as well as for their active over placebo ratio.

Demographic and Baseline Characteristics

Note: since the efficacy data from Hong Kong study were not included in ISE in the original submission, the reviewer incorporated relevant data wherever and whenever possible

Table 2 summarizes characteristics of ITT population at enrollment.

Table 2. Characteristics of Patients at Enrollment, ITT populations (Reviewer's modified Table) (Ref. Table 2.7.3.5 vol. 2.2)

	DEB-96-VAP-14 (pivotal)		DEB-01-VAP-07 (supportive)		DEB-97-VAP-02[1] (Hong Kong)	
Variable	vapreotide (n=98)	placebo (n=98)	vapreotide (n=31)	placebo (n=27)	vapreotide (n=51)	placebo (n=51)
Male sex	67 (68%)	81 (83%)	31 (100%)	31 (100%)	43 (84%)	36 (71%)
Age - years	56 (32-73)	54 (29-75)	54 (28-72)	53 (33-68)	57	55
Disease etiology						
Alcoholism	82 (84%)	84 (86%)			19 (37%)	20 (39%)
Alcohol + other	10 (10%)	8 (8%)				
Viral hepatitis			6 (19%)	4 (15%)	21 (41%)	25 (49%)
Hepatitis + schistosomiasis			25 (81%)	23 (85%)	25 (19%)	23 (18%)
Other	2 (2%)	3 (3%)			2 (2%)	3 (2%)
Disease history						
Ascites	38 (39%)	40 (41%)	19 (61%)	18 (67%)	17 (33%)	17 (33%)
Liver decomp.	9 (9%)	9 (9%)				
Varices	62 (63%)	57 (58%)			24 (47%)	16 (31%)
Prior bleeds	38 (39%)	38 (39%)			17 (74%)	9 (56%)
β-blocker treat.	44 (90%)	35 (83%)	14 (45%)	12 (44%)	17/24 58 (45%)	47 (38%)
Child-Pugh Score						
A	14 (14%)	14 (14%)	10 (35%)	7 (28%)	8 (17%)	6 (12%)
B	42 (43%)	41 (42%)	17 (59%)	15 (60%)	24 (51%)	25 (50%)
C	36 (37%)	39 (40%)	2 (7%)	3 (12%)	15 (31%)	19 (38%)
Hemodynamics						
Hematocrit (%)	30 (12-47)	27 (9-42)	27 (10-42)	27 (11-40)		
Hb (g/dL)	9 (4-14)	9 (3-14)	9 (3-15)	9 (3-13)	9.6	9.6
Origin of bleeding						
Esophageal varices	91 (93%)	95 (97%)	27 (87%)	23 (85%)	38 (75%)	39 (77%)
Gastric varices	2 (2%)	2 (2%)	4 (13%)	4 (15%)	12 (24%)	11 (22%)
Portal hypertension gastropathy	5 (5%)	1 (1%)	4 (13%)	2 (7%)	1 (2%)	1 (2%)

[1] **Note:** available pertinent data for study DEB-97-VAP-02 is added by the reviewer on this table since this study was not originally included in the ISE. Blank boxes denote data for the given parameters are not applicable or available.

The predominant etiology of PHT was different in the study DEB-97-VAP-14 (pivotal study) and study DEB-01-VAP-07 (supportive stuy). In the pivotal study population, the majority of patients (85%) had PHT resulting from cirrhosis of alcoholic origin. In contrast, in the supportive study population, the majority of patients (83%) had PHT resulting from mixed Schistosomial mansoni parasitic and hepatitis C viral infections; there were no patients with cirrhosis of alcoholic origin. In the Hong Kong study DEB-97-VAP-02, the cause of cirrhosis was viral alone (45%) or alcoholism alone (38%).

Although there was a gender imbalance in the pivotal study, this was not considered clinically significant. Overall, the male female ratio was comparable in the pivotal and Hong Kong study. In contrast, only males participated in the supportive study. Information on race was not recorded in any study. Based on Child-Pugh scores, patients in the pivotal and Hong Kong study had more

severe liver disease (class C) than those in the supportive study. The percentage of patients with class C Child-Pugh was 40% in the pivotal study, 38% in the Hong Kong study and 9% in the supportive study and there was no significant different between the treatment groups. A great majority of patients in the supportive study had Child class A and B (88%, 48/54).

Endoscopic Treatment During the Study

Table 3 summarizes the type of endoscopic treatment administered in the ITT population- Data on DEB-97-VAP-02 are added by the reviewer.

Table 3. Endoscopic Treatment Administered, ITT populations , (Ref. Table 2.7.3.6., vol. 2.2 (modified table)

	DEB-96-VAP-14		DEB-01-VAP-07		DEB-97-VAP-02	
Treatment	vapreotide (n=98)	placebo (n=98)	vapreotide (n=31)	placebo (n=27)	vapreotide (n=51)	placebo (n=51)
None*	11 (11%)	9 (9%)	1 (3%)	2 (7%)	-	-
Sclerotherapy	49 (50%)	55 (56%)	24 (77%)	20 (74%)	-	-
Band ligation	30 (31%)	30 (31%)	2 (6%)	2 (7%)	37 (73%)	37 (73%)
Other**	8 (8%)	4 (4%)	4 (12%)	3 (11%)	13 (26%)	11 (22%)

* Include no endoscopy and no endoscopic treatment
**Includes glue and combinations of sclerotherapy ± band ligation ± glue

There were no significant differences between vapreotide and placebo groups in terms of endoscopic treatments administered, although there were differences between treatment utilization in the pivotal and supportive study (Table 3). In the pivotal study about half of patients received sclerotherapy and one third band ligation. The supportive study used predominantly sclerotherapy. In the Hong Kong study, the majority of patients (73%) received band ligation and 24% received Cyanoacrylate and lipidol injection (glue); it appears as if sclerotherapy was not used in this study.

MO comment: Available data indicate that both methods (sclerotherapy and band ligation) of endoscopic treatment produce comparable efficacy in controlling variceal bleeding.

Efficacy Results

Study DEB-96-VAP-14 (pivotal study)

Table 4 summarizes the sponsor's results of the primary endpoint in the ITT and PP populations

Table 4. Primary criterion-ITT and PP populations (Reviewer's Table)

	ITT population			PP population		
	Vapreotide	Placebo	p-value[1]	Vapreotide	placebo	p-value[1]
N	98	98		77	83	
Hemostasis at 5 days	65 (66%)	49 (50%)	0.021	56 (73%)	43 (53%)	0.006

[1]Chi-square test

Assessed by primary efficacy endpoint, vapreotide was superior to placebo in both prespecified ITT and PP populations in the pivotal study (Table 4). In the ITT population, analysis of the primary endpoint at the end of the five-day infusion after endoscopic treatment demonstrated that hemostasis was achieved in 66% (65/98) of patients receiving vapreotide compared with 50% (49/98) of patients receiving placebo, a result that was statistically significant in favor of vapreotide (p=0.021).

Similar results were observed by the sponsor's analysis in the PP population (73% (56/77, vs. 53% 43/83; p=0.006) Table 4.

Agency's Analysis of Primary Endpoint -ITT population

The Agency's statistical reviewer performed ITT analysis by-center to explore whether the superiority of vapreotide to placebo assessed by primary endpoint was dominated by certain center (Table 5). Centers with > 10 patients were analyzed separately as prespecified in the protocol.

Table 5. Proportion difference analysis by center ITT population (Agency's analysis)

CENTER[1]	PLACEBO (P) SUCCESS RATE % (N)	VAPREOTIDE (V) SUCCESS RATE % (N)	DIFFERENCE V – P (95% CI)	If 95% CI LOWER LIMIT > 0
Center 1	50.0 (10)	80.0 (10)	30.0 (-0.15, 0.67)	No
Center 2	54.6 (11)	63.6 (11)	9.0 (-0.34, 0.50)	No
Center 10	40.0 (5)	50.0 (6)	10.0 (-0.50, 0.65)	No
Center 12	66.7 (6)	62.5 (8)	- 4.2 (-0.54, 0.48)	No
Center 14	50.0 (8)	71.4 (7)	21.4 (-0.31, 0.68)	No
Center 18	**38.5 (13)**	**80.0 (15)**	**41.5 (0.02, 0.71)**	**Yes**
Centers with 5 to 10 patients pooled	54.1 (37)	67.7 (34)	13.6 (-0.1, 0.36)	No
Centers with < 5 patients pooled	37.6 (8)	28.6 (7)	-9.0 (-0.58, 0.41)	No
Overall results	**50.0 (98)**	**66.3 (98)**	**16.3 (0.024, 0.30)**	**Yes**

[1] Centers 1, 2, 10, 12, 14, and 18 had more than 10 patients enrolled and were analyzed separately

Table 5 shows that for all centers except center 18, the lower limits of the 95% two-sided confidence interval for the difference on hemostasis rates (vapreotide minus that of placebo) are not greater than zero, indicating that only for center 18 involving 28 patients (28/196, 14%) the hemostasis rate at the end of day-5 is significantly higher in the vapreotide group than the placebo group. This analysis also shows that hemostasis rates at day 5 are numerically higher in vapreotide group than placebo group for most centers but lower than that of placebo for center 12 and the pooled centers with less than 5 subjects. However, based on the statistician's assessment, the heterogeneity across centers are not statistically significant (Breslow-Day test, p=0.83).

An additional ITT analysis excluding subjects from center 18 was performed to investigate whether or not the superiority of vapreotide to placebo reported by the sponsor was driven from center 18 (Table 6).

Table 6. (Agency's table) Proportion difference analysis on primary endpoint -ITT population Excluding center 18

	Placebo (P) success rate % (n)	Vapreotide (V) success rate % (n)	Difference V-P (95% CI)	p-value Chi-square test
ITT population excluding center 18	51.8 (85)	63.9 (83)	12.1 (-0.03, 0.27)	0.11

As shown in Table 6, after excluding subjects at center 18, the effectiveness of vapreotide is no longer superior to that of placebo (63% vs. 51%; p=0.11) for the primary endpoint indicating that the reported results were in fact driven from subjects at center 18.

The significant findings shown at center 18 may be explained, at least partly, by the involvement of a higher percentage of cirrhotic subjects with Child class A and B (81%; 22/27) in center 18 compared with 56% (89/160) of subjects not at center 18 (Table 7). This observation is supported by the sponsor's post hoc analysis of pooled results indicating that vapreotide was superior to placebo for the primary endpoint in subjects with Child class A and B (73% vs. 52%; 95% CI lower limit > 1), but not for subjects with Child class C (58% vs. 48%) (sponsor's table 2.7.3.4, Module 2.2).

Table 7. (Agency's Table) Percent of patients with Child-Pugh class A&B or C

CHILD-PUGH Class	CODE 'A&B' % (n/N)	CODE 'C' % (n/N)
Patients not at Center 18	56 % (89/160)	44% (71/160)
Patients at Center 18	81 % (22/27)	19 % (5/27)

MO comment: Although the Agency's by center analysis of primary endpoint in the ITT population indicate that the superiority of vapreotide to placebo was driven from subjects at center 18, results in most centers indicate trends in favor of vapreotide. Further, although vapreotide was no longer superior to placebo when subjects at center 18 were excluded from the analysis, there was a 12% (63% vs. 51%) therapeutic gain in vapreotide treated subjects which is clinically significant in light of the serious conditions being treated.

When comparison is made with published data, the rate of control of bleeding with vapreotide in this study appears low, compared with that in previous studies using drugs from the same pharmacologic class (Besson I et al. N Engl J Med 1995; Sung JJy et al. Lancet 1995). However, the overall rates of hemostasis observed are similar in recent trials that used comparable criteria set by the Consensus Conference [e.g. 65% with somatostatin in association with sclerotherapy (Avgerinos A et al. Lancet 1997)].

Table 8 summarizes the sponsor's analysis of secondary endpoint in the ITT population.

Table 8. Secondary criteria ITT population (Ref. Table 15, vol. 1.8)

	Vapreotide	Placebo	All	P-value
N	98	98	196	
Endoscopy facilitation:				
– Active bleeding	28 (31%)	43 (46%)	71 (39%)	**p = 0.031**
– White nipple or no sign	63 (69%)	50 (54%)	113 (61%)	
Hemostasis at Tinf+6h (all the patients)	80 (82%)	52 (53%)	132 (67%)	**p = 0.001**
Hemostasis at Tinf+6h /endoscopy already performed at that time	71/86 (83%)	47/85 (55%)	118/171 (69%)	**p = 0.001**
Hemostasis at Tinf+6h /endoscopy not performed at that time	9/12 (75%)	5/13 (38%)	14/25 (56%)	p = 0.214
Rebleeding episodes :				
– Between Tendo+48h and Tendo+120h	3 (3%)	4 (4%)	7 (4%)	p = 0.713
– Between Day 5 and Day 7	5 (5%)	4 (4%)	9 (5%)	p = 1
– Between Day 7 and Day 30	8 (8%)	2 (2%)	10 (5%)	p = 0.100
– Between Day 30 and Day 42	7 (7%)	6 (6%)	13 (7%)	p = 0.846
– Between Day 5 and Day 42	16 (16%)	11 (11%)	27 (14%)	p = 0.379
At least one unit of blood transfused:				
– Between Tendo and Tendo 6h				
– Between Tendo+6h and Tendo+48h	44 (45%)	49 (50%)	93 (47%)	p = 0.474
– Between Tendo+48h and Tendo+120h	25 (26%)	40 (41%)	65 (33%)	**p = 0.006**
– Between Day 5 and Day 7	11 (11%)	12 (12%)	23 (12%)	p = 0.699
– Between Day 7 and Day 30				p = 0.799
– Between Day 30 and Day 42	8 (8%)	9 (9%)	17 (9%)	p = 0.961
	7 (7%)	7 (7%)	14 (7%)	p = 1
	4 (4%)	4 (4%)	8 (4%)	

Table 8. Secondary criteria ITT population (cont)

	Vapreotide	Placebo	All	P-value
N	98	98	196	
Total number of units of blood transfused:				
– Whole 6-week period	2 (0 ; 22)	3 (0 ; 19)	2 (0 ; 22)	p = 0.099
– During the first 5 days	2 (0 ; 8)	2 (0 ; 15)	2 (0 ; 15)	**p = 0.042**
– Between Day 5 and Day 42	0 (0 ; 20)	0 (0 ; 14)	0 (0 ; 20)	p = 0.911
Total duration of hospitalization (days) – All patients	12 (2 ; 42)	12 (1 ; 42)	12 (1 ; 42)	p = 0.224
Total duration (days) of hospitalization (patients surviving at Day 42)	(N = 84) 12 (4 ; 42)	(N = 77) 12 (5 ; 42)	(N = 161) 12 (4 ; 42)	p = 0.853
Number of deaths:				
During the planned 42 days period of the study	14 (14%)	21 (21%)	35 (18%)	p = 0.215
Between Tinf and Tendo+120h	5 (5%)	7 (7%)	12 (6%)	p = 0.551
Between Day 6 and Day 42	9 (9%)	14 (14%)	23 (12%)	p = 0.290

For the secondary endpoints in the ITT population, significant benefits for vapreotide were observed for three of several variables analyzed by the sponsor (Table 8)**:**

- At the time of initial endoscopic procedure, control of bleeding was observed in a significantly greater proportion of patients in the vapreotide group than in the placebo group [64% (63/98) vs. 51% (50/98), p=0.031]. This action can be attributed solely to vapreotide, as it was observed before initiation of endoscopic treatment.
- Control of bleeding also was observed in a significantly greater proportion of patients in the vapreotide group than in the placebo group at both six hours after endoscopy [88% (86/98) vs. 60% (59/98), p=0.00l] and 48 hours after endoscopy [73% (72/98) vs. 54% (53/98), p=0.005].
- During the 5-day treatment period, significantly fewer units of blood were administered to patients in the vapreotide group than in the placebo group [mean, 2.0 vs. 2.8 units, p=0.04 by the log-rank test for Kaplan-Meier estimates].

MO comment: Although the secondary endpoint findings support the primary endpoint, the reader is cautioned that the numerous p-values presented are not adjusted for multiple comparisons that have been performed.

Study DEB-01-VAP-07 (supportive study)

In the ITT population, analysis of the primary endpoint at the end of the 5-day infusion after endoscopic treatment demonstrated that hemostasis was achieved in 71 % (22/31) of patients receiving vapreotide compared with 59% (16/27) of patients receiving placebo, a difference that was not statistical significant (p=0.349). Similar results were observed by the sponsor's analysis for the PP population (83%, 20/24 and 66%, 12/18; p=0.281) (Table 9)

Table 9. Primary endpoint in ITT and PP population (Ref. Module 5, vol. 1.21)

				Placebo		Vapreotide	
				N	% 95%CI	N	% 95%CI
Population	**p-value**	**Test**					
ITT	0.349	Chi sq	NO	11	40.74 [22.39; 61.20]	9	29.03 [14.22; 48.04]
			YES	16	59.26 [38.80; 77.61]	22	70.97 [51.96; 85.78
PP	0.281	Fisher	NO	6	33.33 [13.34; 59.01]	4	16.67 [4.74; 37.38]
			YES	12	66.67 [40.99; 86.66]	20	83.33 [62.62; 95.26]

For multiple secondary endpoints analyzed by the sponsor, there were no significant differences between the treatment groups. The clinical significance of trends in favor of vapreotide observed for survival at 42 days (84%, 26/31 vs. 74%, 20/27; p=0.0373) and treatment success over 42 days (65%, 20/31 vs. 44%, 12/27; p=0.125) is questionable in light of multiple comparisons performed without adjusting for multiplicity and in the face of lack of efficacy for the primary endpoint.

MO comment: Despite the involvement of higher percentage of cirrhotic patients with Child class A and B (88%, 48/54), the supportive study failed to confirm the results observed in the pivotal study. The difference may be explained by the small study size, and at least partly, by the schistosomiasis contribution to PHT. It has been suggested that variceal bleeding secondary to presinusoidal blockade as observed in schistosomiasis, but also during the physical obstruction of the portal vein by thrombus or a tumor, dose not respond to treatment with somatostatin.

Study DEB-97-VAP-02 (terminated study)

In the ITT population, analysis of the primary endpoint at the end of the 5-day infusion after endoscopic treatment demonstrated that hemostasis was achieved in 55% (28/51) of patients receiving vapreotide compared with 51% (26/51) of patients receiving placebo. A difference that is not significantly different (p=0.692). Similar results were observed for the subset analysis assessed at 6 hours as well as 48 hours after the end of endoscopic treatment (Table 10).

Table 10. Primary criterion-ITT population (Ref. amendment vol. 1.3, table 23)

	Vapreotide	Placebo	All	p-value
n	51	51	102	
Hemostasis at Tendo+6h	35 (69%)	27 (53%)	62 (61%)	0.105
Hemostasis at Tendo+48h	30 (59%)	26 (51%)	56 (55%)	0.426
Hemostasis at 5 days	**28 (55%)**	**26 (51%)**	**54 (53%)**	**0.692**

As shown in Table 11, sponsor's analysis of the primary endpoint in the PP populations revealed similar results to that of the ITT population (52%, 22/42 and 50%, 19/38; p=0.832).

Table 11. Primary criterion PP population (Ref. amendment vol. 1.3, Table 26)

	Vapreotide	Placebo	All	p-value
n	42	38	80	
Hemostasis at Tendo+6h	28(67%)	20 (53%)	48 (60%)	0.201
Hemostasis at Tendo+48h	23 (55%)	19 (50%)	42 (53%)	0.670
Hemostasis at 5 days	**22 (52%)**	**19 (50%)**	**41 (51%)**	**0.832**

Table 12 summarizes the sponsor's multiple endpoints analysis in the ITT population.

Table 12. Secondary criteria ITT population (Ref. amendment vol. 1.3, table 24)

	Vapreotide	Placebo	All	p-value
N	51	51	102	
Re Bleeding episodes:				
• During the 6 weeks	6 (75%)	6 (86%)	12 (80%)	1 .000
• Between Tendo+48h and Tendo+120h	4 (10%)	0	4 (5%)	0.043
• Between Day 5 and Day42	2 (50%)	6 (86%)	8 (73%)	0.491
Number of rebleeding episodes30:				0.464
• 1 episode	1 (50%)	5 (83%)	6 (75%)	
• 2 episodes	1 (50%)	1 (17%)	2 (25%)	
At least one unit of blood transfused" :				
• Between Admission and Tendo+6h	35 (69%)	29 (57%)	64 (63%)	0.219
• Between Tendo+6h and Tendo+48h	22 (46%)	25 (53%)	47 (51%)	0.605
• Between Tendo+48h and Tendo+120h	10 (22%)	13 (27%)	23 (25%)	0.567
Total number of units of blood transfused:	N=51	N=51	N=102	
• Whole 6-week period	3 (0 : 24)	3 (0 : 18)	3 (0 : 24)	1.000
• During the firs! 5 days	3 (0 : 24)	2 (0 : 1 3)	2 (0 : 24)	0.579
• Between Day 5 and Day42	N=42 0 (0 : 8)	N=49 0 (0 : 9)	N=91 0 (0 : 9)	0.473
Total duration of hospitalization (days) - All patients	N=50 10 (2 : 33)	N=51 12 (1 ;42)	N=101 11 (1: 42)	0.103
Number of deaths:				
• During the planned 42 days	10 (20%)	4 (8%)	14 (14%)	0.084
• Between Admission and Tendo+120h (day 5)	5 (10%)	2 (4%)	7 (7%)	0.436
• Between Day 6 and Day 42	5 (10%)	2 (4%)	7 (7%)	0 436

For multiple secondary endpoint analyses in the ITT population, the results showed that there was no significant difference for any variables between the treatment groups.

MO comment: Despite the similarities regarding demographics, baseline characteristics or etiology of liver cirrhosis of the populations described in the pivotal study, the findings observed in the Hong Kong study are quite distinct from that of the pivotal study (DEB-97-VAP-14). Hemostasis rate at the end of 5 days (primary endpoint) was quite similar in the two treatment groups in the Hong Kong study. In contrast, vapreotide was superior to placebo for the primary endpoint in the pivotal study. The reasons for such variability in the outcomes are unclear to this reviewer. Based on the reviewer's assessment, the findings of this study could not be explained

by the protocol violations as suggested by the sponsor. This reviewer finds no obvious quantitative or qualitative differences in protocol violations in this study when compared with those described in the pivotal study.

D. Efficacy Conclusions

The reviewer's assessment of efficacy data from three clinical studies, i.e. DEB-96-VAP-14, DEB-01-VAP-07 and DEB-97-VAP-02 showed that the latter two studies did not demonstrate a significant difference between vapreotide and placebo groups for the primary endpoint (hemostasis at the end of 5-day infusion) in both prespecified ITT and PP populations. Whereas, the superiority of vapreotide to placebo was demonstrated in one study (DEB-96-VAP-14) when assessed for the primary endpoint, in both the ITT and PP populations.

However, in study DEB-96-VAP-14, the superiority of vapreotide to placebo was driven by center 18 involving 28 patients (28/196; 14%) whose underlying liver disease was predominantly class A and B as determined by Child-Pugh score. However, the results from most centers show trends in favor of vapreotide. In addition, although the effectiveness of vapreotide was no longer superior to that of placebo when subjects from center 18 were excluded from analysis, there was a 12% (63% vs. 51%) therapeutic gain in vapreotide treated group which is clinically significant in light of the serious conditions being treated.

Based on the assessment of the efficacy data presented, this reviewer concluded that a single clinical study finding of efficacy, unsupported by an independent evidence is not adequate for a conclusion of a substantial evidence of effectiveness. An additional well controlled study is required that confirms the findings from the pivotal study (DEB-96-VAP-14).

VII. Integrated Review of Safety

A. Brief Statement of Conclusions

The safety data appear to be adequately presented. The major drawback of these studies is the small number of patients, i.e. a total of 481 patients received at least one dose of vapreotide. Of these, a total of 222 subjects received one or more doses of vapreotide for treatment of variceal bleeding (the proposed indication). An important contribution of the trials under current application is that they are placebo-controlled studies, thus the control arm provides a background of AEs frequency particularly in this critically ill population. Overall, the incidence of clinical and laboratory AEs, SAEs and deaths was similar between the two treatment groups in variceal bleeding studies, suggesting that many events recorded were a reflection of the patients' underlying medical condition.

In conclusion, the short-term course use of vapreotide therapy was not associated with significant toxicity in the population studied. The short-term course of vapreotide therapy was not associated with the biliary tract abnormalities and cardiac function abnormalities observed as a result pharmacologic activity with extended exposure.

B. Description of Patient Exposure

Planed and mean drug exposure for seven vapreotide studies included in the safety analysis is summarized in Table 13. All subjects in the seven safety studies who received at least one dose of study drug are included in these analyses. The majority of the safety population (88%) was scheduled to receive the proposed dose of 1.2 mg vapreotide for 5 days (46%) or more (42%).

Actual exposure was less than planned, largely due to protocol specified discontinuations of study drug. In the three varcieal bleeding studies, 16% (36/222) of subjects randomized to vapreotide treatment discontinued study drug per protocol because they were found at endoscopy to have their bleeding unrelated to portal hypertension or bleeding due to bilharzias etiology. An additional 10% (23/222) of subjects in the vapreotide groups failed to complete the scheduled 5 day course of treatment because of death due to underlying disease (5%), loss to follow-up (1.8%), use of alternative therapy (1.3%), early discharge (0.9%), withdrawal of consent (0.9%), and other (0.5%). In the pancreatic surgery, 27% (52/186) of subjects randomized to vapreotide treatment discontinued study drug per protocol because at surgery they were found to have inoperable tumors.

Table 13. (Ref Table 2.7.4.2., Mod 2.2) Extent of Exposure to Vapreotide in Safety Population

Study	Treatment Duration (days)			Number at Daily Dose of		Mean Exposure: Daily Dose x Actual Mean Duration
	Planned	Percent Completed 5- or 7-day Course	Actual Mean ± SD	1.2mg	1.5 mg	
Variceal Bleeding Studies						
DEB-96-VAP-14	5	80%	3.8 ±1.9	111	0	4.6 mg
DEB-97-VAP-02	5	67%	2.7 ± 1.7	70	0	3.2 mg
DEB-01-VAP-07	5	66%	4.1 ±1.8	41	0	4.9 mg
Total Variceal Bleeding Studies		74%	3.5 ± 1.9	222	0	4.2 mg
Studies in Other Indications						
DEB-92-VAP-02	90-180		180.6±234.0	0	35	270.9 mg
DEB-93-VAP-09	28		25 .3 ±4.9	0	22	38.0 mg
DEB-95-VAP-02	21		21.0 ±0.0	15	0	25.2mg
DEB-98-VAP-06	7	73%	4.4 ±2.9	186	0	5.3 mg
Total Other Studies				201	57	
Total Studies				424	57	

C. Methods and Specific Findings of Safety Review

Safety studies from three trials under this application were reviewed independently and summarized under section XI of this review.

In the Integrated Summary of Safety, the safety profile for vapreotide was developed from seven trials involving a total of 481 subjects who received at least one dose of vapreotide acetate: three randomized, double blind, placebo controlled studies for the proposed indication; a randomized, double-blind, placebo controlled trial in pancreatic surgery, and three open efficacy studies in carcinoid/neuroendocrine tumors, Crohn's disease, and acromegaly (Table 14).

MO comment: It should be noted that although the total daily dose was comparable in these studies, the mode of administration was different. In the varcieal studies the test drug was administered intravenously, while in the remaining studies it was used subcutaneously.

Table 14. Listing of vapreotide studies (Ref 2.7.4.1, Module 2 vol. 2.2)

Study No. [Location in CTD]	Indication	Study Type	Vapreotide Dose(mg/d) & Route	Duration (days)	# Pts on Study	Vapreotide				Comparator			
						# Pts	Deaths	With draw for AEs	SAE	# Pts	Deaths	With draw for AEs	SAE
Variceal Bleeding Studies													
DEB-96-VAP-14	Variceal bleeding	Randomized, D-B, P-C	1.2 mg IV infusion	5	227	111	19	9	40	116	27	13	46
DEB-97-VAP-02	Variceal bleeding	Randomized, D-B, P-C	1.2 mg IV infusion	5	136	70	9	10	20	66	6	6	21
DEB-01-VAP-07	Variceal bleeding	Randomized, D-B, P-C	1.2 mg IV infusion	5	72	41	6	4	15	31	8	4	14
Other Controlled Trials Used to Establish Safety Profile													
DEB-98-VAP-06	Pancreatic surgery	Randomized, D-B, P-C	1.2 mg SC	7	376	187	0	7	74	189	7	6	82
Other Uncontrolled Trials used to Establish Safety Profile													
DEB-92-VAP-02	Carcinoid tumors	Open	1.5 mg SC infusion	90 - 180	35	35	4	4	7	–	–	–	–
DEB-93-VAP-09	Crohn's disease	Open	1.5 mg SC infusion	28	22	22	0	4	4	–	–	–	–
DEB-95-VAP-02	Acromegaly	Open	1.2 mg SC infusion	21	15	15	0	0	0	–	–	–	–

Demographic and Other Characteristics of Study Population

Demographic characteristics of the pooled populations from the variceal bleeding studies and studies in other indications are summarized in Table 15.

In the variceal bleeding studies, the majority of subjects (81%) were male, whereas in other studies the populations were more evenly divided between sexes. Subjects in the variceal bleeding studies were somewhat younger than those in the other studies; subjects 65 years or older comprised 21% of the safety population in variceal bleeding studies and 42% in studies in other indications. Race was recorded in only in the one study conducted in the USA (pancreatic surgery study DEB-97-VAP-02: 95% white, 4% black subjects).

Table 15. Demographic Characteristics of Safety Population (Ref. Table 2.7.4.3, Module 2, vol. 1.2)

	Variceal Bleeding Studies		Other Studies	
	vapreotide (N=222)	placebo (N=213)	vapreotide (N=259)	placebo (N=189)
Age (years)				
Number reporting age	209	203	259	189
Mean ± SD	55.3 ± 11.0	55.7 ± 10.8	59.1 ± 16.1	61.5 ± 12.7
[Range]	[19 – 78]	[29 – 81]	[17 – 89]	[19 – 86]
18 - 40	21 (10%)	18 (9%)	37 (14%)	13 (7%)
41 - 64	140 (67%)	141 (70%)	115 (45%)	95 (50%)
65 - 75	43 (21%)	41 (20%)	63 (24%)	56 (30%)
>75	5 (2%)	3 (1.5%)	43 (17%)	25 (13%)
Sex				
Male	179 (81%)	174 (82%)	139 (54%)	100 (53%)
Female	43 (19%)	39 (18%)	120 (46%)	89 (47%)

Adverse Events (AEs)

Treatment-emergent AEs reported in ≥ 1% of vapreotide treated subjects in the pooled safety studies are summarized in Table 16.

In general, the adverse event profile was comparable in both treatment groups. In controlled studies, AEs were reported by 81% of subjects receiving 1.2 mg/day vapreotide and 83% of subjects receiving placebo. Comparisons of AE rates by body system showed no significant difference between the treatment groups for most categories, with the exception of higher AEs rates for the placebo group for psychiatric disorders (anxiety, delirium tremens, insomnia); renal and urinary disorders (oliguria, urinary retention), respiratory disorder (dyspnea, pleural effusion). There were no body system categories in which AEs rates were higher for vapreotide than for placebo groups.

Adverse Events 5%-20%: Treatment-emergent adverse events (relationship to drug not established, excluding events related to underlying disease) occurring in 5%-20% of patients receiving vapreotide acetate were: Blood and Lymphatic System: anemia NOS (6.5%); Gastrointestinal Disorders: abdominal pain (6.6%), constipation (9.6%), diarrhea (7.9%), nausea (17.2%), vomiting (7.1%); General Disorders & Administration Site Conditions: pyrexia (18.9%); Metabolism and Nutrition Disorders: hyperglycemia NOS (7.5%); Psychiatric Disorders: insomnia (6.2%); Skin and Subcutaneous Tissue Disorders: pruritus (5.4%).

Adverse Events 0.4%-4%: Treatment-emergent adverse events (relationship to drug not established, excluding events related to underlying disease) reported by at least 2 patients receiving vapreotide acetate were: Blood and Lymphatic System Disorders: coagulopathy (2 patients), leukocytosis (5 patients); Cardiac Disorders: atrial fibrillation (8), cardiac arrest (2), tachycardia NOS (13); Gastrointestinal Disorders: abdominal distention (8), ascites (10), dyspepsia (14), impaired gastric emptying (23), esophageal ulcer (11); General Disorders & Administration Site Conditions: chest pain (8), fatigue (7), hyperpyrexia (4), infusion site phlebitis (4), injection site inflammation (6); Hepatobiliary Disorders: cholelithiasis (4); Investigations: blood pressure increased (4), oxygen saturation decreased (7); Metabolism and Nutrition Disorders: anorexia (5), dehydration (4), diabetes mellitus NOS (5), hypocalcemia (11), hypoglycemia (4), hypokalemia (20), hypomagnesemia (14), hypovolemia (9); Nervous

System Disorders: convulsions NOS (6), dizziness (6), encephalopathy (6), headache (13); Psychiatric Disorders: agitation (7), anxiety (8), confusional state (17); Renal and Urinary Disorders: dysuria (5), oliguria (11), urinary retention(3); Respiratory, Thoracic and Mediastinal Disorders: dyspnea (9), pleural effusion (18), pulmonary edema NOS (7); Vascular Disorders: hypertension (19), hypotension (14), orthostatic hypotension (3).

Table 16. Treatment-Emergent Adverse Events Reported in ≥1% of Vapreotide-treated Subjects – Pooled Studies (Ref. Table 2.7.4.4., Module 2 vol. 1.2)

MedDRA Body System & Preferred Term	Total Safety Population				Variceal Bleeding Studies		
	All Doses N=481	1.2 mg/d N=424	Placebo N=402	p-value*	1.2 mg/d N=222	Placebo N=213	p-value
Blood & lymphatic system disorders	39 (8.1%)	38 (9.0%)	29 (7.2%)	0.6197	3 (0.6%)	6 (2.8%)	
Anemia NOS	31 (6.5%)	30 (7.1%)	13 (3.2%)		---	1 (0.5%)	
Coagulopathy	2 (0.4%)	2 (0.5%)	3 (0.7%)		---	3 (1.4%)	
Leukocytosis	5 (1.0%)	5 (1.2%)	7 (1.7%)		---	---	
Cardiac disorders	45 (9.4%)	43 (10.1%)	29 (7.2%)	0.2528	5 (2.2%)	11 (5.2%)	
Atrial fibrillation	8 (1.7%)	8 (1.9%)	1 (0.2%)		1 (0.4%)	---	
Cardiac arrest	2 (0.4%)	2 (0.5%)	4 (1.0%)		2 (0.9%)	4 (1.9%)	
Tachycardia NOS	13 (2.7%)	13 (3.1%)	12 (3.0%)		---	1 (0.5%)	
Gastrointestinal disorders	208 (43.2%)	202 (47.6%)	195 (48.5%)	0.1178	72 (32.4%)	63 (29.6%)	
Abdominal distension	8 (1.7%)	8 (1.9%)	6 (1.5%)		3 (1.4%)	2 (0.9%)	
Abdominal pain NOS	25 (5.2%)	24 (5.7%)	25 (6.2%)		7 (3.2%)	9 (4.2%)	
Abdominal pain upper	7 (1.5%)	6 (1.4%)	7 (1.7%)		3 (1.4%)	4 (1.9%)	
Ascites	10 (2.1%)	10 (2.4%)	10 (2.5%)		8 (3.6%)	9 (4.2%)	
Constipation	46 (9.6%)	46 (10.8%)	45 (11.2%)		2 (0.9%)	---	
Diarrhea NOS	38 (7.9%)	38 (9.0%)	34 (8.5%)		6 (2.7%)	11 (5.2%)	
Dyspepsia	14 (2.9%)	14 (3.3%)	14 (3.5%)		7 (3.2%)	6 (2.8%)	
Gastrointestinal hemorrhage NOS	8 (1.7%)	8 (1.9%)	7 (1.7%)		3 (1.4%)	4 (1.9%)	
Hematemesis	15 (3.1%)	15 (3.5%)	6 (1.5%)		15 (6.8%)	6 (2.8%)	
Hiccups	7 (1.5%)	7 (1.7%)	7 (1.7%)		---	---	
Impaired gastric emptying	23 (4.8%)	23 (5.4%)	21 (5.2%)		---	---	
Melena	5 (1.0%)	5 (1.2%)	3 (0.7%)		5 (2.3%)	2 (0.9%)	
Nausea	83 (17.3%)	83 (19.6%)	81 (20.1%)		4 (1.8%)	6 (2.8%)	
Esophageal ulcer	11 (2.3%)	11 (2.6%)	18 (4.5%)		11 (5.0%)	18 (8.5%)	
Vomiting NOS	34 (7.1%)	34 (8.0%)	19 (4.7%)		---	1 (0.5%)	

Table 16. Treatment-Emergent Adverse Events Reported in ≥1% of Vapreotide-treated Subjects – Pooled Studies (continued)

MedDRA Body System & Preferred Term	Total Safety Population				Variceal Bleeding Studies		
	All Doses N=481	1.2 mg/d N=424	Placebo N=402	p-value*	1.2 mg/d N=222	Placebo N=213	p-value
General disorders & administration site conditions	168 (34.9%)	154 (36.3%)	129 (32.1%)	0.3741	74 (33.3%)	63 (29.6%)	
Chest pain	8 (1.7%)	8 (1.9%)	11 (2.7%)		2 (0.9%)	3 (1.4%)	
Fatigue	7 (1.5%)	7 (1.7%)	4 (1.0%)		---	---	
Hyperpyrexia	4 (0.8%)	4 (0.9%)	2 (0.5%)		4 (1.8%)	2 (0.9%)	
Infusion site phlebitis	4 (0.8%)	4 (0.9%)	2 (0.5%)		4 (1.8%)	2 (0.9%)	
Injection site inflammation	6 (1.2%)	6 (1.4%)			---	---	
Injection site nodule	7 (1.5%)		1 (0.2%)		---	---	
Nodule	14 (2.9%)	11 (2.6%)			---	---	
Edema peripheral	15 (3.1%)	15 (3.5%)	13 (3.2%)		1 (0.5%)	4 (1.9%)	
Pain NOS	15 (3.1%)	15 (3.5%)	10 (2.5%)		---	---	
Pyrexia	91 (18.9%)	91 (21.5%)	83 (20.6%)		63 (28.4%)	50 (23.5%)	
Hepatobiliary disorders	38 (7.9%)	34 (8.0%)	39 (9.7%)	0.3448	28 (12.6%)	32 (15.0%)	
Cholelithiasis	4 (0.8%)				---	---	
Hepatorenal syndrome	3 (0.6%)	3 (0.7%)	5 (1.2%)		3 (1.4%)	5 (2.3%)	
Esophageal varices hemorrhage	19 (4.0%)	19 (4.5%)	20 (5.0%)		19 (8.6%)	20 (9.4%)	
Infections and infestations	66 (13.7%)	65 (15.3%)	64 (15.9%)	0.3584	17 (7.7%)	21 (9.9%)	
Abdominal abscess NOS	14 (2.9%)	14 (3.3%)	6 (1.5%)		---	---	
Candidial infection NOS	4 (0.8%)	4 (0.9%)	1 (0.2%)		1 (0.5%)	---	
Clostridium colitis	4 (0.8%)	4 (0.9%)	1 (0.2%)		---	---	
Fungal infection NOS	4 (0.8%)	4 (0.9%)	1 (0.2%)		1 (0.5%)	---	
Pneumonia NOS	16 (3.3%)	16 (3.8%)	12 (3.0%)		3 (1.4%)	3 (1.4%)	
Sepsis NOS	7 (1.5%)	7 (1.7%)	7 (1.7%)		4 (1.8%)	5 (2.3%)	
Urinary tract infection NOS	15 (3.1%)	15 (3.5%)	20 (5.0%)		2 (0.9%)	1 (0.5%)	

Table 16. Treatment-Emergent Adverse Events Reported in ≥1% of Vapreotide-treated Subjects – Pooled Studies (continued)

MedDRA Body System & Preferred Term	Total Safety Population				Variceal Bleeding Studies		
	All Doses N=481	1.2 mg/d N=424	Placebo N=402	p-value*	1.2 mg/d N=222	Placebo N=213	p-value
Injury, poisoning & procedural complications	83 (17.3%)	83 (19.6%)	89 (22.1%)	0.0680	3 (1.4%)	5 (2.3%)	
Accidental overdose	2 (0.4%)	2 (0.5%)	1 (0.2%)		2 (0.9%)	1 (0.5%)	
Anastomotic leak	40 (8.3%)	40 (9.4%)	38 (9.5%)		---	---	
Intra-operative hypotension	3 (0.6%)	3 (0.7%)	3 (0.7%)		---	---	
Nausea postoperative	5 (1.0%)	5 (1.2%)	3 (0.7%)		---	---	
Pancreatic fluid collection	5 (1.0%)	5 (1.2%)			---	---	
Post procedural pain	30 (6.2%)	30 (7.1%)	27 (6.7%)		---	1 (0.5%)	
Postoperative infection	4 (0.8%)	4 (0.9%)	3 (0.7%)		---	---	
Seroma	4 (0.8%)	4 (0.9%)	3 (0.7%)		---	---	
Wound infection	9 (1.9%)	9 (2.1%)	16 (4.0%)		---	---	
Investigations	34 (7.1%)	32 (7.5%)	28 (7.0%)	0.9522	2 (0.9%)	5 (2.3%)	
Blood pressure increased	4 (0.8%)	4 (0.9%)			---	---	
Oxygen saturation decreased	7 (1.5%)	7 (1.7%)	6 (1.5%)		---	---	
White blood cell count increased	8 (1.7%)	8 (1.9%)	2 (0.5%)		---	---	
Metabolism and nutrition disorders	76 (15.8%)	76 (17.9%)	81 (20.1%)	0.0923	9 (4.1%)	12 (5.6%)	
Anorexia	5 (1.0%)	5 (1.2%)	6 (1.5%)		---	---	
Dehydration	4 (0.8%)	4 (0.9%)	3 (0.7%)		---	---	
Diabetes mellitus NOS	5 (1.0%)	5 (1.2%)	3 (0.7%)		2 (0.9%)	1 (0.5%)	
Fluid overload	8 (1.7%)	8 (1.9%)	2 (0.5%)		---	---	
Hyperglycemia NOS	36 (7.5%)	36 (8.5%)	33 (8.2%)		7 (3.2%)	6 (2.8%)	
Hypocalcaemia	11 (2.3%)	11 (2.6%)	9 (2.2%)		---	---	
Hypoglycemia NOS	4 (0.8%)	4 (0.9%)	4 (1.0%)		---	2 (0.9%)	
Hypokalaemia	20 (4.2%)	20 (4.7%)	23 (5.7%)		---	2 (0.9%)	
Hypomagnesaemia	14 (2.9%)	14 (3.3%)	14 (3.5%)		---	---	
Hypovolemia	9 (1.9%)	9 (2.1%)	8 (2.0%)		---	---	

Table 16. Treatment-Emergent Adverse Events Reported in ≥1% of Vapreotide-treated Subjects (continued)

MedDRA Body System & Preferred Term	Total Safety Population				Variceal Bleeding Studies		
	All Doses N=481	1.2 mg/d N=424	Placebo N=402	p-value*	1.2 mg/d N=222	Placebo N=213	p-value
Musculoskeltal and connective tissue disorders	21 (4.4%)	20 (4.7%)	27 (6.7%)	0.1250	3 (1.4%)	7 (3.3%)	
Arthralgia	5 (1.0%)	4 (0.9%)	5 (1.2%)		---	1 (0.5%)	
Back pain	10 (2.1%)	10 (2.4%)	11 (2.7%)		1 (0.5%)	2 (0.9%)	
Nervous system disorders	66 (13.7%)	65 (15.3%)	70 (17.4%)	0.1302	46 (20.7%)	47 (22.1%)	
Convulsions NOS	6 (1.2%)	6 (1.4%)	5 (1.2%)		6 (2.7%)	5 (2.3%)	
Dizziness	6 (1.2%)	6 (1.4%)	8 (2.0%)		5 (2.3%)	4 (1.9%)	
Encephalopathy	6 (1.2%)	6 (1.4%)	5 (1.2%)		6 (2.7%)	5 (2.3%)	
Headache	13 (2.7%)	12 (2.8%)	15 (3.7%)		4 (1.8%)	2 (0.9%)	
Hepatic encephalopathy	25 (5.2%)	25 (5.9%)	23 (5.7%)		25 (11.3%)	23 (10.8%)	
Hypoaesthesia	6 (1.2%)	6 (1.4%)	4 (1.0%)		---	---	
Psychiatric disorders	66 (13.7%)	65 (15.3%)	80 (19.9%)	0.0138	9 (4.1%)	15 (7.0%)	
Agitation	7 (1.5%)	7 (1.7%)	4 (1.0%)		---	---	
Anxiety	8 (1.7%)	8 (1.9%)	19 (4.7%)		---	---	
Confusional state	17 (3.5%)	17 (4.0%)	14 (3.5%)		3 (1.4%)	3 (1.4%)	
Delirium tremens	3 (0.6%)	3 (0.7%)	11 (2.7%)		3 (1.4%)	11 (5.2%)	
Insomnia	30 (6.2%)	29 (6.8%)	40 (10.0%)		1 (0.5%)	---	
Renal and urinary disorders	30 (6.2%)	30 (7.1%)	40 (10.0%)	0.0420	6 (2.7%)	13 (6.1%)	
Dysuria	5 (1.0%)	5 (1.2%)	5 (1.2%)		1 (0.5%)	2 (0.9%)	
Oliguria	11 (2.3%)	11 (2.6%)	19 (4.7%)		1 (0.5%)	6 (2.8%)	
Renal failure acute & NOS	8 (1.6%)	8 (1.9%)	7 (1.7%)		3 (1.4%)	4 (1.9%)	
Urinary retention	3 (0.6%)	3 (0.7%)	7 (1.7%)		1 (0.5%)	---	

Table 16. Treatment-Emergent Adverse Events Reported in ≥1% of Vapreotide-treated Subjects (continued)

MedDRA Body System & Preferred Term	Total Safety Population				Variceal Bleeding Studies		
	All Doses N=481	1.2 mg/d N=424	Placebo N=402	p-value*	1.2 mg/d N=222	Placebo N=	p-value
Respiratory, thoracic and mediastinal disorders	73 (15.2%)	73 (17.2%)	96 (23.9%)	0.0011	20 (9.0%)	26 (12.2%)	
Atelectasis	5 (1.0%)	5 (1.2%)	7 (1.7%)		---	1 (0.5%)	
Dyspnea	9 (1.9%)	9 (2.1%)	12 (3.0%)		1 (0.5%)	5 (2.3%)	
Lung disorder NOS	4 (0.8%)	4 (0.9%)	3 (0.7%)		4 (1.8%)	3 (1.4%)	
Pharyngolaryngeal pain	11 (2.3%)	11 (2.6%)	32 (8.0%)		---	---	
Pleural effusion	18 (3.7%)	18 (4.2%)	22 (5.5%)		---	---	
Productive cough	5 (1.0%)	5 (1.2%)	5 (1.2%)		5 (2.3%)	5 (2.3%)	
Pulmonary edema NOS	7 (1.5%)	7 (1.7%)	3 (0.7%)		---	---	
Respiratory failure	14 (2.9%)	14 (3.3%)	4 (1.0%)		1 (0.5%)	---	
Wheezing	5 (1.0%)	5 (1.2%)	4 (1.0%)		1 (0.5%)	---	
Skin & subcutaneous tissue disorders	52 (10.8%)	51 (12.0%)	40 (10.0%)	0.6768	2 (0.9%)	1 (0.5%)	
Pruritus	26 (5.4%)	25 (5.9%)	26 (6.5%)		1 (0.5%)	---	
Rash NOS	13 (2.7%)	13 (3.1%)	3 (0.7%)		---	---	
Vascular disorders	60 (12.5%)	59 (13.9%)	67 (16.7%)	0.0771	15 (6.8%)	29 (13.6%)	
Hemorrhage NOS	2 (0.4%)	2 (0.5%)	8 (2.0%)		2 (0.9%)	8 (3.8%)	
Hypertension NOS	19 (4.0%)	19 (4.5%)	15 (3.7%)		1 (0.5%)	2 (0.9%)	
Hypotension NOS	14 (2.9%)	14 (3.3%)	16 (4.0%)		2 (0.9%)	4 (1.9%)	
Orthostatic hypotension	3 (0.6%)	3 (0.7%)	2 (0.5%)		---	---	
Phlebitis NOS	4 (0.8%)	4 (0.9%)	2 (0.5%)		2 (0.9%)	1 (0.5%)	
Shock	5 (1.0%)	5 (1.2%)	5 (1.2%)		2 (0.9%)	2 (0.9%)	
Shock hemorrhagic	3 (0.6%)	3 (0.7%)	----		3 (1.4%)	---	
Total patients who experienced an AE	374 (77.8%)	344 (81.1%)	332 (82.6%)		158 (71.2%)	151 (70.9%)	

The pharmacologic activity of somatostatin and its analogs is expected to induce a variety of adverse effects including:

- Biliary tract abnormalities (gallstones, sludge without stones, biliary duct dilatation and, rarely, acute cholecystitis, ascending cholangitis, biliary obstruction, cholestatic hepatitis, or pancreatitis), resulting from inhibition of gallbladder contractility and bile secretion: In the vapreotide studies involving a 5 to 7 day course for treatment of variceal bleeding or pancreatic surgery, biliary tract abnormalities were observed in 1.2% (5/409) of vapreotide-treated subjects (2 cholecystitis, 1 bile duct stone, 2 cholangitis) and 1.0% (4/402) of placebo subjects (2 cholangitis, 1 cholecystitis, 1 bile duct obstruction).
- Hypoglycemia or hyperglycemia resulting from alterations in the balance between counter-regulatory hormones, insulin, glucagon and growth hormone: In the vapreotide variceal bleeding and pancreatic surgery studies, hypoglycemia and hyperglycemia,respectively, were reported in 1.0% (4/409) and 8.8% (36/409) of subjects in vapreotide groups and 1.0% (4/402) and 8.2% (33/402) of subjects in placebo groups.
- Hypothyroidism resulting from suppressed secretion of thyroid stimulating hormone: In acromegalic patients receiving chronic treatment with octreotide (another somatostatin analog), 12% developed biochemical hypothyroidism only 8% developed goiter, and 4% required initiation of thyroid replacement therapy. None of these effects were reported in the vapreotide studies for short-term treatment of variceal bleeding and pancreatic surgery.
- Cardiac contraction abnormalities (bradycardia, conduction abnormalities, arrhythmias and EKG changes including QT prolongation, axis shifts, early repolarization, low voltage, R/S transition, and early R wave progression): In acromegalic patients receiving chronic treatment with octreotide, 25% developed bradycardia, 10% developed conduction abnormalities, and 9% developed arrhythmias. In a clinical study in stable cirrhotic patients not undergoing acute variceal bleeding a single intravenous bolus administration of 0.1 mg vapreotide induced a short-lived (20 min) increase in pulmonary arterial and systemic pressure. In clinical trials involving a 5 to 7 day course of treatment for variceal bleeding or pancreatic surgery, bradycardia was reported in 0.2% (1/409) of subjects in vapreotide groups and 0.5% (2/402) subjects in placebo groups; no arrhythmias were reported.
- Gastrointestinal disorders (diarrhea, loose stools, nausea, and abdominal discomfort) due to imbalance of gastrointestinal hormonal-secretory function: In the vapreotide safety population, gastrointestinal disorders included nausea in 20%, diarrhea in 9%, abdominal discomfort in 9%, and vomiting in 8%. [The corresponding adverse event rates for placebo groups were nausea in 20%, diarrhea in 8.5%, abdominal discomfort in 9%, and vomiting in 5%.]

Clinical Laboratory Evaluation

In the variceal bleeding and pancreatic surgery studies, hematology (hemoglobin, erythrocyte count, leukocyte count, platelet count) and blood chemistry parameters (sodium, creatinine, glucose, AST, ALT in all studies; also total bilirubin and alkaline phosphatase in the latest variceal bleeding study and pancreatic surgery study) were measured at baseline (screening or prior to start of infusion) and at the end of infusion. Assays were performed in the local or central laboratory normally used at each investigative site.

Among patients in the variceal bleeding studies, baseline values for laboratory parameters were consistent with the disease state. Parameters consistent with chronic liver disease included mean ALT and AST well above normal range and mean glucose levels at the upper end of normal range in the two studies enrolling mainly patients with alcoholic cirrhosis and well above normal range in the third study enrolling patients with portal hypertension due to viral hepatitis ± schistosomiasis. Mean erythrocyte levels were below the normal range, consistent with acute hemorrhage. Changes observed in laboratory parameters at the end of the vapreotide infusion generally supported the efficacy and pharmacodynamic effects of vapreotide: erythrocyte levels stabilized, consistent with control of hemorrhage, and mean glucose levels decreased markedly, consistent with expected pharmacodynamic effects that may result in hypoglycemia. The decrease in mean leukocytes observed over the course of vapreotide treatment also is consistent with achieving control of bleeding, since leukocyte count often is increased with hemorrhage and infection. Importantly, there were no significant differences between the vapreotide and placebo groups for any laboratory parameter.

SAEs and Death

In the variceal bleeding studies (proposed indication), among the 222 subjects who received at least one dose of vapreotide acetate for treatment of variceal bleeding 74 (33%) experienced SAEs. Disease-related SAEs, including re-bleeding (hematemesis, melena), shock (hemorrhagic, hypovolemic), hepatic encephalopathy, hepatorenal syndrome, hepatocarcinoma, and hepatic failure, accounted for 88% (65/74) of SAEs. SAEs not attributed to the underlying disease included surgery for hiatal hernia (1), surgery for maxilofacial sinus neoplasm (1), neuropathy-Korsakoff syndrome (1), bradycardia and cardiac failure (1), cardiac arrest (1), peritonitis (1), stroke (1), pneumonia and ascites (1), cholelithiasis (1), and acute respiratory distress syndrome (1).

Similarly, 38% (81/213) of subjects who received placebo in variceal bleeding studies experienced SAEs. Among placebo patients, disease-related SAEs accounted for 80% of the total and SAEs not attributed to underlying disease included acute respiratory distress syndrome (1), cardiac arrest (3), cholecystitis (1), abdominal fluid retention and pain (1), pleural effusion (1), pulmonary tuberculosis (1), surgery for umbilical hernia (1), bursitis (1), sepsis/septic shock (2), asthma with asthma crisis (1), allopurinol sensitivity (1), delirium tremens (1), and death NOS(l).

Table 17 summarizes the cause of deaths in variceal bleeding studies summarized by the reviewer from the sponsor's Table 2.7.4.5 listing of death, Module 2.2.

Table 17. Cause of deaths in variceal bleeding studies (Reviewer's Table)

Causes of death	Vapreotide (n =28)	Placebo (n=34)	All 62
	N (%)	N (%)	N (%)
Hematemesis with or without organ failure	11 (39)	12 (35)	23 (37)
Hepatic encephalopathy	7 (25)	7 (21)	14 (22)
Hemorrhagic shock	6 (21)	4 (12)	10 (16)
Cardiac failure/arrest	2 (7)	3 (8)	5 (8)
Septic shock	0	2 (5)	2 (3)
Coagulapathy/pneumonia	1 (3)	1 (2)	2 (3)
ARDS	1 (3)	1 (2)	2 (3)
others	0	4 (12)	4 (6)
Total	28	34	62

Others refers to bleeding secondary to orthopedic surgery (n=1), Duodenal ulcer bleeding (n=1); Death NOS (n=1).

In the variceal bleeding studies a total of 62 deaths occurred during the study that was comparable between treatment groups: 28 in the vapreotide group and 34 in the placebo group (Table 17). Overall, the most common cause of death was hematemesis with or with organ failure (37%), followed by hepatic encephalopathy (22%) and hemorrhagic shock (16%). In general, the cause of death was comparable between the treatment groups except for hemorrhagic shock that was more frequent cause of death in the vapreotide group than in the placebo group (21% vs. 12%).

MO comment: The death rate as well as the causes of deaths was comparable between the two treatments groups, suggesting that the events recorded were a reflection of the pateints' underlying disease.

D. Adequacy of Safety Testing

The sponsor has adequately assessed the safety of vapreotide for the indication sought in the labeling of the drug. The exposure is short term in most studies, similar to the expected use of the drug.

E. Summary of Critical Safety Findings and Limitations of Data

The short-term course use of vapreotide therapy was not associated with significant toxicity in the population studied. The short-term course of vapreotide therapy was not associated with the biliary tract abnormalities and cardiac function abnormalities observed as a result pharmacologic activity with extended exposure.

The main limitation of the safety data is the relatively small number of patients studied. The other limitation is that the mode of administration of the test drug used in no-varcieal bleeding studies was SC.

VIII. Dosing, Regimen, and Administration Issues

Vapreotide is administered by SC or IV infusion. For the proposed indication, the recommended dose is an initial IV bolus injection of 50 µg followed by a continuous IV infusion at the rate of 50 µg/hr (1.2 mg/day) for 5 days.

Dose-optimizing studies were not performed with vapreotide. The dose selection was based on previous studies using similar compounds (somatostatin and its analogue octreotide) for the same indication. Based on a series of previous studies using similar compounds, a comparable dosing and regimen appears to provide acceptable risk/benefit ratio.

IX. Use in Special Populations

A. Evaluation of Sponsor's Gender Effects Analyses and Adequacy of Investigation

Neither efficacy nor safety subgroup analyses for gender were carried out by the sponsor.

In the variceal bleeding studies, the majority of subjects (81%) were male, which is representative of the population with the medical condition.

For the pivotal study, the Agency's subgroup analysis indicates that for males, hemostasis rate was significantly higher in vapreotide group than placebo group (p=0.029). While, for females, the hemostasis rate is only numerically higher in vapreotide group than placebo group (p=0.43). However, the study size is too small to allow for a valid conclusion to be drawn.

B. Evaluation of Evidence for Age, Race, or Ethnicity Effects on Safety or Efficacy

Neither efficacy nor safety subgroup analysis for patients age was carried out by the sponsor. All clinical studies were conducted in foreign countries. Race information was not collected.

The Agency's subgroup analysis for the pivotal study indicates that for patients aged ≤ 65 years, hemostasis rate was significantly higher in vapreotide group than placebo group (p=0.014). Whereas for patients aged > 65 years, hemostasis rate was numerically higher in the vapreotide group than the placebo group (p=0.72). However, the study size is too small to allow for a valid conclusion to be drawn. In varcieal bleeding studies, subjects 65 years or older comprised 21% of the population.

C. Evaluation of Pediatric Program

On August 5, 2003, a request to waive requirements to comply with the Pediatric Rule was submitted to the Agency (S/N 023 to IND 59,287). The request for waiver was on the basis that vapreotide has Orphan Drug Designation. On January 26, 2004, the Agency granted the waiver for pediatric studies for vapreotide for the proposed indication.

D. Comments on Data Available or Needed in Other Populations

None

X. Conclusions and Recommendations

A. Conclusions

The reviewer's assessment of the efficacy data from three clinical studies, i.e. DEB-96-VAP-14, DEB-01-VAP-07 and DEB-97-VAP-02 showed that the latter two studies did not demonstrate a significant difference between vapreotide and placebo group for the primary endpoint (hemostasis at the end of 5-day infusion) in both prespecified ITT and PP populations. Whereas, the superiority of vapreotide to placebo was demonstrated in a single study (DEB-96-VAP-14) when assessed for the primary endpoint, in both the ITT and PP populations.

However, in a study DEB-96-VAP-14, the superiority of vapreotide to placebo was driven by center 18 involving 28 patients (28/196; 14%) whose underlying liver disease was predominantly class A and B as determined by Child-Pugh score. However, the results from most centers show trends in favor of vapreotide. In addition, although the effectiveness of vapreotide was no longer superior to that of placebo when subjects from center 18 were excluded from analysis, there was a 12% therapeutic gain in vapreotide treated group which is clinically significant in light of the serious conditions being treated.

Based on the assessment of the efficacy data presented, this reviewer concluded that a single clinical study finding of efficacy, unsupported by an independent evidence is not adequate for a conclusion of substantial evidence of effectiveness. An additional well controlled study is required that confirms the findings from the pivotal study (DEB-96-VAP-14).

The safety profile for vapreotide was developed from seven clinical trials involving a total of 481 subjects who received at least one dose of vapreotide. Randomized, double-blind, placebo controlled trials comprised 96% of patients in safety database. The variceal bleeding studies (proposed indication) comprised 52% of patients in the safety database.

In general, the AE profile was comparable in both treatment groups. In controlled studies, AEs were reported by 81% of subjects receiving 1.2 mg/day vapreotide and 83% of subjects receiving placebo. There no body system categories in which AEs rates were higher for vapreotide than for placebo

Among the 222 subjects who received at least one dose of vapreotide for treatment of variceal bleeding 33% experienced serious disease-related adverse events (SAEs) such as rebleeding (hematemesis, melena), shock (hemorrhagic, hypovolemic), hepatic encephalopathy, hepatorenal syndrome, hepatocarcinoma, and hepatic failure. Similarly, among 213 patients who received placebo, 38% experienced similar SAEs.

In general, the death rate as well as the cause of deaths was comparable in the two treatments groups. In the variceal bleeding studies a total of 62 deaths occurred during the study that was comparable between treatment groups: 28 in the vapreotide group and 34 in the placebo group Table 21). Overall, the most common cause of death was hematemesis with or with organ failure (37%), followed by hepatic encephalopathy (22%) and hemorrhagic shock (16%).

The reviewer concluded that a short-term course use of vapreotide therapy was not associated with significant toxicity. The safety profile including death rate of vapreotide was comparable with that of placebo, suggesting that many events recorded were a reflection of the patients' underlying medical conditions.

B. Recommendations

- From a clinical perspective, I recommend vapreotide be considered approvable for the indication of acute variceal bleeding related to PHT, in association with endoscopic treatment. The issuance of an approval is dependent up on the submission and review of an additional well controlled clinical trial that confirms the efficacy in the pivotal study. The sponsor plans to provide additional clinical data from a larger Phase III clinical trial (DEB-02-VAP-06) of vapreotide for the proposed indication that was recently completed in Eastern Europe.

- The sponsor should clarify whether or not the proposed commercial formulation was used in clinical trials.

- The proposed Package Insert will need to be changed as dictated by the results of the additional study.

XI. Appendix - Individual More detailed Study Reviews

Disclaimer: Tabular and graphical information is from sponsor's submission unless stated otherwise.

A. Study DEB-96-VAP-14 (pivotal study)

PROTOCOL

Title: The early association of vapreotide to endoscopic treatment for the control of acute variceal bleeding, and prevention of early rebreeding in cirrhotic patients.

Study Summary:

A phase III, randomize, double-blind, placebo controlled, multicenter parallel study using vapreotide administered for 5 days in cirrhotic patients suffering from acute variceal bleeding due to PHT with a follow-up of 6 weeks.

Cirrhotic patients admitted at hospital (time of first hospital admission = Time zero, T_0) with a history of acute hematemesis and/or melena were to be randomized as soon as possible (maximum delay 24 hours after onset of hemorrhage, and 6 hours after admission [To + 6 h]) to receive either vapreotide 50 µg IV bolus in emergency followed by a continuous IV infusion of 50 µg/h for 5 days or placebo. Long-term follow-up (6 weeks): the patients were to be followed up on the 7th, 30th and 42nd day, in order to monitor the status.

Randomization was balanced by blocks of 4 containing an equal number of test drug and placebo. Each center received a consecutively numbered series of sealed boxes containing an equal number of test drug and placebo numbered in increasing order according to the boxes supplied in each center.

After randomization and the beginning of infusion, a therapeutic endoscopy (sclerotherapy or band ligation) was to be performed at the latest 12h following admission at hospital ($T_0+12\ h$) to confirm the origin of bleeding.

The patients in both groups were to have additional sessions of sclerotherapy or band ligation after Day 5 and thereafter every week, as requested by their clinical condition and according to the physician's opinion until the obliteration of all varices was achieved. In case of hemorrhage unrelated to PHT, the infusion was to be stopped and the patient followed 5, 7, 30 and 42 days. All patients were to receive prophylactic antibiotic from day 1 to the first hospital discharge.

MO comment: MO comment: Dose-optimizing studies were not conducted with vapreotide. The dose and regimen selected for the current studies was based on the dose of somatostatin used in previous studies for the same indication. The appropriateness of the selected approach cannot be validated since available data indicate that the conventional dose of somatostatin used by the sponsor to estimate the vapreotide dose is largely empirical. A recent controlled study comparing different schedules of somatostatin in the treatment of acute variceal bleeding suggests that using a higher dose of somatostatin infusion achieves a higher rate of hemostasis than the conventional dose in patients with active variceal bleeding at endoscopy (Mointinoho E et al: J Hepatol 2001). Whether a vapreotide dose that is higher than the dose used in the current submission would produce similar outcomes cannot be determined without a clinical trial.

The 5 day therapy is recommended since it corresponds to the period during which the risk of recurrence of bleeding is the highest. The 6 week study period has been defined by consensus as the period under which all mortality is considered as directly related to the episode of acute hemorrhage.

Objectives

The primary objective was to quantify to which extent vapreotide in association with endoscopic treatment can improve homeostasis at 5 days, i.e. control of initial bleeding and prevention of early rebleeding.

Secondary objectives were to assess: 1) hemostasis and endoscopic facilitation at first endoscopy, percent of cases presenting an active bleeding; 2) hemostasis 6 hours after randomization; 3) the total number of rebleeding episodes per patient after the 6 weeks of study; 4) number of blood units used during the 6 weeks of the study; 4) the number of days in hospital since randomization; and, 5) 7-, 30- and 42-day survival.

Efficacy Criteria

The primary efficacy criterion was hemostasis at 5 days after completion of emergency endoscopic treatment (*Tendo*), defined as achievement of both primary hemostasis (no bleeding from Tendo + 6h to Tendo +48h) and secondary hemostasis (no rebleeding betweenTendo+48h to Tendo+120h).

Secondary efficacy criteria include: 1) hemostasis and endoscopic facilitation at first endoscopy, percent of cases presenting an active bleeding; 2) hemostasis 6 hours after randomization; 3) the total number of rebleeding episodes per patient after the 6 weeks of study; 4) number of blood units used during the 6 weeks of the study; 4) the number of days in hospital since randomization; and, 5) 7-, 30- and 42-day survival.

Primary Efficacy Variables Assessment

To assess the primary endpoint, the sponsor used 3 types of criteria based on Recommendations from Consensus Conference: a) the acute bleeding time-frame during the first 48 hours with 2 different criteria to evaluate primary hemostasis, i.e. bleeding within 6 hour and after 6 hour following the end of endoscopic treatment (Tendo), b) secondary hemostasis was evaluated between 48 hour to 120 hour (Day 3 to 5) for rebleeding.

Primary hemostasis:

Evaluation at Tendo + 6 hrs:

- transfusion requirement ≤ units from Tendo;
- systolic pressure > 80 mm Hg
- pulse rate < 100 bpm

Evaluation between Tendo + 6 hrs to Tendo + 48 hrs:

- no hematemesis;
- transfusion requirement ≤ 2 units from Tendo + 6 hrs
- pulse rate < 100 bpm;
- Hct: no decrease ≥ 10 points in comparison with value of Tendo + 6 hrs

Secondary hemostasis:

Evaluation between Tendo + 48h to Tendo + 120h.

- no rebleeding (hematemesis, melena)

Rebleeding was defined as occurrence of new hematemesis or a new melena after a period of ≥ 24h of stability of vital signs, and with Hct or Hgb as from tend+24h. A rebleeding episode implies that an initial control of the first hemorrhage was obtained.
Failure to control bleeding during the 5-day infusion period:

- persistent and uncontrolled bleeding;
- other drugs necessary to control hematemesis;
- new hematemesis and/or melena;
- death

MO Comment: the definition of the primary endpoint and assessment of the associated parameters were adapted from the Consensus Workshop on Definition, Methodology and Therapeutic Strategies in portal hypertension (De Franchis, R. J Hepatol 2000).

Study Population

Inclusion criteria	**Exclusion criteria**
- Female or male cirrhotic patients aged 18 to 75 years	- Coma
- Hematemesis and/or melena	- Child-Pugh score > 13 in the previous month
- Delay ≤ 24 hours between onset of initial hemorrhage and randomization	- Pregnancy or breast feeding
- Delay ≤ 6 hours between admission and randomization	- Known diffuse Hepatocelullar carcinoma
- Cirrhosis documented by one of the classical clinical signs (ascites, abdominal collateral venous circulation, firm liver with a sharp lower edge, more than 5 spider naevi	- Known complete portal thrombosis
- The patient or his/her relative must sign the consent form	- Non-cirrhotic portal hypertension
	- Bleeding from esophageal varices within the previous 6 weeks
	- Patient already included in another study which ended < 6 weeks
	- Patients already included in another therapeutic study.

MO comment: as judged by the inclusion/exclusion criteria, the study population was adequate for the proposed study

Study Procedure and Assessment

Figure 1. Study schedule (Ref. Module 5, vol. 1. 8, Figure 1)

Data and treatments	**Day 1** admission Tinf to Tendo+24h	**Day 2** Tendo + 48h	**Day 3** Tendo + 72h	**Day 4** Tendo + 96h	**Day 5** Tendo + 120h	**Day 7** follow-up visit	**Day 30** follow-up visit	**Day 42** follow-up visit
Drug infusion	X	X	X	X	X			
Adverse event(s)?	X	X	X	X	X	X	X	X
Therapeutic endoscopy	X					X[1]	X[1]	X[1]
Blood pressure	X	X	X	X	X			
Heart rate	X	X	X	X	X			
Temperature	X	X	X	X	X			
Ht / Hb	X	X	X	X	X			X
Blood sample :								
- RBC	X				X			
- WBC	X				X			
- Platelet count	X				X			
- Na^+	X				X			
- Creatinine	X				X			
- Glycemia	X	X			X			
- AST	X	X			X			
- ALT	X	X			X			
- Vapreotide	X	X						
Transfusion(s)?	X	X	X	X	X	X	X	X
Other treatments ?	X	X	X	X	X	X	X	X
Child-Pugh score	X				X			X
Abdominal sonographic scan					X			

[1] If necessary

Hemodynamic conditions such as blood pressure, pulse, Hematocrit (Ht), transfusion needs were recorded every 6 hours for the first 48 hours; and every 12h between the third and the fifth day (Figure 1).

Forbidden Concomitant Medications

During the first 5-day infusion period, no other medical treatment to control bleeding was to be given. If another medical treatment appeared necessary to control bleeding during that period, the patient was considered as a therapeutic failure. B-blocker and nitrates could be introduced after day 5 if necessary for the long-term management of esophageal or gastric varices.

During the 6 week study period, somatostatin, vasopressin, or their analogs were not permitted. If these drugs were necessary, the patient was considered as a therapeutic failure.

MO comment: Given the 6 weeks study period, the introduction of B-blockers after day 5 may confound the efficacy outcome since B-blockers are the standard long-term therapy prevent variceal rebleeding.

Statistical and Analytical Plans

Efficacy analyses were conducted in two sets of patients: intent-to-treat (ITT) and per protocol (PP) populations. ITT analysis was conducted in all randomized patients, regardless of any protocol deviation and according to the randomized treatment. PP analysis was conducted in all randomized patients according to the treatment actually received, except for those who did not fulfill any of the following situations:

- The patient had non-permitted concurrent treatment;
- The patient had no assessment before going off-treatment due to loss to follow-up, withdrawn consent, or concurrent illness;
- Hemorrhage due to causes other than PHT.

Safety analysis was conducted in all patients who received any dose of vapreotide or placebo.

The null hypothesis (H_0) was that there was no difference between treatments on primary efficacy criterion and the alternative hypothesis was that there was a true difference. The α risk p-values reported were two-sided and the statistical significance nominal limit was set to 0.05. The test of the primary criterion was for *confirmatory* purposes; all other tests performed were for *exploratory* purposes. Therefore the significant level was not adjusted for the latter analyses.

The primary endpoint was analyzed in contingency table by the chi-square test. Rate of hemostasis and two-sided 95% confidence interval (CI) were constructed per treatment arm, as well as for their active over placebo ratio.

No interim statistical analysis was planed. There was no imputation for missing data. For the primary criterion, patients with missing data were considered as failure. In all secondary criteria,

when data used in the analysis were missing, the patient was excluded from that specific analysis.

Determination of Sample Size
Based on the published literature, hemostasis was observed in about 65% of patients with placebo treatment. As a rate of hemostasis of 85% at 5 days on vapreotide could be anticipated for somatostatin or other analogues, 73 patients per treatment arm were required to demonstrate this difference versus placebo, with nominal $\alpha = 0.05$ two-sided and $\beta = 20$. Further to the anticipated 30% rate of patients due to bleeding of non-esophageal varices origin, the number of patients to enroll was increased accordingly, to reach a total of 146 patients with bleeding of esophageal varices origin.

Protocol Amendment

A systemic blind review of all cases was conducted after study completion on February 11, 1999. According to the sponsor, the purpose of this review was to identify the protocol deviations and to allocate the patients to the populations for statistical analysis.

The following conventions on disease indications were defined for the purpose of statistical analysis:

- Stage 1 gastric varices were considered anatomically as esophageal varices,
- In case of a hemorrhage of non-determined origin because of absence of endoscopic examination, the hemorrhage was classified as esophageal varices,
- Esophageal varices associated with gastric varices, and esophageal varices associated with portal hypertensive gastroropathy were considered as esophageal varices.

The definition of the ITT and PP populations was refined:

- ITT analysis was conducted in the randomized patients for whom hemorrhage was due to portal hypertension (esophageal varices, gastric varices and portal hypertensive gastropathy), regardless of any protocol deviation according the randomized treatment. All cases of hemorrhage unrelated to PHT were therefore included in the safety analysis.
- PP analysis was conducted in randomized patients according to the treatment actually received. The following exclusion criteria were added:
    - Hemorrhage due to causes other than esophageal varices in a first step; in a second step, the few cases of gastric varices and portal hypertensive gastropathy included in the ITT analysis;
    - Endoscopic treatment not carried out, except in case of portal gastropathy;
    - Randomization and/or endoscopic treatment carried out outside the permitted time window (maximum delay 24h after onset of hemorrhage, and 6h after admission).
    - An additional analysis was conducted in the subset of the PP population of patients bleeding from esophageal varices (PPEV), to allow for comparison with data in the literature, which often report only bleeding esophageal varices.

MO comment: in response to the reviewer's request for clarification on the timing of protocol amendment, the sponsor indicated that it was after study completion that a systemic blinded review of all cases could occur (later dated October, 7, 2004). Further, it was stated that the blinded review was completed prior to locking the database and performing a statistical analysis. The database was locked in March 1999. The sponsor provided a satisfactory response.

The sponsor also provided a reasonable rationale for classifying a non-determined origin of bleeding (in the absence of endoscopic examination) as esophageal varices. Available data indicate that > 70% of cirrhotic patients with upper gastrointestinal bleeding has esophageal varices. More importantly, such classification would have insignificant impact on the outcome of the study since it only involved 3 patients under this classification: 2 in the placebo and one in the vapreotide group.

RESULTS

Disposition of patients

Two hundred and twenty-seven patients were enrolled and randomized into the study between July 1, 1997 and the October 30, 1998, in 22 centers with unequal size of recruitment.

Table 18. Enrollment per Center (Ref. Table 1, vol. 1.8)

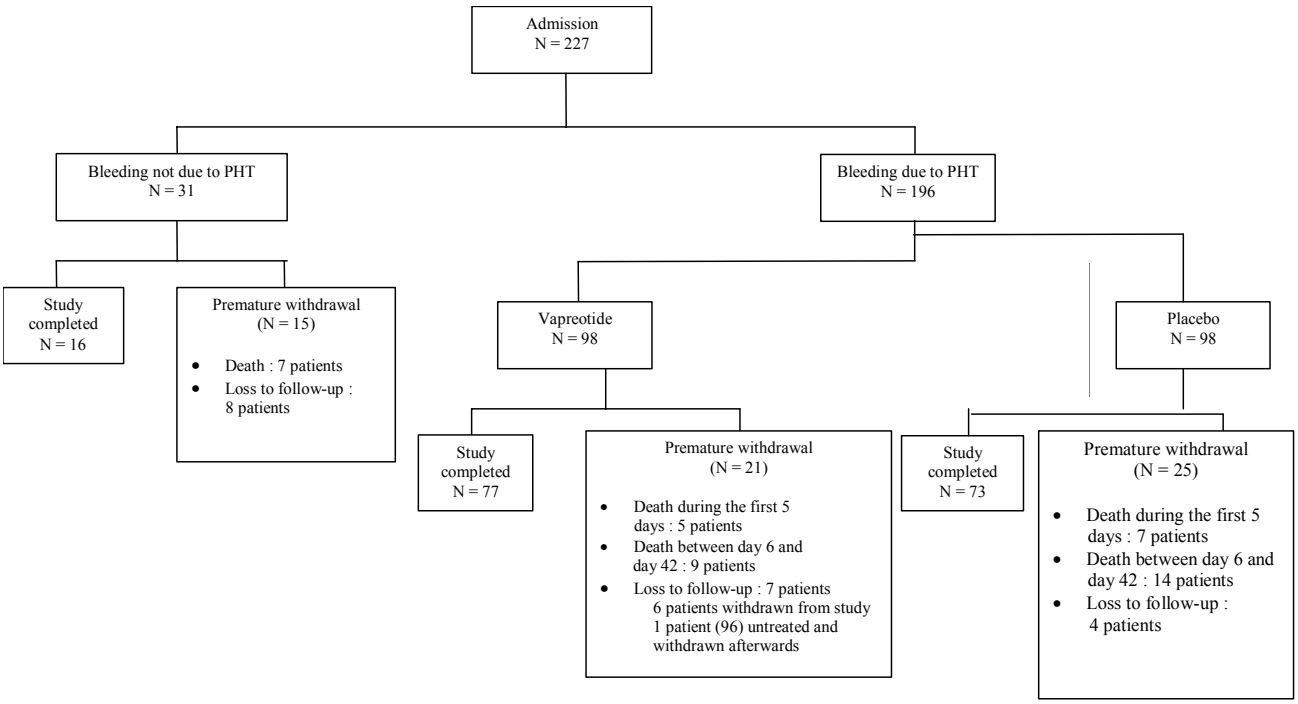
	Treatment Group					
	Placebo		Vapreotide		Total	
	N	%	N	%	N	%
Center number						
1 - Angers	12	10.34	10	9.01	22	9.69
2 - Paris Salpétrière	14	12.07	16	14.41	30	13.22
3 - Paris Beaujon	5	4.31	4	3.60	9	3.96
4 - Paris Villejuif	4	3.45	3	2.70	7	3.08
5 - Paris St Antoine	3	2.59	3	2.70	6	2.64
7 - Lyon	1	0.86	.	.	1	0.44
8 - Nîmes	6	5.17	3	2.70	9	3.96
9 - Aurillac	4	3.45	2	1.80	6	2.64
10 - Lille	6	5.17	8	7.21	14	6.17
11 - Dijon	3	2.59	4	3.60	7	3.08
12 - Poitiers	6	5.17	8	7.21	14	6.17
13 - Limoges	2	1.72	2	1.80	4	1.76
14 - La Réunion	8	6.90	7	6.31	15	6.61
15 - Le Mans	5	4.31	4	3.60	9	3.96
17 - Soisson	3	2.59	3	2.70	6	2.64
18 - Nantes	16	13.79	16	14.41	32	14.10
22 - Nancy/Vandoeuvre	4	3.45	6	5.41	10	4.41
23 - Lens	2	1.72	2	1.80	4	1.76
24 - Caen	3	2.59	2	1.80	5	2.20
25 - Grenoble	2	1.72	1	0.90	3	1.32
26 - Marseille	4	3.45	4	3.60	8	3.52
27 - Clermont-Ferrand	3	2.59	3	2.70	6	2.64
Total	116	100.00	111	100.00	227	100.00

MO comment: It appears that the patients were primarily driven from three centers (1, 2 and 18). Note that the five centers 6, 16, 19, 20 and 21 are not listed on Table 18 because these centers did not recruit patients.

Of the 227 patients, 196 had bleeding due to PHT and were included in the ITT population (98 in each treatment arm), and 31 patients had bleeding unrelated to PHT and were excluded from the efficacy analysis.

One-hundred-fifty (77%) patients in the ITT population completed the study (77 in vapreotide and 73 in placebo group), 46 patients (23%) did not complete the study (21 in vapreotide and 25 in placebo group). Premature withdrawal was due to death in 34 patients: 13 in the vapreotide and 21 in the placebo group; due to loss to follow-up in 11 patients: 7 in the vapreotide and 4 in the placebo group as shown in the Figure 2.

Figure 2 (Ref. Figure 3. vol. 1.8, Module 5)



Protocol Deviations

A total of 36 patients had at least one protocol deviation during the treatment period: 21 in the vapreotide group and 15 in the placebo group (Table 19). The most common protocol deviation was endoscopic treatment not carried out or carried out outside the permitted time window and was balanced between the two treatment arms: 10 in the vapreotide arm and 9 in the placebo arm.

Table 19. Major Protocol Deviation (Ref. Table 3, vol. 1.8)

	Vapreotide	Placebo	All
N	111	116	227
Number of patients with at least one deviation at admission in the study	2 Patients n° 68, 293	0	2
Number of patients with at least one deviation during the treatment period:	20	15	35
List of the deviations during the treatment period:			
– concomitant treatment with β-blocker between Day 1 and Day 5	Patients n°13, 29, 90, 106, 160	Patients n°4, 15, 26	
– concomitant treatment with somatostatin or analogue	Patient n° 56	Patient n° 162	
– endoscopic treatment not carried out or carried out outside the permitted time window,	Patients n° 19, 53, 87, 96, 160, 223, 263, 293, 342, 345	Patients n° 5, 26, 43, 92, 99, 111, 231, 389, 390	
– randomization carried out after the endoscopic treatment or carried out outside the permitted time window,	Patients n° 29, 106	Patients n°26, 101, 225	
– infusion of at least one vial from a box of another patient	Patients n° 9110, 10241	Patient n° 10275	
– inadequate trial	Patients n° 136, 305, 353		
Number of patients with at least one deviation during the whole study	21	15	36

MO comment: the distribution of protocol deviations was comparable between the two treatment groups.

Demographic and Baseline Characteristics (ITT population)

In the ITT population male patients accounted for 83% of the placebo group and 68% of the vapreotide group (Table 20). The median age was 56 years (range, 29 to 75), median weight was 70 kg (range, 36 to 120), and the median height was 170 cm (range, 151 to 190).

Table 20. Demographic Characteristics-ITT population (Ref. Table 5, vol. 1.8)

	Vapreotide	Placebo	All	P-value
N	98	98	196	
Sex ratio	2.2	4.8	3.1	**p = 0.020**
Age (years)	56 (32 ; 73)[1]	54 (29 ; 75)	56 (29 ; 75)	p = 0.976
Weight (kg)	70 (36 ; 106)	70 (48 ; 120)	70 (36 ; 120)	p = 0.902
Height (cm)	170 (152 ; 190)	169 (151 ; 190)	170 (151 ; 190)	p = 0.580

[1] Median (minimum; Maximum)

MO comment: The proportion of males was significantly higher in the placebo group than in vapreotide group. The other demographic characteristics were comparable between the two treatment groups. Information on race was not recorded.

Past and/or Concomitant Diseases

Past or concomitant diseases were reported in 81% of the patients (Table 21). The majority of patients had digestive diseases (40%), 25% had cardio-vascular disease mainly hypertension, and endocrine diseases (24%) with a majority of insulin and non-insulin dependent diabetes mellitus. The two treatment groups were comparable except for abnormal examination of Ear, Nose and Throat (ENT) including 9 malignant neoplasm and lung systems.

Table 21. Past and concomitant diseases at admission-ITT population (Ref. Table 6, vol. 1.8)

	Vapreotide	Placebo	All	P-value
N	98	98	196	
At least 1 past and/or concomitant disease	77 (79%)	81 (83%)	158 (81%)	-
Abnormal clinical examination :				
– Digestive tract	42 (43%)	36 (37%)	78 (40%)	p = 0.381
– Cardio-vascular system	29 (30%)	20 (20%)	49 (25%)	p = 0.138
– Endocrine system	26 (27%)	21 (21%)	47 (24%)	p = 0.403
– ENT/Lungs system	12 (12%)	23 (23%)	35 (18%)	**p = 0.040**
– Bones-joints	11 (11%)	19 (19%)	30 (15%)	p = 0.112
– Nervous system	14 (14%)	15 (15%)	29 (15%)	p = 0.841

Concomitant Treatment

Fifty-four percent of the patients were included in the study with at least one concomitant treatment (Table 22). The most frequent medications used were:

- Alimentary tract and metabolism medications (93%);
- Systemic anti-infectives (91%);
- Cardiovascular medications (53%);
- Nervous system treatment (50%).

Table 22. Concomitant treatments at admission – ITT population (Ref. Table 7, vol. 1.8, Module 5)

	Vapreotide	Placebo	All
N	98	98	196
At least one concomitant treatment before randomization	55 (56%) [46; 66%]	51 (52%) [42; 62%]	106 (54%)
Concomitant treatment during product infusion*			
– At least one	98 (100%)	97 (99%)	195 (99%)
– Alimentary tract and metabolism medication	92 (94%)	90 (93%)	182 (93%)
– General anti-infectives for systemic use medication	90 (92%)	88 (91%)	178 (91%)
– Cardiovascular medication	52 (53%)	52 (54%)	104 (53%)
– Nervous system medication	53 (54%)	44 (45%)	97 (50%)
Concomitant treatment after the end of product infusion*			
– At least one	94 (96%)	92 (94%)	186 (95%)
– Alimentary tract and metabolism medication	86 (91%)	87 (95%)	173 (93%)
– Cardiovascular medication	77 (82%)	80 (87%)	157 (84%)
– General anti-infectives for systemic use medication	73 (78%)	70 (76%)	143 (77%)

History of the Disease

The cause of cirrhosis was mainly alcoholism (85%) and was comparable between the two treatment groups (Table 23). The median time elapsed between clinical and/or histological diagnosis of cirrhosis and inclusion was 1 year. Previous history of ascites was reported in 40% of the patients while previous episode of hepatic encephalopathy was reported in 9% of patients, with no significant difference between the two treatment groups. History of esophageal varices was documented for 61% of the patients, with no difference between the two treatment groups. The median time between diagnosis of esophageal varices and inclusion was 2 years.

Thirty-nine percent of patients in each treatment group had already suffered from bleeding due to PHT. The median time of the occurrence of the last episodes was < 1 year. Forty-six percent of patients were previously treated for PHT, with no significant difference between the 2 treatment groups. Overall, 87% of the patients were previously treated with B-blockers: in 47% as a single therapy, and in 36% in association with endoscopic therapy and there was no significant difference between the treatment groups.

Table 23. History of the disease -ITT population (Ref. Table 8, vol. 1.8)

	Vapreotide	Placebo	All	P-value
N	98	98	196	
Etiology :				p = 0.890
– Alcoholism	82 (84%)	84 (86%)	166 (85%)	
– Alcoholism + viral hepatitis	7 (7%)	7 (7%)	14 (7%)	
Time from diagnosis of cirrhosis to inclusion (years)	2 (0 ; 16)	1 (0 ; 35)	1 (0 ; 35)	p = 0.728
Previous history of ascites	38 (39%)	40 (41%)	78 (40%)	p = 0.815
Previous history of hepatic encephalopathy	9 (9%)	9 (9%)	18 (9%)	p = 0.982
Known esophageal varices	62 (63%)	57 (58%)	119 (61%)	p = 0.410
Time from diagnosis to inclusion (years)	2 (0 ; 16)	2 (0 ; 35)	2 (0 ; 35)	p = 0.976
Previous episode of hemorrhage related to portal hypertension :	38 (39%)	38 (39%)	76 (39%)	p = 0.954
– 1 episode	19 (50%)	18 (47%)	37 (49%)	p = 0.449
– 2 episodes	9 (24%)	7 (18%)	16 (21%)	
– More than 2 episodes	8 (21%)	12 (32%)	20 (26%)	
Previous treatment for portal hypertension :	49 (50%)	42 (43%)	91 (46%)	p = 0.284
• β-blockers				
– alone	44 (90%)	35 (83%)	79 (87%)	p = 0.364
– with endoscopy	23 (47%)	20 (48%)	43 (47%)	
– other	20 (41%)	13 (31%)	33 (36%)	
	1 (2%)	2 (5%)	3 (4%)	

Admission to Hospital and Initiation of Therapy

Patients were admitted to the center in a median delay of 7 hours after the beginning of hemorrhage and was comparable between the treatment groups (Table 24). The product infusion was started in a median delay of 9.45 hrs (range 0:25 to 28:00h) after the beginning of hemorrhage and in a median delay of 2:01 hrs (range, 0:00-8:30) after the admission to the center with no significant difference between the treatment groups. The endoscopic treatment was completed in a median delay 3:50 hrs (range 1:00 to 26:50h) after hospital admission.
The source of hemorrhage was assessed by endoscopy as follow:

- Esophageal varices for 95% of the patients;
- Gastric varices for 2% of the patients;
- PHT gastropathy for 3% of the patients.

The physical obliteration of varices was carried out using mainly sclerotherapy (53%) or band ligation (31%) and was comparable between the treatment groups (Table 24). The median volume of sclerosant (prolidocanol 1%) injection during sclerotherapy was 18 ml (range 1 to 40 ml). The endoscopic therapy was not carried out in 16 patients for various reasons: 9 in the vapreotide group and 7 in the placebo group.

The Child-Pugh score was evaluated between admission to hospital and 24 hrs after the end of endoscopic procedure. The majority of patients was classified as B (42%) or C (38%) and was comparable between the treatment groups. Child classification was missing in 10 patients: 6 in the vapreotide group and 4 in the placebo group (Table 24).

MO comment: Consistent with International Consensuses Conference Recommendation (De Francis. R. J Hepatol 2000), patients were randomized as early as possible after admission and in all cases treatment with study drug was initiated prior to endoscopic diagnosis. In this study, the time elapsed between start of bleeding to drug infusion as well as between admissions to start of infusion was reasonably short.

Table 24. Current episode of acute variceal bleeding-ITT population (Ref. Table 9, vol. 8)

Median (min;max)	Vapreotide	Placebo	All	P-value
N	98	98	196	
Time between hemorrhage and admission in investigator center (hour:min)	7:00 (0:00 ; 23:30)	7:58 (0:00 ; 22:00)	7:00 (0:00 ; 23:30)	p = 0.880
Time between hemorrhage and start of product infusion (hour:min)	9:45 (0:25 ; 23:55)	9:53 (0:30 ; 28:00)	9:45 (0:25 ; 28:00)	p = 0.952
Time between admission and start of product infusion (hour:min)	2:15 (0:00 ; 6:30)	2:00 (0:00 ; 8:30)	2:01 (0:00 ; 8:30)	p = 0.197
Time between the end of endoscopic treatment and admission (hour:min)	3:45 (1:00 ; 26:50)	3:55 (1:05 ; 13:15)	3:50 (1:00 ; 26:50)	p = 0.649
Source of hemorrhage :				
– Esophageal varices	91 (93%)	95 (97%)	186 (95%)	p = 0.307
– Portal hypertensive gastropathy	5 (5%)	1 (1%)	6 (3%)	
– Gastric varices	2 (2%)	2 (2%)	4 (2%)	
Physical obliteration of varices :				p = 0.479
– Sclerotherapy	49 (50%)	55 (56%)	104 (53%)	
– Band ligation	30 (31%)	30 (31%)	60 (31%)	
Child-Pugh score	9 (5 ; 13)	9 (5 ; 15)	9 (5 ; 15)	p = 0.385
– Class A	14 (14%)	14 (14%)	28 (14%)	p = 0.946
– Class B	42 (43%)	41 (42%)	83 (42%)	
– Class C	36 (37%)	39 (40%)	75 (38%)	

The size of esophageal varices was available in 176 patients and was > 5mm in the majority of the patients (70%) and was comparable between the two treatment groups. The red spots were present in varices in the majority of patients (80%) and were comparable between the groups (Table 25).

Table 25. Esophageal Varices – ITT population (Ref. Table 41, vol. 8)

Chi-square test	Treatment Group					
	Placebo		Vapreotide		Total	
	N	%	N	%	N	%
Presence of red spots p = 0.368						
Yes	74	82.22	66	76.74	140	79.55
No	16	17.78	20	23.26	36	20.45
95% CI of presence of red spots	[74.3% - 90.1%]		[67.8% - 85.7%]		-	
Size of varices p = 0.599						
<= 5 mm	25	27.78	27	31.40	52	29.55
> 5 mm	65	72.22	59	68.60	124	70.45
95% CI of <= 5 mm	[18.5% - 37.0%]		[21.6% - 41.2%]		-	
Total	90	100.00	86	100.00	176	100.00

MO comment: Available data indicate that the most important predictive factors related to the risk of bleeding and rebleeding are large variceal size (>5mm), presence of read weal marks in varices and severity of liver dysfunction expressed by the Child class C. These three risk factors appear to present in the majority of patients studied and were comparable between the treatment groups.

Monitoring at Admission

Monitoring of patients was started at initiation of infusion following hospital admission (Table 26). Although the great majority of patients (n=160) did not receive any plasma or macromolecules before reaching the center where the study drug infusion was initiated, the number of patients who received such infusion was higher for those who were subsequently randomized to placebo (n=24) than those who randomized to vapreotide (n=11). This may explain the lower Hct at admission in the placebo group. At the same time, 5% of the patients had already received one blood unit or more, with no difference between groups. Hemodynamic parameters including pulse rate, mean systolic and diastolic blood pressure at admission were comparable between the two treatment groups. However, Hematocrit was lower in placebo group than vapreotide approaching a statistically significant difference (30 % vs. 27%; p=0.053).

Bleeding was manifested as hematemesis with or without melena in 124 of patients (63%) or melena in 31 of patients (16%), and was comparable between the two treatment groups.

MO comment: It appears that the placebo group lost more blood than the vapreotide group.

Table 26. Monitoring at admission – ITT population (Ref. Table 10, vol. 1.8)

	Vapreotide	Placebo	All	P-value
N	98	98	196	
Body temperature (°C)	37.2 ± 0.7	37.2 ± 0.6	37.2 ± 0.6	p = 0.725
Systolic blood pressure (mmHg)	127 ± 23	125 ± 23	126 ± 23	p = 0.491
Diastolic blood pressure (mmHg)	70 ± 14	67 ± 15	68 ± 15	p = 0.075
Mean blood pressure (mmHg)	89 ± 15	86 ± 16	88 ± 16	p = 0.142
Heart rate (bpm)	98 ± 22	104 ± 22	101 ± 22	p = 0.062
Bleeding				
– Hematemesis or hematemesis+ melena	58 (59%)	66 (67%)	124 (63%)	p = 0.153
– Melena	14 (14%)	17 (17%)	31 (16%)	
Hematocrit (%)	30 (12 ; 47)	27 (9 ; 42)	28 (9 ; 47)	p = 0.053
Hemoglobin (g/dl)	9 (4 ; 14)	9 (3 ; 14)	9 (3 ; 14)	p = 0.107
No transfusion of units of blood	94 (96%)	93 (95%)	187 (95%)	p = 1
Transfusion of plasma or macromolecules :				p <0.001
– None	86 (88%)	74 (76%)	160 (82%)	
– Less than 1000 ml	11 (11%)	16 (16%)	27 (14%)	
– At least 1000 ml	-	8 (8%)	8 (4%)	

Table 27. Laboratory results at admission-ITT population (Ref. Table 12. vol. 1.8)

	Vapreotide	Placebo	All	P-value
N	98	98	196	
Erythrocytes (T/L)	2.9 ± 0.7	2.8 ± 0.9	2.8 ± 0.8	P = 0.137
Leukocytes (g/l)	7.2 (1.3 ; 30.7)	8.4 (0.8 ; 22.6)	7.8 (0.8 ; 30.7)	P = 0.183
Thrombocytes (g/l)	98 (18 ; 689)	96 (30 ; 508)	97 (18 ; 689)	P = 0.849
Sodium (mmol/l)	139 (120 ; 149)	138 (120 ; 149)	139 (120 ; 149)	P = 0.916
Creatinine (µmol/l)	75 (39 ; 1073)	80 (48 ; 477)	77 (39 ; 1073)	P = 0.069
Glucose (mmol/l)	7.7 (4.0 ; 39.3)	8.6 (2.6 ; 24.5)	8.3 (2.6 ; 39.3)	**P = 0.040**
AST (UI/L)	52 (6 ; 417)	64 (8 ; 330)	60 (6 ; 417)	P = 0.315
ALT (UI/L)	28 (4 ; 139)	29 (2 ; 210)	29 (2 ; 210)	P = 0.148

Regarding blood test parameters at admission there was no significant difference between the treatment groups, except for serum glucose, which was significantly higher in the placebo group than the vapreotide group (Table 27).

Per protocol population

The results observed on the PP population are presented in Appendix 14.1.3 (85 to 164) and are reported to be similar to those observed for the ITT population, except for the following points:

- At admission, heart rate was significantly higher in placebo group than in vapreotide group (105 ± 23 bpm vs. 98 ± 20 bpm; p=0.047). This difference was accentuated at the end of endoscopic treatment (109 + 22 vs. 98 + 21, respectively)

- At admission, hematocrit was significantly higher in vapreotide group than in placebo group (29 7 vs. 27 8; p=0.02). The difference disappeared at the end of endoscopic treatment (27 5 vs. 28 7, respectively, p=0.308).

MO comment: It appears as if patients in the placebo group lost more blood from variceal bleeding than those in the vapreotide group. It is unclear to what extent could this difference impacted the outcome.

Sponsor's Efficacy Results

In the ITT population, analysis of the primary endpoint at the end of 5-day after endoscopic treatment (Tendo) demonstrated that hemostasis was achieved in 66% of patients receiving vapreotide compared with 53% of patients receiving placebo, a difference that was statistically significant (p=0.00.021) (Table 28). For the subset analyses, significantly higher hemostasis rate was achieved in vapreotide group than placebo group at Tendo+6h and Tend+48h (p=0.001 and p=0.005; respectively), whereas the difference between the treatment groups was not statistically significant for hemostasis between Tendo+6h and Tendo+48h or between Tendo+48h and Tendp+120h.

Table 28. Primary criterion-ITT population (Ref. Table 13, vol. 1.8)

	Vapreotide	Placebo	All	P-value[1]
N	98	98	196	
Hemostasis at 5 days	65 (66%)	49 (50%)	114 (58%)	p = 0.021
– Hemorrhage controlled at Tendo+6h	86 (88%)	59 (60%)	145 (74%)	p = 0.001
– Hemostasis between Tendo+6h and Tendo+48h	74 (76%)	63 (64%)	137 (70%)	p = 0.087
– Hemostasis at Tendo+48h	72 (73%)	53 (54%)	125 (64%)	*p = 0.005*
– Hemostasis between Tendo+48h and Tendo+120h	76 (78%)	70 (71%)	146 (74%)	p = 0.326

1 chi-square test

The sponsor's additional analysis using long-rank test and time to event indicated that the number of patients free of therapeutic failure was significantly higher in the vapreotide group than in placebo group at all times including Day 5 (p=0.017) (Table 29). This finding supports the primary endpoint.

Table 29. Percentage of patients free of therapeutic failure – ITT population (Ref. Table14, vol. 1.8)

Period	p (log-rank test)
Tendo to Tendo+6h	0.0001
Tendo+6h to Tendo+48h	0.003
Tendo to Tendo+48h	0.003
Tendo+48h to Tendo+120h	0.028
Tendo to Tendo+120h	0.017
Tendo to Day 42	0.006
Tendo+120h to Day 42	0.011

Analysis of the primary endpoint in PP as well as PPEV populations is summarized in Table 30 and Table 31, respectively, and are similar to those findings observed in the ITT population. In the PP population, analysis of the primary endpoint at the end of 5-day after endoscopic treatment demonstrated that hemostasis was achieved in 56% of patients receiving vapreotide compared with 43% of patients receiving placebo, a difference that was statistically significant (p=0.006). Similar results were observed in the PPEV, a subgroup of PP population with esophageal varices only (52% vs. 42%; p=0.008).

Table 30. Primary criterion – PP population (Ref. Table 16, vol. 1.8)

	Vapreotide	Placebo	All	P-value[1]
N	77	83	160	
Hemostasis at 5 days	56 (73%)	43 (53%)	99 (62%)	**p = 0.006**
– Hemostasis between Tendo+6h and Tendo+48h	60 (78%)	56 (67%)	116 (73%)	p = 0.139
– Hemostasis at Tendo+48h	58 (75%)	46 (55%)	104 (65%)	**p = 0.008**
– Hemostasis between Tendo+48h and Tendo+120h	66 (86%)	63 (76%)	129 (81%)	p = 0.117

1 Chi-square test

Table 31. Primary criterion PPEV population (Ref. Table 18, vol. 1.8)

	Vapreotide	Placebo	All	P-value[1]
N	72	82	154	
Hemostasis at 5 days	52 (72%)	42 (51%)	94 (61%)	**p = 0.008**
– Hemorrhage controlled at Tendo+6h	65 (90%)	49 (60%)	114 (74%)	**p = 0.001**
– Hemostasis between Tendo+6h and Tendo+48h	56 (78%)	55 (67%)	111 (72%)	p = 0.140
– Hemostasis at Tendo+48h	54 (75%)	45 (55%)	99 (64%)	**p = 0.009**
– Hemostasis between Tendo+48h and Tendo+120h	62 (86%)	62 (76%)	124 (81%)	p = 0.101

1 Chi-square

Agency's Analysis of Primary Endpoint-ITT population

The Agency's statistical reviewer performed analysis by-center to explore whether the superiority of vapreotide to placebo assessed by primary endpoint was dominated by certain center(Table 32). Centers with > 10 patients were analyzed separately as prespecified in the protocol.

Table 32. Proportion difference analysis by center ITT population (Agency's analysis)

CENTER[1]	PLACEBO (P) SUCCESS RATE % (N)	VAPREOTIDE (V) SUCCESS RATE % (N)	DIFFERENCE V – P (95% CI)	If 95% CI LOWER LIMIT > 0
Center 1	50.0 (10)	80.0 (10)	30.0 (-0.15, 0.67)	No
Center 2	54.6 (11)	63.6 (11)	9.0 (-0.34, 0.50)	No
Center 10	40.0 (5)	50.0 (6)	10.0 (-0.50, 0.65)	No
Center 12	66.7 (6)	62.5 (8)	- 4.2 (-0.54, 0.48)	No
Center 14	50.0 (8)	71.4 (7)	21.4 (-0.31, 0.68)	No
Center 18	**38.5 (13)**	**80.0 (15)**	**41.5 (0.02, 0.71)**	**Yes**
Centers with 5 to 10 patients pooled	54.1 (37)	67.7 (34)	13.6 (-0.1, 0.36)	No
Centers with < 5 patients pooled	37.6 (8)	28.6 (7)	-9.0 (-0.58, 0.41)	No
Overall results	**50.0 (98)**	**66.3 (98)**	**16.3 (0.024, 0.30)**	**Yes**

[1] Centers 1, 2, 10, 12, 14, and 18 had more than 10 patients enrolled and were analyzed separately

Table 32 shows that for all centers except center 18, the lower limits of the 95% two-sided confidence interval for the difference on hemostasis rates (vapreotide minus placebo) are not greater than zero, indicating that only in center 18 involving 28 patients (28/196, 14%), the hemostasis rate at the end of day 5 is significantly higher in the vapreotide group than the placebo group. However, the results in most centers show trends in favor of vapreotide except for center 12 and the pooled centers with less than 5 subjects. However, based on statistician's assessment, the heterogeneity across centers are statistically significant (Breslow-Day test, p=0.83).

To investigate whether or not the superiority of vapreotide to placebo reported by the sponsor was driven from center 18, an analysis excluding center 18 was performed.

Table 33. (Agency's table) Proportion difference analysis on primary endpoint ITT population Excluding center 18

	Placebo (P) success rate % (n)	Vapreotide (V) success rate % (n)	Difference V-P (95% CI)	p-value Chi-square test
ITT population excluding center 18	51.8 (85)	63.9 (83)	12.1 (-0.03, 0.27)	0.11

As shown in Table 33, after excluding center subjects of center 18, vapreotide was no longer superior to placebo (p=0.11) for the primary endpoint, i.e. in achieving hemostasis at the end day 5 (63% vs. 51%), indicating that the reported result was in fact driven from center 18 subjects. .

The significant findings shown at center 18 may be explained, at least partly, by involvement of a higher percentage of cirrhotic subjects with Child class A and B (81%; 22/27) in this center 18 compared with 56% (89/160) of subjects not at center 18 (Table 34). This observation is supported by the sponsor's post hoc analysis of pooled results across centers indicating that vapreotide was superior to placebo for the primary endpoint in subjects with Child class A and B (73% vs. 52%; 95% CI lower limit > 1), whereas for Child class C, the difference was not significantly different (58% vs. 48%) (sponsor's Table 2.7.3.4, Module 2.2)

Table 34. (Agency's Table) Percent of patients with Child-Pugh class A&B or C

CHILD-PUGH Class	CODE 'A&B' % (n/N)	CODE 'C' % (n/N)
Patients not at Center 18	56 % (89/160)	44% (71/160)
Patients at Center 18	81 % (22/27)	19 % (5/27)

MO comment: Although the Agency's by center analysis of primary endpoint in the ITT population indicate that the superiority of vapreotide to placebo was driven from center 18, results in most centers indicate a trend in favor of vapreotide. Further, although vapreotide was no longer superior to placebo when subjects at center 18 were excluded from the analysis, there was a 12% (63% vs. 51%) therapeutic gain in vapreotide treated subjects which is clinically significant in light of the serious conditions being treated.

When comparison is made with published data, the rate of control of bleeding with vapreotide in this study appears low, compared with that in previous studies using drugs from the same pharmacologic class (Besson I et al. N Engl J Med 1995; Sung JJy et al. Lancet 1995). However, the overall rates of hemostasis observed are similar in recent trials that used comparable criteria set by the Consensus Conference [e.g. 65% with somatostatin in association with sclerotherapy (Avgerinos A et al. Lancet 1997)].

Table 35 summarizes the sponsor's secondary end point analysis results in ITT population

Table 35. Secondary criteria ITT population (Ref. Table 15, vol. 1.8)

	Vapreotide	Placebo	All	P-value
N	98	98	196	
Endoscopy facilitation:				
– Active bleeding	28 (31%)	43 (46%)	71 (39%)	**p = 0.031**
– White nipple or no sign	63 (69%)	50 (54%)	113 (61%)	
Hemostasis at Tinf+6h (all the patients)	80 (82%)	52 (53%)	132 (67%)	**p = 0.001**
Hemostasis at Tinf+6h /endoscopy already performed at that time	71/86 (83%)	47/85 (55%)	118/171 (69%)	**p = 0.001**
Hemostasis at Tinf+6h /endoscopy not performed at that time	9/12 (75%)	5/13 (38%)	14/25 (56%)	p = 0.214
Rebleeding episodes :				
– Between Tendo+48h and Tendo+120h	3 (3%)	4 (4%)	7 (4%)	p = 0.713
– Between Day 5 and Day 7	5 (5%)	4 (4%)	9 (5%)	p = 1
– Between Day 7 and Day 30	8 (8%)	2 (2%)	10 (5%)	p = 0.100
– Between Day 30 and Day 42	7 (7%)	6 (6%)	13 (7%)	p = 0.846
– Between Day 5 and Day 42	16 (16%)	11 (11%)	27 (14%)	p = 0.379
At least one unit of blood transfused:				
– Between Tendo and Tendo 6h				
– Between Tendo+6h and Tendo+48h	44 (45%)	49 (50%)	93 (47%)	p = 0.474
– Between Tendo+48h and Tendo+120h	25 (26%)	40 (41%)	65 (33%)	**p = 0.006**
– Between Day 5 and Day 7	11 (11%)	12 (12%)	23 (12%)	p = 0.699
– Between Day 7 and Day 30	8 (8%)	9 (9%)	17 (9%)	p = 0.799
– Between Day 30 and Day 42	7 (7%)	7 (7%)	14 (7%)	p = 0.961
	4 (4%)	4 (4%)	8 (4%)	p = 1

Table 35. Secondary criteria ITT population (cont)

	Vapreotide	Placebo	All	P-value
N	98	98	196	
Total number of units of blood transfused:				
– Whole 6-week period	2 (0 ; 22)	3 (0 ; 19)	2 (0 ; 22)	p = 0.099
– During the first 5 days	2 (0 ; 8)	2 (0 ; 15)	2 (0 ; 15)	**p = 0.042**
– Between Day 5 and Day 42	0 (0 ; 20)	0 (0 ; 14)	0 (0 ; 20)	p = 0.911
Total duration of hospitalization (days) – All patients	12 (2 ; 42)	12 (1 ; 42)	12 (1 ; 42)	p = 0.224
Total duration (days) of hospitalization (patients surviving at Day 42)	(N = 84) 12 (4 ; 42)	(N = 77) 12 (5 ; 42)	(N = 161) 12 (4 ; 42)	p = 0.853
Number of deaths:				
– During the planned 42 days period of the study	14 (14%)	21 (21%)	35 (18%)	p = 0.215
– Between Tinf and Tendo+120h	5 (5%)	7 (7%)	12 (6%)	p = 0.551
– Between Day 6 and Day 42	9 (9%)	14 (14%)	23 (12%)	p = 0.290

For the secondary endpoint analysis significant benefits for vapreotide were observed for some of the multiple secondary endpoints analyzed (Table 35): 1) at the time of initial endoscopic procedure, bleeding was observed in a significantly smaller proportion of patients in the vapreotide group than in the placebo group (31% vs. 46%). This action can be attributed solely to vapreotide, as it was observed before initiation of endoscopic treatment; 2) control of bleeding also was observed in a significantly greater proportion of patients in the vapreotide group than in the placebo group at both 6h and 48h after endoscopy (82% vs. 53%); 3) during the 5-day treatment period, significantly fewer units of blood were administered to patients in the vapreotide group than in the placebo group 26% vs. 41%).

MO comment: Although the secondary endpoint findings support the primary endpoints, the reader is cautioned that the numerous p-values presented are not adjusted for multiple comparisons that have been performed.

SAFETY EVALUATION

Extent of exposure

Study drug was infused to all 227 patients who were enrolled into the study. However, this infusion was discontinued in the patients for whom the source of hemorrhage was found at endoscopy as not related to PHT (n=31).

In addition, the infusion was discontinued for 44 patients for other reasons. The main reasons were the following:

- Therapeutic alternative (n=11): 3 in vapreotide and 8 in the placebo group
- Therapeutic alternative associated with an additional endoscopy: 3 in vapreotide and 6 in placebo group)
- Other reasons (4 patients in vapreotide and 2 patients in placebo group)

The lack of initial control of bleeding and/or rebleeding was the main reason for a switch to a therapeutic alternative. The nature of this alternative was either a drug alone (mainly somatostatin, vasopressin or their analogues) or in association to an endoscopic treatment or balloon tamponade.

The median time between start of product infusion and premature discontinuation of infusion was 8 hrs. For 48 patients, the discontinuation took place within 24 hrs following the end of endoscopic treatment. No significant difference was found between the two treatment groups regarding rate of withdrawal, discontinuation due to therapeutic alternative, and median time to withdrawal (Table 36).

Table 36. Cause of early interruption of infusion of study product (Ref. Table 20, vol. 1.8)

	Vapreotide N=111	Placebo N=116
Bleeding not related to portal hypertension	N=13 n° 12, 59, 62, 98, 110, 172, 176, 185, 324, 341, 362, 401, 9176	N=18 n° 1, 16, 58, 91, 94, 108, 133, 143, 170, 230, 233, 261, 323, 343, 344, 361, 9001, 9143
Therapeutic alternative	N=3 n° 64, 93, 223	N=8 n° 63, 99, 111, 166, 227, 275, 355, 9108
Therapeutic alternative and new endoscopy	N=0	N=2 n° 171, 9016
Serious adverse event	N=2 n° 41, 158	N=0
Serious adverse event and therapeutic alternative	N=2 n° 202, 226	N=1 n° 54
Serious adverse event, therapeutic alternative and new endoscopy	N=3 n° 66, 135, 184	N=6 n° 49, 61, 173, 309, 9005, 9091
Serious adverse event followed by death	N=1 n° 74	N=2 n° 5, 144
Death	N=0	N=1 n° 225
Patient decided to withdraw	N=3 n° 136, 160, 353	N=0
Therapeutic endoscopy > To+24h	N=1 n°53	N=1 n°231
Therapeutic endoscopy > To+24h and other reason	N=1 n° 96	N=0
Other	N=4 n° 29, 56, 68, 10241	N=2 n° 26, 10275
Infusion interrupted on sponsor's request	N=0	N=1 n° 162
Total	20	24

Adverse Events (AEs)

Two hundred and eight nine AEs were recorded during the whole study.

By convention, natural complications of cirrhosis (such as rebleeding and encephalopathy) were also recorded as adverse events during the whole study. With these definitions, at least one adverse event occurred in 41% of the patients (42% under placebo and 40% under vapreotide) during study drug infusion.

The most frequently reported adverse events, and especially serious adverse events, were major clinical manifestations of portal hypertension:

- Central and peripheral nervous system disorders (18% of the patients) with a majority of encephalopathy,
- Liver and biliary system disorders (10% of the patients) with a majority of gastro-intestinal hemorrhage,
- "Body as a whole-general disorders" (6 % of the patients): 15% of the adverse events in the vapreotide group and 4% of the adverse events in the placebo group), with mainly hyperpyrexia (2 patients in placebo group and 4 patients in vapreotide group),
- Psychiatric disorders (5% of the patients) with a majority of delirium.
- Respiratory system disorders (5% of the patients), 10 in placebo group and 2 in vapreotide group,).

Intensity of these adverse events was mainly rated as moderate or severe. Most of them were classified as not related to the study drug.

The two treatment groups were comparable for the rate of patients with at least one concomitant symptom or one AE (Table 37). For most represented body system, the rate of patients who experienced an event were comparable between the two treatment groups, except during infusion for events classified in body as a whole organ class (p=0.037): 3 patients in placebo group and 10 patients in vapreotide group with no obvious clinical relevance; and for events classified as psychiatric disorders system organ class (p=0.022): 10 in placebo and 2 in vapreotide group. No difference was observed for the rate of patients with encephalopathy and GI hemorrhage linked to PHT during infusion.

Table 37. Number of patients with ≥ 1 AE (Ref. Table 23, vol. 1.8)

		Treatment Group					
		Placebo		Vapreotide		Total	
		N	%	N	%	N	%
Body system	WHO preferred term						
BODY AS A WHOLE - GENERAL DISORDERS	ASCITES	.	.	1	0.9	1	0.4
	CHEST PAIN	.	.	1	0.9	1	0.4
	FEVER	1	0.9	2	1.8	3	1.3
	HYPERPYREXIA	2	1.7	4	3.6	6	2.6
	INFLUENZA-LIKE SYMPTOMS	.	.	1	0.9	1	0.4
	MULTIPLE ORGAN FAILURE	.	.	1	0.9	1	0.4
	Total Chi-square test p = 0.037	3	2.6	10	9.0	13	5.7
CARDIOVASCULAR DISORDERS, GENERAL	CARDIAC FAILURE	.	.	1	0.9	1	0.4
	CIRCULATORY FAILURE	4	3.4	1	0.9	5	2.2
	HYPERTENSION	1	0.9	.	.	1	0.4
	Total	5	4.3	2	1.8	7	3.1
CENTR & PERIPH NERVOUS SYSTEM DISORDERS	CONVULSIONS	5	4.3	3	3.6	8	3.5
	CRAMPS LEGS	.	.	1	0.9	1	0.4
	ENCEPHALOPATHY Chi-square test p = 0.744	14	12.1	15	13.5	29	12.8
	HEADACHE	1	0.9	.	.	1	0.4
	HYPERTONIA	.	.	1	0.9	1	0.4
	VERTIGO	1	0.9	.	.	1	0.4
	Total Chi-square test p = 0.845	21	18.1	19	17.1	40	17.6
GASTRO-INTESTINAL SYSTEM DISORDERS	ABDOMINAL PAIN	2	1.7	1	0.9	3	1.3
	CONSTIPATION	.	.	1	0.9	1	0.4
	DIARRHOEA	.	.	1	0.9	1	0.4
	DUODENITIS	.	.	1	0.9	1	0.4
	GI HAEMORRHAGE	1	0.9	2	1.8	3	1.3
	NAUSEA	1	0.9			1	0.4
	OESOPHAGEAL ULCERATION HAEMORRHAGE	1	0.9	.	.	1	0.4
	Total Chi-square test p = 0.701	5	4.3	6	5.4	11	4.8

Table 37. Number of patients with ≥ 1 AE (Cont)

		Treatment Group					
		Placebo		Vapreotide		Total	
		N	%	N	%	N	%
Body system	WHO preferred term						
HEART RATE AND RHYTHM DISORDERS	BRADYCARDIA			1	0.9	1	0.4
	CARDIAC ARREST	2	1.7	1	0.9	3	1.3
	TACHYCARDIA SUPRAVENTRICULAR	1	0.9			1	0.4
	Total	*3*	*2.6*	*1*	*0.9*	*4*	*1.8*
LIVER AND BILIARY SYSTEM DISORDERS	COMA HEPATIC	2	1.7			2	0.9
	GI HAEMORRHAGE Chi-*square test p = 0.089*	9	7.8	3	2.7	12	5.3
	HAEMATEMESIS	2	1.7	2	1.8	4	1.8
	HAEMORRHAGE RECTUM	1	0.9			1	0.4
	HEPATIC FAILURE	3	2.6	1	0.9	4	1.8
	MELAENA	.	.	3	2.7	3	1.3
	Total Chi-*square test p = 0.216*	*14*	*12.1*	*8*	*7.2*	*22*	*9.7*
METABOLIC AND NUTRITIONAL DISORDERS	DIABETES MELLITUS	1	0.9	1	0.9	2	0.9
	HYPERGLYCAEMIA	2	1.7	1	0.9	3	1.3
	Total	*3*	*2.6*	*2*	*1.8*	*5*	*2.2*
MYO ENDO PERICARDIAL & VALVE DISORDERS	ANGINA PECTORIS	1	0.9			1	0.4
	Total	*1*	*0.9*	*0*	*0.0*	*1*	*0.4*
NEOPLASM	HEPATIC NEOPLASM	1	0.9			1	0.4
	HEPATIC NEOPLASM MALIGNANT	1	0.9	2	1.8	3	1.3
	Total	*2*	*1.7*	*2*	*1.8*	*4*	*1.8*
PLATELET,BLEEDING & CLOTTING DISORDERS	HAEMATOMA			1	0.9	1	0.4
	HAEMORRHAGE NOS	1	0.9	.		1	0.4
	THROMBOSIS	1	0.9	.	.	1	0.4
	Total	*2*	*1.7*	*1*	*0.9*	*3*	*1.3*
PSYCHIATRIC DISORDERS	DELIRIUM	7	6.0	2	1.8	9	4.0
	NERVOUSNESS	1	0.9	.	.	1	0.4
	WITHDRAWAL SYNDROME	2	1.7	.	.	2	0.9
	Total Chi-square test p = 0.022	*10*	*8.6*	*2*	*1.8*	*12*	*5.3*
RED BLOOD CELL DISORDERS	PANCYTOPENIA	.	.	1	0.9	1	0.4
	Total	*0*	*0.0*	*1*	*0.9*	*1*	*0.4*

Table 37. Number of patients with ≥ 1 AE (Cont)

		Treatment Group					
		Placebo		Vapreotide		Total	
		N	%	N	%	N	%
Body system	WHO preferred term						
RESISTANCE MECHANISM DISORDERS	INFECTION	.	.	1	0.9	1	0.4
	SEPSIS	1	0.9			1	0.4
	URINARY TRACT INFECTION	.	.	1	0.9	1	0.4
	Total	*1*	*0.9*	*2*	*1.8*	*3*	*1.3*
RESPIRATORY SYSTEM DISORDERS	BRONCHOSPASM	.	.	1	0.9	1	0.4
	DYSPNOEA	1	0.9	.	.	1	0.4
	PLEURISY	.	.	1	0.9	1	0.4
	RESPIRATORY DISORDER	5	4.3	3	2.7	8	3.5
	SPUTUM INCREASED	.	.	1	0.9	1	0.4
	Total Chi-*square test p = 0.937*	*6*	*5.2*	*6*	*5.4*	*12*	*5.3*
URINARY SYSTEM DISORDERS	OLIGURIA	1	0.9	.	.	1	0.4
	RENAL FAILURE ACUTE	2	1.7	.	.	2	0.9
	RENAL FUNCTION ABNORMAL	1	0.9	.	.	1	0.4
	Total	*3*	*2.6*	*0*	*0.0*	*3*	*1.3*
VASCULAR (EXTRACARDIAC) DISORDERS	CEREBROVASCULAR DISORDER	.	.	1	0.9	1	0.4
	VASCULITIS	1	0.9	.	.	1	0.4
	Total	*1*	*0.9*	*1*	*0.9*	*2*	*0.9*
WHITE CELL AND RES DISORDERS	LYMPHANGITIS	.	.	1	0.9	1	0.4
	Total	*0*	*0.0*	*1*	*0.9*	*1*	*0.4*

After randomization and within study drug infusion, there were 2 AEs classified by the investigator as possibly related to the study medication (vapreotide), including a mild transient hyperglycemia (patient # 29) and moderate generalized seizures which recovered (#9014). There were 3 AEs probably related to study medication in 2 patients, including diarrhea, hematoma and lymphangitis.

Deaths and Serious Adverse Events (SAEs)

During the study, 86 patients reported at least one SAE. The most frequently reported SAEs were in relationship to rebleeding for esophageal varices. A total of 42 patients died during the study: 17 in the vapreotide group and 25 in the placebo group. There 9 deaths after the end of the study: 4 in vapreotide group and 5 in placebo group. There were no death or SAEs reported during the study which were classified as AEs possibly or probably related to the study medication.

Clinical Laboratory Evaluation

Different laboratory parameters were evaluated before, during and at the end of product infusion. Two sets of parameters, namely glucose and AST-ALT, were monitored to control for potential adverse reactions with vapreotide, while the others were followed for general monitoring purposes.

Somatostatin and its analogues may interfere with glucose homeostasis following inhibition of both insulin and growth hormone release. In the present study, glucose level was initially above normal ranges for 33% of the patients of the placebo group and 27% of the patients of the vapreotide group, and returned within normal ranges at the end of infusion. One case of hyperglycemia and one case of diabetes mellitus were reported for each of the vapreotide and placebo groups.

ALT and AST presented small comparable variations between admission and day 5 in the placebo and vapreotide groups. ALT increased by a median of 4.0 in the placebo group, and by 5.0 in the vapreotide group.

AST decreased by a median of 6.0 in the placebo group, and by a median of 1.0 in the vapreotide group (differences between groups not significant p=0.207 for AST and p=0.941 for ALT).

Reviewer's Safety Conclusions

The short term use of vapreotide therapy was not associated with significant toxicity. The safety profile of vapreotide was comparable with that of placebo, suggesting that many events recorded were a reflection of the patient's underlying medical condition.

B. Study DEB-01-VAP-07 (supportive study)

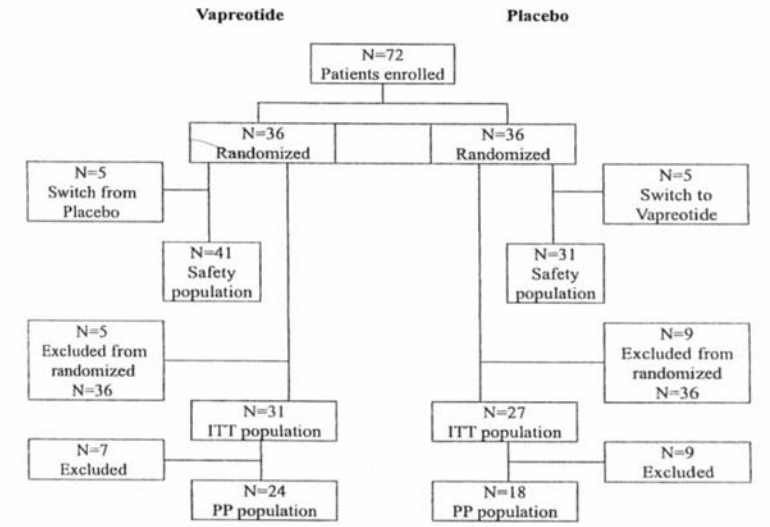
The study design was identical with the pivotal study with the following exception:

- This study was a single center, phase II *pilot* study designed to generate efficacy hypothesis. Thus, the study was not powered to observe statistically significant differences between treatment arms.

- The etiology of liver cirrhosis in the study population was secondary to bilharzia and concomitant chronic viral hepatitis. Patients with liver cirrhosis secondary to pure bilharzia were excluded.

Disposition of Subjects

Figure 3 summarizes the disposition of patients during the study.
Figure 3 (Ref. Module 5, vol. 1.21)



A total of 72 patients were enrolled and randomized into the study at a single center between April 14, 2002 and September 4, 2002. Five patients (# 10, 24, 36, 45, 69) randomized to placebo were found to have on day 3 vapreotide plasma levels above the limit of quantification without identifiable deviation and were included in vapreotide group for safety analysis.

Of the 72 enrolled and randomized patients, the ITT population was defined by excluding 5 patients in the vapreotide group (4 due to pure bilharzia etiology and 1 patient due to bleeding unrelated to PHT) and 9 patient in the randomized placebo group (5 due to pure bilharzia, 3 due to due to bleeding unrelated to PHT and 1 due to absence of endoscopy). Therefore, there were a total of 58 ITT patients.

Protocol Deviation

Table 38. Protocol deviation by treatment group (Ref. vol. 1.21, p-42)

Criteria	Patient
Non-inclusion criteria (pure bilharzia)	Vapreotide: 18, 32 ,42, 5 1 Placebo: 4, 16, 31, 45, 55
Missing Child-Pugh at admission	Vapreotide: 9, 32, 34 Placebo: 7, 21, 27, 46, 54, 55
No endoscopy	Placebo: 21
Study treatment overdose	Vapreotide: 12
Patient randomized to placebo, but vapreotide plasma levels found above quantification level on day 3	10, 24, 36, 45, 69

MO comment: The proportion of protocol deviation was comparable between the two treatment group.

Demographic and Baseline Characteristics

All patients were males. The mean age of patients in the placebo group was 52 years and was comparable with the mean age of patients in the vapreotide group (Table 39).

Table 39. Demographic characteristics - ITT population (modified reviewer's table)

	Placebo (n=27)	Vapreotide (n=31)	p-value
Age (years)			
Mean ± SD (min;max)	52.53 ± 7.88 (32.69;67.68)	53.80 ± 9.74 (28.04;71.76)	0.589
Gender, n (%) Male	27 (100)	31 (100)	

MO comment: Information on race was not recorded.

History of Liver Cirrhosis

The cause of liver cirrhosis was viral hepatitis associated with bilharzia in 83% of the ITT population and was comparable between the two treatment groups. Similar results were observed in the PP population (Table 40).

Table 40. History of Cirrhosis ITT population (Ref. Table 14.1.4, vol. 1.21)

			Placebo (N-27)		Vapreotide (N=31)	
			N	%	N	%
Parameter	p-value	Test				
Bilharzia (pure)			0	0.00	0	0.00
Viral hepatitis (pure)	0.7371	Fisher	4	14.81	6	19.35
Viral-hepatitis B (pure)			0	0.00	0	0.00
Viral-hepatitis C (pure)	0.481	Fisher	3	11.11	6	19.35
Viral-hepatitis B and C	0.466	Fisher	1	3.70	0	0.00
Mixed (hepatitis-bilharzia)	0.737	Fisher	23	85.19	25	80.65
Mixed (hepatitis B-bilharzia)	0.675	Fisher	2	7.41	4	72.90
Mixed (hepatitis C-bilharzia)	0.358	Chi-sq	18	66.67	17	54.84
Mixed (hepatitis B and C-bilharzia)	0.116	Fisher	0	0.00	4	12.90

MO comment: The etiology of the underlying disease in the study population is not representative of the U.S. population.

Child-Pugh Score at Admission

The Child-Pugh score was evaluated between admission to hospital and 24 hours after the end of endoscopic procedure (Table 41). In the ITT population, the majority of the patients were classified as Child B (55%) or A (29%), while only 9% the patients were classified as C. No significant difference was found for Child score between the two treatment groups.

Table 41. Child-Pugh Score at Admission – ITT population (Ref. Table 14.1.5, vol. 1.21))

Child Classification	Placebo n=25	Vapreotide n=29	Total n=54
A	7 (28%)	10 (34%)	17 (31%)
B	15 (60%)	17 (58.6%)	31 (59.2%)
C	**3 (12%)**	**2 (6.8%)**	**5 (9%)**

MO comment: there appears an imbalance in baseline prognostic indicator between this study and the aforementioned pivotal study. In the pivotal study, 40% of the patients suffer from poor liver dysfunction (Child class C) compared with 9% of the patients in this study. This difference may have an impact on the outcome of the study. In cirrhotic patients with acute variceal bleeding, the level of liver dysfunction as expressed by Child-Pugh score is the most important determinant of survival. Subjects with the highest score (Class C) have a poor prognosis.

Origin of Hemorrhage and Endoscopic treatment (ITT population)

In 86% of the ITT population, the principal origin of hemorrhage was esophageal varices and was comparable between the tow treatment groups (Table 42).The main endoscopic treatment applied was sclerotherapy and was similar between the treatment groups.

MO comment: Available data indicate that for control of variceal bleeding, the two endoscopic methods, i.e. sclerotherapy and band ligation produce comparable results.

Table 42. Origin of hemorrhage - ITT population (Ref. Tables 14.1.6 and 14.1.7 vol. 1.21)

	Placebo n = 27	Vapreotide n = 31
Source of bleeding, n (%)	27	31
Esophageal varices	23 (85)	27 (87)
Gastric varices	4 (15%)	4 (13%)
PHT gastropathy	2 (7)	4 (13%)
Endoscopic therapy, n (%)		
Sclerotherapy	22 (81)	28 (90)
Band ligation	2 (7)	2 (6)
Glue or other	3 (3)	4 (12)

Treatment Completion

All patients in the ITT population received study medication. Forty-five patients (78%) in the ITT population completed the 5-day study treatment: 24 (77%) in the vapreotide group and 21 (77%) in the placebo group. Thirty-seven patients (88%) in the PP population completed the treatment: 22 (91%) in the vapreotide and 15 (83%) in the placebo group.

Table 43 summarizes the reasons for treatment discontinuation per treatment arm in the ITT and PP populations. It appears therapeutic alternative was the main reason for discontinuation treatment in both the ITT and PP population.

Tale 43.Treatment discontinuation during the first 5 days (Ref. vol. 1.21, p-46)

Reasons for treatment discontinuation		Placebo		Vapreotide		Total	
		N	%	N	%	N	%
ITT	Therapeutic alternative	3	11.11	3	9.68	6	10.34
	Hospital discharge before day 5	1	3.70	2	6.45	3	5.17
	Death	2	7.41	1	3.23	3	5.17
	Other AE	1	3.70	0	0.00	1	1.72
	Consent withdrawn	1	3.70	2	6.45	3	5.17
	Other cause	1	3.70	1	3.23	2	3.45
PP	Therapeutic alternative	2	11.11	2	8.33	4	9.52
	Hospital discharge before day 5	0	0.00	1	4.17	1	2.38
	Death	2	11.11	0	0.00	2	4.76
	Other AE	1	5.56	0	0.00	1	2.38

Study Completion

In the ITT population 41 patients (70%) completed the study: 23 in the vapreotide group and 18 in the placebo group. In the PP population 35 (83%) patients completed the study: 22 in the vapreotide group and 13 in the placebo group.

Reasons for study discontinuation are presented in Table 44 in the ITT and PP populations. Death was the main cause for not completing the study.

Table 44. Study discontinuation (Ref. vol. 1.21, p-56)

Reason for study premature discontinuation	ITT		PP	
	Placebo	Vapreotide	Placebo	Vapreotide
Death	7	4	5	1
Withdrawal of consent	1	2	0	0
Patient lost to follow up	1	1	0	1
Other	0	1	0	0
Total	9	8	5	2

Concomitant Medication

In the ITT population, the most frequent concomitant medications mentioned were: antacids, drugs for treatment of peptic ulcer and flatulence, anti-bacterial for systemic use, anti-hemorrhagic, bile and liver therapy, diuretics and vitamins. Similar results were observed in the Safety and PP populations.

Antibiotics

During at least five days following the start of study drug administration, almost all patients received antibiotics (mainly Flumox®, a combination of amoxicillin and flucloxacillin).

MO comment: Prophylactic antibiotic therapy is recommended in cirrhotic patients with variceal bleeding.

Anti-hemorrhagic/Antacids
During their hospitalization, most patients (98%) received at least one anti-hemorrhagic drug, mainly etamsylate, tranexamic acid and/or vitamin K. Most patients (98%) were treated with at least one antacid drug (mainly omeprazole, ranitidine and/or Mucogel®) after their randomization in the study.

Beta-blockers/Diuretics
Four patients (one randomized on placebo and three on vapreotide) were treated with beta-blocker (mainly propanolol) before their randomization. Twenty-four patients (12 on placebo, 12 on vapreotide) received a beta-blocker (mainly propanolol) after discontinuation of the study drug. Before randomization, diuretics, mainly furosemide and/or spironolactone, were administered in 22 patients (38%): 9 in the placebo group and 13 in the vapreotide group. Most of them were stopped at randomization.

MO comment: The use of B-blocker during the study period may confound the outcome of the study since B-blockers are indicated for prevention of variceal rebleeding on a long-term basis. However, in this study the use B-blocker was evenly distributed between the treatment groups.

Sponsor's Efficacy Results

In this pilot study, analysis of the primary endpoint in the ITT population demonstrated that during the period of 5 days following completion of endoscopic therapy, the rate of hemostasis was 71% in the vapreotide group compared with 59% in the placebo group, a difference that is not statistically significantly different (p=0.349) (Table 45) . Similar results were observed for the PP population (83% vs. 66%; p=0.281)

Table 45. Primary endpoint in ITT and PP population (Ref. Module 5, vol. 1.21)

				Placebo		Vapreotide	
				N	% 95%CI	N	% 95%CI
Population	p-value	Test					
ITT	0.349	Chi sq	NO	11	40.74 [22.39; 61.20]	9	29.03 [14.22; 48.04]
			YES	16	59.26 [38.80; 77.61]	22	70.97 [51.96; 85.78
PP	0.281	Fisher	NO	6	33.33 [13.34; 59.01]	4	16.67 [4.74; 37.38]
			YES	12	66.67 [40.99; 86.66]	20	83.33 [62.62; 95.26]

For multiple secondary endpoints analyzed, no significant difference was observed between the treatment groups in both ITT and PP patient populations except for survival and treatment success at 42 days in the PP population. A statistically significant difference was observed between the two treatment groups in term of 42-day survival in pp population, with lower death

incidence in the vapreotide group (4.2%) compared with placebo (27.8%) (Table 46). As well, the proportion of patients with treatment success over 42 days was significant higher in the vapreotide group that placebo group (p=0.047) (Table 47).

MO comment: It should be noted that numerous p-values presented are not adjusted for multiple comparisons that have been performed for the secondary endpoints. Further, the clinical significance of these results is questionable in light of the lack of demonstration of significant difference in the primary endpoint.

Table 46. Death occurred between admission and day 42 (Ref. vol. 1.21, p-51)

Population	Treatment	N	%
Safety	Placebo (N=31)	8	25.80
	Vapreotide (N=41)	6	14.63
ITT	Placebo (N=27)	7	25.93
	Vapreotide (N=3 1)	5	16.13
PP	Placebo (N=l 8)	5	27.78
	Vapreotide (N=24)	1	4.17

Table 47. Treatment success over 42 days (Ref. vol. 1.21, p-54)

			Placebo		Vapreotide	
			N	%	N	%
Population	p-value	Test				
ITT	0.125	Chi-sq	12	44.44	20	64.52
PP	0.047	Chi-sq	9	50.00	19	79.17

Reviewer's Efficacy Conclusions:

Despite the involvement of higher percentage of cirrhotic patients with Child class A and B (88%) in this study, the findings failed to confirm the results observed in the pivotal study. The difference may be explained by the small study size, and at least partly, by the schistosomiasis contribution to PHT. Available data suggest that variceal bleeding secondary to presinusoidal blockade as observed in schistosomiasis, but also during the physical obstruction of the portal vein by thrombus or a tumor, dose not respond to treatment with somatostatin.

SAFETY EVALUATION

Extent of Exposure

Seventy two patients in the safety population received the study medication during the study. Mean extent of exposure was 4.1 days for vapreotide group and 3.4 days for placebo group.

Adverse Events (AEs)

Sixty six (92%) patients in the safety population reported a total of 173 AEs during the study (Table 40). The incidence of AEs were comparable between the two treatment groups (about 90% in each treatment group). According to the investigators all AEs observed during the study were not related with the study drug.

SAEs and Death

SAEs were reported in 40% of the ITT population and it was comparable between the two treatment groups: in 36% of patients in vapreotide group and 45% of patients in the placebo group (Table 48). A total of 18 patients died during the study: 6 in vapreotide group and 8 in the placebo group. All SAEs and death were considered not related to the study medication

Table 48. Overview of adverse events (Ref. vol. 1.21, p-58)

	Vapreotide			Placebo			Total		
	N	(%)	(m)	N	(%)	(m)	N	(%)	(m)
Total number of patients	41			31			72		
Patients with adverse events	38	92.68	104	28	90.32	69	66	91.67	173
Intensity									
Mild	19	46.34	31	14	45.16	18	33	45.83	49
Moderate	31	75.61	56	20	64.52	37	51	70.83	93
Severe	12	29.27	17	11	35.48	14	23	31.94	31
Relationship (derived)									
Not related	38	92.68	104	28	90.32	69	66	91.67	173
Related	0	0.00	0	0	0.00	0	0	0.00	0
Serious adverse events	15	36.59	22	14	45.16	21	29	40.28	43
Deaths	6	14.63	6	8	25.81	9	14	19.44	15

N = Number of patients, % = Percentage of patients, (m) = Number of mentions

The most frequently mentioned SOC categories (> 20% of patients), which were related to patient's condition, were (Table 49):

- General disorders and administration site conditions: 80% in the vapreotide group and 68% in the placebo group;
- Gastrointestinal disorder: 43% in the vapreotide group and 32% in the placebo group;
- Hepatobiliary disorders: 26% in the vapreotide group and 32% in the placebo group.

The most frequently mentioned AEs (>20% of patients) were:

- Pyrexia: 78% in the vapreotide group and 64%) in the placebo group;
- Esophageal varcieal hemorrhage: 24% in the vapreotide group and 32% in the placebo group

Table 49. AEs by SOC (Ref. vol. 1.21, p-59)

			Vapreotide			Placebo		
			N	(%)	(m)	N	(%)	(m)
SOC	**p-value**	**Test**						
BLOOD AND LYMPHATIC SYSTEM DISORDERS	1.000	Fisher	1	2.44	1	1	3.23	1
GASTROINTESTINAL DISORDERS	0.316	Chi sq	18	43.90	23	10	32.26	15
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	0.216	Chi sq	33	80.49	40	21	67.74	28
HEPATOBILIARY DISORDERS	0.616	Chi sq	11	26.83	13	10	32.26	12
INFECTIONS AND INFESTATIONS	1.000	Fisher	1	2.44	1	0	0.00	0
INJURY. POISONING AND PROCEDURAL COMPLICATIONS	1.000	Fisher	1	2.44	1	0	0.00	0
METABOLISM AND NUTRITION DISORDERS	1.000	Fisher	2	4.88	2	1	3.23	2
NERVOUS SYSTEM DISORDERS	0.765	Fisher	9	21.95	10	5	16.13	6
PSYCHIATRIC DISORDERS	1.000	Fisher	1	2.44	1	0	0.00	0
RENAL AND URINARY DISORDERS	1.000	Fisher	1	2.44	1	1	3.23	1
RESPIRATORY. THORACIC AND MEDIASTINAL DISORDERS	0.331	Fisher	8	19.51	8	3	9.68	3
SURGICAL AND MEDICAL PROCEDURES	1.000	Fisher	1	2.44	1	0	0.00	0
VASCULAR DISORDERS	1.000	Fisher	2	4.88	2	1	3.23	1

N = Number of patients, % = Percentage of patients, (m) = Number of mentions

Evaluation of Laboratory Parameters

The changes over time in laboratory values were compared between the two treatment groups by analysis of variance. The change over time was for plasma creatinine mean increase of 0.2 mg/dl in the placebo group and 0.1 mg/dl in the vapreotide group. However, the post treatment mean of both groups remained within normal range. Statistically significant difference changes were observed in glucose (mean decrease of 30.4 mg/dl in the placebo group and 42.4 mg/dl in the vapreotide group). These changes were not considered as clinically relevant. Overall, there was no statistically significant difference between treatments for any laboratory parameters

Reviewer's Safety Conclusions

The safety profile of the short-term vapreotide therapy is similar to that of placebo, suggesting that many events recorded were a reflection of the patients' underlying disease.

C. Study DEB-97-VAP-02 (terminated study)

Study DEB-97-VAP-02 is a multicenter, randomized, double-blind, placebo controlled phase III study that was initiated in July 1997 in Hong Kong concurrently with the pivotal study (DEB-96-VAP-14) using identical study design. The estimated sample size was 150 patients. The study was terminated in June 2001 due to a very slow enrollment rate and major protocol violation, consequently, the analysis was only restricted to the safety criteria. Up on the Agency's request, the efficacy data were submitted as an amendment on September 22, 2004.

RESULTS

Disposition of patients

One hundred and thirty-six patients were included and randomized into the study between July 18, 1997 and June 28, 2001, in 5 centers, including Hong Kong (3 centers), Singapore (1 center), and Malaysia (1 center).

Of 136 patients, 104 patients had bleeding due to PHT and were included in the ITT population, and 32 patients had bleeding unrelated to PHT and were excluded from the efficacy analysis (Table 50). The origin of bleeding was esophageal varices in 58% of the patients, gastric varices in 17%, and PHT gastropathy in 1% of patients and not due to PHT in 24% of patients (Table 51).

Table 50. Description of populations studied (Ref. amendment, vol. 1.3, Table 2)

	Vapreotide	Placebo	All
Randomized patients	70	66	136
Safety population	69	65	134
ITT population	51	51	102[1]
PP population	42	38	80

[1] one patient included twice on two different occasions in the study (#66) and 1 patient did not receive any dose of treatment

Table 51. Origin of hemorrhage (Ref. amendment vol. 1.3, Table 1)

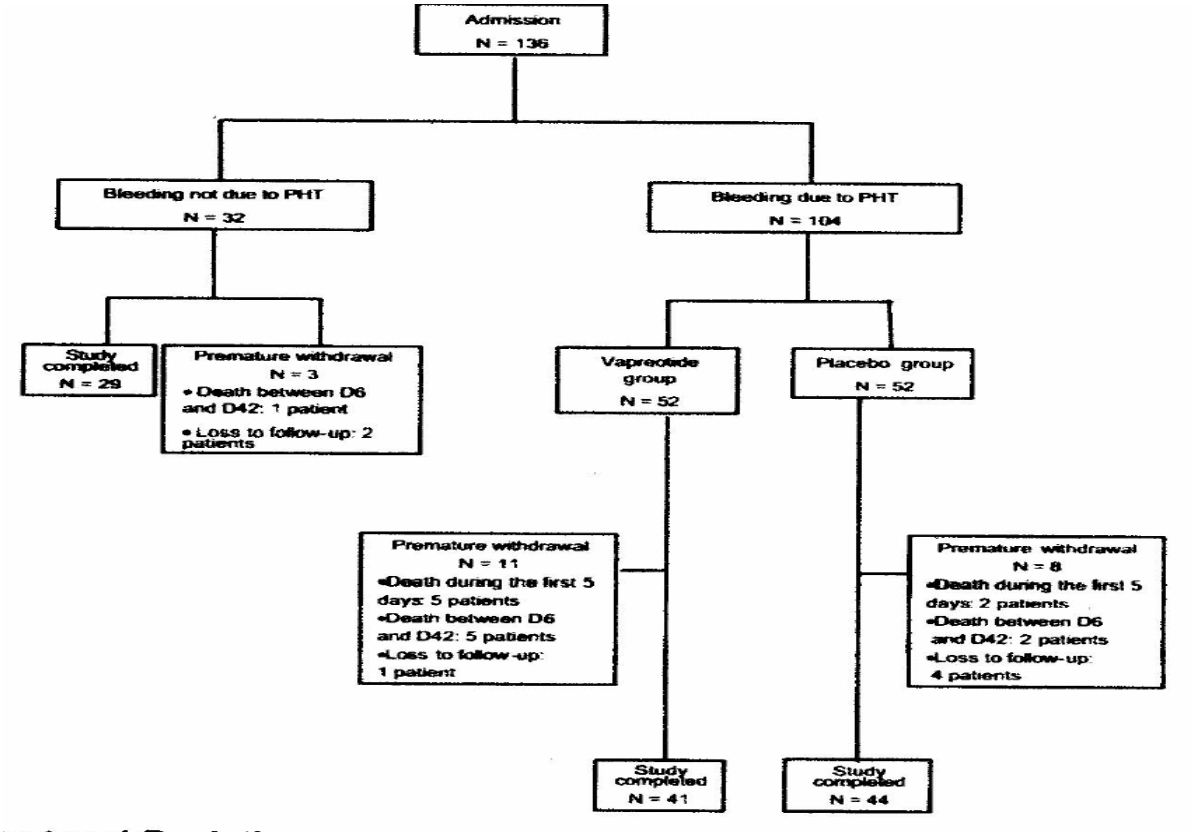
	Vapreotide	Placebo	All
N	70	66	136
Esophageal varices	39 (56%)	40 (61%)	79 (58%)
Gastric varices	12 (17%)	11 (17%)	23 (17%)
Portal hypertensive gastropathy	1 (1%)	1 (2%)	2(1%)
Not due to portal hypertension	18(26%)	14 (21%)	32 (24%)

Twenty-two patients did not complete the study (Figure 4). The reason for premature withdrawal was:

- Death between the first 5 days concerning 7 patients (placebo group: patients n° 205 and 9018; vapreotide group: patients n° 25, 61, 9017, 9031 and 9038);

- Death between Day 6 and Day 42 concerning 8 patients: 7 patients had bleeding due to portal hypertension (placebo group: patient n° 52 and 9201; vapreotide group: patients n° 21, 101. 106, 405 and 9020) and one patient had bleeding not due to portal hypertension (placebo group: patient n° 9039);
- Lost to follow-up concerning 7 patients: 5 patients had bleeding due tot portal hypertension (placebo group: patient n° 20, 28, 65 and 407; vapreotide group: patient n° 9021) and 2 patients had bleeding not due to portal hypertension (placebo group: patient n° 27; vapreotide group: patient n° 44).

Figure 4 (Ref. figure, amendment vole 1.3)



Protocol Deviations

During the whole study, among the patients in ITT population, there were 22 patients with at least one major deviation (13 patients in the placebo group and 9 patients in the vapreotide group) (Table 52).

. The reasons for major protocol violations were:

- Randomization after endoscopy;
- Administration of forbidden treatment;
- Study drug stopped by error,
- Time between hemorrhage and randomization > 24h;

- Error in administration of treatment;
- Received the wrong box of treatment;
- No endoscopic treatment at initial endoscopy.

Table 52. Major protocol deviation – ITT population (Ref. Table 3, amendment vol. 1.3)

	Vapreotide	Placebo	All
N	51	51	102
Number of patients with at least one major deviation during the whole study	9	13	22
List of deviations:			
Randomization after endoscopy	Patients n" 1, 10, 9010	Patients n° 8, 9. 62, 9002, 9004, 70	
Administration of non permitted treatment	Patient n° 61, 98	Patients n° 9, 89, 102	
Study drug stopped by error	Patients n" 54, 9205	Patients n° 93, 9201	
Time between hemorrhage and randomization > 24h	Patient n" 15	Patients n° 9, 22	
Error in administration of treatment	Patient n° 202	Patient n° 53	
Received the wrong box of treatment	Patient n° 1		
No endoscopic treatment at initial hemorrhage		Patient n° 63	

MO comment: The distribution of protocol violations is well balanced between the two treatment groups. This reviewer finds no obvious quantitative or qualitative difference in protocol violations between this study and the pivotal study.

Extent of Exposure

Study drug was infused to 134 patients among the 136 patients who were included. However, this infusion was discontinued in the patients for whom the source of hemorrhage was found at endoscopy as not due to portal hypertension (N=31).
In addition, among the patients with hemorrhage due to portal hypertension, the infusion was discontinued for 23 patients in the ITT population, 16 of which were in the PP population. The main reasons for discontinuation were the following (Table 53):

- Therapeutic alternative;
- Therapeutic alternative associated with a new endoscopy;
- Other reasons.

Patients deemed to have received a full 5 days of infusion should have used 11 vials of product (one for the bolus, and 2 per day for 5 days). Some patients received only 8 vials, while others had used 12 vials, this difference being likely related to discrepancies between the posted and the real infusion rate with the pumps used.

The absence of initial control of hemorrhage and/or massive hemorrhage was the main reasons for a switch to a therapeutic alternative. The nature of alternative was balloon tamponade, or endoscopic treatment, or drug (somatostatin), or the association of several therapeutic

alternatives. The median time between the start of infusion and premature discontinuation of infusion was 7.5 hrs (range 0.2 to 96 hrs).

Table 53. Cause of early interruption of infusion of study product (Ref. amendment vol. 1.3, Table 4)

Reasons of early interruption	Vapreotide	Placebo
Decision of the patient	N = 1 Patient n" 210	-
Death	N = 1 Patient n° 9038	-
Other cause	N = 5 Patients n° 54, 66, 106, 202, 402	N = 4 Patients n° 9, 53, 93, 9201
Therapeutic alternative	N = 5 Patients n° 21 , 25, 88, 9007, 9017	N = 1 Patients n" 9018
Therapeutic alternative and new endoscopy	N = 3 Patients n° 101, 9030, 9031	N = 2 Patient n° 87, 205
Therapeutic alternative and other cause	N = 1 Patient n° 72	
Total	16	7

MO comment: More patients in the vapreotide PP population had an interruption of drug infusion than placebo PP population (9 vs. 3) due to therapeutic alternative, which is indicative of treatment failure.

Demographics and Baseline Characteristics (ITT population)

Male patients accounted for 71% of the placebo group and 84% of the vapreotide group. The mean age was 47 years, the mean weight and height was 58 kg and 161 cm, respectively, and were comparable between the two treatment groups (Table 54).

Table 54. Demographic characteristics – ITT population (Ref. amendment vol. 1.3

	Vapreotide	Placebo	All	P-value
N	51	51	102	
Sex - Male - Female	 43(84%) 8 (16%)	 36 (71%) 15 (29%)	 79 (78%) 23 (23%)	0.097*
Age (years)	57.3112.53	55.7±10.6	56.5±11.6	0.4904
Weight (kg)	N=45 58.5±9.4	N=47 60.4±12.4	N=92 59.5+.11.0	0.41 34
Height (cm)	N=35 161.9*8.1	N=44 161.&8.5	N=79 161.718.3	0.6395

Concomitant Diseases and Concomitant Treatments

At least one past and/or concomitant disease were reported at entry in the study for 75% of the patients, including 78% of the patients in the placebo group and 73% of the patients in the vapreotide group (Table 55). As expected the majority of patients had digestive tract ailments.

The proportion of patients with at least one past and/or concomitant disease at admission was not significantly different between treatment groups.

Table 55. Past and concomitant diseases at admission (Ref. amendment vol. 1.3 table 6)

	Vapreotide	Placebo	All	p-value
N	51	51	102	
At least 1 previous medical history	37 (73%)	40 (78%)	77 (75%)	0.490"
Abnormal clinical examination				
Cardiovascular system	7(11%)	10(13%)	17 (12%)	
ENT/lungs system	3(5%)	5(7%)	8(6%)	
Digestive tract	26 (39%)	28 (36%)	54 (38%)	
Uro-genital tract	5(8%)	4(5%)	9(6%)	
Nervous system	5 (8%)	4 (5%)	9(6%)	
Endocrine system	9 (13%)	11 (14%)	20 (14%)	
Bones-joints	5(8%)	6(8%)	11 (8%)	
Blood	3(5%)	2 (3%)	5(4%)	
Infections/parasites	4 (6%)	7 (9%)	11 (8%)	

At admission, 41% of the patients presented at least one concomitant treatment, including 33% of the patients in the placebo group and 49% of the patients in the vapreotide group, a difference which was not statistically significant (Table 56).

Table 56. Concomitant treatments ad admission- ITT population (Ref. amendment vol. 1.3, table 7)

	Vapreotide	Placebo	All	p-value
N	51	51	102	
At least one concomitant treatment before randomization	25 (49%)	17 (33%)	42 (41%)	0.108°
Concomitant treatment during product infusion				
Alimentary tract and metabolism medication	18 (72%)	14 (82%)	32 (76%)	
General anti-infectives for systemic use medication	2 (8%)	2 (12%)	4 (10%)	
Cardiovascular medication	14 (56%)	11 (65%)	25 (60%)	
Blood and blood forming organs	10 (40%)	9 (53%)	19 (45%)	
Nervous system	2 (8%)	2 (12%)	4 (10%)	
Systemic hormonal preparations, excluding sex hormones	1 (4%)	1 (6%)	2 (5%)	
Antineoplastic and immunomodulating drugs	1 (4%)	0 (0%)	1 (2%)	
Respiratory system	1(4%)	0(0%)	1(2%)	
Other	1 (4%)	0 (0%)	1 (2%)	

MO comment: no prophylactic antibiotic therapy was given systematically in this study.

History of the Disease

The cause of cirrhosis was mainly viral hepatitis alone (45%) or alcoholism alone (38%). These proportions were not significantly different between the two groups (Table 49).

The median time elapsed between clinical and/or histological diagnosis of cirrhosis and inclusion was 3 years (range 0 to 17 years).

Previous history of ascites was reported in 33% of the patients and previous episode of hepatic encephalopathy in 6% of the patients. The presence of esophageal varices was documented for 39% of all patients, with 31% in placebo group and 47% in vapreotide group. Sixty-seven percent of patients had previous episodes of hemorrhage due to portal hypertension, with important differences between the vapreotide and placebo groups suggesting that on average the disease was more serious in the vapreotide group at baseline; a higher amount of patients had more than 2 previous episodes in the vapreotide group (31%) versus the placebo group (11%).

MO comment: The sponsor's assertion that the disease was more serious in vapreotide group than placebo -because of a higher proportion of patients had > 2 episodes of bleeding in vapreotide group versus the placebo group - appears misleading. As shown in Table 49 numerically there are ***5 patients*** *in the vapreotide group and one patient in the placebo group who had > 2 episodes of bleeding. Such a small number of patients will have a negligible impact on the outcome of the study.*

Forty-six percent of patients were previously treated for portal hypertension. Of these patients, 47% (22 patients) were previously treated with endoscopic treatment (with or without further therapy) and 53% (25 patients) with beta-blockers alone (Table 57). A higher number of patients in the vapreotide ITT population had previously received endoscopic treatment (14 patients) compared to placebo (8 patients).

Table 57. History of cirrhosis – ITT population (Ref. amendment vol. 1.3, table 8)

	Vapreotide	Placebo	All	P-value
N	51	51	102	
Etiology:				0.750
Alcoholism alone	19 (37%)	20 (39%)	39 (38)	
Alcoholism/viral hepatitis	3 (6%)	3 (6%)	6 (6%)	
Alcoholism/biliary	1 (2%)	0 (0%)	1 (1%)	
Viral hepatitis alone	21 (41%)	25 (49%)	46 (45%)	
Biliary	2 (4%)	1 (2%)	3 (3%)	
Other	5 (10%)	2 (4%)	7 (7%)	
Time from diagnosis of cirrhosis to inclusion (years)	N-42 2 (0; 17)	N-45 2 (0; 15)	N=87 2 (0; 17)	0.321
Previous history of ascites	17 (33%)	17 (33%)	34 (33%)	1.000
Previous history of hepatic encephalopathy	4 (8%)	2 (4%)	6 (6%)	0.678
Known esophageal varices • Time from diagnosis to inclusion (years)	24 (47%) 2.5 (0:11)	16 (31%) 2 (0 : 13)	40 (39%) 2 (0: 13)	0.105
Previous episodes of hemorrhage due to portal hypertension • 1 episode • 2 episodes • More than 2 episodes	N=24 17 (74%) 10 (63%) 1 (6%) 5 (31%)	N=16 9 (56%) 7 (78%) 1 (11%) 1 (11%)	N=40 26 (67%) 17 (68%) 2 (8%) 6 (24%)	0.433
Previous treatment for portal hypertension:	26 (51%)	21 (41%)	47 (46%)	0.321
• Beta blockers alone	12 (46%)	13 (62%)	25 (53%)	
• Beta blockers/endoscopic treatment	9 (35%)	3 (14%)	12 (26%)	
• Nitrates/endoscopic treatment	0 (0%)	1 (5%)	1 (2%)	
• Endoscopic treatment alone	5(19%)	4 (19%)	9 (19%)	
Type of endoscopic treatment:	N=14	N=8	N=22	
• Band ligation alone	5 (36%)	3 (38%)	8 (36%)	
• Band ligation/cyanoacrylate	1 (7%)	0 (0%)	1 (5%)	
• Band ligation/cyanoacrylate/ sclerotherapy	0 (0%)	1 (13%)	1 (5%)	
• Band ligation/sclerotherapy	1 (7%)	1 (13%)	2(9%)	
• Band ligation/other	1 (7%)	0 (0%)	1 (5%)	
• Cyanoacrylale alone	1 (7%)	1 (13%)	2 (9%)	
• Cyanoacrylale/ sclerotherapy	3 (21%)	0 (0%)	3 (14%)	
• Sclerotherapy alone	2 (14%)	2 (25%)	4 (18%)	

Monitoring

At admission, 42% of the patients presented with hematemesis and/or melena. whereas at the end of endoscopic treatment, 14% of the patients did (Table 58). The proportion of patients with hematemesis and/or melena at admission and at the end of endoscopic treatment was not significantly different between the two treatment groups. Both groups had similar hemoglobin

levels at admission (Table 58). There was no difference between the two treatments groups in the source of hemorrhage or type of endoscopic technique used to treat varices (Table 59).

MO comment: It appears that the proportion of patients having gastric varices in this study (23%) is higher than the pivotal study (2%) and supportive study (13%).

Table 58. Monitoring at admission-ITT population (Ref. amendment vol. 1.3. Table 10)

	Vapreotide	Placebo	All	p-value
N	51	51	102	
Bleeding				0.194
Hematemesis	10 (20%)	12 (24%)	22 (22%)	
Melena	8 (16%)	3 (6%)	11 (11%)	
Hematemesis+ melena	7 (14%)	3 (6%)	10 (10%)	
None	26 (51%)	33 (65%)	59 (58%)	
Hemoglobin (g/dl)	9.5±2.1	9.7±2.6	9.6±2.3	0.739
General complications	7 (14%)	7 (14%)	14 (14%)	1.000
Transfusion	1 (2%)	3 (6%)	4 (4%)	0.617
Infusion of plasma	10 (20%)	9 (18%)	19 (19%)	0.799

Table 59. Current episode of variceal bleeding-ITT population (Ref. amendment vol. 1.3, Table 11)

	Vapreotide	Placebo	All	p-value
N	51	51	102	
Time between hemorrhage and hospitalization (hour;min)	N=49 4:0022 (-8:36:21:54)	N=48 3:18 (0 : 22:18)	N=97 3:18 (-8:36:22:18)	0.629
Source of hemorrhage:				
Esophageal varices	38 (75%)	39 (77%)	77 (76%)	0.818
Portal hypertensive gastropathy	1 (2%)	1 (2%)	2 (2%)	1.000
Gastric varices	12 (24%)	1 (22%)	23 (23%)	0.813
Physical obliteration of varices:				
Cyanoacrylate and lipiodol	13 (26%)	11 (22%)	24 (24%)	0.641
Band ligation	37 (73%)	37 (73%)	74 (73%)	1.00
Other	4 (8%)	2 (4%)	6 (6%)	0.678

Child-Pugh Score

The Child-Pugh score was evaluated between admission to hospital and 24 hrs after the end of endoscopic procedure (Table 60). In the ITT population, the majority of patients were classified as B (50%) or C (35%), and the minority was classified as A (14%). The two treatment groups were comparable in this regard.

Table 60. Child-Pugh score in ITT population (Ref. amendment vol. 1.3, Table 3.28)

	Vapreotide (n=51)	Placebo (n=51)	All (n=102)
Child-Pugh score[1] Mean (SD)	8.66 (2.09)	8.98 (2.32)	8.82 (2.20)
Child class[2]			
A	8 (17%)	6 (12%)	14 (14%)
B	24 (51%)	25 (50%)	49 (50%)
C	15 (31%)	19 (38%)	34 (35%)
95% CI (5 Class C)	[16.9%;41.9%]	24.0%;50.5%]	[24.2%;42.5%]

[1] Class A score=5,6; Class B score=7.9; Class C score ≥ 10
[2] Child classification was missing in 5 patients: 4 in the vapreotide and 1 in the placebo group

Sponsor's Efficacy Analysis Results

Analysis of the primary endpoint in the ITT population demonstrated that during the period of 5-day infusion following completion of endoscopic treatment, hemostasis was achieved in 55% of patients receiving vapreotide compared with in 51% of patients receiving placebo (Table 61), a difference which is not statistically significant (p=0.692). Similar results were observed in the PP population (52% vs. 50%; p=0.832) (Table 62).

Table 61. Primary criterion-ITT population (Ref. amendment vol. 1.3, table 23)

	Vapreotide	Placebo	All	p-value
n	51	51	102	
Hemostasis at Tendo+6h	35 (69%)	27 (53%)	62 (61%)	0.105
Hemostasis at Tendo+48h	30 (59%)	26 (51%)	56 (55%)	0.426
Hemostasis at 5 days	**28 (55%)**	**26 (51%)**	**54 (53%)**	**0.692**

Table 62. Primary criterion PP population (Ref. amendment vol. 1.3, table 26)

	Vapreotide	Placebo	All	p-value
n	42	38	80	
Hemostasis at Tendo+6h	28(67%)	20 (53%)	48 (60%)	0.201
Hemostasis at Tendo+48h	23 (55%)	19 (50%)	42 (53%)	0.670
Hemostasis at 5 days	**22 (52%)**	**19 (50%)**	**41 (51%)**	**0.832**

For secondary endpoint the sponsor performed multiple analyses in the ITT population as shown in Table 63. The results were not statistically significantly different between the treatment groups for any variables, except for rebleeding between Tendo+48h and Tendo+120h in favor of placebo (0.043). Similar results were observed for secondary endpoints in the PP population.

Table 63. Secondary criteria ITT population (Ref. amendment vol. 1.3, table 24)

	Vapreotide	Placebo	All	p-value
N	51	51	102	
Re Bleeding episodes:				
• During the 6 weeks	6 (75%)	6 (86%)	12 (80%)	1 .000
• Between Tendo+48h and Tendo+120h	4 (10%)	0	4 (5%)	0.043
• Between Day 5 and Day42	2 (50%)	6 (86%)	8 (73%)	0.491
Number of rebleeding episodes30:				0.464
• 1 episode	1 (50%)	5 (83%)	6 (75%)	
• 2 episodes	1 (50%)	1 (17%)	2 (25%)	
At least one unit of blood transfused" :				
• Between Admission and Tendo+6h	35 (69%)	29 (57%)	64 (63%)	0.219
• Between Tendo+6h and Tendo+48h	22 (46%)	25 (53%)	47 (51%)	0.605
• Between Tendo+48h and Tendo+120h	10 (22%)	13 (27%)	23 (25%)	0.567
Total number of units of blood transfused:	N=51	N=51	N=102	
• Whole 6-week period	3 (0 : 24)	3 (0 : 18)	3 (0 : 24)	1.000
• During the firs! 5 days	3 (0 : 24)	2 (0 : 1 3)	2 (0 : 24)	0.579
• Between Day 5 and Day42	N=42 0 (0 : 8)	N=49 0 (0 : 9)	N=91 0 (0 : 9)	0.473
Total duration of hospitalization (days) - All patients	N=50 10 (2 : 33)	N=51 12 (1 ;42)	N=101 11 (1: 42)	0.103
Number of deaths:				
• During the planned 42 days	10 (20%)	4 (8%)	14 (14%)	0.084
• Between Admission and Tendo+120h (day 5)	5 (10%)	2 (4%)	7 (7%)	0.436
• Between Day 6 and Day 42	5 (10%)	2 (4%)	7 (7%)	0 436

Reviewer's Efficacy Conclusions

Despite the similarities regarding demographics, baseline characteristics or etiology of liver cirrhosis of the populations described in the two studies, the findings observed in the Hong Kong study are quite distinct from that of the pivotal study (DEB-97-VAP-14). Hemostasis rate at the end of 5 days (primary endpoint) was quite similar in the two treatment groups in the Hong Kong study. In contrast, vapreotide was superior to placebo for the primary endpoint in the pivotal study. The reasons for such variability in the outcomes are unclear to this reviewer. Based on the reviewer's assessment, the findings of this study could not be explained by the protocol violations as suggested by the sponsor. This reviewer finds no obvious quantitative or qualitative differences in protocol violations in this study when compared with those described in the pivotal study.

Safety Evaluation

Extent of Exposure

Study drug was infused to 134 patients among the 136 patients who were included. However, this infusion was discontinued in the patients for whom the source of hemorrhage was found at endoscopy as not due to portal hypertension (n=31).

In addition, among the patients with hemorrhage due to portal hypertension, the infusion was discontinued for 23 patients. The main reasons for discontinuation were the following (Table 64):
- Therapeutic alternative,
- Therapeutic alternative associated with a new endoscopy,
- Other reasons.

The absence of initial control of hemorrhage and/or massive hemorrhage or rebleeding was the main reasons for a switch to a therapeutic alternative. The nature of the alternative was balloon tamponade, or endoscopic treatment, or drug (somatostatin), or the association of several therapeutic alternatives.

The median time between the start of infusion and premature discontinuation of infusion was 7.5 hours (range 0.2 hours to 96 hours).

Table 64. Causes of interruption of infusion (Ref. Table 13, vol. 1.23)

Reasons of early interruption	Placebo	Vapreotide
N	65	69
Bleeding not due to portal hypertension	N = 14 Patients n° 2, 27, 32, 56, 90, 99, 100, 203, 204, 209, 9026, 9028, 9037, 9039,	N = 17 Patients n° 4, 12, 16, 18, 19, 31, 34, 44, 51, 64, 68, 81, 91, 104, 9003, 9016, 9025,
Decision of the patient	-	N = 1 Patient n° 210
Death	-	N = 1 Patient n° 9038
Other cause	N=4 Patients n" 9, 53, 93, 9201	N = 5 Patients n° 54. 66, 106, 202, 402
Therapeutic alternative	N = 1 Patients n° 9018	N = 5 Patients n*21, 25, 88, 9007, 9017
Therapeutic alternative and new endoscopy	N = 2 Patient n° 87, 205	N = 3 Patients n° 101, 9030, 9031
Therapeutic alternative and other cause	-	N = 1 Patient n" 72
Total	7	16

Adverse Events

Safety analysis included all 134 patients who received study medications. The overall rate of patients with at least one adverse event was 75% during the study. There were no significant differences between the treatment groups (Table 65).

Importantly, by convention all major clinical complications of portal hypertension and consequences of advanced cirrhosis were counted as adverse events, especially gastrointestinal rebleeding, encephalopathy, hepatic and renal disorders, and ascites.

Apart from general disorders and administration site conditions such as pyrexia and injection site reactions observed in 48% of the patients, the most frequent adverse events reported during the study were gastro-intestinal disorders (44%), nervous system disorders (22%) and, to a lesser extent, renal and urinary disorders (10%) and hepatobiliary disorders (5%). Infections were reported in 15% of patients. They were classified as not related to the study drugs.

Two patients (3%) in vapreotide group and 3 patients (4.5%) in placebo group experienced mild to moderate hyperglycemia classified as related to study drugs

Adverse events were mainly rated as mild or moderate. Most of them were classified as not related to the study drug.

SAEs and Death

During the study, 41 patients reported at least one SAE. The most frequently reported SAEs were in relationship to rebleeding from esophageal varices, hepatic encephalopathy, and melena. Fifteen deaths occurred during the study: 9 in the vapreotide group and 6 in the placebo group. The sponsor indicates that there were no death nor SAEs reported during the study, which were classified as AEs possibly related to the study medications. Causes of Death are listed in reviewer's Table 21.

Table 65. Number of patients with ≥ 1 AEs during study (Ref vol., 1.23, table 14)

		Treatment Group					
		Placebo		Vapreotide		Total	
		N	%	N	%	N	%
Body system	Preferred term						
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	PYREXIA	30	46.2	28	40.6	58	43.3
	INFUSION SITE PHLEBITIS	5	8.0	5	7.3	10	7.5
	CHEST DISCOMFORT	3	4.6	1	1.5	4	3.0
	OEDEMA PERIPHERAL	3	4.6	1	1.5	4	2.3
	CHEST PAIN	2	3.1	1	1.5	3	2.2
	INJECTION SITE CELLULITIS	1	1.5	1	1.5	2	1.5
	INJECTION SITE ANAESTHESIA	-	-	1	1.5	1	0.8
	INJECTION SITE PAIN	1	1.5	-	-	1	0.8
	INJECTIO SITE THROMBOSIS	-	-	1	1.5	1	0.8
	MALAISE	1	1.5	-	-	1	0.8
	MUCOSAL ULCERATION NOS	-	-	1	1.5	1	0.8
	MULTI-ORGAN FAILURE	1	1.5	-	-	1	0.8
	OEDEMA NOS	1	1.5	-	-	1	0.8
	Total	*34*	*52.3*	*30*	*43.5*	*64*	*47.8*
GASTROINTESTINAL DISORDERES	OESOPHAGEAL ULCER	10	15.4	5	7.3	15	11.2
	DIARRHOEA NOS	9	13.9	2	2.9	11	8.2
	HEAMATEMESIS	4	6.2	7	10.1	11	8.2
	ASCITES	8	12.3	2	2.9	10	7.5
	ABDOMINAL DISTENSION	3	4.6	3	4.4	6	4.5
	MELAENA	4	6.2	2	2.9	6	4.5
	ABDOMINAL PAIN NOS	4	6.2	1	1.5	5	3.7
	GASTRIC ULCER	4	6.2	1	1.5	5	3.4
	ABDOMINAL PAIN UPPER	3	4.6	1	1.5	4	3.0
	GASTRIC ULCER HAEMORRHAGE	2	3.1	2	2.9	4	3.0
	ODYNOPHAGIA	2	3.1	2	2.9	4	3.0
	OESOPHAGEAL VARICES HAEMORRHAGE	2	3.1	2	2.9	4	3.0

Table 65. Number of patients with ≥ 1 AEs during study (Cont)

		Treatment Group					
		Placebo		Vapreotide		Total	
		N	%	N	%	N	%
Body system	Preferred term						
	EPIGASTRIC DISCOMFORT	2	3.1	1	1.5	3	2.2
	GASTROINTESTINAL HAEMORRHAGE NOS	2	3.1	1	1.5	3	2.2
	DUODENAL ULCER	1	1.5	1	1.5	2	1.5
	DYSPEPSIA	1	1.5	1	1.5	2	1.5
	DYSPHAGIA	2	3.1	-	-	2	1.5
	GINGIVAL BLEEDING	2	3.1	-	-	2	1.5
	NAUSEA	2	3.1	-	-	2	1.5
	ABDOMINAL DISCOMFORT	1	1.5	-	-	1	0.8
	CONSTIPATION	-	-	1	1.5	1	0.8
	FREQUENT BOWEL MOVEMENTS	1	1.5	-	-	1	0.8
	GASTRIC VARICES	-	-	1	1.5	1	0.8
	GASTRIC VARICES HAEMORRHAGE	1	1.5	-	-	1	0.8
	GASTROINTESTINAL ULCER NOS	-	-	1	1.5	1	0.8
	INGUINAL HERNIA NOS	1	1.5	-	-	1	0.8
	OESOPHAGEAL STENOSIS ACQUIRED	1	1.5	-	-	1	0.8
	OESOPHAGEAL ULCER HAEMORRHAGE	-	-	1	1.5	1	0.8
	VOMITING NOS	1	1.5	-	-	1	0.8
	Total	*34*	*52.3*	*25*	*36.2*	*59*	*44.0*
NERVOUS SYSTEM DISORDERS	HEPATIC ENCEPHALOPATY	6	9.2	7	10.1	13	9.7
	DIZZINESS	3	4.6	4	5.8	7	5.2
	TREMOR	3	4.6	-	-	3	2.2
	ASTERIXIS	2	3.1	-	-	2	1.5
	HEADACHE NOS	1	1.5	1	1.5	2	1.5
	CEREBRAL INFARCTION	1	1.5	-	-	1	0.8
	COMA HEPATIC	-	-	1	1.5	1	0.8
	CONVULSIONS NOS	-	-	1	1.5	1	0.8

Table 65. Number of patients with ≥ 1 AEs during study (Cont)

		Treatment Group					
		Placebo		Vapreotide		Total	
		N	%	N	%	N	%
Body system	Preferred term						
	ENCEPHALOPATHY NOS	-	-	1	1.5	1	0.8
	GRAND MAL CONVULSION	1	1.5	-	-	1	0.8
	LACUNAR INFARCTION	1	1.5	-	-	1	0.8
	PERONEAL NERVE PALSY	1	1.5	-	-	1	0.8
	Total	*12*	*23.1*	*14*	*20.3*	*29*	*21.6*
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	DYSPNOEA NOS	4	6.2	2	2.9	6	4.5
	PHARYNGITIS	5	7.7	1	1.5	6	4.5
	PRODUCTIVE COUGH	4	6.2	1	1.5	5	3.4
	PLEURAL EFFUSION	1	1.5	1	1.5	2	1.5
	ATELACTASIS	1	1.5	-	-	1	0.8
	CHRONIC OBSTRUCTIVE AIRWAYS DISEASE	1	1.5	-	-	1	0.8
	EPISTAXIS	1	1.5	-	-	1	0.8
	GASPING	1	1.5	-	-	1	0.8
	HAEMOPTYSIS	-	-	1	1.5	1	0.8
	HYPOXIA	-	-	1	1.5	1	0.8
	LUNG DISORDER NOS	1	1.5	-	-	1	0.8
	RESPIRATORY FAILURE	-	-	1	1.5	1	0.8
	Total	*14*	*21.5*	*7*	*10.1*	*21*	*15.7*

Table 65. Number of patients with ≥ 1 AEs during study (Cont)

		Treatment Group					
		Placebo		Vapreotide		Total	
		N	%	N	%	N	%
Body system	Preferred term						
INFECTIONS AND INFESTATIONS	PNEUMONIA NOS	4	6.2	1	1.5	5	3.7
	SEPSIS NOS	2	3.1	2	2.9	4	3.0
	URINARY TRACT INFECTION NOS	1	1.5	1	1.5	2	1.5
	BRONCHOPNEUMONIA	1	1.5	-	-	1	0.8
	ESCHERICHIA INFECTION NOS	-	-	1	1.5	1	0.8
	GRAM-POSITIVE BACTERIAL INFECTION	1	1.5	-	-	1	0.8
	LOWER RESPIRATORY TRACT INFECTION NOS	1	1.5	-	-	1	0.8
	METHICILLIN-RESISTANT STAPHYLOCOCCAL AUREUS INFECTION	1	1.5	-	-	1	0.8
	PERITONOTIS BACTERIAL NPS	1	1.5	-	-	1	0.8
	PNEUMONIA AGGRAVATED	-	-	1	1.5	1	0.8
	PURULENT DISCHARGE	-	-	1	1.5	1	0.8
	SEPTICAEMIA GRAM-POSITIVE	-	-	1	1.5	1	0.8
	STAPHYLOCOCCAL INFECTION NOS	1	1.5	-	-	1	0.8
	STAPHYLOCOCCAL SEPSIS	-	-	1	1.5	1	0.8
	Total	*11*	*16.9*	*9*	*13.0*	*20*	*14.9*
METABOLISM AND NUTRITION DISORDERS	HYPERGLYCAEMIA NOS	4	6.2	4	5.8	8	6.0
	HYPOGLYCAEMIA	2	3.1	-	-	2	1.5
	HYPOKALAEMIA	2	3.1	-	-	2	1.5
	DIABETES MELLITUS NOS	-	-	1	1.5	1	0.8
	FLUID RETENTION	1	1.5	-	-	1	0.8
	GOUT	1	1.5	-	-	1	0.8
	Total	*9*	*13.9*	*5*	*7.3*	*14*	*10.5*

Table 65. Number of patients with ≥ 1 AEs during study (cont)

		Treatment Group					
		Placebo		Vapreotide		Total	
		N	%	N	%	N	%
Body system	Preferred term						
RENAL AND URINARY DISORDERS	URINE FLOW DECREASED	5	7.7	1	1.5	6	4.5
	HAEMATURIA	1	1.5	2	2.9	3	2.2
	ANURIA	1	1.5	1	1.5	2	1.5
	RENAL FAILURE ACUTE	-	-	2	2.9	2	1.5
	DYSURIA	1	1.5	-	-	1	0.8
	RENAL FAILURE NOS	1	1.5	-	-	1	0.8
	RENAL IMPAIRMENT NOS	1	1.5	-	-	1	0.8
	URINARY RETENTION	-	-	1	1.5	1	0.8
	URINE VOLUME DECREASED	1	1.5	-	-	1	0.8
	Total	*10*	*15.4*	*4*	*5.8*	*14*	*10.5*
VASCULAR DISORDERS	HYPOTENSION NOS	4	6.2	1	1.5	5	3.7
	PHLEBITIS NOS	1	1.5	2	2.9	3	2.2
	HYPERTENSION NOS	1	15	1	1.5	2	1.5
	HAEMATOMA NOS	1	1.5	-	-	1	0.8
	Total	*7*	*10.8*	*4*	*5.8*	*11*	*8.2*
HEPATOBILIARY DISORDERS	JAUNDICE NOS	3	4.6	-	-	3	2.2
	BILE DUCT STONE	-	-	1	1.5	1	0.8
	CHOLECYSTITIS ACUTE NOS	-	-	1	1.5	1	0.8
	CHOLECYSTITIS NOS	1	1.5	-	-	1	0.8
	HEPATIC FAILURE	1	1.5	-	-	1	0.8
	HEPATORENAL SYNFROME	1	1.5	-	-	1	0.8
	Total	*5*	*7.7*	*2*	*2.9*	*7*	*5.2*
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	BACK PAIN	2	3.1	1	1.5	3	2.2
	ARTHRALGIA	1	1.5	-	-	1	0.8
	JOINT SWELLING	1	1.5	-	-	1	0.8
	MUSCLE CRAMPS	1	1.5	-	-	1	0.8
	MYALGIA	-	-	1	1.5	1	0.8
	PERIPHERAL SWELLING	1	1.5	-	-	1	0.8
	PLANTAR FASIITIS	-	-	1	1.5	1	0.8
	Total	5	7.7	2	2.9	7	5.2

Table 65. Number of patients with ≥ 1 AEs during study (Cont)

		Treatment Group					
		Placebo		Vapreotide		Total	
		N	%	N	%	N	%
Body system	Preferred term						
PSYCHIATRIC DISORDERS	CONFUSION	2	3.1	3	4.4	5	3.7
	CONFUSION AGGRAVATED	1	1.5	-	-	1	0.8
	DELIRIUM TREMENS	1	1.5	-	-	1	0.8
	DISORIENTATION	1	1.5	-	-	1	0.8
	INSOMNIA	-	-	1	1.5	1	0.8
	Total	*3*	*4.6*	*4*	*5.8*	*7*	*5.2*
CARDIAC DISORDERS	PALPITATIONS	-	-	2	2.9	2	1.5
	BRADYCARDIA NOS	1	1.5	-	-	1	0.8
	CARDIAC ARREST	1	1.5	-	-	1	0.8
	CARDIAC FAILURE NOS	1	1.5	-	-	1	0.8
	TACHYCARDIA NOS	1	1.5	-	-	1	0.8
	Total	*4*	*6.2*	*2*	*2.9*	*6*	*4.5*
INVESTIGATIONS	BLOOD PRESSURE SYSTOLIC DECREASED	2	3.1	-	-	2	1.5
	BACTERIA NOS URINE IDENTIFIED	-	-	1	1.5	1	0.8
	BLOOD PHOSPHATE DECREASED	1	1.5	-	-	1	0.8
	HAEMOGLOBIN DECREASED	-	-	1	1.5	1	0.8
	PARACENTESIS ABDOMEN ABNORMAL	1	1.5	-	-	1	0.8
	Total	*4*	*6.2*	*2*	*2.9*	*6*	*4.5*
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	ACCIDENTAL OVERDOSE	1	1.5	1	1.5	2	1.5
	LACERATION	1	1.5	-	-	1	0.8
	POST PROCEDURAL PAIN	1	1.5	-	-	1	0.8
	SUBCUTANEOUS HAEMATOMA	1	1.5	-	-	1	0.8
	Total	*3*	*4.6*	*1*	*1.5*	*4*	*3.0*

Table 65. Number of patients with ≥ 1 AEs during study (Cont)

		Treatment Group					
		Placebo		Vapreotide		Total	
		N	%	N	%	N	%
Body system	Preferred term						
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	ERYTHEMA	1	1.5	-	-	1	0.8
	PRURITUS NOS	-	-	1	1.5	1	0.8
	RASH PRURITIC	-	-	1	1.5	1	0.8
	Total	*1*	*1.5*	*2*	*2.9*	*3*	*2.2*
BLOOD AND LYMPHATIC SYSTEM DISORDERS	COAGULOPATHY	2	3.1	-	-	2	1.5
	Total	*2*	*3.1*	-	-	*2*	*1.5*
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	BREAST PAIN	-	-	1	1.5	1	0.8
	SCROTAL OEDEMA	1	1.5	-	-	1	0.8
	Total	*1*	*1.5*	*1*	*1.5*	*2*	*1.5*
EYE DISORDERS	CONJUNCTIVAL HAEMORRHAGE	1	1.5	-	-	1	0.8
	Total	*1*	*1.5*	-	-	*1*	*0.8*
IMMUNE SYSTEM DISORDERS	DRUG HYPERSENSITIVITY	1	1.5	-	-	1	0.8
	Total	*1*	*1.5*	-	-	*1*	*0.8*
SURGICAL AND MEDICAL PROCEDURES	UMBILICAL HERNIA REPAIR	1	1.5	-	-	1	0.8
	Total	*1*	*1.5*	-	-	*1*	*0.8*

Overall Reviewer's Conclusions (Hong Kong study)

Despite the similarities regarding demographics, baseline characteristics or etiology of liver cirrhosis of the populations described in the two studied (Hong Kong and pivotal), the findings observed in the Hong Kong study are quite distinct from that of the pivotal study (DEB-97-VAP-14). Hemostasis rate at the end of 5 days (primary endpoint) was quite similar in the vapreotide and placebo groups in the Hong Kong study. In contrast, vapreotide was superior to placebo for the primary endpoint in the pivotal study. The reasons for such variability in the outcomes are unclear to this reviewer. Based on the reviewer's assessment, the findings of this study could not be explained by the protocol violations as suggested by the sponsor. This reviewer finds no obvious quantitative or qualitative differences in protocol violations in Hong Kong study when compared with those described in the pivotal study.

The short term use of vapreotide therapy was not associated with significant toxicity. The safety profile of vapreotide was comparable with that of placebo, suggesting that many events recorded were a reflection of the patient's underlying medical condition

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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmacoepidemiology and Statistical Science
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION
CLINICAL STUDIES

NDA/Serial Number: 21-761
Drug Name: Sanvar (Vapreotide acetate 0.6mg) injection
Indication(s): Treatment of acute variceal bleeding related to portal hypertension in association with endoscopic treatment.
Applicant: H3 Pharma, Inc.
Date(s): March 1, 2004
Review Priority: Standard

Biometrics Division: Division of Biometrics II
Statistical Reviewer: Wen-Jen Chen, Ph.D. (HFD-715)
Concurring Reviewers: Stella Grosser, Ph.D. (HFD-715)

Medical Division: Gastrointestinal and Coagulation Drug Products
Medical Reviewer: Fathia Gibril, MD.
Project Manager: Ms. Diane Moore

Statistical Keywords: Clinical studies; NDA review.

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1.0 EXECTIVE SUMMARY OF STATISTICAL FINDINGS

1.1 Conclusions and Recommendations

- ✓ Based upon the efficacy results shown by the three trials, one notes that the two studies (Studies DEB-01-VAP-07 and DEP-97-VAP-02) did not show vapreotide significantly better than placebo when assessed by the primary endpoint hemostasis at end of Day 5 after endoscopic treatment. Only Study DEB-96-VAP-14 showed the superiority of vapreotide to placebo when assessed by the primary endpoint. However, using ITT population, the superiority of vapreotide to placebo appears to be driven by patients at Center 18 (14% of ITT population; 28/196). In addition, the significant effectiveness of vapreotide shown by Center 18 may be due to relatively a large percent of patients with small esophageal varices in the vapreotide group when compared with patients not at Center 18**.** The superiority of vapreotide to placebo shown by the pivotal Study DEB-96-VAP-14 is not robust.
- ✓ To conclude that a single study is adequate in support of an effectiveness claim, the guidance for industry (Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products, 1998) recommends that the efficacy result should be statistically very persuasive. The Guidance emphasizes that in a multi-center study, a very low p-value (for example, less than .00125) indicates the result is highly inconsistent with the null hypothesis of no treatment effect. Accordingly, for a single study to be considered statistically persuasive in support of the efficacy claim, the p-value for the treatment comparison should be very small. As a result, the superiority of vapreotide to placebo shown by a single pivotal Study DEB-96-VAP-14 is not statistically persuasive.
- ✓ From the statistical perspective, based upon the remarks stated in the section of "Statistical Issues and Collective Evidence", the single pivotal Study DEB-96-VAP-14 does not provide substantial evidence to support the use of vapreotide in the treatment of acute variceal related to portal hypertension associated with endoscopic treatment.

1.2 Brief Overview of Clinical Studies

The applicant conducted three randomized, double-blind, placebo-controlled studies (DEB-96-VAP-14, DEB-01-VAP-07, and DEP-97-VAP-02) to assess the efficacy of vapreotide (Sanvar) for treatment of variceal hemorrhage in patients with portal hypotension. However, the applicant indicated that due to low recruitment rate, Study DEP-97-VAP-02 conducted in Hong Kong was terminated in June 2001. As a result, in this NDA submission, the applicant originally only submitted efficacy results from the two studies (DEB-96-VAP-14 and DEB-01-VAP-07) to support the use of Sanvar in treatment of acute variceal bleeding related to portal hypertension in association with endoscopic treatment. Of the two submitted studies, the applicant indicated that Study DEB-96-VAP-14 conducted in France was a phase III pivotal study while Study DEB-01-VAP-07 conducted in Egypt was a phase IIb pilot study. Later, to respond the agency's information request, dated June 25, 2004, the applicant submitted to the agency the efficacy

results for Study DEP-97-VAP-02.

Based upon results of the analysis of the primary and secondary endpoints provided by the applicant, the early-terminated Study DEP-97-VAP-02 and the pilot Study DEB-01-VAP-07 did not demonstrate significant evidence (for more detail, refer to section 2.1 of "Overview") to support the efficacy of vapreotide in the use of treatment of acute variceal bleeding related to portal hypertension associated with endoscopic treatment. Consequently, in this review, DEP-97-VAP-02 and Study DEB-01-VAP-07 are not further reviewed and the pivotal Study DEB-96-VAP-14 is the focus.

1.3 Statistical Issues and Findings

- For pivotal Study DEB-96-VAP-14, the by-Center efficacy analysis result on the primary endpoint (hemostasis at end of Day 5 after endoscopic treatment) indicates that the rate for vapreotide treated patients is significantly higher than that for placebo only for Center 18 (14 % of ITT patients; 28/196). After excluding patients from Center 18, the efficacy analysis results on both the primary endpoint (hemostasis rate at end of Day 5 after endoscopic treatment) and time to therapeutic failure from end of endoscopy to 5 days after endoscopic treatment do not demonstrate that vapreotide is significantly better than placebo. Thus, the efficacy analysis results on the primary endpoint (hemostasis rate at end of Day 5 after endoscopic treatment) and therapeutic failure (bleeding) assessed from at end of endoscopy to 5 days after end of endoscopic treatment indicate that patients at Center 18 may dominate the superiority of vapreotide to placebo.
- The baseline variable analysis indicates that the odds of the hemostasis at end of Day 5 after endoscopic treatment for patients with small size of esophageal varices is significantly higher than that of patients with large size of esophageal varices. This variable is equally distributed between treatment groups for patients not at Center 18. However, for center 18, the percent of patients in the vapreotide group with small size of esophageal varix is more than three times higher than that in the placebo group. Accordingly, the effectiveness of vapreotide relative to placebo observed for Center 18 may be due to the imbalance in varix sizes.
- For the early-terminated Study DEP-97-VAP-02 and the pilot Study DEB-01-VAP-07, as noted by this reviewer in the section 2.1, "Overview", the efficacy analysis results provided by the applicant did not demonstrate significant evidence to support the efficacy of vapreotide in the treatment of acute variceal bleeding related to portal hypertension associated with endoscopic treatment.

2.0 INTRODUCTION

2.1 Overview

With regards to Sanvar (Vapreotide acetate) injection, the sponsor made the following observations in the study report:

> Bleeding from esophageal varices is one of the major complications of portal hypertension in cirrhotic patients. In these patients, the first acute episode of bleeding is associated with a high mortality. Early re-bleeding during the first few days following the initial episode of variceal bleeding may also be a drect cause of death. If the patient survives the acute episode, bleeding may nevertheless contribute to decompensation of cirrhosis and subsequent mortality.
>
> The splanchnic effects induced by somatostatin and its analogues have been used to control variceal bleeding in cirrhosis. However, controversial results have been reported as to their efficacy to control variceal bleeding. The discrepancies between the different reports published on the subject might be explained by differences in the product, the doses, and the duration of administration that have been used. Another potentially important source of discrepancies is related to the time elapsed between the onset of hemorrhage and the administration of the drug.
>
> The principal question that the present double-blind, placebo-controlled clinical study aimed to address was the extent to which the somatostatin analogue could improve hemostasis with survival at 5 days, when administered as closely as possible to the initial hemorrhage, but in all cases before endoscopy and physical obliteration of varices.

The applicant conducted three randomized, double-blind, placebo-controlled studies (DEB-96-VAP-14, DEB-01-VAP-07, and DEP-97-VAP-02) to assess the efficacy of vapreotide (Sanvar) for treatment of variceal hemorrhage in patients with portal hypotension. However, the applicant indicated that due to low recruitment rate, Study DEP-97-VAP-02 conducted in Hong Kong was terminated in June 2001. As a result, in this NDA submission, the applicant originally only submitted efficacy results from the two studies (DEB-96-VAP-14 and DEB-01-VAP-07) to support the use of in treatment of acute variceal related to portal hypertension in association with endoscopic treatment. Of the two submitted studies, the applicant indicated that Study DEB-96-VAP-14 conducted in France was a phase III pivotal study while Study DEB-01-VAP-07 conducted in Egypt was a phase IIb pilot study. Later, to respond to the agency's information request, dated June 25, 2004, the applicant submitted to the agency the efficacy results for Study DEP-97-VAP-02.

For the pilot Study DEB-01-VAP-07 with 58 patients (31 in vapreotide and 27 in placebo) in the intent-to-treat patient population, the analysis results for the primary endpoint (hemostasis at end of 5 day infusion after endoscopic treatment) performed by the applicant indicated that at significance level of 0.05, the hemostasis rates at end of 5 day infusion after endoscopic treatment were not statistically significantly different between vapreotide and placebo for both intent-to-treat (p=0.35) and per-protocol (p=0.281) patient populations.

As for the secondary endpoint analysis, the applicant performed multiple assessments including the following five analyses using both intent-to-treat and per-protocol patient populations: Survival at 42 days, Treatment success over 42 days (defined as survival with control of initial bleeding and without late recurrence of bleeding), Time to failure (the occurrence of bleeding or death) until day 5, Re-bleeding episodes from Day 5 to Day 42, and Number of blood units transfused. At significance level of 0.05, except for Survival at 42 days (p=0.039) and Treatment success over 42 days (p=0.047) using per-protocol patient population, the analysis results for the five secondary endpoints performed by the applicant indicated that no statistically significant differences between vapreotide and placebo were found for both intent-to-treat and per-protocol

patient populations. Since many secondary endpoint analyses (10 analyses performed using both intent-to-treat and per-protocol populations) were performed, the significant results for Survival at 42 days and Treatment success over 42 days using per-protocol patient population may not be real effect ascribed to vapreotide, but occurred by chance due to multiple comparisons. In addition, these two significance results did not replicate in the pivotal Study DEB-96-VAP-14 (p=0.83 for Surviving at Day 42 and no result reported for Treatment success over 42 days).

Thus, based upon the analysis results from the primary and secondary endpoints provided by the applicant, the pilot Study DEB-01-VAP-07 did not demonstrate significant evidence to support the efficacy of vapreotide in the use of treatment of acute variceal related to portal hypertension associated with endoscopic treatment.

For the early terminated Study DEP-97-VAP-02, with 102 patients (51 in vapreotide and 51 in placebo) in the intent-to-treat patient population, the analysis results for the primary endpoint (hemostasis at end of 5 day infusion after endoscopic treatment) performed by the applicant indicated that at significance level of 0.05, the hemostasis rates at end of 5 day infusion after endoscopic treatment were not statistically significantly different between vapreotide and placebo for both intent-to-treat (p=0.69) and per-protocol (p=0.83) patient populations. In addition, at significance level of 0.05, all secondary endpoints performed by the applicant (including re-bleeding episodes assessed at different time periods, total or at least one unit of blood transfused, and number of deaths assessed at different time periods) were not significant for both ITT and Per-Protocol patient populations. Thus, based upon the analysis results from the primary and secondary endpoints provided by the applicant, Study DEB-97-VAP-02 did not demonstrate any evidence to support the efficacy of vapreotide in the use of treatment of acute variceal bleeding related to portal hypertension associated with endoscopic treatment.

Finally, based upon the remarks/comments made for Studies DEB-01-VAP-07 and DEP-97-VAP-02, in this review, these two studies are not further reviewed and the pivotal Study DEB-96-VAP-14 is the focus.

2.2 Data Sources

This reviewer has reviewed NDA volumes 1.1 in Module 1, volumes 1.1 and 1.2 in Module 2, and volumes 1.8 to 1.22 in Module 5 submitted by the applicant dated March 1, 2004.

3.0 STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

3.1.1 Study DEB-96-VAP-14

Study Design and Endpoints

The major objective of the study was to quantify to what extent Sanvar in association with

endoscopic treatment can improve hemostasis at 5 days, i.e., control of initial bleeding and prevention of early re-bleeding. The secondary objectives of the study were to assess: 1. hemostasis and endoscopic facilitation at first endoscopy, 2. the overall clinical evaluation of hemostasis at 6 hour after randomization, 3. the total number of re-bleeding episodes per patient during the 6 weeks of study; etc.

This was a double-blind, parallel group, randomized, multi-center study using Sanvar administered for 5 days in male or female cirrhotic patients aged 18 to 75 years suffering from acute variceal bleeding. The total study duration was 6 weeks (=42 days). The first day when the patient was admitted at hospital was Day 1 (= randomization); the last day of the study being Day 42. All patients were followed up until Day 42. This 6-week study period has been defined as the period under which all mortality will be considered as directly related to the episode of acute hemorrhage. The planned inclusion period was 18 months, which could be prolonged to achieve the total number of evaluable cases.

Cirrhotic patients admitted (time of first hospital admission = time zero, T_0) either in an Intensive Care Unit, or a classical General Admission Unit for acute hematemesis and/or melena were to be randomized as soon as possible to receive either Sanvar administered 50 µg IV bolus in emergency followed by an IV infusion of 50 µg /h for 5 days, or placebo. This 5-day period following acute hemorrhage was chosen because it encompasses the greatest risk of early re-bleeding from varices. Randomization was balanced by blocks of 4 containing an equal number of Sanvar and placebo treatments.

After randomization and the beginning of infusion, but at the latest 12 hours following admission, the patients underwent endoscopic treatment of their bleeding varices according to their bleeding source. In case of hemorrhage unrelated to portal hypertension (e.g., gastro-duodenal ulcer), the infusion was stopped and the patient followed at 5, 7, 30 and 42 days. Patients were replaced in case of hemorrhage unrelated to portal hypertension.

Sample size was calculated to fulfill the primary objective of the trial, which was to demonstrate that vapreotide could improve hemostasis at 5 days when compared to placebo. Based on published literature, hemostasis was observed in about 65% of patients under placebo treatment. As 85% rate of hemostasis at 5 days on vapreotide could be anticipated for somatostatin or other analogues, 73 patients per treatment arm were required to demonstrate the difference of vapreotide versus placebo by two-sided test with nominal α level equal to 0.05 and power (1 - ß) equal to 0.80.

The primary efficacy endpoint/criterion was hemostasis at end of 5 days after endoscopic treatment (=Tendo). The primary endpoint was the hemostasis during the first two days (as assessed at 6h, and between 6 and 48h after endoscopy) followed by no re-bleeding from Day 3 to Day 5. The secondary efficacy endpoints/criteria were endoscopy facilitation, hemostasis 6 hours after randomization, re-bleeding episodes, blood transfution units, hospital stay, and survival after 7-day, 30-day, and 42-day since randomization.

Statistical Methodologies

Efficacy analyses were conducted in two patient populations: intention-to-treat (ITT) and per protocol (PP). Intention-to-treat analysis was conducted in all randomized patients for whom hemorrhage was due to portal hypertension (esophageal varices, gastric varices, porta1 hypertensive gastropathy), regardless of any protocol deviation and according to the randomized treatment. Per protocol analysis was conducted in ITT population according to the treatment actually received. Safety analysis was conducted in all patients who received any dose of the test medications (Sanvar or placebo).

The null hypothesis (H_0) was that there was no difference between treatments on primary efficacy criterion and the alternative hypothesis (H_a) was that there was a true difference. The risk p-values reported were two-sided and the statistical significance nominal limit was set to 0.05. The test of the primary criterion was for confirmatory purposes. All other tests performed were for exploratory purposes. Therefore the significance level was not adjusted for these analyses.

The primary efficacy endpoint, hemostasis at 5 days after endoscopic treatment, was analyzed in contingency table by the chi-square test. Rate of hemostasis and its two-sided 95% confidence interval (Cl) were calculated per treatment arm.

For the secondary criteria, the chi-square test was performed to analyze endoscopy facilitation, hemostasis at Tinf (Time of beginning of the Infusion) +6h, and re-bleeding at other time points. Blood transfusion units and hospital stay were analyzed by the Wilcoxon rank-sum test. Survival curves of each treatment arm were compared by the log-rank test. Median survival with its 95% confidence interval was presented. Survival at 7-, 30- and 42-day per treatment arm was assessed by the Kaplan-Meier estimate.

Finally, no interim statistical analysis was planned. In addition, there was no imputation for missing data. For the primary criterion, patients with missing data were considered as failure. In all secondary criteria, when data used in the analysis were missing, the patient was excluded from that specific analysis.

Patient Disposition

Two hundred and twenty-seven patients were enrolled and randomized into the study between the 1st of July 1997 and the 30th of October 1998, in 22 centers of unequal size. Thirty-seven percent of the patients were recruited at 3 centers: Nantes (14%), Paris/Salpêtriére hospital (13%), and Angers (10%).

The origin of bleeding was essentially esophageal varices (82%) and was not due to portal hypertension for 14% of the patients. Table 3.1.1.1 presents the origin of hemorrhage.

Table 3.1.1.1 (Sponsor's) Origin of hemorrhage, classified according to statistical convention

	Vapreotide	Placebo	All
N	111	116	227
Esophageal varices	91 (82%)	95 (82%)	186 (82%)
Gastric varices	2 (2%)	2 (2%)	4 (2%)
Portal hypertensive gastropathy	5 (5%)	1 (1%)	6 (3%)
Not due to portal hypertension	13 (12%)	18 (16%)	31 (14%)

In addition, Table 3.1.1.2 presents the disposition of patients by populations studied.

Table 3.1.1.2 (Sponsor's) Disposition of patients by populations studied

	Vapreotide	Placebo	All
ITT population	98	98	196
PP population	77	83	160
PPEV population (esophageal varices only)	72	82	154
Safety population	111	116	227

Of total 227 patients, 196 bleeding due to portal hypertension were enrolled in the ITT patient population, 98 patients in each group. In the ITT population, twenty-one patients in Vapreotide group and twenty-five in placebo group were premature withdrawal. Of the twenty-one premature withdrawals from the Vapreotide group, there were 5 patients dead during the first 5 days, 9 dead between day 6 and day 42, and 7 patients lost to follow-up. However, for those 25 premature withdrawals from the placebo group, there were 7 patients dead during the first 5 days, 14 dead between day 6 and day 42, and 4 patients lost to follow-up.

Demographics and Baseline Characteristics

The demographic characteristics of study subjects in the ITT population were summarized in Table 3.1.1.3 while past and concomitant diseases at admission in the ITT population were presented in Table 3.1.1.4.

Table 3.1.1.3 (Sponsor's) Demographic characteristics for ITT population

	Vapreotide	Placebo	All	P-value
N	98	98	196	
Sex ratio	2.2	4.8	3.1	**p = 0.020**[8]
Age (years)	56 (32 ; 73)[9]	54 (29 ; 75)	56 (29 ; 75)	p = 0.976[10]
Weight (kg)	70 (36 ; 106)	70 (48 ; 120)	70 (36 ; 120)	p = 0.902[10]
Height (cm)	170 (152 ; 190)	169 (151 ; 190)	170 (151 ; 190)	p = 0.580[10]

Table 3.1.1.3 indicated that the median age was 56 years (range 29 to 75), median height was 170 cm (range 151 to 190) and median weight was 70 kg (range 36 to 120). Male patients accounted for 83% of the placebo group and 68º/o of the vapreotide group. The proportion of males was significantly higher in the placebo group than in vapreotide group. The other demographie characteristics were comparable between the two treatment groups.

Table 3.1.1.4 (sponsor's) Past and concomitant diseases at admission for ITT population

	Vapreotide	Placebo	All	P-value
N	98	98	196	
At least 1 past and/or concomitant disease	77 (79%)	81 (83%)	158 (81%)	-
Abnormal clinical examination :				
– Digestive tract	42 (43%)	36 (37%)	78 (40%)	p = 0.381[11]
– Cardio-vascular system	29 (30%)	20 (20%)	49 (25%)	p = 0.138[11]
– Endocrine system	26 (27%)	21 (21%)	47 (24%)	p = 0.403[11]
– ENT/Lungs system	12 (12%)	23 (23%)	35 (18%)	**p = 0.040**[11]
– Bones-joints	11 (11%)	19 (19%)	30 (15%)	p = 0.112[11]
– Nervous system	14 (14%)	15 (15%)	29 (15%)	p = 0.841[11]

Table 3.1.1.4 indicated that past and/or concomitant diseases were reported at entry in the study for 81% of the patients. Blood analysis and infections/parasites examinations were assessed as normal for at least 90% of the patients. Similarly, uro-genital function and nervous function were assessed as normal for at least 85% of the patients. Reported concomitant and/or past diseases were as follows

– Digestive diseases (40%), mainly acquired absence of organs (not elsewhere classified),
– Cardio-vascular diseases (25%), mainly essential (primary) hypertension,
– Endocrine diseases (24%) with a majority of insulin and non-insulin dependent diabetes mellitus,
– Ear, Nose and Throat (ENT) diseases (18%) including 9 malignant neoplasms,
– Bones-joints disorders (15%),
– Nervous system disorders (15%) with a majority of depressive episodes and epilepsy.

Based upon the p-values, the applicant declared that the concomitant diseases for the two treatment groups were comparable except for abnormal examination of ENT and lungs system.

Applicant's Efficacy Analysis Results and Conclusions

Using ITT patient population, Table 3.1.1.5 presented the analysis results for the primary endpoint (hemostasis at 5-days after endoscopic treatment) and the associated assessments by Chi-square test.

Table 3.1.1.5 (Sponsor's) Primary endpoint analysis and the associated assessments – ITT population

	Vapreotide	Placebo	All	P-value
N	98	98	196	
Hemostasis at 5 days	65 (66%)	49 (50%)	114 (58%)	**p = 0.021**[38]
– Hemorrhage controlled at Tendo+6h	86 (88%)	59 (60%)	145 (74%)	**p = 0.001**[38]
– Hemostasis between Tendo+6h and Tendo+48h	74 (76%)	63 (64%)	137 (70%)	p = 0.087[38]
– Hemostasis at Tendo+48h	72 (73%)	53 (54%)	125 (64%)	**p = 0.005**[38]
– Hemostasis between Tendo+48h and Tendo+120h	76 (78%)	70 (71%)	146 (74%)	p = 0.326[38]

Note: Tendo denotes time of end of endoscopy.

Table 3.1.1.5 indicated that in the intention-to-treat analysis, the primary endpoint (hemostasis with survival for the 5-day period) was achieved significantly more often with vapreotide (66% of patients) than placebo (50% of patients; p=0.02).

The applicant indicated that the results of the primary endpoint analysis and the associated assessments using per-protocol population were similar to that using ITT population.

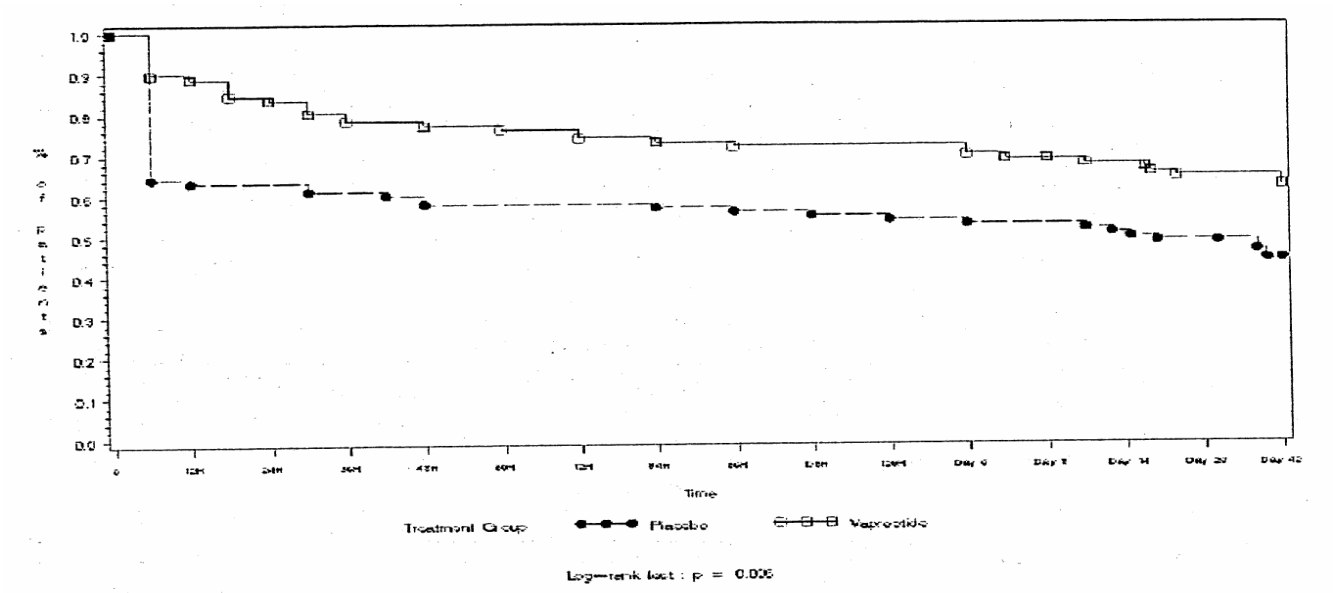
For the analysis of time to variceal bleeding, Table 3.1.1.6 presented the result of time to therapeutic failure at different time periods by Log-rank test while Figure 3.1.1.1 demonstrated the Kaplan-Meier curve for time to therapeutic failure from end of endoscopy to Day 42.

Table 3.1.1.6 (Sponsor's) Time to therapeutic failure at different time periods – ITT population

Period	p (log-rank test)
Tendo to Tendo+6h	0.0001
Tendo+6h to Tendo+48h	0.003
Tendo to Tendo+48h	0.003
Tendo+48h to Tendo+120h	0.028
Tendo to Tendo+120h	0.017
Tendo to Day 42	0.006
Tendo+120h to Day 42	0.011

Note: Tendo denotes time of end of endoscopy.

Figure 3.1.1.1 (Applicant's) Time to therapeutic failure from end of endoscopy to Day 42 – ITT population



Based upon the results using Log-rank test from Table 3.1.1.6, the applicant indicated that time to therapeutic failure was significantly longer (i.e., better) in vapreotide group than in placebo group at all times, including Day 5 (p=0.017) and the overall 6-week period of observation (p=0.006).

In addition, the applicant emphasized that therapeutic failures could occur at any time period (0 to 6h, 6 to 48h, and 48 to 120h), but were observed more frequently during the early phases of infusion, demonstrated in Figure 3.1.1.1.

For the secondary analysis, the applicant analyzed: Local hemostasis (active bleeding at endoscopy), General hemostasis 6 hours after randomization, Number of re-bleeding episodes, Number of units of blood transfused, Duration of hospitalization, Number of deaths, and Child-Pugh score. At significance level of .05, using ITT patient population, the applicant declared that for the following secondary endpoints, study drug vapreotide were significantly better than placebo: active bleeding at endoscopy (p=0.031), hemostasis at 6 hours after randomization (p=0.001), At least one unit of blood transfused between 6 hours after end of endoscopy and 48 hours after end of endoscopy (p=0.006), and Number of blood units transfused during the first 5 days (p=0.042).

The applicant indicated that the secondary endpoint analyses using per-protocol population were similar to that using ITT population.

Finally, the applicant concluded that this study showed that the early association of vapreotide to endoscopic treatment was more effective than placebo for the control of acute variceal bleeding in cirrhotic patients.

Reviewer's Analysis and Comments

In order to validate the sponsor's efficacy claim, this reviewer performs the following two analyses: 1) primary efficacy analysis by center and 2) baseline variable analysis.

1.) Primary efficacy analysis by center

In order to explore whether the superiority of vapreotide to placebo assessed by the primary endpoint, hemostasis at 5 days after endoscopic treatment, was dominated by certain center, this reviewer analyzes the differences in proportions on the primary endpoint to compare the efficacy of vapreotide versus placebo using ITT population. The centers used in this analysis are the centers defined by the applicant. Table 3.1.1.7 presents the result. Data used in this reviewer's analysis were submitted by the applicant on July 21, 2004.

Table 3.1.1.7 (Reviewer's) Proportion difference analysis on hemostasis at 5 days using ITT population

CENTER [T]	PLACEBO (P) SUCCESS RATE % (N)	VAPREOTIDE (V) SUCCESS RATE % (N)	DIFFERENCE V – P (95% CI)	IF 95% CI LOWER LIMIT > 0
Center 1	50.0 (10)	80.0 (10)	30.0 (-0.15, 0.67)	No
Center 2	54.6 (11)	63.6 (11)	9.0 (-0.34, 0.50)	No
Center 10	40.0 (5)	50.0 (6)	10.0 (-0.50, 0.65)	No
Center 12	66.7 (6)	62.5 (8)	- 4.2 (-0.54, 0.48)	No
Center 14	50.0 (8)	71.4 (7)	21.4 (-0.31, 0.68)	No
Center 18	38.5 (13)	80.0 (15)	41.5 (0.02, 0.71)	Yes
Centers with 5 to 10 patients pooled	54.1 (37)	67.7 (34)	13.6 (-0.1, 0.36)	No
Centers with < 5 patients pooled	37.6 (8)	28.6 (7)	-9.0 (-0.58, 0.41)	No
Overall results	50.0 (98)	66.3 (98)	16.3 (0.024, 0.30)	Yes

[t]: Centers 1, 2, 10, 12, 14, and 18 had more than 10 patients enrolled and were analyzed separately;

Table 3.1.1.7 shows that for all centers except Center 18, the lower limits of the 95% two-sided confidence interval on the hemostasis rate difference of vapreotide minus that of placebo are not greater than zero. This result indicates that only for Center 18 with 28 patients, the hemostasis rate at end of Day 5 of vapreotide is significantly higher than that of placebo.

In addition, Table 3.1.1.7 also indicates that the hemostasis rates at Day 5 of vapreotide are numerically higher than placebo for most centers but lower than that of placebo for Center 12 and the collective Centers with fewer than 5 patients. However, Breslow-Day test for heterogeneity across Centers does not show significance (p=0.83), indicating that the impact of

center effect on treatment efficacy comparison is able to be ignored.

In order to further investigate whether the superiority of vapreotide to placebo reported by the applicant (p=0.021, Table 3.1.1.5) is driven by Center 18, this reviewer performs the applicant's method (Chi-square test) to compare the hemostasis rates at end of Day 5 between the two treatment groups using ITT patient population excluding patients from Center 18. Table 3.1.1.8 presents the result.

Table 3.1.1.8 (Reviewer's) Proportion difference analysis on hemostasis at end of Day 5 using ITT population excluding Center 18

	PLACEBO (P) SUCCESS RATE % (N)	VAPREOTIDE (V) SUCCESS RATE % (N)	DIFFERENCE V – P (95% CI)	P-VALUE FOR CHI-SQUARE TEST
ITT Patients excluding Center 18	51.8 (85)	63.9 (83)	12.1 (-0.03, 0.27)	0.11

Table 3.1.1.8 shows that at significance level of 0.05, after excluding patients of Center 18, the effectiveness of vapreotide is no longer superior to that of placebo (p=0.11) assessed by the hemostasis rate at end of Day 5. In addition, after excluding patients of Center 18, the p-value for Log-Rank test on time to therapeutic failure (bleeding) assessed from at end of endoscopy to 5 days after end of endoscopy increases from 0.017 to .096, showing vapreotide is also no longer significantly better than placebo.

Therefore, the efficacy analysis results on the primary endpoint, hemostasis rate at end of Day 5 after endoscopic treatment and therapeutic failure (bleeding) assessed from end of endoscopy to 5 days after end of endoscopy suggest that patients (14%; 28/196) from Center 18 may dominate the superiority of vapreotide to placebo.

2) Baseline variable analysis

The medial officer indicates that patients with large size of esophageal varices or more severe cirrhotic disease are expected to have worse clinical outcomes. Therefore, based upon the medical officer's logic, this reviewer performs the logistic regression analysis to explore the effects of size of esophageal varices and Child-Pugh's classification at entrance on the primary endpoint (hemostasis rate at end of Day 5). In the logistic regression analysis, the size of esophageal varices is classified as large versus small. Similarly, the Child-Pugh's classification at entrance is also divided into two levels: the first level 'A&B" is a combined code of codes A and B while the second level is the code 'C' (more severe). The result of the logistic regression is presented in Table 3.1.1.9.

Table 3.1.1.9 (Reviewer's) Result of the logistic regression analysis using ITT population

Effects	Odds Ratio Estimate	95% Wald Confidence Interval	P-value for testing Odds Ratio
Child- Pugh (Code 'A&B' vs. 'C')	1.47	(0.772, 2.80)	0.24
Size of Varix (Small vs. Large)	2.62	(1.26, 5.46)	0.01*

***: Significance at significance level of .05.**

Table 3.1.1.9 indicates that the odds of hemostasis at end of Day 5 for patients with small size of esophageal varices is 2.62 times higher than that of patients with large size of esophageal varices and at significance level of .05, the 2.62 times higher is significant (p = .01).

Since the size of esophageal varix significantly impact the hemostasis rate at end of Day 5, in order to investigate whether the significant effectiveness for vapreotide versus placebo affected by the distributions on the size of esophageal varix, this reviewer compares the percents of patients with small varix size for vapreotide versus placebo between patients at Center 18 and patients not at Center 18 using ITT population.

Table 3.1.1.10 presents the percents of patients with small and large size of esophageal varices by treatment group separately for patients at Center 18 and not at Center 18.

Table 3.1.1.10 (Reviewer's) Percents of patients with small or large size of esophageal varices using ITT population

ESOPHAGEAL VARIX	SMALL SIZE % (n/N)	LARGE SIZE % (n/N)
Patients not at Center 18		
Vapreotide	27 % (20/73)	73% (53/73)
Placebo	29 % (23/78)	71 % (55/78)
Patients at Center 18		
Vapreotide	54 % (7/13)	46 % (6/13)
Placebo	17 % (2/12)	83 % (10/12)

Note: 20 patients missing values concerning the size of varices.

Table 3.1.1.10 indicates that the percents of patients with small size of esophageal varices between vapreotide (27%) and placebo (29%) are approximately equal for patients not at Center 18. However, for patients at Center 18, the percent of patients with small size of esophageal varices in the vapreotide treatment group is three times higher than that of the placebo group (54% for vapreotide versus 17% for placebo). Since unlike other centers, for Center 18, much higher percents of patients in the vapreotide group had small size of esophageal varices than that of placebo group, the effectiveness of vapreotide significantly better than that of placebo shown by center 18 may be biased in favor of vapreotide due to imbalanced distribution of small-sized varices between the two treatment groups.

3.2 Evaluation of Safety

3.2.1 Study DEB-96-VAP-14

Two hundred and eighty nine adverse events were recorded during the whole study. Between admission to hospital and randomization into the study, 4 patients experienced a total of 5 adverse events. The applicant indicated that these events were considered as concomitant symptoms as study medication was not yet initiated. In the vapreotide group, these events were mild T wave inversion and arteritis classified as serious adverse event. In the placebo group, these events were mild edema with severe sepsis and moderate encephalopathy.

By convention, natural complications of cirrhosis (such as re-bleeding and encephalopathy) were also recorded as adverse events during the whole study. With these definitions, at least one adverse event occurred in 41% (93/227) of the patients (49/116 under placebo and 44/111 under vapreotide) during study drug infusion. The most frequently reported adverse events were major clinical manifestations of portal hypertension:

- Central and peripheral nervous system disorders with a majority of encephalopathy,
- Civer and biliary system disorders with a majority of gastro-intestinal hemorrhage,
- "Body as a whole-general disorders" with mainly hyperpyrexia,
- Psychiatric disorders with a majority of deiirium,
- Respiratory system disorders.

Intensity of these adverse events was mainly rated as moderate or severe. Most of them were classified as not related to the study drug.

During the period following the end of product infusion, at least one adverse event was observed in 39% (88/227) of the patients (47/116 under placebo and 41/111 under vapreotide). The most common events were:

- Liver and biliary system disorders with a majority of hematemesis,
- Gastro-intestinal system disorders with mainly esophageal ulceration,
- Central and peripheral nervous system disorders with mainly encephalopathies,
- "Body as a whole-general disorders" with a majority of ascites,
- Resistance mechanism disorders with a majority of sepsis.

These adverse events were mainly severe, and only a minority was considered to some degree as related to the study drug (placebo or vapreotide).

The two treatment groups were comparable for the rate of patients with at least one concomitant symptom or one adverse event (see Table 3.2.1.1).

Table 3.2.1.1(Applicant's) Concomitant symptoms or adverse events using safety population

	Vapreotide	Placebo	All	P-value
N	111	116	227	
Patients with at least one concomitant symptom before randomization.	2 (2%)	2 (2%)	4 (2%)	p = 1.000[62]
Number of events documented	*2*	*3*	*5*	
Patients with at least one adverse event during product infusion	44 (40%)	49 (42%)	93 (41%)	p = 0.690[63]
Number of events documented	*67*	*85*	*152*	
Patients with at least one adverse event after the end of product infusion	41 (37%)	47 (41%)	88 (39%)	p = 0.580[63]
Number of events documented	*61*	*71*	*132*	
Patients with at least one adverse event during or after the product infusion	71 (61.2%)	68 (61.2%)	139 (61.2%)	p = 0.993[64]

In conclusion, the applicant emphasized that vapreotide was shown to be safe and well tolerated.

4.0 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 GENDER, RACE, AND AGE

Study DEB-96-VAP-14

In order to assess the consistency of the treatment effect of vapreotide across subgroups, this reviewer performs the subgroup analysis using Chi-square test on the primary endpoint of hemostasis at end of Day 5 based upon ITT patient population. Since this NDA submission does not provide data on race, the subgroups analyzed are only for Gender (Male and Female) and Age group (≤ 65 and > 65).

Gender (Females and Males)

Table 4.1.1 presents the results of treatment efficacy comparisons for vapreotide versus placebo by gender.

Table 4.1.1 (Reviewer's) Proportion difference analysis on hemostasis at end of Day 5 using ITT population

	PLACEBO (P) SUCCESS RATE % (N)	VAPREOTIDE (V) SUCCESS RATE % (N)	DIFFERENCE % (V-P)	P-VALUE FOR CHI-SQUARE TEST
Female	52.9 (17)	64.5 (31)	11.6	0.43
Male	49.4 (81)	67.2 (67)	17.8	0.029*

***: Significance at significance level of 0.05.**

Table 4.1.1 indicates that at significance level of 0.05, for males, the hemostasis rate at end of Day 5 after endoscopic treatment for vapreotide is significantly higher than that of placebo

(p=0.029). However, for females, the hemostasis rate at end of Day 5 after endoscopic treatment for vapreotide is only numerically higher than that of placebo (p=0.43).

Age group (≤ 65 and > 65)

Table 4.1.2 presents the results of treatment efficacy comparisons for vapreotide versus placebo by Age group (≤ 65 and > 65).

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Table 4.1.2 (Reviewer's) Proportion difference analysis on hemostasis at end of Day 5 using ITT population

	PLACEBO (P) SUCCESS RATE % (N)	VAPREOTIDE (V) SUCCESS RATE % (N)	DIFFERENCE % (V-P)	P-VALUE FOR CHI-SQUARE TEST
Age ≤ 65	46.8 (79)	66.3 (80)	19.5	0.014*
Age > 65	63.2 (19)	66.7 (18)	3.5	0.72

***: Significance at significance level of 0.05.**

Similarly, Table 4.1.2 shows that at significance level of 0.05, for patients with ages not greater than 65, the hemostasis rate at end of Day 5 after endoscopic treatment for vapreotide is significantly higher than that of placebo (p=0.014). However, for patients with age greater than 65, the hemostasis rate at end of Day 5 for vapreotide is only numerically higher than that of placebo (p=0.72).

4.2 OTHER SPECIAL/SUBGROUP POPULATIONS - Not applicable

5.0 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

- For pivotal Study DEB-96-VAP-14, the by-Center efficacy analysis result on the primary endpoint (hemostasis at end of Day 5 after endoscopic treatment) indicates that the rate for vapreotide treated patients is significantly higher than that for placebo only for Center 18 (14 % of ITT patients; 28/196). After excluding patients from Center 18, the efficacy analysis results on both the primary endpoint (hemostasis rate at end of Day 5 after endoscopic treatment) and time to therapeutic failure from end of endoscopy to 5 days after endoscopic treatment do not demonstrate that vapreotide is significantly better than placebo. Thus, the efficacy analysis results on the primary endpoint (hemostasis rate at end of Day 5 after endoscopic treatment) and therapeutic failure (bleeding) assessed from at end of endoscopy to 5 days after end of endoscopic treatment indicate that patients at Center 18 may dominate the superiority of vapreotide to placebo.
- The baseline variable analysis indicates that the odds of the hemostasis at end of Day 5 after endoscopic treatment for patients with small size of esophageal varices is significantly higher than that of patients with large size of esophageal varices. This variable is equally distributed between treatment groups for patients not at Center 18. However, for center 18, the percent of patients in the vapreotide group with small size of esophageal varix is more than three times higher than that in the placebo group.

Accordingly, the effectiveness of vapreotide relative to placebo observed for Center 18 may be due to the imbalance in varix sizes.

- For the early-terminated Study DEP-97-VAP-02 and the pilot Study DEB-01-VAP-07, as noted by this reviewer in the section 2.1, "Overview", the efficacy analysis results provided by the applicant did not demonstrate significant evidence to support the efficacy of vapreotide in the treatment of acute variceal bleeding related to portal hypertension associated with endoscopic treatment.
- In summary, based upon the efficacy results shown by the three trials, one notes that the two studies (Studies DEB-01-VAP-07 and DEP-97-VAP-02) did not show vapreotide significantly better than placebo when assessed by the primary endpoint hemostasis at end of Day 5 after endoscopic treatment. Only Study DEB-96-VAP-14 showed the superiority of vapreotide to placebo when assessed by the primary endpoint. However, using ITT population, the superiority of vapreotide to placebo appears to be driven by patients at Center 18 (14% of ITT population; 28/196). In addition, the significant effectiveness of vapreotide shown by Center 18 may be due to relatively a large percent of patients with small esophageal varices in the vapreotide group when compared with patients not at Center 18**.** The superiority of vapreotide to placebo shown by the pivotal Study DEB-96-VAP-14 is not robust.
- To conclude that a single study is adequate in support of an effectiveness claim, the guidance for industry (Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products, 1998) recommends that the efficacy result should be statistically very persuasive. The Guidance emphasizes that in a multi-center study, a very low p-value (for example, less than .00125) indicates the result is highly inconsistent with the null hypothesis of no treatment effect. Accordingly, for a single study to be considered statistically persuasive in support of the efficacy claim, the p-value for the treatment comparison should be very small. As a result, the superiority of vapreotide to placebo shown by a single pivotal Study DEB-96-VAP-14 is not statistically persuasive.

5.2 Recommendations

From the statistical perspective, based upon the remarks stated in the section of "Statistical Issues and Collective Evidence", the single pivotal Study DEB-96-VAP-14 does not provide substantial evidence to support the use of vapreotide in the treatment of acute variceal related to portal hypertension associated with endoscopic treatment.

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STATISTICAL REVIEW FOR SPECIAL PROTOCOL

IND & NDA#: 59287 & 21-761

APPLICANT: H3 Pharma, Inc.

NAME OF DRUG: Sanvar (Vapreotide acetate 0.6mg) injection

INDICATION: Treatment of acute variceal bleeding related to portal hypertension in association with endoscopic treatment.

REVIEWER: Wen-Jen Chen, Ph.D., Statistician

MEDICAL DIVISION: Gastroenterology Products

Background

After completing the NDA review for this application, the medical division of Gastrointestinal and Coagulation Drug Products issued an approvable letter, dated December 21, 2004, to inform H3 Pharma, Inc. that before the application may be approved, the applicant needs to address the lack of substantial evidence that demonstrates the efficacy of vapreotide for the use in treatment of acute variceal bleeding related to portal hypertension associated with endoscopic treatment. In particular, the letter indicated that "the applicant needs to provide additional efficacy data from a well- controlled clinical trial."

To address the lack of substantial efficacy evidence, the applicant proposed a single arm trial with 50 patients in a Type A meeting package dated 21 November 2005. The proposed efficacy assessment criteria claimed that the study will be considered positive if the point estimate of the proportion of subjects achieving control of bleeding at the end of the 5-day infusion (i.e., primary endpoint identical to that in the pivotal study) is within 10% of the proportion estimated from the three existing randomized, double-blind, placebo controlled studies (DEB-96-VAP-14, DEB-01-VAP-07, and DEB-02-VAP-06).

From the statistical perspective, this reviewer did not deem that the applicant's one single arm trial can resolve the efficacy issue stated in the approvable letter. However, in a teleconference meeting on February 8, 2006, the medical division accepted the applicant's proposal based upon clinical considerations. Some modifications on the single arm trial were proposed by the FDA and acknowledged by the applicant. The meeting minutes contain the information on the clinical proposal. In order to clarify that from the statistical perspective, the single arm study proposed by the applicant can not resolve the efficacy issue stated in the approvable letter, this reviewer wrote an addendum and put it into the DFS system on February 16, 2006. In the addendum, this reviewer commented on the efficacy issues of the single arm trial by answering the questions posted by the applicant in the Type A meeting package.

In this special protocol application, the applicant essentially followed the agreement between the medical division and the applicant made on February 8, 2006, to design a single-arm (Sanvar) open label study (DEBV-06-VAP-301) using Sanvar administered for 5 days in patients with acute variceal bleeding due to portal hypertension. In the single-arm study, the applicant plans to enroll 70 evaluable subjects (including a minimum of 9 and maximum of 26 patients with Child-Pugh Class C) in the ITT population. As for the statistical efficacy analysis, the applicant indicates that since this is primarily a descriptive study, no formal hypothesis testing will be performed. All efficacy outcomes will be presented as descriptive statistics. Ordinal and continuous data will be presented overall and by center, in the form of descriptive statistics, as number of patients, median, mean, standard deviation, and 95% confidence interval. Categorical data will be presented in the form of contingency tables including the 95% confidence interval. In the analysis of efficacy plan, the applicant does not specify the criterion to assess the efficacy evidence of Sanvar based upon the descriptive statistics developed by the single-arm trial. However, from Question 8 (posted by the applicant in the special protocol) "Does the Division

agree that the study will be deemed successful if the results are quantitatively similar to those in the pivotal French Study DEB-96-VAP-14?", it seems that the applicant intends to compare the 95% confidence interval on the proportion of hemostasis at end of 5 days after endoscopic treatment (primary outcome) calculated by the new single-arm study to the hemostasis rate of Sanvar calculated by the French Study.

Based upon the single-arm study along with the descriptive statistical analysis plan proposed by the applicant, the responses to the following three questions (Questions 1, 8, and 9) requested by the applicant for the special protocol are given below.

Reviewer's response to the applicant's questions

1. **Does the Division agree that a single-arm study will be acceptable?**

Statistical Response: No.

The single-arm (Sanvar) study proposed by the applicant is an un-blinded (open label), non-randomized, and uncontrolled (no placebo or active- controlled arm included) clinical trial. However, ICH E9 "Guidance for Industry, E9 Statistical Principles for Clinical Trials" indicates that the most important design techniques for avoiding bias assessments in clinical trials are blinding and randomization.

Blinding is intended to limit the occurrence of conscious and unconscious bias in the conduct and interpretation of a clinical trial arising from the influence that the knowledge of treatment may have on the recruitment and allocation of subjects, their subsequent care, the attitudes of subjects to the treatments, the assessment of end-points, the handling of withdrawals, the exclusion of data from analysis, and so on.

Randomization introduces a deliberate element of chance into the assignment of treatments to subjects in a clinical trial. During subsequent analysis of the trial data, it provides a sound statistical basis for the quantitative evaluation of the evidence relating to treatment effects. It also tends to produce treatment groups in which the distributions of prognostic factors, known and unknown, are similar. In combination with blinding, randomization helps to avoid possible bias in the selection and allocation of subjects arising from the predictability of treatment assignments.

However, the single-arm trial (DEBV-06-VAP-301) proposed by the applicant is an open-label study; both the investigators and patients know the administered treatment. Accordingly, unlike the blinded trials avoiding a biased efficacy analysis, the single arm trial clearly may induce biased efficacy assessments.

In addition, for the efficacy analysis, the applicant intends to use data from the new single arm study to calculate the 95% confidence interval on the hemostasis rate at end of 5 day infusion after endoscopic treatment for Sanvar and compares it to the hemostasis rate of Sanvar in the

French Study (DEB-96-VAP-14). If the results of the new study are quantitatively similar to those in the French study, then the applicant will claim that the new study successfully demonstrates the efficacy of Sanvar.

In contrast to an efficacy analysis performed in a randomized trial, the efficacy analysis proposed by the applicant in the single-arm trial is a cross-trial comparison analysis. It is noted that the patients enrolled in the new study (DEBV-06-VAP-301) will not be randomized together with those patients enrolled in the French Study (DEB-96-VAP-14). The baseline characteristics of patients enrolled in the new proposed study are very likely not similar to that of patients enrolled in the French study. Accordingly, the efficacy comparison of Sanvar between the new study and the French study will not be a valid comparison. In addition, the applicant does not provide rigorous statistical definition of "results quantitatively similar" in the special protocol. Therefore, deciding whether the results of the new study are quantitatively similar to those in the French study and using that comparison to assess the efficacy of Sanvar lacks a statistical theoretical foundation and the cross-trial comparison analysis is not rest upon a valid randomized basis. As a result, the efficacy analysis method proposed by the applicant can not objectively assess the efficacy of Savar.

In conclusion, from the statistical perspective, based upon the above comments, the single-arm clinical trial is not a well-controlled trial and the proposed analysis method is not statistically sound. The single-arm trial is not acceptable.

8. Does the Division agree that there is no need to demonstrate a statistically robust result? Does the Division agree that the study will be deemed successful if the results are quantitatively similar to those in the pivotal French Study DEB-96-VAP-14?

Statistical Response: No.

The three existing studies (including the French study DEB-96-VAP-14) submitted by the applicant did not provide substantial evidence to demonstrate that Sanvar is an effective drug. An approvable letter, dated December 21, 2004, informed the applicant that before the application may be approved, the applicant needs to address the lack of substantial evidence that demonstrates the efficacy of Sanvar (vapreotide) for the use in treatment of acute variceal bleeding related to portal hypertension associated with endoscopic treatment. In particular, the letter indicated that the applicant needs to provide additional efficacy data from a well-controlled clinical trial.

As commented in the response to Question 1, the single-arm study proposed by the applicant is not a well-controlled clinical trial as required by the approvable letter. In addition, deciding whether the results of the new study are quantitatively similar to those in the French study and using that comparison to assess the efficacy of Sanvar lacks a statistical theoretical foundation and the cross-trial comparison analysis is not rest upon a valid randomized basis. Consequently, from the statistical perspective, the proposed single-arm trial along with its efficacy analysis is deemed not able to provide substantial evidence to demonstrate the efficacy of Sanvar in the treatment of acute variceal bleeding related to portal hypertension in association with endoscopic

treatment. For detailed comments on the issues of the proposed single-arm trial along with its efficacy analysis method, refer to the response to Question 1.

9) Does the Division agree that the proposed study is appropriately designed to resolve the clinical and statistical deficiencies specified in the NDA approvable letter, provided that the results of the ITT population for the primary endpoint are similar to those reported in the vapreotide of the pivotal French Study DEB-96-VAP-14?

Statistical Response: No.

As indicated in the response to Question 1, the single-arm study (DEBV-06-VAP-301) proposed by the applicant is not a well-controlled study as required by the approvable letter. It will not resolve the problem of lack of substantial evidence in the NDA demonstrating the efficacy of Sanvar (vapreotide). Refer to the response to Question 1 for detailed comments on the issue of the proposed single-arm trial.

In addition, as indicated in the response to Question 1, the proposed analysis method is a cross-trial comparison analysis lacking a valid randomized basis and “results quantitative similar” lacks a statistical theoretical foundation. Consequently, it is impossible to objectively assess whether the results of the ITT population for the primary endpoint of the new study are quantitatively similar to those reported in the Vapreotide (Sanvar) arm of the pivotal French Study DEB-96-VAP-14 based on statistical theory.

Therefore, from the statistical perspective, the proposed single-arm study does not provide legitimate assessment to resolve the deficiency specified in the NDA approvable letter.

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Wen-Jen Chen
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[Code of Federal Regulations]
[Title 21, Volume 5]
[Revised as of April 1, 2002]
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[Page 150-152]

TITLE 21--FOOD AND DRUGS

CHAPTER I--FOOD AND DRUG ADMINISTRATION, DEPARTMENT OF HEALTH AND HUMAN SERVICES (CONTINUED)

PART 314--APPLICATIONS FOR FDA APPROVAL TO MARKET A NEW DRUG--Table of Contents

Subpart D--FDA Action on Applications and Abbreviated Applications

Sec. 314.126 Adequate and well-controlled studies.

(a) The purpose of conducting clinical investigations of a drug is to distinguish the effect of a drug from other influences, such as spontaneous change in the course of the disease, placebo effect, or biased observation. The characteristics described in paragraph (b) of this section have been developed over a period of years and are recognized by the scientific community as the essentials of an adequate and well-controlled clinical investigation. The Food and Drug Administration considers these characteristics in determining whether an investigation is adequate and well-controlled for purposes of section 505 of the act. Reports of adequate and well-controlled investigations provide the primary basis for determining whether there is ``substantial evidence'' to support the claims of effectiveness for new drugs. Therefore, the study report should provide sufficient details of study design, conduct, and analysis to allow critical evaluation and a determination of whether the characteristics of an adequate and well-controlled study are present.

(b) An adequate and well-controlled study has the following characteristics:

(1) There is a clear statement of the objectives of the investigation and a summary of the proposed or actual

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methods of analysis in the protocol for the study and in the report of its results. In addition, the protocol should contain a description of the proposed methods of analysis, and the study report should contain a description of the methods of analysis ultimately used. If the protocol does not contain a description of the proposed methods of analysis, the study report should describe how the methods used were selected.

(2) The study uses a design that permits a valid comparison with a control to provide a quantitative assessment of drug effect. The protocol for the study and report of results should describe the study design precisely; for example, duration of treatment periods, whether treatments are parallel, sequential, or crossover, and whether the sample size is predetermined or based upon some interim analysis.

Generally, the following types of control are recognized:

(i) Placebo concurrent control. The test drug is compared with an inactive preparation designed to resemble the test drug as far as possible. A placebo-controlled study may include additional treatment groups, such as an active treatment control or a dose-comparison control, and usually includes randomization and blinding of patients or investigators, or both.

(ii) Dose-comparison concurrent control. At least two doses of the drug are compared. A dose-comparison study may include additional treatment groups, such as placebo control or active control. Dose-comparison trials usually include randomization and blinding of patients or investigators, or both.

(iii) No treatment concurrent control. Where objective measurements of effectiveness are available and placebo effect is negligible, the test drug is compared with no treatment. No treatment concurrent control trials usually include randomization.

(iv) Active treatment concurrent control. The test drug is compared with known effective therapy; for example, where the condition treated is such that administration of placebo or no treatment would be contrary to the interest of the patient. An active treatment study may include additional treatment groups, however, such as a placebo control or a dose-comparison control. Active treatment trials usually include randomization and blinding of patients or investigators, or both. If the intent of the trial is to show similarity of the test and control drugs, the report of the study should assess the ability of the study to have detected a difference between treatments. Similarity of test drug and active control can mean either that both drugs were effective or that neither was effective. The analysis of the study should explain why the drugs should be considered effective in the study, for example, by reference to results in previous placebo-controlled studies of the active control drug.

(v) Historical control. The results of treatment with the test drug are compared with experience historically derived from the adequately documented natural history of the disease or condition, or from the results of active treatment, in comparable patients or populations. Because historical control populations usually cannot be as well assessed with respect to pertinent variables as can concurrent control populations, historical control designs are usually reserved for special circumstances. Examples include studies of diseases with high and predictable mortality (for example, certain malignancies) and studies in which the effect of the drug is self-evident (general anesthetics, drug metabolism).

(3) The method of selection of subjects provides adequate assurance that they have the disease or condition being studied, or evidence of susceptibility and exposure to the condition against which prophylaxis is directed.

(4) The method of assigning patients to treatment and control groups minimizes bias and is intended to assure comparability of the groups with respect to pertinent variables such as age, sex, severity of

disease, duration of disease, and use of drugs or therapy other than the test drug. The protocol for the study and the report of its results should describe how subjects were assigned to groups. Ordinarily, in a concurrently controlled study, assignment is by randomization, with or without stratification.

(5) Adequate measures are taken to minimize bias on the part of the subjects, observers, and analysts of the

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data. The protocol and report of the study should describe the procedures used to accomplish this, such as blinding.

(6) The methods of assessment of subjects' response are well-defined and reliable. The protocol for the study and the report of results should explain the variables measured, the methods of observation, and criteria used to assess response.

(7) There is an analysis of the results of the study adequate to assess the effects of the drug. The report of the study should describe the results and the analytic methods used to evaluate them, including any appropriate statistical methods. The analysis should assess, among other things, the comparability of test and control groups with respect to pertinent variables, and the effects of any interim data analyses performed.

(c) The Director of the Center for Drug Evaluation and Research may, on the Director's own initiative or on the petition of an interested person, waive in whole or in part any of the criteria in paragraph (b) of this section with respect to a specific clinical investigation, either prior to the investigation or in the evaluation of a completed study. A petition for a waiver is required to set forth clearly and concisely the specific criteria from which waiver is sought, why the criteria are not reasonably applicable to the particular clinical investigation, what alternative procedures, if any, are to be, or have been employed, and what results have been obtained. The petition is also required to state why the clinical investigations so conducted will yield, or have yielded, substantial evidence of effectiveness, notwithstanding nonconformance with the criteria for which waiver is requested.

(d) For an investigation to be considered adequate for approval of a new drug, it is required that the test drug be standardized as to identity, strength, quality, purity, and dosage form to give significance to the results of the investigation.

(e) Uncontrolled studies or partially controlled studies are not acceptable as the sole basis for the approval of claims of effectiveness. Such studies carefully conducted and documented, may provide corroborative support of well-controlled studies regarding efficacy and may yield valuable data regarding safety of the test drug. Such studies will be considered on their merits in the light of the principles listed here, with the exception of the requirement for the comparison of the treated subjects with controls. Isolated case reports, random experience, and reports lacking the details which permit scientific evaluation will not be considered.

[50 FR 7493, Feb. 22, 1985, as amended at 50 FR 21238, May 23, 1985; 55 FR 11580, Mar. 29, 1990; 64 FR 402, Jan. 5, 1999; 67 FR 9586, Mar. 4, 2002]

Guidance for Industry

Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
May 1998
Clinical 6

Guidance for Industry

Providing Clinical Evidence of Effectiveness for Human Drugs and Biological Products

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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
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GUIDANCE FOR INDUSTRY[1]

Providing Clinical Evidence of Effectiveness[2] for Human Drug and Biological Products

I. INTRODUCTION

This document is intended to provide guidance to applicants planning to file new drug applications (NDAs), biologics license applications (BLAs), or applications for supplemental indications on the evidence to be provided to demonstrate effectiveness.

This document is also intended to meet the requirements of subsections 403(b)(1) and (2) of the Food and Drug Administration Modernization Act (the Modernization Act) of 1997 for human drug and biological products (P.L. 105-115).[3] Subsection 403(b)(1) directs FDA to provide guidance on the circumstances in which published matter may be the basis for approval of a supplemental application for a new indication. Section III of this guidance satisfies this requirement by describing circumstances in which published matter may partially or entirely support approval of a supplemental application. Subsection 403(b)(2) directs FDA to provide guidance on data requirements that will avoid duplication of previously submitted data by recognizing the availability of data previously submitted in support of an original application to support approval of a supplemental application. Section II of this guidance satisfies this requirement by describing a range of circumstances in which related existing data, whether from an original application or other sources, may be used to support approval of a supplemental application.

In 1962, Congress amended the Federal Food, Drug, and Cosmetic Act to add a requirement that, to obtain marketing approval, manufacturers demonstrate the effectiveness of their products through the conduct of adequate and well-controlled studies. Since then, the issue of what constitutes sufficient evidence of effectiveness has been debated by the Agency, the scientific community, industry, and others. Sound evidence of effectiveness is a crucial component of the Agency's benefit-risk assessment of a new product or use. At the same time, the demonstration of effectiveness represents a major component of drug development time and cost; the amount

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[1] This guidance document represents the agency's current thinking on providing clinical evidence of effectiveness for human drug and biological products. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statute, regulations, or both.

[2] As used in this guidance, the term efficacy refers to the findings in an adequate and well-controlled clinical trial or the intent of conducting such a trial and the term effectiveness refers to the regulatory determination that is made on the basis of clinical efficacy and other data.

[3] The Modernization Act requirements in Section 403 also apply to animal drugs and medical devices. These products will be addressed in separate guidances.

and nature of the evidence needed can therefore be an important determinant of when and whether new therapies become available to the public. The public health is best served by the development of sound evidence of effectiveness in an efficient manner.

The science and practice of drug development and clinical evaluation have evolved significantly since the effectiveness requirement for drugs was established, and this evolution has implications for the amount and type of data needed to support effectiveness in certain cases. As a result of medical advances in the understanding of pathogenesis and disease staging, it is increasingly likely that clinical studies of drugs will be more narrowly defined to focus, for example, on a more specific disease stage or clinically distinct subpopulation. As a consequence, product indications are often narrower, the universe of possible indications is larger, and data may be available from a number of studies of a drug in closely related indications that bear on a determination of its effectiveness for a new use. Similarly, there may be studies of a drug in different populations, studies of a drug alone or in combination, and studies of different doses and dosage forms, all of which may support a particular new use of a drug. At the same time, progress in clinical evaluation and clinical pharmacology have resulted in more rigorously designed and conducted clinical efficacy trials, which are ordinarily conducted at more than one clinical site. This added rigor and scope has implications for a study's reliability, generalizability, and capacity to substantiate effectiveness.

Given this evolution, the Agency has determined that it would be appropriate to articulate its current thinking concerning the quantitative and qualitative standards for demonstrating effectiveness of drugs and biologics. FDA hopes that this guidance will enable sponsors to plan drug development programs that are sufficient to establish effectiveness without being excessive in scope. The guidance should also bring greater consistency and predictability to FDA's assessment of the clinical trial data needed to support drug effectiveness.

Another major goal of this guidance is to encourage the submission of supplemental applications to add new uses to the labeling of approved drugs. By articulating how it currently views the quantity and quality of evidence necessary to support approval of a new use of a drug, FDA hopes to illustrate that the submission of supplements for new uses need not be unduly burdensome.

II. QUANTITY OF EVIDENCE NECESSARY TO SUPPORT EFFECTIVENESS

A. Legal Standards for Drug and Biological Products

Drugs: The effectiveness requirement for drug approval was added to the Federal Food, Drug, and Cosmetic Act (the Act or the FDC Act) in 1962. Between passage of the Act in 1938 and the 1962 amendments, drug manufacturers were required to show only that their drugs were safe. The original impetus for the effectiveness requirement was Congress's growing concern about the misleading and unsupported claims being made by pharmaceutical companies about their drug products coupled with high drug prices. After two years of hearings on these issues, Congress adopted the 1962 Drug Amendments,

which included a provision requiring manufacturers of drug products to establish a drug's effectiveness by "substantial evidence." *Substantial evidence* was defined in section 505(d) of the Act as "evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof."

Since the 1962 Amendments added this provision to the statute, discussions have ensued regarding the quantity and quality of the evidence needed to establish effectiveness. With regard to quantity, it has been FDA's position that Congress generally intended to require at least two adequate and well-controlled studies, each convincing on its own, to establish effectiveness. (See e.g., Final Decision on Benylin, 44 FR 51512, 518 (August 31, 1979); *Warner-Lambert Co. V. Heckler*, 787 F. 2d 147 (3d Cir. 1986)). FDA's position is based on the language in the statute[4] and the legislative history of the 1962 amendments. Language in a Senate report suggested that the phrase "adequate and well-controlled investigations" was designed not only to describe the quality of the required data but the "quantum" of required evidence. (S. Rep. No. 1744, Part 2, 87th Cong. 2d Sess. 6 (1962))

Nevertheless, FDA has been flexible within the limits imposed by the congressional scheme, broadly interpreting the statutory requirements to the extent possible where the data on a particular drug were convincing. In some cases, FDA has relied on pertinent information from other adequate and well-controlled studies of a drug, such as studies of other doses and regimens, of other dosage forms, in other stages of disease, in other populations, and of different endpoints, to support a single adequate and well-controlled study demonstrating effectiveness of a new use. In these cases, although there is only one study of the exact new use, there are, in fact, multiple studies supporting the new use, and expert judgment could conclude that the studies together represent substantial evidence of effectiveness. In other cases, FDA has relied on only a single adequate and well-controlled efficacy study to support approval — generally only in cases in which a single multicenter study of excellent design provided highly reliable and statistically strong evidence of an important clinical benefit, such as an effect on survival, and a confirmatory study would have been difficult to conduct on ethical grounds.

In section 115(a) of the Modernization Act, Congress amended section 505(d) of the Act to make it clear that the Agency may consider "data from one adequate and well-controlled clinical investigation and confirmatory evidence" to constitute substantial

[4] Section 505(d) of the Act uses the plural form in defining "substantial evidence" as "adequate and well-controlled investigations, including clinical investigations." See also use of "investigations" in section 505(b) of the Act, which lists the contents of a new drug application.

evidence if FDA determines that such data and evidence are sufficient to establish effectiveness. In making this clarification, Congress confirmed FDA's interpretation of the statutory requirements for approval and acknowledged the Agency's position that there has been substantial progress in the science of drug development resulting in higher quality clinical trial data.

Biologics. Biological products are approved under authority of section 351 of the Public Health Service Act (PHS Act) (42 U.S.C.§ 262). Under section 351, as in effect since 1944, licenses for biologics have been issued only upon a showing that the products meet standards designed to ensure the "continued safety, purity, and potency" of the products. *Potency* has long been interpreted to include effectiveness (21 CFR 600.3(s)). In 1972, FDA initiated a review of the safety and effectiveness of all previously licensed biologics. The Agency stated then that proof of effectiveness would consist of controlled clinical investigations as defined in the provision for "adequate and well-controlled studies" for new drugs (21 CFR 314.126), unless waived as not applicable to the biological product or essential to the validity of the study when an alternative method is adequate to substantiate effectiveness (21 CFR 601.25 (d) (2)). One such adequate alternative was identified to be serological response data where a previously accepted correlation with clinical effectiveness exists. As with nonbiological drug products, FDA has approved biological products based on single, multicenter studies with strong results.

Although section 123(a) of the Modernization Act amended section 351 of the PHS Act to make it clear that separate licenses are not required for biological products and the establishments at which the products are made, the evidentiary standard for a biological product was not changed: the product must be shown to be "safe, pure, and potent" (section 351 (a)(2) of the PHS Act as amended). In the Modernization Act (section 123(f)) Congress also directed the agency to take measures to "minimize differences in the review and approval" of products required to have approved BLAs under section 351 of the PHS Act and products required to have approved NDAs under section 505(b)(1) of the FDC Act.

B. Scientific Basis for the Legal Standard

The usual requirement for more than one adequate and well-controlled investigation reflects the need for *independent substantiation* of experimental results. A single clinical experimental finding of efficacy, unsupported by other independent evidence, has not usually been considered adequate scientific support for a conclusion of effectiveness. The reasons for this include the following.

- Any clinical trial may be subject to unanticipated, undetected, systematic biases. These biases may operate despite the best intentions of sponsors and investigators, and may lead to flawed conclusions. In addition, some investigators may bring conscious biases to evaluations.

- The inherent variability in biological systems may produce a positive trial result by chance alone. This possibility is acknowledged, and quantified to some extent, in the statistical evaluation of the result of a single efficacy trial. It should be noted, however, that hundreds of randomized clinical efficacy trials are conducted each year with the intent of submitting favorable results to FDA. Even if all drugs tested in such trials were ineffective, one would expect one in forty of those trials to "demonstrate" efficacy by chance alone at conventional levels of statistical significance.[5] It is probable, therefore, that false positive findings (i.e., the chance appearance of efficacy with an ineffective drug) will occur and be submitted to FDA as evidence of effectiveness. Independent substantiation of a favorable result protects against the possibility that a chance occurrence in a single study will lead to an erroneous conclusion that a treatment is effective.

- Results obtained in a single center may be dependent on site or investigator specific factors (e.g., disease definition, concomitant treatment, diet). In such cases, the results, although correct, may not be generalizable to the intended population. This possibility is the primary basis for emphasizing the need for independence in substantiating studies.

- Rarely, favorable efficacy results are the product of scientific fraud.

Although there are statistical, methodologic, and other safeguards to address the identified problems, they are often inadequate to address these problems in a single trial. Independent substantiation of experimental results addresses such problems by providing consistency across more than one study, thus greatly reducing the possibility that a biased, chance, site-specific, or fraudulent result will lead to an erroneous conclusion that a drug is effective.

The need for independent substantiation has often been referred to as the need for replication of the finding. Replication may not be the best term, however, as it may imply that precise repetition of the same experiment in other patients by other investigators is the only means to substantiate a conclusion. Precise replication of a trial is only one of a number of possible means of obtaining independent substantiation of a clinical finding and, at times, can be less than optimal as it could leave the conclusions vulnerable to any systematic biases inherent to the particular study design. Results that are obtained from studies that are of different design and independent in execution, perhaps evaluating different populations, endpoints, or dosage forms, may provide support for a conclusion of effectiveness that is as convincing as, or more convincing than, a repetition of the same study.

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[5] p-value = 0.05, two-tailed, which implies an error rate in the efficacy (false positive) tail of 0.025 or one in forty.

C. The Quantity of Evidence to Support Effectiveness

The following three sections provide guidance on the quantity of evidence needed in particular circumstances to establish substantial evidence of effectiveness. Section 1 addresses situations in which effectiveness of a new use may be extrapolated entirely from existing efficacy studies. Section 2 addresses situations in which a single adequate and well-controlled study of a specific new use can be supported by information from other related adequate and well-controlled studies, such as studies in other phases of a disease, in closely related diseases, of other conditions of use (different dose, duration of use, regimen), of different dosage forms, or of different endpoints. Section 3 addresses situations in which a single multicenter study, without supporting information from other adequate and well-controlled studies, may provide evidence that a use is effective.

In each of these situations, it is assumed that any studies relied on to support effectiveness meet the requirements for adequate and well-controlled studies in 21 CFR 314.126. It should also be appreciated that reliance on a single study of a given use, whether alone or with substantiation from related trial data, leaves little room for study imperfections or contradictory (nonsupportive) information. In all cases, it is presumed that the single study has been appropriately designed, that the possibility of bias due to baseline imbalance, unblinding, post-hoc changes in analysis, or other factors is judged to be minimal, and that the results reflect a clear prior hypothesis documented in the protocol. Moreover, a single favorable study among several similar attempts that failed to support a finding of effectiveness would not constitute persuasive support for a product use unless there were a strong argument for discounting the outcomes in the studies that failed to show effectiveness (e.g., study obviously inadequately powered or lack of assay sensitivity as demonstrated in a three-arm study by failure of the study to show efficacy of a known active agent).

Whether to rely on a single study to support an effectiveness determination is not often an issue in contemporary drug development. In most drug development situations, the need to find an appropriate dose, to study patients of greater and lesser complexity or severity of disease, to compare the drug to other therapy, to study an adequate number of patients for safety purposes, and to otherwise know what needs to be known about a drug before it is marketed will result in more than one adequate and well-controlled study upon which to base an effectiveness determination.

This guidance is not intended to provide a complete listing of the circumstances in which existing efficacy data may provide independent substantiation of related claims; rather, it provides examples of the reasoning that may be employed. The examples are applicable whether the claim arises in the original filing of an NDA or BLA, or in a supplemental application.

1. Extrapolation from Existing Studies

In certain cases, effectiveness of an approved drug product for a new indication, or effectiveness of a new product, may be adequately demonstrated without additional adequate and well-controlled clinical efficacy trials. Ordinarily, this will be because other types of data provide a way to apply the known effectiveness to a new population or a different dose, regimen or dosage form. The following are examples of situations in which effectiveness might be extrapolated from efficacy data for another claim or product.

a. Pediatric uses

The rule revising the Pediatric Use section of product labeling (21 CFR 201.57(f)(9)(iv)) makes allowance for inclusion of pediatric use information in labeling without controlled clinical trials of the use in children. In such cases, a sponsor must provide other information to support pediatric use, and the Agency must conclude that the course of the disease and the effects of the drug are sufficiently similar in the pediatric and adult populations to permit extrapolation from adult efficacy data to pediatric patients. Evidence that could support a conclusion of similar disease course and similar drug effect in adult and pediatric populations includes evidence of common pathophysiology and natural history of the disease in the adult and pediatric populations, evidence of common drug metabolism and similar concentration-response relationships in each population, and experience with the drug, or other drugs in its therapeutic class, in the disease or condition or related diseases or conditions. Examples in which pediatric use labeling information has been extrapolated from adult efficacy data include ibuprofen for pain and loratidine for seasonal allergic rhinitis.

b. Bioequivalence

The effectiveness of alternative formulations and new dosage strengths may be assessed on the basis of evidence of bioequivalence.

c. Modified-release dosage forms

In some cases, modified release dosage forms may be approved on the basis of pharmacokinetic data linking the new dosage form to a previously studied immediate-release dosage form. Because the pharmacokinetic patterns of modified-release and immediate-release dosage forms are not identical, it is generally important to have some understanding of the relationship of blood concentration to response, including an understanding of the time course of that relationship, to extrapolate the immediate-release

data to the modified-release dosage form.

d. Different doses, regimens, or dosage forms

Dose-response relationships are generally continuous such that information about the effectiveness of one dose, dosage regimen, or dosage form is relevant to the effectiveness of other doses, regimens, or dosage forms. Where blood levels and exposure are not very different, it may be possible to conclude that a new dose, regimen, or dosage form is effective on the basis of pharmacokinetic data alone. Even if blood levels are quite different, if there is a well-understood relationship between blood concentration and response, including an understanding of the time course of that relationship, it may be possible to conclude that a new dose, regimen, or dosage form is effective on the basis of pharmacokinetic data without an additional clinical efficacy trial. In this situation, pharmacokinetic data, together with the well-defined pharmacokinetic/pharmacodynamic (PK/PD) relationship, are used to translate the controlled trial results from one dose, regimen, or dosage form to a new dose, regimen, or dosage form (See also section II.C.2.a).

2. Demonstration of Effectiveness by a Single Study of a New Use, with Independent Substantiation From Related Study Data

The discussion that follows describes specific examples in which a single study of a new use, with independent substantiation from study data in related uses, could provide evidence of effectiveness. In these cases, the study in the new use and the related studies support the conclusion that the drug has the effect it is purported to have. Whether related studies are capable of substantiating a single study of a new use is a matter of judgment and depends on the quality and outcomes of the studies and the degree of relatedness to the new use.

a. Different doses, regimens, or dosage forms

As discussed in Sections II.C.1.d, it may be possible to conclude that a new dose, regimen, or dosage form is effective on the basis of pharmacokinetic data without an additional clinical efficacy trial where blood levels and exposure are not very different or, even if quite different, there is a well-understood relationship between blood concentration and response. Where the relationship between blood concentration and response is not so well understood and the pharmacokinetics of the new dose, regimen, or dosage form differ from the previous one, clinical efficacy data will likely be necessary to support effectiveness of a new regimen. In this case, a single additional efficacy study should ordinarily be sufficient. For example, a single controlled trial was needed to support the recent approval of a once

daily dose of risperidone because the once daily and twice daily regimens had different pharmacokinetics and risperidone's PK/PD relationship was not well understood.

b. Studies in other phases of the disease

In many cases, therapies that are effective in one phase of a disease are effective in other disease phases, although the magnitude of the benefit and benefit-to-risk relationship may differ in these other phases. For example, if a drug is known to be effective in patients with a refractory stage of a particular cancer, a single adequate and well-controlled study of the drug in an earlier stage of the same tumor will generally be sufficient evidence of effectiveness to support the new use.

c. Studies in other populations

Often, responses in subsets of a particular patient population are qualitatively similar to those in the whole population. In most cases, separate studies of effectiveness in demographic subsets are not needed (see also discussion of the pediatric population in section II.C.1.a) However, where further studies are needed, a single study would ordinarily suffice to support effectiveness in age, race, gender, concomitant disease, or other subsets for a drug already shown to be generally effective in a condition or to be effective in one population. For example, a single study was sufficient to support tamoxifen use in breast cancer in males.

d. Studies in combination or as monotherapy

For a drug known to be effective as monotherapy, a single adequate and well-controlled study is usually sufficient to support effectiveness of the drug when combined with other therapy (as part of a multidrug regimen or in a fixed-dose combination). Similarly, known effectiveness of a drug as part of a combination (i.e., its contribution to the effect of the combination is known) would usually permit reliance on a single study of appropriate design to support its use as monotherapy, or as part of a different combination, for the same use. For example, a single study of a new combination vaccine designed to demonstrate adequate immune response will ordinarily provide sufficient evidence of effectiveness if the new combination contains products or antigens already proven to be effective alone or in other combinations. These situations are common for oncologic and antihypertensive drugs, but occur elsewhere as well.

e. Studies in a closely related disease

Studies in etiologically or pathophysiologically related conditions, or studies of a symptom common to several diseases (e.g., pain) can support each other, allowing initial approval of several uses or allowing additional claims based on a single adequate and well-controlled study. For example, certain anti-coagulant or anti-platelet therapies could be approved for use in two different settings based on individual studies in unstable angina/acute coronary syndrome and in the postangioplasty state. Because the endpoints studied and the theoretical basis for use of an anti-coagulant or anti-platelet drug are similar, each study supports the other for each claim. Similarly, single analgesic studies in several painful conditions would ordinarily be sufficient to support either a general analgesic indication or multiple specific indications. The recent approval of lamotrigine for treatment of Lennox-Gastaut Syndrome (a rare, largely pediatric, generalized seizure disorder) was based on a single adequate and well-controlled trial, due in part to related data showing efficacy of the drug in partial-onset seizures in adults.

f. Studies in less closely related diseases, but where the general purpose of therapy is similar

Certain classes of drug therapy, such as antimicrobials and antineoplastics, are appropriate interventions across a range of different diseases. For therapies of this type, evidence of effectiveness in one disease could provide independent substantiation of effectiveness in a quite different disease. For example, it is possible to argue that evidence of effectiveness of an antimicrobial in one infectious disease setting may support reliance on a single study showing effectiveness in other settings where the causative pathogens, characteristics of the site of infection that affect the disease process (e.g., structure and immunology) and patient population are similar.[6] Similarly, for an oncologic drug, evidence of effectiveness in one or more tumor types may support reliance on a single study showing effectiveness against a different kind of tumor, especially if the tumor types have a common biological origin.

g. Studies of different clinical endpoints

Demonstration of a beneficial effect in different studies on two different clinically meaningful endpoints could cross-substantiate a claim for

[6] See Division of Anti-Infective Drug Products: Points to Consider in the Clinical Development and Labeling of Anti-Infective Drug Products, October 1992.

effectiveness for each outcome. For example, the initial claim for effectiveness of enalapril for heart failure was supported by one study showing symptom improvement over several months and a second study showing improved survival in a more severely ill population. The two different findings, each from an adequate and well-controlled study, led to the conclusion that enalapril was effective in both treating symptoms and improving survival.

h. Pharmacologic/pathophysiologic endpoints

When the pathophysiology of a disease and the mechanism of action of a therapy are very well understood, it may be possible to link specific pharmacologic effects to a strong likelihood of clinical effectiveness. A pharmacologic effect that is accepted as a validated surrogate endpoint can support ordinary approval (e.g., blood pressure effects, cholesterol-lowering effects) and a pharmacologic effect that is considered reasonably likely to predict clinical benefit can support accelerated approval under the conditions described in 21 CFR 314 Subpart H and 21 CFR 601 Subpart E (e.g., CD4 count and viral load effects to support effectiveness of anti-viral drugs for HIV infection). When the pharmacologic effect is not considered an acceptable effectiveness endpoint, but the linkage between it and the clinical outcome is strong, not merely on theoretical grounds but based on prior therapeutic experience or well-understood pathophysiology, a single adequate and well-controlled study showing clinical efficacy can sometimes be substantiated by persuasive data from a well-controlled study or studies showing the related pharmacologic effect.

For example, a single clearly positive trial can be sufficient to support approval of a replacement therapy such as a coagulation factor, when it is combined with clear evidence that the condition being treated is caused by a deficiency of that factor. Demonstration of physical replacement of the deficient factor or restoration of the missing physiologic activity provides strong substantiation of the clinical effect. The corrective treatment of an inborn error of metabolism could be viewed similarly. In the case of preventive vaccines, one adequate and well-controlled clinical trial may be supported by compelling animal challenge/protection models, human serological data, passive antibody data, or pathogenesis information. The more evidence there is linking effects on the pharmacologic endpoint to improvement or prevention of the disease, the more persuasive the argument for reliance on a single clinical efficacy study.

Note, however, that plausible beneficial pharmacologic effects have often not correlated with clinical benefit, and, therefore, caution must be observed in relying on a pharmacologic effect as contributing to evidence

of effectiveness. For example, pharmacologic effects such as arrhythmia suppression by Type 1 antiarrhythmics and increased cardiac output by phosphodiesterase inhibitors or beta adrenergic inotropes resulted in increased mortality, rather than, as was expected, decreased sudden death and improved outcome in heart failure. The reasons for the absence of an expected correlation between pharmacologic and clinical effects are diverse and can include an incompletely understood relationship between the pharmacologic effect and the clinical benefit and the presence of other pharmacologic effects attributable to a drug in addition to the effect being measured and thought to be beneficial. Generally, the utility of pharmacologic outcomes in providing independent substantiation will be greatest where there is prior experience with the pharmacologic class. Even in this case, however, it is difficult to be certain that a pharmacologic effect that correlates with a clinical benefit accounts for all the clinical benefit or that other effects are not present and relevant.

3. Evidence of Effectiveness from a Single Study

When the effectiveness requirement was originally implemented in 1962, the prevailing efficacy study model was a single institution, single investigator, relatively small trial with relatively loose blinding procedures, and little attention to prospective study design and identification of outcomes and analyses. At present, major clinical efficacy studies are typically multicentered, with clear, prospectively determined clinical and statistical analytic criteria. These studies are less vulnerable to certain biases, are often more generalizable, may achieve very convincing statistical results, and can often be evaluated for internal consistency across subgroups, centers, and multiple endpoints.

The added rigor and size of contemporary clinical trials have made it possible to rely, in certain circumstances, on a single adequate and well-controlled study, without independent substantiation from another controlled trial, as a sufficient scientific and legal basis for approval. For example, the approval of timolol for reduction of post-infarction mortality was based on a single, particularly persuasive (low p-value), internally consistent, multicenter study that demonstrated a major effect on mortality and reinfarction rate. For ethical reasons, the study was considered unrepeatable. The Center for Biologics Evaluation and Research has also approved a number of products based upon a single persuasive study. The Agency provided a general statement in 1995 describing when a single, multicenter study may suffice (60 FR 39181; August 1, 1995), but the Agency has not comprehensively described the situations in which a single adequate and well-controlled study might be considered adequate support for an effectiveness claim, or the characteristics of a single study that could make it adequate support for an effectiveness claim.

Whether to rely on a single adequate and well-controlled study is inevitably a matter of judgment. A conclusion based on two persuasive studies will always be more secure than a conclusion based on a single, comparably persuasive study. For this reason, reliance on only a single study will generally be limited to situations in which a trial has demonstrated a clinically meaningful effect on mortality, irreversible morbidity, or prevention of a disease with potentially serious outcome and confirmation of the result in a second trial would be practically or ethically impossible. For example, sequential repetition of strongly positive trials that demonstrated a decrease in post-infarction mortality, prevention of osteoporotic fractures, or prevention of pertussis would present significant ethical concerns. Repetition of positive trials showing only symptomatic benefit would generally not present the same ethical concerns.

The discussion that follows identifies the characteristics of a single adequate and well-controlled study that could make the study adequate support for an effectiveness claim. Although no one of these characteristics is necessarily determinative, the presence of one or more in a study can contribute to a conclusion that the study would be adequate to support an effectiveness claim.

a. Large multicenter study

In a large multicenter study in which (1) no single study site provided an unusually large fraction of the patients and (2) no single investigator or site was disproportionately responsible for the favorable effect seen, the study's internal consistency lessens concerns about lack of generalizability of the finding or an inexplicable result attributable only to the practice of a single investigator. If analysis shows that a single site is largely responsible for the effect, the credibility of a multicenter study is diminished.

b. Consistency across study subsets

Frequently, large trials have relatively broad entry criteria and the study populations may be diverse with regard to important covariates such as concomitant or prior therapy, disease stage, age, gender or race. Analysis of the results of such trials for consistency across key patient subsets addresses concerns about generalizability of findings to various populations in a manner that may not be possible with smaller trials or trials with more narrow entry criteria. For example, the timolol postinfarction study randomized patients separately within three severity strata. The study showed positive effects on survival in each stratum supporting a conclusion that the drug's utility was not limited to a particular disease stage (e.g., relatively low or high severity).

c. Multiple *studies* in a single study

Properly designed factorial studies may be analyzed as a series of pairwise comparisons, representing, within a single study, separate demonstrations of activity of a drug as monotherapy and in combination with another drug. This model was successfully used in ISIS II, which showed that for patients with a myocardial infarction both aspirin and streptokinase had favorable effects on survival when used alone and when combined (aspirin alone and streptokinase alone were each superior to placebo; aspirin and streptokinase in combination were superior to aspirin alone and to streptokinase alone). This represented two separate (but not completely independent) demonstrations of the effectiveness of aspirin and streptokinase.

d. Multiple endpoints involving different events

In some cases, a single study will include several important, prospectively identified primary or secondary endpoints, each of which represents a beneficial, but different, effect. Where a study shows statistically persuasive evidence of an effect on more than one of such endpoints, the internal weight of evidence of the study is enhanced. For example, the approval of beta-interferon (Betaseron) for prevention of exacerbations in multiple sclerosis was based on a single multicenter study, at least partly because there were both a decreased rate of exacerbations and a decrease in MRI-demonstrated disease activity — two entirely different, but logically related, endpoints.

Similarly, favorable effects on both death and nonfatal myocardial infarctions in a lipid-lowering, postangioplasty, or postinfarction study would, in effect, represent different, but consistent, demonstrations of effectiveness, greatly reducing the possibility that a finding of reduced mortality was a chance occurrence. For example, approval of abciximab as adjunctive treatment for patients undergoing complicated angioplasty or atherectomy was supported by a single study with a strong overall result on the combined endpoint (decreased the combined total of deaths, new infarctions, and need for urgent interventions) and statistically significant effects in separate evaluations of two components of the combined endpoint (decreased new infarctions and decreased need for urgent interventions). In contrast, a beneficial effect on multiple endpoints that evaluate essentially the same phenomenon and correlate strongly, such as mood change on two different depression scales or SGOT and CPK levels postinfarction, does not significantly enhance the internal weight of the evidence from a single trial.

Although two consistent findings within a single study usually provide reassurance that a positive treatment effect is not due to chance, they do not protect against bias in study conduct or biased analyses. For example, a treatment assignment not well balanced for important prognostic variables could lead to an apparent effect on both endpoints. Thus, close scrutiny of study design and conduct are critical to evaluating this type of study.

e. Statistically very persuasive finding

In a multicenter study, a very low p-value indicates that the result is highly inconsistent with the null hypothesis of no treatment effect. In some studies it is possible to detect nominally statistically significant results in data from several centers, but, even where that is not possible, an overall extreme result and significance level means that most study centers had similar findings. For example, the thrombolysis trials of streptokinase (ISIS II, GISSI) had very sizable treatment effects and very low p-values, greatly adding to their persuasiveness. Preventive vaccines for infectious disease indications with a high efficacy rate (e.g., point estimate of efficacy of 80% or higher and a reasonably narrow 95% confidence interval) have been approved based on a single adequate and well-controlled trial.

4. Reliance on a Single, Multicenter Study — Caveats

While acknowledging the persuasiveness of a single, internally consistent, strong multicenter study, it must be appreciated that even a strong result can represent an isolated or biased result, especially if that study is the only study suggesting efficacy among similar studies. Recently, the apparent highly favorable effect of vesnarinone, an inotropic agent, in heart failure (60% reduction of mortality in what appeared to be a well-designed, placebo-controlled, multicenter trial with an extreme p-value) has proven to be unrepeatable. In an attempt to substantiate the finding, the same dose of the drug that seemed lifesaving in the earlier study significantly increased mortality (by 26%), and a lower dose also appeared to have a detrimental effect on survival. Although the population in the second study was, on the whole, a sicker population than in the first, the outcomes in similarly sick patients in each study were inconsistent so this factor does not explain the contradictory results.

When considering whether to rely on a single multicenter trial, it is critical that the possibility of an incorrect outcome be considered and that all the available data be examined for their potential to either support or undercut reliance on a single multicenter trial. In the case of vesnarinone, there were other data that were not consistent with the dramatically favorable outcome in the multicenter study. These data seemed to show an inverse dose-response relationship, showed no suggestion

of symptomatic benefit, and showed no effect on hemodynamic endpoints. These inconsistencies led the Agency, with the advice of its Cardio-Renal Advisory Committee, to refuse approval — a decision borne out by the results of the subsequent study.

This example illustrates how inadequacies and inconsistencies in the data, such as lack of pharmacologic rationale and lack of expected other effects accompanying a critical outcome, can weaken the persuasiveness of a single trial. Although an unexplained failure to substantiate the results of a favorable study in a second controlled trial is not proof that the favorable study was in error — studies of effective agents can fail to show efficacy for a variety of reasons — it is often reason not to rely on the single favorable study.

III. DOCUMENTATION OF THE QUALITY OF EVIDENCE SUPPORTING AN EFFECTIVENESS CLAIM

When submitting the requisite quantity of data to support approval of a new product or new use of an approved product, sponsors must also document that the studies were adequately designed and conducted. Essential characteristics of adequate and well-controlled trials are described in 21 CFR 314.126. To demonstrate that a trial supporting an effectiveness claim is adequate and well-controlled, extensive documentation of trial planning, protocols, conduct, and data handling is usually submitted to the Agency, and detailed patient records are made available at the clinical sites.

From a scientific standpoint, however, it is recognized that the extent of documentation necessary depends on the particular study, the types of data involved, and the other evidence available to support the claim. Therefore, the Agency is able to accept different levels of documentation of data quality, as long as the adequacy of the scientific evidence can be assured. This section discusses the factors that influence the extent of documentation needed, with particular emphasis on studies evaluating new uses of approved drugs.

For the purposes of this section, the phrase *documentation of the quality of evidence* refers to (1) the completeness of the documentation and (2) the ability to access the primary study data and the original study-related records (e.g., subjects' medical records, drug accountability records) for the purposes of verifying the data submitted as evidence. These interrelated elements bear on a determination of whether a study is adequate and well-controlled.

In practice, to achieve a high level of documentation, studies supporting claims are ordinarily conducted in accordance with good clinical practices (GCPs). Sponsors routinely monitor all clinical sites, and FDA routinely has access to the original clinical protocols, primary data, clinical site source documents for on-site audits, and complete study reports.

However, situations often arise in which studies that evaluate the efficacy of a drug product lack the full documentation described above (for example, full patient records may not be available) or in which the study was conducted with less monitoring than is ordinarily seen in commercially sponsored trials. Such situations are more common for supplemental indications because postapproval studies are more likely to be conducted by parties other than the drug sponsor and those parties may employ less extensive monitoring and data-gathering procedures than a sponsor. Under certain circumstances, it is possible for sponsors to rely on such studies to support effectiveness claims, despite less than usual documentation or monitoring. Some of those circumstances are described below.

A. Reliance on Less Than Usual Access to Clinical Data or Detailed Study Reports

FDA's access to primary data has proven to be important in many regulatory decisions. There are also reasons to be skeptical of the conclusions of published reports of studies. Experience has shown that such study reports do not always contain a complete, or entirely accurate, representation of study plans, conduct and outcomes. Outright fraud (i.e., deliberate deception) is unusual. However, incompleteness, lack of clarity, unmentioned deviation from prospectively planned analyses, or an inadequate description of how critical endpoint judgments or assessments were made are common flaws. Typically, journal article peer reviewers only have access to a limited data set and analyses, do not see the original protocol and amendments, may not know what happened to study subjects that investigators determined to be non-evaluable, and thus may lack sufficient information to detect critical omissions and problems. The utility of peer review can also be affected by variability in the relevant experience and expertise of peer reviewers. FDA's experiences with the Anturane Reinfarction Trial, as well as literature reports of the efficacy of tacrine and the anti-sepsis HA-1A antibody, illustrate its concerns with reliance on the published medical literature.

Notwithstanding these concerns, the presence of some of the factors discussed below can make it possible for FDA to rely on studies for which it has less than usual access to data or detailed study reports to partially or entirely (the so-called *paper* filing) support an effectiveness claim. FDA's reliance on a literature report to support an effectiveness claim is more likely if FDA can obtain additional critical study details. Section 1 below describes additional information that, if available, would increase the likelihood that a study could be relied on to support an effectiveness claim. Section 2 describes factors that may make efficacy findings sufficiently persuasive to permit reliance on the published literature alone. Note that the factors outlined in Section 2 are relevant to an assessment of the reliability of literature reports generally, whether alone, or accompanied by other important information as discussed in Section 1.

1. Submission of Published Literature or Other Reports in Conjunction with Other Important Information that Enhances the Reliability of the Data

If a sponsor wishes to rely on a study conducted by another party and cannot obtain the primary data from the study, for most well-conducted studies it is possible to obtain other important information, such as a protocol documenting the prospective plans for the trial, records of trial conduct and procedures, patient data listings for important variables, and documentation of the statistical analysis. FDA has considerable experience evaluating large multicenter outcome studies sponsored by U.S. and European government agencies (NIH, British Medical Research Council) and private organizations (the ISIS studies, the SAVE study) for which there was limited access to primary study data, but for which other critical information was available. Providing as many as possible of the following important pieces of information about a study, in conjunction with the published report, can increase the likelihood that the study can be relied on to support an effectiveness claim:

a. The protocol used for the study, as well as any important protocol amendments that were implemented during the study and their relation to study accrual or randomization.

b. The prospective statistical analysis plan and any changes from the original plan that occurred during or after the study, with particular note of which analyses were performed pre- and post-unblinding.

c. Randomization codes and documented study entry dates for the subjects.

d. Full accounting of all study subjects, including identification of any subjects with on-treatment data who have been omitted from analysis and the reasons for omissions, and an analysis of results using all subjects with on-study data.

e. Electronic or paper record of each subject's data for critical variables and pertinent baseline characteristics. Where individual subject responses are a critical variable (e.g., objective responses in cancer patients, clinical cures and microbial eradications in infectious disease patients, death from a particular cause), detailed bases for the assessment, such as the case report, hospital records, and narratives, should be provided when possible.

f. Where safety is a major issue, complete information for all deaths and drop-outs due to toxicity. For postapproval supplemental uses, however, there is generally less need for the results of lab tests or for details of adverse event reports and, consequently, much more limited documentation may be sufficient (e.g., only for unexpected deaths and previously undescribed serious adverse effects). Exceptions to this

approach would include situations in which the population for the supplemental use is so different that existing safety information has limited application (e.g., thrombolysis in stroke patients versus myocardial infarction patients) or where the new population presents serious safety concerns (e.g., extension of a preventive vaccine indication from young children to infants).

2. Submission of Published Literature Reports Alone

The following factors increase the possibility of reliance on published reports alone to support approval of a new product or new use:

a. Multiple studies conducted by different investigators where each of the studies clearly has an adequate design and where the findings across studies are consistent.

b. A high level of detail in the published reports, including clear and adequate descriptions of statistical plans, analytic methods (prospectively determined), and study endpoints, and a full accounting of all enrolled patients.

c. Clearly appropriate endpoints that can be objectively assessed and are not dependent on investigator judgment (e.g., overall mortality, blood pressure, or microbial eradication). Such endpoints are more readily interpreted than more subjective endpoints such as cause-specific mortality or relief of symptoms.

d. Robust results achieved by protocol-specified analyses that yield a consistent conclusion of efficacy and do not require selected post hoc analyses such as covariate adjustment, subsetting, or reduced data sets (e.g., analysis of only responders or compliant patients, or of an "eligible" or “evaluable” subset).

e. Conduct of studies by groups with properly documented operating procedures and a history of implementing such procedures effectively.

There have been approvals based primarily or exclusively on published reports. Examples include the initial approval of secretin for evaluation of pancreatic function and recent approvals of bleomycin and talc for malignant pleural effusion and doxycycline for malaria.

B. Reliance on Studies with Alternative, Less Intensive Quality Control/On-Site Monitoring

Industry-sponsored studies typically use extensive on-site and central monitoring and auditing procedures to assure data quality. Studies supported by other sponsors may employ less stringent procedures and may use no on-site monitoring at all. An International Conference on Harmonisation guideline on good clinical practices,[7] recently accepted internationally, emphasizes that the extent of monitoring in a trial should be based on trial-specific factors (e.g., design, complexity, size, and type of study outcome measures) and that different degrees of on-site monitoring can be appropriate. In recent years, many credible and valuable studies conducted by government or independent study groups, often with important mortality outcomes, had very little on-site monitoring. These studies have addressed quality control in other ways, such as by close control and review of documentation and extensive guidance and planning efforts with investigators. There is a long history of reliance on such studies for initial approval of drugs as well as for additional indications. Factors that influence whether studies with limited or no monitoring may be relied on include the following:

1. The existence of a prospective plan to assure data quality.

2. Studies that have features that make them inherently less susceptible to bias, such as those with relatively simple procedures, noncritical entry criteria, and readily assessed outcomes.

3. The ability to sample critical data and make comparisons to supporting records (e.g., hospital records).

4. Conduct of the study by a group with established operating procedures and a history of implementing such procedures effectively.

[7] International Conference on Harmonisation Guidance for Industry E6, *Good Clinical Practice: Consolidated Guideline*, April 1996.