

Sanvar[®] (vapreotide acetate) Injection

NDA No. 21-761

**Indication: Adjunctive Therapy to Endoscopic Intervention for the Control of
Acute Esophageal Bleeding as a Result of Portal Hypertension**

Briefing Document for Advisory Committee

Division of Gastrointestinal Drugs

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List of Abbreviations and Definitions of Terms

@6h	Every 6 hours
AASLD	American Association for the Study of Liver Diseases
AE	Adverse event
ALT	Alanine transaminase
AST	Aspartate transaminase
bpm	Beats per minute
CI	Confidence interval
CRFs	Case report forms
DBP	Diastolic blood pressure
DEB	Debiovision Inc.
DIC	Disseminated intravascular coagulation
DMNA	Dimethylnitrosamine
EIA	Enzyme immunoassay
EKG	Electrocardiogram
EVB	Esophageal variceal bleeding
FDA	Food and Drug Administration
GCP	Good Clinical Practices
GIDAC	Gastrointestinal Drugs Advisory Committee
HCC	Hepatocellular carcinoma
HED	Human Equivalent Dose
Hgb	Hemoglobin
HIV/AIDS	Human immunodeficiency virus/acquired immune deficiency syndrome
HVPG	Hepatic venous pressure gradient)
ICH	International Conference on Harmonisation
IRB	Institutional Review Board
ITT	Intention-to-treat
IU	International units
IV	Intravenous
MedDRA	Medical Dictionary for Regulatory Activities
mm Hg	Millimeters of mercury
N	Number of population
n	Number of sample (a subset of N)
NDA	New Drug Application
nM	Nanomole
NOS	Not otherwise specified

OR	Odds ratio
PBO	Placebo
PD	Pharmacodynamic
PK	Pharmacokinetic
PKC	Protein kinase C
RBC	Red blood cells
RCT	Randomized controlled trials
SAE	Serious adverse event
SBP	Systolic blood pressure
SD	Standard deviation
SMS	Somatostatin
SOC	System Organ Class
SPA	Special Protocol Assignment
SSTR	Somatostatin receptor
Tendo	Time at end of endoscopy
TIPS	Transjugular intrahepatic portosystemic shunt
USA	United States
VAP	Vapreotide acetate
VAP-02	Study DEB-97-VAP-02
VAP-06	Study DEB-02-VAP-06
VAP-07	Study DEB-01-VAP-07
VAP-14	Study DEB-96-VAP-14
VAP-301	Study DEBV-VAP/EVB-301
WBC	White blood cells
WHO	World Health Organization

1 Executive Summary

1.1 Overview

This document has been prepared by Debiovision Inc. for the Gastrointestinal Drugs Advisory Committee (GIDAC) of the Food and Drug Administration (FDA) for the meeting scheduled on 19 May 2009. During this meeting the committee will discuss the efficacy and safety of vapreotide acetate (hereafter referred to as vapreotide), a somatostatin analog, for the following indication:

- *As adjunctive therapy to endoscopic intervention for the control of acute esophageal bleeding as a result of portal hypertension*

This document contains a comprehensive summary of the development of vapreotide, and includes preclinical data and a review of clinical data from the vapreotide esophageal variceal bleeding (EVB) development program. These data support the efficacy and safety of vapreotide for control of esophageal variceal bleeding in patients with portal hypertension, and demonstrate that vapreotide:

- improves control of bleeding with survival over 5 days
- improves control of bleeding at time of endoscopy
- has a well-characterized safety profile, with the incidence and type of adverse events (AEs) comparable to placebo
- provides an important therapeutic option for these critically ill patients

1.2 Disease Background

Variceal bleeding associated with portal hypertension is a serious, life-threatening medical emergency, accounting for a higher mortality rate than for any other cause of upper gastrointestinal bleeding (Jamal 2008). Varices are present in 40% to 60% of patients with decompensated cirrhosis (Jamal 2008; Bosch 2008; Pagliaro 1994; Sharara 2001), and their presence and size are related to the underlying cause, duration, and severity of cirrhosis. About one-third of these patients will experience one or more variceal bleeding events (Toubia 2008). Esophageal variceal bleeding (EVB) affects fewer than 50,000 patients in the USA annually (Agency for Healthcare Research and Quality 2008) and, accordingly, qualifies as a rare or orphan disease.

Although advances in resuscitation methods, use of vasoactive drugs, and improved endoscopic techniques have reduced mortality associated with EVB, mortality rates in treated patients remain high, with current estimates ranging from 15% to 26% per bleeding event (Bosch 2008; Bambha 2008; Chalasani 2003; Dy 2003; Stokkeland 2006; Thomopoulos 2006; Mutaner 2009). Additionally, the liver injury produced by bleeding and infection from the index hemorrhage may also result in acute decompensation of cirrhosis with subsequent secondary mortality.

When a patient presents with acute EVB, the primary goal is to control the initial hemorrhage and prevent early rebleeding. Various vasoactive drugs have been studied in this indication, and published meta-analyses of these trials have concluded that the combination of a vasoactive agent with endoscopic treatment is superior to endoscopic treatment alone for control of bleeding (Bañares 2002; de Franchis 2004). Current treatment consensus guidelines recommend that vasoactive drugs (octreotide, vapeotide, terlipressin or somatostatin) should be used as early as possible in patients with suspicion of acute variceal bleeding. Therefore, the current standard of care worldwide is to start treatment with a vasoactive drug as early as possible (ie, at the time of admission) and to initiate endoscopic therapy at time of diagnostic endoscopy (de Franchis 2005).

Achieving prompt control of the initial bleed with a vasoactive drug is associated with a number of clinical benefits. Notably, the addition of a vasoactive drug to endoscopic therapy has been shown to reduce blood transfusion requirements during the critical 5-day period immediately following a hemorrhage (Levacher 1995; Avgerinos 1997; Calès 2001). Additionally, achieving control of bleeding has been shown to be correlated with improved survival (Moitinho 2001).

In clinical practice, endoscopic evaluation and treatment often are delayed up to 12 hours, due to unavailability of facilities and trained personnel or unsuitable patient conditions (Besson 1995). Since the failure to control bleeding is highest during the first hours to days following hemorrhage onset (Burroughs 1989), early pharmacological treatment to fill the gap between the beginning of hemorrhage and the initiation of therapeutic endoscopy offers a beneficial treatment option.

Although the clinical benefits associated with use of vasoactive drugs for treatment of variceal bleeding are widely accepted, no pharmacological treatment is presently approved in the USA for this indication. Octreotide, approved for use in other indications but not for variceal bleeding, is used extensively off-label in combination with endoscopic therapy for this condition.

Consistent with the practice of evidence-based medicine, there is a need for an approved vasoactive drug, proven in clinical studies to be effective and safe for patients with esophageal variceal bleeding. Furthermore, the availability of an approved drug for this indication would ensure that comprehensive labeling is available to provide standardized and accurate guidance regarding patient selection, dosing, and administration, as well as to allow for a structured, ongoing safety surveillance program. Accordingly, Debiovision Inc. is seeking FDA-approval to market vapeotide, a somatostatin analog, for use in treating esophageal variceal bleeding as adjunctive therapy to endoscopic intervention.

1.3 Mechanism of Action

Vapeotide was discovered by Dr. Andrew Schally (1977 Nobel Prize Laureate) at Tulane University. It is a cyclic octapeptide analog of native somatostatin with similar pharmacological effects, but with a longer duration of action. Although the exact mechanisms of action of somatostatin and its analogs in variceal bleeding has not been completely elucidated, this class of vasoactive agents appears to decrease splanchnic and portal-collateral blood flow by inhibiting

the release of vasodilatory peptides such as glucagon, vasoactive intestinal polypeptide, calcitonin gene-related peptide, and substance P (Reichlin 1983; Veal 2003; Reynaert 2003) and inducing vasoconstriction by a protein kinase C (PKC)-dependent mechanism (West 2001).

1.4 Nonclinical Pharmacology and Toxicology

Vapreotide has been shown in an experimental model of portal hypertension due to cirrhosis to decrease hepatic and collateral blood flow. Rats with liver cirrhosis induced by dimethylnitrosamine (DMNA) were used to evaluate the effect of a 30-min infusion of vapreotide (0 or 8 µg/kg/h). This acute exposure to vapreotide significantly decreased spleno-renal shunt blood flow.

Repeated dose toxicity studies in rats and dogs showed no evidence of organ toxicity. Adverse effects commonly observed with vapreotide in these preclinical studies – diarrhea and reduced body weight gain despite normal food consumption – were consistent with the pharmacological effect of somatostatin analogs on gastrointestinal hormonal-secretory function.

1.5 Clinical Pharmacology

Pharmacokinetic (PK) studies of vapreotide following single and multiple intravenous (IV) administration were conducted in healthy volunteers, patients with liver impairment, patients with kidney impairment showed the following:

- Vapreotide is metabolized rapidly to form 2 main metabolites, des-[amido8]-vapreotide (with biological activity) and des-[Trp⁸-NH₂]-vapreotide (with negligible biological activity);
- Vapreotide is rapidly eliminated following IV injection ($t_{1/2}$ ~10 min), with a mean total body clearance of 64 L/h; elimination is predominately by the bile (76%), with the remainder by the kidney;
- PK parameters following a vapreotide IV injection were not different between healthy volunteers and subjects with liver or renal impairment.

1.6 Regulatory History

Based on the annual incidence of acute variceal bleeding in the USA, vapreotide was granted Orphan Drug Status by FDA for the intended indication. A New Drug Application (NDA) was submitted for vapreotide in February 2004. VAP-14 (conducted in France) was included in that submission as the pivotal study and VAP-07 (Egypt) was submitted as supportive evidence of efficacy. The VAP-02 (Hong-Kong) data were included only as additional safety data. The VAP-06 study was ongoing in Eastern Europe at that time.

In an Approvable Letter issued in December 2004, the Agency requested additional efficacy data, stating awareness that the Sponsor had just completed a major trial (VAP-06).

The VAP-06 study, complicated by a major protocol amendment, did not achieve statistical significance, and FDA reiterated their request for additional data to support the efficacy of vapreotide.

Debiovision agreed to conduct a Phase 3 study in the USA. Since early treatment with vasoactive drugs prior to endoscopy had become standard of care by then, Institutional Review Boards (IRBs) viewed inclusion of a placebo arm as unethical for the EVB indication. An active comparator trial was not feasible without an FDA-approved comparator. Therefore, VAP-301 was designed as an open-label, single arm study, with VAP-14 and other EVB studies serving as historical controls. FDA agreed to a Special Protocol Assessment (SPA) for this study, which was initiated in 2006. Under the SPA, it was agreed that the results of VAP-301 would be judged for their clinical significance, along with the results from the previous trials, with the understanding that the study would lack statistical comparisons. The complete response to the Approvable Letter for vapeotide was submitted by Debiovision in September 2008.

1.7 Clinical Development Program

The vapeotide clinical development program for treatment of acute variceal bleeding includes 5 studies conducted in cirrhotic patients with portal hypertension:

- VAP-14 (France): a multicenter, randomized, double-blind, placebo-controlled study. This study was conducted to demonstrate the efficacy of early administration of vapeotide in combination with endoscopic therapy in controlling acute bleeding in cirrhotic patients with variceal bleeding (Calès 2001).
- VAP-301 (USA): a multicenter, historical-controlled, open-label study, a design accepted by FDA under a Special Protocol Assessment (SPA). This study was conducted to show the consistency and relevance of the VAP-14 results.
- VAP-07 (Egypt): a single-center, randomized, double-blind, placebo-controlled study designed as a pilot study to evaluate vapeotide in patients with portal hypertension due to viral hepatitis- and/or schistosomiasis-induced cirrhosis.
- VAP-06 (Eastern Europe): a multicenter, randomized, double-blind, placebo-controlled study. The study was complicated by a major protocol amendment to deal with blood supply shortages.
- VAP-02 (Hong Kong): a multicenter, randomized, double-blind, placebo-controlled study that was terminated early because of a very slow accrual rate resulting in noncompliance with the study protocol that irrevocably jeopardized the validity of the study and safety of the patients.

Safety data from these 5 EVB studies were pooled to assess the safety of vapeotide in the intended indication. In these studies 469 patients received at least one dose of vapeotide. Vapeotide has also been studied for other indications (eg, acromegaly, pancreatic surgery, Crohn's disease, cancer). Safety data from an additional 4 non-EVB studies in which safety data was collected in compliance with regulatory requirements and Good Clinical Practices (GCP), were integrated with the EVB safety data for an extended database consisting of 728 patients who also received at least one dose of vapeotide.

1.8 Clinical Efficacy

The efficacy of vapreotide has been studied in 5 EVB studies: VAP-14, VAP-301, VAP-07, VAP-06, and VAP-02.

The study design adopted for these trials is described in Section 7.1.1. Briefly, all variceal bleeding studies used identical inclusion/exclusion criteria, primary endpoints, study procedures and timelines. Inclusion criteria required cirrhotic patients to have hematemesis and/or melena, start treatment with study drug ≤ 24 hours from initial hemorrhage and ≤ 6 hours from hospital admission, and anticipated to have ≤ 12 hours between admission and end of therapeutic endoscopy. Exclusion criteria included grade IV hepatic encephalopathy, Child Pugh score ≥ 13 , diffuse hepatocellular carcinoma (HCC), complete portal venous thrombosis, and bleeding from esophageal varices within the previous 6 weeks. Because the diagnostic endoscopy was combined with the therapeutic endoscopy, as specified by the protocol, any patient determined to have upper gastrointestinal bleeding not due to portal hypertension had their study drug discontinued and was excluded from the protocol-specified intent-to-treat (ITT) population. These patients were followed for safety.

The study drug regimen consisted of an initial 4 mL IV bolus (vapreotide 50 μ g or placebo) immediately followed by a continuous 4 mL/h IV infusion (vapreotide 50 μ g/h or placebo) for 5 days after completion of the therapeutic endoscopy.

The primary efficacy endpoint for all EVB studies was control of bleeding with survival over 5 days, hereafter referred to as control of bleeding over 5 days. (See Section 7.1.2 for a description of the detailed requirements used to define control of bleeding). Secondary efficacy endpoints included control of bleeding at time of endoscopy; control of bleeding 6 hours after the start of the study drug infusion; control of bleeding at 48 hours (Day 2) after completion of therapeutic endoscopy; number of blood units transfused; and survival at Day 42.

Results from the pivotal VAP-14 study together with supporting information from the other EVB studies, as summarized below, provide evidence of the efficacy of vapreotide for the treatment of acute variceal bleeding, in association with endoscopic treatment:

- VAP-14 is the pivotal trial for demonstration of the efficacy of early administration of vapreotide in association with endoscopic therapy for treatment of EVB (Calès 2001). In this study, vapreotide, compared to placebo, significantly increased the percentage of patients who achieved control of bleeding over 5 days (odds ratio [OR]: 1.97; 95% CI: 1.11, 3.51), increased the percentage of patients with control of bleeding at endoscopy, and decreased the average number of blood transfusions during the 5 days following the index hemorrhage (Table 1). The benefit of vapreotide for control of bleeding was independent of baseline hematocrit, presence or absence of active bleeding at endoscopy, severity of liver impairment (Child-Pugh Class A or B vs C), use of beta-blockers at admission, or type of endoscopic treatment modality.

Table 1 Efficacy Results for VAP-14 (ITT)

	Vapreotide (N=98)	Placebo (N=98)	P- value
Primary endpoint: Control of bleeding over 5 days, n (%)	65 (66%)	49 (50%)	0.021
Secondary endpoints: Control of bleeding:			
• at endoscopy	63 (64%)	50 (51%)	0.031
• 6 hours after initiation of infusion	80 (82%)	52 (53%)	0.001
• 48 hours after endoscopy	72 (73%)	53 (54%)	0.005
Number of blood units per patient Days 1-5, mean (SD)	2.0 ± 2.2	2.8 ± 2.8	0.04
Survival at Day 42	84 (86%)	77 (79%)	0.195

- VAP-301, the open-label study conducted in the USA, had 70 patients in the ITT population and 77% of patients achieved control of bleeding over 5 days. Accounting for expected differences in cirrhosis etiology and type of endoscopic procedure, VAP-301 shows results that are generally consistent with VAP-14. Analyses performed in patient subgroups for etiology and type of endoscopic procedure further demonstrate the clinical relevance of the VAP-14 findings in a USA patient population with EVB. The success rate achieved in VAP-301 for control of bleeding over 5 days (ie, 77%) is also consistent with that reported in 2 meta-analyses of published data on vasoactive treatment with endoscopy compared to endoscopy alone (77% and 74% for the vasoactive + endoscopy group compared to 58% and 53% for the endoscopy alone group [Bañares 2002; de Franchis 2004, respectively]).
- VAP-07, the pilot study in Egypt, that enrolled patients with portal hypertension due primarily to viral hepatitis- and/or schistosomiasis-induced cirrhosis rather than alcoholism, as was the case in VAP-14, showed a trend in favor of treatment with vapreotide for control of bleeding (71% vapreotide vs 59% placebo; p=0.349).
- VAP-06, the Eastern European study, had a major protocol amendment that redefined the primary endpoint. When analyzed as originally planned with the total ITT population (N=267), this study showed no difference between vapreotide and placebo (65% vs 66%). The amendment to the protocol, implemented after 71 patients were enrolled, resulted in differences in treatment practices before and after the amendment that call into question the appropriateness of combining the pre- and post-amendment populations. In addition, the protocol-specified criteria for success included the investigator's opinion on the control of bleeding. When analyzed separately using the same criteria as in the pivotal VAP-14 study (which excluded investigator's opinion and the requirement for a required hematocrit level), the pre-amendment efficacy data (N=65) show a positive trend (63% vapreotide vs 52% placebo), while no difference is seen in the post-amendment data (ITT: N=202) (52% vapreotide vs 51% placebo).

- VAP-02 is the study that was terminated early due to a slow rate of enrollment. The slow accrual contributed to adherence issues with the protocol that irrevocably jeopardized the validity of the study and safety of the patients (ie, at least 2 patients were administered 12 vials of study drug within 6 hours instead of the intended 5 days). Initially submitted solely for evaluation of the safety data, the efficacy results (ITT N=102) were analyzed at the request of FDA. It was agreed that the efficacy results were difficult to interpret, and could not be used to support efficacy. These results are included herein for full disclosure.

Table 2 Percent of Patients with Control of Bleeding Over 5 Days (Primary Endpoint) by EVB Study (ITT)

Study	Vapreotide		Placebo		P-value	Odds Ratio (95% CI)
	n/N	%	n/N	%		
VAP-14 (France)	65/98	66.3	49/98	50.0	0.021	1.97 (1.11, 3.51)
VAP-301 (USA)	54/70	77.1	N/A	N/A	N/A	N/A
VAP-07 (Egypt)	22/31	71.0	16/27	59.3	0.349	1.68 (0.56, 5.00)
VAP-06 (Romania, Bulgaria)	89/136	65.4	87/131	66.4	0.867	0.96 (0.56, 1.64)
VAP-02 (Hong-Kong)	28/51	54.9	26/51	51.0	0.692	1.17 (0.50, 2.74)

N/A = not applicable; VAP-301 had no placebo group.

A meta-analysis of the primary efficacy results from the 4 placebo-controlled trials (VAP-14, VAP-07, VAP-06, and VAP-02) resulted in an odds ratio of 1.33 in favor of vapreotide (95% CI: 0.92, 1.93). A sensitivity analysis, excluding VAP-02 and treating the VAP-06 pre and post amendment results as separate trials, shows an odds ratio of 1.43 (95% CI: 1.01, 2.03). (VAP-301 could not be included in the meta-analysis since it did not have a placebo-control arm). A pooled logistic regression including the VAP-301 data provided materially the same results (odds ratio: 1.44 [95% CI: 1.01, 2.03]).

In conclusion, the results obtained from the pivotal, well-conducted VAP-14, and trends observed in the other evaluable studies, demonstrate that early administration of vapreotide, in association with endoscopic intervention, is effective for the treatment of acute variceal hemorrhage related to portal hypertension.

1.9 Clinical Safety

The safety profile for vapreotide in EVB patients is derived primarily from pooled safety data from the 4 randomized, placebo-controlled EVB studies (RCTs: N=366 vapreotide, N=347 placebo) and supportive data from one single-arm EVB study (n=103 vapreotide). Results for the single-arm EVB study (VAP-301) were compared with those for the 4 EVB RCTs (VAP-14, VAP-02, VAP-06, VAP-07). In all the EVB studies, patients were scheduled to receive a bolus injection of 50 µg vapreotide (or placebo) followed by a continuous IV infusion of 50 µg/h (1.2 mg/d) for 5 days. Per protocol, study treatment was discontinued immediately for patients found at endoscopy to have bleeding unrelated to portal hypertension; these patients were

excluded from ITT analyses, but were followed for safety during the 42-day study period and their data included in the safety database.

Comparison of safety data for the vapreotide (N=366) and placebo (N=347) groups in the pooled EVB RCTs showed that vapreotide is well tolerated in the targeted population:

- Treatment-emergent adverse events (AEs) occurred at comparable rates in the vapreotide and placebo groups overall (75% vs 76%), both during study drug infusion over Days 1-5 (65% vs 66%) and during follow-up over Days 6-42 (26% vs 31%) and by system organ class (SOC). The most frequent AEs in both the vapreotide and placebo groups, occurring in $\geq 5\%$ of patients, were pyrexia, upper gastrointestinal hemorrhage, flatulence, melena, hepatic encephalopathy, and headache.
- Serious adverse events (SAEs) occurred at similar rates in the vapreotide and placebo groups overall (34% vs 39%), during study drug infusion (21% vs 23%) and during follow-up (15% vs 18%). As expected in this study population, the most frequent SAEs in both treatment groups, occurring in $\geq 2\%$ of patients, were disease-related complications: upper gastrointestinal hemorrhage, melena, hepatic encephalopathy, and hemorrhagic shock.
- Deaths during the 42-day study period in the 4 controlled EVB studies occurred at similar rates in the vapreotide and placebo groups (15.0% vs 16.4%);
- The incidence of cytopenias (pancytopenias, thrombocytopenia), although infrequent ($<1\%$), was higher in the vapreotide group than the placebo group. However, based on review of individual cases and considering that cytopenias are an expected disease-related complication in cirrhotic patients, there is no clear safety signal for vapreotide.

VAP-301, conducted in the USA, identified no unexpected AE or safety signal for vapreotide. Although the incidence of some AEs differed between the single-arm VAP-301 study and the pooled EVB RCTs, the observed differences were in events related to expected complications of cirrhosis. The rate of SAEs in VAP-301 was comparable or lower than reported in the pooled EVB RCTs, with the types of SAEs similar. The 6-week mortality rate in the single-arm VAP-301 study was numerically higher (25.2% [26/103]), but it was a smaller sample size and its 95% CI (17.2%, 34.7%) overlapped with those of the larger pooled EVB RCT database (95% CI: 11.5%, 19.1% for vapreotide; and 12.7%, 20.8% for placebo).

A secondary safety database (9-Study Database) contained pooled safety data from the 4 EVB RCTs (N=366 vapreotide patients), VAP-301 (N=103), and 4 non-EVB studies (N=259 vapreotide patients). The 4 non-EVB studies were in other indications (pancreatic surgery, acromegaly, Crohn's disease, and neuroendocrine tumors), had higher dosages (up to 1.5 mg/d), and longer exposures (up to 180 days). Comparisons of AEs between the primary and secondary safety databases reflected differences driven by results from the pancreatic surgery RCT, which had higher rates of anemia, respiratory failure, and events related to the underlying pancreatic disease and surgical procedure.

The safety profile of vapreotide is similar to that reported for somatostatin and somatostatin analogs.

1.10 Benefit – Risk Assessment

Variceal bleeding associated with portal hypertension is an important, life-threatening emergency, accounting for a higher mortality rate than for any other cause of upper gastrointestinal bleeding. The control of bleeding achieved with early administration of vasoactive drugs is associated with important clinical benefits.

Despite the clinical evidence, no pharmacological treatment is currently approved in the USA for this indication, and off-label use of a vasoactive agent has become standard clinical practice. The availability of an approved drug for this indication would ensure:

- Efficacy and safety of the product that have been established in the indicated population and at the labeled dose;
- Comprehensive labeling is available to provide standardized and accurate guidance regarding patient selection, dosing, and administration. This may be especially pertinent in local community hospitals where the availability of standardized, comprehensive drug labeling is important for physician training.
- An ongoing structured safety surveillance program, contributing to the current understanding regarding the risk-benefit profile of the product in this patient population.

Accordingly, due to the small patient population and lack of an approved therapy, vapreotide has been designated an Orphan Drug for this indication.

The efficacy of vapreotide, as adjunctive therapy to endoscopic intervention for the control of acute esophageal bleeding as a result of portal hypertension, has been established in the pivotal VAP-14 study, with supporting information from VAP-301 and other EVB studies. The VAP-14 study (Calès 2001) is recognized as a well-designed, well-conducted study using criteria established by treatment consensus guidelines that remain in effect today (de Franchis 1996; Grace 1998; Garcia-Tsao 2007). In VAP-14, vapreotide significantly increased the percentage of patients who achieved control of bleeding over 5 days, increased the percentage of patients with control of bleeding at endoscopy, and decreased the average number of blood units transfused during the initial 5 days following the index hemorrhage.

This clinical experience provides substantial evidence that vapreotide, when administered prior to endoscopic intervention, is safe and effective for the treatment of acute variceal bleeding. Further, vapreotide can be administered immediately to all patients suspected of esophageal bleeding; treatment can be started even at home or during transfer to the hospital. This is important since about a quarter of deaths occur very early after bleeding onset (Laine 2005). In addition, vapreotide has no special requirements for storage or preparation.

Vapreotide's safety profile has been characterized in clinical trials of patients with EVB and in other indications. Overall, vapreotide has been shown to be well-tolerated, and the incidence and

types of AEs and SAEs associated with vapreotide are comparable to those reported with placebo. In the EVB studies, the most frequently reported AEs for both vapreotide and placebo were pyrexia and upper gastrointestinal hemorrhage, melena, and hepatic encephalopathy.

The 6-week mortality rate was comparable between the vapreotide and placebo groups in the controlled EVB studies (15% vs 16%). In the single-arm VAP-301 study, the mortality rate (25%) was numerically higher than seen in previous vapreotide studies, although the 95% confidence intervals overlap. VAP-301 showed increased rates of deaths due to infection/multiorgan failure, worsening of liver disease, and cardiac/cardiorespiratory arrest, all of which are expected complications in cirrhotic patients with upper gastrointestinal bleeding. Of note, VAP-301 mortality rate is similar to 6-week mortality rates reported in the recent Cochrane Review of somatostatin analogs (mean of 19%, with a range of 3% - 38% in active acute EVB treatment groups).

In summary, vapreotide has a favorable benefit/risk profile. The efficacy and safety results from the vapreotide clinical studies support early administration of vapreotide in patients with acute variceal bleeding, an important advantage in the treatment of this serious, life-threatening, medical emergency.

1.11 Summary and Conclusions

Acute variceal bleeding due to portal hypertension is a serious and life-threatening medical emergency associated with high morbidity and mortality. Consensus guidelines endorse early treatment with vasoactive drugs for patients with EVB, but there are no drugs currently approved for this indication in the USA.

Vapreotide provides clinically meaningful benefits for patients with EVB, including control of bleeding over the critical first 5 days after the index hemorrhage. The efficacy of vapreotide, as adjunctive therapy to endoscopic intervention for the control of acute esophageal bleeding as a result of portal hypertension, has been established in VAP-14 and is supported by other clinical studies. Vapreotide has been shown to be well-tolerated, with AEs and SAEs similar to placebo. The clinical safety results support early administration of vapreotide in all patients suspected of variceal bleeding, an important advantage for the treatment of this medical emergency.

Based on the overall favorable benefit/risk profile, the approval of vapreotide for treatment of EVB in cirrhotic patients is expected to provide important clinical benefits to these critically ill patients.

2 Introduction

2.1 Proposed Indication

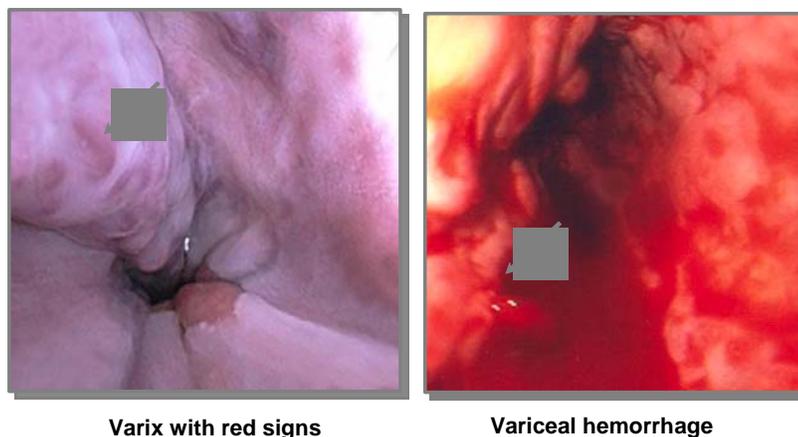
Vapreotide is indicated as adjunctive therapy to endoscopic intervention for the control of acute esophageal bleeding as a result of portal hypertension.

2.2 Management of Esophageal Variceal Bleeding Related to Portal Hypertension

2.2.1 Esophageal Variceal Bleeding

Esophageal variceal bleeding, a serious, life-threatening event, affects fewer than 50,000 patients in the USA annually (Agency for Healthcare Research and Quality 2006). Gastroesophageal varices—portosystemic collaterals formed after pre-existing vascular channels have been dilated by portal hypertension—are present in 40% to 60% of patients with decompensated cirrhosis (Jamal 2008; Bosch 2008; Pagliaro 1994; Sharara 2001). Although most patients with cirrhosis develop varices, only about one-third of these patients will experience one or more variceal bleeding events (Toubia 2008). A prognostic sign of a first esophageal variceal bleed (a bulging varix) is shown in the left-hand picture of Figure 1; and a hemorrhaging varix is shown in the right-hand picture. Prognostic factors for risk of variceal bleeding include Child-Pugh Class C, size of varices, and presence of red wale markings (longitudinal dilated, venules resembling whip marks on the varices – see Figure 1) (North Italian Endoscopic Club 1988).

Figure 1 **Bulging and Hemorrhaging Varices**



Variceal bleeding due to portal hypertension accounts for a higher mortality rate than any other cause of upper gastrointestinal bleeding (Jamal 2008). Historically, mortality after acute variceal hemorrhage if untreated was as high as 50% (Bosch 2008; Bambha 2008; Chalasani 2003; Dy 2003; Stokkeland 2006; Thomopoulos 2006). Advances in resuscitation methods, use of

vasoactive drugs, and improved endoscopic techniques have contributed to reductions in mortality rates, but despite this decline, mortality associated with EVB in treated patients remains high, with current estimates of 15 to 26% per bleeding event.

In the absence of specific treatment, the failure to control acute variceal bleeding or early rebleeding occurs in up to 50% of cases (Toubia 2008; Navarro 1995; Pagliaro 1994). The highest risk of rebleeding is seen in the first 5 days following the index hemorrhage, after which the risk remains increased until the second or third month (Burroughs 1989; Pagliaro 1994). Factors associated with increased risk of early rebleeding (within 5 days) include elevated hepatic venous pressure gradient (HVPG \geq 20 mm Hg), bacterial infection, active bleeding at endoscopy, portal vein thrombosis, Child-Pugh score, shock, and AST levels (per IU increase) (Bosch 2008).

2.2.2 Current Management

The management of variceal bleeding requires simultaneous and coordinated attention to correct hypovolemia, prevention of complications associated with bleeding, to stop the variceal hemorrhage, and to prevent early rebleeding. The first 2 goals, which are independent of the cause of hemorrhage, demand immediate management. Pharmacological treatment with vasoactive drugs can be initiated on the patient's arrival at the hospital or during transfer (de Franchis 2005).

The current treatment consensus guidelines worldwide for suspected acute variceal bleeding recommend starting treatment with a vasoactive drug (terlipressin, somatostatin, vapreotide, or octreotide) as soon as possible following admission and prior to endoscopic therapy (de Franchis 2005). This approach is consistent with guidelines developed by groups of European and American experts and published as the Baveno Consensus Workshops (de Franchis 2005; de Franchis 2000; de Franchis 1996) and American Association for the Study of Liver Disease (AASLD) symposia (Garcia-Tsao 2007; Grace 1998). Clinical experts recognize vasoactive drugs in association with endoscopic treatment as first-line treatment for variceal bleeding (de Franchis 2005; Garcia-Tsao 2007).

Endoscopic therapy is best used in association with vasoactive drugs that should be started as soon as possible before endoscopy. Endoscopic variceal band ligation (ligation and strangulation of varices with rubber bands) is currently the endoscopic treatment of choice for esophageal varices. Endoscopic sclerotherapy (injection of a sclerosing solution into or next to a bleeding varix) may be used if band ligation is technically difficult.

Rescue treatment for EVB includes transjugular intrahepatic portosystemic shunt (TIPS), emergency shunt surgery, and balloon tamponade in rare circumstances (Villanueva 2008; Avgerinos 1998; Burroughs 1996; McCormack 1999).

2.2.3 Vasoactive Drugs

Vasoactive drugs used for EVB include vasopressin and its analog (terlipressin) and somatostatin and its analogs (octreotide, lanreotide, vapreotide). Vasopressin, a potent vasoconstrictor, is not

considered as first-line vasoactive therapy due to its potential for causing severe adverse cardiovascular events (Dell'Era 2008, Döhler 2008). Terlipressin is a long-acting derivative of vasopressin that is associated with fewer adverse effects (Dell'Era 2008). However, due to its general or non-specific vasoconstrictive activity, terlipressin may induce ischemic complications, contraindicating its use in patients with a history of ischemic heart disease, cardiac arrhythmias, vascular diseases of the extremities, or history of cerebral vascular accident (Nevens 2004). Somatostatin and its analogs (octreotide, lanreotide, vapreotide) are devoid of generalized vasoconstrictive effects, presenting a major advantage over vasopressin and terlipressin (Calès 2008).

Although the mechanism of action of somatostatin and its analogs has not been fully elucidated, this class of drugs appears to decrease splanchnic blood flow by inhibiting the release of vasodilatory peptides such as glucagon, vasoactive intestinal polypeptide, calcitonin gene-related peptide, and substance P and also by inducing vasoconstriction by a PKC-dependent mechanism (Abralde 2002; Ferayorni 1996; Groszmann 1999; West 2001). These agents have also been shown to reduce hepatic blood flow, wedged hepatic venous pressure, and azygous blood flow in patients with stable cirrhosis (Groszmann 1999; Ottesen 1998).

Natural somatostatin, octreotide and terlipressin have been approved for use in various European countries for the treatment of acute variceal bleeding, but none are approved in the USA for this indication. Medical institutions in the USA, however, extensively use octreotide off-label in combination with endoscopic therapy for acute variceal bleeding.

Achieving prompt initial control of bleeding with vasoactive drugs is associated with a number of clinical benefits, such as facilitation of endoscopic procedures and prevention of additional complications and secondary mortality resulting from liver hypoxia. In practice, treatment with somatostatin analogs may be initiated immediately, before formal identification of the source of bleeding (an assessment made by endoscopy). Endoscopic evaluation and treatment often are delayed by an average of up to 12 hours, due to unavailability of facilities and trained personnel or unsuitable patient conditions (Besson 1995; Abralde 2007). Since the failure to control bleeding is highest during the first hours to days following the onset of hemorrhage (Burroughs 1989), early active pharmacological treatment to fill the gap between the beginning of hemorrhage and the initiation of therapeutic endoscopy is expected to significantly improve overall hemostasis.

The early administration of vasoactive drugs reduces the rate of active bleeding during endoscopy (Levacher 1995; Avgerinos 1997; Calès 2001), thus producing a clear view that can facilitate diagnostic and therapeutic endoscopic procedures (Avgerinos 1997; Toubia 2008; Zaman 2005; Villanueva 2008). Band ligation is technically difficult to perform during an active bleed as the field of vision is decreased by 30% (Abralde 2007).

The addition of vasoactive drugs to endoscopic management has been found to improve initial control of bleeding at 5 days (Bañares 2002) and to reduce blood transfusion requirements during the initial 5-day period as compared with endoscopic therapy alone (Levacher 1995; Avgerinos 1997; Calès 2001). Moreover, there is evidence that achieving control of bleeding may be

correlated with improved survival. A published trial of somatostatin showed that achievement of control of bleeding at Day 5 according to the Baveno consensus criterion was predictive of survival at 6 weeks (Moitinho 2001; Avgerinos 1997), while other studies of somatostatin (Villanueva 1999), octreotide (Besson 1995), and terlipressin (Escorsell 2000) using somewhat different definitions of hemostasis also have shown a correlation with survival at 6 weeks

2.2.3.1 Clinical Studies of Vasoactive Drugs in EVB

EVB clinical trials are challenging to conduct, and randomized, controlled clinical trials evaluating the efficacy of vasoactive drugs in association with endoscopic treatment versus endoscopic treatment alone or with placebo have reported variable results. Four main factors that contribute to variability with the reported rate of success of control of bleeding in acute variceal bleeding trials include: 1) the patient population enrolled in the trial; 2) the point at which randomization occurs; 3) the treatment schedule; and 4) the criteria used to define success and failure. Although control of bleeding is the endpoint used for most of the trials, its definition varies across trials. Other difficulties with conducting research in this field include the lack of standardized study endpoints, monitoring the composite endpoints specified in consensus guidelines (de Franchis 2005; Garcia-Tsao 2007; Grace 1998), the relatively small number of patients presenting with EVB after exclusionary conditions (Agency for Healthcare Research and Quality 2006), and the routine use of off-label vasoactive drugs (Burroughs 2006) at the time of presentation or earlier during patient transfer. These factors underscore the technical challenges associated with the conduct of adequate clinical trials in EVB and may in part explain why no vasoactive drug has yet been approved for this indication in the USA.

Two published meta-analyses have analyzed the results of trials evaluating the use of a pharmacological agent in combination with endoscopic therapy versus endoscopic therapy alone (Bañares 2002; de Franchis 2004) using control of bleeding as an endpoint. Bañares reported 8 such trials that met the criteria of being randomized, controlled comparisons with endoscopic treatment, which measured one of the following outcomes: initial control of bleeding, control of bleeding at Day 5, mortality at Day 5 and adverse events (Bañares 2002). In a separate review, de Franchis compared and reviewed the same 8 trials in addition to 2 studies reported by Burroughs in 1996 and Levacher in 1995 (de Franchis 2004).

The vapreotide trial (VAP-14; Calès 2001) used the recommended combined endpoint (control of bleeding 5 days after endoscopy with survival) consisting of primary control of bleeding (assessed consecutively at 6 hours and between 6 and 48 hours after endoscopy) and early rebleeding (no rebleeding episodes between 48 hours and 5 days), closely corresponding to the consensus recommendations for assessing control of bleeding (de Franchis 1996, Grace 1998). Results from this study will be presented in detail in Section 8.2.1.

The 2 octreotide studies with the highest success rates in these meta-analyses (Sung 1995; Zuberi 2000) did not use consensus criteria for the primary endpoint reported results for the components individually rather than as a composite endpoint. Furthermore, Zuberi excluded patients with the most severe liver disease (Child Pugh Class C). In another study, a 71% success rate for control

of bleeding following use of terlipressin and glyceryl-nitrate compared to 47% with placebo was demonstrated, but these results were for control of bleeding at 12 hours after administration of the study drug and not at 5 days in accordance with the consensus recommendations (Levacher 1995).

The rate of control of bleeding established with the placebo groups may be considered as a common denominator between the various trials. Although all included a comparator arm that consisted of endoscopic treatment alone, control rates for the placebo arms in these trials ranged from 31% to 94%. These results were likely impacted by differences in study population, treatment schedules, and study outcome criteria. The magnitude of the difference between the active and control arms, however, can be examined for an indication of the effect of the treatment. In trials that were able to show a difference between groups, the magnitude of the difference ranges from 8% to 24%.

3 Brief Regulatory and Development History

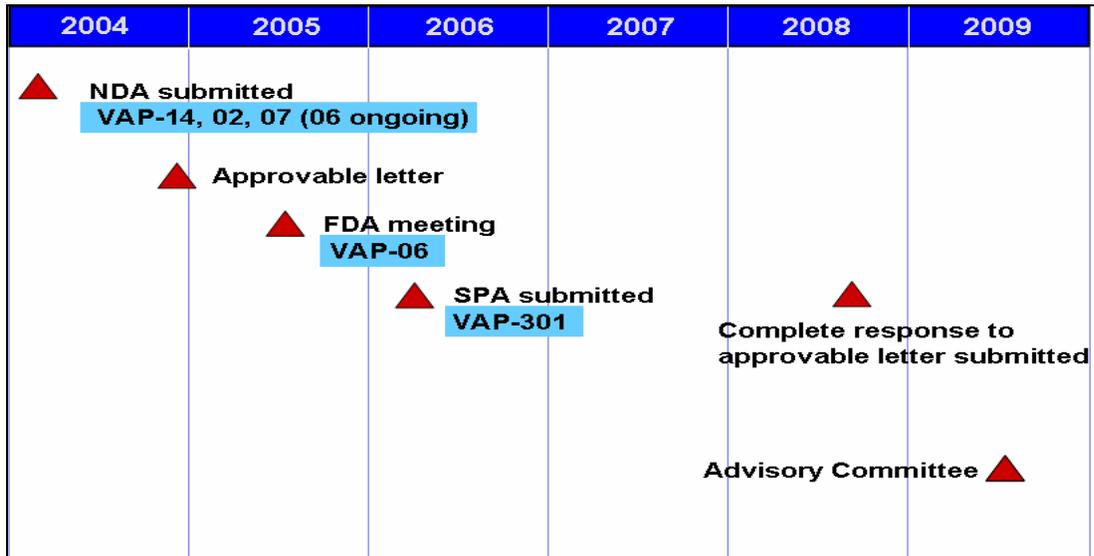
Vapreotide has been studied for use as adjunctive therapy to endoscopic intervention for the control of acute esophageal bleeding as a result of portal hypertension. Based on the annual incidence of acute variceal bleeding in the USA, vapreotide was granted Orphan Drug Status by the FDA. The initial NDA for vapreotide was submitted by Debiovision in February 2004. The results from 3 placebo-controlled studies were included in the NDA (VAP-14 and VAP-07 for efficacy and safety, and VAP-02 for evaluation of safety) and the fourth placebo-controlled study, VAP-06, was ongoing in Eastern Europe. In an Approvable letter issued in December of 2004, the Agency requested additional efficacy data and stated awareness that the Sponsor had just completed a major trial (VAP-06).

Debiovision met with FDA to review the VAP-06 results. Preliminary data on the primary endpoint for the ITT population suggested no meaningful difference between vapreotide and placebo results. However, the study had been compromised by a protocol amendment that impacted the primary endpoint. Debiovision proposed post-hoc analysis on the pre-amendment population. The Agency agreed that the 2 populations pre- and post-amendment should not be combined, but maintained the opinion that additional data were still needed to support the efficacy of vapreotide.

Debiovision agreed to conduct a Phase 3 study in the USA. By that time, use of a vasoactive drug in the treatment of EVB was standard practice and the inclusion of a placebo arm in clinical studies for this life-threatening indication was considered unethical by IRBs. Moreover, given the very large sample size needed to conclude equivalence or superiority and the lack of an FDA-approved comparator, conducting an active-controlled trial was not feasible. Therefore, VAP-301 was designed as an open-label, historical-control Phase 3 study, with VAP-14 and the available literature on octreotide studies serving as historical controls. The FDA accepted VAP-301 under a SPA, a provision FDA may allow when aware of the developmental context in which a clinical protocol is being reviewed (FDA Guidance for Industry May 2002). It was agreed that the results of VAP-301 would be judged on clinical significance, along with results

from the previous EVB studies, with the understanding that the study would lack statistical rigor. The first patient was enrolled in VAP-301 in August 2006 and the trial was completed in June 2008. Debiovision submitted a complete response to the approvable letter for vapreotide in September 2008.

Figure 2 Vapreotide Key Regulatory and Development Milestones



4 Vapreotide Mechanism of Action

Vapreotide was discovered by Dr. Andrew Schally (1977 Nobel Prize Laureate) at Tulane University. Vapreotide is a cyclic octapeptide analog of native somatostatin with similar pharmacological effects, but with a longer duration of action. Although the exact mechanisms of action of somatostatin and its analogs in variceal bleeding has not been completely elucidated, this class of agents appears to decrease splanchnic blood flow by inhibiting the release of vasodilatory peptides such as glucagon, vasoactive intestinal polypeptide, calcitonin gene-related peptide, and substance P (Reichlin 1983; Veal 2003; Reynaert 2003) and by facilitating the vasoconstriction induced by PKC-dependent vasoconstrictors (West 2001).

5 Nonclinical Pharmacology and Toxicology

5.1 Primary Pharmacodynamics

The somatostatin receptor has 5 distinct genes encoding a family of structurally related G-protein coupled receptor subtype molecules, designated as SSTR1-5. A study of subtype selectivity for somatostatin and various analogs, summarized in Table 3, found that the cyclic octapeptide analogs (octreotide, lanreotide, and vapreotide) bind selectively to the human receptors SSTR2, SSTR3, and SSTR5 with affinities comparable to that of somatostatin, but were not reactive with the human receptor SSTR1. Vapreotide and lanreotide showed moderate affinity for SSTR4, while octreotide did not bind to SSTR4 (Patel 1994).

Table 3 Binding of Somatostatin and Somatostatin Analogs to Somatostatin Receptor Subtype, Ki (nM) (Patel 1994)

	SSTR1	SSTR2	SSTR3	SSTR4	SSTR5
Somatostatin	1.1	1.3	1.6	0.53	0.9
Vapeotide	> 1000	5.4	30.9	45	0.7
Octreotide	> 1000	2.1	4.4	> 1000	5.6
Lanreotide	> 1000	1.8	43	66	0.62

Vapeotide has 2 main metabolites des-(amido8)-vapeotide, and des-[Trp8-NH₂]-vapeotide. Somatostatin receptor subtype affinity profiles of vapeotide and its 2 main metabolites were determined by assessing complete displacement with 0.1 to 1000 nM of vapeotide, des-(amido8)-vapeotide, and des-[Trp8-NH₂]-vapeotide from cells expressing each type of the 5 somatostatin receptor subtypes, SSTR1–5 (Reubi, Debiopharm internal report, 2001). As expected, vapeotide showed high affinity for SSTR2 and SSTR5. Compared with vapeotide, the des-(amido8) metabolite had 2- to 3-fold lower affinity for all SSTR subtypes and des-[Trp8-NH₂]-vapeotide had 30- to 50-fold less affinity. Based on these findings, the author concluded that at therapeutic concentrations of vapeotide, des-(amido8)-vapeotide exhibits biological activity but the activity of des-[Trp8-NH₂]-vapeotide is negligible.

5.1.1 Effects on Portal Hypertension

The acute and chronic effects of vapeotide were investigated in rats with cirrhosis induced by dimethylnitrosamine (DMNA) (Moal 1998; Oberti 1998; Veal 2000; Veal 2003). To study acute effects, hemodynamic measurements were made prior to and after a 30-minute infusion of vapeotide (0 or 8 µg/kg/h) in male rats (10 per group) with DMNA-induced cirrhosis. Results, summarized in Table 4, showed that acute administration of vapeotide significantly decreased splenic-renal shunt blood flow but not splenic porto-systemic shunt blood flow (Veal 2000). After the vapeotide infusion, portal pressure was reduced slightly, but the difference was not statistically significant.

Table 4 Acute Hemodynamic Effects of Vapreotide in Rats with DMNA-induced Cirrhosis (Veal 2000)

Measurement	Saline	Vapreotide	P-value
Mean arterial pressure:			
Baseline (mm Hg)	93 ± 10	95 ± 16	NS
Variation at 30 minutes (%)	-9 ± 15	-13 ± 12	NS
Portal pressure:			
Baseline (mm Hg)	17 ± 2	16 ± 2	NS
Variation at 30 minutes (%)	-2 ± 10	-9 ± 10	NS
Splenic renal shunt blood flow:			
Baseline (ml/min)	8.5 ± 4.6	5.1 ± 5.1	NS
Variation at 30 minutes (%)	-4 ± 15	-26 ± 32	<0.05
Splenic porto-systemic shunt:			
Baseline (%)	93 ± 7	68 ± 7	<0.05
Variation at 30 minutes (%)	1 ± 27	0 ± 15	NS

To study chronic hemodynamic effects, rats (20 per group) were given subcutaneous implants of vapreotide (0 or 4.8 mg) 2 days after starting DMNA injections (Moal 1998). As controls, another 2 groups (10 per group) were given subcutaneous implants of vapreotide (0 or 4.8 mg) without DMNA injections. The hemodynamic effects on anesthetized animals, assessed by the transit time ultrasound technique, and effects on liver fibrosis, assessed by liver collagen surface density, were studied 5 weeks after initiation of DMNA injections. DMNA induced a similar degree of cirrhosis in both the vapreotide and control groups (Table 5). Treatment with vapreotide caused a significant (56%) reduction in spleno-renal shunt blood flow, but no significant effect on portal pressure in cirrhotic rats. In these studies, plasma concentrations of vapreotide were significantly higher in the cirrhotic rats suggesting reduced intrahepatic blood flow and increased hepatic exposure to the drug is possibly linked to reduced metabolism and clearance consistent with the metabolism and excretion of vapreotide.

Table 5 Chronic Hemodynamic Effects of Vapreotide in Rats with DMNA-induced Cirrhosis (Moal 1998)

	Sham rats		DMNA-treated rats	
	Control	Vapreotide	Control	Vapreotide
Portal pressure (mm Hg)	8.9 ± 1.7	9.2 ± 1.4	16.5 ± 2.2	15.5 ± 2.1
Spleno-renal shunt blood flow (mL/min)	0.19 ± 0.09	0.28 ± 0.14	2.51 ± 1.70	1.10 ± 1.40 ^a
Cardiac index (mL/min/100g)	24 ± 5	21 ± 4	56 ± 11	35 ± 10 ^a
Liver collagen surface density (%)	1.9 ± 0.4	2.7 ± 0.7	9.0 ± 2.0	10.5 ± 1.7
Plasma vapreotide (ng/mL)	N/A	5.2 ± 2.5	N/A	17.5 ± 24.5 ^b

^a p < 0.05 vapreotide vs control in DMNA-treated rats.

^b p < 0.05 DMNA vs sham rats treated with vapreotide.

Most recent results comparing the hemodynamic effects of acute and chronic vapreotide administration in rats with DMNA-induced cirrhosis (Veal 2003), were consistent with previous

reports leading the authors to conclude that the acute administration of vapreotide decreased collateral circulation blood flow while chronic administration attenuated its development. In this model, vapreotide appears to have a vasoconstrictive effect on splanchnic collateral circulation.

5.2 Toxicology

Repeated-dose toxicity studies in rats and dogs showed no evidence of direct organ toxicity. Toxicities commonly observed with vapreotide, such as diarrhea and reduced body weight gain despite normal food consumption, were consistent with the pharmacological effects of vapreotide on gastrointestinal hormonal-secretory function and are consistent with those reported for somatostatin and octreotide. In repeated dose studies in dogs, fluid was observed in the knee joint of some dogs. Although no consistent modifications of synovial membranes were observed, a possible treatment-related effect on physiological maturation of the articular cartilage and on epiphyseal growth plates of the femur and tibia could not be excluded.

Genotoxicity studies showed no mutagenic activity for vapreotide, assessed by the induction of DNA base-pair substitution or frameshift mutations in *Salmonella typhimurium* strains or *Escherichia coli* WP2 uvrA bacteria; induction of 6-thioguanine-resistant mutants in Chinese Hamster V79 cells; induction of unscheduled DNA synthesis in primary rat hepatocytes; induction of chromosomal aberrations in human lymphocytes; or induction of micronucleus in mouse polychromatic erythrocytes.

No maternal toxicity, fetal toxicity, or teratogenic effects were observed when pregnant rats and rabbits were given repeated subcutaneous injections of vapreotide during days 6-15 (18) of gestation. However, embryotoxicity was observed in rats given 2.4 mg/kg/d, evidenced by a statistically significant increase in resorbed fetuses/total implantations. Accordingly, vapreotide is contraindicated in pregnant women.

Preclinical data for vapreotide indicate no safety concerns with respect to the potential for delaying ventricular repolarization (QT/QTc interval prolongation).

- No pro-arrhythmic potential was observed in *in vitro* safety pharmacology studies in dog ventricular tissues at vapreotide concentrations up to 200 ng/mL (more than 100-fold higher than mean steady-state concentration of 1.45 ng/mL observed in humans with recommended dosing regimen and 50-fold higher than the estimated maximum plasma concentration of 4 ng/mL in healthy volunteers receiving a 50 µg/mL bolus injection) (Study IPST 701126-1; Study IPST 701126-2).
- No prolongation in QT/QTc intervals was observed in dogs given vapreotide infusions with doses up to 1.2 mg/kg/day for 28 days (Study DEB-00-VAP-05).

6 Clinical Pharmacokinetics and Pharmacodynamics

6.1 Pharmacokinetics

Pharmacokinetic studies of vapreotide acetate following a single IV administration were conducted in healthy volunteers as well as in separate groups of patients with liver and renal

impairment. Vapreotide was eliminated rapidly in both healthy subjects and subjects with liver impairment as reflected by a high clearance rate and short half-life (~10 min) (Table 6). The rapid elimination of vapreotide also was confirmed by a low mean residence time of vapreotide in the systemic circulation (~14 min) (Study H3P-02-VAP-09). No significant differences in pharmacokinetic (PK) parameters were noted between healthy subjects and subjects with liver or renal impairment.

Table 6 Pharmacokinetic Assessment of Vapreotide after Single Intravenous Bolus Administration

Population, Study	Dose	Assay Method ^a	AUC (µg•h/L)	t _{1/2} (h)	Cl (L/h)
Healthy Volunteers:					
Study H3P-02-VAP-09 (n=6)	600 µg	EIA	17.7 ± 9.08	0.13 ± 0.05	44.9 ± 27.6
Study DEB-99-VAP-05 (n=8)	600 µg	EIA	19.1 ± 6.67	0.49 ± 0.27	35.6 ± 14.2
Liver Impairment:					
Study H3P-02-VAP-09					
Moderate (Child-Pugh A,B) (n=5) ^b	600 µg	EIA	23.0 ± 25.7	0.17 ± 0.10	48.2 ± 30.2
Severe (Child-Pugh C) (n=6)	600 µg	EIA	14.0 ± 6.42	0.25 ± 0.11	53.3 ± 30.3
Renal Impairment					
Study H3P-02-VAP-09 (n=6)	600 µg	EIA	18.0 ± 5.32	0.21 ± 0.13	35.9 ± 6.51

Abbreviations: EIA = enzyme immunoassay

^aThe EIA used an antibody that did not cross-react with the metabolite.

^bExcludes results from one subject (0003CHA) with half-life > 3 times the mean (4.34h).

The terminal half-life of vapreotide following IV injection in patients with impaired renal function is very short and equivalent to that in healthy subjects (~10 min), so less than 10% of the administered dose would be present at 12 hours after IV administration, or when an IV infusion is discontinued (Study H3P-02-VAP-09).

Pharmacokinetic parameters from studies in patients with stable cirrhosis (Study DEB-95-VAP-03) and impaired liver function (Study H3P-02-VAP-09) also suggest no potential for drug accumulation during a 5-day IV infusion. The concentration at steady state may be estimated by dividing the infusion rate by the plasma clearance (Rowland 1989). From the plasma clearance rates obtained in the vapreotide studies in patients with impaired liver function (~51 L/h from EIA analyses), concentration at steady state after a continuous infusion of 50 µg/h to patients with impaired liver function may be estimated to be 0.98 ng/mL.

The pharmacokinetic profile of vapreotide was evaluated in a subset of patients (n=24) enrolled in VAP-07; these patients had bleeding esophageal varices and received a bolus of vapreotide of 50 µg, followed by the constant infusion of 50 µg/h for 5 days. The plasma concentration of vapreotide at steady state was assayed after 72 hours of infusion. The mean drug level was 1.45 ng/mL, with levels ranging from 0.31 to 5.85 ng/mL. Using the information obtained in patients with liver cirrhosis following a single IV injection (Table 6), it is possible to estimate that the vapreotide volume of distribution will range from 12.1 L to 19.2 L. With this volume of distribution, vapreotide maximal plasma concentration after a bolus of 50 µg was estimated to be 4.1 ng/mL. The average vapreotide clearance at steady state is 34.5 L/h. The fact that the

concentration of vapreotide at steady state and its clearance (after 72 h) are similar to the values estimated following a single IV injection suggests no potential for drug accumulation..

6.2 Pharmacodynamics

Studies designed to investigate a PK/PD relationship for vapreotide in cirrhotic patients with acute variceal bleeding have not been conducted. Based on a consideration of published literature and advice from experts in the field, it was concluded that it is not possible to establish a pharmacokinetic/pharmacodynamic (PK/PD) relationship in cirrhotic patients experiencing active acute variceal hemorrhage for the following reasons:

- Because the exact mechanisms of action of somatostatin and its analogs in variceal bleeding are not known, there is currently no known biological surrogate that would enable definition of a direct relationship between the kinetics of somatostatin (or somatostatin analog) and the pharmacodynamic effects observed in bleeding patients.
- Hemodynamic parameters such as portal pressure are under the control of multiple parameters in cirrhosis. Therefore, they do not represent reliable surrogate markers that enable the evaluation of the pharmacologic action of somatostatin and its analogs.

6.2.1 Drug-Drug Interactions

No formal drug-drug interaction studies have been performed with vapreotide. An evaluation of the potential for drug interactions is summarized below:

- **Drug metabolism interactions:** Vapreotide is a peptide that is degraded by non-specific proteases present in the plasma and in different tissues. Since these peptidases are not subject to saturable kinetics, enzymatic degradation of vapreotide should not be subject to pharmacodynamic interactions. Interaction with the metabolism of drugs metabolized via the cytochrome P450 system also is not expected.
- **Interaction with elimination pathways:** Studies in animals have shown that vapreotide is eliminated by both renal and biliary routes. Renal elimination is expected to involve primarily glomerular filtration of the unbound moiety of vapreotide, the molecular weight of which (1,100) is largely below the threshold of filtration (60,000). Additionally, glomerular filtration is a nonsaturable mechanism. No system of active and saturable renal secretion of peptides is known currently, so no interaction for renal elimination of vapreotide is expected. The biliary route of elimination is favored by the lipophilicity of vapreotide. No active biliary transport of peptides has been described and competition for saturation by biliary elimination is not expected.
- **Interaction with binding to plasma proteins:** Binding to plasma proteins accounts for 80% of the plasma concentration of vapreotide (Study DEB-94-PRE.CL-VAP-

- 02). At the plasma concentrations of vapreotide observed in clinical situations, the majority of albumin binding sites remained free (e.g., at a very high clinical level of 40 nM vapreotide plasma concentration, or 45.3 ng/mL, less than 0.005% of total albumin binding sites are occupied by vapreotide). Therefore, very little interaction resulting from displacement of other protein-bound substances is expected.
- **Physical incompatibilities with other drugs:** In solution, vapreotide tends to precipitate at pH higher than 5. Accordingly, instructions for use recommend that vapreotide should be administered alone.
 - **Pharmacodynamic interactions:** Similar to other somatostatin analogs, vapreotide inhibits the secretion of glucagon (resulting in hypoglycemia) and insulin (resulting in hyperglycemia). Because slight hyperglycemia can occur, instructions for use caution that vapreotide has the potential to interact with treatments used for diabetes mellitus.
 - **Other possible interactions:** The potential for vapreotide to interact with other drugs used in cirrhosis was examined in the Phase 3 clinical trial in cirrhotic patients with acute variceal bleeding (Calès 2001; Study VAP-14). Among the 98 patients treated with vapreotide in this clinical trial, concomitant medications included anti-infective agents (92% of patients), laxatives (51%), drugs for treatment of peptic ulcers (49%), anxiolytics (28%), beta-blockers (28%), insulin (18%), potassium-sparing agents (19%), and diuretics (12%). No interactions between vapreotide and these concomitant medications were reported.

7 Clinical Development Program

7.1 Overview of Clinical Studies

Five studies were conducted in patients with acute variceal bleeding. These studies are summarized in Table 7. The first EVB study conducted was VAP-14, a phase 3 double-blind, placebo-controlled study initiated in July 1997 in France. The results of this trial, published in 2001 in the *New England Journal of Medicine* by Calès P et al, demonstrated that vapreotide in combination with endoscopic therapy controlled acute variceal bleeding in cirrhotic patients with portal hypertension. Another randomized, placebo-controlled study VAP-02 was initiated in Hong Kong at the same time (July 1997) using the same study design, but was terminated 4 years later (Aug 2001) due to a very slow rate of recruitment which contributed to problems with adherence to the protocol that irrevocably jeopardized the validity of the study and the safety of patients. A third study, VAP-07, a randomized, single-center Phase 2 pilot study was initiated in Egypt in April 2002, again using the same study design as VAP-14. In VAP-07, the majority (83%) of patients had cirrhosis due to a combination of viral hepatitis and schistosomiasis, while in VAP-14, the etiology was predominately alcohol-related (85%).

The fourth, randomized, placebo-controlled study, VAP-06, was initiated in 2004 in Eastern Europe (Romania and Bulgaria), using the same design as VAP-14, except that the definition for the primary efficacy endpoint included the requirement to meet a target hematocrit of 27%.

VAP-14 did not have a protocol-specified required hematocrit level but rather a target hematocrit. The study sites suffered chronic shortages of blood and experienced significant delays in obtaining requested blood units, which interfered with the conduct of the study because of the required target hematocrit level. After 71 patients had been randomized (70 received study drug), the protocol was amended to reduce the target hematocrit to 21%. Another 210 patients were randomized after the amendment was implemented.

As described in Section 3, since the VAP-06 results were compromised by the post-initiation amendment, FDA further requested additional efficacy data. A fifth study, VAP-301, using an open-label, historical-controlled design was negotiated and accepted as appropriate for resolving the outstanding request for additional evidence of efficacy by FDA under an SPA, VAP-301 was initiated in the USA in 2006 and completed during the summer of 2008.

Table 7 Overview of Vapreotide EVB Studies

Study (Country)	Design	ITT Population	
		Vapreotide	Placebo
VAP-14 (France)	Phase 3, placebo-controlled, 22 centers	98	98
VAP-02 (Hong Kong) ^a	Phase 3, Placebo-controlled, 5 centers	51	51
VAP-07 (Egypt)	Phase 2, Placebo-controlled, 1 center	31	27
VAP-06 (Romania and Bulgaria)	Phase 3, Placebo-controlled, 8 centers	136	131
VAP-301 (USA)	Phase 3, Historical-controlled, open-label, 15 centers	70	--

^a Study terminated due to very slow accrual rate resulting in issues with adherence to the study protocol that irrevocably jeopardized the validity of the study and safety of the patients.

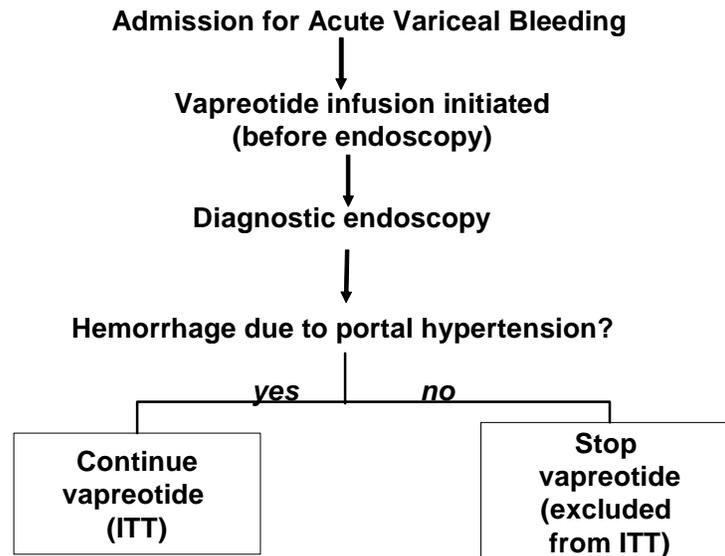
For the safety discussion, vapreotide has been studied in 45 studies of various indications, of which 36 were investigator-initiated pilot studies with no or only sporadic safety reporting. The safety discussion for vapreotide in this document will focus principally on a primary database consisting of safety data from the 4 placebo-controlled, double-blind EVB studies (VAP-14, VAP-02, VAP-06, and VAP-07), along side the safety data from the single-arm, open-label study (VAP-301). Nine vapreotide studies with safety data collected per clinical trial standards were analyzed for safety as a secondary database (9-Study Database): 5 EVB studies and 4 non-EVB studies (indications: pancreatic surgery, carcinoid/neuroendocrine tumors, Crohn’s disease, and acromegaly). For completeness, safety data from the 9-Study Database were reviewed for any potential safety signal that might not have been detected in the EVB studies.

7.1.1 Study Design for EVB Studies

All of the EVB studies had the same study design with respect to dosing regimen, inclusion/exclusion criteria, and primary endpoint, with minor differences in the components of the endpoint. Figure 3 provides an overview of the study flow. Study drug was to be initiated prior to diagnostic endoscopy. During endoscopy, those patients found to have a hemorrhage unrelated to portal hypertension, as pre-specified in the study protocol, had the study drug

infusion stopped and received treatment that was specific for their disease. These patients were excluded from the protocol-specified intent-to-treat (ITT) population and followed for safety.

Figure 3 Design of EVB Studies



The exclusion of patients with bleeding not due to portal hypertension after randomization is common to most trials conducted in this indication (Gotzsche 2008). This exclusion criterion is only detected at the time of endoscopy (and hence after randomization). Since the source of hemorrhage is not affected by treatment, exclusion of patients that do not meet this requirement (ie, with bleeding not due to portal hypertension) does not introduce bias into the ITT comparison. As is common practice in these trials, the primary analysis is conducted in the resulting subset of patients randomized. This modified intent-to-treat population is in keeping with convention in the field, and we refer to it as the intent-to-treat (ITT) population.

7.1.2 Study Endpoints

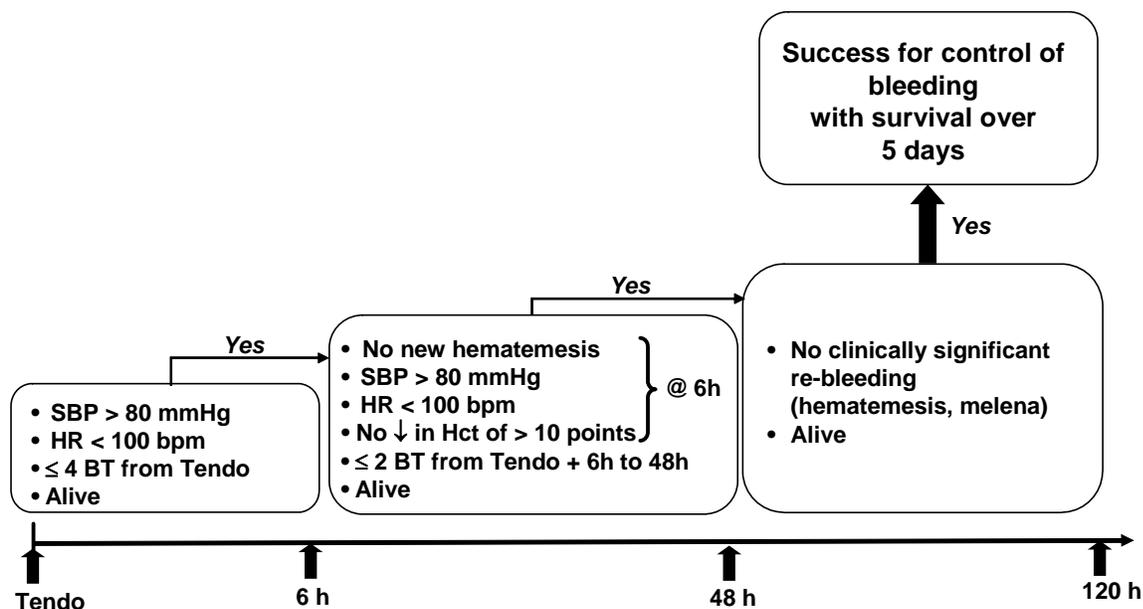
Control of bleeding is the primary goal of treatment for EVB. The vapreotide EVB studies used a composite primary efficacy criterion for *control of bleeding with survival over 5 days* (which will hereafter be referred to throughout this document as *control of bleeding over 5 days*).

The definitions for successful control of acute bleeding were adapted from the international consensus guidelines on portal hypertension (de Franchis 1996; Grace 1998) and confirmed in recent published guidelines (Garcia-Tsao 2007). The conditions for achieving success for attainment of the primary endpoint were very rigorous, as shown in Figure 4, and as follows:

- During the first 6 hours after endoscopy (Tendo = time from end of endoscopy), the patient had to:
 - survive;
 - receive ≤ 4 units of blood;
 - have systolic blood pressure (SBP) > 80 mm Hg; and
 - have a heart rate < 100 bpm.
- Between 6 and 48 hours, the patient had to:
 - survive;
 - experience no new hematemesis;
 - receive ≤ 2 units of blood;
 - have no more than a 10 point decrease in hematocrit;
 - have SBP > 80 mm Hg (measured every 6 hours [$@ 6h$]); and
 - have a heart rate < 100 bpm (measured $@ 6h$).
- Between 48 and 120 hours (end of infusion), the patient had to:
 - survive;
 - have no clinically significant rebleeding (defined as hematemesis or melena with at least one of the following Baveno criteria: (i) a decrease in SBP ≥ 20 mm Hg as compared with the average of the 2 preceding values; (ii) an increase in heart rate ≥ 20 bpm as compared with the average of the 2 preceding values; and (iii) a decrease in hematocrit of ≥ 5 points as compared with the preceding value).

If all of these criteria were met at the end of the 5-day infusion, the patient was considered a success for control of bleeding over 5 days.

Figure 4 Primary Efficacy Criteria (per Baveno Consensus Guidelines)



Secondary efficacy endpoints included:

- Control of bleeding at the time of diagnostic endoscopy;
- Control of bleeding 6 hours after initiation of study drug;
- The number of units of blood administered; and
- Survival at Day 42.

7.1.3 Patient Population

Consistent with international treatment consensus guidelines (de Franchis 2005, Garcia-Tsao 2007, Grace 1998), cirrhotic patients presenting with upper digestive tract bleeding who met all inclusion/exclusion criteria were enrolled as early as possible after admission and, in all cases, treatment with study drug was initiated prior to endoscopic diagnosis of the source of the bleeding. Patients were eligible for participation if they met the following criteria:

- Aged 18 to 75 yrs;
- Hematemesis and/or melena with unequivocal history of cirrhosis;
- ≤ 24 h between onset of initial hemorrhage and initiation of study drug;
- ≤ 6 h between admission and initiation of study drug;
- Anticipated time interval ≤ 12 h between admission and end of therapeutic endoscopy.

Important exclusion criteria, similar to those for studies of other vasoactive agents for treatment of variceal hemorrhage in cirrhotic patients (Besson 1995; Escorsell 2000; Primignani 1995; Silvain 1993; Villanueva 1999), included grade IV hepatic encephalopathy, which is a contraindication to endoscopy, Child-Pugh score ≥ 13 , and diffuse hepatocellular carcinoma, which are conditions that can cause mortality independently of the presence of variceal bleeding.

7.1.4 Dose Selection

No formal dose-finding studies have been conducted with vapreotide. The regimen selected for the EVB studies (50 μg IV bolus followed by IV infusion of 50 $\mu\text{g}/\text{h}$ for 5 days) is identical to the regimen used in similar studies of octreotide in cirrhotic patients with variceal hemorrhage (Besson 1995; Kravetz 1996; Sung 1995). In addition, this dose of vapreotide falls within the range of the human equivalent dose (HED) of vapreotide computed from the dose-levels that were studied in rats with portal hypertension resulting from cirrhosis (Study DEB-94-PRE-/cl-VAP-03). Given that variceal bleeding is a life-threatening medical emergency, administration of the bolus dose in addition to the infusion is believed to be important for treatment efficacy. Somatostatin boluses cause transient, but dramatic, decreases in portal pressure, porto-collateral blood flow (Cirera 1995), and variceal pressure (Nevens 1994). Studies exploring the impact of duration of somatostatin (Avgerinos 2000) and octreotide (Romaozinho 1996) therapy for treatment of acute variceal hemorrhage demonstrated that there was improved efficacy for control of hemostasis with a 5-day infusion compared with a 2-day infusion.

7.1.5 Statistical Methodology

Continuous parameters were presented in the form of descriptive statistics per treatment arm, as median, mean, standard deviation, standard error, min-max, 95% confidence interval (95% CI). Categorical parameters were presented per treatment arm as contingency tables with absolute, percentage frequencies 95% CI.

Baseline characteristics and efficacy:

Categorical parameters were analyzed in contingency table by the chi-square test or Fisher's exact test when frequencies were < 5 . The 2-sided 95% CI was constructed per treatment arm. Student's t-test or Wilcoxon rank-sum test analyzed continuous parameters if the normal distribution was not verified. Survival curves were compared by the log-rank test.

Efficacy:

For the randomized multicenter studies, preliminary analysis on hemostasis was conducted with the Cochran-Mantel-Haenszel test to analyze the following factors: treatment, center, and treatment-by-center interaction. A lack of significant treatment-by-center interaction was considered as a justification for pooling data over all centers. A logistic regression was conducted in order to explain variation in the primary criterion. For all randomized studies a log-rank tests were performed in order to compare survival curves.

Safety:

All patients who received at least one dose of study drug were included in the analysis of safety. This included the patients who received vapreotide up to the time of the diagnostic endoscopy and were determined not to have bleeding due to portal hypertension.

All adverse events were summarized by body system and WHO preferred terminology within each treatment group and globally. Events were tabulated in 2 different ways, by the number and percentage of patients who experienced events and by the number of times each event occurred. Laboratory parameters at pre- and end-of-treatment as well as change from pre-treatment levels were presented as summary statistics and were compared between treatment groups by Student's t-test, or a Wilcoxon test if normal distribution was not verified. Shift tables based on laboratory normal ranges were presented for each study treatment.

For represented body system, frequencies of patients who experienced an event were compared between the 2 treatment groups by the chi-square test or by Fisher's exact test when expected cells frequencies were < 5 .

8 Clinical Efficacy

8.1 Overview of Efficacy

The efficacy of vapreotide as adjunctive therapy to endoscopic intervention for the treatment of acute esophageal bleeding as a result of portal hypertension has been established in the pivotal VAP-14 study together with supporting information from VAP-301 and other EVB studies

(VAP-07, and VAP-06). All of the EVB studies used the same primary endpoint for efficacy in accordance with consensus guidelines. The study drug regimen consisted of an IV bolus (vapreotide 50 µg or placebo) followed by continuous IV infusion (vapreotide 50 µg/h or placebo) for 5 days.

- VAP-14 demonstrated the efficacy of early administration of vapreotide in association with endoscopic therapy in cirrhotic patients with variceal bleeding with respect to the primary and secondary endpoints as follows:
 - Higher rate of control of bleeding over 5 days (66% vapreotide vs 50% placebo; p=0.02) (primary endpoint)
 - Higher rate of control of bleeding at the time of endoscopy (64% vs 51%; p=0.031)
 - Higher rate of control of bleeding at 6 hours post-initiation of the infusion (82% vs 53%; p=0.001)
 - Higher rate of control of bleeding at 48 hours (Day 2) after endoscopy (73% vs 54%; p=0.005)
 - Fewer blood transfusions required during Days 1-5 (2.0 vs 2.8; p=0.04).
 - A trend in survival benefit at Day 42 (86% vs 79%; p=0.195)
 - The effectiveness of vapreotide for control of bleeding was found to be independent of baseline hematocrit, presence or absence of active bleeding at endoscopy, severity of liver impairment (Child-Pugh Class A or B vs C), use of beta-blocker treatment at admission, or type of endoscopic treatment modality.
- VAP-301, accounting for expected differences in cirrhosis etiology and endoscopic procedure, shows results that are generally consistent with VAP-14, with 77% of patients achieving control of bleeding over 5 days. Analyses performed in patient subgroups for etiology and type of endoscopic procedure further demonstrate the clinical relevance of the VAP-14 findings in the USA patient population with EVB. The success rate achieved in VAP-301 for control of bleeding over 5 days (ie, 77%) is also consistent with that reported in 2 meta-analyses of published data on vasoactive treatment with endoscopy compared to endoscopy alone (77% and 74% for the vasoactive + endoscopy group compared to 58% and 53% for the endoscopy alone group [Bañares 2002; de Franchis 2004, respectively]).
- VAP-07, the pilot study that enrolled patients with portal hypertension due primarily to viral hepatitis- and/or schistosomiasis-induced cirrhosis rather than alcoholism alone as in VAP-14, showed a trend in favor of treatment with vapreotide for control of bleeding over 5 days (71% vapreotide vs 59% placebo; p=0.349).
- VAP-06, when analyzed as originally planned, showed no difference between vapreotide and placebo (65% vs 66%). An amendment to the protocol that was implemented after

71 patients were enrolled changed the treatment protocol and the primary endpoint (to require significantly fewer blood transfusions). Differences in treatment practices before and after the amendment call into question the appropriateness of combining the pre- and post-amendment populations. In addition, the protocol-specified criteria for success included the investigator's opinion on the control of bleeding. When analyzed separately using the same criteria as in the pivotal VAP-14 study (which excluded investigator's opinion and requirement for a target hematocrit), the pre-amendment efficacy data (N=65) show a positive trend (63% vapreotide vs 52% placebo), while no difference is seen in the post-amendment (N=202) (52% vapreotide vs 51% placebo).

- VAP-02, a multicenter, randomized, double-blind, placebo-controlled study (ITT N=102) was terminated early due to the slow rate of enrollment (136 patients over 4 years; only 16 in 2001) which contributed to adherence issues with the protocol that irrevocably jeopardized the validity of the study and safety of the patients (ie, at least 2 patients were administered 12 vials of study drug within 6 hours instead of the intended 5 days). Initially submitted solely for evaluation of the safety data, the efficacy results were analyzed at the request of FDA. It was agreed that the efficacy results were difficult to interpret, and could not be used to support efficacy. These results are included herein for full disclosure.
- A meta-analysis of the primary efficacy results from the 4 placebo-controlled trials (VAP-14, VAP-07, VAP-06, and VAP-02) resulted in an odds ratio of 1.33 in favor of vapreotide (95% CI: 0.92, 1.93). A sensitivity meta-analysis, excluding VAP-02 and treating VAP-06 pre and post amendment results as separate trials, shows an odds ratio of 1.43 (95% CI: 1.01, 2.03). (VAP-301 could not be included in the meta-analysis since it did not have a placebo-control arm). A pooled logistic regression including the VAP-301 data provided materially the same results (odds ratio: 1.44 [95% CI: 1.01, 2.03]).

In conclusion, the results obtained from the pivotal, well-conducted VAP-14 study, and trends observed in the other evaluable studies, demonstrate that early administration of vapreotide, in association with endoscopic intervention, is effective for the treatment of acute variceal hemorrhage related to portal hypertension.

8.2 Efficacy Studies

An overview of the 5 EVB studies that evaluated the efficacy of vapreotide for the intended indication is provided in Table 8.

Table 8 Vapreotide Clinical Studies in Variceal Hemorrhage

Study	Countries	Study Period	Design	# Centers	No. Patients Safety/ITT Populations	
					Vapreotide	Placebo
VAP-14	France	1997-1998	Randomized, double-blind, placebo-controlled	22	111/98	116/98
VAP-07	Egypt	Apr – Sept 2002	Randomized, double-blind, placebo-controlled	1	41/31	31/27
VAP-06	Romania, Bulgaria	2003-2004	Randomized, double-blind, placebo-controlled	8	144/136	134/131
VAP-06 Pre-amendment					36/32	34/33
VAP-06 Post-amendment					108/104	100/98
VAP-02	Hong-Kong	1997 -2001	Randomized, double-blind, placebo-controlled	5	70/51	66/51
VAP-301	USA	2006-2008	Single-arm, open-label	15	103/70	N/A

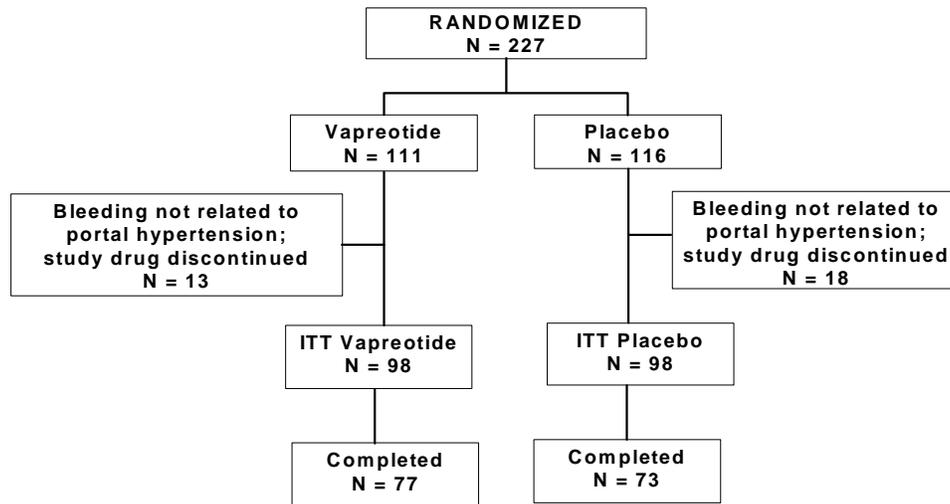
N/A = not applicable; VAP-301 was a single-arm study.

8.2.1 Study VAP-14

In VAP-14, 227 patients with cirrhosis who were hospitalized for acute upper gastrointestinal bleeding were randomly assigned to receive vapreotide (50 µg IV bolus injection followed by an IV infusion at a rate of 50 µg/h for 5 days) or placebo.

Per protocol, 31 patients (13 vapreotide and 18 placebo patients) who had bleeding found at endoscopy to be due to causes other than portal hypertension or who had no diagnostic endoscopy performed were excluded from the ITT population. The patient disposition for VAP-14 is shown in Figure 5.

Figure 5 Patient Disposition: VAP-14



Of the 98 patients in each treatment arm, 78 vapreotide and 74 placebo patients completed the 5-day infusion period; and 77 vapreotide and 73 placebo patients were followed until death or completion of the 42-day study period. Forty-six patients (21 vapreotide; 25 placebo) prematurely discontinued the study. Of the 21 vapreotide patients, 5 patients died during the first 5 days; 9 patients died between Days 6 and 42; and 7 patients were lost to follow-up. Of the 25 placebo patients who prematurely discontinued the study, 7 patients died during the first 5 days, 14 patients died between Days 6 and 42, and 4 patients were lost to follow up.

The sample size for VAP-14 was calculated to fulfill the primary objective, which was to demonstrate that vapreotide could improve control of bleeding over 5 days when compared to placebo. Based on published literature (Besson 1995; Sarin 1992; Sarin 1996), control of bleeding was observed in about 65% of patients under placebo treatment. As a rate of control of bleeding at 5 days on vapreotide of 85% could be anticipated for somatostatin or other analogs, 73 patients per treatment group were required to demonstrate this difference versus placebo, with nominal $\alpha = 0.05$ (2-sided) and $\beta = 0.20$. Sample size calculation used the formula for comparing 2 binomial proportions, without correction for continuity (Machin 1987). 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 209 patients.

Demographic and Baseline Characteristics

The vapreotide and placebo groups were comparable in age, height, and weight (Table 9). The vapreotide group had a lower percentage of males, and on average had numerically lower heart rates, higher blood pressures, higher hematocrits, and a lower percentage had external signs of bleeding at admission (defined by hematemesis and/or melena that occurred or was observed during examination of the patient at admission as opposed to the index hemorrhage).

Table 9 Demographic and Other Characteristics at Hospital Admission: VAP-14 (ITT)

	Vapreotide N = 98	Placebo N = 98
Gender : Male	67 (68%)	81 (83%)
Age (yr)	N=98	N=98
Mean (SD)	54.9 (10.8)	55.0 (11.1)
Median (Range)	56.0 (32.0 – 73.0)	54.0 (29.0 - 75.0)
Weight (kg)	N = 96	N = 92
Mean (SD)	72.0 (14.7)	72.7 (15.4)
Median (Range)	70.0 (36.0 – 106.0)	70.0 (48.0 – 120.0)
Height (cm)	N = 91	N = 90
Mean (SD)	168.7 (8.0)	168.4 (7.9)
Median (Range)	170.0 (152.0 – 190.0)	169.0 (151.0 – 190.0)
Hematocrit at admission (%)	N = 93	N = 96
Mean (SD)	29.0 (6.9)	26.5 (7.9)
Median (Range)	29.5 (12.0 – 47.0)	27.0 (9.0 – 42.3)
SBP at admission (mmHg)	N = 98	N = 97
Mean (SD)	127.4 (23.0)	125.1 (22.6)
Median (Range)	130.0 (70.0 – 180.0)	122.0 (73.0 – 183.0)
DBP at admission (mmHg)	N = 96	N = 97
Mean (SD)	70.3 (14.0)	66.6 (15.1)
Median (Range)	70.0 (37.0 – 111.0)	68.0 (30.0 – 101.0)
Heart Rate at admission (bpm)	N = 97	N = 96
Mean (SD)	97.8 (21.6)	103.7 (22.3)
Median (Range)	96.0 (57.0 – 152.0)	104.0 (57.0 – 170.0)
External Bleeding at Admission	N=98 72 (73.5%)	N=98 83 (84.7%)

The 2 treatment groups were comparable at admission for disease characteristics related to cirrhosis (Table 10).

Table 10 Baseline Disease Characteristics: VAP-14 (ITT)

	Vapreotide N = 98	Placebo N = 98
Underlying cause of cirrhosis:		
Alcoholism only	83 (84.7%)	84 (85.7%)
Viral hepatitis only	3 (3.1%)	3 (3.1%)
Alcoholism plus viral hepatitis	9 (9.2%)	7 (7.1%)
Other	3 (3.1%)	4 (4.1%)
Child-Pugh Class	N = 92	N = 94
A	14 (15.2%)	14 (14.9%)
B	42 (45.7%)	41 (43.6%)
A or B	56 (60.9%)	55 (58.5%)
C	36 (39.1%)	39 (41.5%)
Prothrombin Activity (%)	N = 98	N = 97
Mean (SD)	53.3 (14.9)	48.2 (16.5)
Median (Range)	52 (20.0 – 90.0)	50 (14.0 – 84.0)
Bilirubin (mg/dL)	N = 98	N = 97
Mean (SD)	3.5 (4.7)	3.5 (3.8)
Median (Range)	2.3 (0.4 – 34.6)	2.3 (0.4 – 20.2)
Ascites	N = 98	N = 97
Absent	62 (63.3%)	65 (67.0%)
Mild-Moderate	22 (22.4%)	22 (22.7%)
Severe-Refractory	14 (14.3%)	10 (10.3%)
Hepatic Encephalopathy	N = 98	N = 97
Absent	84 (85.7%)	77 (79.4%)
Mild (I-II)	9 (9.2%)	17 (17.5%)
Severe (III-IV)	5 (5.1%)	3 (3.1%)
Previous episode of hemorrhage related to portal hypertension:	N = 97	N = 98
0 episode	59 (60.8%)	60 (61.2%)
1 episode	19 (19.6%)	18 (18.4%)
≥ 2 episodes	17 (17.5%)	19 (19.4%)
Unknown	2 (2.1%)	1 (1.0%)

The rates of concomitant treatment before randomization, during study drug infusion, and after the end of infusion are shown in Table 11. Fewer patients randomized to vapreotide, compared to placebo, received transfusions of plasma or macromolecules at admission (11% vs 24%).

Table 11 Concomitant Treatments: VAP-14 (ITT)

	Vapreotide N = 98 n (%)	Placebo N = 98 n (%)
At least one concomitant treatment before randomization	55 (56%)	51 (52%)
Transfusion of plasma or macromolecules at admission		
None	86 (88%)	74 (76%)
Less than 1000 mL	11 (11%)	16 (16%)
At least 1000 mL	---	8 (8%)
Concomitant medication during product infusion ^a		
At least one medication	98 (100%)	97 (99%)
Alimentary tract and metabolism	92 (94%)	90 (93%)
General anti-infectives for systemic use	90 (92%)	88 (91%)
Cardiovascular	52 (53%)	52 (54%)
Nervous system	53 (54%)	44 (45%)
Concomitant treatment after the end of product infusion ^a		
At least one medication	94 (96%)	92 (94%)
Alimentary tract and metabolism	86 (91%)	87 (95%)
General anti-infectives for systemic use	73 (78%)	70 (76%)
Cardiovascular	77 (82%)	80 (87%)

^a Only main items are included in this table.

The mean time between hemorrhage and start of study drug infusion was (hr:min) 9:45 and 9:53 for the vapreotide and placebo groups. The groups were also similar in the mean time from admission to start of the product infusion (2:15 vs 2:00).

Endoscopic treatment was initiated a mean (\pm SD) of 2.3 \pm 1.5 hours after admission. Study patients received endoscopy a mean (\pm SD) of 2.6 \pm 3.3 hours after the infusion was initiated.

The source of the variceal hemorrhage was determined during the endoscopic procedure following randomization. Almost all of the patients (95%) had esophageal varices (Table 12).

Table 12 Source of Hemorrhage: VAP-14 (ITT)

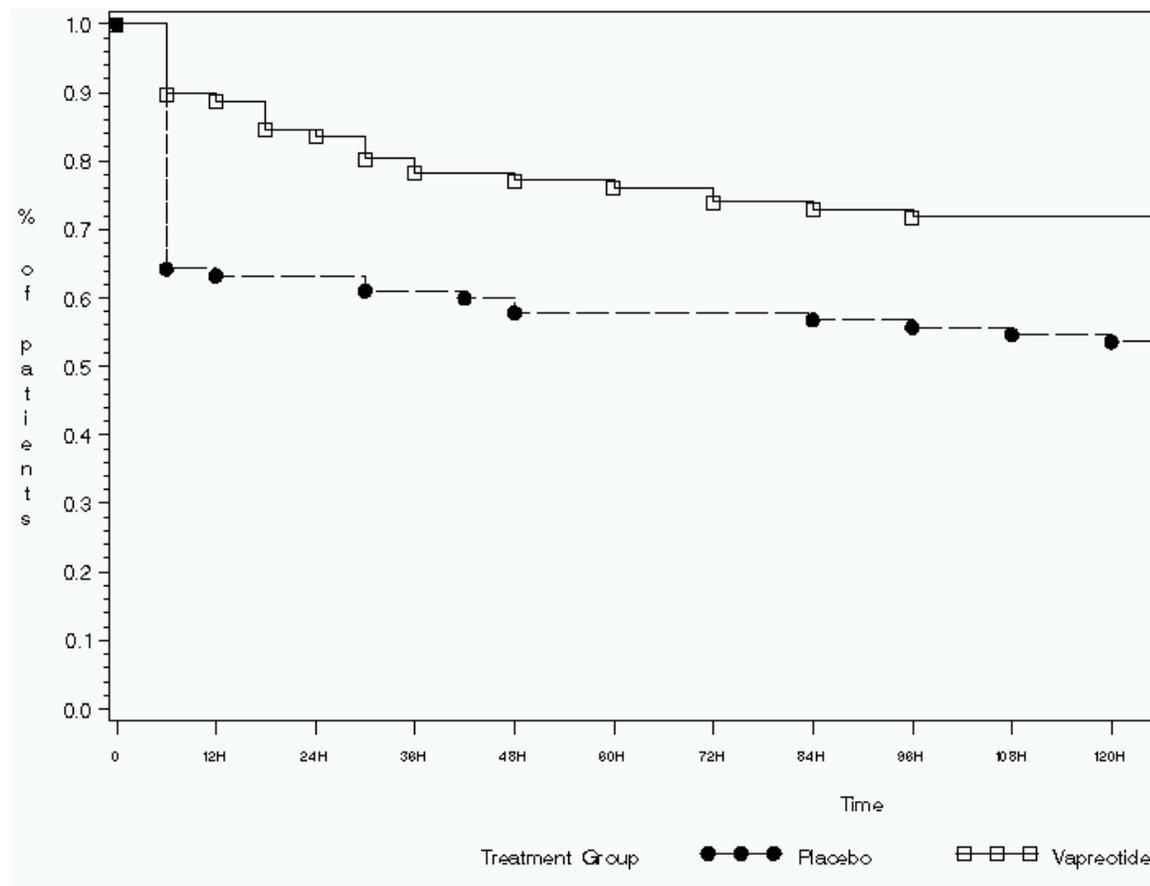
	Vapreotide N = 98 n (%)	Placebo N = 98 n (%)
Esophageal varices	91 (93%)	95 (97%)
Gastric varices	2 (2%)	2 (2%)
Portal hypertensive gastropathy	5 (5%)	1 (1%)

Efficacy Results

Vapreotide, compared to placebo, significantly increased the percentage of patients who achieved control of bleeding over the first 5 days (primary endpoint) (66% vs 50%; p=0.021) (odds ratio: 1.97 [1.11, 3.51]).

Failures could occur at any time period after the end of endoscopic treatment (time 0 on graph), but were observed more frequently early during treatment with study drug (Figure 6). Control of bleeding was achieved in the vapreotide and placebo groups for 82% vs 53% of patients within the first 6 hours after initiation of study drug infusion (p=0.001), and 73% vs 54% of patients 48 hours after endoscopy (p=0.005).

**Figure 6 Percentage of Patients with Control of Bleeding Over Time:
VAP-14 (ITT)**



Because of baseline differences between the treatment groups in various parameters, additional analyses were performed to assess the impact of those differences on the primary outcome. Cochran-Mantel-Haenszel tests on the ITT population confirmed the statistically significant treatment effect after adjusting for each parameter that was imbalanced at baseline. Table 13 provides the p-values and odds ratios for those analyses.

Table 13 Primary Endpoint (Control of Bleeding Over 5 Days) Adjusted for Baseline Imbalances: VAP-14 (ITT)

Baseline Parameter	Vapreotide N=98 Mean ± SD or % of patients	Placebo N=98 Mean ± SD or % of patients	P- value ^a	Primary Endpoint ^b Adjusted for Parameter P-value ^c	Odds Ratio ^b VAP/PBO (95% CI)	Homo- geneity P-value ^d
Unadjusted				0.021	1.97 (1.11, 3.51)	0.038
Heart rate (bpm)	98 ± 22	104 ± 22	0.062	0.048	1.80 (1.00, 3.25)	0.115
Mean SBP (mmHg)	89 ± 15	86 ± 16	0.141	0.046	1.82 (1.00, 3.29)	0.649
Mean DBP (mmHg)	70 ± 14	67 ± 15	0.075	0.040	1.87 (1.03, 3.41)	0.317
Hematocrit (%)	29 ± 7	27 ± 8	0.053	0.029	1.98 (1.07, 3.64)	0.564
External bleeding at admission	73.5%	84.7%	0.053	0.029	1.91 (1.07, 3.41)	0.264
Transfusion of plasma or macromolecules	11.3%	24.5%	0.017	0.019	2.02 (1.12, 3.66)	0.498

Abbreviations: VAP = vapreotide; PBO = placebo; SBP = systolic blood pressure; DBP = diastolic blood pressure

^a Student's t-test or Wilcoxon test comparing vapreotide and placebo groups for differences in baseline parameters.

^b Control of bleeding with survival over Day 5.

^c Cochran-Mantel-Haenszel test comparing primary efficacy endpoint between treatment groups (ITT) adjusted for baseline variable.

^d Homogeneity of treatment effect p-value; Breslow-Day test.

The benefit of vapreotide was apparent across all study centers that enrolled patients in VAP-14. No significant difference was seen among centers in terms of relative treatment effect (Cochran-Mantel-Haenszel test p=0.75), and no single center was disproportionately responsible for the favorable effect observed. Table 14 shows the odds ratio for the primary endpoint when each center that enrolled more than 10 patients is removed from the analysis for center effect. Centers that enrolled less than 5, or 5 to 10, patients were grouped and then removed. The key observation is that the odds ratios are consistent and the 95% confidence intervals for the primary analysis overlap when the different centers are removed.

Table 14 Test for Center Effect: VAP-14 (ITT)

	Odds Ratio (95% CI)
ITT – All Centers (N=196)	1.97 (1.11, 3.51)
Center Removed from Equation	Odds Ratio when Specified Center(s) Removed
#18 (n=28)	1.65 (0.89, 3.05)
#2 (n=22)	2.04 (1.11, 3.78)
#1 (n=20)	1.84 (1.00, 3.37)
#14 (n=15)	1.94 (1.06, 3.52)
#12 (n=14)	2.09 (1.15, 3.80)
#10 (n=11)	2.02 (1.11, 3.67)
All centers with 5-10 patients (n=71)	2.11 (1.03, 4.33)
All centers with <5 patients (n=15)	2.15 (1.17, 3.95)

The benefit of vapreotide was consistent across a range of subpopulations. The higher percentage of patients with control of bleeding over 5 days in the vapreotide group was shown to be independent of type of endoscopic treatment performed (band ligation; sclerotherapy), Child-Pugh Class (A/B; C), size of varices (≤ 5 mm; > 5 mm), and concomitant use of β -blockers (Table 15).

Table 15 Control of Bleeding Over 5 Days by Subgroups: VAP-14 (ITT)

	Vapreotide n/N (%)	Placebo n/N (%)	Odds Ratio (95% CI)
Overall	65/98 (66%)	49/98 (50%)	1.97 (1.11, 3.51)
Endoscopic Treatment			
Band ligation only	23/30 (77%)	18/30 (60%)	2.19 (0.72, 6.70)
Sclerotherapy only	31/49 (63%)	26/55 (47%)	1.92 (0.88, 4.22)
Child-Pugh Class			
A or B	41/56 (73%)	29/55 (53%)	2.45 (1.11, 5.42)
C	21/36 (58%)	19/39 (49%)	1.47 (0.60, 3.67)
Size of Varices			
≤ 5 mm	21/27 (78%)	18/25 (72%)	1.36 (0.39, 4.79)
> 5 mm	36/59 (61%)	28/65 (43%)	2.07 (1.01, 4.24)
Prior β -blockers			
No	34/54 (63%)	31/63 (49%)	1.75 (0.86, 3.68)
Yes	31/44 (70%)	18/35 (51%)	2.25 (0.89, 5.69)

Secondary Endpoints

Statistically significant benefits for vapreotide also were observed for 4 prospectively defined secondary endpoints related to achieving control of bleeding: at the time of initial endoscopic procedure; at 6 hours after initiation of the study drug infusion; at 48 hours after endoscopy; units of blood transfused during the study, and survival at Day 42 (Table 16).

Table 16 Secondary Endpoints: VAP-14 (ITT)

Secondary Endpoint	Vapreotide N = 98	Placebo N = 98	P-value
Control of bleeding, n (%)			
At endoscopy	63 (64%)	50 (51%)	0.031
6 hours after initiation of infusion	80 (82%)	52 (53%)	0.001
48 hours after endoscopy	72 (73%)	53 (54%)	0.005
Blood units transfused over 5 days, mean ± SD	2.0 ± 2.2	2.8 ± 2.8	0.04 ^a
Survival at Day 42	84 (86%)	77 (79%)	0.195

^a Log-rank test for Kaplan-Meier estimates.

Survival at Day 42, showed a trend in favor of vapreotide, but was not statistically significantly different between the vapreotide and placebo groups (86% [84/98] vs 79% [77/98], p=0.195). To explore the survival data, an analysis was performed using both arms of the VAP-14 ITT population (N=196) to evaluate the extent to which mortality at 6 weeks could be predicted by the primary endpoint (control of bleeding over 5 days). Death at 6 weeks was analyzed according to success/failure for the primary endpoint. A significant association (p=0.0003, chi-square) between control of bleeding over 5 days and death at 6 weeks was observed.

8.2.2 Study VAP-301

The main objective of the historical-controlled, open-label USA study, VAP-301, as agreed with FDA in an SPA, was to provide confirmation of the efficacy of early administration of vapreotide in combination with endoscopic treatment for the control of acute variceal bleeding. The lack of an approved active comparator in the USA ruled out an active-controlled trial, and using a placebo arm was considered unethical by the time this study was initiated in 2006. It was agreed with FDA that the success rate achieved in this study would be evaluated for clinical significance compared to the results achieved in the VAP-14 study and the results reported in the available literature on octreotide. Formal statistical tests and comparisons were not planned in the protocol.

Sample size was calculated to provide the point estimate with 95% CI for the primary outcome, control of bleeding over 5 days. With an expected rate of 70% and 70 evaluable patients in the ITT population, the 95% CI for the proportion was estimated to have a half-width of 10%. For secondary outcomes, the worst-case (for a proportion of 50% success) is a confidence interval half-width of 11.5%. Sample size considerations were based solely on the primary outcome. Sample size calculations used the formula for estimation of a binomial proportion, and all sample size calculations were carried out using the PASS software system (*Hintze, J. NCSS and PASS 2001* (<http://www.ncss.com/>)). The total number of patients enrolled was monitored according to the proportion of patients with bleeding due to portal hypertension to reach a total of 70 patients with portal hypertension.

Fifteen centers in the USA enrolled 103 patients with cirrhosis who were hospitalized for acute upper gastrointestinal bleeding. All patients received vapreotide (50 µg IV bolus followed by a continuous IV infusion at a rate of 50 µg/h for 5 days). Study patients completed diagnostic (and therapeutic) endoscopy a mean (\pm SD) 5:09 (\pm 2.26) hours after admission.

Of the 103 patients enrolled, 33 patients were excluded from the ITT population, ie, had their study drug infusion discontinued at the time of the diagnostic endoscopy. This included 31 patients whose bleeding was due to causes other than portal hypertension and 2 patients who were discontinued by the investigator (one for respiratory complications that prevented endoscopy and the other because he had previously participated in this study).

In order to be consistent with current medical practice in the USA for treatment of EVB, the study protocol required 2 amendments after initiation of the study, neither of which deviated from the original study design or assessment of efficacy criteria, nor had an effect on the safety of patients. The first amendment permitted time intervals for assessments to be extended from 30 to 60 minutes for the first 48 hours and from 60 to 90 minutes between 48 and 120 hours. The second modification allowed the use of volumetric pumps in addition to syringe pumps to administer the study drug.

8.2.2.1 Study Populations

VAP-301 was conducted to show consistency with the results obtained with vapreotide for the treatment of EVB in the pivotal VAP-14 study. In the following sections, the results from VAP-301 are shown along side the results from VAP-14 for ease of presentation.

Key demographic and baseline characteristics for the ITT population in VAP-301, and the combined treatment groups in VAP-14 are summarized in Table 17 and Table 18. Patient characteristics at enrollment were similar in both studies. The majority of patients were middle-aged (mean age of 53 and 55 years in the VAP-301 and VAP-14) males (76% in both studies) with external signs of bleeding at physical examination subsequent to hospitalization for the index bleeding event (70% and 73%). Mean values for vital signs, hematocrit, and hemoglobin levels also were comparable for the vapreotide groups in both studies.

Table 17 Demographic and Baseline Characteristics by Study and Treatment Group: VAP-301 and VAP-14 (ITT)

	VAP-301 Vapreotide N=70	VAP-14 (Vapreotide & Placebo) N=196
Gender : Male	53 (76%)	148 (76%)
Age (yr)	N=70	N=196
Mean (SD)	53.3 (8.4)	54.9 (10.9)
Median (Range)	52.0 (27.9 – 71.8)	55.5 (29.0 - 75.0)
Weight (kg)	N=69	N=188
Mean (SD)	84.1 (21.9)	72.3 (15.0)
Median (Range)	80.9 (41.4-146.4)	70.0 (36.0 – 120.0)
Height (cm)	N=67	N=181
Mean (SD)	174.2 (9.9)	168.6 (7.9)
Median (Range)	175.3 (155-198)	170.0 (151 – 190)
Hematocrit at admission (%)	N=70	N=189
Mean (SD)	28.8 (6.2)	27.7 (7.5)
Median (Range)	29.4 (15.3-42.0)	28.0 (9.0 – 47.0)
SBP at admission (mmHg)	N=69	N=195
Mean (SD)	117.0 (21.2)	126.3 (22.8)
Median (Range)	113.0 (77.0-183.0)	127.0 (70.0-183.0)
DBP at admission (mmHg)	N=69	N=193
Mean (SD)	66.8 (14.7)	68.4 (14.6)
Median (Range)	66.5 (28.5-95.0)	70.0 (30.0-111.0)
Heart Rate at admission (bpm)	N=69	N=193
Mean (SD)	98.3 (21.0)	100.7 (22.1)
Median (Range)	96.5 (61.0-155.0)	100.0 (57.0-170.0)

The etiology of cirrhosis was more complex in the VAP-301 study than in the pivotal VAP-14 study. In VAP-14, 85% of disease was attributed to alcoholism alone and only 8% to combined alcoholism and viral hepatitis. In contrast, 33% of disease in VAP-301 was attributed to alcoholism alone, with 29% attributed to combined alcoholism and viral hepatitis, and 14% to viral hepatitis alone. The more complex etiology in VAP-301 is consistent with that recently reported for patients hospitalized in the USA for complications of portal hypertension. Specifically, it has been observed that from 1998 to 2003, the prevalence of hepatitis C-related advanced liver disease increased from 12.9% to 23.7% and that of combined alcoholism and hepatitis C virus infection increased from 5.6% to 11.2% (Nguyen 2007).

Hepatic encephalopathy (20% vs 17%) and ascites (57% vs 35%), which are characteristic of end-stage decompensated cirrhosis, were more prevalent in VAP-301 than VAP-14.

**Table 18 Baseline Disease Characteristics by Study and Treatment Group:
 VAP-301 and VAP-14 (ITT)**

	VAP-301 (Vapreotide) N=70	VAP-14 (Vapreotide & Placebo) N=196
Underlying cause of cirrhosis:		
Alcoholism only	23 (32.9%)	167 (85.2%)
Viral hepatitis only	10 (14.3%)	6 (3.1%)
Alcoholism plus viral hepatitis	20 (28.6%)	16 (8.2%)
Other ^a	17 (24.3%)	7 (3.6%)
Child-Pugh Class	N=69	N=186
A	12 (17.4%)	28 (15.1%)
B	31 (44.9%)	83 (44.6%)
A or B	43 (62.3%)	111 (59.7%)
C	26 (37.7%)	75 (40.3%)
Bilirubin (mg/dL)	N=69	N=195
Mean (SD)	3.6 (5.0)	3.5 (4.3)
Median (Range)	1.9 (0.4-31.5)	2.3 (0.4-34.6)
Ascites	N=70	N=195
Absent	30 (42.9%)	127 (65.1%)
Mild-Moderate	34 (48.6%)	44 (22.6%)
Severe-Refractory	6 (8.6%)	24 (12.3%)
Hepatic Encephalopathy	N=70	N=195
Absent	56 (80.0%)	161 (82.6%)
Mild (I-II)	13 (18.6%)	26 (13.3%)
Severe (III-IV)	1 (1.4%)	8 (4.1%)
Previous episode of hemorrhage, n (%)	N=70 30 (42.9%)	N=195 76 (39.0%)
Origin of bleeding, n (%)	N=70	N=196
Esophageal varices	66 (94%)	186 (95%)
Gastric varices	3 (4%)	4 (2%)
Portal hypertensive gastropathy	1 (1%)	6 (3%)

^a Includes alcoholism/hemachromatosis, biliary, non-alcoholic fatty liver, disease and fatty liver, drug-induced, sclerosing cholangitis, autoimmune hepatitis, cryptogenic, alpha1-antitrypsin deficiency, unknown, and not applicable (patient who did not meet inclusion criteria because the etiology of portal hypertension was undifferentiated carcinoma).

8.2.2.2 Study Treatment

Patients in both studies received the same dose and schedule of study drug. Of the 70 ITT patients in VAP-301, 61 completed the 5-day vapreotide infusion period. Not unexpectedly, the proportions of patients who had band ligations and who had sclerotherapy differed between studies (Table 19). In the pivotal VAP-14 study, 53% of patients had sclerotherapy and 31% had band ligation. Subsequent to completion of the VAP-14 study, band ligation became the

preferred endoscopic treatment (Villanueva 2006). Reflecting this trend, 86% of patients in VAP-301 had band ligation and only 4% had sclerotherapy.

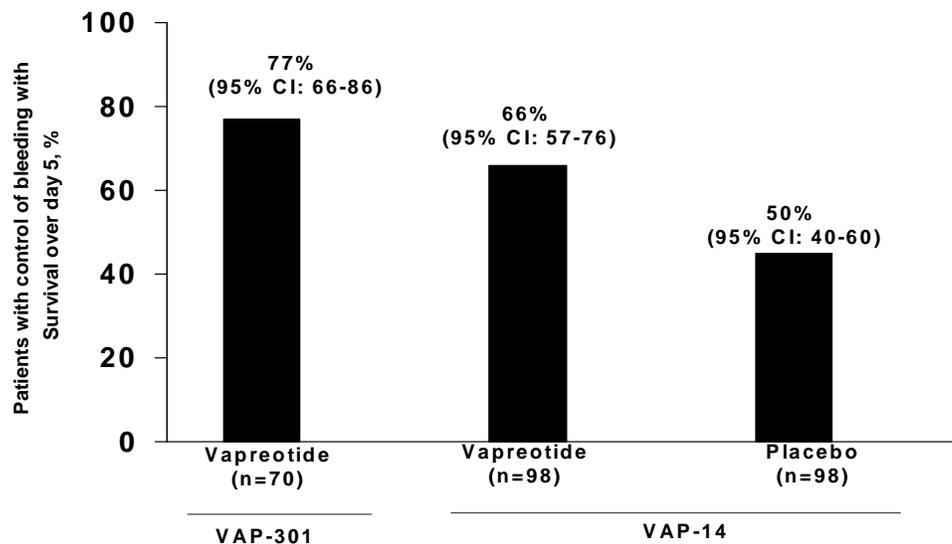
**Table 19 Endoscopic Therapy Modality by Study and Treatment Group:
 VAP-301 and VAP-14 (ITT)**

Endoscopic Therapy Modality	VAP-301 (vapreotide) N=70 n (%)	VAP-14 (vapreotide & placebo) N=196 n (%)
No diagnostic endoscopy	0 (0%)	4 (2%)
Sclerotherapy only	3 (4%)	104 (53%)
Band Ligation only	60 (86%)	60 (31%)
Sclerotherapy and band ligation	4 (6%)	2 (1%)
Other	0 (0%)	10 (5%)
None	3 (4%)	16 (8%)

8.2.2.3 Efficacy Results in VAP-301

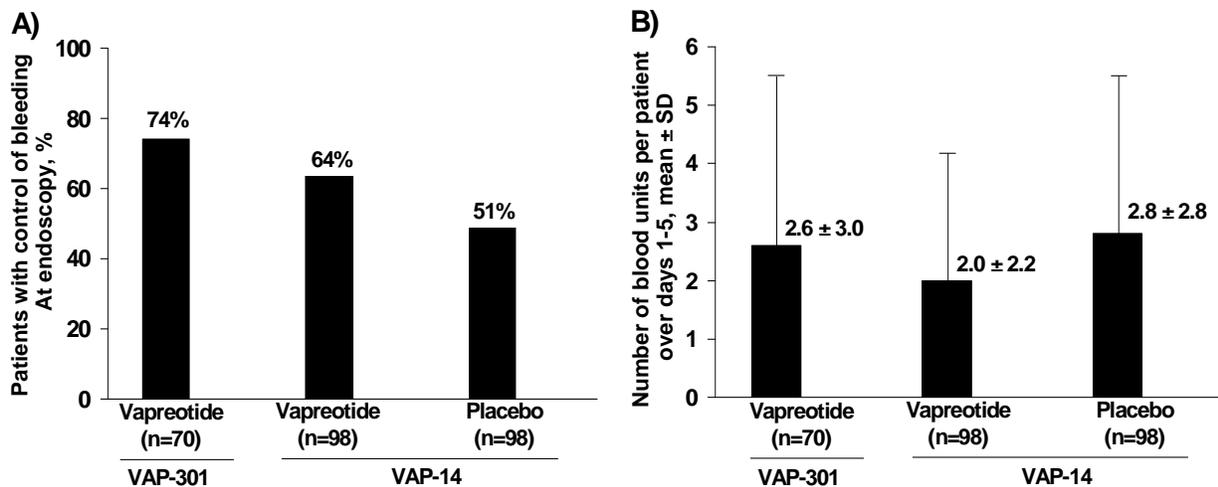
The success rate for control of bleeding over 5 days (ie, the primary endpoint) was 77% in the VAP-301 compared to 66% for the vapreotide and 50% for the placebo groups in VAP-14 (Figure 7).

**Figure 7 Primary Efficacy Endpoint: Control of Bleeding Over 5 Days:
 VAP-301 and VAP-14 (ITT)**



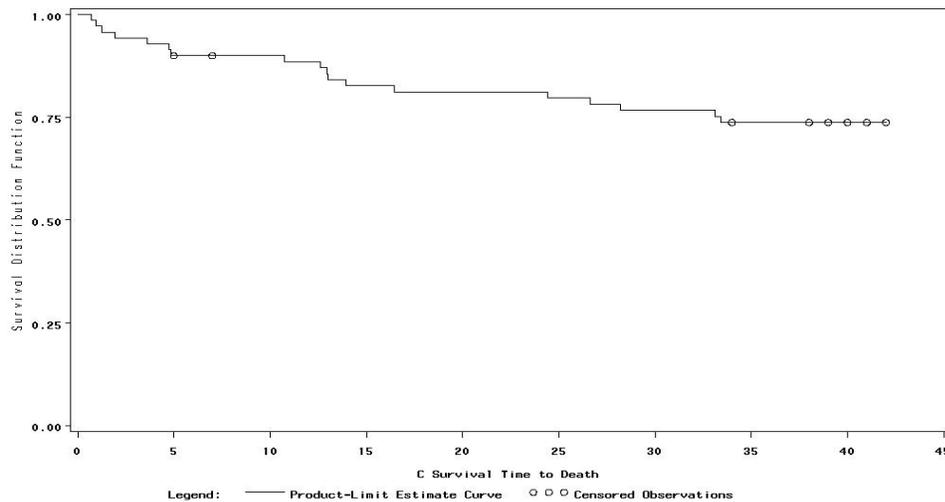
Endoscopic facilitation (control of bleeding at time of endoscopy) was defined as the absence of active bleeding at endoscopy and the ability to determine the origin of hemorrhage. In the ITT populations, control of bleeding at time of endoscopy was achieved in 74% of patients in VAP-301 and 64% of patients treated with vapreotide in VAP-14 compared to 51% of patients in the VAP-14 placebo group (Figure 8A). During the first 5 days following the index hemorrhage, patients in VAP-301 required an average of 2.6 units of blood. The average number of units of blood transfused per patient in VAP-301 was slightly higher than the average number of units required for the vapreotide group in VAP-14 (Figure 8B). Differences in the practice of transfusional medicine may partly account for these differences.

Figure 8 Secondary Endpoints: VAP-301 and VAP-14 (ITT):
A) Control of Bleeding at Endoscopy; and
B) Number of Blood Units Per Patient Over Days 1-5



Eighteen of the 70 ITT patients died in VAP-301 (26% [95% CI: 17%, 38%]) compared to 14% for vapreotide and 21% placebo ITT groups in VAP-14. As shown in Figure 9, the majority of deaths in VAP-301 (11/18; 61%) occurred after the 5-day treatment period with vapreotide. The cause of deaths experienced in VAP-301, including the 18 deaths in the ITT population and the additional 8 deaths in the safety population are discussed in Safety Section 9.8.

Figure 9 Kaplan-Meier Survival Curve (Time to Death): VAP-301



8.2.2.4 Subgroup Analyses for VAP-301 and VAP-14

8.2.2.4.1 Endoscopic Therapy Modality

At the time VAP-14 was conducted both band ligation and sclerotherapy were used routinely. By the time VAP-301 was conducted, band ligation had been proven superior to sclerotherapy (Villanueva 2006). Accordingly, the 2 studies differed in the percentage of patients in which band ligation was performed. To further establish the relevance of VAP-14 to a USA clinical setting, subgroup analyses by endoscopic treatment were performed in VAP-301 and VAP-14.

Similar percentages of vapreotide patients in each study who had band ligation met the primary endpoint (78% in VAP-301 and 77% in VAP-14) (Table 20). Too few patients in VAP-301 received sclerotherapy without banding (n=3) to make a meaningful comparison with sclerotherapy outcomes in VAP-14. A higher percentage of patients in VAP-301 might be expected to achieve the primary efficacy endpoint as was observed for the overall results (77% vs 66% for VAP-301 and VAP-14 vapreotide group, respectively) because of the predominate use of band ligation. However, univariate logistic regression analyses of the vapreotide groups showed no significant association between the endoscopic treatment modality and achievement of the primary endpoint.

Table 20 Subgroup Analysis of Proportion of Patients Meeting Primary Endpoint by Endoscopic Therapy Modality: VAP-301 and VAP-14 (ITT)

	VAP-301 Vapreotide N=70 n/N (%)	VAP-14 Vapreotide N=98 n/N (%)	VAP-14 Placebo N=98 n/N (%)
Band ligation	47/60 (78%)	23/30 (77%)	18/30 (60%)
Sclerotherapy	3/3 (100%)	31/49 (63%)	26/55 (47%)

8.2.2.4.2 Patients with Alcoholism and Viral Hepatitis

In the VAP-301 ITT population, 29% (20/70) of patients compared with only 8% (16/196) of ITT patients in VAP-14 presented with alcoholism and viral hepatitis. Table 21 shows the percentage of patients in these subgroups who achieved control of bleeding over 5 days. Acknowledging that the numbers of patients with alcoholism and viral hepatitis were small in the VAP-14 treatment groups, the data support the benefit of vapreotide over placebo in both subpopulations.

Table 21 Comparison of Primary Endpoint for Subgroups With and Without Alcoholism Plus Viral Hepatitis: VAP-301 and VAP-14 (ITT)

Primary Endpoint	VAP-301		VAP-14 Vapreotide		VAP-14 Placebo	
	Alcoholism + viral hepatitis (N=20)	Without combined etiology (N=50)	Alcoholism + viral hepatitis (N=9)	Without combined etiology (N=89)	Alcoholism + viral hepatitis (N=7)	Without combined etiology (N=91)
Control of Bleeding Over 5 Days	17 (85%)	37 (74%)	7 (78%)	58 (65%)	2 (29%)	47 (52%)

8.2.2.5 Comparison of VAP-301 Results to Octreotide Published Literature

As a placebo-controlled trial could not be conducted, it was agreed with FDA that the VAP-301 study results would be evaluated for clinical significance in light of the efficacy results achieved in the pivotal VAP-14 study, and results reported in the available published literature on octreotide. While the results achieved in VAP-14 provide a straightforward comparator (identical study design [without the placebo arm], same eligibility criteria, endpoints and outcome criteria), the results reported in the literature for octreotide are more complex to synthesize and interpret.

Three meta-analyses (Bañares 2002; de Franchis 2004; and Gotzsche 2008 Cochrane Review), and the trials studied therein, were reviewed. The 2008 Cochrane Review, while the most recent, did not report on control of bleeding at 5 days using Baveno criteria, and therefore, is excluded from this summary.

As discussed in Section 2.2.3.1, clinical studies of the treatment of acute esophageal varices are complicated to perform and are difficult to compare across studies unless the same design is used. Potential sources of heterogeneity between trials are:

- 1) The patient population included in the trial;
- 2) The point at which randomization occurs;
- 3) The treatment schedule; and
- 4) The criteria used to define success and failure.

Given the substantial heterogeneity in design and conduct of the published trials, and the lack of a control arm in VAP-301, a formal meta-analysis including this trial would not be feasible or reasonable. However, a qualitative comparison between the results of the current trial and the published literature may provide some useful information.

Bañares and colleagues (2002) report the proportion with 5-day control of bleeding as 0.77 (95% CI: 0.73, 0.81) in the active treatment arms and 0.58 (95% CI: 0.53, 0.63) in the placebo arm. This review includes trials of octreotide and vapreotide in combination with endoscopic therapy versus endoscopic therapy alone. Similarly, de Franchis (2004) reports the success proportion in the active-arm as 0.74 and in the placebo arm as 0.53 (confidence intervals not presented). This review includes trials of terlipressin, octreotide, or vapreotide and endoscopic therapy versus endoscopic therapy alone.

The proportion with 5-day control of bleeding in the current study is 0.77, which is very close to the rates estimated for active treatment in the 2 meta-analyses. In addition, this proportion is significantly higher than the estimated placebo-arm rates in the 2 meta-analyses (2-sided exact binomial $p < 0.001$ for both tests).

Conclusion

Synthesis of meta-analytic results on vasoactive treatment for control of bleeding should be interpreted with caution. There are many sources of heterogeneity in the published literature, including, but not restricted to, those cited above.

Interpretation of historical-controlled trials as part of meta-analyses should also be done with caution due to the absence of a comparator arm. For reasons noted above, a placebo arm was infeasible in VAP-301 trial; however, qualitative interpretation of the results of this trial in the context of the meta-analysis is feasible provided it is done with sufficient care.

However, given these limitations, the published literature on vasoactive treatment along with endoscopy compared to endoscopy alone is suggestive that the combined treatment does improve control of bleeding over endoscopic treatment alone, with the proportion with control of bleeding in the active arm in the range of 0.74 to 0.78 with relatively narrow confidence intervals.

The proportion with control of bleeding in the current historical-controlled trial was in line with the results from the literature, suggesting that vapreotide in the current study is comparable to the other vasoactive treatments studied. Further, this proportion is significantly different from the placebo proportion reported in the published meta-analyses. This evidence is not sufficient to determine non-inferiority, but provides the best available evidence given the constraints on randomized trials in this indication.

8.2.2.6 Conclusions for VAP-301

The single-arm, open-label study, VAP-301 helps to demonstrate the relevance of the VAP-14 results for the current EVB patient population in the USA. The primary endpoint (control of bleeding over 5 days) was achieved in 77 % of patients. The results for the primary efficacy endpoint were supported by the percentage of patients who achieved each of the protocol-

specified secondary efficacy criteria. Facilitation of the endoscopy was achieved in 74% of patients and over the 5 days of treatment, the patients required a mean of 2.6 units of blood.

The success rate achieved in VAP-301 for control of bleeding over 5 days (ie, 77%) compared favorably with the 66% achieved in the VAP-14 vapreotide group overall, and the success rates in the subgroup who had band ligation, the endoscopic procedure used more frequently in VAP-301. The 77% success rate is also consistent with that reported in 2 meta-analyses of published data on vasoactive treatment with endoscopy compared to endoscopy alone (77% and 74% for the vasoactive + endoscopy group compared to 58% and 53% for the endoscopy alone group [Bañares 2002; de Franchis 2004, respectively]).

In conclusion, the results of VAP-301 support the effectiveness of vapreotide shown in the pivotal VAP-14 study.

8.2.3 Other EVB Studies

As previously presented, studies in the EVB indication are difficult to conduct. Three additional placebo-controlled EVB studies of vapreotide were conducted; all 3 had confounding factors that compromised the interpretation of the efficacy data. Their efficacy results are summarized in this section.

8.2.3.1 Study VAP-07 (Egypt)

VAP-07 was a single-center, double-blind, placebo-controlled pilot study conducted in Egypt. In this trial, 72 patients were enrolled with cirrhosis and portal hypertension due to viral hepatitis and schistosomiasis and were hospitalized for acute variceal bleeding. Patients were randomly assigned to receive vapreotide (50 µg IV bolus injection followed immediately by an IV infusion at a rate of 50 µg/h for 5 days) or placebo within 6 hours after admission, followed by therapeutic endoscopy within 12 hours after admission. After the protocol-specified exclusion of 14 patients who had their infusions stopped after diagnostic endoscopy—9 (4 vapreotide, 5 placebo) who had pure schistosomiasis, 4 (1 vapreotide, 3 placebo) whose bleeding was found at diagnostic endoscopy to be due to causes other than portal hypertension, and 1 placebo patient who had no endoscopy—the ITT population included 58 patients: 31 in the vapreotide group and 27 in the placebo group.

The primary endpoint, survival and control of bleeding over 5 days, was achieved in 71% (22/31) of patients receiving vapreotide compared with 59% (16/27) of patients receiving placebo (Table 22). The sample size for this pilot study was small and not designed to show a significant difference between the two arms. Although the difference between the treatment groups did not reach statistical significance ($p=0.349$), a trend that favored vapreotide was observed.

Table 22 Control of Bleeding over 5 Days: VAP-07 (ITT)

Primary Endpoint	Vapreotide N=31 n (%)	Placebo N=27 n (%)	P-value	Odds Ratio (95% CI)
Control of Bleeding over 5 Days	22 (71%)	16 (59%)	p=0.349	1.68 (0.56, 5.00)

8.2.3.2 Study VAP-06 (Romania and Bulgaria)

VAP-06 was a multicenter, double blind, placebo-controlled, Phase 3 trial conducted at 8 sites in Romania and Bulgaria. The study design was the same as VAP-14, except an hematocrit level of 27% was included in the definition of success (ie, patients whose hematocrit fell below 27% were deemed failure; in the VAP-14 the hematocrit level of 27% was included as a target, not a hard endpoint). Sample size was calculated based on VAP-14, which had a difference of ~17% between vapreotide and placebo treatment groups (67% vs 50%). A total of 262 patients with portal hypertension (131 per treatment group) would be required to demonstrate a difference of at least 17%, with nominal $\alpha = 0.05$ (2-sided) and $\beta = 0.20$.

Patients with cirrhosis who were hospitalized for acute upper gastrointestinal bleeding were randomly assigned to receive vapreotide (50 μ g IV bolus followed by a continuous IV infusion at a rate of 50 μ g/h for 5 days) or placebo within 6 hours after hospital admission. The diagnostic (and therapeutic) endoscopy was performed a mean of 3:16 hours and 2:45 hours after hospital admission for the vapreotide and placebo groups, respectively.

Post-Initiation Study Amendment

The investigational sites in Romania and Bulgaria suffered chronic shortages of blood and experienced significant delays in obtaining requested blood units. These chronic blood supply shortages and concern from the investigators resulted in a major protocol amendment after enrollment of 70 patients.

This protocol amendment changed the required hematocrit value from $27 \pm 1\%$ to $21 \pm 1\%$. This change resulted in a significant modification of patient treatment, reflected in a markedly lower number of blood transfusions administered after the amendment. With a target hematocrit of 21%, only about 18% of patients in the post-amendment population were eligible for transfusions according to their baseline values, despite admission for acute hemorrhage. This is in contrast to the pre-amendment population, where 57% of patients at baseline were below the target hematocrit of 27%, a value similar to that in the pivotal VAP-14 Study (45% of patients at baseline had a hematocrit below 27%). The mean number of blood units transfused before the amendment was 1.8 units in the vapreotide group and 3.0 units in the placebo groups; while after the amendment the mean number of units was 1.4 units in both treatment groups.

The amendment also introduced a subjective assessment by the investigator that could override the objective criteria to determine if bleeding was controlled or not.

Results from the protocol-specified analysis of the full VAP-06 ITT show no difference between the vapreotide and placebo groups (Table 23). The lower hematocrit requirement (the level designated to trigger transfusion) may have resulted in inadequate resuscitation measures in the post-amendment population.

This revision to the primary endpoint, inadequate resuscitation, and the resulting clinically important changes in treatment practice make evaluation of the pre- and post-amendment populations together questionable. When analyzed as distinct populations using the same criteria as in VAP-14 (no hematocrit requirement and no investigator opinion in assessing the primary endpoint), the results in the pre-amendment population show a trend in favor of vapreotide for control of bleeding over 5 days (Table 23). The magnitude of the effect observed between the vapreotide and placebo groups in the pre-amendment population for VAP-06 was similar to that observed in VAP-14. No effect of treatment is observed in the post-amendment population.

Table 23 Control of Bleeding over 5 Days: VAP-06 (ITT)

Database	Vapreotide		Placebo		P-value	Odds Ratio (95% CI)
	N=136	n (%)	N=131	n (%)		
VAP-06 Amended protocol criteria		89 (65.4%)		87 (66.4%)	0.87	0.96 (0.56, 1.64)
VAP-14 criteria ^a		73 (53.7%)		67 (51.2%)	0.68	1.11 (0.67, 1.84)
VAP-06 Pre-Amendment ^a	N=32	20 (62.5%)	N=33	17 (51.5%)	0.37	1.57 (0.58, 4.22)
VAP-06 Post-Amendment ^a	N=104	53 (51.5%)	N=98	50 (51.0%)	0.99	1.00 (0.57, 1.73)

%=proportion of patients who achieved control of bleeding over 5 days (primary endpoint).

^a Success rate was assessed using the criteria from VAP-14, which did not have a protocol-specified target hematocrit level.

8.2.3.3 Study VAP-02 (Hong-Kong)

VAP-02 was a multicenter, randomized, double-blind, placebo-controlled, Phase 3 study in cirrhotic patients suffering from acute variceal bleeding conducted in 5 centers in Asia (Hong-Kong, Singapore, and Malaysia). Sample size was calculated based on expected control of bleeding in 60% of placebo patients and 85% of vapreotide patients. To demonstrate a 25% difference versus placebo with nominal $\alpha = 0.05$ (2-sided) and $\beta = 0.20$, at least 49 patients per treatment group would be required. Due to the anticipated 30% rate of ineligible patients due to bleeding of non-esophageal varices origin, the number of patients was increased to ~72 per treatment group to ensure 50 patients with bleeding esophageal varices.

A total of 136 patients were randomized to receive either vapreotide (50 μg IV bolus injection followed by an IV infusion of 50 $\mu\text{g}/\text{h}$ for 5 days), or placebo. After randomization and the beginning of infusion, the patients underwent endoscopic treatment. Of the 136 patients randomized, 2 did not receive treatment; the safety population was 134 (69 vapreotide; 65 placebo). The ITT population, defined in the protocol as those patients found at endoscopy to have bleeding related to portal hypertension, was 102 patients (51 vapreotide; 51 placebo).

The study was terminated early without any interim analysis due to a slow rate of enrollment (136 patients over 4 years; only 16 in 2001) that led to protocol noncompliance and jeopardized the validity of the study and safety of the patients (ie, at least 2 patients were administered 12 vials of study drug within 6 hours instead of the intended 5 days).

Control of bleeding with survival over 5 days, the primary endpoint, was achieved in 54.9% (28/51) vs 51.0% (26/51) of the vapreotide and placebo patients ($p=0.692$). The efficacy results of the study are difficult to interpret in view of the large number of protocol violations. All randomized patients were included in the safety assessments.

8.2.4 Combined Analyses of the Primary Efficacy Endpoint

A meta-analysis of the results was conducted on the primary efficacy endpoint (control of bleeding over 5 days) in the trials of vapreotide used in conjunction with endoscopy for treatment of variceal bleeding.

Methods

All prospectively randomized, controlled clinical studies of vapreotide were considered for inclusion in the meta-analysis, and the historical-controlled VAP-301 trial for inclusion in pooled analyses. Outcomes were standardized (to the extent possible) to agree with the Baveno II consensus criteria (de Franchis 1996), which were used as the primary outcome in the pivotal VAP-14 trial. Summary statistics (odds ratios) were computed for each trial. A meta-analysis of all trials judged suitable for combination was conducted.

Pooled estimates of treatment success proportions were computed using unweighted results of the studies, and exact binomial confidence limits were computed for the pooled estimate of proportions. A random-effects meta-analysis was performed of the odds ratio using the DerSimonian and Laird technique. A pooled logistic regression analysis with study as a covariate was performed, including the VAP-301 historical-controlled study. All statistical analyses were conducted using Stata/SE software version 10.0 and SAS version 9.1.

Results

There were 4 placebo-controlled studies and one historical-controlled study of vapreotide that evaluated control of bleeding in cirrhotic patients with acute variceal bleeding due to portal hypertension. Table 24 provides summary efficacy statistics for these studies.

Because Study VAP-301 was a historical-controlled open-label study, it was not included in the formal meta-analysis but is presented in Table 24 and included in the pooled logistic regression for completeness.

Table 24 Primary Efficacy Results for Studies Included in Meta-Analysis

Study	Success	Vapreotide		Placebo		Odds Ratio (95% CI)
		N	%	N	%	
VAP-14	Yes	65	66.3	49	50.0	1.97 (1.11, 3.51)
	No	33	33.7	49	50.0	
	Total	98		98		
VAP-07	Yes	22	71.0	16	59.3	1.68 (0.56, 5.00)
	No	9	29.0	11	40.7	
	Total	31		27		
VAP-06 ^a	Yes	89	65.4	87	66.4	0.96 (0.56, 1.64)
	No	47	34.6	44	33.6	
	Total	136		131		
VAP-02	Yes	28	54.9	26	51.0	1.17 (0.50, 2.74)
	No	23	45.1	25	49.0	
	Total	51		51		
VAP-301	Yes	54	77.1	NA	NA	NA
	No	16	22.9	NA	NA	
	Total	70		NA		

^a Total ITT population (both pre- and post-amendment data) analyzed by protocol criteria and did not use investigator opinion in determination of primary endpoint.

The summary odds ratio from the 4 placebo-controlled studies, including the full population by protocol criteria for VAP-06 was 1.33 (95% CI: 0.92, 1.93; p=0.134, heterogeneity test p=0.299). The forest plot from this analysis is presented in Figure 10.

As discussed previously, VAP-02 was a study terminated early due to major protocol noncompliance and VAP-06 had a post-initiation protocol amendment that revised the definition of the primary criterion. Therefore, a meta-analysis was performed excluding VAP-02 and treating VAP-06 as 2 separate trials (pre- and post-amendment). For comparison across studies, the results were calculated using the same outcome criteria as VAP-14, which were also those used in VAP-07 and VAP-301. Table 25 provides summary efficacy statistics showing results for the sensitivity meta-analysis. The summary odds ratio from the 3 placebo-controlled studies, including both the pre- and post-amendment data from VAP-06 analyzed as separate data, was 1.43 (95% CI: 1.01, 2.03; p=0.044, heterogeneity test p=0.401). The Forest plot from this analysis is presented in Figure 11.

Figure 10 Forest Plot of Meta-Analysis Results (VAP-14, VAP-07, VAP-02, and VAP-06)

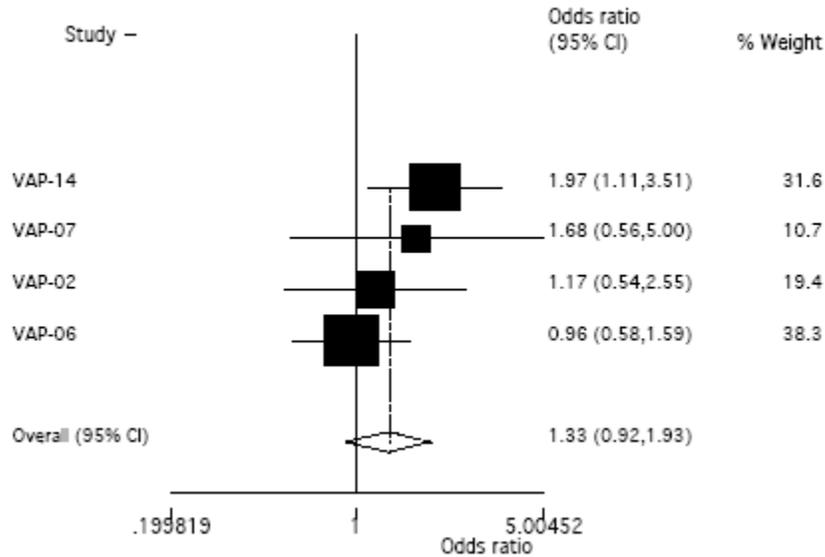


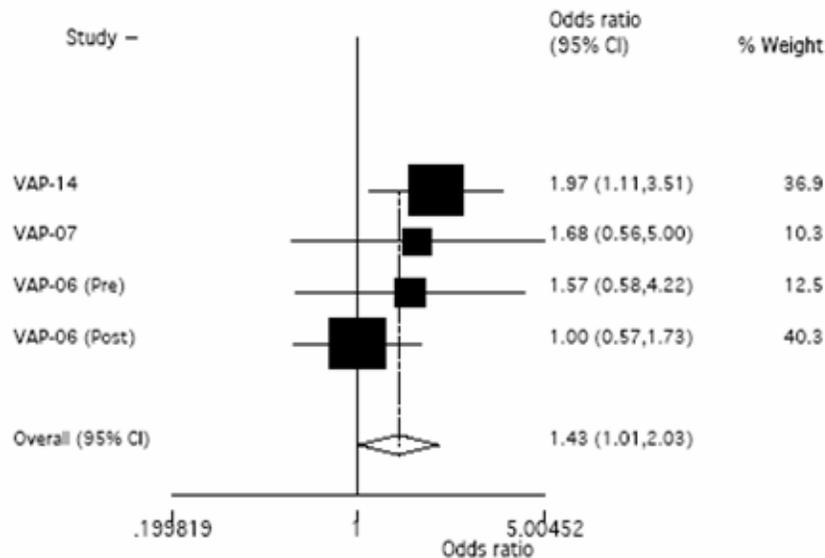
Table 25 Primary Efficacy Results for Studies Included in Sensitivity Meta-Analysis

Study	Success	Vapreotide		Placebo		Odds Ratio (95% CI)
		N	%	N	%	
VAP-14	Yes	65	66.3	49	50.0	1.97 (1.11, 3.51)
	No	33	33.7	49	50.0	
	Total	98		98		
VAP-07	Yes	22	71.0	16	59.3	1.68 (0.56, 5.00)
	No	9	29.0	11	40.7	
	Total	33		27		
VAP-06 Pre-amendment ^a	Yes	20	62.5	17	51.5	1.57 (0.58, 4.22)
	No	12	37.5	16	48.5	
	Total	32		33		
VAP-06 Post-amendment ^a	Yes	53	51.0	50	51.0	1.00 (0.57, 1.73)
	No	51	49.0	48	49.0	
	Total	104		98		
VAP-301	Yes	54	77.1	N/A	N/A	N/A
	No	16	22.9	N/A	N/A	
	Total	70		N/A		

N/A = not applicable; study did not have a placebo group.

^aData were recomputed using VAP-14 criteria for the primary endpoint.

Figure 11 Forest Plot of Meta-Analysis (VAP-14, VAP-07, VAP-06 pre-amendment and VAP-06 post-amendment)



The proportion with control of bleeding in the combined studies VAP-14, VAP-06, VAP-07 and VAP-301 was 64% (95% CI: 59%, 69%) for vapreotide versus 52% (95% CI: 45%, 58%) for placebo. A pooled logistic regression analysis including all data from the 4 trials (including VAP-301), with study as covariate, showed an odds ratio of 1.44 (95% CI: 1.01, 2.03).

The proportion with control of bleeding in the historical-controlled VAP-301 study (77%, 95% CI: 66%, 86%) is at the higher end of the range of control rates reported in the other studies, and is broadly consistent with the previous evidence.

Conclusion

The meta-analysis that excluded VAP-02 and treated VAP-06 as 2 separate studies and the pooled analysis both show a statistically significant effect of vapreotide on the primary outcome. The 4 studies give results that are consistent, and the combined odds ratio suggests a substantial effect. These data provide statistically significant evidence of a positive effect of vapreotide in association with endoscopic treatment for control of bleeding due to portal hypertension.

8.3 Efficacy Conclusions

The efficacy of vapreotide has been demonstrated in a robust, multicenter, well-controlled clinical study, VAP-14, that was designed with a primary efficacy endpoint (ie, control of bleeding with survival over 5 days) that is in accordance with the criteria defined in consensus guidelines for well-designed treatment of variceal bleeding. In that study, vapreotide significantly increased the percentage of patients who achieved control of bleeding over 5 days, increased the percentage of patients with control of bleeding at endoscopy, and decreased the

average number of blood units transfused in the first 5 days following the index hemorrhage. These benefits were maintained after the data were adjusted for any differences in baseline characteristics.

The results of 2 other placebo-controlled studies (VAP-06 and VAP-07), show evidence of trends that are consistent with the efficacy of vapreotide shown in the pivotal VAP-14 study. Additionally, the results of the open-label USA study (VAP-301) are also consistent with the results of VAP-14. In comparison with VAP-14, patients in VAP-301 had more complex disease, with a higher proportion of disease attributed to combined alcoholism and viral hepatitis and viral hepatitis alone, and more patients presenting with signs of end-stage decompensated cirrhosis (ie, hepatic encephalopathy and ascites). Additionally, more patients in VAP-301 received band ligation than in the VAP-14 study, in which sclerotherapy was the predominant type of endoscopic treatment modality used. Despite these differences in patient population and endoscopic modalities, the percentage of patients achieving control of bleeding in VAP-301 was consistent with those of VAP-14, in the overall study population, and as well in the subgroups with similar disease etiology and type of endoscopic procedures performed.

In summary, the 66% success rate for the primary efficacy endpoint of control of bleeding over 5 days in the pivotal VAP-14 study (66% [95% CI: 42%, 84%]) is supported by the open-label VAP-301 study (77% [95% CI: 66%, 86%]) and the sensitivity meta-analysis of the 3 EVB vapreotide trials (60% [95% CI: 54%, 66%]). Together, these data demonstrate the efficacy of vapreotide with therapeutic endoscopy for treatment of acute variceal hemorrhage related to portal hypertension.

9 Clinical Safety

9.1 Safety Overview

The safety profile for vapreotide in EVB patients is derived primarily from pooled safety data from the 4 randomized placebo-controlled (RCTs) EVB studies (N=366 vapreotide, N=347 placebo) and supportive data from the single-arm EVB study (N=103 vapreotide). Results for the single-arm EVB study (VAP-301) were compared with those for the 4 EVB RCTs (VAP-14, VAP-02, VAP-06, VAP-07). In all the EVB studies, patients were scheduled to receive a bolus injection of 50 µg vapreotide (or placebo) followed by a continuous IV infusion of 50 µg/h (1.2 mg/d) for 5 days. Per protocol, study treatment was to be discontinued immediately for patients found at endoscopy to have bleeding unrelated to portal hypertension; these patients were excluded from ITT analyses, but were followed for safety during the 42-day study period and their data included in the safety database.

Comparison of safety data for the vapreotide (N=366) and placebo (N=347) groups in the pooled EVB RCTs showed that vapreotide is well tolerated in the targeted population:

- Treatment-emergent adverse events (AEs) occurred at comparable rates in the vapreotide and placebo groups overall (75% vs 76%), both during study drug infusion over Days 1-5 (65% vs 66%) and during follow-up over Days 6-42 (26% vs 31%) and by system

organ class (SOC). The most frequent AEs in both the vapreotide and placebo groups, occurring in $\geq 5\%$ of patients, were pyrexia, upper gastrointestinal hemorrhage, flatulence, melena, hepatic encephalopathy, and headache.

- Serious adverse events (SAEs) occurred at similar rates in the vapreotide and placebo groups overall (34% vs 39%) during study drug infusion (21% vs 23%) and during follow-up (15% vs 18%). As expected in this study population, the most frequent SAEs in both treatment groups, occurring in $\geq 2\%$ of patients, were disease-related complications: upper gastrointestinal hemorrhage, melena, hepatic encephalopathy, and hemorrhagic shock.
- Deaths during the 42-day study period in the 4 controlled EVB studies occurred at similar rates in the vapreotide and placebo groups (15.0% vs 16.4%);
- The incidence of cytopenias (pancytopenias, thrombocytopenia), although infrequent ($<1\%$), was higher in the vapreotide group than the placebo group. However, based on review of individual cases and considering that cytopenias are an expected disease-related complication in cirrhotic patients, there is no clear safety signal for vapreotide.

VAP-301, conducted in the USA, identified no unexpected AE or safety signal for vapreotide. Although the incidence of some AEs differed between the single-arm VAP-301 study and the pooled EVB RCTs, the observed differences were in events related to expected complications of cirrhosis. The rate of SAEs in VAP-301 was comparable or lower than reported in the pooled EVB RCTs, with the types of SAEs similar. The 6-week mortality rate in the single-arm VAP-301 study was numerically higher (25.2% [26/103]), but it was a smaller sample size and its 95% confidence interval (17.2% – 34.7%) overlapped with those of the larger pooled EVB RCT database (95% CI: 11.5%, 19.1% for vapreotide; and 12.7%, 20.8% for placebo).

A secondary safety database (9-Study Database) contained pooled safety data from the 4 EVB RCTs (N=366 vapreotide patients), VAP-301 (N=103), and 4 non-EVB studies (N=259 vapreotide patients). The 4 non-EVB studies were in other indications (pancreatic surgery, acromegaly, Crohn's disease, and neuroendocrine tumors), had higher dosages (up to 1.5 mg/d), and longer exposures (up to 180 days). Comparisons of AEs between the primary and secondary safety databases reflected differences driven by results from the pancreatic surgery RCT, which had higher rates of anemia, respiratory failure, and events related to the underlying pancreatic disease (caused by the tumours) and surgical procedure.

The safety profile of vapreotide is similar to that reported for somatostatin and somatostatin analogs.

9.2 Safety Studies

The safety profile for vapreotide in EVB patients is derived primarily from pooled safety data from the indicated EVB patient population: pooled data from 4 randomized placebo-controlled EVB RCTs (VAP-14, VAP-02, VAP-06, and VAP-07; N=366 vapreotide, N=347 placebo) and additional safety data from the single-arm EVB study (VAP-301; N=103 vapreotide). This

database will be referred to as the “EVB Database.” Results for the single-arm VAP-301 study are presented separately from the 4 EVB RCTs, since the lack of a control arm in that study makes interpretation of its results more difficult.

In addition to the EVB database, which is the primary safety database there are 3 additional safety databases:

- “Non-EVB Database”: pooled data from 4 additional vapreotide studies for various indications (pancreatic surgery, acromegaly, Crohn’s disease, and neuroendocrine tumors) that enrolled 259 patients who received vapreotide. With daily exposures of 1.2 or 1.5 mg and treatment durations ranging from 5 to 180 days, this database provides information on patients with greater exposure to vapreotide from studies that collected safety data in accordance with GCPs (see next bullet).
- “9-Study Database”: pooled data from the EVB Database and the Non-EVB Database (N=728 vapreotide; N=536 placebo). The protocols for all studies included in the EVB and Non-EVB databases were approved by the respective IRB/Independent Ethics Committee at each investigational site and were conducted in accordance with the Declaration of Helsinki. Adverse event data were obtained from objective measurements, clinical assessment of patients by study staff, and from information volunteered by patients and obtained by study staff from direct query. Although there was some variation in wording across study protocols, SAEs in each of the studies in this database included those events meeting one of the criteria defined in ICH Guideline E2A: *Clinical Safety Data Management: Definitions and Standards for Expedited Reporting*.
- “All Studies Database”: pooled data on 1,222 patients who received at least one dose of vapreotide from the EVB Database, the Non-EVB Database, and 36 investigator-initiated studies in various indications. The 36 investigator-initiated studies had 494 patients exposed to vapreotide, with daily exposures to vapreotide ranging from 0.01 to 6 mg and treatment durations ranging from 1 to 1620 days. The additional 36 studies did not systematically collect AEs but deaths, SAEs, and AEs leading to treatment discontinuations were reported.

The indications for all 45 vapreotide studies (5 EVB, 4 Non-EVB; and 36 Investigator-initiated studies) are provided in Appendix 1. A tabular summary describing the primary and secondary databases used for safety assessment is provided in Table 26.

Table 26 Summary of Databases Analyzed for Safety

Safety Database	Description	Vapreotide Patients N	Placebo Patients N
Primary Safety Database			
EVB Database	4 EVB RCTs	366	347
	VAP 301 (single arm)	103	0
	5 EVB studies (4 EVB RCT + VAP-301)	469	347
Secondary Safety Databases			
Non-EVB Database	4 Studies in non-EVB indications ^a	258	189
9-Study Database (<i>EVB + Non-EVB Databases</i>)	9 Studies with systematic safety reporting	728	536
All Studies Database^b	Includes EVB and Non-EVB Databases plus 36 investigator- sponsored studies (with 494 patients) in various indications	1222	613 placebo 17 active comparator

^a Indications include pancreatic surgery, acromegaly, Crohn’s disease, and neuroendocrine tumors; these studies, as did the EVB studies, collected AEs in accordance with GCP.

^b Other indications include various types of cancer, painful syndrome, AIDS-associated diarrhea, migraine and cluster headaches, Crohn’s disease, acromegaly, GI fistula, post-operative pain, Sheehan syndrome, vipoma, stable cirrhosis, and ulcerative colitis (see Appendix 1).

Adverse events in the 4 EVB RCTs and the 4 Non-EVB studies were originally coded using MedDRA Version 6 and AEs in the single-arm VAP-301 were originally coded using MedDRA Version 9. In order to harmonize the terms in the safety database, AEs for all studies were transcoded to MedDRA Version 10.

For tabular summaries of AE incidence, AEs were summarized based on MedDRA System Organ Class (SOC) and Preferred Term. For a given category, a patient could contribute no more than a single count to that category’s incidence, even if the patient had multiple events within the category. Treatment group differences were assessed with the 2-tailed Fisher’s exact test; p-values were not constructed as formal tests of hypothesis associated with Type I and Type II error values, but were used to numerically assess differences between vapreotide and placebo groups and identify adverse events of possible interest.

9.3 Exposure

Duration of exposure in the studies included in the 9-Study Database is summarized in Table 27. The majority of patients in this database who received vapreotide were scheduled to receive the proposed daily dose of 1.2 mg vapreotide (50 µg vapreotide followed by a continuous IV infusion of 50 µg/h) for at least 5 days. The mean drug exposure is lower than would be expected because it includes patients with bleeding unrelated to portal hypertension for whom study drug was stopped with the diagnostic endoscopy as per protocol.

In the EVB studies, 17% of patients assigned to vapreotide and 12% of patients assigned to placebo discontinued study drug per protocol because they were found at endoscopy to have bleeding unrelated to portal hypertension or bleeding due to a pure schistosomiasis etiology or undetermined cause of bleeding. These patients were included in the safety databases.

Table 27 Extent of Exposure to Vapreotide in Safety Populations by Study

Study	Treatment Duration (days)			Number of Patients at Daily Dose		Mean Exposure: Daily Dose x Actual Mean Duration
	Planned	Percent VAP group completed 5- or 7-day course	Actual mean \pm SD	1.2 mg	1.5 mg	
EVB Studies						
VAP-14	5	70%	3.8 \pm 1.9	111	0	4.6 mg
VAP-02	5	54%	2.5 \pm 1.7	70 ^a	0	3.0 mg
VAP-07	5	69%	4.2 \pm 1.8	41	0	5.0 mg
VAP-06	5	82%	4.6 \pm 1.4	144 ^b	0	5.5 mg
VAP-301	5	59%	3.3 \pm 2.3	103	0	4.0 mg
Total		70%	3.8 \pm 1.9	469	0	4.6 mg
Non-EVB Studies (indication)						
DEB-92-VAP-02 (neuroendocrine tumors/carcinoids)	90-180	N/A	180 \pm 234	0	35	270.9 mg
DEB-93-VAP-09 (Crohn's disease)	28	N/A	25.3 \pm 4.9	0	22	38.0 mg
DEB-95-VAP-02 (acromegaly)	21	N/A	21.0 \pm 0.0	15	0	25.2 mg
DEB-98-VAP-06 (pancreatic surgery)	7	73%	4.4 \pm 2.9	186 ^a	0	5.3 mg
Total				201	57	

^a Two patients did not have duration records, one patient in VAP-02 and one patient in DEB-98-VAP-06, and therefore, were not included in the exposure analysis.

^b Both pre- and post-amendment vapreotide patients

9.4 Demographic and Baseline Characteristics of Study Population

Demographic characteristics of the EVB and Non-EVB databases are summarized in Table 28. In the EVB studies the majority of patients were male, whereas in other studies the populations were more evenly divided between sexes.

Baseline risk factors for complications in EVB (Laine 2005) also are summarized in Table 28. The vapreotide and placebo groups from the EVB RCTs were well balanced for disease etiology and prognostic risk factors of disease severity (assessed by Child-Pugh score), prior variceal bleeding, and presence of hepatic encephalopathy and ascites.

The vapreotide group from the EVB RCTs and VAP-301 had similar percentage of patients with decompensated cirrhosis as indicated by Child-Pugh Class C, presence of hepatic encephalopathy, and ascites. However, disease etiology was more complex in VAP-301 than in the earlier EVB RCTs. In particular, a higher percentage of patients in VAP-301 had disease due to combined alcoholism and viral hepatitis.

Table 28 Demographic Characteristics of Safety Population

Demographic Characteristic	4 EVB RCTs		Single-arm VAP-301 Vapreotide N=103	4 Non-EVB Studies	
	Vapreotide N=366	Placebo N=347		Vapreotide N=259	Placebo N=189
Age					
N	352	337	103	259	189
Mean ± SD, years	54.6 ± 11.0	55.1 ± 10.5	52.6 ± 8.5	59.1 ± 16.1	61.5 ± 12.7
[Range], years	[18 – 78]	[18 – 81]	[27 – 71]	[17 – 89]	[19 - 86]
18 – 64, n (%)	280 (80%)	274 (81%)	93 (90%)	152 (59%)	108 (57%)
≥65, n (%)	72 (20%)	63 (19%)	10 (10%)	106 (41%)	81 (43%)
Sex					
Male, n (%)	281 (77%)	256 (74%)	77 (75%)	139 (54%)	100 (53%)
Female, n (%)	85 (23%)	91 (26%)	26 (25%)	120 (46%)	89 (47%)
Disease etiology, n (%)	N=356	N=339	N=103		
Alcoholism alone	195 (55%)	193 (57%)	39 (38%)	N/A	N/A
Viral hepatitis alone	69 (19%)	76 (22%)	14 (14%)	N/A	N/A
Alcoholism + viral hepatitis	36 (10%)	28 (8%)	28 (27%)	N/A	N/A
Other/unknown	56 (16%)	42 (12%)	22 (21%)	N/A	N/A
Risk factors for complications, n/N (%)					
Child-Pugh class B-C	286/344 (83%)	273/323 (85%)	81/99 (82%)	N/A	N/A
Child-Pugh Class C	123/344 (36%)	130/323 (40%)	37/99 (37%)	N/A	N/A
Hepatic encephalopathy	50/366 (14%)	67/345 (19%)	18/103 (17%)	N/A	N/A
Ascites	186/365 (51%)	172/344 (50%)	57/103 (55%)	N/A	N/A
Prior variceal bleeding	83/291 (29%)	72/288 (25%)	37/103 (36%)	N/A	N/A

N/A = not applicable to non-EVB studies.

9.5 Summary of Treatment-Emergent Adverse Events

The incidences of AEs, SAEs, or discontinuations in vapreotide-exposed were comparable to those in the placebo patients in the 4 EVB RCTs and the Non-EVB Database (Table 29). The single-arm VAP-301 had similar rates of AEs, SAEs, and discontinuations due to AEs as the EVB RCTs, but had a higher rate of deaths, which are discussed in more detail in Section 9.8.

Table 29 Summary of AEs, SAEs, Discontinuations Due to AEs, and Deaths

Safety Outcome	4 EVB RCTs		VAP-301	4 Non-EVB Studies	
	Vapreotide (n=366)	Placebo (n=347)	Vapreotide (n=103)	Vapreotide (n=259)	Placebo (n=189)
Patients with AE	275 (75%)	262 (76%)	72 (70%)	560 (77%)	445 (83%)
Patients with SAE	124 (34%)	134 (39%)	36 (35%)	245 (34%)	216 (40%)
Discontinuation due to AE ^a	25 (7%)	39 (11%)	9 (9%)	64 (9%)	44 (8%)
Death (Days 1-42)	55 (15%)	57 (16%)	26 (25%) ^b	86 (12%)	67 (13%)

^a Includes discontinuations due to AE, including those resulting in death by Day 5, and discontinuations due to death as a result of worsening of underlying disease and leading to death.

^b Mortality rates reported in the Efficacy section are for the ITT population (N=70). The rates shown here are for the Safety Populations (N=103).

9.6 Common Adverse Events in Variceal Bleeding Studies

9.6.1 Treatment-Emergent Adverse Events

Treatment-emergent adverse events (AEs) reported in the EVB Database are summarized by MedDRA System Organ Class (SOC; body system) and time period (during study drug infusion, ie, Days 1-5, and during follow-up, ie, Days 6-42) in Table 30.

For the EVB RCTs, AE rates overall were comparable for the vapreotide and placebo groups both during study drug infusion (Days 1-5) and during follow-up (Days 6-42). Overall, 65% of patients receiving vapreotide and 66% of patients receiving placebo experienced AEs during the study drug infusion. A lower rate of AEs was reported in both groups during the follow-up period, 26% in the vapreotide group and 31% in the placebo group.

Comparison of AE rates by body system for the EVB RCTs showed no significant differences in the type of AEs reported between vapreotide and placebo groups, with the exception of a higher rate of Investigation events (ie, laboratory results reported as AEs) for the placebo group during study drug administration, and trends toward higher rates of hepatobiliary disorders and infections for the placebo group during the follow-up period. There were no body system for which AEs rates were significantly higher (or showed trends) for vapreotide compared to placebo groups.

Comparison of AE rates by body system for the vapreotide groups in the pooled EVB RCTs and VAP-301 showed a higher rate in VAP-301 during study drug infusion (Days 1-5) for blood and lymphatic system disorders (7.8% vs 1.9%), cardiac disorders (6.8% vs 3.0%), infections and infestations (12.6% vs 3.6%), and metabolism and nutrition disorders (17.5% vs 3.0%). During the follow-up period (Days 6-42), the AE rate by body system was higher in VAP-301 for hepatobiliary disorders (12.6% vs 4.1%) and respiratory, thoracic and mediastinal disorders (6.8% vs 1.1%). The significance of these findings is unclear due to the lack of a placebo control. The difference in the rate of infections and infestations was driven by a higher rate of bacteremias, bacterial peritonitis, pneumonia, and septic shock in VAP-301 (Table 31). A recent retrospective study of 231 patients with acute variceal bleeding at 4 large academic tertiary care

centers in the USA found that 29% of patients developed infectious complications (bacterial peritonitis or bacteremia or central line infection) and 11% developed aspiration pneumonia during the hospitalization following the acute episode of bleeding (Chalasanani 2003).

The difference in the rate of metabolic and nutrition disorders was driven by an increase in hypokalemia, hypomagnesemia, and metabolic acidosis (Table 31). The higher rate of metabolic and nutrition disorders in VAP-301 compared to the EVB RCTs (22.3% vs 3.6%) was driven by higher rates in hypokalemia (10.7% vs 0%), hypomagnesemia (2.9% vs 0.3%), and metabolic acidosis (3.9% vs 0%). Most of these electrolyte base disorders were mild and recovered. It is possible that the increased rate of these disorders reported in the recent study reflected more frequent monitoring in a current emergency care setting.

The most frequent AEs in the pooled EVB RCTs are summarized in Table 31, along with the rates observed in the single-arm VAP-301 study. In the pooled EVB RCTs, the rates were reasonably comparable between vapreotide and placebo groups, overall (Days 1-42), during the infusion period (Days 1-5), and during the follow-up period (Days 6-42). Most of these common AEs were expected disease-related complications (Laine 2005) and occurred in comparable rates between the vapreotide and placebo groups; these included upper gastrointestinal hemorrhage, melena, hepatic encephalopathy, encephalopathy, hemorrhagic shock, esophageal ulcer, and hepatorenal syndrome. Although gastrointestinal disorders and hyperglycemia have been reported for somatostatin and its analogs based on its mechanism of action, there was no difference in the rates of AEs for these events between vapreotide and placebo groups in the pooled EVB RCTs.

Event rates were almost always higher during the infusion period than during follow-up. Only the rate of hepatorenal syndrome was higher in the follow-up period (1.1% vs 1.4% for the vapreotide and placebo groups in the EVB RCTs) than during study drug infusion (0.5% vs 0.3%).

For most AEs, the rates in the single-arm VAP-301 study were comparable to those reported for the vapreotide group from the pooled EVB RCTs. However, during study drug infusion (Days 1-5), rates for common AEs were higher in VAP-301 for nausea and lower in VAP-301 for upper gastrointestinal hemorrhage, pyrexia, headache, hepatic encephalopathy, chest pain, abdominal pain, and dyspepsia. Additionally, several additional events were commonly observed ($\geq 2\%$) during the infusion period for VAP-301 that were not common in the pooled EVB RCTs, including hypokalemia (9.6% vs 0%), renal failure (4.9% vs 0%), metabolic acidosis (3.9% vs 0%), hypomagnesemia (2.9% vs 0.3%), pneumonia (2.9% vs 0.5%), pleural effusion (2.9% vs 0.5%), hypotension (2.9% vs 0.3%), pain (2.9% vs 0%), and psychomotor hyperactivity (2.9% vs 0.8%).

Event rates during the follow-up period were higher in VAP-301 than in the vapreotide group from the pooled EVB RCTs for esophageal varices hemorrhage (5.8% vs 0%), renal failure (5.8% vs 0.3%), pneumonia (3.9% vs 0%), septic shock (3.9% vs 0%), respiratory failure (3.9% vs 0.3%), abdominal pain (3.9% vs 0.3%), diarrhea (2.9% vs 0.5%), coagulopathy (2.9% vs 0%), hypotension (2.9% vs 0.3%), and cough (2.9% vs 0%), and lower in the VAP-301 group for

upper gastrointestinal hemorrhage (3.9% vs 6.6%). All of these events are expected disease-related complications in patients with advanced cirrhosis and upper gastrointestinal bleeding (Laine 2005) and the significance of these findings is unclear due to the lack of a placebo control.

The higher rate of renal failure in VAP-301 than the earlier EVB RCTs (5.8% vs 0.3%) is also consistent with recent reports. In a large case series of cirrhotic patients with gastrointestinal hemorrhage (82% variceal), 11% of patients developed renal failure; hypovolemia and poor liver function were the only factors independently predictive of the development of renal failure (Cardenas 2001).

Table 30 Summary of Treatment-Emergent Adverse Events in EVB Studies by System Organ Class and Time Period

MedDRA System Organ Class	Days 1-5 (study drug infusion), n(%)				Days 6-42 (post-treatment follow-up), n(%)			
	4 EVB RCTs			VAP-301	4 EVB RCTs			VAP-301
	Vapreotide N=366	Placebo N=347	P-value	Vapreotide N=103	Vapreotide N=366	Placebo N=347	P-value	Vapreotide N=301
Total Patients with AEs	239 (65%)	230 (66%)		57 (55%)	97 (26%)	107 (31%)		35 (34%)
Blood & lymphatic system disorders	7 (1.9%)	3 (0.9%)	0.3420	8 (7.8%)	2 (0.5%)	2 (0.6%)	1.000	5 (4.9%)
Cardiac disorders	11 (3.0%)	12 (3.5%)	0.7324	7 (6.8%)	6 (1.6%)	6 (1.7%)	0.9258	3 (2.9%)
Ear & labyrinth disorders	1 (0.3%)	1 (0.3%)	1.000		---	---		---
Endocrine disorders	2 (0.5%)	1 (0.3%)			---	---		1 (1.0%)
Eye disorders	---	---			---	1 (0.3%)		---
Gastrointestinal disorders	129 (35.2%)	127 (36.6%)	0.7065	14 (13.6%)	55 (15.0%)	58 (16.7%)	0.5375	12 (11.7%)
General disorders & administration site conditions	100 (27.3%)	91 (26.2%)	0.8076	12 (11.7%)	12 (3.3%)	18 (5.2%)	0.2045	7 (6.8%)
Hepatobiliary disorders	33 (9.0%)	38 (11.0%)	0.3885	8 (7.8%)	15 (4.1%)	24 (6.9%)	0.0981	13 (12.6%)
Infections & infestations	13 (3.6%)	9 (2.6%)	0.4596	13 (12.6%)	8 (2.2%)	15 (4.3%)	0.1065	10 (9.7%)
Injury poisoning & procedural complications	2 (0.5%)	2 (0.6%)	1.000	2 (1.9%)	6 (1.6%)	11 (3.2%)	0.1805	1 (1.0%)
Investigations	1 (0.3%)	7 (2.0%)	0.0337	3 (2.9%)	---	2 (0.6%)		1 (1.0%)
Metabolism & nutrition disorders	11 (3.0%)	10 (2.9%)	0.9223	18 (17.5%)	2 (0.5%)	6 (1.7%)	0.1669	6 (5.8%)
Musculoskeletal & connective tissue disorders	4 (1.1%)	4 (1.2%)	1.000	3 (2.9%)	2 (0.5%)	3 (0.9%)	0.6787	2 (1.9%)
Neoplasms benign, malignant & unspecified	1 (0.3%)	1 (0.3%)		2 (1.9%)	4 (1.1%)	1 (0.3%)		---
Nervous system disorders	47 (12.8%)	55 (15.9%)	0.2515	7 (6.8%)	6 (1.6%)	8 (2.3%)	0.5217	1 (1.0%)
Psychiatric disorders	15 (4.1%)	18 (5.2%)	0.4891	7 (6.8%)	3 (0.8%)	6 (1.7%)	0.2769	1 (1.0%)
Renal & urinary disorders	5 (1.4%)	5 (1.4%)	1.000	5 (4.9%)	2 (0.5%)	2 (0.6%)	1.000	7 (6.8%)
Reproductive system & breast disorders	1 (0.3%)	---		---	---	1 (0.3%)		---
Respiratory, thoracic & mediastinal disorders	22 (6.0%)	24 (6.9%)	0.6228	11 (10.7%)	4 (1.1%)	9 (2.6%)	0.1660	7 (6.8%)
Skin & subcutaneous disorders	4 (1.1%)	2 (0.6%)	0.6868	---	---	2 (0.6%)		2 (1.9%)
Surgical & medical procedures	---	---			3 (0.8%)	1 (0.3%)		---
Vascular disorders	17 (4.6%)	19 (5.5%)	0.6126	6 (5.8%)	7 (1.9%)	11 (3.2%)	0.2847	6 (5.8%)

--- : no events reported

Table 31 AEs Occurring in \geq 2% of Vapreotide Patients in EVB Studies

MedDRA System Organ Class Preferred Term	Days 1-42, n (%)			Days 1-5 (drug infusion), n (%)			Days 6-42 (Follow-up), n (%)		
	4 EVB RCTs		VAP-301	4 EVB RCTs		VAP-301	4 EVB RCTs		VAP-301
	Vapreotide N=366	Placebo N=347	Vapreotide N=103	Vapreotide N=366	Placebo N=347	Vapreotide N=103	Vapreotide N=366	Placebo N=347	Vapreotide N=103
Blood & lymphatic system disorders									
Coagulopathy	---	3 (0.9%)	3 (2.9%)	---	2 (0.6%)	1 (1.0%)	---	1 (0.3%)	3 (2.9%)
Gastrointestinal disorders									
Abdominal pain	15 (4.1%)	15 (4.3%)	6 (5.8%)	15 (4.1%)	12 (3.5%)	2 (1.9%)	1 (0.3%)	4 (1.2%)	4 (3.9%)
Abdominal pain upper	14 (3.8%)	14 (4.0%)	1 (1.0%)	11 (3.0%)	13 (3.7%)	1 (1.0%)	4 (1.1%)	1 (0.3%)	---
Diarrhea	9 (2.5%)	15 (4.3%)	3 (2.9%)	7 (1.9%)	11 (3.2%)	---	2 (0.5%)	5 (1.4%)	3 (2.9%)
Dyspepsia	11 (3.0%)	8 (2.3%)	2 (1.9%)	11 (3.0%)	8 (2.3%)	1 (1.0%)	---	---	1 (1.0%)
Esophageal ulcer	7 (1.9%)	11 (3.2%)	---						
Esophageal varices hemorrhage	3 (0.8%)	3 (0.9%)	7 (6.8%)	3 (0.8%)	3 (0.9%)	1 (1.0%)	---	---	6 (5.8%)
Flatulence	42 (11.5%)	37 (10.7%)	---	41 (11.2%)	37 (10.7%)	---	1 (0.3%)	---	---
Melena	38 (10.4%)	37 (10.7%)	2 (1.9%)	31 (8.5%)	33 (9.5%)	---	7 (1.9%)	5 (1.4%)	2 (1.9%)
Nausea	8 (2.2%)	9 (2.6%)	7 (6.8%)	7 (1.9%)	7 (2.0%)	6 (5.8%)	1 (0.3%)	3 (0.9%)	1 (1.0%)
Upper gastrointestinal hemorrhage	54 (14.8%)	50 (14.4%)	5 (4.9%)	34 (9.3%)	27 (7.8%)	1 (1.0%)	24 (6.6%)	24 (6.9%)	4 (3.9%)
General disorders & administrative site conditions									
Chest pain	18 (4.9%)	15 (4.3%)	1 (1.0%)	17 (4.6%)	14 (4.0%)	1 (1.0%)	1 (0.3%)	1 (0.3%)	---
Pain	---	---	5 (4.9%)	---	---	3 (2.9%)	---	---	2 (1.9%)
Pyrexia	85 (23.2%)	74 (21.3%)	5 (4.9%)	80 (21.9%)	71 (20.5%)	4 (3.9%)	7 (1.9%)	7 (2.0%)	1 (1.0%)
Infections & infestations									
Bacterial peritonitis	---	2 (0.6%)	3 (2.9%)	---	1 (0.3%)	2 (1.9%)	--	1 (0.3%)	2 (1.9%)
Pneumonia	3 (0.8%)	3 (0.9%)	7 (6.8%)	2 (0.5%)	1 (0.3%)	3 (2.9%)	---	2 (0.6%)	4 (3.9%)
Septic shock	---	2 (0.6%)	5 (4.9%)	---	---	1 (1.0%)	---	2 (0.6%)	4 (3.9%)
Hepatobiliary disorders									
Hepatic encephalopathy	33 (9.0%)	31 (8.9%)	5 (4.9%)	27 (7.4%)	24 (6.9%)	4 (3.9%)	4 (1.1%)	10 (2.9%)	2 (1.9%)
Hepatorenal syndrome	7 (1.9%)	6 (1.7%)	2 (1.9%)	2 (0.5%)	1 (0.3%)	---	4 (1.1%)	5 (1.4%)	2 (1.9%)

--- : no events reported

Table 31 AEs Occurring in ≥ 2% of Vapreotide Patients in EVB Studies (continued)

MedDRA System Organ Class Preferred Term	Days 1-42, n (%)			Days 1-5 (drug infusion), n (%)			Days 6-42 (Follow-up) n (%)		
	4 EVB RCTs		VAP-301	4 EVB RCTs		VAP-301	4 EVB RCTs		VAP-301
	Vapreotide N=366	Placebo N=347	Vapreotide N=103	Vapreotide N=366	Placebo N=347	Vapreotide N=103	Vapreotide N=366	Placebo N=347	Vapreotide N=103
Metabolism & nutrition disorders									
Hyperglycemia	11 (3.0%)	9 (2.6%)	4 (3.9%)	10 (2.7%)	6 (1.7%)	3 (2.9%)	1 (0.3%)	2 (0.6%)	1 (1.0%)
Hypokalemia	---	3 (0.9%)	11 (10.7%)	---	3 (0.9%)	10 (9.6%)	---	---	1 (1.0%)
Hypomagnesemia	1 (0.3%)	---	3 (2.9%)	1 (0.3%)	---	3 (2.9%)	---	---	---
Metabolic acidosis	---	---	4 (3.9%)	---	---	4 (3.9%)	---	---	1 (1.0%)
Nervous system disorders									
Encephalopathy	11 (3.0%)	9 (2.6%)	---	10 (2.7%)	7 (2.0%)	---	1 (0.3%)	---	---
Headache	26 (7.1%)	34 (9.8%)	5 (4.9%)	24 (6.6%)	32 (9.2%)	5 (4.9%)	2 (0.5%)	3 (0.9%)	---
Psychiatric disorders									
Psychomotor hyperactivity	3 (0.8%)	1 (0.3%)	3 (2.9%)	3 (0.8%)	---	3 (2.9%)	---	1 (0.3%)	---
Renal & urinary disorders									
Renal failure	1 (0.3%)	3 (0.9%)	10 (9.7%)	---	2 (0.6%)	5 (4.9%)	1 (0.3%)	1 (0.3%)	6 (5.8%)
Respiratory, thoracic & mediastinal disorders									
Cough	2 (0.5%)	3 (0.9%)	4 (3.9%)	2 (0.5%)	2 (0.6%)	1 (1.0%)	---	1 (0.3%)	3 (2.9%)
Pleural effusion	2 (0.5%)	1 (0.3%)	3 (2.9%)	2 (0.5%)	1 (0.3%)	3 (2.9%)	---	---	---
Respiratory failure	3 (0.8%)	---	5 (4.9%)	2 (0.5%)	---	1 (1.0%)	1 (0.3%)	---	4 (3.9%)
Vascular disorders									
Hypotension	2 (0.5%)	5 (1.4%)	6 (5.8%)	1 (0.3%)	2 (0.6%)	3 (2.9%)	1 (0.3%)	3 (0.9%)	3 (2.9%)
Shock hemorrhagic	11 (3.0%)	8 (2.3%)	---	7 (1.9%)	5 (1.4%)	---	3 (0.8%)	3 (0.9%)	---

--- : no events reported

9.6.2 Hematologic and Other Laboratory Abnormalities

Per protocol, laboratory parameters including hematologic (hemoglobin, red blood cells [RBC], white blood cells [WBC], platelet count) and blood chemistry (glucose, creatinine, aspartate transaminase [AST], alanine transaminase [ALT], sodium) were to be measured at baseline (Day 1, prior to initiating study drug infusion) and Day 5 (end of study drug infusion). With the exception of platelet count, protocol-specified laboratory parameters were available at baseline and Day 5 for 70% - 83% of patients (varied with analyte) in the EVB RCTs and for 56% - 62% of patients in VAP-301. No platelet counts were available from VAP-06 and VAP-07 and only 34% of patients in VAP-301 had RBC counts at baseline and Day 5.

Laboratory parameters were categorized as low (below the lower limit of normal), normal, or high (above the upper limit of normal) based on the normal ranges established at each investigational site. For patients who completed Day 5 safety assessments in the pooled EVB RCTs, baseline values for key parameters for vapreotide and placebo groups were well balanced and consistent with a population of cirrhotic patients with variceal bleeding: the majority of patients had low platelet count, low RBC, elevated glucose, and elevated ALT (or AST). In the pooled EVB RCTs, baseline WBC was high in about one-fifth of patients and low in about one-eighth.

Results for baseline values in VAP-301 were comparable to the pooled EVB RCTs except fewer patients in VAP-301 had high glucose levels and more patients had high WBC (Table 32).

Table 32 Laboratory Parameters at Baseline in EVB studies

Baseline Values	4 EVB RCTs		VAP-301
	Vapreotide N=366 ^a	Placebo N=347 ^a	Vapreotide N=103 ^a
RBC, N	299	294	35
Low	272 (91.0%)	266 (89.6%)	29 (82.9%)
Normal	27 (9.0%)	28 (9.5%)	6 (17.1%)
High	0 (0%)	0 (0%)	0 (0%)
WBC, N	309	300	63
Low	40 (12.9%)	37 (12.3%)	6 (9.5%)
Normal	207 (67.0%)	190 (63.3%)	35 (55.6%)
High	62 (20.1%)	73 (24.3%)	22 (34.9%)
Platelet count, N	169	160	62
Low	131 (77.5%)	122 (76.3%)	40 (64.5%)
Normal	25 (14.8%)	28 (17.5%)	21 (33.9%)
High	13 (7.7%)	10 (6.3%)	1 (1.6%)
Glucose, N	287	279	63
Low	2 (0.7%)	4 (1.4%)	6 (9.5%)
Normal	96 (33.4%)	86 (30.8%)	35 (55.6%)
High	187 (65.2%)	189 (67.7%)	22 (34.9%)
ALT, N	300	280	58
Low	5 (1.7%)	3 (1.1%)	0 (0%)
Normal	161 (53.7%)	135 (48.2%)	36 (62.1%)
High	134 (44.7%)	142 (50.7%)	22 (37.9%)
AST, N	257	247	58
Low	1 (0.4%)	0 (0%)	0 (0%)
Normal	63 (24.5%)	44 (17.8%)	11 (19.0%)
High	193 (75.1%)	203 (82.2%)	47 (81.0%)
Creatinine, N	304	293	64
Low	41 (13.5%)	28 (9.6%)	3 (4.7%)
Normal	215 (70.7%)	210 (71.7%)	53 (82.8%)
High	48 (15.8%)	55 (18.8%)	8 (12.5%)

^a Note: Percentages are based on the number of patients with available data at both Baseline and Day 5.

Changes in laboratory parameters from baseline to Day 5 for the pooled EVB RCTs and VAP-301 are summarized in Table 33. Similar proportion of patients whose values shifted were observed for both the vapreotide and placebo groups from the pooled EVB RCTs, with decreases in WBC and glucose for approximately 30% of patients and decreases in platelet count for approximately 10% of patients.

Changes in laboratory parameters for VAP-301 were similar to those observed for the vapreotide group from pooled EVB RCTs, though a higher percentage of decreases from baseline in RBC (14%), WBC (36%), and platelet count (18%) were observed in VAP-301. Overall there were no differences in changes from baseline values.

Table 33 Changes in Laboratory Parameters from Baseline to End of Study Drug Infusion in EVB Studies

Laboratory Parameter at Day 5 ^a	4 EVB RCTs		VAP-301
	Vapreotide N=366 ^b	Placebo N=347 ^b	Vapreotide N=103 ^b
RBC, N	299	294	35
No change from baseline	267 (89.3%)	259 (88.1%)	29 (82.9%)
Increase from baseline	16 (5.4%)	19 (6.5%)	1 (2.9%)
Decrease from baseline	16 (5.4%)	16 (5.4%)	5 (14.3%)
WBC, N	309	300	63
No change from baseline	191 (61.8%)	171 (57.0%)	34 (54.0%)
Increase from baseline	24 (7.8%)	24 (8.0%)	6 (9.5%)
Decrease from baseline	94 (30.4%)	105 (35.0%)	23 (36.5%)
Platelet count N	153	160	62
No change from baseline	124 (81.0%)	138 (86.3%)	50 (80.6%)
Increase from baseline	13 (8.5%)	4 (2.5%)	1 (1.6%)
Decrease from baseline	16 (10.5%)	18 (11.3%)	11 (17.7%)
Glucose, N	287	279	63
No change from baseline	177 (61.7%)	148 (53.0%)	34 (54.0%)
Increase from baseline	38 (13.2%)	41 (14.7%)	6 (9.5%)
Decrease from baseline	72 (25.1%)	90 (32.3%)	23 (36.5%)
ALT, N	300	280	58
No change from baseline	229 (76.3%)	224 (80.0%)	48 (82.8%)
Increase from baseline	33 (11.0%)	30 (10.7%)	4 (6.9%)
Decrease from baseline	38 (12.7%)	26 (9.3%)	6 (10.3%)
AST, N	257	247	58
No change from baseline	214 (83.3%)	212 (85.8%)	52 (89.7%)
Increase from baseline	18 (7.0%)	17 (6.9%)	3 (5.2%)
Decrease from baseline	25 (9.7%)	18 (7.3%)	3 (5.2%)
Creatinine, N	304	293	64
No change from baseline	216 (71.1%)	206 (70.3%)	55 (85.9%)
Increase from baseline	47 (15.5%)	34 (11.6%)	2 (3.1%)
Decrease from baseline	41 (13.5%)	53 (18.1%)	7 (10.9%)

^a “No change from baseline” means the patient’s lab value remained within the same lab value range (low, normal or high). An “increase from baseline” means the patient’s lab value shifted from low to normal or high, or from normal to high; a “decrease from baseline” means the patient’s lab value shifted from normal to low, or from high to normal or low.

^b Percentages are based on the number of patients with available data at both Baseline and Day 5.

9.7 Serious Adverse Events in Variceal Bleeding Studies

The most frequent serious adverse events (SAEs) reported in the pooled EVB RCTs and in the single-arm VAP-301 are summarized in Table 34 by body system and type of AE (Preferred Term) and by time period. All of these common SAEs are expected complications in cirrhotic patients with variceal bleeding (Laine 2005): upper gastrointestinal hemorrhage, esophageal varices hemorrhage, melena, hepatic encephalopathy, hepatorenal syndrome, hepatic coma, coma, shock, hemorrhagic shock, cardiorespiratory arrest, and pneumonia. In the pooled EVB RCTs, similar SAE rates were observed for the vapreotide and placebo groups, thus no safety concerns were identified. The SAEs reported in VAP-301 were similar in types with comparable or lower rates as reported in the EVB RCTs.

Table 34 SAEs Occurring in ≥ 1% of Patients in EVB Placebo-Controlled Studies

MedDRA System Organ Class Preferred Term	Days 1-42, n (%)			Days 1-5 (drug infusion), n (%)			Days 6-42 (Follow-up), n (%)		
	4 EVB RCTs		VAP-301	4 EVB RCTs		VAP-301	4 EVB RCTs		VAP-301
	Vapreotide N=366	Placebo N=347	Vapreotide N=103	Vapreotide N=366	Placebo N=347	Vapreotide N=103	Vapreotide N=366	Placebo N=347	Vapreotide N=103
Cardiac disorders									
Cardio-respiratory arrest	5 (1.4%)	4 (1.2%)	1 (1.0%)	3 (0.8%)	4 (1.2%)	1 (1.0%)	2 (0.5%)	---	---
Gastrointestinal disorders									
Melena	36 (9.8%)	36 (10.4%)	1 (1.0%)	30 (8.2%)	33 (9.5%)	---	5 (1.4%)	4 (1.2%)	1 (1.0%)
Upper gastrointestinal hemorrhage	43 (13.1%)	44 (12.7%)	2 (1.9%) ^a	28 (7.7%)	22 (6.3%)	---	23 (6.3%)	22 (6.3%)	2 (1.9%) ^a
Hepatobiliary disorders									
Esophageal varices hemorrhage	3 (0.8%)	3 (0.9%)	5 (4.9%) ^a	2 (0.5%)	---	1 (1.0%)	---	3 (0.9%)	4 (3.9%) ^a
Hepatic coma	4 (1.1%)	5 (1.4%)	---	1 (0.3%)	4 (1.2%)	---	3 (0.8%)	1 (0.3%)	---
Hepatic encephalopathy	19 (5.2%)	17 (4.9%)	---	15 (4.1%)	10 (2.9%)	---	3 (0.8%)	7 (2.0%)	---
Hepatorenal syndrome	7 (1.9%)	6 (1.7%)	1 (1.0%)	2 (0.5%)	1 (0.3%)	---	4 (1.1%)	5 (1.4%)	1 (1.0%)
Infections & infestations									
Pneumonia	3 (0.8%)	---	1 (1.0%)	3 (0.8%)	---	---	---	---	1 (1.0%)
Nervous system disorders									
Coma	3 (0.8%)	1 (0.3%)	---	1 (0.3%)	1 (0.3%)	---	2 (0.5%)	---	---
Vascular disorders									
Shock	4 (1.1%)	2 (0.6%)	---	2 (0.5%)	1 (0.3%)	---	2 (0.5%)	1 (0.3%)	---
Shock hemorrhagic	11 (3.0%)	8 (2.3%)	---	7 (1.9%)	5 (1.4%)	---	3 (0.8%)	3 (0.9%)	---

--- : no events reported

^a During the follow-up period, VAP-301 patients had a higher rate of esophageal varices hemorrhage (7.7% vs 0%) and a lower rate of upper gastrointestinal hemorrhage (1.9% vs 6.3%). Assuming that these Preferred Terms were used interchangeably to describe re-bleeding events, then VAP-301 had a rate of re-bleeding during follow-up that was comparable to that in vapreotide group from the pooled EVB RCTs (6.3% vs 5.8%).

9.8 Deaths in Variceal Bleeding Studies

Deaths and primary cause of death in the pooled EVB RCTs and VAP-301 are summarized by time period in Table 35. During the period of study drug infusion (Days 1-5), the mortality rate was similar for the vapreotide and placebo groups from the EVB RCTs (6.6% vs 6.9%) and for the single-arm VAP-301 (8.7%). However, during the follow-up period the death rate was higher in VAP-301 (16.5%) than in the vapreotide and placebo groups from the EVB RCTs (8.5% vs 9.5%). Accordingly, the 6-week mortality was higher in VAP-301 (25.2%) than in the vapreotide and placebo groups from the pooled EVB RCTs (15.0% vs 16.4%) however, the 95% CIs overlap (17.2% - 34.7% for VAP-301 vs 11.5% - 19.1% for vapreotide in VAP-14), suggesting that the difference may result from the small sample size. A recent Cochrane report that analyzed 6-week mortality in EVB studies employing somatostatin analogs (Gotzsche 2008) reported a mean rate of 19%, with a range of 3% - 38% in active acute EVB treatment groups. In addition, it is possible that the higher mortality in VAP-301 reflects the more complex disease etiology, particularly the combination of alcoholism and viral hepatitis. Additionally, there were 6 patients in VAP-301 with HIV/AIDS, all of whom died on study.

In the EVB RCTs, most deaths resulted from uncontrolled bleeding/re-bleeding or worsening of liver disease. The higher mortality rate in the VAP-301 study compared with the EVB RCTs was driven by increased rates of deaths due to infection/multiorgan failure (9.7% vs 1.1%), worsening of liver disease (6.8% vs 4.8%), and cardiac/cardiorespiratory arrest (2.9% vs 0.8%), all of which are expected complications in cirrhotic patients with upper gastrointestinal bleeding. As discussed, infections, particularly spontaneous bacterial peritonitis, are common in cirrhotic patients with variceal bleeding (Bleichner 1986) and are associated with failure to control bleeding, early rebleeding, and mortality (Goulis 1998; Vivas 2001). As a further complication, accelerated intravascular coagulation and fibrinolysis are found in 30% of patients with advanced liver disease and these patients are prone to develop disseminated intravascular coagulation if sepsis occurs (Amitrano 2002). Cirrhotic cardiomyopathy is present in the majority of cirrhotic patients who have reached Child Pugh stage B or C (Baik 2007) and is exacerbated by hemorrhage. Additionally, cardiopulmonary complications occur in 23-50% of cirrhotic patients with variceal bleeding (Lipper 1991). Renal failure also may be precipitated by a variceal bleed and is associated with increased mortality (Cardenas 2001).

Table 35 Deaths Occurring in Vapreotide EVB Studies

Cause of Death	Days 1-42, n (%)			Days 1-5 (drug infusion), n (%)			Days 6-42 (Follow-up), n (%)		
	4 EVB RCTs		VAP-301	4 EVB RCTs		VAP-301	4 EVB RCTs		VAP-301
	Vapreotide N=366	Placebo N=347	Vapreotide N=103	Vapreotide N=366	Placebo N=347	Vapreotide N=103	Vapreotide N=366	Placebo N=347	Vapreotide N=103
Total deaths	55 (15.0%)	57 (16.4%)	26 (25.2%)	24 (6.6%)	24 (6.9%)	9 (8.7%)	31 (8.5%)	33 (9.5%)	17 (16.5%)
Uncontrolled bleeding/ recurrence of bleeding leading to hemorrhagic shock ^a	27 (7.4%)	30 (8.6%)	5 (4.9%)	15 (4.1%)	16 (4.6%)	2 (1.9%)	13 (3.6%)	14 (4.0%)	3 (2.9%)
Worsening of liver disease ^b	18 (4.9%)	15 (4.3%)	7 (6.8%)	7 (1.9%)	5 (1.4%)	1 (1.0%)	11 (3.0%)	11 (3.2%)	6 (5.8%)
Infection/multiorgan failure ^c	3 (0.8%)	5 (1.4%)	10 (9.7%)	---	---	4 (3.9%)	3 (0.8%)	5 (1.4%)	5 (4.9%)
Cardiac/cardiorespiratory arrest ^d	2 (0.5%)	4 (1.2%)	3 (2.9%)	1 (0.3%)	2 (0.6%)	2 (1.9%)	1 (0.3%)	2 (0.6%)	1 (1.0%)
Cerebrovascular accident	2 (0.5%)	---	---	1 (0.3%)	---	---	1 (0.3%)	---	---
Renal failure	1 (0.3%)	---	---	---	---	---	1 (0.3%)	---	---
Respiratory distress/acute respiratory distress syndrome/ respiratory failure	1 (0.3%)	2 (0.6%)	---	---	1 (0.3%)	---	1 (0.3%)	1 (0.3%)	1 (1.0%)
Death (not otherwise specified)	1 (0.3%)	1 (0.3%)	1 (1.0%)	---	---	---	1 (0.3%)	1 (0.3%)	1 (1.0%)

^a Includes upper gastrointestinal hemorrhage, melena, duodenal ulcer hemorrhage, rectal hemorrhage, hemorrhagic shock, hypovolemic shock, shock.

^b Includes hepatic encephalopathy, hepatorenal syndrome, hepatic neoplasm, hepatic cirrhosis hepatic failure, hepatic coma.

^c Includes peritonitis/ascites infection, pneumonia, fungemia, sepsis/septic shock, multiorgan failure (included because cases of multiorgan failure also had infection/sepsis).

^d Cardiac/cardiorespiratory arrest resulting from severe bleeding and hemorrhagic shock included in the uncontrolled bleeding category, not herein.

-- : no events reported

9.9 Discontinuations Due to Adverse Events in Variceal Bleeding Studies

The determination of treatment discontinuation in association with an adverse event was handled differently from study to study, depending on investigator assessment and interpretation. In some cases, death was recorded as a discontinuation of study drug due to an adverse event and in others it was not. Additionally, in some cases treatment discontinuations were recorded as related to an AE when they were, in fact, due to protocol-specified discontinuations upon finding bleeding unrelated to portal hypertension at diagnostic endoscopy or for a protocol violation. A careful review of safety data from each EVB study revealed 12 discontinuations associated with an AE, compared with 17 discontinuations due to death caused by worsening of underlying liver disease, 7 discontinuations due to death caused by uncontrolled index hemorrhage leading to hemorrhagic shock, 47 discontinuations for administration of alternative therapy for initial bleeding or re-bleeding, and 3 discontinuations due to accidental overdose (Table 36).

Table 36 Treatment Discontinuations in Vapreotide EVB Studies

Treatment Discontinuation Due to:	4 EVB RCTs		VAP-301 Vapreotide N=103 n (%)
	Vapreotide N=366 n (%)	Placebo N=347 n (%)	
Adverse Event:			
Cardiovascular event	2 (0.5%)	3 (0.9%)	2 (1.9%)
Multiorgan failure/infection	---	1 (0.3%)	2 (1.9%)
Leukopenia	---	---	1 (1.0%)
Thrombophlebitis at infusion site	1 (0.3%)	---	---
Worsening of baseline underlying liver disease followed by death	8 (2.1%)	5 (1.4%)	4 (3.9%)
Uncontrolled bleeding (hemorrhagic shock) followed by death	6 (1.6%)	2 (0.6%)	---
Administration of alternative treatment for initial bleeding or re-bleeding ^a	20 (5.5%)	27 (7.8%)	---
Accidental overdose ^b	2 (0.5%)	1 (0.3%)	---

--- : no events reported

^a Patients who recovered from the rebleeding.

^b Three patients in VAP-02 received on Day 1 the study drug planned for 5 days (6 mg vapreotide for 2 of the patients).

The 3 patients (2 vapreotide; 1 placebo) who had accidental overdoses of study drug were enrolled in VAP-02. One vapreotide patient received study drug over 2 hours that should have been given over 12 hours. The study drug was discontinued when the error was detected. No AEs were reported for this patient during the period of drug administration. Approximately 6 hours after study drug was discontinued the patient had a re-bleeding episode and was treated with another vasoactive agent. The other vapreotide patient received the content of 12 vials of study drug (6 mg) over ~6 hours rather than the intended 5 days (at 50 µg/h). Study drug was discontinued when the error was detected. The patient experienced mild and transient abdominal

pain and transient hyperglycemia that resolved with treatment the same day. These 2 AEs were considered by the investigator as probably related to the study drug overdose.

9.10 Adverse Events of Interest in Variceal Bleeding Studies

Uncommon events (< 2% of EVB patients) that occurred in the vapreotide group but not in the placebo group in the pooled EVB RCTs; events that occurred at a markedly higher rate in VAP-301 than in the pooled EVB RCTs; and events that led to treatment discontinuation and could have been related to the pharmacodynamic effect of vapreotide increasing pulmonary wedge pressure during the infusion period are summarized in Table 37. These events were investigated in detail as potential safety signals. Results of investigations, summarized in subsections below, did not identify a safety signal and suggest that these low frequency events were expected complications of cirrhotic patients experiencing variceal bleeding, with imbalances between vapreotide and placebo groups in the EVB RCTs a reflection of small sample size.

Table 37 Adverse Events of Interest in EVB Studies

MedDRA System Organ Class Preferred Term	Days 1-5 (drug infusion), n (%)			Days 6-42 (follow-up), n (%)		
	4 EVB RCTs		VAP-301	4 EVB RCTs		VAP-301
	Vapreotide N=366	Placebo N=347	Vapreotide N=103	Vapreotide N=366	Placebo N=347	Vapreotide N=103
Blood & lymphatic system disorders						
Anemia	---	---	2 (1.9%)	---	1 (0.35)	1 (1.0%)
Disseminated intravascular coagulation	---	---	1 (1.0%)	1 (0.3%)	---	1 (1.0%)
Leukopenia	---	---	2 (1.9%)	---	---	---
Pancytopenia	2 (0.5%)	---	1 (1.0%)	---	---	---
Thrombocytopenia	5 (1.4%)	1 (0.3%)	1 (1.0%)	1 (0.3%)	---	1 (1.0%)
Cardiac disorders						
Atrial fibrillation	1 (0.3%)	---	1 (1.0%)	1 (0.3%)	---	1 (1.0%)
Cardiac failure (& congestive) ^a	---	1 (0.3%)	---	1 (0.3%)	1 (0.3%)	---
Renal & urinary disorders						
Renal failure/Renal failure acute	2 (0.5%)	3 (0.9%)	5 (4.9%)	1 (0.3%)	1 (0.3%)	6 (5.8%)
Respiratory, thoracic & mediastinal disorders						
Acute respiratory distress Syndrome/Respiratory distress	---	2 (0.6%)	2 (1.9%)	1 (0.3%)	1 (0.3%)	1 (1.0%)
Dyspnea ^a	1 (0.3%)	5 (1.4%)	1 (1.0%)	---	2 (0.6%)	---
Pulmonary congestion ^a	---	---	---	---	---	---
Pulmonary edema ^a	---	---	1 (1.0%)	---	---	1 (1.0%)
Respiratory failure/Acute respiratory failure ^a	2 (0.5%)	1 (0.3%)	1 (1.0%)	1 (0.3%)	---	4 (3.9%)

^a Events potentially related to pharmacodynamic effect of vapreotide increasing pulmonary wedge pressure
 --- : no events reported

9.10.1 Hematopoietic Abnormalities During Infusion Period

Pancytopenia was reported for 3 patients receiving vapreotide and no placebo patients:

- A patient with alcoholic cirrhosis had pancytopenia at baseline (Hgb 7.6 g/dL; WBC 1300/mm³; platelet count 40,000/mm³) and showed a slight worsening of platelet count at Day 5 (Hgb 8.7 g/dL; WBC 1400/mm³; platelet count 23,000/mm³) that was judged by the investigator to be clinically insignificant and unrelated to study medication;
- A patient with cirrhosis due to schistosomiasis and hepatitis C had splenomegaly and anemia at baseline (Hgb 7.4 g/dL; RBC 2.97; WBC 6000/m³; platelet count not determined) and developed leukopenia at Day 5 (Hgb not determined; RBC 3.61; WBC 1600/mm³; platelet count not determined). Since pancytopenia is associated with both advanced liver disease and schistosomiasis infection, it is difficult to ascertain an effect of vapreotide on the WBC for this patient. The investigator considered that the pancytopenia was unrelated to study medication;
- A patient with cirrhosis due to autoimmune hepatitis (receiving immunosuppressive therapy with azathioprine and steroids) had abnormal hematologic parameters at baseline (Hgb 10.3 g/dL; WBC 14,750/mm³; platelet count 55,000/mm³). Assessments at Day 5 showed worsened thrombocytopenia and normalized WBC (Hgb 9.6 g/dL; WBC 6700/mm³; platelet count 44,000/mm³). Since pancytopenia is associated with advanced liver disease, autoimmune hepatitis, and immunosuppressive treatment, it is difficult to ascertain an effect of vapreotide on the pancytopenia for this patient. The investigator considered that the pancytopenia was unrelated to study medication.

Leukopenia was reported for 2 patients receiving vapreotide in VAP-301:

- A patient with alcoholic cirrhosis had leukopenia at baseline (Hgb 8.9 g/dL; WBC 4000/mm³; platelet count 75,000/mm³) that worsened during day 3 of the infusion (WBC 2800/mm³ at the last assessment before terminating the infusion). The vapreotide infusion was discontinued on day 3 and the WBC recovered to baseline values by 12 hours after discontinuation of the infusion (single measurement: WBC 4400/mm³). Follow-up assessment at 6 months showed low WBC (3400/mm³) similar to values observed before discontinuation of the vapreotide infusion. The investigator considered the leukopenia to be due to hypersplenism secondary to cirrhotic portal hypertension and unrelated to study drug.
- A patient with cirrhosis due to primary sclerosing cholangitis, as well as a history of ulcerative colitis (receiving immunosuppressive therapy with azathioprine) and anemia of chronic disease, had low normal hematologic parameters and baseline (Hgb 8.9 g/dL; WBC 5100/mm³; platelet count 79,000/mm³) and showed leukopenia and thrombocytopenia at Day 5 (Hgb 10.2 g/dL; WBC 2000/mm³; platelet count 48,000/mm³).

Thrombocytopenia was reported for 8 vapreotide patients and one placebo patient. Six of these events occurred during Days 1-5 and 2 events occurred during Days 6-42. All 6 of the events during study drug infusion (5 vapreotide, 1 placebo) were reported by a single center in the VAP-06 study; since platelet counts were not collected in this study, it is difficult to attribute the relationship to study medication. The 2 events reported in the follow-up period occurred in

VAP-301. One event was attributed by the investigator as secondary to immunosuppressive therapy following liver transplant and the other event occurred in a patient with multiple complications of an irreversible end-stage liver disease (cachexia, infection, coagulopathy, renal insufficiency).

Disseminated intravascular coagulation (DIC) was reported for 3 vapreotide patients and no placebo patients:

- A patient who presented at baseline with coagulopathy, acute liver failure, renal failure (creatinine 1.9 mg/dL), metabolic acidosis, elevated WBC, significant gingival bleeding (even after packing by oral and maxillofacial surgery), and suspected vitamin C deficiency, was enrolled in the study and the following day was placed on continuous renal replacement therapy due to high creatinine levels and low urine output. The investigator continued the study drug infusion. The patient's liver function worsened and WBC increased. On Day 4, she developed sepsis and DIC. The patient's family decided to withdraw care and the patient died on Day 5. The investigator considered all events to be unrelated to study treatment.
- A patient presenting with alcoholic hepatitis and ascites was found at diagnostic endoscopy to have bleeding unrelated to portal hypertension. Per protocol, the vapreotide infusion was discontinued. Twelve days following discontinuation of vapreotide, the patient experienced hematochezia and subsequently developed renal insufficiency, DIC, and septic shock, leading to death the same day.
- A patient who completed the 5-day course of vapreotide treatment with no complication or re-bleeding had an upper digestive re-bleeding episode 6 days after completing vapreotide treatment that was followed by DIC leading to pulmonary embolism and renal insufficiency that was considered an acute expression of the pulmonary embolism. The following day that patient had another rebleed and died from hemorrhagic shock. The investigator considered these events to be unrelated to study treatment.

It should be noted that cytopenias, including thrombocytopenia, leucopenia, and anemia, alone or in combination have been reported in 6% to 77% of patients with varying degrees of cirrhosis (Bashour 2000; Qamar 2008, 2009). A recent study analyzed a database of 213 patients with compensated cirrhosis without esophageal varices who were followed for approximately 9 years until the development of varices or variceal bleeding (39% of patients) or completion of the study (Qamar 2009). At baseline, thrombocytopenia (platelet count $<150,000/\text{mm}^3$) was present in 78%, leukopenia (WBC $<4000/\text{mm}^3$) in 23.5%, and anemia (Hgb <13.5 g/dL for men and 11.5 g/dL for women) in 21% of patients. Multivariate analysis showed that thrombocytopenia plus leukopenia, increased hepatic venous pressure gradient (HVPG), and Child Pugh score were independently associated with death or transplant during the follow-up period. Patients with thrombocytopenia plus leukopenia also were more likely to develop clinical decompensation and clinically significant portal hypertension (HVPG >10 mm Hg).

In considering the occurrence of DIC, accelerated intravascular coagulation and fibrinolysis are found in 30% of patients with advanced liver disease and these patients are prone to develop DIC if sepsis occurs (Amitrano 2002).

These events were rare, and no difference from baseline laboratory values was noted in the EVB database (see Table 32).

Based on review of these cases and expected disease-related complications in cirrhotic patients, there is no clear safety signal for vapreotide with respects to hematologic events.

9.10.2 Renal Failure

Although a similar rate of renal failure/renal failure acute was reported for the vapreotide and placebo groups in the EVB RCTs (0.8% [3/366] vs 1.2% [4/347] for vapreotide and placebo groups, respectively), a higher incidence was reported in VAP-301 (9.7% [10/103]). Five of the 10 cases reported in VAP-301 occurred during the vapreotide infusion. In 2 of these cases renal function recovered with the stabilization of baseline disease, upper gastrointestinal bleeding, and alcohol withdrawal syndrome, respectively. Four of the 10 patients in VAP-301 had elevated creatinine at baseline or established renal insufficiency that worsened with severity of bleeding or infection. The other cases reported in VAP-301 occurred in a context of a severe hemorrhage (from varices or other source) complicated by other organ system failures or infection (liver failure, DIC, pneumonia and septic shock).

In reviewing these cases, it should be considered that renal failure may be precipitated by a variceal bleed. In a large case series of cirrhotic patients with gastrointestinal hemorrhage (82% variceal), hypovolemia and poor liver function were the only factors independently predictive of renal failure (Cardenas 2001). The same study found that the only two predictors of in-hospital mortality were the presence of hypovolemic shock and renal failure (67% mortality vs 3% in patients without either of these factors). Based on review of these cases and expected disease-related complications in cirrhotic patients, and considering the lack of a placebo group, the increased incidence of renal failure in the VAP-301 study does not provide a clear safety signal for vapreotide with respect to renal failure.

9.10.3 Events Potentially Related to Vapreotide Effects on Pulmonary Wedge Pressure

Events reviewed as potentially related to vapreotide effects on pulmonary wedge pressure included dyspnea, pulmonary edema, respiratory congestion, respiratory failure, and cardiac failure during study drug infusion.

During study drug infusion there were no apparent differences between vapreotide and placebo groups in the EVB RCTs with respect to the rate of these events and similar rates were observed for VAP-301. Of the 3 cases of respiratory failure reported during the vapreotide infusion in the EVB RCTs and VAP-301 study, 2 cases occurred in alcoholic cirrhotic patients who had Mallory-Weiss tear as the cause of bleeding and developed pneumonia following endoscopy. The other patient had respiratory failure secondary to massive hemorrhage with massive blood

product transfusions. Of the 2 cases of acute respiratory distress reported during vapreotide infusion in VAP-301, one developed acute respiratory distress syndrome in the context of hepatorenal syndrome and the other had pseudomonas pneumonia.

During the follow-up period, 2 vapreotide patients from the EVB RCTs (0.6%) and 5 from VAP-301 (4.9%) developed respiratory failure, respiratory distress or acute respiratory distress compared with a single placebo patient (0.3%). One vapreotide patient from the EVB RCTs developed respiratory failure secondary to a re-bleeding episode (6 days after completing study drug infusion), followed by disseminated intravascular coagulation that led to pulmonary embolism. All 5 patients in VAP-301 developed respiratory distress or respiratory failure secondary to infectious pneumonia.

All these cases, both during and after study drug infusion, could be considered complications of the underlying disease, as pneumonia is a common complication in alcoholic cirrhotic patients with variceal bleeding due to the risk of aspiration during endoscopy.

9.10.4 Cardiovascular Adverse Events

In the pooled EVB RCTs, there was no apparent difference in the overall rate of cardiac events between the vapreotide and placebo groups (5.5% vs 4.6%). As shown in Table 37, 4 vapreotide patients were reported to have an episode of atrial fibrillation compared to no placebo patient (2 in EVB RCTs and 2 in VAP-301). Two of the 4 patients had atrial fibrillation during the treatment period. In one case, atrial fibrillation occurred on Day 1 and resolved following a dose of digoxin; the infusion was continued through 5 days with no recurrence of atrial fibrillation. In the second case, a patient who presented at enrollment with cachexia, pneumonia urinary tract infection, renal insufficiency, and irreversible end-stage liver disease experienced intermittent episodes of atrial fibrillation on Day 2 of the infusion; the infusion was continued for 5 days and the patient continued to experience recurring episodes of atrial fibrillation over the next 23 days.

No cases of Torsade or ventricular fibrillation were reported during any vapreotide infusion, and no cases of ventricular tachycardia were reported during the EVB studies. One case of ventricular tachycardia was observed in a placebo patient in the 9-Study Database.

9.11 Safety Profile from the 9-Study Database (EVB and Non-EVB Pooled Data)

The larger sample size of vapreotide-exposed patients contained in the 9-Study Database did not identify any unexpected safety concern with the use of vapreotide. As previously mentioned, this database contained patients exposed to vapreotide for longer durations (up to 180 days). The most frequent AEs in the 9-Study Database are summarized in Table 38, along with the corresponding event rates for the pooled EVB RCTs and the single-arm EVB study (VAP-301). In the 9-Study Database, there were no marked differences in event rates between vapreotide and placebo groups, except that the vapreotide group had higher rates of anemia (4.7% vs 2.4%) and respiratory failure (2.9% vs 0.7%) and lower rates of expected complications from pancreatic surgery, including anastomotic leak (5.5% vs 7.1%), urosepsis (2.5% vs 4.4%), and incision site infection (1.8% vs 3.2%). The imbalances in anemia and respiratory failure were driven by cases

reported for the pancreatic surgery study; considered alone, there were no imbalances in anemia and respiratory failure between the vapeotide and placebo groups in that study.

Table 38 AEs Occurring in ≥ 2% of Vapreotide Patients in the Pooled EVB and Non-EVB (9-Study) Database

MedDRA System Organ Class Preferred Term	4 EVB RCTs		VAP-301 Vapreotide N=103	9-Study Database (Pooled EVB and Non-EVB)		
	Vapreotide N=366	Placebo N=347		Vapreotide N=728	1.2 mg/day Vapreotide N=671	Placebo N=536
Blood & lymphatic system disorders						
Anemia	---	1 (0.3%)	3 (2.9%)	34 (4.7%)	33 (4.9%)	13 (2.4%)
Coagulopathy	---	4 (1.2%)	3 (2.9%)	5 (0.7%)	5 (0.7%)	5 (0.9%)
Cardiac disorders						
Tachycardia	---	1 (0.3%)	3 (2.9%)	16 (2.2%)	16 (2.4%)	13 (2.4%)
Gastrointestinal disorders						
Abdominal pain	15 (4.1%)	14 (4.3%)	6 (5.8%)	38 (5.2%)	37 (5.5%)	30 (5.6%)
Abdominal pain upper	14 (3.8%)	14 (4.0%)	1 (1.0%)	19 (2.6%)	18 (2.7%)	19 (3.5%)
Constipation	3 (0.8%)	1 (0.3%)	1 (1.0%)	48 (6.6%)	48 (7.2%)	46 (8.6%)
Diarrhea	9 (2.5%)	15 (4.2%)	3 (2.9%)	44 (6.0%)	44 (6.6%)	40 (7.5%)
Dyspepsia	11 (3.0%)	8 (2.3%)	2 (1.9%)	20 (2.7%)	20 (3.0%)	16 (3.0%)
Esophageal ulcer	7 (1.9%)	11 (3.2%)	---	7 (1.0%)	7 (1.0%)	11 (2.1%)
Esophageal varices hemorr.	3 (0.8%)	3 (0.9%)	7 (6.8%)			
Flatulence	42 (11.5%)	37 (10.7%)	---	44 (6.0%)	44 (6.6%)	40 (7.5%)
Impaired gastric emptying	--	---	---	23 (3.2%)	23 (3.4%)	21 (3.9%)
Melena	38 (10.4%)	37 (10.7%)	2 (1.9%)	40 (5.5%)	40 (6.0%)	36 (6.7%)
Nausea	8 (2.2%)	9 (2.6%)	7 (6.8%)	95 (13.0%)	95 (14.2%)	84 (15.7%)
Upper GI hemorrhage	54 (14.8%)	50 (14.4%)	5 (4.9%)	60 (8.2%)	60 (8.9%)	50 (9.3%)
Vomiting	2 (0.5%)	3 (0.9%)	2 (1.9%)	38 (5.2%)	38 (5.7%)	21 (3.9%)
General disorders & administrative site conditions						
Chest pain	18 (4.9%)	15 (4.3%)	1 (1.0%)	25 (3.4%)	25 (3.7%)	22 (4.1%)
Edema peripheral	2 (0.5%)	4 (1.2%)	1 (1.0%)	16 (2.2%)	16 (2.4%)	13 (2.4%)
Pain	---	---	5 (4.9%)	7 (1.0%)	7 (1.0%)	8 (1.5%)
Pyrexia	85 (23.2%)	74 (21.3%)	5 (4.9%)	119 (16.3%)	119 (17.7%)	107 (20.0%)
Hepatobiliary disorders						
Hepatic encephalopathy	33 (9.0%)	31 (8.9%)	5 (4.9%)	38 (5.2%)	38 (5.7%)	31 (5.8%)
Hepatorenal syndrome	7 (1.9%)	6 (1.7%)	2 (1.9%)	9 (1.2%)	9 (1.3%)	7 (1.3%)

Table 38 AEs Occurring in $\geq 2\%$ of Vapreotide Patients in the Pooled EVB and Non-EVB (9-Study) Database (continued)

MedDRASystem Organ Class Preferred Term	4 EVB RCTs		VAP-301 Vapreotide N=103	9-Study Database (Pooled EVB and Non-EVB)		
	Vapreotide N=366	Placebo N=347		Vapreotide N=728	1.2 mg/day Vapreotide N=671	Placebo N=536
Infections & infestations						
Abdominal abscess	---	---	---	14 (1.9%)	14 (2.1%)	6 (1.1%)
Bacterial peritonitis	---	2 (0.6%)	3 (2.9%)	3 (0.4%)	3 (0.4%)	3 (0.6%)
Pneumonia	3 (0.8%)	3 (0.9%)	7 (6.8%)	23 (3.2%)	23 (3.4%)	13 (2.4%)
Septic shock	---	2 (0.6%)	5 (4.9%)	5 (0.7%)	5 (0.7%)	3 (0.6%)
Urosepsis	---	---	---	18 (2.5%)	18 (2.7%)	23 (4.4%)
Injury, poisoning & procedural complications						
Anastomotic leak	---	---	---	40 (5.5%)	40 (6.0%)	38 (7.1%)
Incision site infection	---	---	---	13 (1.8%)	13 (1.9%)	17 (3.2%)
Procedural pain	---	---	---	29 (4.0%)	29 (4.3%)	21 (3.9%)
Metabolism & nutrition disorders						
Hyperglycemia	11 (3.0%)	9 (2.6%)	4 (3.9%)	44 (6.0%)	44 (6.6%)	36 (6.7%)
Hypoglycemia	---	2 (0.6%)	1 (1.0%)	13 (1.8%)	13 (1.9%)	9 (1.7%)
Hypokalemia	---	3 (0.9%)	11 (10.7%)	20 (2.7%)	20 (3.0%)	23 (4.3%)
Hypomagnesemia	1 (0.3%)	---	3 (2.9%)	31 (4.3%)	31 (4.6%)	23 (4.3%)
Hyponatremia	---	---	1 (1.0%)	18 (2.5%)	18 (2.7%)	14 (2.6%)
Metabolic acidosis	---	---	4 (3.9%)	6 (0.8%)	6 (0.9%)	3 (0.6%)
Musculoskeletal & connective tissue disorders						
Back pain	1 (0.3%)	3 (0.9%)	4 (3.9%)	15 (2.1%)	15 (2.2%)	12 (2.2%)
Nervous system disorders						
Encephalopathy	11 (3.0%)	9 (2.6%)	---	11 (1.5%)	11 (1.6%)	9 (1.7%)
Headache	26 (7.1%)	34 (9.8%)	5 (4.9%)	40 (5.5%)	39 (5.8%)	47 (8.8%)
Psychiatric disorders						
Confusional state	4 (1.1%)	3 (0.9%)	---	17 (2.3%)	17 (2.5%)	14 (2.6%)
Insomnia	6 (1.6%)	3 (0.9%)	2 (1.9%)	37 (5.1%)	36 (5.4%)	43 (8.0%)
Psychomotor hyperactivity	3 (0.8%)	1 (0.3%)	3 (2.9%)	6 (0.8%)	6 (0.9%)	1 (0.2%)
Renal & urinary disorders						
Renal failure	1 (0.3%)	3 (0.9%)	10 (9.7%)	13 (1.8%)	13 (1.9%)	6 (1.1%)

Table 38 AEs Occurring in $\geq 2\%$ of Vapreotide Patients in the Pooled EVB and Non-EVB (9-Study) Database (continued)

MedDRA System Organ Class Preferred Term	4 EVB RCTs		VAP-301 Vapreotide N=103	9-Study Database (Pooled EVB and Non-EVB)		
	Vapreotide N=366	Placebo N=347		Vapreotide N=728	1.2 mg/day Vapreotide N=671	Placebo N=536
Respiratory, thoracic & mediastinal disorders						
Cough	2 (0.5%)	3 (0.9%)	4 (3.9%)	6 (0.8%)	6 (0.9%)	6 (1.1%)
Pharyngolaryngeal pain	2 (0.5%)	7 (2.0%)	1 (1.0%)	13 (1.8%)	13 (1.9%)	33 (6.2%)
Pleural effusion	2 (0.5%)	1 (0.3%)	3 (2.9%)	22 (3.0%)	22 (3.3%)	22 (4.1%)
Respiratory failure	3 (0.8%)	---	5 (4.9%)	21 (2.9%)	21 (3.1%)	4 (0.7%)
Skin & subcutaneous tissue disorders						
Pruritis	4 (1.1%)	2 (0.6%)	---	29 (4.0%)	28 (4.2%)	27 (5.0%)
Rash	---	1 (0.3%)	1 (1.0%)	14 (1.9%)	14 (2.1%)	5 (0.9%)
Vascular disorders						
Hypertension	1 (0.3%)	2 (0.6%)	2 (1.9%)	18 (2.5%)	18 (2.7%)	15 (2.8%)
Hypotension	2 (0.5%)	5 (1.4%)	6 (5.8%)	21 (2.9%)	21 (3.1%)	17 (3.2%)
Shock hemorrhagic	11 (3.0%)	8 (2.3%)	---	11 (1.5%)	11 (1.6%)	8 (1.5%)

9.12 Safety Discussion and Conclusions

The safety profile for vapreotide in EVB patients is derived primarily from pooled safety data from 4 randomized placebo-controlled EVB RCTs (VAP-14, VAP-02, VAP-06, and VAP-07; N=366 vapreotide, N=347 placebo) and one single-arm study (VAP-301; N=103 vapreotide). Results show that vapreotide is well tolerated in the targeted population:

- The incidences of treatment-emergent adverse events (AEs) were comparable in the vapreotide and placebo groups overall, both during study drug infusion over Days 1-5 and during follow-up over Days 6-42 and by system organ class (SOC). The most frequent AEs in the vapreotide and placebo groups, occurring in $\geq 5\%$ of patients, were pyrexia, upper gastrointestinal hemorrhage, flatulence, melena, hepatic encephalopathy, and headache.
- Serious adverse events (SAEs) occurred at similar rates in the vapreotide and placebo groups overall and during study drug infusion and follow-up and by SOC. As expected in this study population, the most frequent SAEs, occurring in $\geq 2\%$ of patients, were disease-related complications: upper gastrointestinal hemorrhage, melena, hepatic encephalopathy, and hemorrhagic shock.
- Deaths during the 42-day study period occurred at similar rates in the vapreotide and placebo groups (15.0% vs 16.4%) and due to similar causes, largely complications of bleeding and worsening of underlying liver disease.
- A review of infrequent AEs associated with the blood or lymphatic system (including pancytopenia, thrombocytopenia, and leukopenia); AEs potentially related to increases in pulmonary wedge pressure; and AEs associated with cardiotoxicity, including the potential for QTc prolongation concluded that there were no clear safety signals for vapreotide.

Safety data from the single-arm VAP-301 study were generally consistent with the data from the pooled EVB RCTs and revealed no safety signals. While the VAP-301 study and EVB RCTs had a comparable incidence of AEs, the VAP-301 study had a higher incidence of infections (19.4% vs 6.0%) and metabolic complications (hypokalemia, hypomagnesemia, metabolic acidosis: 22.3% vs 3.6%), which are expected complications in cirrhotic patients. A higher mortality rate during the follow-up period in the VAP-301 study (16.5% vs 8.5%) may have reflected the more complex disease etiology, particular an increased percentage of patients with combined alcoholism and viral hepatitis (27% vs 10%). Additionally, there were 6 patients in VAP-301 with HIV/AIDS, all of whom died on study. It is difficult to assess the significance of these differences due to the lack of a placebo control in VAP-301.

Importantly, the patient populations in the EVB studies, particularly VAP-301, are representative of patients in the general population of cirrhotic patients who require emergency treatment for acute variceal bleeding.

Safety of vapreotide is further confirmed by the 9-Study Database with 728 vapreotide-exposed patients. Including the investigator-initiated studies (All Studies Database), a total of 1,222

patients have been exposed to vapreotide, in varying indications, for up to a year, and with much larger doses without evidence of any unexpected adverse effects related to the use of vapreotide.

10 Benefits and Risks of Vapreotide

10.1 Vasoactive Therapy in EVB

Variceal bleeding associated with portal hypertension is a serious, life-threatening emergency, accounting for a higher mortality rate than for any other cause of upper gastrointestinal bleeding.

The control of bleeding achieved with early administration of vasoactive drugs is associated with important clinical benefits. For example, combination therapy for EVB with vasoactive agents and endoscopic intervention has been shown to reduce blood transfusion requirements during the critical 5-day period immediately following the index hemorrhage as compared with endoscopic therapy alone (Levacher 1995; Avgerinos 1997; Calès 2001). Additionally, there is evidence that adequate control of the initial hemorrhage and prevention of early rebleeding over 5 days may be correlated with improved 6-week survival (VAP-14; VAP-301; Moitinho 2001). Achieving initial control of bleeding in patients with EVB may also facilitate endoscopic procedures, and in particular, band ligation. Consensus recommendations specify that vasoactive drugs should be used systematically and as early as possible in patients with suspicion of variceal bleeding.

Despite the clinical evidence, no pharmacologic treatment is currently approved in the USA for this indication, and off-label use of a vasoactive agent has become standard practice. The availability of an approved drug for this indication would ensure:

- Efficacy and safety of the product have been established in the indicated population and at the labeled dose;
- Comprehensive labeling is available to provide standardized and accurate guidance regarding patient selection, dosing, and administration. This may be especially pertinent in local community hospitals where the availability of standardized, comprehensive drug labeling is important for physician training.
- An ongoing structured safety surveillance program, contributing to the current understanding regarding the risk-benefit profile of the product in this patient population.

Accordingly, Debiovision Inc. is seeking an indication for vapreotide as adjunctive therapy to endoscopic intervention for the control of acute esophageal bleeding from portal hypertension. Vapreotide has been designated an Orphan Drug for this indication.

10.2 Benefits of Vapreotide

The efficacy of vapreotide, as adjunctive therapy to endoscopic intervention for the control of acute esophageal bleeding as a result of portal hypertension, has been established in the pivotal VAP-14 study, with supporting information from VAP-301 and other EVB studies.

The VAP-14 study (Calès 2003) is recognized as a well-designed, well-controlled study (Bañares 2002; de Franchis 2004) that is based on criteria established by consensus guidelines

(de Franchis 1996; Grace 1998; Gracia-Tsao 2007). In VAP-14, vapreotide significantly increased the percentage of patients who achieved control of bleeding over 5 days, increased the percentage of patients with control of bleeding at endoscopy, and decreased the average number of blood units transfused during the initial 5 days following the index hemorrhage.

Supportive studies, including a pilot study (VAP-07) and two other placebo-controlled trials (VAP-06 and VAP-02) that were compromised due to serious executional problems, did not achieve statistically significant outcomes. Nonetheless, in a meta-analysis of the 4 vapreotide placebo-controlled trials, the odds ratio was 1.33 (95% CI: 0.92, 1.93) in favor of vapreotide.

The open-label VAP-301 study provides additional information regarding treatment with vapreotide in a contemporary USA setting. Accounting for several baseline differences between VAP-301 and VAP-14, the VAP-301 success rate and subgroup results show consistency with the clinical benefits observed in VAP-14.

This clinical experience provides substantial evidence that vapreotide, when administered prior to endoscopic intervention, is safe and effective for the treatment of acute variceal bleeding. Further, vapreotide can be administered immediately to all patients suspected of esophageal bleeding; treatment can be started even at home or during transfer to the hospital. This is important since about a quarter of deaths occur very early after bleeding onset (Laine 2005). In addition, vapreotide has no special requirements for storage or preparation.

10.3 Risks of Vapreotide

Vapreotide's safety profile has been characterized in clinical trials of patients with EVB and in other indications. The incidence and types of AEs and SAEs associated with vapreotide are comparable to those reported with placebo. In the EVB studies, the most frequently reported AEs for both vapreotide and placebo were pyrexia and upper GI hemorrhage. The most frequent SAEs were disease-related complications: upper gastrointestinal hemorrhage, melena, hepatic encephalopathy.

The 6-week mortality rate was comparable between the vapreotide and placebo groups in the controlled EVB studies (15% vs 16%). In the single-arm VAP-301 study, the mortality rate of 25% was numerically higher than previously seen in vapreotide studies, although the 95% CIs overlap. Compared with the EVB RCTs, VAP-301 showed increased rates of deaths due to infection/multiorgan failure, worsening of liver disease, and cardiac/cardiorespiratory arrest, all of which are expected complications in cirrhotic patients with upper gastrointestinal bleeding. The mortality rate in VAP-301 is consistent with 6-week mortality rates reported in the recent Cochrane Review of somatostatin analogs (mean of 19%, with a range of 3% - 38% in active acute EVB treatment groups) and other recent literature.

The overall safety profile of somatostatin analogs has been well established in over 20 years of use in other indications and the safety results observed with vapreotide are consistent with experience acquired with this class of vasoactive agents. The wide spectrum of pharmacological activity of somatostatin analogs has the potential to cause a variety of AEs, including biliary tract abnormalities, hypo- or hyperglycemia, hypothyroidism, gastrointestinal disorder, and cardiac

conduction abnormalities. However, no safety signals of this nature have been observed with 5-day exposure to vapreotide in patients with EVB administered the standard dosage regimen (ie, 50 µg/h), or with longer-term exposures in patients treated for other disease indications.

In summary, vapreotide has a favorable benefit/risk profile, with demonstrated efficacy and no clinically meaningful safety risks in patients with EVB.

11 Summary and Conclusion

Acute variceal bleeding due to portal hypertension is a serious and life-threatening medical emergency associated with high morbidity and mortality. Consensus guidelines endorse early treatment with vasoactive drugs for patients with EVB, but there are no drugs currently approved for this indication in the USA.

Vapreotide provides clinically meaningful benefits for patients with EVB, including control of bleeding over the critical first 5 days after the index hemorrhage. The efficacy of vapreotide, as adjunctive therapy to endoscopic intervention for the control of acute esophageal bleeding as a result of portal hypertension, has been established in VAP-14 and is supported by other clinical studies. Vapreotide has been shown to be well-tolerated, with AEs and SAEs similar to placebo. The clinical safety results support early administration of vapreotide in all patients suspected of variceal bleeding, an important advantage for the treatment of this life-threatening medical emergency.

Based on the overall favorable benefit/risk profile, the approval of vapreotide for treatment of EVB in cirrhotic patients is expected to provide important clinical benefits to these critically ill patients.

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Appendix 1 List of 45 Clinical Studies of Vaptotide Acetate

List of Studies Included in the Safety Analysis																	
Study Number	Indication	Study type	Vapreotide dose (mg)	Treatment Duration (Days)	Comparator	Patients enrolled	# of CRFs	Vapreotide					Comparator				
								Patients enrolled	Deaths	Withdrawals due to AEs	Number of Patients with SAEs	Number of SAEs	Patients enrolled	Deaths	Withdrawals due to AEs	Number of Patients with SAEs	Number of SAEs
VARICEAL BLEEDING STUDIES (EVb Studies)																	
DEB-96-VAP-14	VARICEAL BLEEDING IN CIRRHOSIS	DOUBL E-BLIND	1.2	5	PLACEBO	227	227	111	19	9	40	63	116	27	13	46	71
DEB-97-VAP-02	VARICEAL BLEEDING IN CIRRHOSIS	DOUBL E-BLIND	1.2	5	PLACEBO	136	136	70	9	10	20	34	66	6	6	21	39
DEB-01-VAP-07	VARICEAL BLEEDING IN CIRRHOSIS	DOUBL E-BLIND	1.2	5	PLACEBO	72	72	41	6	4	15	22	31	8	4	14	21
DEB-02-VAP-06	VARICEAL BLEEDING IN CIRRHOSIS	DOUBL E-BLIND	1.2	5	PLACEBO	278	278	144	22	10	49	97	134	19	7	53	98
DEBV-VAP/EVB-301	VARICEAL BLEEDING IN CIRRHOSIS	OPEN	1.2	5	.	103	103	103	26	6	36	57
SUBTOTAL						816	816	469	82*	39	160	273	347	60*	30	134	229
* Note : These numbers include 4 deaths not counted in Table 29; the 4 deaths occurred after the 42-Day study period.																	
OTHER STUDIES																	
DEB-92-VAP-02	NEUROENDOCRINE TUMORS/CARCINOID	OPEN	1.5	90 - 180	.	35	35	35	4	4	7	8
DEB-93-VAP-09	CROHN'S DISEASE	OPEN	1.5	28	.	22	22	22	0	4	4	4
DEB-95-VAP-02	ACROMEGALY	OPEN	1.2	21	.	15	15	15	0	0	0	0
DEB-98-VAP-06	PANCREATIC SURGERY	DOUBLE-BLIND	1.2	7	PLACEBO	376	376	187	0	7	74	168	189	7	6	82	151
SUBTOTAL						448	448	259	4	15	85	180	189	7	6	82	151
SUPPORTIVE STUDIES																	
DEB-86-VAP-01	ACROMEGALY	OPEN	0.25	1	.	10	0	10	0	0	0	0
DEB-86-VAP-02	SHEEHAN SYNDROME	OPEN	0.25	1	.	8	0	8	0	0	0	0
DEB-87-VAP-01	GI FISTULA	OPEN	1	8 - 21	.	52	52	52	0	0	0	0
DEB-87-VAP-02	PANCREAS CA	OPEN	1.5	MIN 60	.	18	15	18	0	0	0	0
DEB-87-VAP-03	NEUROENDOCRINE TUMORS/CARCINOID	OPEN	1.2	60- 1400	.	23	23	23	0	0	0	0

List of Studies Included in the Safety Analysis																	
Study Number	Indication	Study type	Vapreotide dose (mg)	Treatment Duration (Days)	Comparator	Patients enrolled	# of CRFs	Vapreotide					Comparator				
								Patients enrolled	Deaths	Withdrawals due to AEs	Number of Patients with SAEs	Number of SAEs	Patients enrolled	Deaths	Withdrawals due to AEs	Number of Patients with SAEs	Number of SAEs
DEB-87-VAP-04	PULMONARY CA	OPEN	1.2	20 - 69 S	.	4	4	4	0	0	0	0
DEB-87-VAP-05	CHONDROCARCINOMA	OPEN	1.2	84	.	3	3	3	0	0	0	0
DEB-88-VAP-01	AIDS ASSOCIATED DIARRHEA	OPEN	1.8	14 - 140	.	36	37	36	0	2	0	0
DEB-88-VAP-02	GASTRINOMA	OPEN	1.2	190	.	1	1	1	0	0	0	0
DEB-88-VAP-03	VIPOMA	OPEN	1.2	75	.	1	1	1	0	0	0	0
DEB-88-VAP-04	OTHER CA	OPEN	1.2	36 - 99	.	6	6	6	0	0	0	0
DEB-89-VAP-01	GI FISTULA	OPEN	1	8 - 21	.	27	26	27	1	2	2	3
DEB-89-VAP-02	PANCREAS CA	OPEN	1.5	30	.	21	0	21	0	0	0	0
DEB-89-VAP-03	NEUROENDOCRINE TUMORS/CARCINOID	OPEN	1.2	36 - 535	.	13	13	13	0	0	0	0
DEB-90-VAP-01	GI FISTULA	DOUBLE-BLIND	1	20	PLACEBO	34	34	20	2	2	2	4	14	1	3	3	3
DEB-91-VAP-04	ACROMEGALY	OPEN	1.5	7	.	11	11	11	0	0	0	0
DEB-91-VAP-05	ACROMEGALY	OPEN	1.5	10	.	9	0	9	0	0	0	0
DEB-91-VAP-06	ACROMEGALY	OPEN	1.2	12	.	3	0	3	0	0	0	0
DEB-91-VAP-10	PANCREAS CA	OPEN	6	60 - 223	.	14	11	14	0	0	0	0
DEB-91-VAP-11	PAINFUL SYNDROME	OPEN	1	3	.	3	0	3	0	0	0	0
DEB-91-VAP-12	NEUROENDOCRINE TUMORS/CARCINOID	OPEN	1.2	48 - 185	.	2	2	2	0	0	0	0
DEB-92-VAP-01	GI FISTULA	OPEN	1.5	20	.	19	19	19	4	3	6	7
DEB-92-VAP-03	AIDS ASSOCIATED DIARRHEA	OPEN-VAP/CONV	1.5	14 - 28	CONVENTIONAL	39	39	22	3	4	6	6	17	1	2	3	4
DEB-92-VAP-10	BREAST CA	OPEN	1	10	.	1	0	1	0	0	0	0
DEB-93-	ULCERATIVE COLITIS	OPEN	2	28	.	5	5	5	0	0	0	0

List of Studies Included in the Safety Analysis																	
Study Number	Indication	Study type	Vapreotide dose (mg)	Treatment Duration (Days)	Comparator	Patients enrolled	# of CRFs	Vapreotide					Comparator				
								Patients enrolled	Deaths	Withdrawals due to AEs	Number of Patients with SAEs	Number of SAEs	Patients enrolled	Deaths	Withdrawals due to AEs	Number of Patients with SAEs	Number of SAEs
VAP-11																	
DEB-93-VAP-13	PAIN RELATED TO HERPES	OPEN	1.5	7	.	12	12	12	0	0	0	0
DEB-93-VAP-14	POST-OPERATIVE PAIN	OPEN	1	5	.	14	14	14	0	0	0	0
DEB-93-VAP-16	POST-OPERATIVE PAIN	DOUBLE-BLIND	2	3	PLACEBO	41	41	21	0	0	0	0	20	0	0	0	0
DEB-93-VAP-18	MIGRAINE AND CLUSTER HEADACHE	OPEN	1.5	4 - 95	.	11	11	11	0	1	0	0
DEB-93-VAP-21	AIDS ASSOCIATED DIARRHEA	DOUBLE-BLIND	1.5	21	PLACEBO	14	0	8	1	1	2	2	6	0	1	3	5
DEB-93-VAP-22	POST-OPERATIVE PAIN	DOUBLE-BLIND	2	3	PLACEBO	58	58	29	0	0	0	0	29	0	0	0	
DEB-93-VAP-23	PROSTATE CA	OPEN	3	90 - 240	.	2	0	2	0	0	0	0
DEB-94-VAP-05	PROSTATE CA	OPEN	3	44 - 168	.	20	20	20	0	3	1	1
DEB-94-VAP-20	BREAST CA	OPEN	6	84	.	14	0	14	0	0	0	0
DEB-95-VAP-03	STABLE CIRRHOSIS	DOUBLE-BLIND	0.2	1	PLACEBO	16	16	8	0	0	0	0	8	0	0	0	
DEB-96-VAP-20	PROSTATE CA	OPEN	3	90- 1620	.	19	0	19	0	0	0	0
DEB-97-VAP-12	NEUROENDOCRINE TUMORS/CARCINOID	OPEN	0.01	1	.	4	0	4	0	0	0	0
SUBTOTAL						588	474	494	11	18	19	23	94	2	6	9	12
OVERALL TOTAL						1852	1738	1222	97	73	265	477	630	69	42	225	392