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APPLICATION NUMBER

21-007/SE7-006

21-039/SE7-006

Medical Review(s)

**Medical Review
Supplemental NDA (Traditional Approval)
NDA 21-007/006
NDA 21-039/006
(SE-7)**

Date Submitted: July 13, 2000
Date Received: July 14, 2000
Date Assigned: July 18, 2000
Date Completed: May 14, 2001

Applicant: Glaxo Wellcome Inc.
Five Moore Drive
Research Triangle Park, NC 27709

Drug: (3S)-tetrahydro-3-furyl N-((1S,2R)-3-(4-amino-N-isobutylbenzenesulfonamido)-1-benzyl-2-hydroxypropyl) carbamate

Generic: amprenavir

Trade: Agenerase®

Dosage forms: Capsules and Oral Solution

Indication: Treatment of HIV-1 infection in combination with other antiretroviral agents.

Related INDs: IND []

Related Documents: MO review of accelerated approval application, July 14, 1999
Stats review of accelerated approval application, March 29, 1999

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Table of Contents

	<u>Page</u>
Executive Summary	3
Recommendation	3
Additional Phase 4 Studies and Marketing Restrictions	3
Risk Communication to Patients and Healthcare Providers	3
Summary of Clinical Findings	3-9
Regulatory History/Milestones	3
Financial Disclosure	4
Overview of Clinical Program	4
Efficacy Summary	4
Safety Summary	6
Recommended Warnings	6
Safety of Agenerase in Relation to Other Protease Inhibitors	7
Unresolved Safety Issues	7
Dose Selection	7
Dose Modification Recommendations	7
Unresolved Dosing Issues	7
Special Populations	7
Foreign Marketing Experience	8
Review of Package Insert	8
Overall Assessment and Conclusions	9
APPENDIX 1: Review of Clinical Trial PROAB3001	10-14
APPENDIX 2: Review of Clinical Trial PROAB3006	15-21
APPENDIX 3: Review of Clinical Trial	22-24
APPENDIX 4: Review of Clinical Trial PROAB3004	25-26

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EXECUTIVE SUMMARY

This executive summary contains the Recommendation and the Summary of Clinical Findings for NDAs 21-007 and 21-039, Agenerase® (amprenavir capsules and oral solution, APV), for the treatment of HIV-1 infection in combination with other antiretroviral agents.

- **Recommendation**

Based on a review of the data submitted by GlaxoSmithKline in support of traditional approval of NDAs 21-007 and 21-039, it is recommended that this application be approved for use in combination with other antiretroviral agents for the treatment of HIV-1 infection.

The approval recommendation is based on demonstration of antiviral activity in treatment-naïve and nucleoside-experienced, but protease inhibitor (PI)-naïve, HIV-infected adults. However, the high frequency of discontinuations early after initiation of APV treatment due primarily to non-serious gastrointestinal-related adverse events, the pill burden (eight capsules BID), the inferior anti-HIV activity compared to indinavir among PI-naïve patients, and the lack of efficacy data in PI-experienced patients represent limitations to APV's utility.

There were no new safety issues identified in this review compared to the profile described in the review of the accelerated approval application. The safety profile in children and adults is essentially similar.

- **Phase 4 Studies and Marketing Restrictions**

The applicant agreed to 11 Phase 4 commitments at the time the application for accelerated approval was approved. The applicant will be reminded of three outstanding commitments in the approving letter for this application. There are no recommendations for new Phase 4 studies or marketing restrictions.

- **Risk Communication to Patients and Healthcare Professionals**

Three statements regarding points to consider when initiating AGENERASE were added to the Indications and Usage section of the label: (1) in a study of PI-naïve patients, amprenavir was significantly less effective than indinavir, (2) there are no data on response to treatment with amprenavir in PI-experienced patients, and (3) mild to moderate gastrointestinal adverse events led to significant numbers of discontinuations during the first 12 weeks of APV therapy.

SUMMARY OF CLINICAL FINDINGS

- **Regulatory History/Milestones**

The initial IND for APV (originally designated as 141W94) was submitted in January 1995. The NDA was submitted in October 1998. Approval of the NDA under 21CFR Subpart H (accelerated approval regulations) occurred on April 15, 1999. Subsequent to approval the applicant completed the two primary clinical trials that supported accelerated approval and has submitted the final reports in support of conversion to traditional approval.

- **Financial Disclosure**

Pursuant to 21 CFR 54.2(e) the financial certification statement provided by the applicant was reviewed.

Site-by-site analyses demonstrated that none of the sites biased the primary results of the studies.

- **Overview of Clinical Program**

Trade name: Agenerase®
Class: HIV-1 protease inhibitor
Formulation: Capsules and Oral Solution
Dosage: 2400 mg/day (adults and adolescents >12 years of age)
22.5 mg/kg BID or 17 mg/kg TID (children 4 years of age and older)

The applicant requested traditional approval for Agenerase® (amprenavir, APV), a protease inhibitor for the treatment of HIV-1 infection, when used in combination with other antiretroviral agents in adult and pediatric patients. In support of traditional approval, the applicant submitted 48-week safety and efficacy results from two phase 3 studies in adults, data from two pediatric studies, and six phase 1 and phase 2 supportive studies¹ in which patients were exposed to APV.

Study PROAB3001 was a randomized, double-blind study that evaluated the efficacy and safety of APV 1200 mg BID versus placebo (PLA) when used in combination with zidovudine (ZDV) 300 mg BID and lamivudine (3TC) 150 mg BID in 232 relatively healthy HIV-infected, antiretroviral naïve patients. Study PROAB3006 was an open-label, 48-week equivalence-design study that compared APV to indinavir (IDV) on a background of nucleoside analogues in treatment-experienced, but PI-naïve adults.

The applicant also submitted data from two studies conducted in PI-naïve and -experienced pediatric patients, and PROAB3004.

- **Efficacy Summary**

The final results of the two principal efficacy studies support traditional approval of APV because both demonstrated that APV has antiviral activity when used as a component of an antiretroviral regimen.

Study PROAB3001 demonstrated that addition of APV to the combination of ZDV/3TC resulted in superior antiviral activity compared to ZDV/3TC in reducing plasma HIV RNA to <400 c/ml after 24 weeks of treatment, 53% versus 11%, respectively. Through 48 weeks of treatment, 41% of patients assigned to APV/ZDV/3TC achieved HIV RNA <400 c/mL. Because most patients assigned to the ZDV/3TC discontinued or changed their antiretroviral therapy by week 24, comparisons of antiviral activity between the two treatment arms after week 24 are of little relevance.

The results were not unexpected as three drug regimens have generally produced superior antiviral activity compare to two drug regimens. Of concern, however, is the rate of success for the APV arm, 40%, which historically is low for an initial PI-based treatment regimen in HIV-infected individuals.

In study PROAB3006, the population had been pretreated with nucleoside analogues, but was naïve to protease inhibitors. In this population, only 30% of APV-treated patients achieved HIV RNA <400 c/mL at week 48; this was significantly lower than patients treated with IDV, 49% (95% confidence interval 8%, -24%), (p<0.05). In addition, the IDV arm produced a significantly greater

¹ The six supportive trials were PROA2001, PROA2003, CNA2004, CNAB2006, CNA2007, and PRO30010. Preliminary data from these studies were reviewed during consideration of the accelerated approval application. At that time, as now, it was not possible to assess APV's contribution to efficacy because the studies were small, often single-arm studies in which APV was generally administered with other antiretroviral agents. A review of the safety data from these studies did not raise any new safety signals and demonstrated an overall similar adverse event profile as described in the larger phase 3 studies.

mean increase in CD4 cell counts compared to APV, +144 versus +97, respectively; the clinical relevance of this difference is unknown.

A number of possibilities for APV's poor performance in this study were evaluated:

- It was possible that unbalance in the background nucleoside analogues might have limited the ability to specifically attribute any observed differences to one of the randomized PIs. This did not seem to be the case since the distribution of background nucleoside analogues was similar between the treatment arms and there did not appear to be a difference in genotypic or phenotypic resistance profiles among patients who experienced virologic failure.
- It was possible that the high early discontinuation rate due to non-serious adverse events from the APV arm affected the assessment of efficacy. This appeared to be the case when the week 24 data were reviewed, however, by the end of the 48-week study period discontinuations due to adverse events had equalized between the treatment arms.
- It was possible that genotypic and/or phenotypic resistance to APV may have led to more treatment failures in that arm. At baseline, there was no difference in the proportion of patients with genotypic mutations or phenotypic susceptibility to APV or IDV; primarily patients demonstrated genotypic and phenotypic resistance to nucleoside analogues. Genotypic and phenotypic analyses were performed on HIV-1 isolates from a subset of patients enrolled in the trial. Genotypic analysis of HIV-1 isolates from 48 patients failing APV and NRTI therapy demonstrated either single or different combinations of protease mutations V32I, M46I/L, I47V, I50V, I54L/M and I84V in 31 patients. Most of these mutations were also observed in APV resistant isolates selected in vitro.

Phenotypic analysis of HIV-1 isolates from 21 patients treated with APV in combination identified isolates from 15 patients that exhibited a 4- to 17-fold decrease in susceptibility to APV in vitro compared to wild-type virus.

Overall, however, there appeared to be similar rates of acquisition of key protease mutations between the two treatment arms.

- It was possible that the therapeutic failure of APV may have also been due to inadequate drug exposure and/or lack of adherence; insufficient pharmacokinetic/pharmacodynamic and no compliance data were submitted to determine if these factors were responsible for the inferiority of APV compared to IDV.

In conclusion, the efficacy results from study PROB3006 demonstrate that in nucleoside analogue-experienced, PI-naïve, patients APV was less efficacious than indinavir. The response to therapy with APV among PI-experienced patients has not been evaluated, except in a very small number of children. Updated antiviral activity data from two pediatric studies demonstrated that APV is active, but less so in patients who had received previous treatment with protease inhibitors.

• **Safety Summary**

The safety of APV has been adequately assessed. The application contained safety data from over 4,000 patients exposed to APV in clinical trials and expanded access programs. In addition, multiple post-marketing safety reports were reviewed. There were no new safety problems identified during the review of the traditional approval application or the post-marketing reports.

The most common clinical adverse events leading to APV discontinuation included gastrointestinal events (abdominal pain, diarrhea, gaseous symptoms, nausea and vomiting) that occurred primarily during the first 12 weeks of therapy. Skin rashes and perioral paresthesia were the second most common reasons for discontinuations.

Overall, rash (all grades), with and without systemic symptoms, occurred in approximately 28% of clinical trials patients (234/840). Of these, 4% were graded as severe (grade 3/4) and there were two cases of Stevens-Johnson syndrome (representing 1% of all rashes). There have been additional post-marketing reports of rash, with and without systemic symptoms as well as reports of Stevens-Johnson syndrome. Therefore, the WARNING about Stevens-Johnson syndrome will be retained in the APV label.

Other commonly occurring adverse events included depression and paresthesias (oral and peripheral). Elevated transaminases, elevated triglycerides, elevated glucose levels and de novo diabetes, and cholesterol, were common APV-related laboratory abnormalities.

The frequency of hypertriglyceridemia, hypercholesterolemia, hyperglycemia, and hemolytic anemia among APV-treated patients were similar to rates reported for other PI. Some patients treated with APV experienced buffalo hump, central adiposity, peripheral fat wasting or other unspecified lipodystrophy. Although there were fewer cases among patients treated with APV than IDV, the difference was not sufficient to justify a claim that APV has fat redistribution-sparing effects.

Post-marketing adverse events appear to be similar to those identified in the review of the accelerated and traditional approval applications. The adverse event profile between adult and pediatric patients also appears to be similar. There were no apparent propylene glycol-related events among pediatric patients treated with the oral solution formulation of APV.

Early discontinuations due to non-serious gastrointestinal events likely limited the accurate assessment of APVs' antiviral activity since patients who discontinued due to adverse events were classified as treatment failures in the efficacy analyses. Unfortunately, these events likely truly limit APVs' general use since many patients do not appear willing to tolerate bothersome adverse events.

- **Recommended Warnings**

There are no new recommended WARNINGS. All information in the current WARNINGS section will be retained, as there were no data submitted to suggest that they should be revised or reduced.

- **Safety of Agenerase® in Relation to Other Protease Inhibitors**

Hypertriglyceridemia, hypercholesterolemia, hyperglycemia, diabetes mellitus, hemolytic anemia, increased bleeding in hemophiliacs have been identified as related to treatment with protease inhibitors. These metabolic abnormalities have been reported in patients treated with APV.

- **Unresolved Safety Issues**

There are no unresolved safety concerns at this time.

- **Dose Selection**

Dose-escalation, pharmacokinetic studies and pharmacodynamic modeling were submitted and reviewed during consideration of the accelerated approval application. The 1200 mg BID dose was chosen because a greater proportion of subjects receiving this dose were expected have trough concentrations of amprenavir at or above the EC_{50} , compared to lower doses. During the review of the accelerated approval application, the medical and biopharmaceutical reviewers concluded that higher doses were not considered because large increments of dose would be

required to produce small decreases in circulating HIV RNA. With the current limitations of the current formulation, administration of larger doses of APV was not considered feasible. The applicant is currently investigating the safety and activity of APV co-administered with pharmacokinetic enhancing doses of ritonavir.

APV must be administered with food, but not with a high-fat meal. The total daily dose of APV (2400 mg) requires patients to ingest a total of 16 large capsules per day (eight twice per day).

- **Dose Modification Recommendations**

Dose reductions are recommended for patients with hepatic insufficiency and those receiving certain co-administered drugs. These recommendations are outlined in the current label and will be retained. No new recommended dose modifications were submitted in this application.

- **Unresolved Dosing Issues**

There are no data on dosing protease inhibitor-experienced patients.

- **Special Populations**

Data from the clinical trials were analyzed to assess potential differences in responses between males and females, and Caucasians and non-whites; there were no apparent differences in antiviral responses or safety among these analyses.

Geriatrics

The Agenerase® label contains information for elderly patients consistent with 21 CFR 201.57. No new safety or efficacy information from elderly patients was submitted in this application.

Pediatrics

Dosing instructions for pediatric patients was established during the accelerated approval review and provided in the currently approved label. The current recommended dose of APV oral solution is 22.5 mg/kg BID or 17 mg/kg TID per day for patients 4-12 years of age or 13-16 years of age who were <50 kg. For all pediatric populations the maximum daily dose of APV is 2800 mg/day. APV oral solution is contraindicated in infants and children below the age of 4 years due to the potential toxicity from the excipient propylene glycol.

Updated data from two ongoing clinical studies

- **Foreign Marketing Experience**

Agenerase® Capsules and Oral Solution are approved for use in patients three years of age and older in the following countries: Switzerland, Israel, Japan, Brazil, Mexico, Uruguay, Chile, Argentina, Columbia, Ghana, Madagascar, Malawi, and the European Union.

- **Review of Package Insert**

Based on this review, the APV label underwent the following revisions:

- The indication was revised to read "AGENERASE (amprenavir) in combination with other antiretroviral agents is indicated for the treatment of HIV-1 infection."
- Statements were added to the INDICATION and USAGE section to identify important clinical limitations that clinicians and patients should consider when considering initiating therapy with APV.
- Because study PROAB3001 utilized a control arm no longer considered acceptable, the presentation was revised to provide only a brief description of results.
- The description of study PROAB3006 was revised to highlight the antiviral and immunologic differences between APV and indinavir identified upon review of the 48-week data.
- The frequencies of adverse events were updated in the ADVERSE REACTIONS section.
- Information related to genotypic/phenotypic resistance to APV was added to the MICROBIOLOGY section.
- The Pediatric Use section was revised to reflect the larger number of pediatric patients studied.

On May 11, 2001, the applicant submitted labeling that contained all the agreed upon revisions.

OVERALL ASSESSMENT AND CONCLUSIONS

The results of the trials reviewed in this application demonstrate that APV has antiviral activity; this was best demonstrated by the results of study PROAB3001. Inferior long-term antiviral efficacy of APV compared to IDV, the high frequency of non-serious dose-limiting gastrointestinal events, and the lack of information on the response to treatment with APV among PI-experienced patients represent important clinical limitations to APV's first-line use. However, APV represents another therapeutic option and there are likely patients who would benefit from its use, although data in this application do not permit identification of specific subpopulations. Co-administration of APV with ritonavir may represent a methodology for reducing the pill burden and enhancing activity; we await such data. Therefore this application should be approved to allow continued availability of APV to HIV-infected patients 4 years of age and older.

/s/

Russell Fleischer, PA-C, MPH
Senior Clinical Analyst

Concurrence: -
HFD-530/ActgDir/Birnkrant
HFD-530/MTL/Cvetkovich

CC:
HFD-530/NDAs 21-007, 21-039
HFD-530/Division File
HFD-725/Stats/Bhore/Soon
HFD-530/Micro/Lmishra/ORear
HFD-530/BioPharm/DiGiacinto/Reynolds

APPENDIX 1

Clinical Trial PROAB3001

"A Phase III Trial to Evaluate the Safety and Antiviral Efficacy of 141W94 in Combination with RETROVIR and EPIVIR compared to RETROVIR and EPIVIR Alone in Patients with HIV Infection."

Twenty-four-week data from this study supported accelerated approval of amprenavir (APV). For a detailed description and discussion of the 24-week data, please refer to Dr. John Martin's Medical and Dr. Greg Soon's Statistical reviews. The applicant has submitted the final study report to support traditional approval.

Design

Study PROAB3001 was a randomized, double-blind phase 3 study that evaluated the efficacy and safety of APV 1200 mg BID versus placebo when used in combination with zidovudine (ZDV) 300 mg BID and lamivudine (3TC) 150 mg BID in 232 HIV-infected, antiretroviral naïve patients. Patients were stratified based on baseline HIV RNA levels: $\geq 10,000$ to $30,000$, $>30,000$ to $100,000$, and $>100,000$ c/mL.

Randomized therapy was to continue until all subjects completed 48 weeks unless a protocol-defined switch criterion was met, defined as two consecutive (within 3 weeks) plasma levels of HIV RNA ≥ 400 copies/ml at week 16 or thereafter, or progression to CDC Class C event after four weeks on study. Patients who met a switch criterion could be treated with one of six options: (1) continue randomized therapy; (2) switch to open-label APV; (3) add abacavir (ABC); (4) change nucleoside RT inhibitor(s); (5) add another approved protease inhibitor; (6) change to any other approved protease inhibitor; or (7) discontinue from the study.

Study Population and Patient Disposition

A total of 232 patients were enrolled and 221 received study drug. Patients were predominantly male (89%), Caucasian (75%), median 35 years of age (range 16 to 62) with a median plasma HIV RNA of $4.68 \log_{10}$ c/mL and a median CD4 cell count of 424 cells/mm³.

Eighty-nine percent of PLA- and 52% of APV-treated patients discontinued randomized therapy. The primary reasons for discontinuation from the APV arm were adverse events (31%) and virologic failure (24%). Eighty-one percent of patients assigned to the ZDV/3TC arm discontinued their assigned treatment due to virologic failure (81%).

Review of Efficacy

Please refer to Dr. Bhoré's statistical review for a comprehensive analysis of the final efficacy results.

The primary efficacy endpoint was the proportion of subjects having <400 HIV RNA c/ml (assay) at 48 weeks who did not progress to a CDC Class C event or death. The proportion of patients with HIV RNA <50 c/mL was a secondary endpoint. Virologic responses through week 48 are presented graphically in Figure 1. Antiviral responses at weeks 24 and 48 are presented in tabular form in Table 1.

Figure 1

Virologic Response Through Week 48, PROAB3001

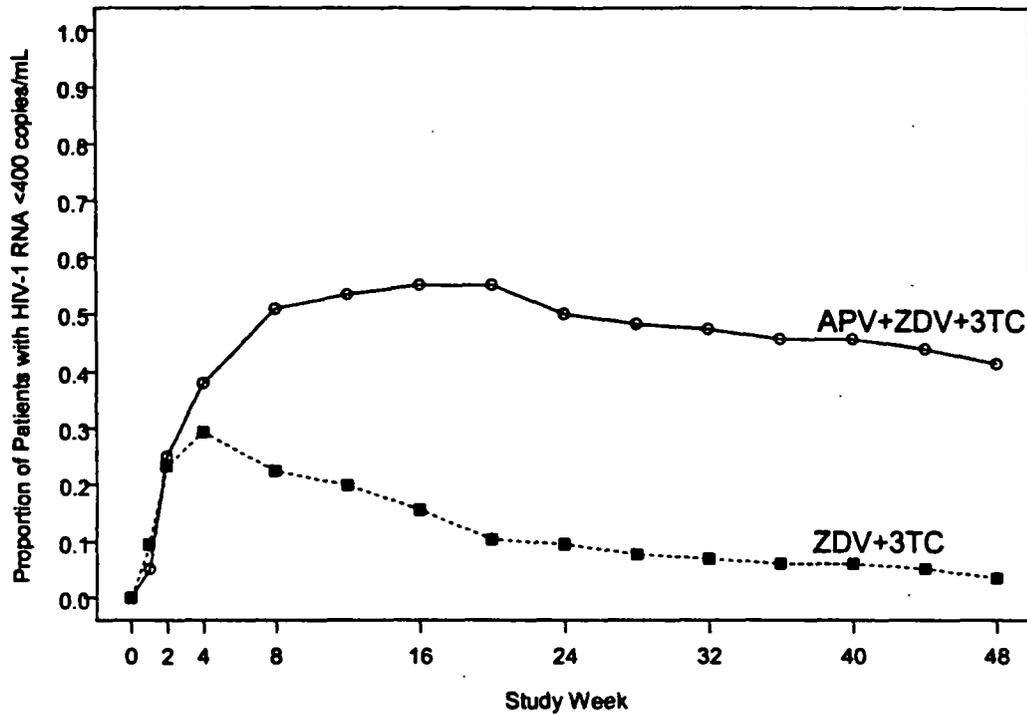


Table 1. Summary of week 24 and 48 antiviral responses

Treatment Arm	24 Weeks		48 Weeks	
	<400 c/mL	<50 c/mL	<400 c/mL	<50 c/mL
APV+ZDV+3TC (n=116)	53%	47%	41%	34%
ZDV+3TC (n=116)	13%	4%	3%	1%

Because of the high rates of discontinuations and switching of antiretroviral therapy among patients assigned to the ZDV/3TC arm, the antiviral response beyond week 24 was not reliable.

Comment: The data demonstrate that APV has antiviral activity when added to a background of two nucleoside analogues.

A review of antiviral response by baseline HIV RNA strata showed that 51% (19/37), 42% (23/55), and 25% (6/24) of patients who entered the study with HIV RNA $\geq 10,000$ to 30,000, $>30,000$, and $>100,000$ c/mL, respectively, had HIV RNA <400 c/mL at week 48.

Comment: Although the numbers are small, these results suggest that APV may be less efficacious in patients with viral load levels $>100,000$ c/mL.

There were 87 patients who switched from randomized PLA to a regimen containing open-label APV. There was a relatively early response evidenced by approximately 60% of patients achieving HIV RNA <400 c/mL by week 4 following the switch to APV. However, by weeks 24 and 48, the response diminished: 54% were <400 c/mL at week 24 and only 21% were <400 c/mL at week 48. Of note, 80/87 of the patients who added APV also added abacavir plus at least one other antiretroviral agent.

Comment: Because the majority of patients added more than one new antiretroviral agent it was not possible to directly assess the contribution of APV to any subsequent antiviral responses.

Review of Safety

The review of safety is based on 221 patients who received at least one dose of study medication.

- **Deaths and Non Fatal Serious Adverse Events**

No deaths occurred in this study.

APV-related serious adverse events included rash, elevated ALT/AST, hypertriglyceridemia, hyperglycemia, depression, neutropenia, anemia, vomiting and shortness of breath. Most of these events occurred early in the study and were described in the review of the accelerated approval application.

Comment: The serious adverse events are consistent with the adverse event profile previously described for APV.

- **Adverse Events Leading to Study Discontinuation**

A total of 21 APV-treated patients (19%) discontinued study medication due to adverse events. The APV-related events leading to discontinuation were gastrointestinal (abdominal pain, nausea, vomiting, diarrhea) and rash/pruritis; most events were grade 1 and 2 in severity.

Comment: Early occurrence of non-serious gastrointestinal events and rash leading to medication discontinuation was noted in the previous review of 24-week data. Discontinuations due to events graded as mild to moderate indicate these were distressing enough to cause discontinuation of APV therapy.

- **Common Adverse Clinical and Laboratory Events**

Selected treatment-emergent adverse events that occurred with significantly more frequency in the APV treatment group (regardless of relationship to study drug) are summarized in Table 2.

Table 2. Selected adverse events

Event	APV (N=113)	PLA (N=109)
Nausea	74%	50%
Vomiting	34%	17%
Diarrhea/loose stools	39%	35%
Gaseous symptoms	33%	43%

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Paresthesia		
Oral/perioral	26%	6%
Peripheral	10%	4%
Rash	27%	6%
Depressive/mood disorders	16%	4%

Comment: There were no appreciable differences in the frequency of adverse events reported in the accelerated approval application and the data reviewed in this final study report.

Selected laboratory abnormalities related to treatment with APV are presented in Table 4.

Table 3. Selected laboratory abnormalities

Parameter	APV (n=111)	PLA (n=108)
↑ Glucose (all grades)	45%	31%
Grade 3&4	<1%	<1%
↑ Triglycerides (all grades)	41%	27%
Grade 3&4	-	<1%
↑ Cholesterol (all grades)	7%	3%
Grade 3&4	-	-

Source: Table 87.

There were no appreciable differences between treatment groups with respect to elevations of transaminase or bilirubin levels, reductions in white blood cell counts, platelets, albumin, potassium or sodium levels.

Comment: The rates of elevated glucose and triglyceride levels are higher in the APV group. This was not unexpected since all the currently approved protease inhibitors, including APV, have been shown to elevate these parameters to varying degrees.

- **Safety Events of Special Interest**

Although a causal relationship has not yet been fully established, hypertriglyceridemia, hypercholesterolemia, hyperglycemia, diabetes mellitus, hemolytic anemia, increased bleeding in hemophiliacs and fat redistribution syndrome have been identified among patients treated with protease inhibitors and, therefore, would likely occur in patients treated with APV.

Seventy-nine patients who received APV experienced elevated triglyceride levels in either the randomized or open-label phase; the majority of which were grade 1-2 elevations. Only three patients experienced a grade 3-4 elevation. No patient discontinued the study due to elevated triglycerides.

No patients treated with APV experienced greater than grade 2 hypercholesterolemia. Four diabetics were enrolled, two in each treatment group. One diabetic in the APV arm maintained normal glucose levels throughout the study while the other required treatment with insulin for consistently elevated glucose levels. One diabetic originally assigned to the ZDV/3TC group experienced grade 4 glucose levels after switching to APV.

One patient in the APV arm experienced hemolytic anemia and was discontinued from the study.

No hemophiliacs were enrolled in the study.

One patient developed a "buffalo hump" 139 days after initiating APV in the open-label phase of the study.

Comment: In the cases described above, elevations in triglycerides and glucose and development of a buffalo hump were temporally related to APV. Exposure to APV results in similar types and frequencies of metabolic abnormalities as other members of the protease inhibitor class.

- **Overall Assessment**

The results demonstrated that APV, when administered in combination with ZDV/3TC, provided additional antiviral activity compared to ZDV/3TC alone in a population of relatively healthy, treatment-naïve, HIV-1 infected adults. Although the study demonstrated superior activity, this was not surprising given that PI-containing regimen was compared to a dual nucleoside combination. The rate of antiviral suppression in the APV arm was lower than expected for an initial protease inhibitor-based regimen.

No new safety concerns were identified during the review of the final study report reflecting data of at least 48 weeks duration. The primary and most important APV-related toxicities included gastrointestinal events (nausea, vomiting, diarrhea), rash, hyperglycemia, hypertriglyceridemia, paresthesias (predominantly oral/perioral), psychiatric events (depressive and mood disorders), and elevations of liver enzymes. These toxicities are described in the current APV label and will be retained and updated.

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APPENDIX 2

Clinical Trial PROAB3006

"A Phase 3 Trial to Compare the Safety and Antiviral Efficacy of 141W94 with Indinavir in Combination with Nucleoside Reverse Transcriptase Inhibitor (NRTI) Therapy in NRTI Experienced, Protease Inhibitor (PI) Naive HIV-1 Infected Patients."

The 24-week data from this study was submitted in support of accelerated approval of amprenavir (APV). For a detailed description and discussion of the interim data, please refer to Dr. John Martin's Medical and Dr. Greg Soon's Statistical reviews. The applicant submitted the final study report to support traditional approval.

Design

This was a randomized, open-label, multicenter, phase 3 study that compared the efficacy and safety of amprenavir (APV) with indinavir (IDV) when used in combination with NRTIs in 504 HIV-infected, NRTI-experienced adult patients. Patients were randomized 1:1 to receive APV (1200 mg BID) or IDV (800 mg TID) on a background of NRTIs. Patients were stratified by HIV RNA (≥ 400 -10000, $>10,000$ -100,000, $>100,000$ c/ml) and according to whether at least one NRTI was changed at entry.

Study Population and Disposition

There were 504 patients enrolled (254 to APV and 250 to IDV); 486 were treated. Patients were a median of 37 years of age (range 20 to 71), predominantly male (80%) and Caucasian (72%). At entry, patients had a median baseline HIV RNA of $3.92 \log_{10}$ c/ml (and a median CD4 cell count of 400 cells/mm³). The disposition of patients at the end of the study is summarized in Table 1.

Table 1. Patient disposition through week 48 by treatment group, number of patients

	APV	IDV
Number randomized	254	250
Number treated	245	241
Number (%) discontinued randomized therapy	125	104
Reason for discontinuation		
Adverse event	41	31
Met switch criteria ^a	21	12
Consent withdrawn	8	6
Non-compliance	4	4
Lost to follow-up	15	9
Protocol violation	1	-
Pregnancy	1	3
Other	3	2

Source: Table 3 and Supporting Table 4, and review of individual case report forms.

a. Failure to achieve a reduction from baseline in HIV-1 RNA $\geq 0.7 \log_{10}$ by week 8 or if HIV-1 RNA ≥ 400 c/mL at any visit from week 16 onwards.

Comment: A disproportionate number of discontinuations from the APV arm due to adverse events occurred during the first 12 weeks of the study. During the second half of the study, more patients discontinued from the IDV arm primarily due to renal complications, which is consistent with long-term exposure to IDV.

Review of Efficacy

The primary endpoint for the study was the proportion of patients with HIV RNA levels <400 c/mL, and who had not progressed to a new CDC Category C event or death.

Other analyses evaluated the proportion of subjects with plasma HIV RNA <50 c/mL, disease progression, and HIV-RT and PI genotype and phenotype evaluations. Safety evaluation included adverse events and clinical laboratory values.

For a detailed assessment of the statistical analyses of efficacy, please see Dr. Bhoré's Statistical Review. The virologic response and results of the outcomes of randomized treatment are presented in Figure 1 and Table 2.

Figure 1.

Virologic Response Through Week 48, PROAB3006

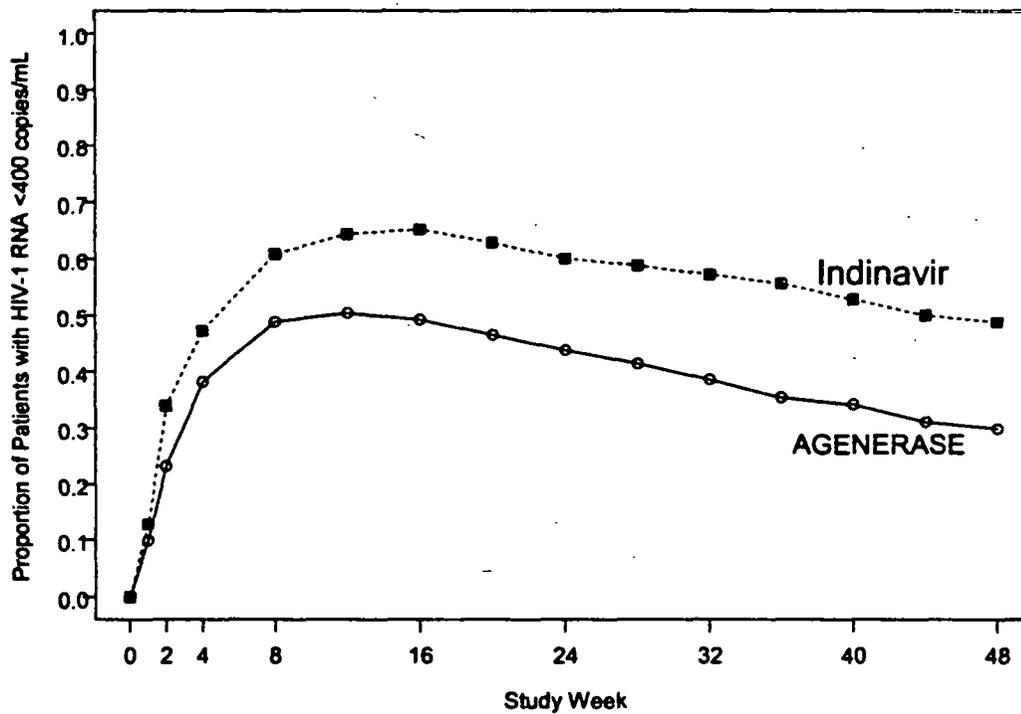


Table 2. Outcomes of randomized patients through week 48

Week 48 Status	APV (N=254)	IDV (N=250)
Responder ^a	30%	49%
Virologic failure ^b	38%	26%
Discontinued due to adverse events ^c	16%	12%
Discontinued due to other reasons ^d	16%	13%

a. Achieved virologic response (two consecutive viral load <400 c/mL and maintained it at week 24 and 48).

- b. Includes viral rebound and failure to achieve confirmed HIV RNA <400 c/mL at weeks 24 and 48.
- c. Classified as treatment failures in the analysis.
- d. Includes loss to follow up, consent withdrawn, non-compliance, pregnancy, other reasons for withdrawals, and those who never initiated treatment.

The difference in the proportion of those with HIV <400 c/ml at 48 weeks (19%) is statistically significant in favor of IDV, 95% CI (-27%, -10%) (p<0.05).

The main reason for virologic failure was rebound of viral load following suppression to <400 c/mL; there were more patients in the APV arm who failed for this reason than in the IDV arm, 25% versus 19%, respectively. It is notable that twice as many patients in the APV arm failed to achieve HIV RNA <400 c/mL, 4% versus 2% in the IDV arm.

Assessment of the proportions of patients with HIV RNA <50 c/mL could not be accurately assessed because samples were not evaluated until week 16 of the study.

Comment: Treatment with APV in nucleoside analogue-experienced, but PI-naïve, patients was significantly less effective compared to treatment with IDV in this patient population. The high early rate of discontinuations from the APV arm due to adverse events, 16% versus 8%, appeared to be at least partially responsible for the lower response rate in the APV arm at week 24. In the analysis of the 48-week data, however, there were significantly more patients who had achieved and subsequently lost virologic response in the APV arm. There were too few patients with baseline HIV RNA >100,000 c/mL (20 per treatment arm) to confidently assess antiviral response in this group of patients.

At baseline, there was no difference in the proportion of patients with genotypic mutations or phenotypic susceptibility to APV or IDV; primarily patients demonstrated genotypic and phenotypic resistance to nucleoside analogues. Genotypic and phenotypic analyses were performed on HIV-1 isolates from a subset of patients enrolled in the trial. Genotypic analysis of HIV-1 isolates from 48 patients failing APV and NRTI therapy demonstrated either single or different combinations of protease mutations V32I, M46I/L, I47V, I50V, I54L/M and I84V in 31 patients. Most of these mutations were also observed in APV resistant isolates selected in vitro.

Phenotypic analysis of HIV-1 isolates from 21 patients treated with APV in combination identified isolates from 15 patients that exhibited a 4- to 17-fold decrease in susceptibility to APV in vitro compared to wild-type virus.

Comment: Overall, there appeared to be similar rates of acquisition of key protease mutations between the two treatment arms.

The median changes from baseline in CD4 cell counts were +42 cells/mm³ (APV) and +88 cells/mm³ (IDV) at week 24, and at week 48, the median change was +97 cells/mm³ and +144 cells/mm³ in the two treatment arms, respectively. These differences were statistically significant.

Comment: APV produced an inferior immunologic response as measured by increases in CD4 cell counts from baseline. Sustained differences in CD4 cell counts of this magnitude may be clinically significant.

There were three APV-treated patients and six IDV-treated patients who experienced a CDC Category C event. In the APV arm the events included recurrent pneumonia, pulmonary mycobacterium tuberculosis and Pneumocystis carinii pneumonia. The events in the IDV arm included immunoblastic lymphoma (2), esophageal candidiasis, Kaposi's sarcoma, disseminated histoplasmosis and HIV encephalopathy.

Comment: There were too few clinical events to assess the impact of the two treatments on disease progression.

The applicant raised a number of possible reasons that could have compromised the overall comparison of efficacy: the open-label design, the choice of background NRTI's, the provision of real-time viral load results to investigators, and discontinuations due to mild/moderate intolerance to APV.

Comment: An open label design is inherently risky because patients and clinicians are aware of treatment assignments and may be influenced by adverse events and apparent lack of efficacy. The applicant was advised to blind the APV-IDV comparison.

The choice of background NRTIs was equally distributed between the treatment arms, as was the presence at baseline and end of treatment genotypic mutations and phenotypic resistance.

The provision of real-time viral load is consistent with current medical practice and likely guided management of patients who were receiving apparently failing therapy. Thus, it is not clear how the applicant determined that this may have compromised the analyses of efficacy.

Discontinuations due to adverse events were classified as treatment failures in the analyses, which may have underestimated APVs' antiviral activity at week 24. However, by the end of the study the discontinuation rates due to adverse events were similar between the treatment arms. Thus, the high discontinuation rate due to non-serious adverse events demonstrated that APV was difficult to tolerate, and that many patients opted to stop APV rather than continue to experience toxicities.

Two additional possibility for therapeutic failure of APV was investigated, inadequate drug exposure and/or lack of adherence; insufficient pharmacokinetic/pharmacodynamic and no compliance data were submitted to determine if these factors were responsible for the inferiority of APV compared to IDV.

Review of Safety

The review of safety includes information on 486 patients who received at least one dose of study medication.

• Deaths

There were two deaths in this study.

Patient #2581 was a 32 year-old Black female with a history of asthma and pulmonary hypertension at entry who died shortly thereafter due to pulmonary hypertension. This death did not appear to be drug-related.

Patient #6302 was a 31 year old male treated with IDV for approximately 5 months. Eight months after his last dose of study medication the patient died due to end stage AIDS encephalopathy. This death was also not determined to be drug-related.

• Non-Fatal Serious Adverse Events

Serious adverse events occurred in 43 and 47 APV and IDV recipients, respectively. The types of events and their frequencies were similar between treatment groups, except for psychiatric-related events among six APV recipients (primarily exacerbation of pre-existing depression with and without suicidal ideation, and alcohol and drug abuse) versus 2 IDV

recipients (homicidal/suicidal ideation and drug abuse). APV-related serious adverse events included rash, convulsions, syncope, and abnormalities of liver function. There were no cases of Stevens-Johnson syndrome reported in this study.

- **Discontinuations due to Adverse Events**

Similar proportions of patients discontinued due to adverse events, 16% from the APV arm and 12% from the IDV arm. Discontinuations from the APV arm were due primarily to mild to moderate in severity gastrointestinal events including nausea, vomiting, diarrhea, and abdominal pain; the majority of discontinuations occurred during the first 12 weeks of APV therapy. Increased liver function tests, fatigue, headache, muscle pains and behavioral disorders were other reasons for discontinuation.

The events leading to discontinuation from the IDV group were generally consistent with prolonged exposure to IDV, including abdominal pain, vomiting, urinary calculi, renal signs, flank pain, renal failure and lipodystrophy.

Comment: Although by the end of the study the rates of discontinuations were similar, it is important to point out that over 80% of the patients who discontinued APV did so prior to week 12 of the study.

- **Common Clinical and Laboratory Events**

Previous data demonstrate that APV causes gastrointestinal symptoms, rashes, paresthesias and depression in a significant number of patients. The frequencies of these selected adverse events (all grades), regardless of relationship to drug, are included in Table 3.

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Table 3. Selected adverse events

Event	APV (n=245)	IDV (n=241)
Nausea	43%	35%
Vomiting	24%	20%
Diarrhea/loose stools	60%	41%
Gaseous symptoms	17%	10%
Paresthesia		
Oral/perioral	31%	2%
Peripheral	14%	10%
Rash	20%	15%
Depressive/mood disorders	9%	13%

Source: Tables 54 and 55.

Previous data demonstrated that APV causes elevations of triglycerides, glucose, cholesterol and transaminase levels. The frequency of these laboratory abnormalities, all grades and grades 3&4, occurring in APV and IDV recipients are presented in Table 4.

Table 4. Selected laboratory abnormalities, proportion of patients.

Parameter	APV (n=237)	IDV (n=239)
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↑ Glucose (all grades) Grade 3&4	53 <1	58 4
↑ Triglycerides (all grades) Grade 3&4	56 7	52 6
↑ Cholesterol (all grades) Grade 3&4	13 <1	15 0

Source: Table 69 and supporting table 96.

Comment: There were no significant differences in the frequency of the above laboratory abnormalities between treatment groups. These events are known toxicities of protease inhibitors and were expected to occur in patients treated with IDV and APV. Not presented are drug-related bilirubin and transaminase elevations that occurred more frequently in IDV recipients, this finding was not unexpected. The numbers are small so the data do not support a claim that APV is less hepatotoxic than IDV.

- **Safety Events of Special Interest**

The incidences of hypertriglyceridemia, hypercholesterolemia, hyperglycemia, diabetes mellitus, hemolytic anemia, increased bleeding in hemophiliacs and fat redistribution were assessed.

Hypertriglyceridemia was observed in equal proportions of patients (54% in the APV arm and 52% in the IDV arm), the majority of which were Grade 1 or 2 in severity. A similar proportion of patients had elevated triglycerides reported as an adverse event. Nine and seven APV- and IDV-treated patients, respectively, discontinued treatment for elevated triglycerides.

Thirteen APV-treated and 14% IDV-treated patients experienced elevated cholesterol levels, there was only one case of a Grade 3 elevation in the APV arm. Overall, there were more patients treated with APV who experienced a cholesterol level >240 mg/dL, 26%, versus 17% in the IDV arm.

Elevated glucose levels were reported in 125 (51%) and 138 (58%) of APV and IDV-treated patients during the randomized phase, respectively.

Seventeen diabetic patients entered the study, six in the APV arm and 11 in the IDV arm. One APV treated patient experienced worsening diabetes compared to four in the IDV arm. *De novo* diabetes was diagnosed in two patients in each treatment group.

No cases of hemolytic anemia were reported.

Four hemophiliacs were enrolled in the study and all were randomized to the IDV arm; three experienced hemorrhagic adverse events (hemarthrosis, gingival bleeding, hematuria).

More patients in the IDV arm were reported to have experienced fat redistribution (buffalo hump, central adiposity, peripheral fat wasting, or other unspecified lipodystrophy) compared to those in the APV arm, 29 versus nine. Of note, eight of the APV and 27 of the IDV-treated patients were receiving concomitant treatment with d4T, a nucleoside analogue that has been linked to lipodystrophy. Time to onset was from 57 to 340 days in the APV arm and 46 to 483 in the IDV arm.

Comment: There was no significant difference in these special interest safety events between the two protease inhibitors. The difference in lipodystrophy may have been confounded by the co-administration of d4T in most patients.

- **Overall Assessment**

APV produced inferior antiviral and immunologic activity compared to IDV when added to a background of nucleoside analogues in relatively healthy protease inhibitor-naive patients. By week 48, significantly more APV recipients had experienced virologic failure of randomized therapy compared to those randomized to IDV. The proportion of patients with HIV RNA <400 c/ml and no CDC class C event was 30% versus 46% for APV versus IDV, respectively; this difference was statistically significant ($p=0.014$). With respect to increases in CD4 cell counts, there was a significantly greater treatment effect in the IDV group compared to the APV group, +150 cells/mm³ versus +94 cells/mm³, respectively. These data suggest that APV may not be the optimal choice as a first-line PI.

By the end of the study, the proportion of patients who discontinued study treatment due to adverse events was similar between treatment arms. However, a disproportionate number of APV-treated patients discontinued by week 12 due to mild to moderate gastrointestinal adverse events. During the second half of the study, more patients discontinued APV than IDV due to virologic failure.

There were no new safety concerns raised in the review of the final study report. The most common adverse events associated with APV therapy include mild to moderate severity gastrointestinal events (nausea, vomiting, diarrhea/loose stools, and gaseous symptoms). These events led to APV discontinuation primarily during the first 12 weeks of therapy. Small numbers of amprenavir recipients developed hypertriglyceridemia, hyperglycemia, diabetes mellitus, hypercholesterolemia or lipodystrophy.

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APPENDIX 4
Clinical Study PROAB3004

"A Phase III, Open-Label Trial to Evaluate the Safety, Antiviral Efficacy and Pharmacokinetics of 141W94 Plus Current Therapy in HIV-1 Infected Children."

Design

This study was originally designed as a randomized, double-blind placebo-controlled phase 3 trial comparing APV to placebo in combination with two nucleoside reverse transcriptase inhibitors (NRTIs). Due to changes in the recommended approach to treatment of children and difficulties in recruitment, the study was amended to an open-label, non-comparative design. An interim report of antiviral activity, pharmacokinetics, and safety were previously reviewed and formed the basis for the pediatric dosing recommendations in the current APV label. The study concluded in April 2000 and the applicant has submitted the final study report in this NDA.

Patients who could swallow capsules received either the 150 mg or 50 mg soft gelatin capsules at a dose of 1200 mg BID or 20 mg/kg BID depending on age and weight. Subjects who could not swallow capsules received the APV oral solution (15 mg/ml) at a dose of 1.5 ml/kg, BID (22.5 mg/kg, BID). All patients also received at least two NRTIs. Treatment was for 48 weeks.

• **Study Population and Disposition**

A total of 229 patients were enrolled (109 PI-naïve and 120 PI-experienced). At baseline 50% of patients were females, 48% were black, 28% were Caucasian, and 21% were Hispanic. Ninety-three percent of patients acquired their HIV infection through vertical/perinatal transmission. The median age was 7 years of age (range 2-19 years), the median viral load was 4.59 log₁₀ c/mL, and the median CD4 cell count was 528 cells/mm³.

Of the 229 enrolled, 228 were treated, and 153 (80 PI-naïve and 73 PI-experienced) completed the study.

The reasons for discontinuation among PI-naïve patients were relatively evenly distributed between adverse events, consent withdrawn, loss to follow-up, insufficient viral response and other. Among PI-experienced patients, adverse events and insufficient viral response were the largest contributors to discontinuation; 11/47 and 20/47, respectively.

• **Antiviral and Immunologic Activity**

The 48-week antiviral and immunologic results are summarized in Table 1.

Table 1. 48-week antiviral and immunologic response

	PI-naïve (n=109)	PI-experienced (n=120)
HIV-RNA <10,000 c/mL	52%	26%
HIV-RNA <400 c/mL	26%	8%
Median change HIV-RNA	-0.93 log ₁₀ c/mL	-0.36 log ₁₀ c/mL
Median change CD4s	+91 cells/mm ³	+26 cells/mm ³

The median baseline viral load for PI-experienced patients was 4.96 log₁₀ c/mL; and 84% of these patients entered with HIV RNA >10,000 c/mL. APV produced a very limited response in this population. It does not appear that this was due to resistance to APV as there was a high proportion of baseline viral isolates susceptible to APV, despite previous exposure to other protease inhibitors.

- **Review of Safety**

There was one death. Subject 7430 was a two-year-old black male who died due to respiratory failure 105 days after initiation of APV. This child entered the study with a history of PCP pneumonia. Approximately 15 weeks into the study he developed a low-grade fever, respiratory symptoms, abdominal pain and diarrhea. A diagnosis of PCP pneumonia, adenovirus infection, pancreatitis, hypokalemia, anemia and congestive heart failure were made. His respiratory status decreased and he died approximately 3 weeks later, the death was determined by the investigator not to be study drug related.

Gastrointestinal complaints (vomiting, diarrhea, loose stools, nausea, abdominal pain), rash, fever, headaches, and cough were the most common adverse events reported among study subjects, and were the primary reasons for treatment discontinuations. Hyperglycemia, hypertriglyceridemia, abnormal fat distribution were reported infrequently.

- **Overall Assessment**

This study demonstrated that APV has activity in both PI-naïve and PI-experienced children. The poor antiviral response among PI-experienced patients appeared to be due to early discontinuations due to gastrointestinal intolerance. Although poorly tolerated, APV was generally safe with an adverse event profile in pediatric patients similar to that in adults. There were no propylene glycol-related adverse events reported in this study.

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