EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

22 April 2010
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Evaluation of Medicines for Human Use

CHMP variation assessment report

Invented name/Name: **Reyataz**
International non-proprietary name/Common name: **atazanavir sulphate**

Type II Variation: EMEA/H/C/000494/II/0057

Variation Assessment Report as adopted by the CHMP with all information of a commercially confidential nature deleted.

Indication summary (as last approved):	Treatment of HIV-1 infection
Marketing Authorisation Holder (MAH):	Bristol-Myers Squibb Pharma EEIG

1. Scope of the variation and changes to the dossier

Scope of the variation:	Extension of indication for Reyataz capsules to include the treatment of HIV-infected children and adolescents above the age of 6 in combination with other antiretroviral medicinal products.
Rapporteur: **Co-Rapporteur:**	Pierre Demolis Rafe Suvarna
Product presentations affected:	See Annex A to the Opinion
Dossier modules/sections affected:	Module 1, 2 and 5
Product Information affected:	SmPC, Annex II and PL (Attachment 1 - changes highlighted)

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2. Steps taken for the assessment

Submission date:	11 December 2008
Start of procedure:	21 December 2008
Rapporteur's assessment report circulated on:	05 March 2009
Co-Rapporteur's assessment report circulated on:	13 February 2009
Rapporteur's and Co-Rapporteur's joint assessment report circulated on:	16 March 2009
Request for supplementary information and extension of timetable adopted by the CHMP on:	2 April 2009
MAH's responses submitted to the CHMP on:	20 August 2009
Rapporteur's and Co-Rapporteur's joint preliminary assessment report on the MAH's responses circulated on:	13 October 2009
Rapporteur's and Co-Rapporteur's joint updated assessment report on the MAH's responses circulated on:	21 October 2009
Request for second supplementary information and extension of timetable adopted by the CHMP on:	22 October 2009
MAH's responses submitted to the CHMP on:	02 December 2009
Rapporteur's assessment report on the MAH's responses to second RSI circulated on:	03 February 2010
Rapporteur's assessment report circulated on:	16 February 2010
Request for third supplementary information and extension of timetable adopted by the CHMP on:	18 February 2010
MAH's responses to third RSI submitted to the CHMP on:	22 March 2010
Rapporteur's and Co-Rapporteur's joint updated assessment report on the MAH's responses to third RSI circulated on:	14 April 2010
Rapporteur's updated assessment report after revised SPC and Applicant's responses to third RSI circulated on:	20 April 2010
CHMP opinion:	22 April 2010

3. Scientific data provided by the Marketing Authorisation Holder

3.1. Introduction

Reyataz (atazanavir; ATV) is an azapeptide HIV-1 protease inhibitor (PI). The compound selectively inhibits the virus-specific processing of viral Gag-Pol proteins in HIV-1 infected cells, thus preventing formation of mature virions and infection of other cells. It is indicated for the treatment of HIV-1 infected adults in combination with other antiretroviral medicinal products. Based on available virological and clinical data, no benefit is expected in patients with strains resistant to multiple protease inhibitors (≥ 4 PI mutations).

Reyataz is currently approved as 100 mg, 150 mg, 200 mg and 300 mg capsules of atazanavir as well as a 50 mg/1.5 g oral powder (oral powder containing 1.5 g of powder per levelled measuring spoon, equivalent to 50 mg of atazanavir expressed as free base in a multidose HPDE bottle with a measuring spoon) for use in adults only. The oral powder has so far not been marketed in the EU.

As of the end of 2007, an estimated 33.2 million people worldwide – 30.8 million adults and 2.5 million children younger than 15 years – were living with HIV/AIDS. An estimated 370,000 children under the age of 15 became infected with HIV in 2007 (Source: UNAIDS). In western and central Europe, an estimated 740,000 persons were living with HIV in 2006. In 2005, 27,555 new HIV diagnoses were reported by 26 European countries, of which 1% (275) were children < 15 years of age and 10% (2,755) were young people aged between 15 and 24 years.

HIV-related mortality and opportunistic and other related infections have significantly decreased in HIV-infected children in the era of HAART. More specifically, since the introduction of NNRTI- or PI-containing combinations, HIV mortality in children in resource-rich countries has decreased by 70%. However, off-label use of ARV drugs approved for treatment of HIV-1 infection in adults only, in the absence of appropriate paediatric formulations and dose recommendations, is not uncommon. Consequently, there continues to be a need for effective and tolerable therapeutic agents for use in the paediatric population.

The use of PIs has been a major breakthrough in the therapy for HIV-1 infection, substantially reducing morbidity and mortality in infected individuals. However, the long-term use of the currently licensed PIs is often hampered by different factors such as poor compliance due to a high pill burden and/or poor palatability of oral solutions, as well as food restrictions, side effects with impact on the quality of life and the emergence of resistant virus that is no longer inhibited by the medicine used.

Atazanavir has pharmacokinetics that allow once daily dosing in adults, which makes a paediatric development program desirable as adherence could be expected to improve with such a regimen in this population.

This type II variation sought an extension of the indication for Reyataz hard capsules to include HIV-1 infected paediatric patients 6 years of age and older in combination with other antiretroviral medicinal products.

An extension application (EMEA/H/C/494/X/58) for the addition of a sachet presentation for the oral powder, where each sachet contains 1.5 g oral powder equivalent to 50 mg atazanavir free base, for use in HIV-1 infected paediatric patients from 3 months to <6 years of age weighing 5 to <25 kg in combination with other medicinal products was submitted in parallel. However, the CHMP in its D120 List of Questions concluded that this line extension was not approvable since data obtained from study AI424020 were considered to be inadequate to support the dose recommendations for ATV/RTV according to body weight bands proposed by the MAH for the powder formulation. In particular, there were concerns that doses may be inadequate based on the virological response rates (at the < 50 c/ml level) observed in treatment-naïve and treatment–experienced children. This was especially critical in light of the fact that the PPK analysis performed by the MAH suggested that, when compared to adult patients, AUC and Cmax would be higher in this population whereas Ctrough would be lower (especially in children of lower weight, i.e. 5-10 kg).

On 10 August 2009, the MAH informed the CHMP on his decision to withdraw the application for a unit-dose sachet for the Reyataz oral powder for children 3 months of age and older up to 25 kg in the treatment of HIV-1 infection. The reason for this withdrawal was that the CHMP concern raised in relation to a valid dose recommendation for younger children (major objection) could not be adequately addressed by the dataset currently available. The MAH, nevertheless, assured the Committee that the withdrawal will have no impact on ongoing paediatric clinical trials involving Reyataz. In addition, no compassionate use programme for Reyataz oral powder in sachet is affected by this withdrawal. The MAH confirmed that he would further investigate and collect data with the use of Reyataz oral powder for children between 3 months to 6 years of age and that a PIP would be submitted to the PDCO for agreement.

Therefore, even though the MAH is still encouraged to adequately develop the medicinal product in children younger than 6 years of age to answer a medical need, the MAH's current choice to only maintain the application in children above the age of 6 within this current extension of indication for Reyataz capsules was supported by the CHMP.

One single clinical study (AI424020 also referenced to as PACTG 1020-A), as well as one PKK modelling analysis were submitted in support of this variation. This study includes data on the powder and therefore on the younger children. These data are being discussed, where necessary, in this report even though they are not limited to the population and pharmaceutical form, for which an indication is sought.

Atazanavir is authorised in the EU only with the concomitant use of ritonavir as a pharmacokinetic enhancer ("boosting"). In line with the adult MA, the MAH is not seeking an indication for unboosted atazanavir in the paediatric population (either using the powder in sachets or the hard capsules). However, data for unboosted atazanavir were obtained during the clinical study and some are included in this report for completeness.

The MAH initially proposed the following changes to section 4.1 and 4.2 of the SPC, in addition to changes in sections 4.8, 5.1 and 5.2 (deletions are indicated by strikethrough, additions are indicated by underlined):

3.1.1. Therapeutic indications

Reyataz capsules are indicated for the treatment of HIV-1 infected adults and paediatric patients 6 years of age and older in combination with other antiretroviral medicinal products.

In antiretroviral treatment experienced adult patients, the demonstration of efficacy is based on a study comparing REYATAZ 300 mg once daily in combination with ritonavir 100 mg once daily with lopinavir/ritonavir, each regimen in combination with tenofovir. Based on available virological and clinical data, no benefit is expected in patients with strains resistant to multiple protease inhibitors (≥ 4 PI mutations). The choice of REYATAZ in treatment experienced patients should be based on individual viral resistance testing and the patient's treatment history.

3.1.2. Posology and method of administration

Therapy should be initiated by a physician experienced in the management of HIV infection.

Adults: the recommended dose of REYATAZ is 300 mg once daily taken with ritonavir 100 mg once daily and with food. Ritonavir is used as a booster of atazanavir pharmacokinetics.

Paediatric Patients (6 years to less than 18 years of age): The dose of REYATAZ capsules for paediatric patients is based on body weight as shown in Table 1 and should not exceed the recommended adult dose. REYATAZ capsules must be taken with food.

REYATAZ oral powder is available for paediatric patients from 3 months of age and older up to 25 kg. (see Summary of Product Characteristics for REYATAZ oral powder). For paediatric patients who have reached 6 years of age, switching to REYATAZ capsules is encouraged as soon as they are able to swallow capsules.

Paediatric Patients (less than 3 months of age): REYATAZ has not been studied in children less than 3 months of age and is not recommended because of the potential risk of kernicterus.

Table 1: Dose for Paediatric Patients (6 years to less than 18 years of age) for REYATAZ capsules with ritonavir

Body Weight (kg)	REYATAZ dose	ritonavir dosea
15 to less than 20	150 mg	100 mg
20 to less than 40	200 mg	100 mg
at least 40	300 mg	100 mg

a Ritonavir capsules or oral solution.

Concomitant therapy: If REYATAZ with ritonavir is co-administered with didanosine, it is recommended that didanosine be taken 2 hours after REYATAZ with ritonavir. REYATAZ with ritonavir must be taken with food .

Patients with renal impairment: no dosage adjustment is needed .

Patients with hepatic impairment: REYATAZ with ritonavir has not been studied in patients with hepatic impairment. REYATAZ with ritonavir should be used with caution in patients with mild hepatic impairment. REYATAZ should not be used in patients with moderate to severe hepatic impairment.

Method of administration: for oral administration. The capsules should be swallowed whole.

3.2. Non clinical aspects

Environmental Risk assessment

An Environmental Risk Tier B Assessment has been conducted for the initial Marketing Authorisation Application (MAA). It is agreed that Reyataz is unlikely to pose any risks to the environment.

Toxicology

The decision to initiate a study of ATV in children was based on non-clinical findings that showed that ATV produces no selective developmental toxicity and no effects on reproductive function or fertility at exposures generally equivalent to those observed in both adult and paediatric patients. This was confirmed in the reproductive and developmental toxicity studies previously conducted with ATV. These studies showed that ATV had no effect on growth, development, and reproductive performance of progeny in rats. In addition ATV had no effect on fertility, reproductive performance, gestation, parturition, and lactation of the parental generation in rats; or on embryonic and foetal development in rats and rabbits.

These non-clinical findings were shown in the current clinical study (PACTG 1020-A), which studied the safety and efficacy of ATV or ATV/RTV in 183 paediatric patients for at least up to 48 weeks, and which identified no new safety signals and which found that the overall safety in paediatric patients was comparable to that in adults.

Overall post-marketing authorisation non-clinical toxicity was also recently reviewed in the non-clinical overview in the 5-year Renewal (August 2008). In addition, the MAH will conduct post-marketing surveillance in Europe to collect additional safety information on HIV-infected children exposed to atazanavir in real-life settings.

Therefore, the MAH proposed that the existing clinical data in paediatric patients, the commitment to conduct additional post-marketing surveillance in paediatric patients and the existing non-clinical toxicity data support the proposed paediatric indication and that the use of animals to conduct additional non-clinical juvenile toxicity studies is not warranted.

Discussion on Toxicology

The MAH considered additional juvenile toxicity studies as not necessary, based mainly on the review of reproduction toxicity studies. No adverse effect on fertility was noted in rats in spite of altered oestrous cycling in female, no teratogenic effect was reported in either rats or rabbits, and offspring development was not significantly affected in the pre-post-natal toxicity study. However, the justification for lack of juvenile toxicity is mainly based on the review of reproduction toxicity studies, which is questionable; it is unclear whether the trans-placental or milk transfer was enough to achieve a systemic exposure in foetuses and pups that could provide a safety margin for the main toxicological findings in adults.

In addition, it should be mentioned that the main target organ in repeat-dose toxicity (rats and dogs) was the liver. Potential differences in PK due to different transporter, cytochrome, and clearance activities that could be expected in juvenile animals and/or children have not been discussed either. Besides, the MAH has not provided a discussion of the reduced safety margins for the Cmax-dependent toxicological findings taking into account that the Cmax in children is higher than that in adults.

However, clinical experience exists in both adults and children. For all the above mentioned reasons, it is considered that the preclinical data have limited value to support the proposed indication. It is also noted that no major system known to develop significantly during childhood, e.g. CNS, reproductive system, skeletal system, was identified as target organ in toxicity studies. Overall, the safety of Reyataz in children should be based on the clinical observations; therefore, the lack of specific toxicity studies in juvenile animals is considered acceptable.

3.3. Clinical aspects

Clinical Pharmacology

Population Pharmacokinetic (PPK) studies

The dataset used for the PPK modelling was pooled from three adult studies and one paediatric study. The PPK analysis was performed with 3939 atazanavir concentration values from 227 HIV-infected adult and paediatric subjects (732 and 3207 concentration values from 60 and 167 adult and paediatric subjects, respectively) who participated in the following 4 clinical studies: 3 adult studies (AI424008, AI424089, and AI424137), and 1 paediatric study (AI424020), which is discussed in detail in the section on clinical efficacy and safety further below.

The pharmacokinetics (PK) of atazanavir has been evaluated previously in healthy and HIV infected subjects. Atazanavir demonstrates nonlinear pharmacokinetics with greater than dose-proportional increases in AUC and Cmax values over the dose range of 200-800 mg once daily. Atazanavir has PK parameters that support once-daily dosing. The mean elimination half-life of atazanavir in healthy and HIV-infected subjects was approximately 7 hours at steady state following a dose of 400 mg daily. Steady-state is achieved between Days 4 and 8, with an accumulation of approximately 2.3-fold. For this reason, only steady-state data were used in the analysis of PPK and dose was tested as a covariate on one or more of the PK parameters of the linear PK model to account for potential dose-dependent kinetics.

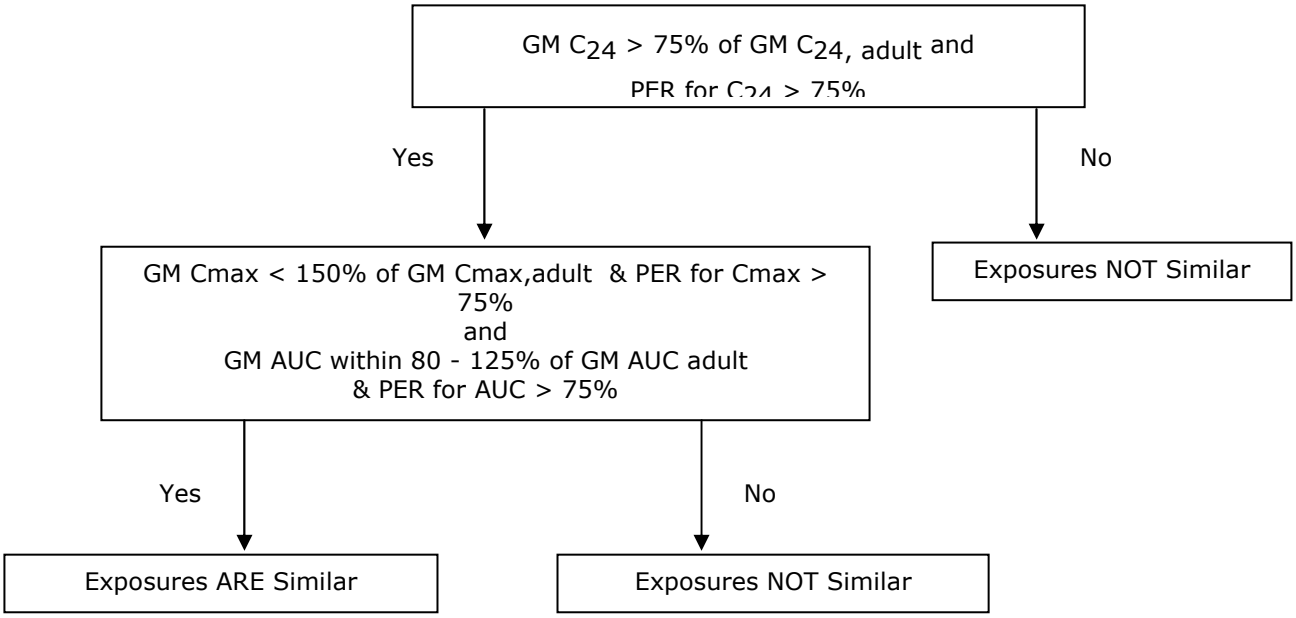
Population PK studies AI424008, AI424089, AI424137 conducted in adults characterised the steady state PK data of atazanavir in HIV infected adult subjects using a PPK modelling approach to determine body weight (BWT)-based paediatric doses for the powder and capsule formulations of boosted (in combination with low-dose ritonavir) and unboosted atazanavir. A nonlinear mixed-effects compartmental PPK model was developed to characterise the pharmacokinetics of atazanavir and to investigate the covariate effects of intrinsic and extrinsic factors on atazanavir PK parameters. Paediatric doses that produced exposures similar to those used to treat HIV-infected adults were determined by employing a model-based simulation approach. Similarity of paediatric atazanavir exposures following unboosted atazanavir and atazanavir/ritonavir dosing regimens with the corresponding target adult exposures was determined.

The predictive performance of the final PPK model was evaluated by simulated data using the final model parameter estimates and conducting a posterior predictive check (PPC). The final model parameter estimates (θ, Ω, Σ) were assumed to have a multivariate normal distribution with mean vector set to the population parameter estimates and covariance matrix set to the covariance matrix of the estimates. The multivariate normal distribution was used as an approximate asymptotic posterior distribution to generate 1000 sets of population parameter values. These population parameters values were then used to generate 1000 simulated datasets conditioning on the designs, dose regimens and covariates in the observed dataset.

For each simulated dataset as well as the observed dataset, the non-compartmental estimates (means and standard deviations) of C24, AUC (steady state area under concentration-time curve at time 0 to 24 hr), and Cmax were calculated and used as PPC statistics. For each PPC statistic, the observed statistic was compared to selected percentiles (5th, median, 95th) of the 1000 simulated statistics. Plots of these statistics were stratified by the 8 age groupings as defined in the paediatric study (Study AI424020) along with 2 additional groupings for the adult patients receiving label recommended atazanavir alone or in combination with ritonavir.

Model-based simulations were performed to support paediatric dosing recommendations based on a bridging strategy, by determining paediatric doses that resulted in steady-state exposures (C24, Cmax, and AUC) similar to target exposures achieved in HIV-infected adults receiving 400 mg QD atazanavir or 300 mg QD atazanavir + 100 mg QD ritonavir. The following decision tree was used to establish similarity of paediatric and adult exposures for the ritonavir boosted atazanavir regimen (Figure 1):

Figure 1: Decision Tree to Support the Boosted ATV Dose Recommendation for ARV-treatment Naïve and Experienced Patients



Where GM is the geometric mean; C24,adult, Cmax,adult, and AUC adult are the target ATV C24, Cmax, and AUC distributions in adults, determined by model-based simulation of ATV/RTV doses of 300/100 mg (based on the currently recommended adult dose for antiviral-treatment naïve patients); PER is the percentage of subjects attaining exposures (C24, Cmax and AUC) within 10th and 90th percentiles of the target adult exposures

Based on the PK/PD analyses from studies AI424089 and AI424138 performed in ARV-naïve patients, the C24 GM level of ≥ 500 ng/ml (75% adult C24 GM) is predicted to be able to achieve good antiviral efficacy for RTV boosted ATV (300/100mg). This prediction is consistent with the clinical results in the AI424020 study in which 88% of ARV naïve paediatric patients treated with the ATV/RTV capsule formulation achieved < 400 c/ml, despite the fact that >40% of the patients took lower than proposed ATV doses in this dose-finding study.

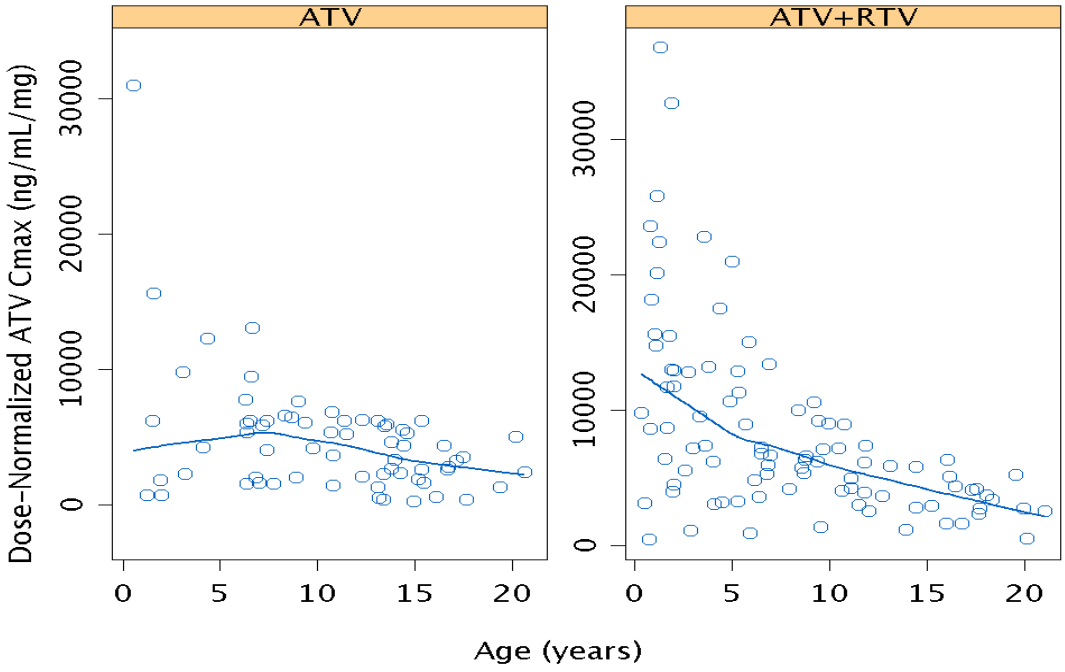
The following covariate effects were included in the final model: an age effect on Ka (the first-order absorption rate constant), body weight effects on V/F (apparent volume of distribution) and CL/F (apparent clearance), ritonavir co-medication effects on CL/F and Frel (relative bioavailability), and a formulation effect on Frel. These covariate effects were important determinants informing the BWT-based dose recommendations for paediatric patients receiving atazanavir capsules or powder formulation alone or in combination with ritonavir. While the atazanavir exposure similarity criteria as defined were dependent on whether patients are ARV-treatment naïve or experienced, the covariate parameter for this effect was neither influential nor included in the final model. Therefore, the final PPK model does not predict differences in atazanavir exposures between ARV-treatment naïve and experienced patients receiving a given dosing regimen.

The PPK analysis dataset included all available PK data from the 3 clinical studies in adult HIV-infected subjects and all intensive PK data from study AI424020 that were available as of 2-March-2007. The PPK dataset used for model development excluded approximately 7% of the available atazanavir concentrations determined by the FDA due to issues with bioanalytical analyses. The dataset used was compared to the dataset including the 7% results questioned by the FDA. The MAH stated that the exclusion of the FDA-identified data does not appear to be influential on the parameter estimation.

Dose-Normalised Observed Cmax vs. Age at Week 1 for Paediatric Patients in Study AI424020

While body weight, ritonavir co-medication and formulation were important factors affecting the overall extent of atazanavir exposure (e.g. AUC), the age effect was an important determinant for ka with increasing ka in younger patients. This effect translated into a higher Cmax with decreasing age as can be observed in the figure below. Note that Cmax sharply increased for paediatric patients less than 10 years of age.

Figure 2: Dose-Normalized Observed Cmax vs. Age at Week 1 for Paediatric Patients in Study AI424020



The final model predicted that younger children and infants have an increased apparent rate of atazanavir absorption resulting in a higher Cmax as compared to adolescents and adults. The model also predicted increases in V/F and CL/F with increasing body weight as one would expect in a pooled analysis across such a wide range of body weights (4.5 kg - 121 kg). The ritonavir co-medication effects on CL/F and relative bioavailability predict substantially higher atazanavir exposures for patients receiving atazanavir in combination with ritonavir as compared to atazanavir alone which is consistent with previous reports of the drug-drug interaction effect between atazanavir and ritonavir. Finally, the model predicts an approximate 35.5% reduction in bioavailability for the powder formulation relative to capsules.

The final model included ritonavir co-medication effects parameterised as simple dichotomous effects (presence or absence) and did not take into consideration of the actual dose of ritonavir. No apparent ritonavir dose trends were observed for the C0 and Frel parameters, while an apparent

trend between ritonavir dose and CL/F was observed. Since the ritonavir dose administered was based on body surface area (BSA) and there is a body weight effect on CL/F, it was unclear if the apparent ritonavir dose trend observed could be fully explained by the correlation between ritonavir dose and body weight or whether the ritonavir dose explains additional variation in CL/F that is not explained by body weight.

In further investigations the ritonavir dose as administered in the paediatric study did not appear to explain additional variation in atazanavir exposure beyond the simple dichotomous effect. The ritonavir dose recommendations (80 mg for ritonavir liquid formulation and 100 mg for ritonavir capsule formulation) were chosen on the basis of the clinical judgment consistent with the atazanavir/ritonavir dose ratios studied in the paediatric study AI424020.

Results - Dose Recommendations and Predictions of Atazanavir Exposure

The following doses were proposed as a result of the simulation studies:

Table 1: Simulation Results of ATV Exposure Parameters in Paediatric Patients at Proposed ATV Capsule Doses in Combination with RTV

BWT Range (kg)	ATV / RTV Dose (mg)	C_{24} (%CV) (ng/ml)	PER (%)	C_{max} (%CV) (ng/ml)	PER (%)	AUC (%CV) (ng·hr/ml)	PER (%)
15 to <20	150 / 100	504 (99.5%)	76.8	5213 (78.7%)	81.4	42902 (77.0%)	82.0
20 to <40	200 / 100	562 (98.9%)	78.0	4954 (81.7%)	80.7	42999 (78.5%)	81.0
≥40	300 / 100	691 (98.5%)	78.1	5040 (84.6%)	79.4	46777 (80.6%)	79.4
Adult (ref)	**300 / 100**	**661 (95.2%)**	80	**4153(85.9%)**	80	**40615 (80.6%)**	80

Conclusion by the MAH

- Steady-state atazanavir concentration-time profiles in adult and paediatric HIV-infected populations were adequately described by a C_0-delinked one-compartment model with first-order absorption.
- The following covariates were found to have an effect on atazanavir PK parameters: age, body weight, ritonavir co-medication, and formulation. Atazanavir CL/F and V/F increase with body weight, and CL/F is 40.9% lower in patients receiving ritonavir co-medication. The relative bioavailability (F_{rel}) of atazanavir increases with ritonavir co-medication, and was 35.5% lower for the atazanavir powder formulation relative to the capsule formulation.
- The final PPK model does not predict differences in atazanavir exposures between ARV-treatment naïve and experienced patients receiving a given dosing regimen.
- Body weight-based powder and capsule atazanavir doses were determined for HIV-infected paediatric patients weighing more than 10 kg, such that the exposures following these doses were comparable to those of atazanavir capsule doses used to treat HIV-infected adults

Discussion on PPK model

This report summarises a standard modelling and simulation approach based on PKK from 3 adult and 1 paediatric study aiming to predict paediatric doses that would produce exposures similar to those used to treat HIV-infected adults with atazanavir. The exposure targets in adults were determined by a model- based simulation of an atazanavir dose of 400mg for atazanavir alone and 300mg/100mg for atazanavir/ritonavir combined.

The exposure similarity criteria were that the geometric mean (GM) for C24 should lie >75% of that in adults and PER for C24 >75%. The selected target for ATV Ctrough is expected to provide a

satisfactory rate of virologic suppression. However, the CHMP would like to underline that similarity criteria were based on results from studies performed in adult naïve patients. It remains unclear whether the selection of acceptance criteria would also be appropriate for the use of boosted ATV in paediatric experienced patients. However, in accordance with its therapeutic use in adults, Reyataz will be mainly used in the paediatric population for naïve patients or moderately experienced patients.

In the simulations of the BWT-based dosing the variability is extensive with CV% >100% for C24. Model estimated and observed variability in ATV PK do indeed appear to be largely consistent, as demonstrated by the posterior predictive check (PPC) and visual predictive check (VPC) assessments. The PPC results indicate that the observed %CV tends to be large (>100%) across the study groups but are generally comparable to the model simulated median and are contained within the model simulated 5th - 95th interval. In general, it is concluded that the variability based on simulation is consistent with the variability of the observed data.

Atazanavir without low dose ritonavir is not authorised for the treatment of HIV infected adults in the EU and the MAH does not seek authorisation for it in paediatric patients. Therefore the following discussion focuses on use of atazanavir/ritonavir. The model predicted that age, body weight, presence of ritonavir and atazanavir formulation were relevant factors affecting exposure to atazanavir with different dosing regimens.

PK data showed a trend towards lower atazanavir Cmin but higher Cmax and AUC in children compared to adults. The effect was less pronounced when atazanavir was combined with low dose ritonavir. The doses proposed as a result of modelling and simulation for the capsule for most weight brackets appear similar to adult doses within the margin set.

The ritonavir dose recommended for co-administration with atazanavir was not optimally explored. However, the only availability of the 100mg capsule limits the possibility of tailoring the dose and the resort to the oral solution raised the issue of poor acceptability.

Clinical efficacy

A single study (AI 424020) was submitted in support of the application. This ongoing study with a planned total duration of 96 weeks (plus potential extension in South Africa) was initiated on 16 November 2000. The report presented is the 48 week interim report of the step 1 phase of the study, using a database lock date of 4 February 2008. The protocol was initially developed to evaluate atazanavir without ritonavir and later modified to include regimens of atazanavir with low-dose ritonavir. The protocol was revised to allow for new sites in South Africa to participate in the study (Protocol Version 5, dated 23 September 2003).

The MAH states that the laws and regulatory requirements of all countries participating in this study were adhered to and that this study was conducted in accordance with Good Clinical Practice (GCP), as defined by the International Conference on Harmonization (ICH) and for US sites in accordance with the United States Code of Federal Regulations, Title 21, Part 50.

Study Design

Study AI 424020 (PACTG 1020-A) is a multicentre, open-label phase 1/2 study to determine the pharmacokinetics, safety, and efficacy results for the dose-finding in antiretroviral naïve and experienced paediatric subjects aged 91 days to 21 years infected with HIV. Both the unboosted

and the boosted treatment regimen were combined with 2 nucleoside reverse transcriptase inhibitors (NRTIs).

Primary Objectives
To determine the PK profile and dosing schedule for atazanavir and atazanavir/ritonavir in combination with 2 NRTIs in HIV-infected paediatric subjects for the powder and capsule formulation, respectively.

- To determine the safety and tolerability of atazanavir and atazanavir/ritonavir in combination with 2 NRTIs in HIV-infected paediatric subjects

Secondary Objectives
To assess the antiretroviral activity of atazanavir and atazanavir/ritonavir containing regimens as measured by viral load response in PI treatment-experienced and naïve study subjects

- To assess the development of virological resistance as measured by genotypic and phenotypic assays during treatment with atazanavir and atazanavir/ritonavir

Study participants
HIV – infected treatment naïve and experienced subjects aged 91 days to 21 years were eligible for enrolment if they met the following criteria:

- Qualifying plasma HIV RNA of ≥ 5,000 copies/ml
- Antiretroviral treatment-naïve or treatment-experienced subjects who were able to add 2 new NRTIs as part of the therapeutic regimen or who showed genotypic evidence of sensitivity to 2 NRTIs
- Phenotypic sensitivity to ATV (resistance index ratio of < 10) despite failing 2 or more courses of a PI-containing regimen after at least 12 weeks of therapy.

Exclusion criteria
Active hepatitis or acute serious and invasive infection requiring therapy at the time of study enrolment

- Documented history of cardiac conduction abnormality(ies) or significant cardiac dysfunction, or a history of undefined syncope for which a cause of cardiac conduction abnormalities could not be ruled out
- Family history of QTc interval syndrome, Brugada syndrome or right ventricular dysplasia or with a corrected QTc interval at screening of > 440 ms
- Prolonged PR interval of > 200 ms for candidates 13 years of age or older or a PR interval > 98th percentile for candidates < 13 years of age at screening ECG
- One of the following cardiac rhythm abnormalities documented on the screening ECG: type I second degree atrioventricular (AV) block while awake, type II second degree AV block at any time, complete AV block at any time, or age-adjusted heart rate < 2nd percentile)

Treatments
Eligible subjects were assigned to treatment groups, stratified by age, atazanavir formulation (powder or capsule), and concomitant administration of ritonavir.

Step 1 (dose-finding) was conducted in the US and South Africa, and consisted of 2 parts:

Part A (groups 1- 4): atazanavir plus 2 NRTIs (excluding abacavir sulfate [ABC, Ziagen] and tenofovir disoproxil fumarate [TDF, Viread]).
Part B (groups 5- 8): atazanavir/ritonavir plus 2 NRTIs (excluding ABC and TDF).

(At the time of initial protocol development only Groups 1 - 4 were implemented. The study was later modified to include regimens of atazanavir with ritonavir in Groups 5 - 8.)

Step 2 will only be open to South African subjects who are virologically responding to treatment when the last enrolee into either part of Step 1 (Part A or Part B) has completed 96 weeks of

treatment (end of Step 1). Step 2 will continue in South Africa until atazanavir is approved and readily available. The subjects who participated in Study AI424020 were enrolled at a total of 36 sites: 34 in the US and 2 in South Africa.

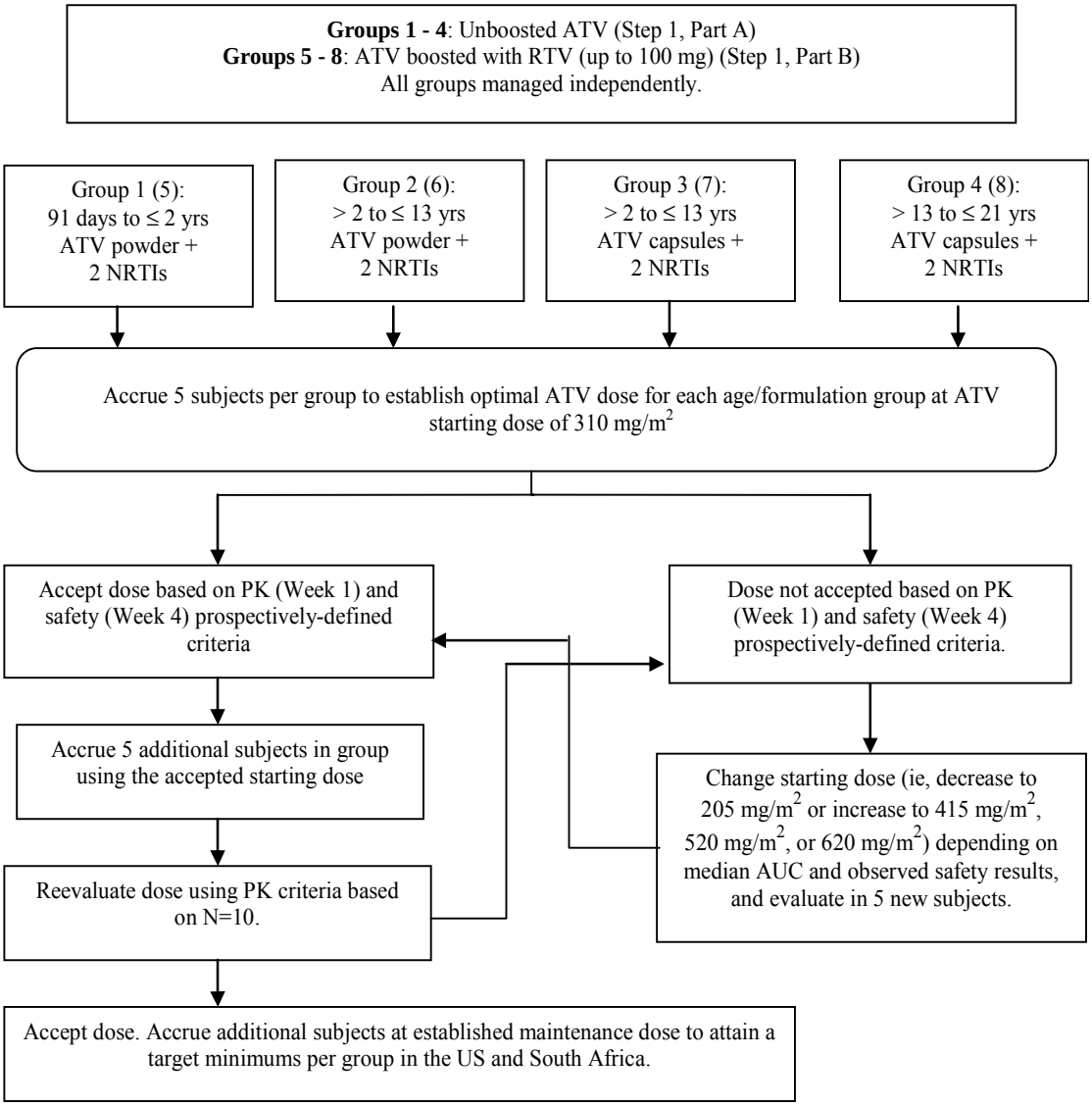
Table 2 Stratification and Regimens Used

ATV without RTV	ATV with RTV	Formulation	Age Ranges
Group 1	Group 5	Powder	Infants 3 months to ≤ 2 years
Group 2	Group 6	Powder	Children > 2 to ≤ 13 years
Group 3	Group 7	Capsules	Children > 2 to ≤ 13 years
Group 4	Group 8	Capsules	Adolescents > 13 to ≤ 21 years

The protocol considered Adolescents as > 13 yrs to 21 yrs; subgroup tables for this report used the following categories: Adolescents >13 yrs to ≤ 18 yrs and Adults >18 yrs.

All groups began at 310 mg/m2 of atazanavir QD; the boosted groups (groups 5- 8) also received ritonavir 100 mg/m2 QD (liquid, up to 100 mg QD or 100 mg capsule). All groups escalated or decreased atazanavir doses based on PK exposure targets and safety criteria.

Figure 3 Study Diagram - Step 1 (AI424020)



The atazanavir powder (50mg/1.5g) provided 50mg per scoop. The atazanavir capsules were supplied as 50, 100 and 200 mg strength. Ritonavir (Norvir, Abbott Laboratories) was supplied as soft gelatin capsules containing 100 mg ritonavir and as an oral solution (80 mg/ml). For all subjects, atazanavir was administered orally QD with food. Morning dosing was recommended, but evening dosing was permitted after intensive PK sampling had been completed and the final dose level of atazanavir had been determined for the group. For subjects receiving the atazanavir powder formulation, the appropriate amount of powder was mixed with a small amount of applesauce, milk, yogurt, or baby formula. Additionally, if preferred by the study patient and/or treating physician, the powder could be mixed with water, but only if dosing of this water-drug suspension is given with a light meal.

Atazanavir dosing was based on body surface area (BSA) calculations for each subject based upon height and weight measurements. Subjects automatically had dose increases based on an increase in body weight of ≥ 25%. Repeat 24-hour PK evaluations were done 2 weeks after initiation of a new atazanavir dose, in the event that further dose changes were needed at this time.

Nucleoside backbone therapy was determined on the basis of the viral genotypic and phenotypic resistance profile and/or the subject's treatment history. The choice of concomitant NRTI was at the investigator's discretion; NRTIs were to be used in combinations recommended in the US Guideline for the Use of Antiretroviral Agents. The NRTIs ABC and TDF were not permitted. Additionally, for subjects receiving the powder formulation of atazanavir, the use of zalcitabine (ddC) for subjects previously treated with didanosine (ddI) and vice versa was not allowed. Dosage and administration of concomitant NRTIs were to be consistent with the manufacturer's prescribing information.

Dose selection
Since treatment-experienced subjects were to be enrolled in this study and in anticipation of higher clearance in younger subjects, the starting dose for each group was initially chosen based on the atazanavir 600 mg QD PK data in HIV-infected adults in AI424008. In MAH sponsored adult trials, a once daily 400-mg dose of atazanavir had resulted in the majority of patients having trough levels above the IC90 (approximately 60 ng/ml, when adjusted for human serum protein binding). The expected inter-patient variability for AUC values is 30% to 50%. Thus, the PACTG 1020-A team decided on a minimum acceptable AUC value of 15,000 ng•h/ml for the study, believing that this value will provide trough levels in the range of the minimum trough target of 60 ng/ml.

In light of the previously mentioned expected variability of AUC values of up to 50%, the protocol team had set a population AUC target for BMS-232632 at 45,000 ng•h/ml. An AUC value of 45,000 ng•h/ml was selected as it was thought to cover the approximately 2-fold higher rate of hepatic clearance observed in young children versus adults taking protease inhibitors. Further, this exposure (projected from PK simulations) is similar to that of 600 mg QD, well tolerated by adult patients in BMS AI424-008.

PK sampling schedule
Two (2) 24h PK profiles were carried out, the first on day 7, the 2nd in week 56. Random samples were performed in week 12, 24, 36 and 72. Repeat 24-hour PK evaluations were done 2 weeks after initiation of a new atazanavir dose. Summaries and listings for PK parameters were based on age group defined as: 3 months to < 6 months, ≥ 6 months to ≤ 2 years > 2 years to < 6 years, ≥ 6 years to ≤13 years, > 13 years to ≤ 18 years and >18 years to 21 years.

Dose modification based on PK data:
All groups began at 310 mg/m2 of atazanavir QD; the boosted groups (groups 5-8) also received ritonavir 100 mg/m2 QD. All groups escalated or decreased atazanavir doses based on PK exposure targets (after week 1) and safety criteria (after week 4):

Acceptance criteria part A (groups 1-4), atazanavir alone:

- no patient out of 5 had AUC < 15,000 ng.h/ml,
- at least 4 of the 5 patients reached an AUC > 30,000 ng.h/ml, and
- at least 4 of the patients reached Cmin ≥60 ng/ml.

Five (5) subjects were to be enrolled in each group to receive the starting dose of atazanavir in the appropriate formulation and with or without ritonavir.

- If prospectively defined dose acceptance criteria, based upon intensive PK assessments made at Week 1 and safety data collected through Week 4, were not met, the atazanavir starting dose was either decreased or increased in the same group of 5 subjects.
- If dose acceptance criteria were met, an additional 5 subjects were enrolled at the same dose and the regimen evaluated once more with 10 total subjects. (In addition, for safety, there

could be no life-threatening toxicities, one or fewer Grade 3 or 4 toxicities (excluding bilirubin), and no more than 2 subjects could have a bilirubin level > 5.1 x ULN.)

- If still satisfying the dose acceptance criteria after 10 subjects, the group fully enrolled at that dosing cohort and treatment in Step 1 continued until 96 weeks after the last subject was enrolled in the respective study part.
- In case adjustment was necessary, repeat pharmacokinetic studies were to be performed 14 days after dose adjustment to confirm adequate AUC values.

Criteria for evaluation and endpoints

Pharmacokinetic Variables

The primary PK parameters were AUC(TAU) (referred as AUC 0-24 in the protocol), and Cmin (trough concentration). Clearance (CL/F), elimination half-life (T-half), peak concentration (Cmax), and time to peak concentration (Tmax) were secondary PK parameters. Standard non-compartmental techniques were used to assess PK parameters. Analysis population were all treated subjects. Subjects had intensive, 24-hour PK sampling at Week 1, and again at Week 56 for those who continued on study. Intensive, 24-hour PK sampling was also to be performed 2 weeks after a new dose of atazanavir had been initiated. A single 1.5 ml venous blood sample was obtained for population PK evaluations at Weeks 12, 24, 36, 72, 96 and every 24 weeks after Week 96 until the end of the study. These random PK samples were to be collected at least 3 hours after dose of atazanavir had been taken, and the time from the last dose of study medication was to be recorded.

Efficacy

The main efficacy endpoints included the following virologic and immunologic parameters:

- Proportion achieving a 1 log10 reduction from baseline in HIV RNA level at Week 48 (VOLS)
- Proportion of subjects with HIV RNA < 400 c/ml and < 50 c/ml at Week 48 (VR)
- Time to loss of virologic response (TLOVR) at Week 48
- Log10 c/ml HIV RNA change from baseline at Week 48
- CD4 cell count and CD4 percent change from baseline at Week 48
- CD8 cell count and CD8 percent change from baseline at Week 4

For the VR analysis, subjects with HIV RNA ≥ 50 c/ml (or ≥ 400 c/ml), or who discontinued prior to the scheduled visit were considered failures in this analysis (Non-Completer = Failure [NC = F]). The VR-OC analysis was similar to the VR analysis except that subjects who discontinued prior to the scheduled Week 48 visit were excluded from this analysis (Non-Completer = Missing [NC = M], "Observed Cases").

TLOVR defined responders at Week 48 as subjects with confirmed HIV RNA < 50 c/ml (or < 400 c/ml) through Week 48 without intervening virologic rebound or treatment discontinuation. Virologic rebound was defined as confirmed on-treatment HIV RNA ≥ 50 c/ml (or ≥ 400 c/ml) or last on-treatment HIV RNA ≥ 50 c/ml (or ≥ 400 c/ml) followed by discontinuation. Subjects were considered failures in this analysis if they experienced a virologic rebound at or before Week 48, discontinued at or before Week 48, never responded by Week 48, or had missing HIV RNA at Week 48 and beyond.

Resistance Profiles

Plasma for phenotypic and genotypic resistance was collected from all subjects during screening. For the resistance analysis of the Week 48 CSR, samples were collected from MAH-identified-subjects who had a virological rebound with at least 1 on treatment HIV RNA > 2000 c/ml on or after the rebound, or who discontinued the study therapy with the last on-treatment HIV RNA > 2000 c/ml.

Safety

Safety endpoints included the frequency of adverse events (AEs), serious adverse events (SAEs), deaths, discontinuation due to AEs, laboratory abnormalities, and electrocardiograms. Grade 4 clinical or laboratory observations triggered discontinuation of atazanavir and concomitant ARV (including ritonavir) therapy. Analysis population was all treated subjects (SAEs and deaths used all enrolled subjects). Non-serious AEs were illnesses, and any signs and symptoms that appeared or worsened during the course of the trial. SAEs were required to be reported based on the PACTG 1020-A protocol definition that follows reporting requirements as defined in the current US Division of AIDS Serious Adverse Experience Reporting Manual. All Grade 3 and 4 laboratory abnormalities suspected to be an adverse drug reaction were mandated to be reported as an SAE. Therefore, under the protocol definition, asymptomatic Grade 3 (3.0 - 7.5 x ULN) and Grade 4 (> 7.5 x ULN) bilirubin elevations, were required to be reported as SAEs.

Protocol Deviations

Forty (40) subjects (22%) had at least 1 eligibility deviation: 24% in the atazanavir alone group and 20% in the atazanavir/ritonavir group. Fourteen (14) subjects (8%) had at least 1 protocol deviation during the treatment period. Eleven (11) subjects (6%) were receiving prohibited concomitant medication (antiretroviral therapies other than the regimens used in the study): 4 subjects in the atazanavir group and 7 subjects in the atazanavir/ritonavir group. For deviations related to PK, sample collection times deviating ≥ 30% from nominal times were considered significant time deviations.

Discussion on study design

The primary objective of this study was to establish a paediatric dosage regimen for atazanavir alone and atazanavir with ritonavir. PK studies were done on Day 7 after starting treatment to ensure measurements at steady state. In case a change of dose was necessary, a repeat PK profile was performed after 2 weeks. Another 24h profile was performed at week 56 for subjects who received a dose within 25% of the accepted dose.

No sample size calculation was provided, group sizes were determined by consensus decision between MAH and protocol group.

The separation of the study into two parts A and B investigating different treatments in 4 age strata each results in 8 subgroups. Each of these subgroups includes varying proportions of treatment naïve and treatment experience patients. The use of two different formulations further adds to complexity, as the study results indicate that the 2 formulations may not bioequivalent. This makes the interpretation of the study results very difficult as very few patients have been investigated in each of the sub-groups.

Outcomes

In the following sections, treatment regimens are referred to as atazanavir (Groups 1 - 4) and atazanavir/ritonavir (Groups 5 - 8). To facilitate the description of the data throughout the text, the protocol-defined age categories are referred to as Infants (3 mo to ≤ 2 yrs); Children (> 2 yrs to ≤ 13 yrs), and Adolescents (> 13 yrs to ≤ 21 yrs). Although the protocol considered Adolescents as > 13 yrs to 21 yrs, the subgroup tables for this report used the following categories: Adolescents > 13 yrs to ≤ 18 yrs and Adults > 18 yrs.

Baseline Demographics

Of the 183 enrolled subjects, 182 subjects (99%) were treated: 85 with atazanavir alone and 97 with atazanavir/ritonavir. A total of 116 subjects received capsules and 66 subjects received the powder formulation. Of the 182 treated patients, 81 were ART naïve (31 in the atazanavir group,

50 in the atazanavir/ritonavir group) and 101 were treatment experienced (57 received atazanavir, 47 received atazanavir/ritonavir).

The age distribution differs between atazanavir and atazanavir/ritonavir group as very few subject < 2 years of age were enrolled in group 1 (atazanavir alone), increasing the median age of the atazanavir alone cohort. There are more black/mixed subjects in the atazanavir/ritonavir group, reflecting enrolment in South Africa in part B of the study, where no white subjects were enrolled.

Discontinuation of treatment prior to or on the Week 24 visit was 16% overall, 16% each in both atazanavir (n= 14) group and the atazanavir/ritonavir group (n=16). The most common (≥ 3% overall) reasons were toxicity, protocol compliance issues, and request for treatment discontinuation. By week 48 a total of 27 (32%) of subjects had withdrawn from the atazanavir group. In the atazanavir/ritonavir group, there were 22 (12%) withdrawals in total. The most common (≥ 3% overall) reason for withdrawal after week 24 was clinical events or disease progression and protocol compliance issues.

The median baseline HIV RNA plasma levels were 4.72 log10 c/ml, median baseline CD4 cell absolute numbers were 450 cells/mm3, and the median baseline CD4 cell percentage was 18%. Mean and median HIV RNA levels were similar for the atazanavir and the atazanavir/ritonavir group, while CD4 count was higher in the atazanavir/ritonavir group.

Overall, the majority of treated subjects (55%) received ARV therapy prior to study entry (atazanavir alone 64%; atazanavir/ritonavir 48%) More subjects (54%) had prior NRTI experience than prior PI experience (41%) and prior non-nucleoside reverse transcriptase inhibitor (NNRTI) experience (34%). Median length of ARV treatment was 321.6 weeks, with treatment length for NRTI/ nucleotide reverse transcriptase inhibitor (NtRTI) (333.1 weeks) > PI (178.1 weeks) > NNRTI (86.4 weeks). The proportions of ARV-experienced subjects were 45% in Infants, 57% in Children, 59% in Adolescents, and 56% in Adults. The median time on prior ARVs was 43.7 weeks in Infants, 303.6 weeks in Children and 562.9 weeks in Adolescents. Naïve patients were younger than experienced patients and were mainly black patients, from Africa.

Median duration of treatment was 88.1 weeks (range 0.7 to 361.1 weeks). Median time on therapy was 97.6 weeks (range 0.7 to 361.1 weeks) for subjects receiving atazanavir (Groups 1 - 4) and 82.1 weeks (range 1.0 to 233.9 weeks) for subjects receiving atazanavir/ritonavir (Groups 5 - 8). The atazanavir/ritonavir group started later than the atazanavir group; therefore, overall exposure on atazanavir/ritonavir was much shorter than for the atazanavir group.

The most common initial NRTI backbone combination therapies were 3TC+d4T (43%), 3TC+ZDV (20%), and d4T+ddI (20%) (Table 6.4 and Table S.4.4). All other NRTI backbone combination therapies were used by ≤ 4% of subjects overall.

Pharmacokinetic results - atazanavir with ritonavir

The initial dosing cohort of 310 mg/m2 for Group 5 and 6 met the PK criteria set forth in the protocol. While AUC in group 5 was comparable to adults, Cmin was lower although all patients exceeded the target limit of 120ng/ml.

In contrast to the patients in Group 6, who were also 2 - 13 years of age but using the powder formulation, the PK from the initial dosing cohort of 310 mg/m2 for Group 7 (capsule formulation) did not meet the PK criteria set forth in the protocol because they were higher than allowed per protocol targets (median AUC > 60 µg•h/ml) and were notably higher than those that would be

observed in adults receiving atazanavir 300 mg with ritonavir 100 mg QD. The target dose for this Group was reduced to 205 mg/m2 and this dose met the protocol-specified PK criteria.

The PK initial dosing cohort of 310 mg/m2 in Group 8 did not meet the PK criteria because they were higher than allowed per protocol targets (median AUC> 60 µg•h/ml). The target dose for Group 8 was reduced to 205 mg/m2 and this dose met the protocol-specified PK criteria. It should be noted that 6 of 10 subjects received a dose in excess of the currently recommended atazanavir adult dose of 300 mg with ritonavir 100 mg in ARV-experienced subjects and some subjects in this group had a BSA ≥ 2 m2.

Table 4.1 shows the PK parameters in subjects who received protocol accepted ATV capsule dose (205 mg/m²) + RTV.

Table 4.1: Summary Statistics for ATV Pharmacokinetic Parameters in Group 7 and 8 (ATV capsule + RTV, 2 years to 21 years)

Pharmacokinetic Parameter	205 mg/m^2			
	> 2 to < 6 years	*≥ 6 to ≤13 years*	*> 13 to ≤ 18 years*	*>18 to 21 years*
	N = 3	**N = 18**	**N = 10**	**N = 3**
AUC(TAU) (µg•h/mL) - Geometric Mean (CV%)	56.3 (13)	43.0 (35)	45.0 (34)	42.4 (4)
Median	55.4	43.7	41.2	42.4
[Range]	[49.8-64.7]	[23.7-82.5]	[26.2-77.4]	[40.5-44.3]
Cmax (ng/mL) - Geometric Mean (CV%)	6419 (14)	4556[a] (33)	3711 (46)	3775 (14)
Median	5991	4933	4257	3998
[Range]	[5875-7515]	[1948-7678]	[1614-6821]	[3210-4191]
Cmin (ng/mL) - Geometric Mean (CV%)	647 (76)	560[a] (60)	1090[b] (60)	614 (15)
Median	483	603	1015	653
[Range]	[389-1441]	[141-1708]	[409-2763]	[511-692]
ATV Dose (mg) Median	150	200	400	350
[Range]	[150-200]	[150-400]	[250-500]	[350-350]
Weight (kg) Mean (std)	21.1 (7.17)	32.6 (14.28)	77.3 (25.79)	60.6 (2.91)
Median	20.0	30.9	86.2	61.9
[Range]	[14.6-28.8]	[17.5-72.9]	[37.5-121.9]	[57.3-62.7]

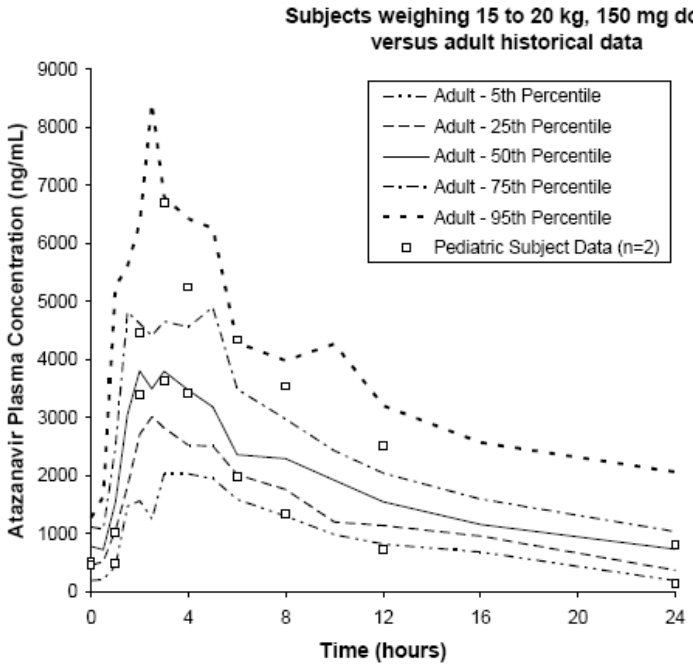
Source: AI424020 CSR Appendix S.8.2.1A and Supplemental Table S.8.2.1G

[a] n=17

[b] N=9

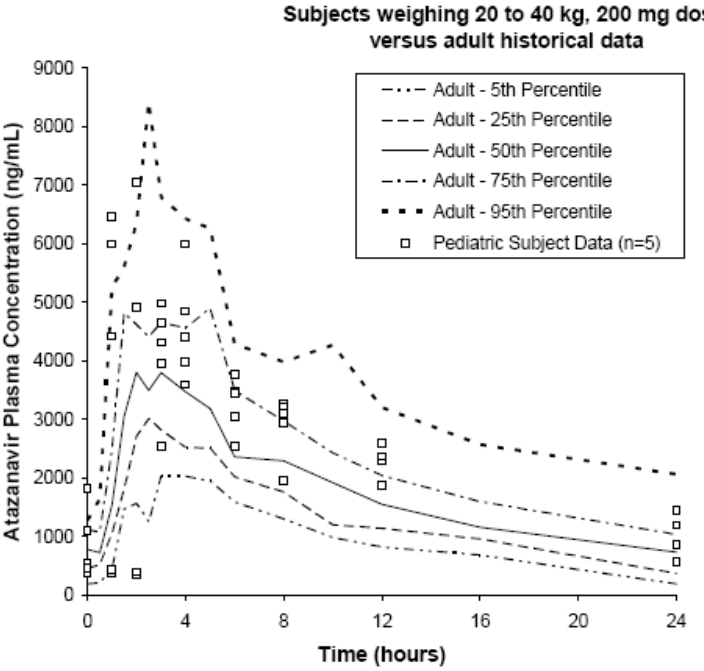
The following figures shows the observed paediatric concentration time profiles by the weight groups identified in comparison to the 5th, 25th 50th, 75th and 95th percentiles of observed adult data.

Figure 4.2B: **Observed Individual ATV Concentration Time Data in Pediatric Patients Who Receiving ATV Capsule + RTV vs Historical Adult Exposures By Weight and Dose: Subjects Weighing 15 to 20 kg, 150 mg**



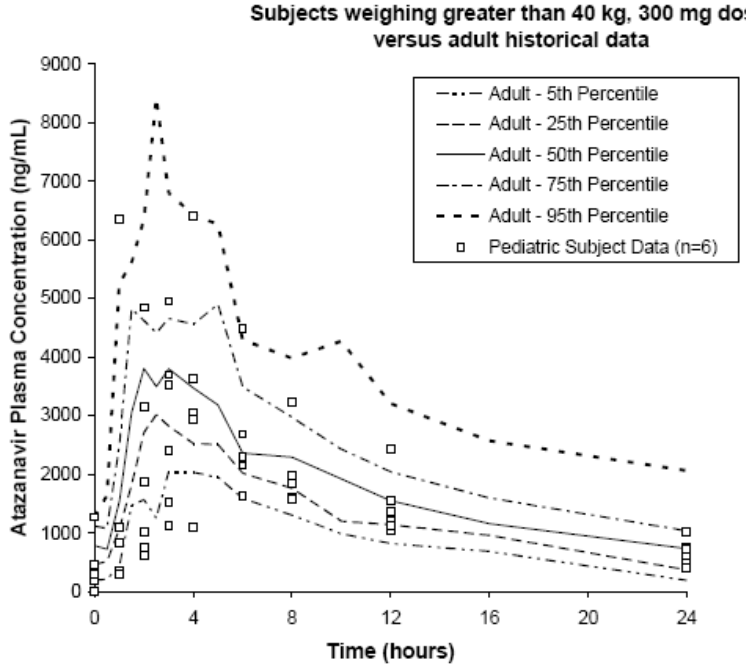
Source table: AI424020 CSR Appendix 8.2.1A; Adult historical data: AI424137 and AI424089 CSR

Figure 4.2D: **Observed Individual ATV Concentration Time Data in Pediatric Patients Who Receiving ATV Capsule + RTV vs Historical Adult Exposures By Weight and Dose: Subjects Weighing 20 to 40 kg, 200 mg**



Source table: AI424020 CSR Appendix 8.2.1A; Adult historical data: AI424137 and AI424089 CSR

Figure 4.2I: **Observed Individual ATV Concentration Time Data in Pediatric Patients Who Receiving ATV Capsule + RTV vs Historical Adult Exposures By Weight and Dose: Subjects Weighing Greater Than 40 kg, 300 mg**



Source table: AI424020 CSR Appendix 8.2.1A; Adult historical data: AI424137 and AI424089 CSR

The above graphs presenting the observed ATV concentration-time profiles for paediatric patients receiving the recommended RTV-boosted ATV by weight bands are reassuring since the observed paediatric data well fit the historical adult data and mainly fall within the 5th to 95th percentiles. As the PPK modelling arrived at dosing recommendations based on BWT and the study was performed using a BSA approach, the following comparison of % difference in dose, together with an assessment of the differences in exposure parameters was provided.

Table 6 provides a comparison of BSA-based boosted capsule ATV doses given in AI424020 with the corresponding BW-based doses.

Table 6: Comparison of Proposed BW Based and BSA Based ATV Capsule Doses Boosted with RTV

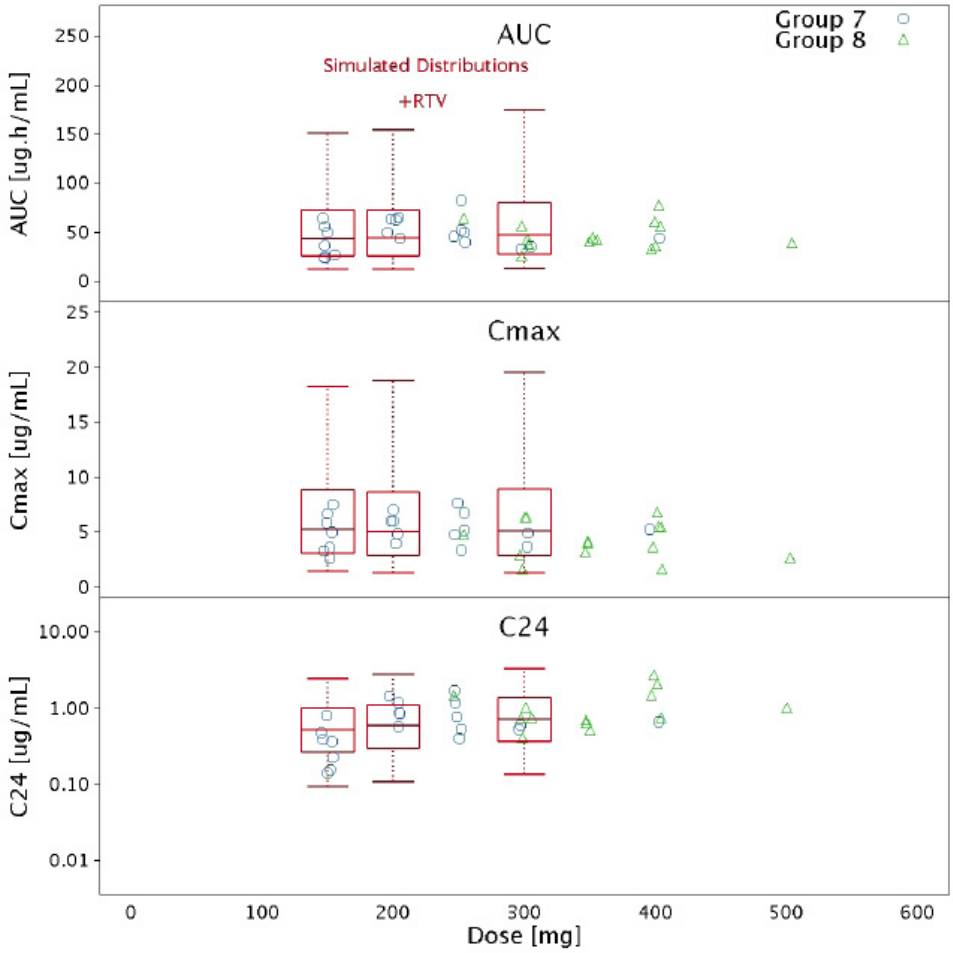
		ATV Doses			
BW Range (kg)	No. of Subject [a]	Proposed BW Based (mg)[b]	Protocol-accepted BSA Based (mg/m^2)	BSA Based in Clinical Study (mg/m^2)[c]	% Difference[d]
15 to < 20	3	150	205	205 (205 - 231)	0 (0 - 0)
20 to < 40	14	200	205	204 (181 - 225)	0 (-25 - 25)
≥ 40	17	300	205	200 (189 - 216)	16.7 (-16.7 - 66.7)

[a] No. of subjects in Study AI424020 who received RTV boosted ATV capsules at protocol accepted BSA-based dose (205 mg/m^2)
[b] Daily ATV dose to be used with RTV 100mg.
c Protocol-accepted BSA-based ATV doses in Study AI424020, presented as median (range)
[d] Calculated as (BSA-based doses in clinical study × BSA - Proposed BW-based doses)/Proposed BW based doses × 100, and presented as median (range)

When comparing the proposed BW-based derived from the modelling/simulation to the BSA-based doses administered in the clinical study, it is noteworthy that these doses are similar except for the > 40 kg weight-band where the BSA-based dose is higher than the BWT-based dose. This is related to the fact that in the clinical study AI424020, patients were allowed to receive ATV doses higher than 300 mg, since ATV doses were not capped at the recommended adult dose. However, the proposed BWT-based doses for this application are capped at the 300 mg adult dose.

Figures 6.1 presents comparisons of model-simulated exposures (using the final model parameter estimates) at the proposed BW-based dosing with the observed exposures at the protocol-accepted BSA-based dosing in Study AI424020 (ATV capsule doses boosted with RTV).

Figure 6.1: **Comparison of Exposures (AUC, C_{max}, and C_{24}) at Proposed BW Based and BSA Based Dosing (ATV Capsule Boosted with RTV)**



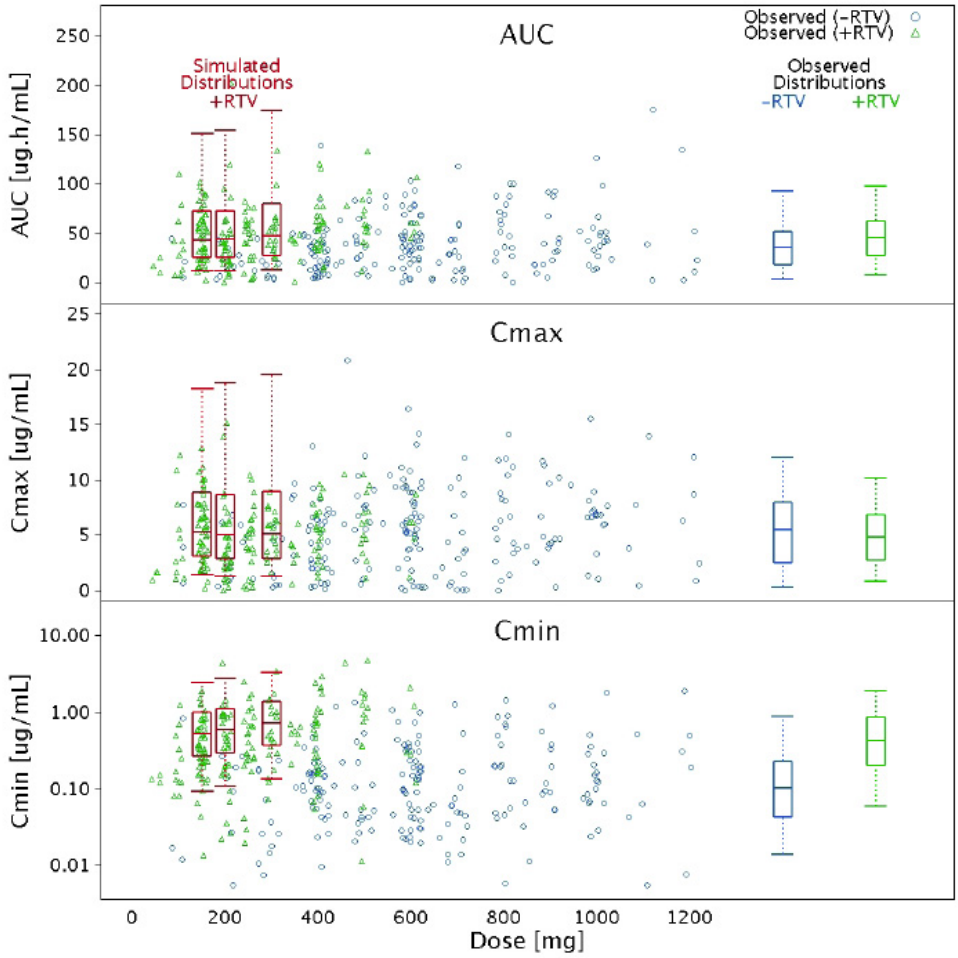
Note 1: Distributions of model-simulated exposures are plotted at the proposed BW based doses, and compared with observed exposures at the BSA based doses determined by non-compartmental analysis.

Note 2: The distributions are represented by median (horizontal line), boxes (interquartile range), and whiskers (5th and 95th percentiles).

The observed C24 in AI424020 extend over the range of simulated exposure for summary measure of C24 produced by all the proposed ATV doses. AUC and Cmax ranges from the proposed BW-based doses extend beyond the observed values in subjects who received ATV capsules boosted with RTV (Group 7 and 8 in AI424020).

But, these exposure levels have been observed in AI424020 when data from all subjects are plotted (Figure 6.2), including those who received unboosted ATV and ATV powder formulation with and without RTV.

Figure 6.2: **Comparison of Exposures (AUC, C_{max}, and C_{24}) at Proposed BW Based and BSA Based Dosing**



Note: Distributions of model-simulated exposures are plotted at the proposed BW based doses, and compared with observed exposures at the BSA based doses determined by non-compartmental analysis.

Overall, the MAH concluded that in addition to offer clinical convenience, the proposed BWT-based dosing recommendations provide:

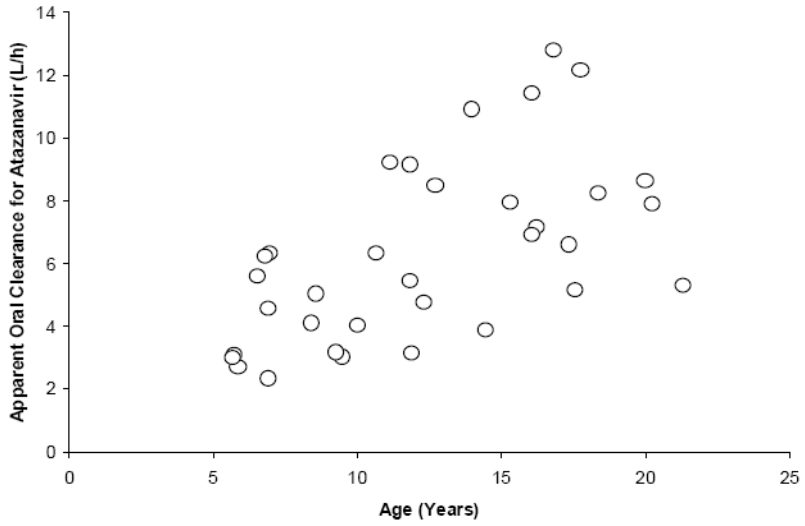
- adequate Cmin levels that are similar to the BSA-based doses accepted in Study AI424020 and are supported by PK/PD data from adult studies;
- AUC levels that are comparable to that in adults; and
- Cmax levels that are within the observed exposure range supported by clinical safety.

Clearance Evaluation for atazanavir <u>with</u> ritonavir

For atazanavir with ritonavir, the apparent oral clearance of both the powder and the capsule increased with age and the range of observations overlapped considerably at all ages except the extremes. When adjusted for by BWT or BSA, the clearance was decreased slightly with age (more notably with BWT) and variability was noted to be higher in younger subjects. The MAH concluded that the reduction in oral clearance per kg with age explains the higher per kg doses required in younger subjects to achieve similar AUC values.

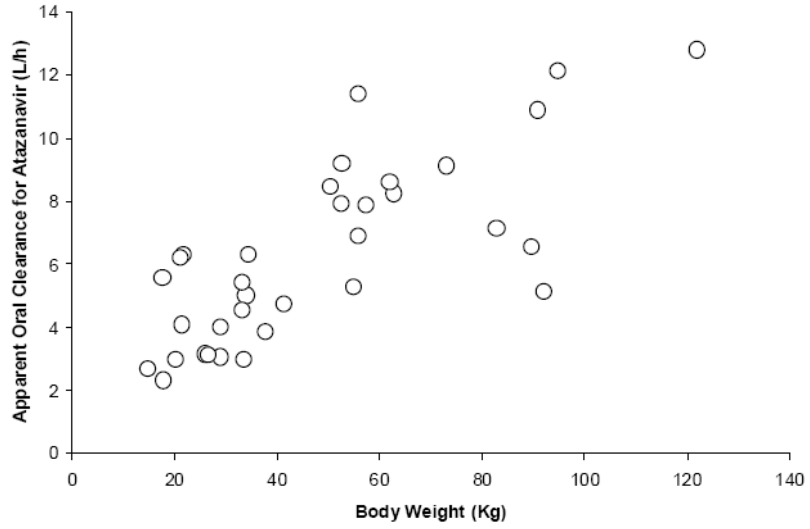
Thirty-four (34) paediatric subjects, aged 5.6 to 21.6 years old, who received the protocol-accepted ATV capsule at a dose of 205 mg/m² plus RTV, provided valid dose finding PK. Figures 10.1 and 10.2 below showed scatter plots of individual CL/F vs. age and body weight, respectively.

Figure 10.1 **Scatter Plot of Individual Apparent Oral Clearance vs Age in Subjects Who Received Accepted Dose in Group 7 and 8 (ATV 205 mg/m2 + RTV)**



Source: AI424020 CSR Appendix 8.2.1A

Figure 10.2 **Scatter Plot of Individual Apparent Oral Clearance vs Body Weight in Subjects Who Received Accepted Dose in Group 7 and 8 (ATV 205 mg/m^2 + RTV)**

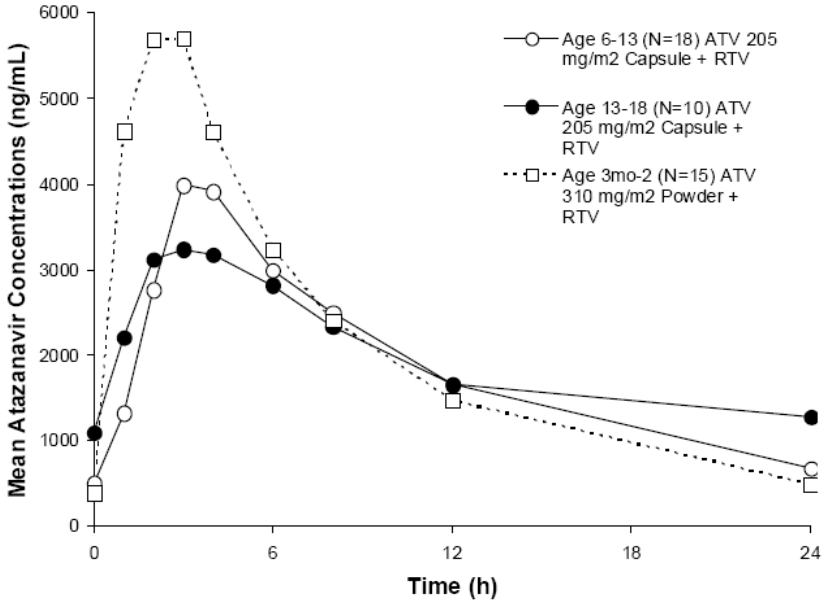


Source: AI424020 CSR Appendix 8.2.1A

As can be seen in the scatter plots above, CL/F for ATV appears to be correlated to both age and body weight; as expected, age and BW are themselves correlated. These observed data are consistent with the finding from the final population PK model that CL/F increases with body weight with a power coefficient to 0.6. Although AUC are largely similar between the different age groups

receiving the accepted ATV capsule dose, there was an apparent tendency of higher Cmax and lower Cmin, or greater peak-to-trough ratio, in younger children (Figure 10.3).

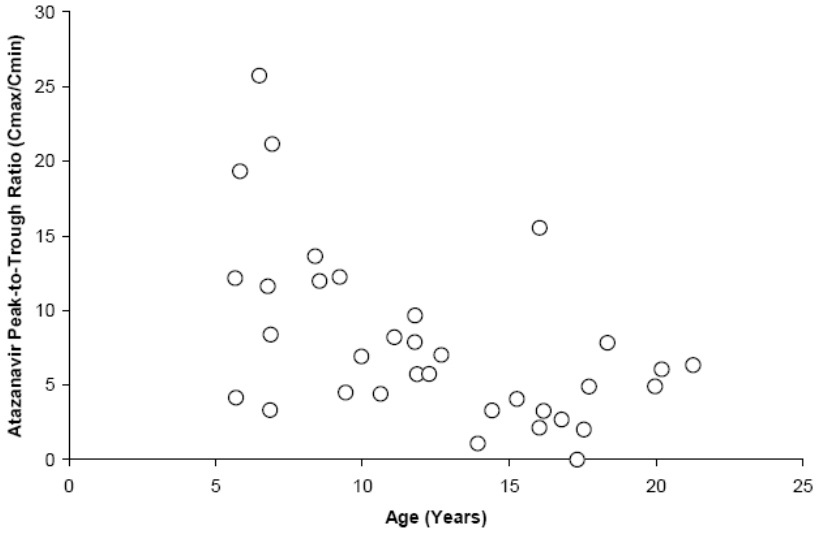
Figure 10.3: **Mean Plasma Concentration-Time Profiles for Atazanavir in Patients Age 6-13 and 13-18 Receiving ATV 205 mg/m^2 Capsule + RTV vs in Patients Age 3mo-2 Receiving ATV 310 mg/m^2 Powder + RTV**



Source: AI424020 CSR Appendices 8.2.1A and 8.3.1A

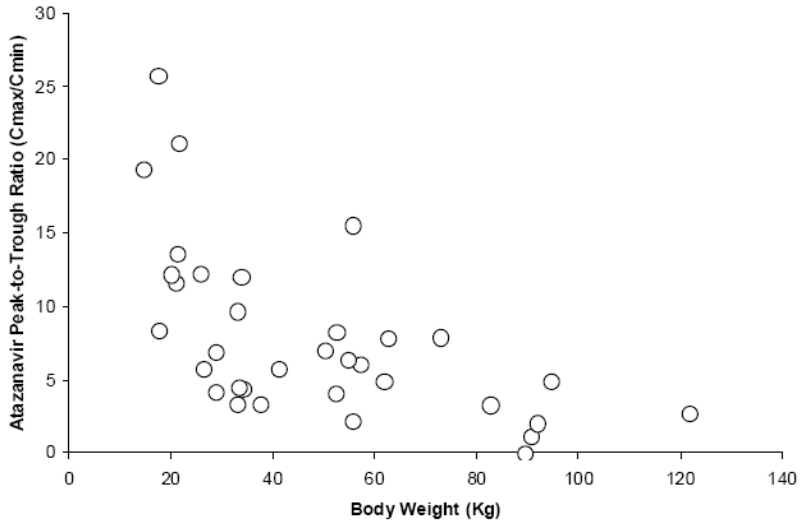
Besides an apparent ATV CL/F vs. age relationship, in children who received the ATV capsule formulation and RTV, ATV peak-to-trough ratio appeared to be inversely correlated with age (Figure 10.4) and body weight (Figure 10.5).

Figure 10.4 **Scatter Plot of Individual Peak-to-Trough Ratio (Cmax/Cmin) vs Age in Subjects Who Received Accepted Dose in Group 7 and 8 (ATV 205 mg/m^2 + RTV)**



Source: AI424020 CSR Appendix 8.2.1A

Figure 10.5 **Scatter Plot of Individual Peak-to-Trough Ratio (Cmax/Cmin) vs Body Weight in Subjects Who Received Accepted Dose in Group 7 and 8 (ATV 205 mg/m^2 + RTV)**



Source: AI424020 CSR Appendix 8.2.1A

In the final population PK model, developed based on data including both boosted and unboosted regimen, powder and capsule formulation, age was found to be a significant covariate on the first order oral absorption rate constant Ka in that younger age was associated with a higher rate of absorption. This model identified that the covariate effect is consistent with the higher Cmax observed in younger children (Figure 10.3).

However, how younger age could result in faster decline in ATV plasma concentrations and consequently lower Cmin is not clear. It cannot be ruled out though that younger age and

corresponding lower body weight may potentially alter the plasma concentration time profile of ATV through pharmacokinetic processes other than the overall CL/F, such as apparent volume of distribution. The more pronounced peak to trough ratio seen with powder formulation may also reflect the effect of age because the majority of patients who took the powder formulation were younger than 6 years old. Note, however, in Figure 10.5 that the apparent trend in peak-to-trough ratio and body weight seems to level off at body weight > 30 kg. A greater peak-to-trough ratio is mainly observed in younger children. In patients aged 6 years and older, the scope of the proposed extension of indication, this concern is quite alleviated.

Confirmatory PK observations at week 56
At 56 weeks, a total of 20 subjects age > 2 yrs to 13 yrs of age taking a dose of powder were within 25% of the accepted dose of 310 mg/m2 and 11 subjects in the same age group (Group 7) were within 25% of 205 mg/m2 for the capsule. The PK for powder at 310 mg/m2 with ritonavir at Week 56 were comparable to that observed in the dose finding exercise, but for the capsule, they were lower and more variable. The MAH states that closer examination of the data reveals that three subjects taking the capsule had relatively low atazanavir exposures. Two (2) of these subjects with low exposures had available pre-dose concentration data which were below the limit of quantitation (BLQ), suggestive of poor adherence. The third subject did not a have a pre-dose value reported, but concentrations for this subject never exceeded 1000 ng/ml, which would be unusual for atazanavir with ritonavir.

Additionally, there were 3 subjects > 13 yrs to 18 yrs of age taking a dose of capsule within 25% of 205 mg/m2 with ritonavir at 56 weeks on study. Although the number of observations was small, the AUC(TAU), Cmax and Cmin values from the three subjects between from > 13 to 18 years of age were higher than the adults at atazanavir/ritonavir 300/100 once daily. Each of the subjects received 400 mg of atazanavir with ritonavir.

Pharmacokinetic results - ritonavir

The range of ritonavir exposures overlaps across groups, with a trend toward lower exposures in the adolescents and adults. The MAH states that the difference in ritonavir exposure does not appear to produce marked differences in atazanavir exposure across these groups as AUC values are similar and the highest atazanavir Cmins were associated with the lowest ritonavir AUC in Group 8.

Pharmacokinetics by Region and prior treatment status

There is an apparent regional effect in the pharmacokinetics of atazanavir without ritonavir. Differences in exposures based on region suggest that patients in South Africa have lower exposures and may have higher clearance or lower bioavailability or both compared to US based patients. Similarly, treatment experienced patients have higher exposures compared to treatment naïve patients when receiving atazanavir alone.

Both regional and prior treatment status differences are not seen to a large extend after atazanavir/ritonavir. In Groups 5-8 Cmin is lower for South African patients compared to US patients and in treatment naïve patients compared to those with treatment experience, but in all patients the preset criteria were met. The MAH states that as US patients are expected to have a higher body weight, and as clearance declines with weight, it would be expected that lower doses per kg would be needed as body size increases. The proportion of treatment naïve patients was larger in the African subjects and the MAH suggests that treatment experience assessment is likely to be confounded by regional assessment.

Discussion on Pharmacokinetics

Atazanavir with ritonavir

The addition of ritonavir to atazanavir considerably reduces the clearance of atazanavir and the peak to trough ratio. Generally, the PK profiles in the paediatric groups are closer to the adult PK parameters than for atazanavir alone. However, the ratio of ritonavir to atazanavir was not justified, neither the ritonavir dose of 100mg/m2 across all age groups. Data presented suggest higher exposure (compared to adults) for ritonavir in all groups except Group 8.
Week 56 confirmatory PK data is difficult to adequately interpret, as compliance was unfortunately not collected in the study.

The primary endpoint of the study was dose determination. However, the data presented leave some doubt about the appropriateness of the doses selected. Efficacy should hence be used to support or reject the proposed doses. A comparison of % difference in dose with the suggested weight based dosing and the BSA based dosing used in the clinical studies showed comparability. The provided data support the proposed BWT-based doses. However, the safety issue, especially the cardiac tolerance (see safety part), will have to be kept under close scrutiny, in view of the higher predicted values for Cmax and AUC compared to observed values.

As previously underlined, when comparing atazanavir PK results for patients receiving ritonavir-boosted atazanavir as a capsule formulation, one can observe that mean Cmax values are higher in younger patients (<13 years) compared to older patients (>13 years), whereas mean Cmin values are lower in younger patients compared to older patients. Regarding mean AUC values, a consistency is noted for patients in the whole age range from 6 to 13 years.

Efficacy Results
The efficacy section presents results for all treated subjects at Week 48 as of database lock date 4 February 2008. Analysis population: all treated subjects, non- completers were treated as failures (NC=F analysis). Table 7 provides an overall summary of efficacy for all treated subjects. The atazanavir and atazanavir/ritonavir groups included both ARV-naïve and -experienced subjects.

Table 7 Efficacy Summary at Week 48- Treated Subjects

		Number of Subjects n/N (%)		
Secondary Endpoint	**LOQ**	**ATV[a] N = 85**	**ATV/RTV[a] N = 97**	**Overall[a] N = 182**
VOLS		41/85 (48)	65/97 (67)	106/182 (58)
VR	< 400 c/ml	34/85 (40)	59/97 (61)	93/182 (51)
	< 50 c/ml	22/85 (26)	45/97 (46)	67/182 (37)
VR-OC	< 400 c/ml	34/58 (59)	59/75 (79)	93/133 (70)
	< 50 c/ml	22/58 (38)	45/75 (60)	67/133 (50)
TLOVR response	< 400 c/ml	37/85 (44)	61/97 (63)	98/182 (54)
	< 50 c/ml	26/85 (31)	44/97 (45)	70/182 (38)
HIV RNA mean change from baseline, $\log_{10}$ c/ml		-1.84	-2.46	-2.20
CD4 median change from baseline, cells/mm3		185	288	245

Includes both ARV-naïve and ARV-experienced subjects
HIV - human immunodeficiency virus, LOQ - limits of quantification, RNA - ribonucleic acid, SE - standard error, TLOVR - time to loss of virologic response, VOLS - virologic one log suppression, VR - virologic response, VR-OC - virologic response based on observed cases

Virologic One Log Suppression (VOLS)

The proportion of all treated subjects who achieved VOLS was 58% overall (48% ATV; 67% ATV/RTV). VOLS within regimens and subgroup categories is shown in Table 8.

Table 8 Virologic One Log Suppression (VOLS) at Week 48 - Treated Subjects

	ATV[a] N = 85		**ATV/RTV[a] N = 97**		**Overall[a] N = 182**	
Secondary Endpoint	**n/N**	**%**	**n/N**	**%**	**n/N**	**%**
VOLS	41/85	48	65/97	67	106/182	58
Age						
Infant	3/8	38	15/21	71	18/29	62
Children	27/42	64	44/56	79	71/98	72
Adolescents	10/32	31	5/14	36	15/46	33
Adults	1/3	33	1/6	17	2/9	22

Table 8 Virologic One Log Suppression (VOLS) at Week 48 - Treated Subjects

	ATV[a] N = 85		ATV/RTV[a] N = 97		Overall[a] N = 182	
Secondary Endpoint	**n/N**	**%**	**n/N**	**%**	**n/N**	**%**
Formulation						
Powder	9/19	47	39/47	83	48/66	73
Capsule	32/66	48	26/50	52	58/116	50
Prior Treatment Status						
Naïve	19/31	61	40/50	80	59/81	73
Experienced	22/54	41	25/47	53	47/101	47
Region						
US	27/63	43	32/57	56	59/120	49
South Africa	14/22	64	33/40	83	47/62	76

[a] Includes both ARV-naïve and ARV-experienced subjects

Virologic Response (VR) for HIV RNA < 400 c/ml and < 50 c/ml at Week 48

Overall, the proportion of treated subjects who achieved VR (HIV RNA < 400 c/ml) was 51%, 40% in the ATV alone group and 61% in the ATV/RTV Group (9). Virologic response within regimens and subgroup categories is shown in Table 9.

Table 9 Virologic Response (VR: HIV RNA < 400 c/ml) at Week 48 - Treated Subjects

	ATV[a]		ATV/RTV[a]		Overall[a]	
Secondary Endpoint	**n/N**	**%**	**n/N**	**%**	**n/N**	**%**
VR	**34/85**	**40**	**59/97**	**61**	**93/182**	**51**
Age						
Infant	3/8	38	15/21	71	18/29	62
Children	22/42	52	39/56	70	61/98	62
Adolescents	8/32	25	5/14	36	13/46	28
Adults	1/3	33	0/6	0	1/9	11
Formulation						
Powder	8/19	42	37/47	79	45/66	68
Capsule	26/66	39	22/50	44	48/116	41
Prior Treatment Status						
Naïve	18/31	58	39/50	78	57/81	70
Experienced	16/54	30	20/47	43	36/101	36
Region						
US	20/63	32	27/57	47	47/120	39
South Africa	14/22	64	32/40	80	46/62	74

[a] Includes both ARV-naïve and ARV-experienced subjects

Results for VR (HIV RNA < 50 c/ml) were consistent with those for VR (HIV RNA < 400 c/ml) (Table 10). The overall VR (HIV RNA < 50 c/ml) was 37%, 26% for ATV alone and 46% for ATV/RTV.

Table 10 VR (HIV RNA < 50 c/ml) at Week 48 - Treated Subjects

	ATV[a]		ATV/RTV[a]		Overall[a]	
Secondary Endpoint	**n/N**	**%**	**n/N**	**%**	**n/N**	**%**
VR	**22/85**	**26**	**45/97**	**46**	**67/182**	**37**
Age						
Infant	3/8	38	9/21	43	12/29	41
Children	14/42	33	32/56	57	46/98	47
Adolescents	5/32	16	4/14	29	9/46	20
Adults	0/3	0	0/6	0	0/9	0
Formulation						
Powder	5/19	26	26/47	55	31/66	47
Capsule	17/66	26	19/50	38	36/116	31
Prior Treatment Status						
Naïve	14/31	45	33/50	66	47/81	58
Experienced	8/54	15	12/47	26	20/101	20
Region						
US	11/63	17	17/57	30	28/120	23
South Africa	11/22	50	28/40	70	39/62	63

The virologic response in study AI424020 is detailed below for each age strata by distinguishing the naïve and experienced patients in the atazanavir/ritonavir treatment groups.

Virologic response at week 24 and 48 by treatment experience with ATV capsule in Children (6 years -<18 years)

	Virologic Response **Responder/Evaluable (%)**	
	ATV/RTV (N=16) ARV- naïve	**ATV/RTV (N=25) ARV-experienced**
Week 24		
VOLS	14/16 (88)	11/25 (44)
VR 400 c/ml	13/16 (81)	10/25 (40)
VR 50 c/ml	12/16 (75)	9/25 (36)
VR-OC 400 c/ml	13/15 (87)	10/19 (53)
VR-OC 50 c/ml	12/15 (80)	9/19 (47)
Week 48		
VOLS	14/16 (88)	11/25 (44)
VR 400 c/ml	14/16 (88)	8/25 (32)
VR 50 c/ml	13/16 (81)	6/25 (24)
VR-OC 400 c/ml	14/15 (93)	8/16 (50)
VR-OC 50 c/ml	13/15 (87)	6/16 (38)

The actual number of children aged 6-18 years, i.e. the target population for this extension indication, and treated by RTV-boosted ATV as a capsule formulation is quite limited (16 naïve patients and 25 experienced patients). Therefore, post-marketing surveillance in this population will be key. A marked difference (around 2-fold) is observed between the rate of responders in naïve patients and experienced patients. In naïve patients, the rate of responders is quite satisfactory (around 80%); it is much less satisfactory in experienced patients (around 40%). However, it is acknowledged that based on PK/PD characteristics and the clinical experience gained in adults, this

ATV/RTV is not a suitable option for multi-resistance patients. The poor results obtained in experienced paediatric patients underline this observation.

Virologic response at week 24 and 48 by age category with ATV capsule - Treated patients

	Virologic Response **Responder/Evaluable (%)**		
	ATV/RTV (N=30) >2 years -<=13 years	**ATV/RTV (N=14) 13 years -<=18 years**	**ATV/RTV (N=6) >18 years**
Week 24			
VOLS	20/30 (67)	6/14 (43)	1/6 (17)
VR 400 c/ml	19/30 (63)	5/14 (36)	1/6 (17)
VR 50 c/ml	18/30 (60)	4/14 (29)	1/6 (17)
VR-OC 400 c/ml	19/26 (73)	5/10 (50)	1/4 (25)
VR-OC 50 c/ml	18/26 (69)	4/10 (40)	1/4 (25)
Week 48			
VOLS	20/30 (67)	5/14 (36)	1/6 (17)
VR 400 c/ml	17/30 (57)	5/14 (36)	0/6 (0)
VR 50 c/ml	15/30 (50)	4/14 (29)	0/6 (0)
VR-OC 400 c/ml	17/24 (71)	5/9 (56)	0/1 (0)
VR-OC 50 c/ml	15/24 (63)	4/9 (44)	0/1 (0)

The rate of responders tends to be higher in younger patients than in older patients.

Virologic response at week 24 and 48 by age category in ARV naïve - Treated patients

	Virologic Response **Responder/Evaluable (%)**			
	ATV/RTV (N=14) 3 months -<=2 years	**ATV/RTV (N=29) >2 years -<=13 years**	**ATV/RTV (N=4) 13 years -<=18 years**	**ATV/RTV (N=3) >18 years**
Week 24				
VOLS	10/14 (71)	26/29 (90)	3/4 (75)	1/3 (33)
VR 400 c/ml	8/14 (57)	26/29 (90)	2/4 (50)	1/3 (33)
VR 50 c/ml	5/14 (36)	24/29 (83)	1/4 (25)	1/3 (33)
VR-OC 400 c/ml	8/11 (73)	26/29 (90)	2/3 (67)	1/2 (50)
VR-OC 50 c/ml	5/11 (45)	24/29 (83)	1/3 (33)	1/2 (50)
Week 48				
VOLS	10/14 (71)	27/29 (93)	2/4 (50)	1/3 (33)
VR 400 c/ml	10/14 (71)	27/29 (93)	2/4 (50)	0/3 (0)
VR 50 c/ml	7/14 (50)	25/29 (86)	1/4 (25)	0/3 (0)
VR-OC 400 c/ml	10/10 (100)	27/29 (93)	2/3 (67)	0/1 (0)
VR-OC 50 c/ml	7/10 (70)	25/29 (86)	1/3 (33)	0/1 (0)

Virologic response at week 24 and 48 by age category in ARV experienced - Treated patients

	Virologic Response **Responder/Evaluable (%)**			
	ATV/RTV (N=7) 3 months -<=2 years	**ATV/RTV (N=27) >2 years -<=13 years**	**ATV/RTV (N=10) 13 years -<=18 years**	**ATV/RTV (N=3) >18 years**
Week 24				
VOLS	5/7 (71)	15/27 (56)	3/10 (30)	0/3 (0)
VR 400 c/ml	4/7 (57)	14/27 (52)	3/10 (30)	0/3 (0)
VR 50 c/ml	2/7 (29)	9/27 (33)	3/10 (30)	0/3 (0)
VR-OC 400 c/ml	4/6 (67)	14/23 (61)	3/7 (43)	0/2 (0)
VR-OC 50 c/ml	2/6 (33)	9/23 (39)	3/7 (43)	0/2 (0)
Week 48				
VOLS	5/7 (71)	17/27 (63)	3/10 (30)	0/3 (0)
VR 400 c/ml	5/7 (71)	12/27 (44)	3/10 (30)	0/3 (0)
VR 50 c/ml	2/7 (29)	7/27 (26)	3/10 (30)	0/3 (0)
VR-OC 400 c/ml	5/6 (83)	12/20 (60)	3/6 (50)	-
VR-OC 50 c/ml	2/6 (33)	7/20 (35)	3/6 (50)	-

VOLS: Virologic One Log Suppression
VR-OC: Virologic Response – Observed Cases

Virologic Response-Observed Cases

In total 133 subject were observed until at least week 48, 58 in the atazanavir alone and 75 in the atazanavir/ritonavir cohort. Overall, the proportion of treated subjects who achieved VR (HIV RNA < 400 c/ml) based on observed cases (VR-OC) was 70%, 59% in the atazanavir alone group and 79% in the atazanavir/ritonavir group. Results for VR-OC (HIV RNA < 50 c/ml) were consistent with those for VR-OC (HIV RNA < 400 c/ml).

Time to Loss of Virologic Response (TLOVR) at Week 48

The proportion of subjects who were responders for HIV RNA <400 c/ml at Week 48 based on the TLOVR was 54% overall, 44% in the atazanavir alone group and 63% in the atazanavir/ritonavir group. Based on HIV RNA< 400 c/ml, in the atazanavir alone group, 39% were classed as virological failures, 18 % suffered a rebound and 21% were never suppressed. In the atazanavir/ritonavir group, 23% were failures with 11% suffering a rebound and 11% never suppressed. At Week 48, the overall mean HIV RNA decrease from baseline was -2.20 log10 c/ml (-1.84 log10 c/ml atazanavir, -2.46 log10 c/ml atazanavir/ritonavir)

Immunologic response

Treatment-naïve subjects had a median increase from baseline in CD4 cell counts of 237 cells/mm3 and treatment-experienced subjects had a median increase from baseline in CD4 cell counts of 127 cells/mm3. Overall, CD8 cell counts decreased while on study therapy. The mean change from baseline overall at Week 48 in CD8 count was -411 cells/mm3 (atazanavir -233 cells/mm3 and atazanavir/ritonavir -540 cells/mm3)

Resistance

For the resistance analysis of the Week 48, samples were collected from MAH-identified-subjects who had a virologic rebound with at least 1 on-treatment HIV RNA > 2000 c/ml on or after the rebound, or who discontinued the study therapy with the last on-treatment HIV RNA > 2000 c/ml.

Genotypic resistance

Of the 81 ART naïve subjects:

Nineteen (19) had baseline genotypic resistance profiles (10/31 in the atazanavir group and 9/50 in the atazanavir/ritonavir group). Among the 10 isolates from atazanavir subjects, there were no

substitutions consisting of thymidine associated mutations (TAMs), there were no baseline protease inhibitor (PI) substitutions or RT substitutions. In the atazanavir/ritonavir group, the single baseline substitutions were PI (A71V), NNRTI (K103N), and reverse transcriptase (RT) substitutions (M41L).

Newly emergent genotypic resistance profiles were observed for 3/31 ART-naïve subjects in the atazanavir group (all 3 isolates had RT substitutions) and for 7/50 ART-naïve subjects in the atazanavir/ritonavir group. Two of the 7 isolates from the atazanavir/ritonavir subjects had RT substitutions; 2/7 had M184M/V, and there were no PI substitutions observed.

Of the 101 ART-experienced subjects:
In the atazanavir group, 53 of 54 subjects had baseline genotypes. At baseline, 25/53 had PI substitutions, 45/53 had RT substitutions and 25/53 had NNRTI substitutions. In the atazanavir/ritonavir group, 30 of the 47 subjects had baseline genotypes. Minor and major PI substitutions observed at baseline included L33F (7%), M46I/L (10%), A71I/V/N/T (23%), I84I/V (7%), N88N/D (7%), and L90M (13%); 26/30 had RT substitutions and 19/30 had NNRTI substitutions.

Newly emergent genotypic resistance profiles were observed for 42/54 ARV-experienced subjects in the atazanavir group. Minor and major PI substitutions emerged in 15 of these 42, 13/42 had RT substitutions. Newly emergent genotypic resistance profiles were observed for 21/47ARV-experienced subjects in the atazanavir/ritonavir group; 3 had PI substitutions and RT substitutions each.

Phenotypic resistance
Phenotypic cut-offs for sensitivity for PIs used in this analysis were: atazanavir > 2.2, indinavir > 2.1, lopinavir > 9, nelfinavir > 3.6, ritonavir > 2.5, and saquinavir > 1.7. Among treatment-naïve subjects, 18 subjects (7/31 atazanavir and 11/50 atazanavir/ritonavir) had baseline phenotypic data available. There was no demonstrable phenotypic resistance to any NRTI, NNRTI or PI in the atazanavir/ritonavir group. In the atazanavir group, one subject had phenotypic resistance to 3TC.

Among treatment-experienced subjects, 46/54 subjects had baseline phenotypic testing (44 were phenotypable) in the atazanavir group and there was demonstrable phenotypic resistance to multiple antiretroviral classes including atazanavir (25%) and ritonavir (23%). In atazanavir/ritonavir group, 28/47 subjects had phenotypic testing at baseline (25 were phenotypable). There was demonstrable phenotypic resistance to multiple antiretroviral classes including atazanavir (20%) and ritonavir (24%).

On-study phenotypic resistance profiles although collected for ARV-naïve subjects and ARV-experienced subjects, was only available for subjects with viral load rebounds of HIV RNA > 2000 c/ml, on-study or at the time of discontinuation.

In the treatment-naïve group, 4/31 (13%) subjects in the atazanavir group and 8/50 (16%) in the atazanavir/ritonavir group had both baseline and on study phenotypic resistance profiles. Among subjects in the atazanavir group, 2 out of 4 subjects tested showed the emergence of any new drug resistance on study (1 subject developed phenotypic resistance to atazanavir and 1 to 3TC), compared to 4 out of 8 in the atazanavir/ritonavir group (2 subjects had resistance emerge to 3TC and, and 1 subject had resistance emerge to DDI and 1 subject had resistance emerge to NFV).

In the treatment-experienced group, 34/54 (63%) subjects in the atazanavir group (34/34 phenotypable) and 18/47 (38%) in the atazanavir/ritonavir group (17/18 phenotypable) had both

baseline and on study phenotypic resistance profiles. Among subjects in the atazanavir group, there were demonstrable phenotypic resistance to multiple antiretroviral classes including 3TC (12%), ABC (12%), AMP (3%), D4T (9%), atazanavir (12%), ddI (21%), LPV (3%), NFV and NVP (3% each), ritonavir (3%), SQV (9%), TDF (12%), and ZDV (9%). In atazanavir/ritonavir group, there were demonstrable phenotypic resistance to multiple antiretroviral classes including 3TC and ABC (18% each), AMP and atazanavir (6% each), ddI (12%), LPV (12%), NFV (6%), NVP (6%), ritonavir (6%), SQV (6%), and ZDV (12%).

Discussion on Efficacy

Treatment experienced patients (55% of all included) included 41% of subjects with prior PI experience and the median length of ARV treatment was 5 years. Although the study was not primarily intended to assess efficacy the following observations are made:

Atazanavir alone

Overall 40% of subjects had HIV RNA <400 c/ml at week 48 and 26% were <50c/ml. Only 25% of adolescents had HIV RNA <400 c/ml and 16% were <50c/ml. Results for treatment experienced patients were 30% and 15% for HIV RNA <400 and <50 c/ml, the equivalent figures for treatment naïve subjects were 58 and 45%. Results seen for atazanavir alone were less favourable than those for atazanavir/ritonavir seen in paediatric subjects in this study. Virological response to atazanavir alone does also not achieve levels comparable to that seen in adults receiving atazanavir/ritonavir. The data presented do not support unboosted atazanavir for treatment of HIV infected subjects and the MAH has not requested this indication.

Atazanavir with ritonavir

Overall 61% of subjects had HIV RNA <400 c/ml at week 48 and 46% had <50c/ml. Of the 97 patients included, 48% of patients were treatment naïve. Treatment naïve patients had HIV RNA <50 c/ml in 66% of cases. This does not compare favourably to figures from studies in adults where 78% of treatment naïve patients had HIV RNA <50 c/ml at week 48 (study 138 BMS, see SmPC Reyataz hard capsules). Treatment experienced subjects had HIV RNA < 400c/ml in 43% and <50c/ml in 26%. Again, this does not compare favourably to adult figures of 53% <400c/ml and 36% <50c/ml (study 045, see SmPC Reyataz hard capsules). Mean HIV RNA decrease from baseline was -2.84 log10 for treatment naïve patients and -1.95 log10 for treatment experienced subjects. Comparable figures for adults were -3.09 log10 for treatment naïve and -1.93 log10 for experienced patients. Immunological parameters were similar.

The doses used were selected based on Day 7 PK and Day 40 safety data and not on the virological response. Data must be interpreted with caution, particularly in view of the small numbers of subjects that remain in each subgroup when results are separated between ART naïve and experienced patients.

With no active control arm in this study, which is the usual situation in studies with ARTs in children, and with difficulties in making inter-study comparisons, it can only be stated that the response rates to atazanavir/ritonavir were seemingly lower than would be expected from studies with atazanavir/ritonavir in adults.

The primary objective of the study was to establish a dose regimen in children. While the doses accepted (except for the dose for subjects from 5- <10kg) have met the MAH's preset exposure criteria, demonstration of clinical efficacy and safety are used to establish that the correct dose was selected for each age or weight bracket. Here, however, the very small subgroups make a full interpretation of the data difficult.

Resistance

On study resistance data were obtained from treatment naïve and experienced subjects who experienced virologic failure and had at least 2000c/ml HIV RNA. Newly emergent genotypic resistance profiles were observed for 10 ART-naïve subjects. As only 19 of the 81 ART naïve subjects had genotype profiles done at baseline, 10 out of 19 subjects tested on both occasions had virus with emergent genotypic resistance. Similarly, it appears from the data presented that newly emergent genotypic resistance profiles were observed in 63/83 viruses from ART-experienced subjects that were genotyped.

Of the 12 viruses from ART naïve subjects that were phenotyped at baseline and on study, 6 had evidence of newly emergent phenotypic resistance while on treatment. Among the 51 viruses from ART-experienced patients that were phenotyped at baseline and on- study the study report states that there was demonstrable phenotypic resistance to multiple antiretroviral classes. However it is not possible to discern the numbers of viruses that demonstrated resistance to multiple classes.

Virological failure (at < 50c/ml level) was observed in 22 of the 81 ART naïve patients and in 58 out of 101 ART experienced patients. It would appear that not every patient who experienced virological failure had newly emergent resistance. The reason for those remaining cases of virological failure is unclear, adherence or unpredictable exposure may have played a role.

Clinical safety - Data from study AI424020

Patient exposure

Median duration of treatment was 88.1 weeks (range 0.7 to 361.1 weeks). Median time on therapy was 97.6 weeks (range 0.7 to 361.1 weeks) for subjects receiving ATV alone (Part A, Groups 1 - 4) and 82.1 weeks (range 1.0 to 233.9 weeks) for subjects receiving ATV/RTV (Part B, Groups 5 - 8).

All Grades of Adverse Events

The most common adverse events (AEs) were laboratory abnormalities. Among the laboratory abnormalities; blood bilirubin unconjugated increased (92%) was the most common. AEs of any grade that were not laboratory abnormalities included cough (76%), pyrexia (47%), vomiting (45%), rash (40%), rhinorrhoea (39%), nasal congestion (33%), diarrhoea (31%), ocular icterus (23%), headache (23%), skin lesion (20%), and lymphadenopathy (22%).

Deaths

Three subjects died during the study; these 3 deaths were considered by the investigator not to be related to atazanavir. The causes of death were as follows: acute respiratory distress syndrome and sepsis (atazanavir, age 16, death 239 days after discontinuation of study drug), congestive heart failure secondary to HIV cardiomyopathy (atazanavir, age 13, death 136 days after discontinuation of study drug), and pneumonia and renal failure (atazanavir/ritonavir, age 23 months, death while on study medication).

Serious Adverse events

Overall serious AEs (SAEs) were reported for 48% of subjects. The most common SAEs were laboratory abnormalities. Among the laboratory abnormalities, blood bilirubin increase (36%) was the most common. The most frequently reported (>10%) Grade 2-4 AEs that were not laboratory abnormalities were cough (21%) and pyrexia (20%). By age group, SAEs were reported more often in Adolescents (63%) than in Children (44%) and Infants (34%). SAEs were reported more frequently (≥10% difference) in treatment-experienced subjects compared with treatment-naïve

subjects. Overall, 53% of subjects who received capsules and 39% who received powder had reported SAEs.

Differences in SAE rates between the subgroups arise from the different composition of the subpopulations in the AI424020 study. In the report, safety data were analysed and presented by treatment regimen, age group, formulation, prior treatment status, and region. Higher rates of SAEs were observed in ART-experienced subjects compared to ART-naïve subjects (56% vs. 38%), and in subjects from US compared to subjects from Africa (52% vs. 40%), especially in ATV/RTV group (52% vs. 35%) (Table 3.1).

Table 3.1: Serious Adverse Events - Enrolled Subjects by Category

	ATV N = 85		ATV/RTV N = 98		Overall N = 183	
	n/N	%	n/N	%	n/N	%
Overall	**44/85**	**52**	**44/98**	**45**	**88/183**	**48**
Age						
Infant	4/8	50	6/21	29	10/29	34
Children	19/42	45	24/56	43	43/98	44
Adolescents	20/32	63	9/14	64	29/46	63
Adults	1/3	33	5/7	71	6/10	60
Formulation						
Powder	11/19	58	15/47	32	26/66	39
Capsule	33/66	50	29/51	57	62/117	53
Prior treatment status						
Naive	13/31	42	18/51	35	31/82	38
Experienced	31/54	57	26/47	55	57/101	56
Region						
US	33/63	52	30/58	52	63/121	52
South Africa	11/22	50	14/40	35	25/62	40

Source: Table 8.3B, AI424020 CSR.

On the other hand, 95% of ART-experienced subjects were from North America, indicating that these 2 factors were highly correlated. Higher percentages of ART-experienced subjects and US subjects were also observed in the capsule formulation relative to the powder and in adolescents relative to children. These subcategory analyses were intended to be descriptive only, as there were multiple baseline and on-study confounding factors within each subgroup that obscure comparisons. To further obfuscate the issue, the subgroups had different median time on study therapy, overall and by treatment. The study was not designed to single out factors that could cause a higher rate of SAEs and the MAH does not want to speculate based on possible random variation due to the amount of overlap of each of the factors.

PR Interval Prolongation

Based on actual ECG measurements, 44 subjects (24%) overall had asymptomatic AV block, 26 (31%) treated with atazanavir alone and 18 (19%) treated with atazanavir/ritonavir. Two (2)of the 44 cases were second degree AV block (one subject had a rare Mobitz type 1 second degree AV block that resolved without discontinuing study medication, a second subject experienced a Mobitz type 1 second degree AV block during sleep, which the investigators considered a normal variant in healthy children and which was not graded as per protocol). Of the 44 AV blocks measured, 5

subjects had an AV block reported as a SAE. Two subjects were discontinued from the study due to first degree AV block.

Other cardiac abnormalities
Grade 2-4 cardiac AEs were reported in 8 subjects, all of the 8 subjects received atazanavir alone (9%). These events were reported as AEs or SAEs by the investigator. One subject who received 800mg atazanavir twice daily instead of once for 3 days showed QRS prolongation with intraventricular conduction delay, with a return to normal after interruption of the study medication.

Cardiac Toxicity
According to the MAH, the therapeutic margin for cardiac toxicity in the paediatric population is consistent with that already established in adults. AI424020 is a dose-finding study that targets adult AUCs reference values of 45,000 ng*h/ml, which in adults are associated to average Cmax values of 4,400 ng/ml, and for which safety has been established. In adults, concentration dependent cardiac toxicity relates to the finding of asymptomatic PR prolongation driven by Cmax. Asymptomatic PR prolongation was observed more frequently in AI424020 than previously reported in adult trials.
This observation is expected given the higher Cmax values achieved on average in this study. Of note, Cmax values as high as 20,000 ng/ml (at least 3 times the adult average values) were well tolerated in paediatric subjects treated in this study. As Table 6.1 shows, although 32 of 182 subjects had Cmax above 7000 ng/ml for at least 8 weeks, only 4 of them were treated with ATV/RTV capsules (which is the proposed mode of dosing supported by this application).

Table 6.1 presents a summary of the subjects with the highest Cmax values (15-20 µg/ml) and the corresponding PR interval, confirming the tolerability of this drug in the upper bound of the therapeutic range in the paediatric population.

Table 6.1 PR Interval in Subjects with Cmax >15,000 ng/mL

Patient Identifier	Age (years)[a]	Treatment	Study Day	Cmax (ng/mL)	PR Interval (ms)	Reason for D/C
AI424020-105191	6	ATV	394	16,452	Trough predosing: 162-164 Post dosing 164-172	Site closure
AI424020-800045	3	ATV/RTV	8	15,207	Trough predosing: 120-124 Postdosing: 134-160	N/A
AI424020-500306	15	ATV	7	15,569	Trough predosing: 155-164 Post dosing: 153-198	Subject did not return for visits
AI424020-501315	6	ATV	525	20,802	Trough predosing: 140 138-152	Virologic failure

Source: AI424020 CSR Appendices 7.9B and 8.4.1
[a] At enrollment
D/C = discontinuation; N/A = not applicable (subject remained on treatment)

No other concentration-safety cardiac toxicity (i.e., QTc prolongation) was observed in the paediatric population, consistent with adults. In a definitive ECG study in healthy adults, there was no concentration-dependent effect of ATV on the QTc interval (using Fridericia's correction). In 1793 HIV-infected subjects receiving antiretroviral regimens, QTc prolongation was comparable in the ATV and comparator regimens. No healthy subject or HIV-infected subject treated with ATV in BMS studies had a QTc interval >500 msec. Consistent with the adult observations, QTc prolongations in the AI424020 study were infrequent, with only one subject experiencing a QTcB interval prolongation of 482 msec (highest QTcF 441 msec). This subject had a prolonged QTcB (440-446 msec) at baseline.

Intraventricular conduction delay has been reported very rarely with atazanavir therapy in adults, and only in the setting of known cardiac conduction abnormalities at baseline, in contrast to PR prolongation, which is observed more frequently. Based on the data from the AI424020 study, it is not anticipated that paediatric patients would be at increased risk for cardiac failure due to conduction delay relative to adults. Four subjects in this study had investigator-documented QRS widening reported in the case report form. Of those, only one (Subject AI424020-800262) actually had a true prolongation relative to age with a value of 0.1 sec (normal for age: up to 0.08 sec). This subject had a history of cardiac abnormality and core pulmonare prior to enrolment and was treated with ATV unboosted at a dose of 1,100 mg QD (this dose not supported in this submission).

Hyperbilirubinemia, Jaundice, and Ocular Icterus in Overall Treated Subjects
In this study, any lab abnormality ≥ Grade 1 was reported as an AE. As an AE, hyperbilirubinemia (Grade 2-4) was reported in 65% of subjects overall (55% atazanavir, 73% atazanavir/ritonavir) Grade 3-4 total bilirubin levels were reported in 39% of subjects overall (41% atazanavir, 37% atazanavir/ritonavir). In addition, ocular icterus was reported in 5% of subjects, and jaundice was reported in 2% of subjects. Increased blood bilirubin levels/jaundice led to discontinuation of 5 atazanavir treated subjects (6%) and 4 atazanavir/ritonavir treated subjects (4%).

Among the subset of subjects age ≥3 months and <18 years (treatment naïve and treatment experienced), hyperbilirubinemia was reported as an AE (Grade 2-4) in 75% of subjects, Grade 3-4 total bilirubin levels were reported in 38% of those subjects overall.

Using the reporting requirements criteria as defined in the 2004 U.S Division of AIDS (DAIDS) Serious Adverse Experience Reporting Manual and a uniform upper limit of normal (ULN) of 1.2 mg/dl, the proportions of subjects in the paediatric cohort (excluding the 9 young adults age 18- 21) with normal baseline total bilirubin and Grade 3 to 4 on-study total bilirubin were 45%, 46%, and 44% for the overall population, atazanavir alone group, and atazanavir/ritonavir group, respectively. Using the DAIDS criteria, the proportions of subjects who received powder with normal baseline and Grade 3 to 4 on-study total bilirubin were 36%, 47%, and 32% for the overall population, atazanavir alone group, and atazanavir/ritonavir group, respectively.

Discontinuation of Study Therapy Related to Adverse Events
Discontinuations related to AEs were reported for 15% of subjects, 17 (20%) treated with atazanavir and 10 (10%) treated with atazanavir/ritonavir. 15 subjects (10 treated with atazanavir and 5 treated with (atazanavir/ritonavir) discontinued with the reason specified as 'toxicity'. In addition, 12 subjects had additional information on the discontinuation page that indicated the reason for discontinuing could have been related to an AE. Seven (7) out of 12 were treated in the atazanavir group and 5 were treated in the atazanavir/ritonavir group

Discontinuations related to cardiovascular events, including first degree heart block (n= 2), worsening of cardiomyopathy, QTcB interval > 470 msec, prolonged PR interval and bradycardia, and worsening cardiac condition (reported in 2 subjects), were reported in 3% of subjects overall (all received atazanavir alone). Five (5) atazanavir-treated subjects (6%) and 4 atazanavir/ritonavir treated subjects (4%) discontinued in relation to increased bilirubin levels/jaundice; 3 of these discontinuations were mandated by the protocol. In addition, 3 atazanavir-treated subjects (4%) and 0 atazanavir/ritonavir treated subjects were discontinued due to vomiting. Discontinuations due to other AEs were reported in 1 or 2 subjects in each group. A higher proportion of Adolescents (10/46, 22%) compared with Infants (3/29, 10%) and Children (13/98, 13%) had treatment discontinued related to AEs.

Treatment-emergent Diagnoses
The most common treatment-emergent diagnoses (Total ≥ 10%) were otitis media acute (28%), tinea infection (16%), pneumonia (15%), pharyngitis (14%), acute sinusitis (13%), acarodermatitis (11%), and impetigo (10%)

Discussion on Safety

The overall number of AEs is rather higher than would be expected.

In the atazanavir alone group, 10 (12%) subjects withdrew because of toxicity and a further 2 requested discontinuation. In the atazanavir/ritonavir group, 5 (5%) subjects withdrew due to toxicity and a further 5 requested discontinuation of treatment. Discontinuations due to adverse events were more frequent than seen in adult studies (5%), where discontinuations increased with dose.

Death occurred in 3 cases during the observed period, in 2 cases the patients were no longer on the study drug at the time of death. A causal link with the study medication was not considered to be likely.

The safety data observed in the current paediatric study confirmed the previously observed safety data in adults (prolongations in PR interval and occurrence of AV block in patients treated by ATV). These adverse events are dose-dependent. Therefore, since children are expected to present higher Cmax values than adults, this adverse event will have to be kept under close scrutiny in children.

Forty-four (44) paediatric patients (24%) presented an AV block in this study, 26 treated with ATV alone (31%) and 18 treated with ATV/RTV (19%). The higher percent of AV block in patients treated with unboosted ATV is in line with the higher total daily doses and Cmax observed in this group compared to RTV-boosted ATV.

This cardiotoxicity although even observed in adults may raise some specific concerns for the paediatric population insofar that:
- children are expected to present higher Cmax values than adults
- given that cardiotoxicity management is more likely required in the adult population than in paediatric population, performing a cardiac monitoring (outside specialised units) may reveal more complex in the paediatric clinical practice than in the adult clinical practice.

Therefore, clear message should be given as regards the precaution to be taken before and during the treatment by atazanavir/RTV in children.

The SmPC was improved to better cover the cardiac toxicity of atazanavir and the specificity for the paediatric population. Section 4.8 of the SmPC was revised to include the adverse events of PR prolongation and AV block with the relative incidence observed in adults and in children. Section 4.4 was revised to include a warning, relative to the risk of PR prolongations and AV blocks, clearly differentiating both populations of adults and children. The SmPC was further updated regarding the precaution (cardiac monitoring) to be taken before and during the treatment with atazanavir/RTV in paediatric patients taking into account the cardiotoxicity of the medicinal product. Further update on co-administration with drugs known as also prolonging the PR.

Hyperbilirubinaemia and jaundice were seen to a similar extent as observed in adult studies.

Generally, the safety profile in children and adolescents appears similar to that in adults, although most AEs seem to occur with higher frequencies in this paediatric study. Comparison between the age brackets indicate a higher frequency of SAEs in adolescents compared to children and infants.

3.4. Pharmacovigilance system

Risk Management Plan

The MAH provided an updated RMP: version 2.2 from 12 March 2010, which is summarised in table 40 (see next page).
Table summary of the Risk Management Plan.

Table 40: Action Plan for Safety Concerns

Safety concern	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimization activities (routine and additional)
Important Identified Risks		
Cardiac conduction abnormalities	Routine PV activities (eg, monitoring, evaluation, and reporting of individual AE and literature reports, periodic aggregate safety data analysis, signal detection via MST/MRG, timely update of safety label)	**4.4 Special warnings and precautions for use** Dose related asymptomatic prolongations in PR interval with REYATAZ have been observed in clinical studies. Caution should be used with medicinal products known to induce PR prolongations. In patients with pre-existing conduction problems (second degree or higher atrioventricular or complex bundle-branch block), REYATAZ should be used with caution and only if the benefits exceed the risk (see section 5.1). *Paediatric population* Asymptomatic PR interval prolongation was more frequent in paediatric patients than adults. Asymptomatic first- and second-degree AV block was reported in paediatric patients (see section 4.8). Caution should be used with medicinal products known to induce PR prolongations. In paediatric patients with pre-existing conduction problems (second degree or higher atrioventricular or complex bundle-branch block), REYATAZ should be used with caution and only if the benefits exceed the risk. Cardiac monitoring is recommended based on the presence of clinical findings (e.g., bradycardia). **4.5 Interaction with other medicinal products and other forms of interaction** *Calcium channel blockers*: Bepridil: Co-administration with bepridil is contraindicated (see section 4.3). Diltiazem 180 mg QD (atazanavir 400 mg QD): No significant effect on atazanavir concentrations was observed. There was an increase in the maximum PR interval compared to atazanavir alone. Co administration of diltiazem and

Table 40:	Action Plan for Safety Concerns	
Safety concern	**Proposed pharmacovigilance activities (routine and additional)**	**Proposed risk minimization activities (routine and additional)**
		REYATAZ/ritonavir has not been studied. The mechanism of diltiazem/atazanavir interaction is CYP3A4 inhibition. An initial dose reduction of diltiazem by 50% is recommended, with subsequent titration as needed and ECG monitoring. Verapamil: Serum concentrations of verapamil may be increased by REYATAZ/ritonavir due to CYP3A4 inhibition. Caution should be exercised when verapamil is co-administered with REYATAZ/ritonavir. **4.8 Undesirable effects** *Cardiac disorders:* rare: oedema, palpitation *Vascular disorders*: uncommon: hypertension; Paediatric population: Both asymptomatic first-degree (23%) and second-degree (1%) atrioventricular block were reported in paediatric patients. **4.9 Overdose** Human experience of acute overdose with REYATAZ is limited. Single doses up to 1,200 mg have been taken by healthy volunteers without symptomatic untoward effects. At high doses that lead to high drug exposures, jaundice due to indirect (unconjugated) hyperbilirubinemia (without associated liver function test changes) or PR interval prolongations may be observed (see sections 4.4 and 4.8).
Hyperbilirubinemia	Routine PV activities (eg, monitoring, evaluation, and reporting of individual AE and literature reports, periodic aggregate safety data analysis, signal detection via MST/MRG, timely update of safety label)	**4.4 Special warnings and precautions for use** Co-administration of REYATAZ with ritonavir in doses greater than 100 mg once daily has not been clinically evaluated. The use of higher ritonavir doses might alter the safety profile of atazanavir (cardiac effects, hyperbilirubinemia) and therefore is not recommended. <u>Hyperbilirubinemia</u> Reversible elevations in indirect (unconjugated) bilirubin related to inhibition of UDP-glucuronosyl transferase (UGT) have occurred in patients receiving REYATAZ (see section 4.8). Hepatic transaminase elevations that occur with elevated bilirubin in patients receiving REYATAZ should be evaluated for alternative etiologies. Alternative antiretroviral therapy to REYATAZ may be considered if jaundice or scleral icterus is unacceptable to a patient. Dose reduction of atazanavir is not recommended because it may result in a loss of therapeutic effect and development of resistance. Indinavir is also associated with indirect (unconjugated) hyperbilirubinemia due to inhibition of UGT. Combinations of REYATAZ and indinavir have not been studied and co-

Table 40:	Action Plan for Safety Concerns	
Safety concern	**Proposed pharmacovigilance activities (routine and additional)**	**Proposed risk minimization activities (routine and additional)**
		administration of these medicinal products is not recommended (see section 4.5). **4.5 Interaction with other medicinal products and other forms of interaction** *Indinavir:* indinavir is associated with indirect unconjugated hyperbilirubinemia due to inhibition of UGT. Co-administration of REYATAZ/ritonavir and indinavir is not recommended (see section 4.4). **4.6 Pregnancy and lactation** There are no adequate data from the use of atazanavir in pregnant women. Studies in animals have not shown evidence of selective developmental toxicity or effects on reproductive function and fertility (see section 5.3). REYATAZ should be used during pregnancy only if the potential benefit justifies the potential risk. It is not known whether REYATAZ administered to the mother during pregnancy will exacerbate physiological hyperbilirubinemia and lead to kernicterus in neonates and infants. In the prepartum period, additional monitoring and alternative therapy to REYATAZ should be considered. **4.8 Undesirable effects** *Laboratory abnormalities* The most frequently reported laboratory abnormality in patients receiving regimens containing REYATAZ and one or more NRTIs was elevated total bilirubin reported predominantly as elevated indirect [unconjugated] bilirubin (87% Grade 1, 2, 3, or 4). Grade 3 or 4 elevation of total bilirubin was noted in 37% (6% Grade 4). Among experienced patients treated with REYATAZ 300 mg once daily with 100 mg ritonavir once daily for a median duration of 95 weeks, 53% had Grade 3-4 total bilirubin elevations. Among naive patients treated with REYATAZ 300 mg once daily with 100 mg ritonavir once daily for a median duration of 96 weeks, 48% had Grade 3-4 total bilirubin elevations (see section 4.4). Two percent of patients treated with REYATAZ experienced concurrent Grade 3-4 ALT/AST and Grade 3-4 total bilirubin elevations. The most frequently reported laboratory abnormality in paediatric patients receiving REYATAZ was elevation of total bilirubin (≥ 2.6 times ULN , Grade 3-4) which occurred in 45% of patients. Patients co-infected with hepatitis B and/or hepatitis C virus

Table 40:	Action Plan for Safety Concerns	
Safety concern	**Proposed pharmacovigilance activities (routine and additional)**	**Proposed risk minimization activities (routine and additional)**
		Among 1,151 patients receiving atazanavir 400 mg once daily, 177 patients were co-infected with chronic hepatitis B or C, and among 655 patients receiving atazanavir 300 mg once daily with ritonavir 100 mg once daily, 97 patients were co-infected with chronic hepatitis B or C. Co-infected patients were more likely to have baseline hepatic transaminase elevations than those without chronic viral hepatitis. No differences in frequency of bilirubin elevations were observed between these patients and those without viral hepatitis. The frequency of treatment emergent hepatitis or transaminase elevations in co-infected patients was comparable between REYATAZ and comparator regimens (see section 4.4). **4.9 Overdose** Human experience of acute overdose with REYATAZ is limited. Single doses up to 1,200 mg have been taken by healthy volunteers without symptomatic untoward effects. At high doses that lead to high drug exposures, jaundice due to indirect (unconjugated) hyperbilirubinemia (without associated liver function test changes) or PR interval prolongations may be observed (see sections 4.4 and 4.8). Treatment of overdose with REYATAZ should consist of general supportive measures, including monitoring of vital signs and ECG, and observations of the patient's clinical status. If indicated, elimination of unabsorbed atazanavir should be achieved by emesis or gastric lavage. Administration of activated charcoal may also be used to aid removal of unabsorbed drug. There is no specific antidote for overdose with REYATAZ. Since atazanavir is extensively metabolised by the liver and is highly protein bound, dialysis is unlikely to be beneficial in significant removal of this medicinal product.
Nephrolithiasis	Routine PV activities (eg, monitoring, evaluation, and reporting of individual AE and literature reports, periodic aggregate safety data analysis, signal detection via MST/MRG, timely update of safety label)	**4.4 Special warnings and precautions for use** Nephrolithiasis has been reported in patients receiving REYATAZ (see section 4.8). If signs or symptoms of nephrolithiasis occur, temporary interruption or discontinuation of treatment may be considered. **4.8 Undesirable effects** *Renal and urinary disorders*: Uncommon: nephrolithiasis, hematuria, proteinuria, pollakiuria Rare: kidney pain
Potential risk[a]		
QT prolongation	Routine PV activities (eg, monitoring, evaluation, and reporting of individual AE and	**4.4 Special warnings and precautions for use** Particular caution should be used when prescribing REYATAZ in association with

Table 40:	Action Plan for Safety Concerns	
Safety concern	**Proposed pharmacovigilance activities (routine and additional)**	**Proposed risk minimization activities (routine and additional)**
	literature reports, periodic aggregate safety data analysis, signal detection via MST/MRG, timely update of safety label)	medicinal products which have the potential to increase the QT interval and/or in patients with pre-existing risk factors (bradycardia, long congenital QT, electrolyte imbalances (see sections 4.8 and 5.3).
Kernicterus	Routine PV activities (eg, monitoring, evaluation, and reporting of individual AE and literature reports, periodic aggregate safety data analysis, signal detection via MST/MRG, timely update of safety label)	**4.2 Posology and method of administration** *Paediatric Patients (less than 3 months of age)*: REYATAZ has not been studied in children less than 3 months of age and is not recommended because of the potential risk of kernicterus.
Missing information		
Pregnancy and lactation	Routine PV activities (eg, monitoring, evaluation, and reporting of individual AE and literature reports, periodic aggregate safety data analysis, signal detection via MST/MRG, timely update of safety label). The Antiretroviral Pregnancy Registry, a prospective, observational study collects and evaluates data on the outcomes of pregnancy exposures to antiretroviral products in HIV-1 infected women.	**4.6 Pregnancy and lactation** There are no adequate data from the use of atazanavir in pregnant women. Studies in animals have not shown evidence of selective developmental toxicity or effects on reproductive function and fertility (see section 5.3). REYATAZ should be used during pregnancy only if the potential benefit justifies the potential risk. It is not known whether REYATAZ administered to the mother during pregnancy will exacerbate physiological hyperbilirubinemia and lead to kernicterus in neonates and infants. In the prepartum period, additional monitoring and alternative therapy to REYATAZ should be considered. It is not known whether atazanavir is excreted in human milk. Studies in rats have demonstrated that atazanavir is excreted in the milk. It is therefore recommended that mothers being treated with REYATAZ not breast-feed their infants. As a general rule, it is recommended that HIV infected women not breast-feed their infants in order to avoid transmission of HIV.
Renal impairment	Routine PV activities (eg, monitoring, evaluation, and reporting of individual AE and literature reports, periodic aggregate safety data analysis, signal detection via MST/MRG, timely update of safety label)	**4.2 Posology and method of administration** Patients with renal impairment: no dosage adjustment is needed (see section 5.2). REYATAZ with ritonavir is not recommended in patients undergoing haemodialysis (see sections 4.4 and 5.2). **4.4 Special warnings and precautions for use** No dosage adjustment is needed in patients with renal impairment. However, REYATAZ with ritonavir is not recommended in patients undergoing hemodialysis (see sections 4.2 and 5.2). **5.2 Pharmacokinetic properties**

Table 40:	Action Plan for Safety Concerns	
Safety concern	**Proposed pharmacovigilance activities (routine and additional)**	**Proposed risk minimization activities (routine and additional)**
		Impaired renal function: in healthy subjects, the renal elimination of unchanged atazanavir was approximately 7% of the administered dose. There are no pharmacokinetic data available for REYATAZ with ritonavir in patients with renal insufficiency. REYATAZ (without ritonavir) has been studied in adult patients with severe renal impairment (n=20), including those on haemodialysis, at multiple doses of 400 mg once daily. Although this study presented some limitations (i.e., unbound drug concentrations not studied), results suggested that the atazanavir pharmacokinetic parameters were decreased by 30% to 50% in patients undergoing hemodialysis compared to patients with normal renal function. The mechanism of this decrease is unknown. (See sections 4.2 and 4.4.)
Hepatic impairment	Routine PV activities (eg, monitoring, evaluation, and reporting of individual AE and literature reports, periodic aggregate safety data analysis, signal detection via MST/MRG, timely update of safety label). The collaborative epidemiologic D:A:D study (see Table 9) is collecting safety data, including hepatic, in HIV-infected subjects treated with combination antiviral therapy.	**4.2 Posology and method of administration** Patients with hepatic impairment: REYATAZ with ritonavir should be used with caution in patients with mild hepatic impairment. REYATAZ must not be used in patients with moderate to severe hepatic impairment (see sections 4.3, 4.4, and 5.2). **4.4 Special warnings and precautions for use** *Patients with coexisting conditions* Atazanavir is primarily hepatically metabolised and increased plasma concentrations were observed in patients with hepatic impairment (see sections 4.2 and 4.3). The safety and efficacy of REYATAZ has not been established in patients with significant underlying liver disorders. Patients with chronic hepatitis B or C and treated with combination antiretroviral therapy are at an increased risk for severe and potentially fatal hepatic adverse events. In case of concomitant antiviral therapy for hepatitis B or C, please refer also to the relevant Summary of Product Characteristics for these medicinal products (see section 4.8). Patients with pre-existing liver dysfunction, including chronic active hepatitis, have an increased frequency of liver function abnormalities during combination antiretroviral therapy and should be monitored according to standard practice. If there is evidence of worsening liver disease in such patients, interruption or discontinuation of treatment must be considered. **5.2 Pharmacokinetic properties** Impaired hepatic function: atazanavir is metabolised and eliminated primarily by the liver. The effects of hepatic impairment on the pharmacokinetics of atazanavir after a 300 mg dose with ritonavir have not been studied. Concentrations of atazanavir with or without ritonavir are expected to be

Table 40: Action Plan for Safety Concerns

Safety concern	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimization activities (routine and additional)
		increased in patients with moderately or severely impaired hepatic function (see sections 4.2, 4.3, and 4.4).
Pediatric population: • Safety data in pediatric patients < 6 years (<15 kg) • Limited safety data in children 6 years to less than 18 years of age.	Routine PV activities (eg, monitoring, evaluation, and reporting of individual AE and literature reports, periodic aggregate safety data analysis, signal detection via MST/MRG, timely update of safety label)	**4.2 Posology and method of administration** *Paediatric patients (less than 6 years of age):* REYAYAZ is not recommended in paediatric patients less than 6 years of age due to insufficient data on pharmacokinetics, safety, and efficacy. REYATAZ has not been studied in children less than 3 months of age and is not recommended because of the potential risk of kernicterus. REYATAZ oral powder must not be used in paediatric patients unable to swallow capsules due to insufficient data on pharmacokinetics, safety, and efficacy. **5.2 Pharmacokinetic properties** *Paediatric patients:* The pharmacokinetic parameters for atazanavir at steady state in paediatric patients were predicted by the population pharmacokinetic model and are summarized in Table 4 of the SmPC by weight ranges that correspond to recommended doses

[a] For potential off-label use in pediatric patients < 6 years of age, please refer to section 1.9.5

The updated RMP version 2.2 was agreed and accepted by the CHMP.

3.5. Overall discussion and benefit-risk assessment

Reyataz (atazanavir) is currently only indicated in HIV infected adults in combination with other antiretroviral medicinal products. Atazanavir has pharmacokinetics that allow once daily dosing in adults, which makes a paediatric development program desirable as adherence could be expected to improve with such a regimen in this population. Also, the introduction of a formulation allowing use in small children would be desirable.

The clinical development of antiretrovirals in children should focus on the dose selection. Its purpose is not the duplication of the clinical efficacy and safety demonstration obtained in adult patients. The selected dose should achieve comparable exposures in children as those observed in adults. Based on the underlying rational that this will lead to a comparable efficacy and safety profile of the medicine, no further clinical data would be required to support a positive benefit risk balance in this population.

However, during the initial evaluation, it was concluded that the dose selection of atazanavir boosted with ritonavir in the MAH's claimed paediatric indication, i.e. in children above 3 months of age, was far from being adequately substantiated by the MAH in support of the claimed extension of indication in children. Indeed, both the clinical study (AI424020/PACTG1020A) and the PPK analysis that supported the indication suffered from critical deficiencies. As a consequence a major objection was raised by the CHMP.

The followings issues have been addressed by the MAH within the submitted responses.

The main concern was a greater peak-to-trough ratio in children as compared to adult patients. From the data provided by the MAH, it was confirmed that mean Cmax values were higher, whereas mean Cmin values were lower in younger patients compared to older patients. However, mean AUC values were similar for patients in the whole age range from 6 to 13 years. Overall, it is clear that a greater peak-to-trough ratio was mainly observed in the youngest children and that in patients aged 6 years and older, this concern was quite alleviated with a significant less higher peak-to-trough ratio.

In response to the CHMP concern the MAH has only retained the limit of 6 years of age in its revised claim for the paediatric extension. Nonetheless the CHMP agreed with this proposal given the limitation of the data in younger children. The MAH is still encouraged to adequately develop the medicine in younger children than 6 years of age to answer a medical need.

Another concern raised was the absence of clinical data to substantiate the BW-based dosing recommended regimen, since only BSA-based doses were investigated in the clinical study. In responses to this concern, the MAH provided data comparing the proposed BW-based (derived from the modelling/simulation) to the BSA-based doses (administered in the clinical study). Based on these data the BW-based dosing can be accepted, all the more that it is more convenient in clinical practice.

As expected based on the clinical experience in adults, a much better response rate is obtained in antiretroviral naïve than in experienced children. This further illustrates the limitations of atazanavir/RTV to be used in moderately experienced patients. The benefit/risk of atazanavir/RTV in antiretroviral experienced paediatric patients was extensively discussed. Due to the very limited number of antiretroviral experienced children no clinical cut off could be determined in these patients. The indication was granted to allow the use of this boosted PI in some ARV experienced children (e.g. in children having stopped their boosted PI for intolerance or poor adherence, before having accumulated multiple PI resistance). However, strong warnings were included to make prescribers aware of the limitations of the data and results in experienced patients: "Atazanavir/ritonavir is not

effective in viral strains harbouring multiple mutations of resistance. While in adults no benefit can be expected in patients with ≥4 PI mutations, in treatment experienced children even lower numbers of PI mutations may be predictive of a lack of benefit."

It is worth noting that when focusing on the target population of the claimed indication, i.e. children aged 6-18 years, it only consists of 16 antiretroviral naïve patients and 25 antiretroviral experienced patients (please see discussion above). The indication was revised to highlight this limited amount of data. Even if it is acknowledged that it is not so far from the limitation of the database for other boosted PIs in paediatric patients, this is nevertheless very limited and requires reinforced post-marketing surveillance in this population (through the RMP). The MAH committed to submit a protocol for its involvement with the PENTA foundation cohorts to follow the paediatric population.

Based on the clinical experience gained in adults, hyperbilirubinemia represents the most salient aspect of the safety profile of atazanavir. As in adults, hyperbilirubinemia accounts for the most frequent serious adverse event observed in children. Nevertheless, it is admitted that hyperbilirubinemia, although frequent, is a manageable adverse event and does not give rise to serious safety concerns. Of note, this nevertheless may have some potential psychosocial impact in the adolescent population.

In addition to that, it is important to have a particular focus to the cardiotoxicity findings in the paediatric study submitted.

Forty-four (44) paediatric patients (24%) presented an AV block in this study, 26 treated with ATV alone (31%) and 18 treated with ATV/RTV (19%). This appears to be more frequent than in adults. The higher percent of AV block in patients treated with unboosted ATV was in line with the higher total daily doses and Cmax observed in this group compared to RTV-boosted ATV. The safety data observed in the current paediatric study confirmed the previously observed safety data in adults (prolongations in PR interval and occurrence of AV block in patients treated by ATV). These adverse events are dose-dependent.

This cardiotoxicity although even observed in adults may raise some specific concerns for the paediatric population insofar that

- children are expected to present higher Cmax values than adults
- given that cardiotoxicity management is more likely required in the adult population than in paediatric population, performing a cardiac monitoring (outside specialised units) may result to be more complex in children in clinical practice than in adults.

Therefore, sections 4.4 and 4.8 of the SmPC were revised to give a clear message as regards the precaution to be taken before and during the treatment by atazanavir/RTV in children.

3.6. Changes to the product information

Summary of Product Characteristics

Section 4.1 Therapeutic indications
The indication was extended for the treatment of HIV 1 infected paediatric patients 6 years of age and older in combination with other antiretroviral medicinal products.
The indication was revised to add Reyataz co-administration with low dose ritonavir.
A sentence was included to highlight that the indication was based on very limited data available from children aged 6 to less than 18 years. The indication was further amended to reflect that the clinical cut off (number of PI mutation) was applicable only for adults since it could not be determined for children.

Section 4.2 Posology and method of administration
This section was updated and the proposed dose of Reyataz capsules for paediatric patients is based on body weight. This section was revised to alert that Reyataz is not recommended in paediatric patients less than 6 years of age due to insufficient data on pharmacokinetics, safety, and efficacy. Furthermore, Reyataz has not been studied in children less than 3 months of age and is not recommended especially taking into account the potential risk of kernicterus.

Section 4.4 Special warnings and precautions for use
A strong warning was include alerting that Atazanavir/ritonavir is not effective in viral strains harbouring multiple mutations of resistance. While in adults no benefit can be expected in patients with ≥4 PI mutations, in treatment experienced children even lower numbers of PI mutations may be predictive of a lack of benefit.

The SmPC was improved to better cover the cardiac toxicity of atazanavir and the specificity for the paediatric population. This section was revised to include a warning, relative to the risk of PR prolongations and AV blocks, clearly differentiating both populations of adults and children. This section was further updated regarding the precaution (cardiac monitoring) to be taken before and during the treatment with atazanavir/RTV in paediatric patients taking into account the cardiotoxicity of the medicinal product. Further update on co-administration with drugs known as also prolonging the PR.

Section 4.8 Undesirable effects
This section was revised to include the adverse events of PR prolongation and AV block with the relative incidence observed in adults and in children and elevation of total bilirubin, the most frequently reported laboratory abnormality in paediatric patients.

Section 5.1 Pharmacodynamic properties
A sentence was introduced to make clear that the clinical data derived from this study are inadequate to support the use of atazanavir (with or without ritonavir) in children below 6 years of age.
The information on the study was further improved and a table was inserted detailing for the 25 antiretroviral paediatric patients the response rate depending on the number of PI mutations (as made for adults): 0-2; 3 and >4.

Section 5.2 Pharmacokinetic properties
This section was revised and improved with pharmacokinetic data for paediatric patients.

The PL was updated accordingly.

Annex II was updated with the last approved version of the RMP.

4. Conclusion

On 22 April 2010 the CHMP considered this Type II variation to be acceptable and agreed on the amendments to be introduced in the Summary of Product Characteristics, Annex II and Package Leaflet.