28 April 2016
EMA/340991/2016
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Reyataz

International non-proprietary name: atazanavir / atazanavir sulfate

Procedure No. EMEA/H/C/000494/X/0094/G

Note

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

Table of contents

List of abbreviations

3TC	lamivudine
ABC	abacavir
ADI	acceptable daily intake
AE	adverse event
AIDS	acquired immunodeficiency syndrome
ALT	alanine transaminase
ARV	antiretroviral
AST	aspartate transaminase
ATV	atazanavir; BMS-232632; Reyataz
AUC	area under the concentration-time curve
$AUC_{(TAU)}$	area under concentration-time curve in 1 dosing interval
AV	atrioventricular
BCS	Biopharmaceutics Classification System
BMS	Bristol-Myers Squibb Company
CDC	Centers for Disease Control
CHMP	Committee for Medicinal Products for Human Use
CLT/F/kg	apparent total oral clearance adjusted for body weight
C_{max}	maximum concentration
C*min*	plasma concentration 24 hours post-dose
CQA	Critical Quality Attribute
CSR	clinical study report
C_{trough}	trough concentration
ddI	didanosine
DILI	drug-induced liver injury
DoE	Design of experiments
DRV	darunavir
ECG	electrocardiogram
EFSA	European Food Safety Authority
EMA	European Medicines Agency
EU	European Union

FMEA Failure mode effects analysis

FTC emtricitabine

FUM Follow-Up Measure

GC Gas chromatography

HAART highly active antiretroviral therapy

HDPE High Density Polyethylene

HIV human immunodeficiency virus

HPLC High performance liquid chromatography

ICH International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use

IEC Independent Ethics Committee

IR Infrared

IR:ATR Infrared with Attenuated Total Reflectance accesory

IRB Institutional Review Board

ITT intent-to-treat

LAS lactic acidosis syndrome

LFT liver function test

LLDPE Linear Low Density Polyethylene

LPLV last patient last visit

LPV lopinavir

NNRTI non- nucleoside reverse transcriptase inhibitor

NRTI nuclestide reverse transcriptase inhibitor

PD pharmacodynamic(s)

PDCO Paediatric Committee

PENTA Paediatric European Network for the Treatment of AIDS

Ph. Eur. European Pharmacopoeia

PI protease inhibitor

PIP Paediatric Investigation Plan

PK pharmacokinetic(s)

PPK population pharmacokinetic(s)

QbD Quality by design

QCC quartile composite C_{trough}

QD once daily

QTPP	Quality target product profile
RfM	request for modification
RH	Relative Humidity
RMP	Risk Management Plan
RNA	ribonucleic acid
RTV	ritonavir
SAE	serious adverse event
SHL	symptomatic hyperlactatemia
SmPC	Summary of Product Characteristics
ULN	upper limit of normal

1. Background information on the procedure

1.1. Submission of the dossier

The Marketing Authorisation Holder, Bristol-Myers Squibb Pharma EEIG, (MAH) submitted to the European Medicines Agency (EMA) on 3 March 2015, an application for a grouping of variations in accordance with Article 7(2) of Commission Regulation (EC) No 1243/208, consisting of an extension of the marketing authorisation, a type II C.1.6.a variation and a Type IB C.1.11.z. variation for Reyataz.

The MAH applied for an extension of the marketing authorisation consisting of the addition of a new strength and pharmaceutical form (50mg oral powder) to support the extension of the target population covered by the authorised therapeutic indication for Reyataz to treat HIV-1 infected paediatric patients of at least 3 months of age and weighing at least 5 kg, in combination with other antiretroviral medicinal products.

The MAH applied for the following indication for the 50mg oral powder:

REYATAZ oral powder, co-administered with low dose ritonavir, is indicated in combination with other antiretroviral medicinal products for the treatment of HIV-1infected paediatric patients at least 3 months of age and weighing at least 5kg (see section 4.2).

Based on available virological and clinical data from adult patients, no benefit is expected in patients with strains resistant to multiple protease inhibitors (≥4PI mutations). The choice of REYATAZ in treatment experienced adult and paediatric patients should be based on individual viral resistance testing and the patient's treatment history (see sections 4.4 and 5.1).

For the approved 100mg, 150mg, 200mg and 300mg hard capsules, the applicant requested the following variations:

Extension of Indication to include the treatment of HIV-1 infected paediatric patients aged 6 to less than 18 years with strains resistant to multiple protease inhibitors (≥4PI mutations).

As a consequence, sections section 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC were updated in light of new paediatric data.

The Package Leaflet and the RMP (v.10) are updated in accordance.

Update of the RMP (v.10) to address the requirement of lack of long-term safety data and the inclusion of category 3 additional pharmacovigilance activities, interim long term safety reports from Stage 2 (follow-up part) of Studies AI424397 and AI424451 up to the study completion. This RMP also includes an update of paediatric-related data and minor revisions concerning nephrolithiasis.

The requested variations proposed amendments to the Summary of Product Characteristics, Annex II, Labelling and Package Leaflet.

The legal basis for this application refers to:

Article 19 of Commission Regulation (EC) No 1234/2008 and Annex I (point 2 c and d) thereof – Extension of marketing authorisation.

Article 15 of Commission Regulation (EC) No 1234/2008 – Notification procedure for minor variations of type IB.

Article 16 of Commission Regulation (EC) No 1234/2008 – "Prior Approval" procedure for major variation of type II.

Article 7(2) of Commission Regulation (EC) No 1234/2008- Grouping of variations.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on MAH's own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

Information on Paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0098/2014 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0098/2014 was completed.

The PDCO issued an opinion on compliance for the PIP P/0098/2014.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific Advice

The applicant received Scientific Advice from the CHMP on 21 June 2012 and 30 May 2013 The Scientific Advice pertained to quality, non-clinical and clinical aspects of the dossier.

Licensing status

Reyataz oral powder has been given a Marketing Authorisation in the United States on 02 June 2014.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Joseph Emmerich

- The application was received by the EMA on 3 March 2015.
- The procedure started on 26 March 2015.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 16 June 2015. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 12 June 2015.

- PRAC assessment overview, adopted by PRAC on 9 July 2015.
- During the meeting on 23 July 2015, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 23 July 2015.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 26 November 2015.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 4 January 2016.
- PRAC RMP Advice and assessment overview, adopted on 14 January 2016.
- During the CHMP meeting on 28 January 2016, the CHMP agreed on a list of outstanding issues to be addressed in writing by the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 29 March 2016.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP members on 15 April 2016.
- During the meeting on 28 April 2016, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for the group of variations for Reyataz.

2. Scientific discussion

2.1. 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 and children aged 6 years and older in combination with other antiretroviral medicinal products.

Reyataz is currently approved as 100 mg, 150 mg, 200 mg and 300 mg capsules of atazanavir. An oral Powder (50 mg/1.5 g oral powder, equivalent to 50 mg atazanavir free base) for use in adults only was approved but has not been marketed in the EU.

The current capsule dosing recommendations for paediatric patients at least 6 years of age are 150, 200, and 300 mg ATV (all with 100 mg RTV) for patients with body weights of 15 - < 20 kg, 20 - < 40 kg, and ≥40 kg, respectively. The adult dose is 300 mg ATV, also with 100 mg RTV.

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 (containing aspartame 10%) for use in HIV-1 infected paediatric patients from 3 months to <6 years of age weighing 5 to <25 kg was submitted in 2009.

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 and the PPK analysis that supported the indication suffered from critical deficiencies. As a consequence a major objection was raised by the CHMP.

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 C_{min} 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. The CHMP agreed with this proposal given the limitation of the data in younger children. In conclusion, on the basis of study AI424020, the indication of Reyataz was only extended to children ≥ 6 years of age with the current marketed capsules.

The current application (EMEA/H/C/000494/X/0094/G) for Reyataz consists of:

- Line extension with the addition of an oral powder presentation (50 mg/sachet),
- Extension of indication to paediatric patient at least 3 months of age and weighing at least 5 kg.

This new application is supported by 2 clinical studies (AI424397 and AI424451) and a PK/PD analysis.

Paediatric indications of the other PIs in EU:

Protease Inhibitor	Paediatric formulations	EU Indication
Kaletra	Oral solution	Children ≥ 2 years
Prezista	Oral solution	Children ≥ 3 years and ≥ 15 kg
Telzir	Oral suspension	Children ≥ 6 years and ≥ 25 kg
Aptivus	Oral solution	Children ≥ 2 years
Invirase	None	Adolescents ≥ 16 years

According the current approved protease inhibitors for use in the paediatric population, there is a clinical need for children under 2 years of age. Therefore, a line extension of Reyataz for infants and children ≥ 3 months of age and ≥ 5 kg is welcomed.

Two studies, AI424397 and AI424451, evaluated the PK, dose regimen, and efficacy and safety of atazanavir following administration of the ATV oral powder formulation. Previously, the relative bioavailability of the ATV powder formulation (10% aspartame) initially used in paediatric clinical trials had been assessed in Study AI424025. A taste assessment study (AI424466) was conducted in healthy adult subjects to compare the initial 10% aspartame formulation with the proposed 4.2% aspartame containing formulation.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as oral powder containing 50 mg of atazanavir (as sulphate) as active substance.

Other ingredients are: aspartame (E951), sucrose and orange vanilla flavour.

The product is available in polyester film/aluminum/polyethylene sealant film sachets, as described in section 6.5 of the SmPC.

2.2.2. Active Substance

The active substance, atazanavir sulphate, used in the manufacture of Reyataz powder for oral use is the same being used for the approved Reyataz 100 mg, 150 mg, 200 mg and 300 mg hard. No new information on the active substance has been provided within this line extension application.

2.2.3. Finished Medicinal Product

Description of the product and pharmaceutical development

The aim of this line extension was to develop an alternative formulation to the currently marketed hard capsules, adequate for paediatric use (patients from 3 months to 6 years who may have difficulties in swallowing capsules) with a suitable strength to provide appropriate dose increments.

The finished product is an off-white to pale yellow powder packaged in sachets containing atazanavir sulphate (equivalent to 50 mg of atazanavir base), aspartame and sucrose as sweeteners, and orange vanilla flavour. Each sachet dosage unit contains 1500 mg of oral powder. The lowest possible unit strength was chosen in order to achieve flexible dosing across all body weights.

Atazanavir sulphate is a non-hygroscopic, ionisable compound, thus its aqueous solubility and partition coefficient are pH-dependent. The solubility of atazanavir sulphate is pH-dependant. It is classified as a low solubility and highly permeable drug according to the Biopharmaceutics Classification System

(BCS class II). Atazanavir is produced as a non-solvate The oral powder manufacturing process does not have an impact on the active substance crystalline form.

The strategy for formulation and process development followed a quality by design (QbD) approach.

The quality target product profile (QTPP) used to guide development was: a powder for oral use with acceptable taste containing 50 mg of atazanavir per sachet, targeted for patients ranging from 3 months to 8 years. The product is to be packaged in PET/Al/LLDPE sachets and should offer rapid dissolution and absorption in the gastrointestinal tract. It should meet the specifications and have a shelf-life of at least 24 months at room temperature.

The critical quality attributes (CQAs) of the finished product are: appearance, identity, assay, content uniformity, impurities and microbial limits.

The product development aimed at obtaining a powder of acceptable taste in the targeted paediatric population (3 months to 8 years), which could be easily poured from the sachet to ensure complete drug delivery, and showing rapid dissolution and absorption.

A powder for oral multidose suspension was first considered. The first prototype (prototype I) formulation was tested in a human relative bioavailability study which showed that its bioavailability was lower relative to the registered Reyataz hard capsules formulation with respect to atazanavir Cmax and $AUC_{(INF)}$. It was hypothesized that one of the excipients selected was responsible for the lower bioavailability. Therefore, the development of powder for oral suspension was discontinued.

A modified dispersible powder formulation (prototype II) was thus developed. A second relative bioavailability study with the revised formulation indicated similar bioavailability with respect to atazanavir $AUC_{(INF)}$ to that of the Reyataz hard capsules formulation. Therefore, the revised II formulation was selected for further development.

This formulation was further modified to comply with the Paediatric Investigation Plan (PIP) request from the EMA Paediatric Committee (PDCO) to reduce the level of one of the exicipients proposed to levels below the limit set by the EU Food Safety Authority acceptable daily intake for all recommended doses based on age/weight group. . The formulation was adjusted to ensure an acceptable palatability and sweetness and the same drug substance to total excipient ratio were maintained. A number of prototype formulations using various high intensity sweeteners were further developed and evaluated for stability. Based on the outcome of the stability study, two prototype formulations were selected to be carried through in an adult taste studyagainst the previously revised formulation. Based on these results, the final formulation for further development and commercialisation was selected.

A biowaiver for the reduced aspartame formulation used in Phase 3 clinical studies and proposed for commercialisation was requested and accepted based on:

- Demonstration of high permeability of the active pharmaceutical ingredient.
- Demonstration that the change in formulation will not affect gastric emptying, secretion, and/or pH;
- Comparison of the compositions of the formulations, showing that the overall drug-to-total excipient ratio is unchanged.
- Demonstration of similar dissolution profiles between the revised and final formulations in different media.

The phase 2 and 3 clinical trials were conducted using a multi-dose bottle presentation. Later, phase 3 clinical trials were conducted using 50 mg sachet dosage unit presentation. The sachet presentation

was developed to reduce the risk of adulteration and miss counting the number of scoops especially for doses ≥150 mg. The sachet presentation utilised the same bulk blend composition and manufacturing process as that used for the multi-dose bottle presentation.

All excipients are well known pharmaceutical ingredients which are commonly used as taste masking agents in paediatric formulations. Aspartame and sucrose (sweeteners) comply with the requirements of the Ph.Eur. monographs. An in-house monograph was presented for the non-compendial excipient orange-vanilla flavor (flavouring agent). This was considered acceptable. However, the applicant is recommended to evaluate the feasibility to develop an alternative method for identity. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.1.1 of this report. The assurance of the active and excipient compatibility is confirmed by the long term stability study of the finished product.

In addition, in–use compatibility studies were conducted to support the stability of atazanavir sulphate powder for oral use dispersed in food vehicles. They are described in the stability section of this report.

The manufacturing development was evaluated through the use of a failure mode effect analysis (FMEA) method in order to define critical process steps and process parameters that may have an influence on the finished product quality attributes. The risk identification was based on the experience from formulation development, process design and scale-up studies. The development adequately addressed the impact of the milling/mixing process parameters on the quality attributes of the blend, performing a Failure Mode and Effect Analysis (FMEA) and several design of experiments (DOE).Sachet filling has also been sufficiently studied. The proposed overfill has been adequately justified. The appropriateness of the filling process parameters were demonstrated by extensive sampling from nine commercial batches.

With regards to the proposed QC dissolution method, attempts were made by the applicant to improve its discriminatory power. Method parameters that could potentially have an impact on the discriminating ability of the method were also assessed. The dissolution experiments performed indicate that the dissolution profile remains unaffected by altering the studied method parameters.

Moreover the chosen conditions for the dissolution method were able to discriminate the prototype and final formulations which showed different *in vivo* behaviour, demonstrating the *in vivo* relevance of the method. Considering the formulation and the manufacturing process, the proposed QC dissolution method is deemed acceptable.The primary packaging proposed for marketing is foil laminated sachets made from PET (Polyethylene Terephthalate)/Al(Aluminium)/LLDPE (Linear Low Density Polyethylene). Appropriate testing standards have been described for the laminated foil of the sachet and for the LLDPE bag used to store the final powder blend. The sealant film of the sachet that comes in contact with the product as well as the LLDPE material of the bulk bag comply with in the EU 10/2011 directive and subsequent revisions.

The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Manufacture of the product and process controls

The manufacturing process includes a series of high-impact milling and high-shear mixing operations followed by filling the final blend into sachet dosage units. As mentioned in the stability section of the report, bulk holding time was also validated.

Transportation of the final blend from the site of manufacture to the site of sachet filling was validated. Overall, the manufacturing process description is sufficiently detailed and the process parameters

ranges are in line with those defined during process development. In process controls are deemed sufficient.

Based on the amount on knowledge gained during development and since the manufacturing process is a standard process, in line with the EMA guideline on process validation (EMA/CHMP/CVMP/QWP/BWP/70278/2012-Rev1), a process validation scheme to be conducted at commercial scale prior to marketing has been presented.

Product specification

The finished product release specifications include appropriate tests for this kind of dosage form: description, identification (HPLC, IR:ATR), assay (HPLC), uniformity of dosage units (Ph. Eur.), impurities (HPLC), dissolution (Ph. Eur.) and microbial limits (Ph. Eur). The proposed acceptance criteria are supported by commercial batch results and stability data and are in line with ICH guidance where applicable.

The proposed specification is supported by data from eleven commercial scale batches, stability data and formulation and process development data. The absence of a test for water content has been adequately justified.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay has been presented.

Batch analysis results are provided for eleven commercial scale batches confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

The finished product is released on the market based on the above release specifications, through traditional final product release testing.

Stability of the product

Stability data of three commercial scale batches of finished product stored for up to 24 months under long term conditions (5 °C and 30 °C / 75% RH) and for up to 6 months under accelerated conditions at 40 °C / 75% RH according to the ICH guidelines were provided. The stability batches of medicinal product are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

In addition, one batch was tested after exposure to the stress condition of 50 °C, seven freeze-thaw cycles (between -20 °C and 40 °C / 75% RH), and exposure to 30 °C / 75% RH and room light in an open sachet.

A bulk stability study was also conducted on one batch of atazanavir powder for oral use packaged in the bulk container through 12 months of storage at 30 °C / 65% RH.

Samples were tested for appearance, assay, related substances, aspartame degradant, water content and dissolution. Identification, content uniformity and microbial quality were also assessed in long term studies. The analytical procedures used have been appropriately validated and are stability indicating.

No significant changes were observed in the long-term stability studies apart from a slight change in colour after 24 months storage at 30 °C / 75% RH with no impact on assay or degradation products.

Stability results from accelerated studies also showed a change in powder colour after 6 months storage), and a slight increase of aspartame degradant within the specification limits. No trends were observed in any of the other parameters.

The results from the stress study showed an increase in aspartame degradant at 50 °C . No change was observed in any of the other parameters. In the freeze-thaw cycling studies all parameters remained with acceptance criteria and only a slight increase in total impurities was evidenced. The open-sachet studies showed an increase in water content in the light-exposed and protected samples, with no impact on the other parameters. They also showed that the powder is not sensitive to room light exposure.

As mentioned in the manufacture section of the report, bulk holding time was also evaluated and validated. The results showed little or no change in mean potency, total impurities, water content or dissolution, and appearance. A change in powder colour and a slight increase of aspartame degradant results were observed. Also, two leachables from the container were identified at the 12-month time point. The levels of these leachables were below the reporting level through 9 months storage. Other parameters showed no significant changes. The applicant investigated the possibility of using an alternative packaging material, but no alternative was found. Based on a toxicological evaluation of these leachables, it was concluded that the levels observed at the 12 month time-point present negligible risk to children. Nevertheless, these are controlled in the finished product specification. Therefore, the proposed bulk container and bulk storage period of six months are deemed acceptable at the time of opinion. However, the applicant is recommended to continue the efforts to substitute the proposed bulk product container with a different container that does not generate them, while assuring acceptable bulk stability. Since the product is to be administered by dispersing the powder in food vehicles, compatibility in –use studies were also conducted on three batches of finished product after storage for 0, 12 and 24 months at 30 °C / 75% RH, using different vehicles for dispersion according to a matrixing plan. The product mixed with food/vehicle was stored for up to 2 hours at 30 °C / 75% RH room-light exposed or protected. The results from these studies demonstrated that the product mixed with food/vehicle is not sensitive to room light exposure. Also, there was no significant change in the parameters tested, except for an increase in aspartame degradant for the powder mixed with some of the vehiclesNevertheless, the estimated intake of this degradant is significantly below the ADI levels (FAO, WHO). These data support the recommendation in the SmPC (section 6.6) that administration should be done within one hour of preparation.

Based on available stability data, the proposed shelf-life of 36 months without special storage conditions, and the in–use shelf-life after mixing with food or beverage of up to 1 hour at temperatures not above 30 °C, as stated in the SmPC (section 6.3) are acceptable.

Adventitious agents

All excipients used in the manufacture of the finished product are non-animal derived materials, with the exception of sucrose. In the processing of sucrose, animal-derived bovine bone charcoal is used as a filtering agent. The charcoal is covered by a valid TSE CEP.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

No new information on the active substance has been provided within this line extension application. The active substance has already been assessed as active substance in the already authorised Reyataz 100, 150, 200 and 300 mg hard capsules.

Information on development, manufacture and control of the finished product has been presented in a satisfactory manner.

The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and

uniform performance in clinical use. Nevertheless, the applicant is recommended to further evaluate the feasibility to develop alternative method for the identification flavouring agent orange vainilla flavor, and to continue his efforts to substitute the current drug product bulk container with an alternative container that does not generate the leachables observed.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.2.6. Recommendations for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

-Although the specifications for the non-compendial excipient are considerate adequate at the time of opinion, the applicant is recommended to evaluate the feasibility to develop an alternative method for identity testing.

-The proposed bulk product container is deemed acceptable. It has been demonstrated that the leachables observed present negligible risk to children. However, the applicant is recommended to continue the efforts to substitute the proposed bulk product container with a different container that does not generate them, while assuring acceptable bulk stability.

2.3. Non-clinical aspects

The MAH has not submitted any new non-clinical data in support of this application, but has provided a short justification based notably on the lack of nonclinical findings that preclude the paediatric use of Reyataz and the available clinical data in the paediatric population.

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 <25 Kg was submitted 2009. No non-clinical data have been submitted to support this variation (notably no toxicity study in juvenile animals of a relevant species). Therefore the CHMP stated that the MAH should provide an up-to date non-clinical overview, highlighting what is new and what is form the initial marketing authorisation application, with all the relevant published and/or proprietary data to support the indication for children of 3 months of age and older up to 25 kg. The safety of the use of atazanavir should be discussed in particular for infants, toddlers and children.

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.

Despite the lack of answer to the toxicology concern raised during the last extension application (EMEA/H/C/494/X/58) in 2009, it appears that no specific concerns were identified by the NcWG during the Paediatric Investigational Plan agreed on 27 October 2010. Therefore the lack of specific toxicity studies in juvenile animals could be considered as acceptable. Moreover, it is 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. 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 peri /post-natal toxicity study.

2.3.1. Ecotoxicity / environmental risk assessment

An updated environmental risk assessment (ERA) for atazanavir was recently conducted as part of the atazanavir/cobicistat fixed dose combination MAA filing (EVOTAZ, EMEA/H/C/003904). Although paediatric patients ages 3 months to 6 years are being added to current patient population for atazanavir (6 years and older), this group of patients was not excluded from the prevalence values used in the most recent ERA for atazanavir (which used a conservative assumption for HIV-1 prevalence of the total population) and has be considered in the PEC calculation in MAA filing EMEA/H/C/003904.

The doses of atazanavir (200-300 mg/day) for the new formulation are lower than what was used in the most recent PEC calculation (400 mg/day); accordingly the PEC calculation shown below which uses 400 mg/day can be considered conservative. The most recent calculation is shown in Equation 1.

Equation 1

$PEC_{sw\text{-}refined}$ = (DOSEai* Fpen (1-Metab))/(WasteWinhab * Dilution)

PEC_{SW}	Predicted environmental concentration in surface water	
$DOSE_{ai}$	Maximum daily dose consumed per inhabitant	400 mg/inh-d
Fpen	Market penetration	0.013
Metab	Removal by human metabolism	0
WASTEWinhab	Amount of wastewater per inhabitant per day	200 L/(inh-d)
Dilution	Dilution factor	10 (Default)

PECSW-refined = [400mg/(inh-d) * 0.0013 * (1-1)]/[200 L/inb-d) * 10]

PECSW-refined = 0.0026 mg/L

PECSW-refined = 2.6 µg/L

2.3.2. Discussion on non-clinical aspects

No new non-clinical data have been submitted in support of this application. Atazanavir is authorised (150, 200, and 300 mg hard capsules) and extensive non-clinical data are available with Atazanavir. There are also comprehensive paediatric clinical data that adequately support the proposed paediatric population and indication. The CHMP considered that no new non-clinical data are required in support of this application.

2.3.3. Conclusion on the non-clinical aspects

The CHMP considered that there are no non-clinical objections and/or concerns that will preclude the approval of the extension application.

2.4. Clinical aspects

2.4.1. Introduction

The clinical development plan for ATV in paediatric patients was initially based on findings from Study AI424020 (also designated as Paediatric AIDS Clinical Trials Group 1020-A) that exhibited comparable safety of the combination of ATV/ritonavir (RTV) to those in the adult studies.

The data from Study AI424020 were previously submitted and reviewed to support the currently approved ATV capsule dosing in paediatric patients 6 years and older in the European Union (EU) and other countries.

Two studies, AI424397 (PRINCE I) and AI424451 (PRINCE II) as well as a relative bioavailability study in adults (AI424025), and the results of a taste assessment study in adult healthy volunteers (AI424466) were submitted in support of this application.

PRINCE I and PRINCE II evaluated the PK, dose regimen, and efficacy and safety of atazanavir following administration of the ATV oral powder formulation, coadministered with ritonavir, in paediatric patients aged ≥ 3 months to < 11 years with HIV infection.

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

Table 1: Tabular overview of clinical studies

Type of Study	Study Identifier	Objective(s) of the Study	Study Design & Type of Control	Test Products; Dosage Regimen; Route of Administration	No. of Subjects	Diagnosis of Subjects	Duration of Treatment
Phase 3b, efficacy, safety, and PK	AI424397	To assess the efficacy, safety, and PK of ATV powder and RTV optimized regimens in a cohort of ARV-naive or -experienced pediatric subjects with HIV (Week 48 analysis)	Prospective, open-label, international, multicenter, nonrandomized, 2-stage study in pediatric subjects	ATV oral powder (50 mg/sachet) at doses recommended per protocol (150 mg for 5 - < 10 kg; 200 mg for 10 - < 15 kg; 250 mg for 15 - < 25 kg weight once daily) and RTV oral solution (80 mg/mL) once daily	Total treated: 56	Pediatric subjects with HIV ≥ 3 months to < 5 years and 6 months of age and weighing ≥5 - < 25 kg	Stage 1: 48 weeks Stage 2: until subjects are 18 years or indication is approved locally
Phase 3b, efficacy, safety, and PK	AI424451	To assess the efficacy, safety, and PK of ATV powder and RTV optimized regimens in a cohort of ARV-naive or -experienced pediatric subjects with HIV (interim analysis)	Prospective, open-label, international, multicenter, nonrandomized, 2-stage study in pediatric subjects	ATV oral powder (50 mg/sachet) at doses recommended per protocol (150 mg for 5< 10 kg; 200 mg for 10 - < 15 kg; 250 mg for 15 - < 25 kg weight once daily) and RTV oral solution (80 mg/mL) once daily	Total treated: 99	Pediatric subjects with HIV ≥3 months to < 11 years and weighing ≥ 5 - < 35 kg	Stage 1: 24 weeks Stage 2: until subjects are 18 years or indication is approved locally
Phase 1 bioavailability study	AI424025	To assess the bioavailability of ATV from a powder formulation vs. a capsule formulation	Open-label, randomized, 4-treatment, 4-period, single-dose, crossover study	Treatment 1: 400 mg ATV in 12 g oral powder with 4 oz applesauce Treatment 2: 400 mg ATV in 12 g oral powder with 50 mL water Treatment 3: 400 mg ATV (2 x 200 mg) capsule Treatment 4: ATV 2 x 200 mg capsule with 4 oz applesauce	Total treated: 8	Healthy adult volunteers	Single dose of each treatment
Phase 1 taste assessment study	AI424466	To compare the overall sweetness, palatability, and safety of 2 new ATV powder formulations to the current ATV	Double-blind, randomized, 3-treatment, 3-period, 3-sequence, crossover study	Treatment A: 15 mg/5 mL current ATV powder Treatment B: 15 mg/5 mL ATV powder with 4.2% aspartame Treatment C: 15 mg/5 mL ATV powder with	Total treated: 12	Healthy adult volunteers	Single dose of each treatment

		powder formulation		4.2% aspartame + Sucralose			

2.4.2. Pharmacokinetics

Posology

The recommended dose of Reyataz capsules in adults is 300 mg once daily taken with ritonavir 100 mg once daily and with food. Currently, the paediatric dosing using capsules is detailed in the **Error! Reference source not found.**:

Table 2: Current dose for paediatric patients (6 years to less than 18 years of age) for Reyataz capsules with Ritonavir

Body weight (kg)	Reyataz once daily dose	Ritonavir once daily dose[a]
15 to less than 20	150 mg	100 mg[b]
20 to less than 40	200 mg	100 mg
At least 40	300 mg	100 mg

[a] Ritonavir capsules, tablets or oral solution
[b] Ritonavir oral solution no lower than 80 mg and not more than 100 mg may be used for paediatric patients from 15 kg to less than 20 kg who cannot swallow ritonavir capsules/tablets

Reyataz oral powder is the addition of this extension. It is available for paediatric patients at least 3 months of age and weighing at least 5 kg. For patients who have reached 6 years of age, switching to Reyataz capsules is encouraged as soon as they are able to swallow capsules.

Table 3: Proposed dose for paediatric patients (at least 3 months of age and weighting at least 5 kg) for Reyataz oral powder with Ritonavir

Body weight (kg)	Reyataz once daily dose	Ritonavir once daily dose
At least 5 to less than 15	200 mg (4 sachets[a])	80 mg[b]
At least 15 to less than 25	250 mg (5 sachets[a])	80 mg[b]
At least 25	300 mg (6 sachets[a])	100 mg[c]

a Each sachet contains 50 mg of Reyataz
b Ritonavir oral solution
c Ritonavir oral solution or capsule/tablets

It has to be underlined that as part of the response to the D120 LOQ, the POPPK dataset was updated with paediatric data from studies AI424397 and AI424451. Although the updated model supports the originally proposed oral powder dosing recommendations for ATV, the capsule dosing recommendations were revised:

Table 4: Proposed revised dose for paediatric patients (6 years to less than 18 years of age) for Reyataz capsules with Ritonavir

Body weight (kg)	Reyataz once daily dose	Ritonavir once daily dose[a]
15 to less than 20	200 mg	100 mg[b]
At least 20	300 mg	100 mg

[a] Ritonavir capsules, tablets or oral solution
[b] Ritonavir oral solution no lower than 80 mg and not more than 100 mg may be used for paediatric patients from 15 kg to less than 20 kg who cannot swallow ritonavir capsules/tablets

Reyataz oral powder must be taken QD with food.

Development

Atazanavir powder for oral use was developed for use in paediatric patients who are unable to swallow a solid oral dosage form. The original ATV powder formulation contained 10% aspartame, which exceeded the acceptable daily intake of 40 mg/kg/day as determined by the European Food Safety Authority (EFSA) in paediatric subjects in lower weight bands. Based on a Paediatric Committee (PDCO) request, the ATV oral powder was reformulated with reduced aspartame (4.2%) and sucrose substitution.

The relative bioavailability of the ATV oral powder that was initially used in paediatric clinical trials was assessed in Study AI424025. The other clinical PK studies provided were studies AI424397 (PRINCE I)

and AI424451 (PRINCE II). Main PK parameters are summarized in **Error! Reference source not found.**.

Table 5: Summary statistics of ATV oral powder PK parameters for studies AI424397 and AI424451 combined

Treatment Group [N]	ATV/ RTV Regimen	Cmax (ng/mL) Geo.Mean (%CV) Min-Max	AUC(TAU) (ng•h/mL) Geo.Mean (%CV) Min-Max	Cmin (ng/mL) Geo.Mean (%CV) Min-Max	Tmax (h) Median (Min-Max)	CLT/F (L/h) Geo.Mean (%CV) Min-Max	CLT/F/kg (L/h/kg) Geo.Mean (%CV) Min-Max
5 to < 10 kg [20]	150/80	4131 (55) 1110-9660	32503 (61) 10441-94352	336 (76) 11.4-1330	1.58 (1.40-12.0)	4.61 (60) 1.6-14.4	0.65 (62) 0.2 - 1.8
5 to < 10 kg [10]	200/80	4466 (59) 607-12200	39519 (54) 6268-93597	550 (60) 101-1330	1.60 (1.4-4.0)	5.06 (122) 2.1-31.9	0.66 (105) 0.3-3.4
10 to < 15 kg [18]	200/80	5197 (53) 390-15000	50305 (67) 6697-189971	572 (111) 11.2-4870	1.97 (1.00-6.00)	3.98 (118) 1.1-29.9	0.32 (122) 0.1 - 2.6
15 to < 25 kg [32]	250/80	5394 (46) 1480-11400	55687 (45) 19309-121141	686 (68) 177-2570	2.54 (1.43-8.00)	4.49 (58) (2.06-12.9)	0.24 (55) 0.095 - 0.645
25 to < 35 kg [8]	300/100	4209 (52) 1160-8950	44329 (63) 7172-117805	468 (104) 51.2-3010	3.42 (1.5-6.1)	6.77 (127) 2.5-41.8	0.25 (107) 0.1-1.2

2.4.2.1. Methods

Analytical methods

Bristol-Myers Squibb Company conducted the bioanalytical assay for ATV using a validated high performance liquid chromatography-tandem mass spectrometry (LC-MS/MS method). This analytical method was used in the clinical pharmacology study, AI424025. Tandem Labs, a bioanalytical contract research organization, conducted the analytical assay for ATV and ritonavir (RTV) using this validated LC-MS/MS method. The analytical method was also used in the paediatric clinical studies, AI424397 and AI424451.

MAH Atazanavir plasma LC-MS/MS Method

Atazanavir was measured in human plasma by a validated high performance LC-MS/MS method. All plasma samples were obtained from blood collected into tubes containing potassium ethylene-diamine-tetraacetic acid (EDTA) as an anticoagulant and processed by an off-line solid phase extraction (SPE) method. The validated method fulfilled all requirements and recommendations regarding linearity, precision, accuracy, sensitivity, and specificity at the time of the study. The data from the method validation runs demonstrated that the range of reliable response was 1 to 1,000 ng/mL, with a lower limit of quantitation (LLOQ) of 1 ng/mL. Stability data were established as follows: bench-top stability in human plasma for at least 24 hours, 2 freeze-thaw cycles, and long-term stability at -20°C for 2 weeks. Samples from all studies were analysed within these periods of known stability.

Tandem Laboratories Atazanavir and Ritonavir plasma LC-MS/MS Method

Atazanavir and RTV were simultaneously measured in human plasma by a validated high performance LC-MS/MS method. All plasma samples were obtained from blood collected into tubes containing potassium EDTA as an anticoagulant and processed by an off-line SPE method. This method fulfilled all

current requirements and recommendations regarding linearity, precision, accuracy, sensitivity, and specificity. The data from the method validation runs demonstrated that the range of reliable response were 10.0 to 10,000 ng/mL, with an LLOQ of 10.0 ng/mL for ATV and 5.0 to 5,000 ng/mL, with an LLOQ of 5.0 ng/mL for RTV. Stability data were established as follows: bench-top stability for at least 24 hours, 6 freeze-thaw cycles, processed sample stability for at least 143 hours at room temperature, and long-term stability at -20°C for at least 777 days. Samples from all studies were analysed within these periods of known stability.

Table 6: Summary of bioanalytical methods used in clinical PK studies

Document Control No.	Analyte	Sample Matrix	Method	Regression Model	Standard Curve Range (ng/mL)	Assay Precision (%CV[b])		Accuracy (% Deviation[c])	Stability (RT,[d] F/T,[e] LTS[f])	Study No.
						Inter-	Intra-			
910066951	ATV	Human Plasma EDTA	LC-MS/MS[a]	Linear Weighted, $1/x^2$	1-1,000	≤ 5.17%	≤ 6.65%	± 3.2%	RT = 24 hr, F/T = 2 cycles, LTS = 2 weeks @ -20°C;	AI424025
930017944	ATV	Human Plasma EDTA	LC-MS/MS[a]	Quadratic Weighted, $1/x^2$	10.0-10,000	≤ 5.8%	≤ 6.5%	± 3.7 %	RT = 24h, F/T = 6 cycles at -20°C, processed sample stability 143 hr at RT, LTS = 777 days @ -20°C	AI424397 AI424451
	RTV			Quadratic Weighted, $1/x^2$	5.0-5,000	≤ 6.2%	≤ 8.9%	± 1.6%		

a LC-MS/MS = high performance liquid chromatography with tandem mass spectrometry.
b %CV = coeffiecient of variance.
c %Dev = % deviation from nominal.
d RT = room temperature.
e F/T = freeze-thaw.
f LTS = long-term stability (frozen)

2.4.2.2. Pharmacokinetic data analysis

AI424025:

Relevant pharmacokinetic parameters of ATV were estimated using a non-compartmental analysis (NCA). The following pharmacokinetic parameters were provided: AUC_{inf}, C_{max}, T_{max}, $T_{1/2}$ and relative bioavailability (calculated as $\frac{Geometric\ Mean\ AUC_{Inf,powder}}{Geometric\ Mean\ AUC_{Inf,capsule}} * 100$).

AI424397 (PRINCE I) and AI424451 (PRINCE II):

At week 2, the following relevant pharmacokinetic parameters of ATV were estimated using a non-compartmental analysis (NCA):

- C_{max},
- AUC_{tau} (Area under the concentration-time curve, in 1 dosing interval from time 0 to 24 hours post observed dose),
- C_{min} (Plasma concentration 24 hours post observed dose. Pre-observed dose concentration is used as an estimate of C_{min} if sample 24 hours post dose is not collected.),
- T_{max},
- CLT/F (calculated as Dose/AUC_{tau}),
- CLT/F/Kg.

2.4.2.3. Statistical analysis

AI424025:

ANOVA was performed on ln-transformed AUC_{inf} and C_{max} and confidence intervals were calculated.

The ANOVA model included evaluation of sequence, subject nested into sequence, period and treatment effects.

AI424397 (PRINCE I) and AI424451 (PRINCE II):

Summary statistics were performed on the PK parameters calculated.

2.4.2.4. Absorption

Bioequivalence

Study AI424025 compared powder and capsule formulations in different conditions.

Study AI424025: was an open-label, randomized, 4-treatment, 4-period, single-dose, crossover study balanced for first-order residual effects to assess the bioavailability of a 400 mg dose of ATV in a 12-g oral powder formulation (10% aspartame formulation) relative to the capsule formulation dose of 400 mg. Eight healthy subjects received the following 4 treatments in a random sequence:

- 400 mg ATV in a modified 12-g powder formulation mixed with 4 ounces applesauce,
- 400 mg ATV in a modified 12-g powder formulation mixed with 50 mL water,
- 400 mg ATV dose (2 x 200 mg capsules) with water (reference treatment),
- The contents of 2 x 200 mg ATV capsules mixed with 4 ounces applesauce.

The study took place from 10/02/2000 to 16/12/2000. This study was performed in accordance with GCP. The clinical phase was conducted at the Clinical Pharmacology Unit of the BMS clinical research centre (Hamilton, NJ, USA). Assays for drug concentration, PK analysis and statistical analysis were performed by BMS.

Information on batch and description of study drugs is given in Table 7.

Table 7: Study drug information for AI424025

Drug	Strength	Formulation	Route	Batch Number	Description
BMS-232632	400 mg	Oral powder	oral	N00006	Off-white to pale yellow powder free from visible evidence of contamination
BMS-232632	200 mg	capsule	oral	C99274	Two-piece gray opaque size 0, hard gelatin capsule filled with white to light yellow granules which may appear as powder

All treatments were administered within 5 minutes of completing a light meal. Each period was separated by 72 hours and < 2 weeks. Blood samples for PK analysis were collected at pre-dose and up to 24 hours after each dose of study drug. Samples were taken pre-dose and 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 5, 6, 8, 12, 18 and 24 hours after dosing, in labelled tubes containing K_3EDTA.

Sample size of eight subjects was justified.

2.4.2.5. Study conduct and results

Eight subjects entered the study. One subject withdrew consent after having received the first period dose, and was not replaced. Seven subjects completed the study and were included in the PK analysis. All subjects were male, and their age ranged from 28 to 41 years old.

Atazanavir was readily absorbed following oral administration of single doses of 400 mg of ATV in an oral formulation mixed with applesauce or water, as intact capsules, or as capsule contents mixed with applesauce. Median peak plasma concentrations were achieved in 1.5 to 2 hours, with a mean half-life of approximately 5 hours.

Table 8: Summary statistics for ATV in Study AI424025

PK Parameter	Treatment A (N=7)	Treatment B (N=7)	Treatment C (N=7)	Treatment D (N=7)
Cmax (ng/mL) Geo.Mean (%CV)	2244.19 (55)	2112.54 (32)	2912.09 (34)	2078.61 (42)
AUC(INF) (ng.h/mL) Geo.Mean (%CV)	9932.67 (40)	10424.46 (31)	10115 (42)	9226.57 (42)
Tmax (h) Median (Min, Max)	1.50 (1.00, 2.00)	1.50 (1.50, 3.00)	1.50 (1.00, 2.00)	2.00 (1.50, 3.00)
T-HALF (h) Mean (SD)	4.48 (0.78)	4.68 (0.60)	5.05 (1.61)	4.90 (0.94)

Treatments: A = ATV 400 mg in 12 g oral powder formulation mixed with 4 oz of applesauce; B = ATV 400 mg in 12 g oral powder formulation mixed with 50 mL of water; C = ATV 400 mg (2 x 200 mg) in a capsule formulation; D = contents of 2 x 200 mg ATV capsules mixed with 4 oz applesauce

Relative to the capsule formulation, ATV maximum plasma concentration (C_{max}) was approximately 22%, 27%, and 28% lower, following administration of the oral powder mixed with applesauce, the oral powder mixed with water, and the capsule contents mixed with applesauce, respectively. However, ATV area under the plasma concentration-time curve from time zero to infinite time in all 3 test treatments was similar to the reference capsule formulation; the ratio of geometric mean 90% confidence interval (CI) for the oral powder mixed with applesauce and water was contained within the usual criteria to conclude bioequivalence (0.80 to 1.25) with regard to ATV AUC_{inf}, while the lower bound of the 90% CI for ATV AUC_{inf} was just below 0.80 for the capsule contents mixed with applesauce.

Table 9: Summary of results of bioequivalence for ATV PK parameters in Study AI424025

PK Parameter	Treatment	Adjusted Geometric Mean	Ratio of Geometric Means Relative to Capsule Point Estimate (90% CI)
Cmax (ng/mL)	A	2360.79	0.777 (0.610, 0.990)
	B	2205.30	0.726 (0.570, 0.925)
	C	3037.65	---
	D	2178.75	0.717 (0.563, 0.913)
AUC(INF) (ng.h/mL)	A	10184.18	0.998 (0.867, 1.149)
	B	10668.97	1.046 (0.908, 1.204)
	C	10204.40	---
	D	9362.17	0.917 (0.797, 1.056)

Treatments: A = ATV 400 mg in 12 g oral powder formulation mixed with 4 oz of applesauce; B = ATV 400 mg in 12 g oral powder formulation mixed with 50 mL of water; C = ATV 400 mg (2 x 200 mg) in a capsule formulation; D = contents of 2 x 200 mg ATV capsules mixed with 4 oz applesauce

Although this study was small (N=7), and was not powered to assess bioequivalence, based on ATV AUC_{inf}, the ATV oral powder appeared to provide similar overall systemic exposures (i.e., AUC_{inf}) to the ATV capsule. While ATV C_{max} was slightly lower with the powder relative to the capsule, C_{max} is not the expected PK parameter driving efficacy. Therefore, this formulation (with 10% aspartame) was selected for development in paediatric subjects. Results from this study supported the further assessment of this ATV oral powder formulation in the paediatric dose-finding study, AI424020. This ATV oral powder formulation was also utilized in Studies AI424397 and AI424451.

2.4.2.6. Influence of food

In study AI424025, the oral powder (10% aspartame) was given in fed condition, and was mixed with either applesauce or water. There was no strict bioequivalence test between those two arms, but the PK parameters were in similar ranges between the two arms.

2.4.3. Pharmacokinetics in target population

In Studies AI424397 and AI424451, the PK of ATV were evaluated following administration of the ATV oral powder formulation (assessed in Study AI424025) in paediatric patients with HIV infection aged 3 months to < 11 years. The dose range of ATV studied was 150 to 300 mg in subjects weighing 5 to < 35 kg, stratified by body weight, administered with RTV. The dosing regimens for these studies were selected using a PPK modelling and simulation approach, and the model included covariates such as body weight on clearance and relative bioavailability of different formulations in paediatric subjects. This model was used to aid in selecting dosing regimens that were predicted to provide systemic exposures to ATV (when boosted with RTV) that were comparable to those observed in adults.

RTV-boosted ATV systemic exposures in paediatric were subjects similar to those demonstrated to be efficacious in the adult population.

AI424397 (PRINCE I)

Study AI424397 (PRINCE I) is an ongoing prospective, single arm, open-label, international, multicentre study to evaluate the safety, efficacy, and PK of ATV oral powder boosted with RTV liquid with an optimized nucleoside reverse transcriptase inhibitor (NRTI) background therapy in HIV-infected paediatric patients 3 months to < 6 years of age. A secondary objective of the study was to assess the PK profile of ATV oral powder with RTV in paediatric subjects in terms of ATV Cmax and area under the plasma concentration-time curve (AUC). There are 3 treatment groups in the study, based on body weight:

- 5 to < 10 kg treated with ATV 150 mg once daily (QD),
- 10 to < 15 kg treated with ATV 200 mg QD,
- 15 to < 25 kg treated with ATV 250 mg QD,

Each with RTV 80 mg oral solution QD and with an optimized NRTI background therapy. These doses of ATV oral powder in paediatric subjects were selected based on ATV systemic exposures that were projected by PK modelling and simulation to be similar to those observed in adults treated with ATV 300 mg capsule formulation given with RTV 100 mg QD.

Study AI424397 consisted of 2 stages. In Stage 1, all subjects were administered ATV oral powder (with RTV) at doses according to body weight. Subjects entered Stage 2 when they either reached an age of 6 years, reached a body weight of 25 kg, or if they had received treatment with ATV oral powder for 48 weeks in Stage 1. Intensive PK assessments and trough PK samples were collected during Stage 1 only.

Intensive PK sampling was conducted at Week 2 in all subjects with samples collected up to 24 hours post-dose. There were 20, 18, and 15 subjects with evaluable ATV PK data in the 5 to < 10 kg, 10 to < 15 kg, and 15 to < 25 kg weight bands, respectively.

Table 10: Summary statistics of ATV PK parameters in Study AI424397

Treatment Group [N]	Cmax (ng/mL) Geo.Mean (%CV) Min - Max	AUC(TAU) (ng•h/mL) Geo.Mean (%CV) Min - Max	Cmin (ng/mL) Geo.Mean (%CV) Min - Max	Tmax (h) Median (Min - Max)	CLT/F (L/h) Geo.Mean (%CV) Min - Max	CLT/F/kg (L/h/kg) Geo.Mean (%CV) Min - Max
5 kg to < 10 kg [20]: ATV/RTV 150/80 mg QD	4131 (55) 1110-9660	32503 (61) 10441-94352	336 (76) 11.4-1330	1.58 (1.40-12.0)	4.61 (60) 1.6-14.4	0.65 (62) 0.2-1.8
10 kg to < 15 kg [18]: ATV/RTV 200/80 mg QD	5197 (53) 390-15000	50305 (67) 6697-189971	572 (111) 11.2-4870	1.97 (1.00-6.00)	3.98 (118) 1.1-29.9	0.32 (122) 0.1-2.6
15 kg to < 25 kg [15]: ATV/RTV 250/80 mg QD	6172 (37) 3560-10400	61485 (36) 31599-117171	698 (67) 238-2410	1.83 (1.40-6.00)	4.07 (36) 2.1-7.9	0.24 (38) 0.1-0.5

Geometric mean (CV) ATV Cmax, AUC(TAU), and Cmin in HIV-infected adult patients (N=10) treated with ATV/RTV 300/100 mg QD are 4422 (58) ng/mL, 46073 (66) ng.h/mL, 636 (97) ng/mL, respectively.

Following administration of ATV oral powder with RTV oral solution, ATV was rapidly absorbed, with median time of maximum plasma concentration (T_{max}) across the groups ranging from 1.5 to 2 hours. Geometric mean area under the plasma concentration-time curve over 1 dosing interval [AUC_{tau}], C_{max}, and plasma concentration 24 hours post-dose (C_{min}) increased with increasing dose. Apparent oral clearance (CLT/F) of ATV was relatively similar between the 3 treatment groups, while ATV apparent oral clearance adjusted for body weight (CLT/F/kg) was highest in the lowest weight band (5 to < 10 kg) and decreased as the weight bands increased.

The variability in the ATV PK parameters from the lowest 2 weight bands was relatively high, with the 10 to < 15 kg weight band demonstrating the highest variability, while variability was considerably lower in the highest weight band (15 to < 25 kg). The variability in ATV C_{min} was relatively large for all weight bands, with the greatest variability observed within the 10 to < 15 kg weight band.

An additional analysis was conducted for a subset of subjects in the 5 to < 10 kg weight band aged 3 to < 6 months in order to explore age-related differences in ATV systemic exposures in very young subjects.

Table 11: Summary statistics of ATV PK parameters in subjects aged 3 to less than 6 months in Study AI424397

Treatment Group [N]	Cmax (ng/mL) Geo.Mean (%CV) Min - Max	AUC(TAU) (ng•h/mL) Geo.Mean (%CV) Min - Max	Cmin (ng/mL) Geo.Mean (%CV) Min - Max	Tmax (h) Median (Min - Max)	CLT/F (L/h) Geo.Mean (%CV) Min - Max	CLT/F/kg (L/h/kg) Geo.Mean (%CV) Min - Max
3 to < 6 months	3240 (61) 1110-7960	25875 (57) 15635-57672	383 (64) 235-1040	1.5 (1.4-12.0)	5.80 (41) 2.6-9.6	0.87 (47) 0.3-1.6

In this subset (all subjects were in the 5 to < 10 kg weight band treated with ATV/RTV 150/80 mg QD), geometric mean values for ATV C_{max} and AUC_{tau} appeared to be slightly lower than those ATV systemic exposures of the broader treatment group (Table 10), while the geometric mean ATV C_{min} value was similar to the geometric mean observed in the broader treatment group. Geometric mean ATV CLT/F and CLT/F/kg for this subset of subjects was higher than that observed for the broader treatment group; however, the range of ATV CLT/F and CLT/F/kg values observed in this subset was largely similar to that observed for the broader treatment group. Overall, the ATV systemic exposures for these 9 subjects were distributed within the range observed for the rest of the subjects in Treatment A.

Overall, geometric mean ATV C_{max}, AUC_{tau}, and C_{min} at the doses administered in each weight band increased with increasing ATV dose; however, individual ATV systemic exposure data for the 3 weight bands demonstrated considerable overlap.

AI424451 (PRINCE II):

Study AI424451 (PRINCE II) is an ongoing, prospective, single arm, open-label, international, multicentre study to evaluate the safety, efficacy, and PK of ATV oral powder boosted with RTV with an optimized NRTI background therapy in HIV-infected paediatric subjects 3 months to < 11 years of age. A secondary objective of the study is to describe the PK profile of ATV oral powder with RTV only for subjects in an age/weight group or receiving a dose that did not have intensive PK assessed in Study AI424397.

Study AI424451 consists of 2 stages. In Stage 1, all subjects are administered ATV oral powder (with RTV) at doses according to body weight. Subjects enter Stage 2 when they either have received 48 weeks of ATV oral powder treatment or reach a body weight of 35 kg. Intensive PK assessments and trough PK samples are collected during Stage 1 only.

Intensive PK sampling was conducted at Week 2 only for subjects in an age/weight group as follows:

- Subjects who entered the study weighing 25 to < 35 kg.
- Subjects who became 6 years of age during Stage 1 of the study and received an increase in the ATV dose and had intensive PK sampling approximately 2 weeks after initiation of the new dose.
- Subjects who became 6 years of age during Stage 1, but did not increase their dose of ATV, and intensive PK sampling was conducted at a regularly scheduled Stage 1 visit.
- Subjects enrolled in the new 5 to < 10 kg weight band receiving ATV 200 mg with RTV 80 mg.

Ten subjects in the 5 to < 10 kg weight band treated with ATV/RTV 200/80 mg had evaluable intensive PK. Twenty-five subjects with evaluable intensive PK data in Study AI424451 were between the ages of 6 and 11 years; 17 were in the 15 to < 25 kg weight band and treated with ATV/RTV 250/80 mg QD, and 8 were in the 25 to < 35 kg weight band and treated with ATV/RTV 300/100 mg QD. Intensive PK collection stopped for subjects who were between the ages of 6 and 11 years in Stage 1 and treated with ATV/RTV 250/80 mg QD during the study, because a sufficient number of samples had already been collected to draw meaningful conclusions.

Table 12: Summary statistics of ATV Pharmacokinetic Parameters in Study AI424451

Treatment Group [N]	Cmax (ng/mL) Geo.Mean (%CV) Min - Max	AUC(TAU) (ng•h/mL) Geo.Mean (%CV) Min - Max	Cmin (ng/mL) Geo.Mean (%CV) Min - Max	Tmax (h) Median (Min - Max)	CLT/F (L/h) Geo.Mean (%CV) Min - Max	CLT/F/kg (L/h/kg) Geo.Mean (%CV) Min - Max
5 to < 10 kg [10]: ATV/RTV 200/80 mg QD	4466 (59) 607-12200	39519 (54) 6268-93597	550 (60) 101-1330	1.60 (1.4-4.0)	5.06 (122) 2.1-31.9	0.66 (105) 0.3-3.4
15 to < 25 kg [17]: ATV/RTV 250/80 mg QD[a]	4789 (55) 1480-11400	51027 (53) 19309-121141	675 (70) 177-2570	2.72 (1.5-8.0)	4.90 (64) 2.1-12.9	0.24 (64) 0.1-0.6
25 to < 35 kg [8]: ATV/RTV 300/100 mg QD	4209 (52) 1160-8950	44329 (63) 7172-117805	468 (104) 51.2-3010	3.42 (1.5-6.1)	6.77 (127) 2.5-41.8	0.25 (107) 0.1-1.2

Geometric mean (CV) ATV Cmax, AUC(TAU), and Cmin in HIV-infected adult patients (N=10) treated with ATV/RTV 300/100 mg QD are 4422 (58) ng/mL, 46073 (66) ng.h/mL, and 636 (97) ng/mL, respectively

Following administration of ATV oral powder with RTV, ATV was rapidly absorbed, with median T_{max} across the 3 weight bands ranging from 1.6 to 3.4 hours, with the lowest weight band (5 to < 10 kg) exhibiting the most rapid absorption and the highest weight band (25 to < 35 kg) exhibiting the least

rapid absorption. While ATV C_{max} in the 15 to < 25 kg weight band treated with ATV/RTV 250/80 mg seemed slightly higher than the other 2 weight bands, the geometric mean C_{max} was comparable between the 5 to < 10 kg weight band treated with ATV/RTV 200/80 mg and the 25 to < 35 kg weight band treated with ATV/RTV 300/100 mg. Geometric mean ATV AUC_{tau} was lowest in the 5 to < 10 kg weight band treated with ATV/RTV 200/80 mg while the highest geometric mean AUC_{tau} was observed in the 15 to < 25 kg weight band, also treated with ATV/RTV 200/80 mg. The lowest geometric mean ATV C_{min} was observed in the 25 to < 35 kg weight band treated with ATV/RTV 300/100 mg, while the highest geometric mean ATV C_{min} was observed in the 15 to < 25 kg weight band treated with ATV/RTV 200/80 mg. Variability was high (%CVs of 64% to 127%); however, geometric mean ATV CLT/F was largely consistent between the 3 weight bands. When adjusted for body weight, geometric mean ATV CLT/F/kg was highest in the lowest weight band (5 to < 10 kg weight band treated with ATV/RTV 200/80 mg) and was comparable between the 15 to < 25 kg weight band treated with ATV/RTV 200/80 mg and 25 to < 35 kg weight band treated with ATV/RTV 300/100 mg.

2.4.3.1. Across-studies analysis

Dose selection

The ATV dosing regimens (when given with RTV) for the clinical studies were selected using a one compartment POPPK modelling and simulation approach, with covariates such as body weight on clearance and relative bioavailability of different formulations included in the model. The model was used to select ATV/RTV dosing regimens that were predicted to provide ATV systemic exposures in paediatric patients similar to those observed in the adult population.

Doses proposed

The following table summarises the proposed doses for the paediatric weight cohorts and the resulting exposure in terms of C_{min}, C_{max} and AUC.

Table 13: Summary Statistics of ATV PK Parameters for the Proposed Dosing Recommendations

PK Parameter	5 - < 10 kg ATV/RTV 200/80 mg QD (N=10)	10 - < 15 kg ATV/RTV 200/80 mg QD (N=18)	15 - < 25 kg ATV/RTV 250/80 mg QD (N=32)	25 - < 35 kg ATV/RTV 300/100 mg QD (N=8)	HIV-infected Adults ATV/RTV 300/100 mg QD (N=10)
Cmax (ng/mL)	4466 (59)	5197 (53)	5394 (46)	4209 (52)	4422 (58)
AUC (ng.h/mL)	39519 (54)	50305 (67)	55687 (45)	44329 (63)	46073 (66)
Cmin (ng/mL)	550 (60)	572 (111)	686 (68)	468 (104)	636 (97)

Dose justification for the 5- <10kg weight band

Two doses of atazanavir (150 mg and 200mg, both given with ritonavir 80 mg) were evaluated. Observed exposure parameters are shown in

.

Table 14: Summary statistics of ATV oral powder PK Parameters for Studies AI424397 and AI424451 combined

Treatment Group [N]	ATV/ RTV Regimen	Cmax (ng/mL) Geo.Mean (%CV) Min-Max	AUC(TAU) (ng•h/mL) Geo.Mean (%CV) Min-Max	Cmin (ng/mL) Geo.Mean (%CV) Min-Max	Tmax (h) Median (Min-Max)	CLT/F (L/h) Geo.Mean (%CV) Min-Max	CLT/F/kg (L/h/kg) Geo.Mean (%CV) Min-Max
5 to < 10 kg [20]	150/80	4131 (55) 1110-9660	32503 (61) 10441-94352	336 (76) 11.4-1330	1.58 (1.40-12.0)	4.61 (60) 1.6-14.4	0.65 (62) 0.2 - 1.8
5 to < 10 kg [10]	200/80	4466 (59) 607-12200	39519 (54) 6268-93597	550 (60) 101-1330	1.60 (1.4-4.0)	5.06 (122) 2.1-31.9	0.66 (105) 0.3-3.4
10 to < 15 kg [18]	200/80	5197 (53) 390-15000	50305 (67) 6697-189971	572 (111) 11.2-4870	1.97 (1.00-6.00)	3.98 (118) 1.1-29.9	0.32 (122) 0.1 - 2.6
15 to < 25 kg [32]	250/80	5394 (46) 1480-11400	55687 (45) 19309-121141	686 (68) 177-2570	2.54 (1.43-8.00)	4.49 (58) (2.06-12.9)	0.24 (55) 0.095 - 0.645
25 to < 35 kg [8]	300/100	4209 (52) 1160-8950	44329 (63) 7172-117805	468 (104) 51.2-3010	3.42 (1.5-6.1)	6.77 (127) 2.5-41.8	0.25 (107) 0.1-1.2

Subjects in the 5 to <10 kg weight band in Study AI424451 treated with ATV/RTV 200/80 mg demonstrated higher geometric mean ATV systemic exposures than those treated with ATV/RTV 150/80 mg in Study AI424397. In particular, the higher dose provided an ATV $_{Cmin}$ that more closely resembles ATV C_{min} in HIV-infected adults.

Dose justification for the 10- <15 kg weight band

Intensive PK sampling in 4397 (200/80 mg): systemic ATV exposures in this weight band were reported to be comparable to adults treated with ATV/RTV 300/100 mg. Mean ATV C_{min} is similar to that observed in adults treated with ATV/RTV 300/100 mg (686 ng/mL versus 636 ng/mL). One of 18 subjects (6%) in the 10 to < 15 kg weight band (ATV/RTV 200/80 mg) had an ATV Cmax that exceeded the 90th percentile of the prediction interval in adult patients.

Dose justification for the 15- <25 kg weight band

The PK of ATV in subjects weighing 15 to < 25 kg treated with ATV/RTV 250/80 mg QD were assessed in both Studies AI424397 and AI424451; subjects in this weight band in Study AI424397 were < 6 years of age (range: 2.8 to 5.4 years), while subjects in this weight band in Study AI424451 were approximately 6 years of age and older (range: 5.9 to 9.6 years).

Geometric mean ATV C_{max} and $AUC_{(TAU)}$ in this group treated with ATV/RTV 250/80 mg in Study AI424451 were somewhat lower than the same weight band in Study AI424397 (same dose), where subjects were older; however, geometric mean ATV C_{min} was very similar between the 2 groups, and when PK data for this weight band between the 2 studies were combined, the geometric mean ATV C_{max}, $AUC_{(TAU),}$ and C_{min} were largely consistent with those observed in adults treated with ATV/RTV 300/100 mg QD.

Dose justification for the 25- <35 kg weight band

In these subjects, ATV C_{max} and $AUC_{(TAU)}$ were similar to adults treated with ATV/RTV 300/100 mg. Geometric mean ATV C_{min} in these subjects was lower compared to adult subjects (468 ng/mL relative to 636 ng/mL, respectively); however, variability was high at over 100%.

While Study AI424451 had an upper body weight limit of 35 kg, the proposed dose of ATV powder for subjects weighing more than 35 kg who cannot swallow ATV capsule is 300 mg (with 100 mg of RTV), the same dose as for subjects weighing 25 to < 35 kg. The currently recommended capsule dose of ATV in paediatric subjects weighing 40 kg or more is 300 mg as well, and given the similar bioavailability demonstrated in Study AI424025 between the oral powder and capsule, a dose of 300 mg oral powder is expected to provide exposures in paediatric subjects between 35 and 40 kg that are similar to adults treated with ATV/RTV 300/100 mg.

Exposure comparison to adults

As part of the D120 LOQ, a major objection was raised since the dose selection was considered as inadequately substantiated by the PPK model. The applicant was asked to enrich and update the PPK model to ensure that the effects of weight and age were adequately captured in the model.

A particular concern was raised for the lowest weight band (5-10 kg), with a small number of children to substantiate the dose (n=10) and a poor response rate observed (<20% of patients with HIV RNA <50 copies/ml at week 24 in PRINCE II).

As part of the applicant's responses to the D120 LOQ, the atazanavir (ATV) population pharmacokinetic (PPK) dataset was updated to include observed data from Studies AI424397 and AI424451 and the original one-compartment model, first-order absorption and elimination re-evaluated for goodness of fit with the updated dataset. The results of that investigation revealed some misspecification in the original model. The population PK dataset was enriched with the 89 subjects of studies PRINCE 1 (AI424137) and PRINCE 2 (AI424397). The PPK model was then revised. In the revised PPK model the data were best described by a two-compartment model. As stated by the applicant, the two-compartment model incorporated the key covariate elements from the one-compartment model. Specifically, the effect of gender and body weight on ATV CL/F and body weight on central volume (V2/F) were retained. The following additional covariate effects were subsequently explored and included in the final model: age (described with a maturation function) and age-dependent ritonavir (RTV) effects on ATV CL/F, RTV coadministration effects on relative bioavailability of ATV, and ATV formulation-dependent absorption lag-times.

As discussed by the applicant, the original one-compartment C0-delinked PPK model predicted an approximate 35% reduction in ATV bioavailability from the powder formulation relative to capsule; however, it was postulated this finding was confounded with age because the powder formulation was predominantly used by younger patients who have higher ATV clearance (when adjusted for body weight). In the revised PPK assessment, in which the disposition of ATV is described by a 2-compartment model incorporating gender, body weight, a maturation function, and RTV coadministration as a categorical covariate with a proportional shift in ATV CL/F based on 3 age groups (< 6 months, 6 months to < 1 year, ≥1 year), formulation had no significant impact on either the absorption rate constant or ATV bioavailability, suggesting similar exposures are expected from the powder and capsule.

The applicant underlines that this is in line with the small BE study in adults (see Day 80 reports, a small (n=7) comparative bioavailability study (AI424025), between the capsule and the powder (10% aspartame) not powered to demonstrate BE but showing similar AUC and trend for lower Cmax with the oral powder).

On the basis of this now assumed comparable bioavailability between the capsule and the oral powder formulation, the applicant is now reconsidering the capsule dosing regimen as detailed below for children below 25 kg, recommending to increase the dose from 150 mg to 200 mg in children from 15

to 20 kg and from 200 mg to 300 mg for children from 20 kg (while this adult dose was previously recommended from 40 kg). However, this puts more weight in PK simulation as compared to the cumulative clinical experience gained in children for years with the currently recommended schedule regimen.

Dose of Reyataz capsule

Current authorised dose

Body Weight	Reyataz once daily	Ritonavir once daily
15- <20 kg	150 mg	100 mg
20 - <40 kg	200 mg	100 mg
≥40 kg	300 mg	100 mg

Applicant's proposal for a revised dose

Body Weight	Reyataz once daily	Ritonavir once daily
15- <20 kg	200 mg	100 mg
≥20 kg	300 mg	100 mg

Dose of Reyataz powder

Body Weight	Reyataz once daily	Ritonavir once daily
≥5- <15 kg	200 mg	80 mg
≥15- <25 kg	250 mg *Correspondance capsule* *≥15- <20 kg:* *revised dose 200 mg* *original dose 150 mg* *≥20-<25 kg:* *revised dose 300 mg* *original dose 200 mg*	80 mg *Correspondance capsule* *≥15- <20 kg:* *revised dose 100 mg* *original dose 100 mg* *≥20-<25 kg:* *revised dose 100 mg* *original dose 100 mg*
≥25 kg	300 mg *Correspondance capsule* *original dose ≥25-<40 kg: 200 mg*	100 mg *Correspondance capsule* *original dose ≥25-<40 kg: 100 mg*

Using the revised PPK model, tabulated exposures at several dose levels in the relevant age groups are presented. A visual comparison of observed paediatric data and observed adult data was provided, and predicted C_{min} was evaluated against the similarity criteria applied for the paediatric line extension for the capsule formulation in 2009. Graphical comparison of predicted C_{max} and AUC with adult data was not provided. Of note, the requested adult reference data was missing in the responses. It would be expected that the reference taken (mentioned target adult $ATVC_{24}$ mean=631.88 ng/ml) is adequately substantiated by data derived from the optimal ritonavir boosted regimen.

Based on these revised PK data submitted, the same dose of Reyataz powder (200/80 mg) is proposed for the 10-15 kg weight group, where the predefined PK criteria are met and the dose is considered acceptable for this weight band. In the 15-20 kg weight band, the 200 mg dose meets the predefined criteria while the 250 mg dose does meet C24 criteria, but exceeds AUC and Cmax criteria by a relatively small margin. The 250 mg dose is nevertheless proposed for the powder as it was the dose evaluated in both clinical studies, which seems reasonable. A dose of 200 mg is proposed for the capsule formulation and based on PK data does indeed seem preferable to the presently approved 150 mg dose, which does not meet the similarity criteria. A dose of 200 mg in this weight band is not expected to be associated with higher Cmax and AUC than observed in the adult population or in in paediatric population (< 15 kg weight bands).

However, following the revised PPK model, it appeared that some concerns could be resolved for several weight bands:

- In the 5-10 kg weight band, the revised model predictions result in lower mean C24 and Cmax compared to the earlier model. None of the predicted doses met acceptance criteria, however the 200 mg dose matches criteria more closely and seems more appropriate than the 150 mg dose, particularly when taking the observed data into account as well. Predicted ATV C24 misses the similarity criteria by a minor margin, which is not considered clinically relevant, however Cmax is higher than considered acceptable. Of note, predicted Cmax was higher and C24 lower than observed values. It is of concern that the modelled and observed data do not match well in this age group, where clinical data have also proven to be very difficult to interpret. It would appear that further development of the model is required to support dosing in this age group. The applicant was required to investigate further development of the PPK model to improve the fit in this age group. A modified, or additional, maturation function may be required for the very young, alternatively the effect of ritonavir in these individuals may need modification in the model. Based on the available data as presented, the dose of 200/80 mg may be acceptable.

- In the 20-25 kg weight band, a dose of 250 mg/80 mg is proposed for the powder formulation and this does appear appropriate as it is the dose evaluated in the clinical studies and the PK criteria are met. For the capsule formulation, a dose of 300 mg/100 mg is proposed which requires further justification. Simulated data suggest that the presently approved 200 mg dose matches the predefined criteria and in addition this dose has been used in clinical practice for some time. The proposed dose of 300 mg does not meet the predefined criteria and there is no supporting clinical data. Predicted exposure parameters are higher than in the adult population (there are no observed data). The applicant should clarify if post-marketing clinical data are available suggesting that the presently approved dose of 200 mg for the capsule formulation may be suboptimal in terms of efficacy and provide any other available data in support of the new dose proposal in this group. With the data available at present, a dose of 200mg (which is anyway given with a slightly higher dose of RTV of 100mg compared to the 80mg administered when the powder formulation is used) may be more appropriate in this weight group.

- In the 25-40 kg weight band, a dose of 300 mg is now proposed for both the capsule and the powder formulation. This does imply a 50% increase of the approved dose (for the capsule formulation), and there is extremely little clinical experience and hence safety data at this dose level. The same considerations with regard to observed efficacy with the approved dose, and evaluation of safety implications of the proposed higher dose outlined for the 20-25kg weight band apply here. If the dose for the capsule formulation is to be changed based on PK modelling only, it is of particular relevance that the model can be shown to be robust. Hence, observed and predicted PK parameters in these weight groups should be compared and model performance reported. Boxplots of observed and predicted ATV C24, Cmax and AUC relative to adult values should be presented for comparison for the 200, 250 and 300 mg dose. Without sufficient supportive data, the proposed increase of the dose in these weight bands does not appear justified at present.

The PPK model submitted was further revised to include a modified maturation function for the characterization of the age-related impact of RTV coadministration on ATV apparent oral clearance (CLT/F), as well as a new maturation function describing the impact of age on ATV bioavailability, resulting in an improvement in the characterization of the time-course of ATV concentrations in paediatric subjects.

The comparison of simulated ATV exposures with adult reference values is below:

Weight Band	Dose	Simulated C24 (ng/mL)	$C24_{ped}/C24_{adult}$	C24 PER (%)	Simulated Cmax (ng/mL)	$Cmax_{ped}/Cmax_{adult}$	Cmax PER (%)	Simulated AUC (ng/mL)	AUC_{ped}/AUC_{adult}	AUC PER (%)
5 to < 10	200	533.8	0.81	79	4740	1.60	70	43312	1.15	74
	250	667.2	1.02	84	5926	2.00	60	54140	1.44	69
	300	800.7	1.22	88	7111	2.40	52	64968	1.73	62
10 to < 15	200	629.2	0.96	86	4619	1.56	73	48496	1.29	78
	250	786.5	1.20	91	5773	1.95	63	60620	1.62	70
	300	943.8	1.44	94	6928	2.34	54	72743	1.94	61
15 to < 20	200	582.1	0.89	85	3784	1.28	75	43495	1.16	81
	250	727.6	1.11	90	4730	1.59	68	54369	1.45	75
	300	873.1	1.33	93	5675	1.91	61	65243	1.74	67
20 to < 25	200	535.8	0.82	84	3442	1.16	80	34272	0.91	78
	250	669.7	1.02	89	4302	1.45	75	42840	1.14	75
	300	803.7	1.23	93	5163	1.74	69	51408	1.37	70
25 to < 35	200	503.0	0.77	82	2820	0.95	81	34082	0.91	81
	250	628.7	0.96	88	3524	1.19	80	42603	1.14	81
	300	754.4	1.15	91	4229	1.43	76	51124	1.36	77
35 to < 40	200	464.5	0.71	79	2451	0.83	80	29537	0.79	79
	250	580.6	0.89	87	3063	1.03	82	36921	0.98	82
	300	696.7	1.06	90	3676	1.24	80	44305	1.18	81

The proposed doses of Reyataz were as follows:

Weight Band (kg)	ATV Oral Powder		ATV Capsule in ≥6 Years of Age/15 kg	
	ATV dose (mg)	RTV dose (mg)	ATV dose (mg)	RTV dose (mg)
5 to <10	200	80	NR	---
10 to <15	200	80	NR	---
15 to <20	250	80	200	100
20 to <25	250	80	200	100
25 to <35	300	100	300	100
35 to <40	300	100	300	100
≥40	300	100	300	100

NR: not recommended

Based on this newly revised PPK model, the ATV oral powder doses remained unchanged:

- In the 5-10 kg and 10-15 kg weight bands, the revisions made to the PPK model result in better agreement between predicted and observed data in this weight band, and substantiate the dose of ATV oral powder 200 mg + RTV 80 mg. This dose meets the pre-defined target exposure acceptance criteria for ATV C24 (C24 > 75% of adult C24 [631.88 ng/ml], and PER C24 > 75%).

- In the 15-20 kg and 20-25 kg weight bands, the dose of ATV powder 250 mg + RTV 80 mg meets the target acceptance criteria for ATV C24. The simulated Cmax in these weight groups are higher than those observed in adults (59% and 45% respectively), which may due to the under-estimation of the simulated adult Cmax. Indeed, the observed geometric mean ATV Cmax in subjects of these weight groups are respectively only 22% and 13% higher than the observed geometric mean ATV Cmax in adults. In addition, there is no trend between ATV exposure and severity of adverse events of interest.

- In the 25-35 kg and 35-40 kg weight bands, the dose of ATV powder 300 mg + RTV 100 mg meets the target acceptance criteria for ATV C24 and Cmax. A dose of 250 mg would also be selected, but 300 mg was chosen to be in accordance with the new proposed capsules doses in these weight bands. In addition, this dose was demonstrated to be safe in Study AI424451.

However, the ATV capsule doses were further revised:

- In the 15-20 kg weight band, the currently approved capsule dose of ATV (150 mg) was updated to 200 mg, consistently with the previous PPK model submitted for the D120 LOQ. Indeed, the newly revised PPK model still demonstrates that the 150 mg dose does not meet target acceptance criteria with regard to ATV C24 (the geometric mean ratio for simulated ATV C24 between pediatric and adult subjects is 0.67, below the minimum threshold of 0.75). Although there have been no reports of suboptimal or reduced efficacy with post-marketing use of this dose in this weight band, it is possible that a small percentage of patients could have suboptimal exposures to ATV using a 150 mg dose with RTV. A higher capsule dose of 200 mg in the 15 to <20 kg weight band meets target acceptance criteria for all three ATV PK parameters, including Cmax. No trend between ATV exposure and severity of adverse events of interest is expected based on this model. The dose of ATV capsule 200 mg is more closely resembles those of ATV powder, avoiding discrepancy in case of switch from powder to capsule formulation.

- In the 20-25 kg weight band, the dose of ATV capsule at 300 mg proposed in the responses to the D120 LOQ is decreased at 200 mg (which is the current ATV capsule dose in this weight group). Indeed, a 300 mg dose does not meet target exposure acceptance criteria, particularly with regard to ATV Cmax, with simulated values that exceed the maximum acceptable threshold, and there is no available clinical data with this dose in this weight band.

- In the 25-35 kg and 35-40 kg weight bands, the updated dose of ATV capsule at 300 mg is maintained. The newly revised PPK model demonstrates that ATV doses of 250 mg and 300 mg, when given with RTV, meet the target exposure acceptance criteria in these pediatric subjects, with one minor exception: in the 25-35 kg weight band, the geometric mean ratio of simulated ATV AUC in pediatric subjects to adults at a 300 mg dose is 1.36, slightly above the maximum threshold of 1.25; however the percentage of subjects with simulated ATV AUC between the 10th and 90th percentile of adult AUC is 77% and meets acceptance criteria. With the dose of 300 mg, no change in ATV posology will be required in case of switch from powder to capsule formulation, with a safety profile expected to be similar to that in adults.

Finally the MAH proposed an intermediate position for the dosing recommendation, i.e. for the 35-40 kg weight band to recommend a 300/100 mg for both the oral powder and the capsule formulations instead of a 250/80 mg for the oral powder and 200/100 for the capsule formulation. Indeed, the applicant considers that based on the updated PPK model, the 200/100 mg might be borderline for the capsule formulation.

The CHMP final recommendation is the following:

Weight bands (kg)	ATV oral Powder		ATV Capsule In >6 y/o/15kg	
	ATV dose (mg)	RTV dose (mg)	ATV dose (mg)	RTV dose (mg)
5-<10	200	80	NR	
10-<15	200	80	NR	
15-<20	250	80	200	100
20-<25	250	80	200	100
25-<35	250	80	200	100
35-<40	~~250~~ ***300***	~~80~~ ***100***	~~200~~ ***300***	~~100~~ ***100***
≥40	300	100	300	100

2.4.4. Pharmacodynamics

A PK/PD analysis was performed taking into account the subjects from PRINCE I and II studies (patients from 3 months to 11 years of age weighing 5 kg to <35 kg treated with RTV-boosted ATV powder). For more details on PRINCE studies, refer to efficacy section.

Overall, 146 subjects are included in this PK/PD analysis: 72 (49%) were male and 74 (51%) were female. Forty subjects (27%) were White, 83 subjects (57%) were Black/African American, 1 subject was Asian, and 22 subjects (15%) were classified as "Other".

The following PK parameters were measured for ATV:

- Composite C_{trough} (= within subject geometric mean of all available $C_{troughs}$),
- Composite IQ (= steady-state ATV C_{trough}/protein binding-adjusted EC90 for ATV against HIV at baseline for each subject).

Table 15: Summary Statistics for ATV Composite IQ and Baseline EC_{90}

	5 to <10 kg (ATV 150 mg)	5 to <10 kg (ATV 200 mg)	10 to <15 kg	15 to <25 kg	25 to <35 kg	Combined
Inhibitory Quotient	N = 42	N = 10	N = 37	N = 46	N = 8	N = 143
Geometric Mean (%CV)	7.23 (73.1)	12.5 (75.9)	10.7 (83.3)	11.4 (68.7)	17.2 (71.4)	10.1 (79.8)
Baseline EC_{90} (ng/mL)	N = 43	N = 10	N = 37	N = 48	N = 8	N = 146
Geometric Mean (%CV)	44.4 (27.0)	35.3 (34.9)	43.8 (24.3)	46.8 (33.6)	44.5 (23.2)	44.3 (29.7)

Following multiple daily dosing of ATV oral powder with RTV at doses of ATV that provide systemic exposures similar to adults treated with the recommended ATV/RTV 300/100 mg QD, ATV composite C_{trough} was lowest in the 5 to < 10 kg weight band treated with ATV/RTV 150/80 mg. The lower composite C_{trough} is consistent with a lower dose of ATV and is consistent with the intensive PK data reported in Study AI424397 that prompted an amendment to Study AI424451 to assess a higher dose of ATV (200 mg) in this weight band to determine whether higher ATV systemic exposures could be achieved.

When ATV composite C_{trough} was distributed into 4 quartiles (ATV quartile composite C_{trough}, ATV QCC), this analysis demonstrated that ATV composite C_{trough} was evenly distributed between the 4 quartiles in each weight band, with the exception of the 5 to < 10 kg weight band treated with ATV/RTV 150/80 mg, where 40% of subjects had an ATV composite C_{trough} in the lowest quartile and the 25 to < 35 kg

weight band, where 63% of subjects had a composite ATV C_{trough} in the highest quartile; however, the sample size was small in this weight band, and all 4 quartiles were still represented in this weight band.

Geometric mean (%CV) composite ATV C_{trough} in adult patients treated with ATV/RTV 300/100 mg QD from Study AI424089 was 670 (63) ng/mL. The geometric mean (%CV) composite C_{trough} for all paediatric subjects combined in this analysis was 448 (77) ng/mL, approximately 33% lower than that observed in adult patients. However, geometric mean composite ATV C_{trough} in paediatric patients still exceeds the population protein-binding adjusted 90% effective concentration (EC90) for wild type virus (14 ng/mL) and the protein-binding adjusted EC90s reported in paediatric subjects included in this assessment (44.3 ng/mL).

Inhibitory quotient (IQ) links the efficacy-driven PK parameter with the sensitivity of the patient isolates of HIV. The composite IQ for all paediatric subjects combined was 10.1. This is markedly lower than the geometric mean composite IQ of 42 reported in HIV-infected adults treated with ATV/RTV 300/100 mg in Study AI424089. This marked difference in IQ is likely driven by the differences in baseline protein-binding adjusted EC90 between the 2 populations as well as to a lesser extent by the difference in composite ATV C_{trough} in the 2 populations (670 ng/mL in adults versus 448 ng/mL in paediatric subjects). Paediatric patients had a geometric mean baseline protein-binding adjusted EC90 of 44.3 ng/mL, compared to 13 ng/mL in adult patients, suggesting that paediatric patients, in general, may have less susceptible virus than adults. However, Studies AI424397 and AI424451 enrolled both treatment-naive and treatment-experienced patients, while Study AI424089 only enrolled treatment-naive adults. It is possible that prior treatment history could impact individual viral susceptibility to ATV. Nevertheless, with the exception of the 5 to < 10 kg weight band treated with ATV/RTV 150/80 mg, the majority of paediatric subjects had a composite IQ between 10 and 100, suggesting that ATV powder doses administered in these paediatric trials are capable of achieving and maintaining suppressive ATV concentration margins over susceptible viruses.

2.4.5. Discussion on clinical pharmacology

From previous studies mainly in the adult population the pharmacokinetics of atazanavir is known to exhibit a non-linear disposition with greater than dose-proportional increases in AUC and C_{max}. Atazanavir is principally metabolised by CYP3A4 isozyme to oxygenated metabolites. Metabolites are then excreted in the bile as either free or glucuronidated metabolites, renal excretion of unchanged drug is low. The mean elimination half-life of ATV subjects was approximately 7 hours at steady state. Steady-state is achieved between Days 4 and 8, with an accumulation of approximately 2.3-fold. ATV should be taken with food. No difference in PK between treatment naïve and experienced subjects had been identified in the POPPK model, neither were race or gender identified as relevant for exposure.

Paediatric PK data presented stem from the intense PK sampling performed during stage 1 of the study at around week 2. All data were generated with the ATV powder formulation containing 10% aspartame. The proposed formulation of ATV powder containing 4.2% aspartame was used in stage 2 of the study in those subjects who remained on the powder formulation after stage 1. Intense PK data were not collected during stage 2. Due to the minor change in formulation, CHMP had advised that a study demonstrating bioequivalence between the two ATV powder formulations is not required.

In the present studies, the PK of atazanavir was evaluated after two weeks of treatment, under presumed steady state conditions. Intensive PK data were available from 88 subjects from 5 weight cohorts, with dosing was based on body weight. The variability in the PK observed PK data is high. As had been previously described in the paediatric population, absorption rate seemed be higher in

younger children and CLT/F/kg seems to be inversely related to age. As a result, C_{max} tends to be higher and C_{min} tends to be lower in children than in adults, so that greater peak/trough ratios are observed. This effect is more pronounced in the absence of ritonavir.

AUC and C_{min} (the latter being the most relevant PK parameter linked to PD) across the studies showed that the posology of ATV/RTV 200/80 mg (powder) is more appropriate than the ATV/RTV 150/80 mg (powder) for the 5-<10 kg weight range. Additionally, PK/PD analysis show a lower rate of virologic success in the lowest ATV QCC, where a large proportion of subjects come from the 5-<10 kg (ATV 150 mg) group, suggesting a suboptimal virologic response of ATV 150 mg.

However, despite an increased dose of ATV from 150 mg to 200 mg, it should be highlighted that PK parameters associated to efficacy (AUC and Cmin) are lower in the group 5-<10 kg than those of the other weight groups and in adults.

Initially, a major objection was raised since the dose selection was considered as inadequately substantiated by the PPK model. The applicant was asked to enrich and update the PPK model to notably ensure that the effects of weight and age were adequately captured in the model.

A particular concern was raised for the lowest weight band (5-10 kg), with a small number of children to substantiate the dose (n=10) and a poor response rate observed (<20% of patients with HIV RNA <50 copies/ml at week 24 in PRINCE II).

As part of the applicant's responses to the D120 LOQ, the atazanavir (ATV) population pharmacokinetic (PPK) dataset was updated to include observed data from Studies AI424397 and AI424451 and the original one-compartment model, first-order absorption and elimination re-evaluated for goodness of fit with the updated dataset. The results of that investigation revealed some misspecification in the original model. The population PK dataset was enriched with the 89 subjects of studies PRINCE 1 (AI424137) and PRINCE 2 (AI424397). The PPK model was then revised. In the revised PPK model the data were best described by a two-compartment model. As stated by the applicant, the two-compartment model incorporated the key covariate elements from the one-compartment model. Specifically, the effect of gender and body weight on ATV CL/F and body weight on central volume (V2/F) were retained. The following additional covariate effects were subsequently explored and included in the final model: age (described with a maturation function) and age-dependent ritonavir (RTV) effects on ATV CL/F, RTV coadministration effects on relative bioavailability of ATV, and ATV formulation-dependent absorption lag-times.

As discussed by the applicant, the original one-compartment C0-delinked PPK model predicted an approximate 35% reduction in ATV bioavailability from the powder formulation relative to capsule; however, it was postulated this finding was confounded with age because the powder formulation was predominantly used by younger patients who have higher ATV clearance (when adjusted for body weight). In the revised PPK assessment, formulation had no significant impact on either the absorption rate constant or ATV bioavailability, suggesting similar exposures are expected from the powder and capsule.

On the basis of this now assumed comparable bioavailability between the capsule and the oral powder formulation, the applicant is now reconsidering the capsule dosing regimen for children below 25 kg, recommending to increase the dose from 150 mg to 200 mg in children from 15 to 20 kg and from 200 mg to 300 mg for children from 20 kg (while this adult dose was previously recommended from 40 kg).

Overall, it is of concern that the modelled and observed data do not match well in the 5-10 kg group, where clinical data have also proven to be very difficult to interpret. It would appear that further

development of the model is required to support dosing in this age group. The applicant should investigate further development of the POPPK model to improve the fit in this age group. A modified, or additional, maturation function may be required for the very young, alternatively the effect of ritonavir in these individuals may need modification in the model.

Moreover, the applicant should clarify if post-marketing clinical data are available suggesting that the presently approved dose of 200 mg for the capsule formulation may be suboptimal in terms of efficacy and provide any other available data in support of the new dose proposal in this group. The potential safety implications for such an increased dose will also have to be thoroughly evaluated. Given the increased exposures associated with this dose, particular concerns would be cardiac and hepatic effects as well as DDI. It is acknowledged that part of the rational for proposing the 300 mg dose is to prevent that subjects switching from powder to capsule should receive a lower dose, which seems reasonable. However, this could be achieved by discouraging switching for subjects < 25 kg (instead of <20kg) to avoid this scenario.

Finally, the choice of the ritonavir dose, which was the same for all subjects < 25kg, was justified. Data suggest that effect of RTV on ATV bioavailability is not explained by an effect on CYP3A4 as it is consistent across the age/ weight range. The company should clarify if an effect of RTV on ATV bioavailability not resulting from CYP3A4 inhibition, has been described before for ATV or for other PIs. The MAH should discuss the potential mechanisms involved and present any corroborating data available.

The PPK model was updated to include a modified maturation function for the characterization of the age-related impact of RTV co-administration on ATV apparent oral clearance (CLT/F), as well as a new maturation function describing the impact of age on ATV bioavailability, resulting in an improvement in the characterization of the time-course of ATV concentrations in paediatric subjects. This newly revised PPK model, like the Day 120 model, predicts that a range of doses will provide target ATV exposures, including the currently recommended capsule doses in most weight bands for children 6 years of age and older. This new model does appear more robust in particular for the 5-10 kg weight band, although some underprediction of C24 is still observed.

Regarding the weight bands 5 to 25 kg, the exposure/response evaluations did not give rise to safety concerns as far as can be judged based on the model-predicted exposures at the time of any AE. The MAH has decreased the dose of capsule formulation for subjects weighing 20-25 kg from 300 mg to 200 mg. This dose is the same as the already approved dose and hence supported by both clinical data and revised PPK model.

The applicant proposed the higher dose of ATV/rtv 300/100mg for the weight bands 25 to 40 kg. Yet the similarity between observed PK parameters in this weight bracket with the 300mg dose to the PK parameters in adults is based on a very small group of subjects. Simulated data favour the dose of 250mg. It is acknowledged that maintaining viral suppression is of the highest relevance in the target population, but it seems somewhat difficult to justify changing the dose of the approved capsule formulation from 200 mg to 300mg, in particular when considering that the 200mg dose has also been used in clinical trials with the capsule formulation and meets the target criteria for similarity, while the 300 mg dose does not. In order to both minimize the gap when switching from the powder to the capsule formulation in children from 25 kg to < 35 kg and to avoid revising the capsule formulation given the experience gained, the CHMP recommended approving a dose of 250mg/80 mg for the powder formulation and to keep the dose for the capsule formulation unchanged at 200/100mg. It is acknowledged that the dose of 250 mg has not been evaluated in clinical trials in the 25 to < 35 kg weight band, but doses of 200mg and 300mg have been used in clinical trials in this population, even though the cohorts were very small as described above.

2.4.6. Conclusions on clinical pharmacology

The PPK model has been significantly improved from the original application, with updated PK data from the PRINCE studies as well as through the inclusion of additional covariates for notably covering modified maturation function for the characterization of the age-related impact of RTV co-administration on ATV apparent oral clearance (CLT/F), as well as a new maturation function describing the impact of age on ATV bioavailability. This overall result in a good fit to data in all age groups.

In conclusion, the final dosing recommendation for the oral powder and capsule formulation took into account the PPKPOP, the need to minimize the gap between oral and capsule formulation as well as the need to minimize the deviation from the original capsule dosing recommendation. It is acknowledged that these dosing recommendations mainly rely on PPKPOP and clinical experience.

Weight band	ATV oral powder / RTV	ATV capsule / RTV
5-<15 kg	200/80 mg	NR
15-<35 kg	250/80 mg	200/100 mg
≥ 35 kg	300/100 mg	300/100 mg

2.5. Clinical efficacy

2.5.1. Main studies

The pivotal studies for this line and indication extension of Reyataz are AI424397 (PRINCE I) and AI424451 (PRINCE II).

The design of Study AI424451, apart from the inclusion of a higher weight band (i.e., 25 - < 35 kg dosed with 300 mg of ATV/80 mg RTV), differed from Study AI424397 in that the primary safety endpoint was revised to be evaluated once the last subject enrolled had reached a minimum of 24 weeks duration in Stage 1 (it was originally 48 weeks). As such, not all subjects have reached 48 weeks in this study. Another significant difference was the addition of a cohort of subjects weighing 5 - < 10 kg dosed with 200 mg of ATV powder formulation boosted with 80 mg RTV. This group was added to assess whether exposures could be enhanced above those observed at a dose of 150 mg ATV/80 mg RTV given to subjects in this weight band in Study AI424397.

AI424397 – PRINCE I study

Methods

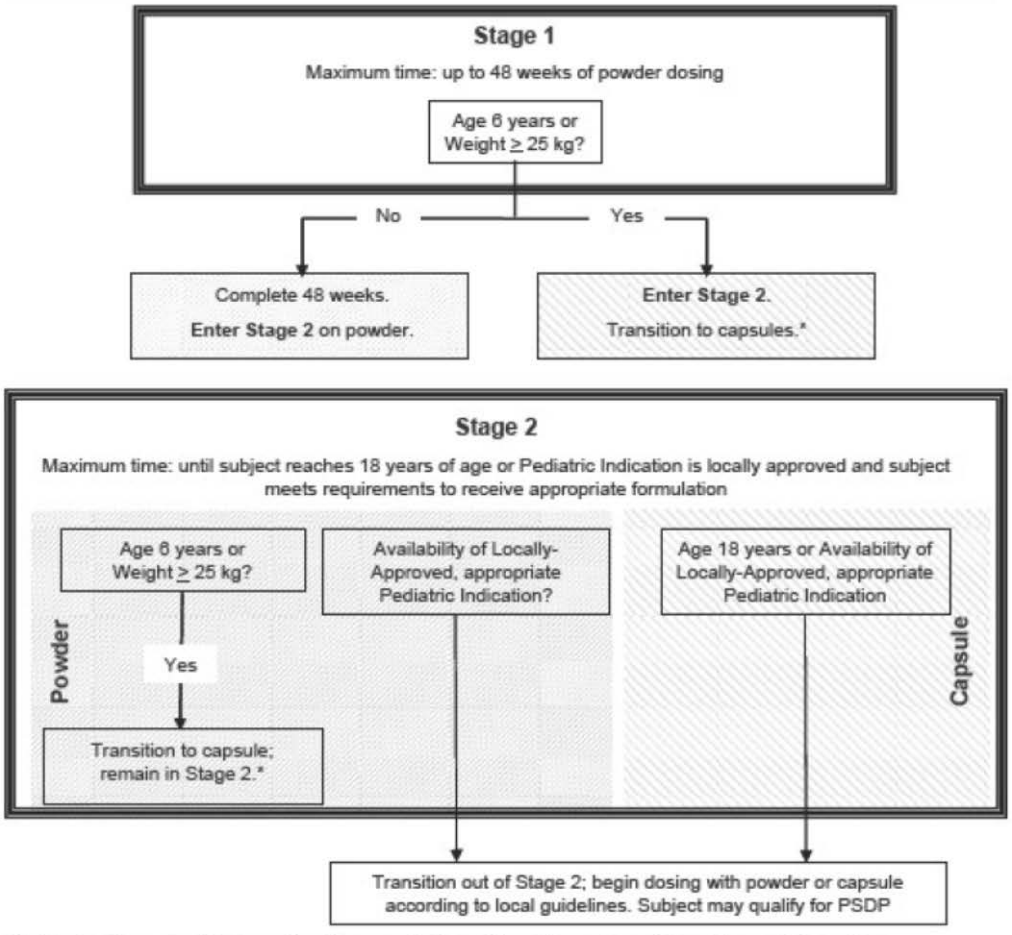
Title	A Prospective Single Arm, Open-label, International, Multicenter Study to Evaluate the Safety, Efficacy and Pharmacokinetics of Atazanavir (ATV) Powder Boosted with Ritonavir (RTV) Liquid with an Optimized NRTI Background Therapy, in HIV Infected Pediatric Patients Greater Than or Equal to 3 Months to Less Than 6 Years.
Study participants	- HIV-infected pediatric subjects ≥ 3 months to < 5 years and 6 months of age. - Weight between 5 kg and 25 kg at Day 1. - ARV naive or experienced (without prior exposure to ATV). - HIV RNA value ≥ 1000 c/ml. - Genotypic sensitivity to ATV and to NRTI backbone.
Treatments	ATV powder **(10% aspartame)** + RTV oral solution + 2 NRTIs (excluding TDF)
Objectives	The primary objective was to describe the safety of ATV powder formulation boosted with RTV liquid-based highly active antiretroviral therapy (HAART) regimens in pediatric subjects dosed

	through 48 weeks (or a minimum of 24 weeks for subjects who are 5.5 years of age at the time of study start). Secondary objectives are: • To describe efficacy of ATV powder formulation, as measured by proportion of subjects with a virologic response (HIV RNA levels < 50 copies/mL and < 400 copies/ml) through Week 48. • To describe the pharmacokinetic (PK) profile of ATV powder formulation with RTV in pediatric subjects in terms of ATV Cmax, Cmin and AUC.
Study design	Phase 3b prospective, international, multicenter, nonrandomized, 2-stage study of a cohort of HIV-infected pediatric subjects ≥ 3 months to < 5 years and 6 months of age.

Age ≥ 3 months to < 5 years, 6 months: 50 subjects treated with powder formulation

Body Weight (kg)	Target # of Subjects	ATV Dose (mg)	RTV Dose (mg)	
5 to less than 10	min of 6* and max of 20	150	80	+ approved NRTI backbone (tenofovir is prohibited)
10 to less than 15	min of 10 and max of 20	200	80	
15 to less than 25	min of 10 and max of 20	250	80	

* A minimum of 6 subjects from this weight band must be ≥ 3 months to < 6 months of age.



*Subjects who are unable to swallow the capsule formulation after an 8 week transition period must be discontinued from the study.

Outcomes/ endpoints	**Efficacy**: The proportions of subjects with HIV RNA < 50 c/mL and < 400 c/mL are being evaluated at each scheduled visit through Week 48, including the change from baseline in HIV RNA, CD4 cell count, and CD4 percentages. **Safety**: Safety assessments include vital signs, physical measurements, deaths, AEs including CDC Class C AIDS events, laboratory measurements and ECG results. **Pharmacokinetics**: At Week 2, serial blood samples were collected over a 24-hour period for plasma concentrations in order to assess the steady-state PK of ATV and RTV. **Other**: Palatability of ATV powder and RTV oral solution is being assessed through a survey from Weeks 4 to 48.

Sample size	Sample size was not based on power calculations. Approximately 50 subjects distributed among the 3 weight bands were planned for this study. A minimum number of treated subjects were to have been assigned per weight band: • 6 subjects between 5 - < 10 kg • 10 subjects between 10 - < 15 kg • 10 subjects between 15 - < 25 kg. A target sample size of 50 treated subjects can detect with 80% probability, a safety event that occurs at a per subject incident rate of 3.2%, and can produce an exact binomial 95% CI within ± 14% for a response rate of 50%.
Statistical methods	No statistical comparisons between weight bands were conducted. **Efficacy**: All efficacy endpoints were secondary, and focused on the ATV powder formulation. Values after the start of ATV capsule were excluded. The response rates through Week 48 were assessed with the Snapshot algorithm. Response rates through Week 48 for Week 48 ATV powder cohort (treated subjects who did not switch to ATV capsule at or before analysis Week 48) used a modified intent-to-treat (ITT) analysis. Response rates through Week 48 for treated subjects used observed values. Response rates were presented with exact binomial 95% CI. **Safety**: Safety evaluations were based on data on ATV powder through Week 48. **PK**: The derived PK parameters, Cmax, Tmax, AUC(TAU), Cmin, CLT/F, and CLT/F/kg obtained at the Week 2 visit for ATV and RTV were summarized by baseline weight band.

Patient disposition

Eighty-two subjects were enrolled, and 56 subjects (68%) were treated. Among these subjects, 46 subjects (82%) completed the Stage 1 treatment period. Nine subjects (16%) discontinued ATV powder before Week 48, and the most common reason for discontinuation of ATV powder was AE (5 subjects).Two subjects were withdrawn due to lack of efficacy, and one each due to poor compliance and withdrawal of consent.

Of the 45 subjects entering Stage 2, 41 (73%) were still on ATV powder at Week 48, and 4 subjects had to transition from powder to capsules during stage 1. At database lock date of 07-Oct-2014, 31 subjects (55%) were still ongoing in Stage 2. Eleven subjects (20%) have discontinued in Stage 2, and the most common reasons for discontinuation were subject withdrew consent and lost to follow up (5% each).

Conduct of the study

This study was conducted in accordance with Good Clinical Practice.

Overall, 6 subjects (11%) had on-treatment protocol deviations (2 subjects in each of the 3 weight bands): 4 subjects continued in the study after a study drug interruption > 14 days, and 2 subjects received prohibited concomitant medication > 3 days.

There were 7 amendments to the protocol. The main major changes were:

- additional visits;

- the addition of an IDMC;

- the switch in background NRTIs in case of confirmed viral rebound between 400 and 10,000 c/ml associated with a genotypic and/or phenotypic resistance to one or more NRTI without genotypic and/or phenotypic resistance to ATV or due to treatment-limiting NRTI toxicity;

- the change of the whole treatment regimen, including ATV, in subjects with confirmed virologic failure or virologic rebound above 1000 copies/mL;

- the modification of the definition of virologic failure in accordance with the updated 2011 DHHS paediatric guidelines and clarified the virologic failure criteria to discontinue a subject in the study.

Demographics

At baseline, the overall median age was 29 months (range: 3 - 65 months). The majority of subjects were Black/African American (57%), and half of the subjects were male. The majority of subjects were recruited in Africa (68%). The majority of subjects were ARV naive (61%) and this was similar in all weight cohorts. The overall median HIV RNA was 5 $\log_{10}$ c/mL, and the majority of subjects had HIV RNA > 100,000 c/mL (57%). Overall median CD4 count was 1,004 cells/mm3, and median CD4 percent was 24%.

Baseline data

Table 16: Summary of demographic characteristics

	B/L Weight 5 - < 10 kg N = 21	B/L Weight 10 - < 15 kg N = 19	B/L Weight 15 - < 25 kg N = 16	Combined 10 - < 25 kg N = 35	TOTAL N = 56
AGE AT BASELINE (MONTHS)					
N	21	19	16	35	56
MEAN	7.3	35.4	52.1	43.0	29.6
MEDIAN	6.0	35.0	55.0	44.0	28.5
MIN , MAX	3, 15	21, 54	34, 65	21, 65	3, 65
Q1 , Q3	4.0, 10.0	23.0, 46.0	45.5, 60.0	33.0, 55.0	9.0, 49.5
STANDARD DEVIATION	4.05	11.63	10.49	13.85	20.72
GENDER (%)					
MALE	11 (52.4)	7 (36.8)	10 (62.5)	17 (48.6)	28 (50.0)
FEMALE	10 (47.6)	12 (63.2)	6 (37.5)	18 (51.4)	28 (50.0)
RACE (%)					
WHITE	2 (9.5)	3 (15.8)	6 (37.5)	9 (25.7)	11 (19.6)
BLACK/AFRICAN AMERICAN	13 (61.9)	12 (63.2)	7 (43.8)	19 (54.3)	32 (57.1)
ASIAN	0	1 (5.3)	0	1 (2.9)	1 (1.8)
OTHER	6 (28.6)	3 (15.8)	3 (18.8)	6 (17.1)	12 (21.4)
ETHNICITY (%)					
NOT HISPANIC/LATINO	0	0	1 (6.3)	1 (2.9)	1 (1.8)
NOT REPORTED	21 (100)	19 (100)	15 (93.8)	34 (97.1)	55 (98.2)
COUNTRY (%)					
CHILE	1 (4.8)	2 (10.5)	3 (18.8)	5 (14.3)	6 (10.7)
MEXICO	2 (9.5)	3 (15.8)	4 (25.0)	7 (20.0)	9 (16.1)
PERU	1 (4.8)	0	1 (6.3)	1 (2.9)	2 (3.6)
SOUTH AFRICA	17 (81.0)	13 (68.4)	8 (50.0)	21 (60.0)	38 (67.9)
THAILAND	0	1 (5.3)	0	1 (2.9)	1 (1.8)
REGION (%)					
AFRICA	17 (81.0)	13 (68.4)	8 (50.0)	21 (60.0)	38 (67.9)
ASIA	0	1 (5.3)	0	1 (2.9)	1 (1.8)
NORTH AMERICA	2 (9.5)	3 (15.8)	4 (25.0)	7 (20.0)	9 (16.1)
SOUTH AMERICA	2 (9.5)	2 (10.5)	4 (25.0)	6 (17.1)	8 (14.3)

Table 17: Summary of HIV disease characteristics at baseline

	B/L Weight 5 - < 10 kg N = 21	B/L Weight 10 - < 15 kg N = 19	B/L Weight 15 - < 25 kg N = 16	Combined 10 - < 25 kg N = 35	TOTAL N = 56
HIV RNA (LOG10 C/ML)					
N	21	19	16	35	56
MEAN	4.77	4.83	4.18	4.54	4.62
MEDIAN	5.00	5.00	4.28	4.81	5.00
MIN , MAX	2.8, 5.0	4.0, 5.0	3.1, 5.0	3.1, 5.0	2.8, 5.0
Q1 , Q3	5.00, 5.00	4.75, 5.00	3.47, 4.97	4.16, 5.00	4.50, 5.00
STANDARD DEVIATION	0.602	0.268	0.727	0.617	0.617
HIV RNA CATEGORIES (C/ML) (%)					
< 30,000	3 (14.3)	2 (10.5)	9 (56.3)	11 (31.4)	14 (25.0)
30,000 - 100,000	0	7 (36.8)	3 (18.8)	10 (28.6)	10 (17.9)
> 100,000	18 (85.7)	10 (52.6)	4 (25.0)	14 (40.0)	32 (57.1)
CD4 (CELLS/MM^3)					
N	16	13	10	23	39
MEAN	1594.1	1107.4	661.1	913.3	1192.6
MEDIAN	1814.5	1002.0	668.5	865.0	1004.0
MIN , MAX	84, 3451	46, 2172	106, 1019	46, 2172	46, 3451
Q1 , Q3	954.5, 2119.5	846.0, 1171.0	496.0, 911.0	571.0, 1019.0	654.0, 1898.0
STANDARD DEVIATION	897.19	643.25	302.60	560.65	784.08
NOT REPORTED	5	6	6	12	17
CD4 PERCENT (%)					
N	16	14	11	25	41
MEAN	25.4	22.0	27.5	24.4	24.8
MEDIAN	23.5	22.0	27.0	24.0	24.0
MIN , MAX	2, 49	1, 40	6, 42	1, 42	1, 49
Q1 , Q3	21.0, 30.5	17.0, 27.0	22.0, 36.0	20.0, 28.0	21.0, 28.0
STANDARD DEVIATION	12.11	9.35	9.85	9.77	10.61
NOT REPORTED	5	5	5	10	15
CD4 PERCENT CATEGORIES (%)					
< 15	2 (9.5)	2 (10.5)	1 (6.3)	3 (8.6)	5 (8.9)
15 - < 25	7 (33.3)	6 (31.6)	4 (25.0)	10 (28.6)	17 (30.4)
>= 25	7 (33.3)	6 (31.6)	6 (37.5)	12 (34.3)	19 (33.9)
NOT REPORTED	5 (23.8)	5 (26.3)	5 (31.3)	10 (28.6)	15 (26.8)
PRIOR ARV USE					
ARV NAIVE	13 (61.9)	12 (63.2)	9 (56.3)	21 (60.0)	34 (60.7)
ARV EXPERIENCED	8 (38.1)	7 (36.8)	7 (43.8)	14 (40.0)	22 (39.3)
NOT REPORTED	0	0	0	0	0

Results

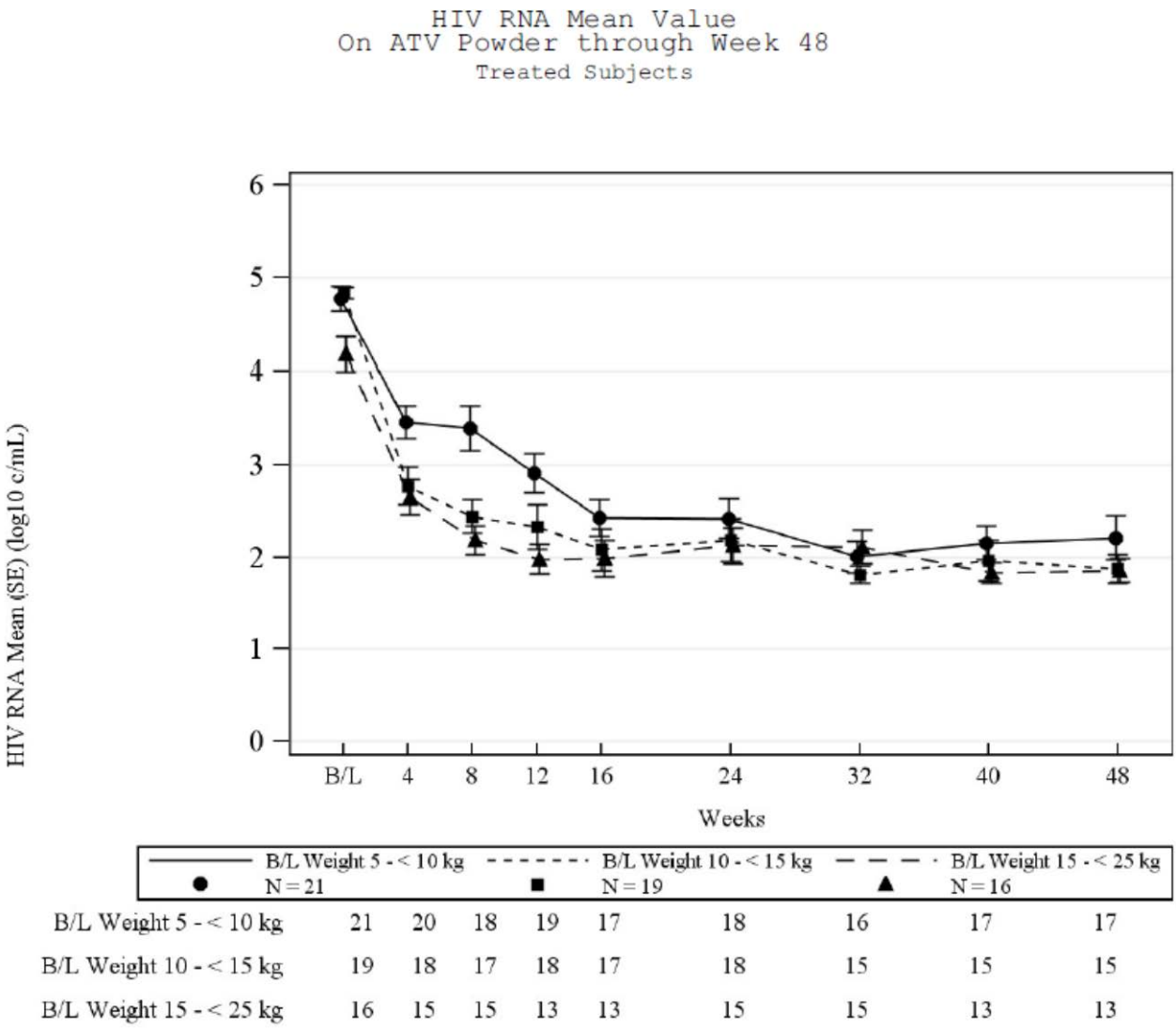
At Week 48 on the ATV powder cohort, 74% of subjects had HIV RNA < 400 c/mL and 61% of subjects had HIV RNA < 50 c/mL. Virologic response (the proportion of subjects with HIV RNA < 400 c/mL and < 50 c/mL) increased with higher baseline weight band.

Table 18: Efficacy snapshot outcome at Week 48 on modified ITT analysis – ATV powder cohort

Treatment Outcomes	B/L Weight 5 - < 10 kg N=21	B/L Weight 10 - < 15 kg N=19	B/L Weight 15 - < 25 kg N=14	Combined 10 - < 25 kg N=33	TOTAL N=54
HIV RNA < 50 c/mL					
VIROLOGIC SUCCESS	10 (47.6)	13 (68.4)	10 (71.4)	23 (69.7)	33 (61.1)
VIROLOGIC FAILURE	7 (33.3)	5 (26.3)	4 (28.6)	9 (27.3)	16 (29.6)
HIV RNA >= 50c/mL	7 (33.3)	2 (10.5)	3 (21.4)	5 (15.2)	12 (22.2)
DISCONTINUED DUE TO VIROLOGIC FAILURE	0	2 (10.5)	0	2 (6.1)	2 (3.7)
DISCONTINUED DUE TO OTHER REASONS AND HIV >= 50 c/mL AT TIME OF DISCONTINUATION	0	1 (5.3)	1 (7.1)	2 (6.1)	2 (3.7)
OBT CHANGED	0	0	0	0	0
NO VIROLOGIC DATA IN ANALYSIS WEEK WINDOW	4 (19.0)	1 (5.3)	0	1 (3.0)	5 (9.3)
DISCONTINUED DUE TO AE OR DEATH	4 (19.0)	1 (5.3)	0	1 (3.0)	5 (9.3)
DISCONTINUED DUE TO OTHER REASONS AND HIV RNA < 50c/mL AT TIME OF DISCONTINUATION	0	0	0	0	0
MISSING DATA IN WINDOW BUT ON TREATMENT	0	0	0	0	0
HIV RNA < 400 c/mL					
VIROLOGIC SUCCESS	14 (66.7)	14 (73.7)	12 (85.7)	26 (78.8)	40 (74.1)
VIROLOGIC FAILURE	3 (14.3)	4 (21.1)	2 (14.3)	6 (18.2)	9 (16.7)
HIV RNA >= 400c/mL	3 (14.3)	1 (5.3)	1 (7.1)	2 (6.1)	5 (9.3)
DISCONTINUED DUE TO VIROLOGIC FAILURE	0	2 (10.5)	0	2 (6.1)	2 (3.7)
DISCONTINUED DUE TO OTHER REASONS AND HIV >= 400 c/mL AT TIME OF DISCONTINUATION	0	1 (5.3)	1 (7.1)	2 (6.1)	2 (3.7)
OBT CHANGED	0	0	0	0	0
NO VIROLOGIC DATA IN ANALYSIS WEEK WINDOW	4 (19.0)	1 (5.3)	0	1 (3.0)	5 (9.3)
DISCONTINUED DUE TO AE OR DEATH	4 (19.0)	1 (5.3)	0	1 (3.0)	5 (9.3)
DISCONTINUED DUE TO OTHER REASONS AND HIV RNA < 400c/mL AT TIME OF DISCONTINUATION	0	0	0	0	0
MISSING DATA IN WINDOW BUT ON TREATMENT	0	0	0	0	0

HIV RNA changes from baseline

At Week 48, the overall mean (median) change from baseline in HIV RNA was -2.66 (-3.06) $\log_{10}$ c/Ml. In the 5-<10 kg, 10-<15 kg, and 15-<25 kg groups, the mean (median) change from baseline in HIV RNA was -2.61 (-3.31), -2.93 (-3.31), and -2.40 (-2.59) log10 c/mL respectively.



B/L Weight 5 - < 10 kg	21	20	18	19	17	18	16	17	17
B/L Weight 10 - < 15 kg	19	18	17	18	17	18	15	15	15
B/L Weight 15 - < 25 kg	16	15	15	13	13	15	15	13	13

The mean (median) change from baseline in HIV RNA was -2.90 (-3.25) log_{10} c/mL and -2.52 (-2.89) log_{10} c/mL in ARV-experienced and -naive subjects, respectively.

CD4 cell count changes from baseline

At Week 48, the overall mean (median) change from baseline in CD4 cell count was 397 (363) cells/mm^3. In the 5-<10 kg, 10-<15 kg, and 15-<25 kg groups, the mean (median) change from baseline in CD4 cell count was 550 (491), 225 (274), and 374 (363) cells/mm^3 respectively.

The mean (median) change from baseline in CD4 cell count was 182 (213) cells/mm3 and 493 (520) cells/mm3 in ARV-experienced and -naive subjects, respectively.

Virologic resistance

By Week 48, a total amount of 14 subjects met the criteria for virologic failure. Nine of these subjects had paired genotypic data (data at baseline and on treatment) and 6 had paired phenotypic resistance testing data. Six subjects (43%) were ARV experienced and 8 subjects (57%) were ARV naive.

None of the subjects acquired phenotypic resistance to ATV, ATV/RTV, or any NRTI or NNRTI. None of the subjects developed any major PI substitution to ATV or ATV/RTV. One ARV-naive subject in the 10-

<15 kg weight band developed M36M/I and 1 ARV-naive subject in the 5-<10 kg weight band developed H69K/R. One ARV-experienced subject in the 15-<25 kg weight band developed I72I/V substitution, and 1 ARV-naive subject in the 5-<10 kg weight band developed L19I/R.

Palatability

Palatability survey on ATV powder (10% aspartame) and RTV oral solution was performed at each visit. Throughout the study, the majority of subjects took their dose of ATV mixed with milk or water. The majority of subjects had no trouble completing their doses of ATV and RTV (91% and 87%, respectively).

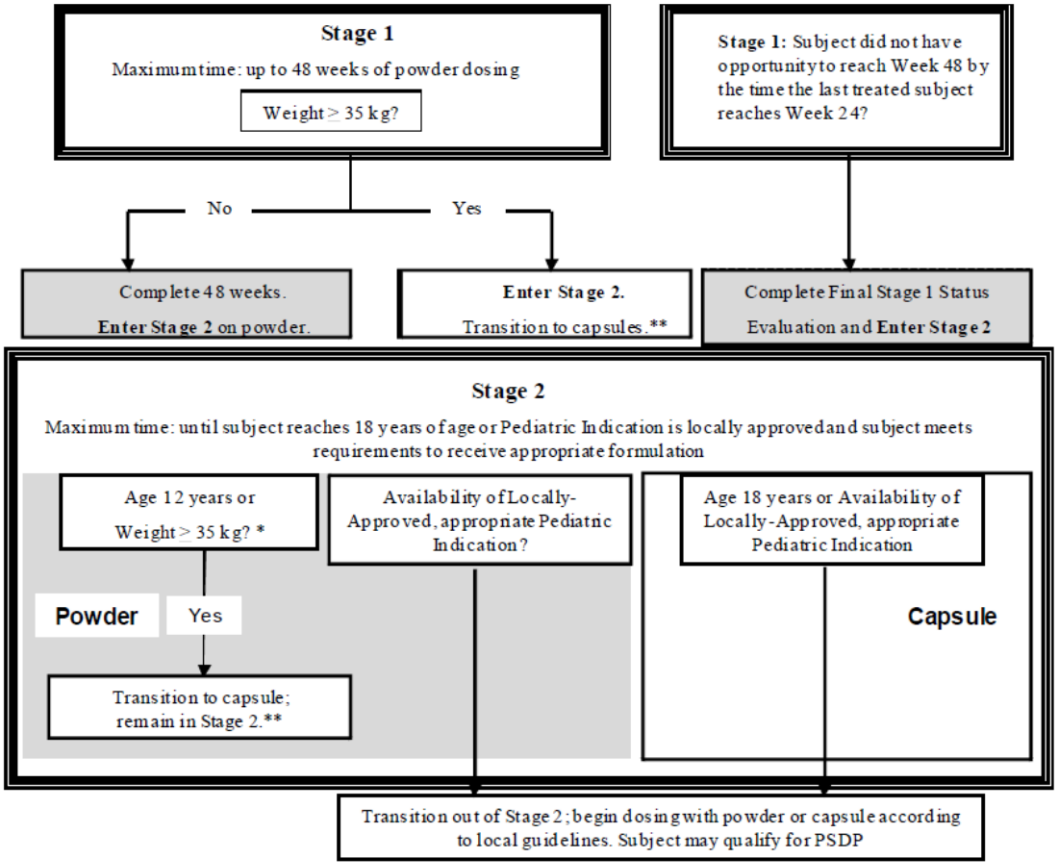
AI424451 – PRINCE II study

Methods

Title	A Prospective Single Arm, Open-label, International, Multicenter Study to Evaluate the Safety, Efficacy and Pharmacokinetics of Atazanavir (ATV) Powder Boosted with Ritonavir (RTV) with an Optimized NRTI Background Therapy, in HIV Infected, Antiretroviral, Naive and Experienced Pediatric Subjects From 3 Months to Less Than 11 Years.
Study participants	- HIV-infected pediatric subjects ≥ 3 months to < 11 years of age. - Weight between 5 kg and 35 kg at Day 1. - ARV naive or experienced (without prior exposure to ATV). - Genotypic sensitivity to ATV and to NRTI backbone.
Treatments	ATV powder (10% aspartame then 4.2% aspartame) + RTV oral solution + 2 NRTIs (excluding TDF)
Objectives	The primary objective was to describe the safety of ATV powder formulation boosted with RTV liquid-based highly active antiretroviral therapy (HAART) regimens in pediatric subjects dosed through 24 weeks. Secondary objectives are: • To describe efficacy of ATV powder formulation, as measured by proportion of subjects with a virologic response (HIV RNA levels < 50 copies/mL and < 400 copies/ml) at Week 24 and Week 48. • To describe the pharmacokinetic (PK) profile of ATV powder formulation with RTV in pediatric subjects in terms of ATV Cmax, Cmin and AUC.
Study design	Phase 3b prospective, international, multicenter, nonrandomized, 2-stage study of a cohort of HIV-infected pediatric subjects ≥ 3 months to < 11 years of age.

Age ≥ 3 months to < 11 years: Minimum 56 subjects treated with ATV powder formulation for 24 weeks

Body Weight (kg)	Target # of Subjects	ATV Dose (mg)	RTV Dose (mg)	
5 to less than 10	Minimum of 5	150	80	+ approved NRTI backbone (tenofovir is prohibited)
	Minimum of 6	200	80	
10 to less than 15	Minimum of 10	200	80	
15 to less than 25	Minimum of 10	250	80	
25 to less than 35	No Minimum	300	100	
The study will commit to enroll a minimum of 30 ARV experienced patients treated with ATV powder for a minimum of 24 weeks.				



* Subjects are required to switch to capsules when they reach 35 kg and/or 12 years of age. However, subjects who reach a weight of 25 kg and/or 6 years of age during Stage 2 may, at the discretion of the investigator and caregiver, choose to attempt switch to the solid dosage forms of ATV/RTV. Careful consideration should be given to the time of switch as subjects who are unable to swallow capsule after an 8-week transition period must be discontinue from Stage 2.

** Subjects who are unable to swallow the capsule formulation after an 8 week transition period must be discontinued from the study.

Outcomes / endpoints	**Efficacy**: The proportions of subjects with HIV RNA < 50 c/mL and < 400 c/mL are being evaluated at each scheduled visit through Week 24 and Week 48, including the change from baseline in HIV RNA, CD4 cell count, and CD4 percentages. **Safety**: Safety assessments include vital signs, physical measurements, deaths, AEs including CDC Class C AIDS events, laboratory measurements and ECG results. **Pharmacokinetics**: Intensive PK assessments for ATV Cmax, C_{min}, and AUC(TAU) were conducted in paediatric subjects weighing ≥ 25 to < 35 kg and/or who were ≥ 6 to < 11 years of age, and for subjects enrolling in the new ≥ 5 - < 10 kg cohort (200 mg ATV and 80 mg RTV). Trough plasma concentrations (C_{trough}) of ATV and RTV were also determined for all subjects from Week 4 though a minimum of 24 weeks and up through 48 weeks in Stage 1. **Other**: Palatability of ATV 10% aspartame powder and RTV oral solution is being assessed through a survey from Weeks 1 to 48. After protocol Amendment 07 approval, subjects ongoing on ATV 10% aspartame powder in Stage 2 who switched to ATV 4.2% aspartame powder had palatability survey and a 5-point facial hedonic scale (only for subjects who were ≥ 3 years old in Stage 2) assessments at time from switch and afterwards, as long as the subjects were on ATV 4.2%

	aspartame powder or up to maximum of 1 year.
Sample size	A total of approximately 95 subjects was planned for this study in order to treat approximately 10-15 subjects in the new 5-<10 kg (200 mg ATV and 80 mg RTV) cohort and have a minimum number of 56 treated subjects with 48 weeks of follow up on ATV powder based on an expected drop-out rate of approximately 30%. A minimum number of subjects with at least 24 weeks of follow up was planned for the following weight bands: - Minimum 5 subjects (on 150 mg ATV powder and 80 mg RTV) between 5-<10 kg - Minimum 6 subjects (on 200 mg ATV powder and 80 mg RTV) between 5-<10 kg - Minimum 10 subjects between 10-<15 kg - Minimum 10 subjects between 15-<25 kg. A target sample size of 95 treated subjects can detect with 80% probability, a safety event that occurs at a per subject incident rate of 1.7%, and can produce an exact binomial 95% CI within ± 10.5% for a response rate of 50.5%.
Statistical methods	No statistical comparisons between weight bands were conducted. **Efficacy**: All efficacy endpoints were secondary, and focused on the ATV powder formulation. Values after the start of ATV capsule were excluded. The response rates through Week 24 and Week 48 were assessed with the Snapshot algorithm. Response rates through Week 24 for Week 24 ATV powder cohort (treated subjects who did not switch to ATV capsule at or before analysis Week 24) and through Week 48 for Week 48 ATV powder cohort used a modified intent-to-treat (ITT) analysis. Response rates through Week 48 for treated subjects used observed values. Response rates were presented with exact binomial 95% CI. **Safety**: Safety evaluations were based on data on ATV powder through Week 48. **PK**: The derived PK parameters, C_{max}, T_{max}, AUC(TAU), C_{min}, CLT/F, and CLT/F/kg obtained at the Week 2 visit for ATV and RTV were summarized by baseline weight band.

Results

Participant flow and numbers analysed

Ninety-nine subjects were treated, and 67 subjects (68%) completed the Stage 1 treatment period. Thirty-two subjects (32%) did not complete Stage 1, and the most common reasons for discontinuation were a lack of efficacy (11%), AEs (7%), and withdrew consent (4%).

Table 19: Patient disposition

	B/L Weight 5 - < 10 kg (ATV 150mg)	B/L Weight 5 - < 10 kg (ATV 200mg)	B/L Weight 10 - < 15 kg	B/L Weight 15 - < 25 kg	B/L Weight 25 - < 35 kg	Total
TREATED	23	12	21	35	8	99
COMPLETED STAGE 1 TREATMENT PERIOD	15 (65.2)	4 (33.3)	16 (76.2)	26 (74.3)	6 (75.0)	67 (67.7)
DID NOT COMPLETE STAGE 1 TREATMENT PERIOD	8 (34.8)	8 (66.7)	5 (23.8)	9 (25.7)	2 (25.0)	32 (32.3)
REASONS FOR NOT COMPLETING STAGE 1 TREATMENT PERIOD	8 (34.8)	8 (66.7)	5 (23.8)	9 (25.7)	2 (25.0)	32 (32.3)
LACK OF EFFICACY	3 (13.0)	1 (8.3)	3 (14.3)	3 (8.6)	1 (12.5)	11 (11.1)
ADVERSE EVENT	1 (4.3)	2 (16.7)	2 (9.5)	1 (2.9)	1 (12.5)	7 (7.1)
SUBJECT WITHDREW CONSENT	1 (4.3)	2 (16.7)	0	1 (2.9)	0	4 (4.0)
LOST TO FOLLOW-UP	1 (4.3)	1 (8.3)	0	0	0	2 (2.0)
POOR/NON-COMPLIANCE	0	1 (8.3)	0	2 (5.7)	0	3 (3.0)
SUBJECT NO LONGER MEETS STUDY CRITERIA	1 (4.3)	1 (8.3)	0	1 (2.9)	0	3 (3.0)
OTHER	1 (4.3)	0	0	1 (2.9)	0	2 (2.0)
ONGOING IN STAGE 1 TREATMENT PERIOD	0	0	0	0	0	0
SUBJECTS CONTINUING IN THE STUDY AFTER STAGE 1 [1]	15 (65.2)	5 (41.7)	16 (76.2)	27 (77.1)	7 (87.5)	70 (70.7)
STAGE 2 TRANSITION TO CAPSULE	0	0	0	3 (8.6)	2 (25.0)	5 (5.1)
STAGE 2	15 (65.2)	4 (33.3)	16 (76.2)	23 (65.7)	4 (50.0)	62 (62.6)
OFF-TREATMENT FOLLOW-UP	0	1 (8.3)	0	1 (2.9)	1 (12.5)	3 (3.0)
SUBJECTS NOT CONTINUING IN THE STUDY [1]	8 (34.8)	7 (58.3)	5 (23.8)	8 (22.9)	1 (12.5)	29 (29.3)

Conduct of the study

This study was conducted in accordance with Good Clinical Practice.

Four subjects (4%) had relevant on-treatment protocol deviations: 2 subjects used a prohibited medication for > 3 days (rifampicin and fluticasone) and 2 subjects continued in the study after study drug interruptions > 14 days.

There were 8 amendments to the protocol. The main major changes were:

- the increase of inclusion upper age limit from 7.5 years to < 11 years of age because a weight of 25 to < 35 kg corresponds more to a HIV-infected paediatric child of approximately 10 years old;

- the addition of a new 5-<10 kg cohort with a higher ATV dose (200 mg ATV and 80 mg RTV) to assess if exposures can potentially be enhanced with a higher ATV dose;

- the switch of all subjects in Stage 2 who were still on the 10% aspartame ATV oral powder formulation to the new 4.2% aspartame ATV oral powder formulation and collected palatability/acceptability data at the time of switch and after the switch for a maximum duration of 1 year;

- the modification of the primary endpoint study duration from 48 weeks to a minimum of 24 weeks and key secondary objectives.

- the change of the whole treatment regimen, including ATV, in subjects with confirmed virologic failure or virologic rebound above 1000 copies/mL;

- the modification of the definition of virologic failure in accordance with the updated 2011 DHHS paediatric guidelines and clarified the virologic failure criteria to discontinue a subject in the study.

Baseline data

Table 20: Summary of demographic characteristics

	B/L Weight 5 - < 10 kg (ATV 150mg) N = 23	B/L Weight 5 - < 10 kg (ATV 200mg) N = 12	B/L Weight 10 - < 15 kg N = 21	B/L Weight 15 - < 25 kg N = 35	B/L Weight 25 - < 35 kg N = 8	Total N = 99
AGE AT BASELINE (MONTHS)						
N	23	12	21	35	8	99
MEAN	8.4	10.5	37.4	67.2	93.4	42.5
MEDIAN	5.0	5.5	36.0	68.0	86.5	41.0
MIN, MAX	3, 25	3, 30	15, 69	35, 115	79, 120	3, 120
Q1, Q3	3.0, 12.0	3.0, 17.0	29.0, 45.0	52.0, 80.0	81.5, 106.0	12.0, 71.0
STANDARD DEVIATION	6.42	9.21	12.44	16.70	15.53	31.58
GENDER (%)						
MALE	11 (47.8)	6 (50.0)	9 (42.9)	17 (48.6)	5 (62.5)	48 (48.5)
FEMALE	12 (52.2)	6 (50.0)	12 (57.1)	18 (51.4)	3 (37.5)	51 (51.5)
RACE (%)						
WHITE	2 (8.7)	2 (16.7)	12 (57.1)	13 (37.1)	3 (37.5)	32 (32.3)
BLACK/AFRICAN AMERICAN	19 (82.6)	6 (50.0)	7 (33.3)	20 (57.1)	5 (62.5)	57 (57.6)
OTHER	2 (8.7)	4 (33.3)	2 (9.5)	2 (5.7)	0	10 (10.1)
ETHNICITY (%)						
HISPANIC/LATINO	0	1 (8.3)	2 (9.5)	1 (2.9)	0	4 (4.0)
NOT HISPANIC/LATINO	1 (4.3)	1 (8.3)	1 (4.8)	1 (2.9)	0	4 (4.0)
NOT REPORTED	22 (95.7)	10 (83.3)	18 (85.7)	33 (94.3)	8 (100.0)	91 (91.9)
GEOGRAPHIC REGION (%)						
AFRICA	20 (87.0)	10 (83.3)	8 (38.1)	21 (60.0)	5 (62.5)	64 (64.6)
EUROPE	0	0	3 (14.3)	6 (17.1)	0	9 (9.1)
NORTH AMERICA	2 (8.7)	1 (8.3)	9 (42.9)	4 (11.4)	2 (25.0)	18 (18.2)
SOUTH AMERICA	1 (4.3)	1 (8.3)	1 (4.8)	4 (11.4)	1 (12.5)	8 (8.1)
COUNTRY (%)						
ARGENTINA	0	1 (8.3)	1 (4.8)	2 (5.7)	0	4 (4.0)
BRAZIL	0	0	0	1 (2.9)	0	1 (1.0)
CHILE	1 (4.3)	0	0	1 (2.9)	1 (12.5)	3 (3.0)
MEXICO	1 (4.3)	1 (8.3)	7 (33.3)	4 (11.4)	2 (25.0)	15 (15.2)
POLAND	0	0	1 (4.8)	0	0	1 (1.0)
ROMANIA	0	0	0	1 (2.9)	0	1 (1.0)
RUSSIA	0	0	1 (4.8)	3 (8.6)	0	4 (4.0)
SOUTH AFRICA	20 (87.0)	10 (83.3)	8 (38.1)	21 (60.0)	5 (62.5)	64 (64.6)
SPAIN	0	0	1 (4.8)	2 (5.7)	0	3 (3.0)
UNITED STATES OF AMERICA	1 (4.3)	0	2 (9.5)	0	0	3 (3.0)

	B/L Weight 5 - < 10 kg (ATV 150mg) N = 23	B/L Weight 5 - < 10 kg (ATV 200mg) N = 12	B/L Weight 10 - < 15 kg N = 21	B/L Weight 15 - < 25 kg N = 35	B/L Weight 25 - < 35 kg N = 8	Total N = 99
HIV RNA (LOG10 C/ML)						
N	23	12	21	35	8	99
MEAN	4.60	5.45	4.91	4.77	4.44	4.82
MEDIAN	5.00	5.43	5.00	4.90	4.51	5.00
MIN, MAX	2.0, 5.9	4.4, 5.9	3.9, 5.9	3.8, 5.7	3.4, 5.7	2.0, 5.9
Q1, Q3	4.28, 5.00	5.34, 5.84	4.76, 5.00	4.30, 5.00	3.59, 5.16	4.41, 5.28
STANDARD DEVIATION	0.939	0.459	0.460	0.449	0.892	0.682
HIV RNA CATEGORIES (C/ML) (%)						
< 30,000	6 (26.1)	1 (8.3)	5 (23.8)	10 (28.6)	4 (50.0)	26 (26.3)
30,000 - 100,000	5 (21.7)	1 (8.3)	3 (14.3)	11 (31.4)	2 (25.0)	22 (22.2)
> 100,000	12 (52.2)	10 (83.3)	13 (61.9)	14 (40.0)	2 (25.0)	51 (51.5)
CD4 COUNT (CELLS/MM^3)						
N	20	11	13	27	8	79
MEAN	2244.6	2138.9	841.9	723.4	610.8	1313.7
MEDIAN	2234.5	2168.0	888.0	724.0	604.5	928.0
MIN, MAX	160, 5703	857, 3235	131, 1588	201, 1383	433, 785	131, 5703
Q1, Q3	1489.0, 2892.0	1489.0, 2722.0	561.0, 1177.0	538.0, 912.0	535.5, 694.0	615.0, 1998.0
STANDARD DEVIATION	1232.71	736.42	488.17	282.90	115.52	1015.30
CD4 COUNT CATEGORIES (CELLS/MM^3) (%)						
50 - < 200	1 (4.3)	0	2 (9.5)	0	0	3 (3.0)
200 - < 350	0	0	1 (4.8)	3 (8.6)	0	4 (4.0)
350 - < 500	1 (4.3)	0	0	2 (5.7)	2 (25.0)	5 (5.1)
500 - < 750	0	0	3 (14.3)	11 (31.4)	5 (62.5)	19 (19.2)
750 - < 1000	1 (4.3)	1 (8.3)	3 (14.3)	7 (20.0)	1 (12.5)	13 (13.1)
1000 - < 1500	2 (8.7)	2 (16.7)	3 (14.3)	4 (11.4)	0	11 (11.1)
1500 - < 2000	2 (8.7)	2 (16.7)	1 (4.8)	0	0	5 (5.1)
>= 2000	13 (56.5)	6 (50.0)	0	0	0	19 (19.2)
NOT REPORTED	3 (13.0)	1 (8.3)	8 (38.1)	8 (22.9)	0	20 (20.2)
CD4 PERCENT (%)						
N	21	11	15	30	8	85
MEAN	28.7	31.2	21.2	24.5	30.8	26.4
MEDIAN	29.0	30.0	21.0	25.0	31.5	27.0
MIN, MAX	8, 50	10, 49	5, 44	9, 53	16, 52	5, 53
Q1, Q3	22.0, 33.0	27.0, 36.0	10.0, 29.0	17.0, 31.0	22.5, 35.0	19.0, 33.0
STANDARD DEVIATION	10.88	11.26	10.88	9.59	11.04	10.82
CD4 PERCENT CATEGORIES (%)						
< 15	3 (13.0)	1 (8.3)	4 (19.0)	5 (14.3)	0	13 (13.1)
15 - < 25	3 (13.0)	1 (8.3)	5 (23.8)	8 (22.9)	3 (37.5)	20 (20.2)
>= 25	15 (65.2)	9 (75.0)	6 (28.6)	17 (48.6)	5 (62.5)	52 (52.5)
NOT REPORTED	2 (8.7)	1 (8.3)	6 (28.6)	5 (14.3)	0	14 (14.1)
PRIOR ARV USE (%)						
ARV NAIVE	5 (21.7)	2 (16.7)	13 (61.9)	14 (40.0)	3 (37.5)	37 (37.4)
ARV EXPERIENCED	18 (78.3)	10 (83.3)	8 (38.1)	21 (60.0)	5 (62.5)	62 (62.6)

At baseline, the majority of subjects had normal laboratory test results. However, Grade 3 or 4 results were reported for some subjects: Grade 3 amylase (18%), Grade 3 ALT (3%), Grade 4 amylase (2%), Grade 3 low calcium, low chloride, and low sodium (1% each), and Grade 4 ALT and AST (1% each).

At baseline, 29% of subjects had abnormal ECG findings (4 subjects [17%], 3 subjects [25%], 6 subjects [29%], 12 subjects [34%], and 4 subjects [50%] in the 5-<10 kg [ATV 150 mg], 5-<10 kg [ATV 200 mg], 10-<15 kg, 15-<25 kg, and 25-<35 kg groups, respectively). The most common abnormal findings were left axis deviation or left ventricular hypertrophy by voltage criteria only or sinus tachycardia; none were consistent with QT or PR prolongation, exclusion criteria for this study.

Overall, 83% of subjects had used prior medications. The most commonly used prior medications were sulfamethoxazole/trimethoprim (61%), acetaminophen (58%), amoxicillin (44%), multivitamins (35%), amoxicillin/clavulanic acid (28%), and iron (21%).

Virologic response – mITT analysis

At Week 24 on the ATV powder cohort (n=99), 66% of subjects had HIV RNA < 400 c/mL and 47% of subjects had HIV RNA < 50 c/mL. In ARV-experienced and -naive subjects, the proportion of subjects with HIV RNA < 400 c/mL (65% and 68%, respectively) and < 50 c/mL (47% and 46%, respectively) was similar.

At Week 48 on the ATV powder cohort (n=80), 65% of subjects had HIV RNA < 400 c/mL and 45% of subjects had HIV RNA < 50 c/mL. In ARV-experienced and -naive subjects, the proportion of subjects with HIV RNA < 400 c/mL (60% and 73%, respectively) and < 50 c/mL (46% and 43%, respectively) was similar.

HIV RNA changes from baseline

The overall mean (median) change from baseline in HIV RNA was -2.53 (-2.80) log_{10} c/mL at Week 24 and -2.71 (-2.90) log_{10} c/mL at Week 48.

In the 5-<10 kg (ATV 150 mg), 5-<10 kg (ATV 200 mg), 10-<15 kg, 15-<25 kg and 25-<35 kg groups, the mean (median) change from baseline in HIV RNA was:

- At Week 24: -2.10 (-2.17), -3.07 (-3.68), -2.69 (-3.17), -2.66 (-2.80) and -2.24 (-2.08) log10 c/mL, respectively.

- At Week 48: -2.31 (-2.76), -4.06 (-4.06), -2.91 (-3.10), -2.70 (-2.62) and -3.97 (-3.97) log_{10} c/mL; respectively (Note: There was only 1 subject in the 25-<35 kg group and 2 subjects in the 5-<10 kg [ATV 200 mg] group.)

CD4 cell count changes from baseline

The overall mean (median) change from baseline in CD4 cell count was 214 (134) cells/mm^3 at Week 24 and 133 (215) cells/mm^3 at Week 48.

Virologic resistance

By Week 48, a total amount of 36 subjects met the criteria for virologic failure. Twenty-one of these subjects had paired genotypic data (data at baseline and on treatment) and 17 had paired phenotypic resistance testing data. Eleven subjects (31%) were ARV naive and 25 subjects (69%) were ARV experienced.

Five subjects developed a M184V mutation, and all 5 exhibited phenotypic resistance for emtricitabine (FTC) and lamivudine (3TC). One subject developed a major ATV mutation (I84V). This subject had ATV C_{trough} values below the LLOQ due to rifabutin co-administration.

Palatability

Palatability survey on ATV powder (10% aspartame) and RTV was performed at each visit. Throughout the study, the majority of subjects took their dose of ATV mixed with milk or water, and palatability/acceptability of ATV powder was higher than for RTV: At Week 24, 87% and 81% of subjects did not have any trouble taking their doses of ATV and RTV, respectively. At Week 48, 83% and 74% of subjects did not have any trouble taking their doses of ATV and RTV, respectively.

After the switch to ATV formulation with lower percentage of aspartame, the palatability survey on ATV powder (4.2% aspartame) and RTV was performed: At Week 24, 30/30 (100%) and 27/30 (90%) of subjects had no problem taking their doses of ATV and RTV, respectively. At Week 48, 15/15 (100%) and 14/15 (93%) of subjects had no problem taking their doses of ATV and RTV, respectively.

The Facial Hedonic Scale was used to describe the palatability of the new ATV 4.2% aspartame powder formulation for subjects on ATV powder formulation in Stage 2 subjects who were ≥ 3 years old. At

Day 1/time of switch from ATV powder (10% aspartame) to the ATV powder (4.2% aspartame), 17 subjects (65%) rated the ATV powder (4.2% aspartame) taste as "good" or "super good." At 24 weeks of treatment with ATV powder (4.2% aspartame), 15/18 subjects (83%) rated the ATV powder (4.2% aspartame) taste as "good" or "super good." At 48 weeks of treatment with ATV powder (4.2% aspartame), all 9 subjects rated the ATV powder (4.2% aspartame) taste as "super good."

Summary of efficacy for trials AI424397 (PRINCE I) and AI424451 (PRINCE II)

Error! Reference source not found. and **Error! Reference source not found.** summarise the efficacy results from the main studies supporting the present application:

Table 21: AI424397 – PRINCE I Study

Title: A Prospective Single Arm, Open-label, International, Multicenter Study to Evaluate the Safety, Efficacy and Pharmacokinetics of Atazanavir (ATV) Powder Boosted with Ritonavir (RTV) Liquid with an Optimized NRTI Background Therapy, in HIV Infected Pediatric Patients Greater Than or Equal to 3 Months to Less Than 6 Years.				
Design	Phase 3b prospective, international, multicenter, nonrandomized, 2-stage study of a cohort of HIV-infected pediatric subjects ≥ 3 months to < 5 years and 6 months of age.			
	Duration of main phase:		48 weeks	
Hypothesis	Exploratory in pediatric subjects			
Participants	- HIV-infected pediatric subjects ≥ 3 months to < 5 years and 6 months of age. - Weight between 5 kg and 25 kg at Day 1. - ARV naive or experienced (without prior exposure to ATV). - HIV RNA value ≥ 1000 c/ml. - Genotypic sensitivity to ATV and to NRTI backbone.			
Treatments groups (by weight)	5 to <10 kg		ATV/RTV 150/80 mg QD + 2 NRTIs (excluding TDF). N = 21	
	10 to <15 kg		ATV/RTV 200/80 mg QD + 2 NRTIs (excluding TDF). N = 19	
	15 to <25 kg		ATV/RTV 250/80 mg QD + 2 NRTIs (excluding TDF). N = 16	
Endpoints and definitions	Efficacy endpoint	% subjects with HIV-1 RNA <50 c/mL	At Week 48, using FDA Snapshot algorithm. mITT and Observed Values analyses.	
		% subjects with HIV-1 RNA <400 c/mL	At Week 48, using FDA Snapshot algorithm. mITT and Observed Values analyses.	
		Change from baseline in plasma HIV-1 RNA		
		Change from baseline in CD4 cell count		
	Safety endpoints	Vital signs, physical measurements, deaths, AEs including CDC Class C AIDS events, laboratory measurements and ECG results.		
Database lock	03 December 2012 (Week 48 completed)			
Results and Analysis				
Analysis description	**Primary Analysis – Week 48 results**			
Analysis population and time point description	Intent to treat Time point: Week 48			
Descriptive statistics and estimate variability	Treatment weight group	5-<10 kg ATV 150 mg	10-<15 kg ATV 200 mg	15-<25 kg ATV 250 mg
	Number of subject	21	19	16
	Subjects with HIV-1 RNA <50 c/mL at W48 (%)	47.6	68.4	71.4
	Subjects with HIV-1 RNA <400 c/mL at W48 (%)	66.7	73.7	85.7

	Mean (median) change from Baseline in HIV-1 RNA (log10 c/ml at Week 48)	-2.61 (-3.31)	-2.93 (-3.31)	-2.40 (-2.59)
Analysis description	**Secondary Analysis – Week 48 results**			
Analysis population and time point description	Per protocol Time point: Week 48			
Descriptive statistics and estimate variability	Treatment weight group	5-<10 kg ATV 150 mg	10-<15 kg ATV 200 mg	15-<25 kg ATV 250 mg
	Number of subject	17	15	13
	Subjects with HIV-1 RNA <50 c/mL at W48 (%)	58.8	86.7	76.9
	Subjects with HIV-1 RNA <400 c/mL at W48 (%)	82.4	93.3	92.3

Additionally at Week 48, in ARV-experienced and -naive subjects, the proportion of subjects with HIV RNA < 400 c/mL (75% and 74%, respectively) and < 50 c/mL (60% and 62%, respectively) was similar.

A total amount of 14 subjects met the criteria for virologic failure. Nine of these subjects had paired genotypic data (data at baseline and on treatment) and 6 had paired phenotypic resistance testing data. None of the subjects acquired phenotypic and genotypic resistance to ATV.

Table 22: AI424451 – PRINCE II study

Title: A Prospective Single Arm, Open-label, International, Multicenter Study to Evaluate the Safety, Efficacy and Pharmacokinetics of Atazanavir (ATV) Powder Boosted with Ritonavir (RTV) with an Optimized NRTI Background Therapy, in HIV Infected, Antiretroviral, Naive and Experienced Pediatric Subjects From 3 Months to Less Than 11 Years.			
Design	Phase 3b prospective, international, multicenter, nonrandomized, 2-stage study of a cohort of HIV-infected pediatric subjects ≥ 3 months to < 11 years of age.		
	Duration of main phase:		48 weeks
Hypothesis	Exploratory in pediatric subjects		
Participants	- HIV-infected pediatric subjects ≥ 3 months to < 11years of age. - Weight between 5 kg and 35 kg at Day 1. - ARV naive or experienced (without prior exposure to ATV). - Genotypic sensitivity to ATV and to NRTI backbone.		
Treatments groups (by weight)	5 to <10 kg		ATV/RTV 150/80 mg QD + 2 NRTIs (excluding TDF). N = 23
	5 to <10 kg		ATV/RTV 200/80 mg QD + 2 NRTIs (excluding TDF). N = 12
	10 to <15 kg		ATV/RTV 200/80 mg QD + 2 NRTIs (excluding TDF). N = 21
	15 to <25 kg		ATV/RTV 250/80 mg QD + 2 NRTIs (excluding TDF). N = 35
	25 to <35 kg		ATV/RTV 300/80 mg QD + 2 NRTIs (excluding TDF). N = 8
Endpoints and definitions	Efficacy endpoint	% subjects with HIV-1 RNA <50 c/mL	At Week 48, using FDA Snapshot algorithm. mITT and Observed Values analyses.
		% subjects with HIV-1 RNA <400 c/mL	At Week 48, using FDA Snapshot algorithm. mITT and Observed Values analyses.
		Change from baseline in plasma HIV-1 RNA	
		Change from baseline in CD4 cell count	
	Safety endpoints	Vital signs, physical measurements, deaths, AEs including CDC Class C AIDS events, laboratory measurements and ECG results.	

Database lock	09 October 2014 (Ongoing)					
Results and Analysis						
Analysis description	**Primary Analysis – Week 48 results**					
Analysis population and time point description	Intent to treat Time point: Week 48					
Descriptive statistics and estimate variability	Treatment weight group	5-<10 kg ATV 150 mg	5-<10 kg ATV 200 mg	10-<15 kg ATV 200 mg	15-<25 kg ATV 250 mg	25-<35 kg ATV 300 mg
	Number of subject	23	1	20	34	2
	Subjects with HIV-1 RNA <50 c/mL at W48 (%)	47.8	0	30.0	52.9	50.0
	Subjects with HIV-1 RNA <400 c/mL at W48 (%)	60.9	100.0	70.0	64.7	50.0
	Mean (median) change from Baseline in HIV-1 RNA (log10 c/ml at Week 48)	-2.31 (-2.76)	-4.06 (-4.06)	-2.91 (-3.10)	-2.70 (-2.62)	-3.97 (-3.97)
Analysis description	**Secondary Analysis – Week 24 results**					
Analysis population and time point description	Intent to treat Time point: Week 24					
Descriptive statistics and estimate variability	Treatment weight group	5-<10 kg ATV 150 mg	5-<10 kg ATV 200 mg	10-<15 kg ATV 200 mg	15-<25 kg ATV 250 mg	25-<35 kg ATV 300 mg
	Number of subject	23	12	21	35	8
	Subjects with HIV-1 RNA <50 c/mL at W24 (%)	43.5	16.7	47.6	54.3	62.5
	Subjects with HIV-1 RNA <400 c/mL at W24 (%)	65.2	41.7	71.4	68.6	75.0
	Mean (median) change from Baseline in HIV-1 RNA (log10 c/ml at Week 24)	-2.10 (-2.17)	-3.07 (-3.68)	-2.69 (-3.17)	-2.66 (-2.80)	-2.24 (-2.08)
Analysis description	**Secondary Analysis – Week 24 results**					
Analysis population and time point description	Per protocol Time point: Week 24					
Descriptive statistics and estimate variability	Treatment weight group	5-<10 kg ATV 150 mg	5-<10 kg ATV 200 mg	10-<15 kg ATV 200 mg	15-<25 kg ATV 250 mg	25-<35 kg ATV 300 mg
	Number of subject	21	7	19	29	7
	Subjects with HIV-1 RNA <50 c/mL at W24 (%)	47.6	28.6	52.6	65.5	71.4
	Subjects with HIV-1 RNA <400 c/mL at W24 (%)	71.4	71.4	78.9	82.8	85.7

Additionally at Week 24, in ARV-experienced and -naive subjects, the proportion of subjects with HIV RNA < 400 c/mL (65% and 68%, respectively) and < 50 c/mL (47% and 46%, respectively) was similar.

A total amount of 36 subjects met the criteria for virologic failure. Twenty-one of these subjects had paired genotypic data (data at baseline and on treatment) and 17 had paired phenotypic resistance testing data. One subject developed a major ATV mutation (I84V). This subject had ATV C_{trough} values below the LLOQ due to rifabutin co-administration.

Analysis performed across trials

Pooled analysis

Due to their similar design and population, studies PRINCE I and II were pooled. The efficacy results are as follows:

Results and Analysis						
Analysis description	**Primary Analysis – Week 48 results**					
Analysis population and time point description	Intent to treat Time point: Week 48					
Descriptive statistics and estimate variability	Treatment weight group	5-<10 kg ATV 150 mg	5-<10 kg ATV 200 mg	10-<15 kg ATV 200 mg	15-<25 kg ATV 250 mg	25-<35 kg ATV 300 mg
	Number of subject	44	1	39	48	2
	Subjects with HIV-1 RNA <50 c/mL at W48 (%)	47.7	0	48.7	58.3	50.0
	Subjects with HIV-1 RNA <400 c/mL at W48 (%)	63.6	100.0	71.8	70.8	50.0
Analysis description	**Secondary Analysis – Week 24 results**					
Analysis population and time point description	Intent to treat Time point: Week 24					
Descriptive statistics and estimate variability	Treatment weight group	5-<10 kg ATV 150 mg	5-<10 kg ATV 200 mg	10-<15 kg ATV 200 mg	15-<25 kg ATV 250 mg	25-<35 kg ATV 300 mg
	Number of subject	44	12	40	51	8
	Subjects with HIV-1 RNA <50 c/mL at W24 (%)	38.6	16.7	50.0	54.9	62.5
	Subjects with HIV-1 RNA <400 c/mL at W24 (%)	61.4	41.7	75.0	68.6	75.0

At Week 48, respectively 62% and 79% of subjects in the ARV-experienced and -naive groups had HIV RNA < 400 c/mL, and respectively 50% and 54% of subjects in the ARV-experienced and –naïve groups had HIV RNA < 50 c/mL. It appears to be an observed association between higher proportions of virologic success and ARV naïve status in the majority of intra-weight band comparisons, although in certain instances the efficacy outcomes are similar between ARV naïve and ARV experienced subjects.

Table 23: Virologic Success at Week 48 by ARV Pre-treatment Status – Snapshot Analyses (PRINCE I and PRINCE II)

	Number of Subjects (%)							
	5-<10 kg ATV 150 mg		5-<10 kg ATV 200 mg	10-<15 kg		15-<25 kg		25-<35 kg
	Prince 1 N = 21	Prince II N = 23	Prince II[a] N = 12	Prince I N = 19	Prince II N = 20	Prince I N = 14	Prince II N = 34	Prince II N =2
Snapshot								
HIV RNA <50 c/mL								
Naive	3/7 (42.9)	1/5 (20.0)	0/2	8/10 (80.0)	5/12 (41.7)	4/5 (80.0)	7/13 (53.8)	0/0
Experienced	7/14 (50.0)	10/18 (55.6)	0/1	5/9 (55.6)	1/8 (12.5)	6/9 (66.7)	11/21 (52.4)	1/2 (50.0)
HIV RNA< 400 c/mL								
Naive	6/7 (85.7)	3/5 (60.0)	0/0	8/10 (80.0)	10/12 (83.3)	5/5 (100)	9/13 (69.2)	0/0
Experienced	8/14 (57.1)	11/18 (61.1)	1/1 (100)	6/9 (66.7)	4/8 (50.0)	7/9 (77.8)	13/21 (61.9)	1/2 (50.0)

a Week 24 results are shown for the 200 kg weight group as only 1 subject had reached Week 48.

The antiviral efficacy seems slightly higher in subjects with baseline viral load < 100,000 c/ml compared to ≥ 100,000 c/ml: at week 48, the rates of HIV RNA < 50 c/ml are 57% (36/63) and 46% (33/71), and the rates of HIV RNA < 400 c/ml are 73% (46/63) and 65% (46/71), respectively. As regards the baseline NRTI background, Kivexa was mostly used (58.2% of subjects), the other backgrounds mainly consisted of AZT/3TC (15%) and ABC/AZT (13.4%). The best response rates were observed with Kivexa (HIV RNA < 50 c/ml and < 400 c/ml at week 48 at 63% and 79.5%, respectively) compared to AZT-based NRTI backgrounds (HIV RNA < 50 c/ml and < 400 c/ml at week 48 around 25-30% and 40-50%, respectively).

Table 24: Virologic Outcome at Week 48 - Eligible Week 48 ATV Powder Cohort (Integrated Analysis PRINCE I and PRINCE II)

	Number of Subjects (%)				
	5-<10 kg (ATV 150 mg) N = 44	10-<15 kg N = 39	15-<25 kg N = 48	25-<35 kg N = 2	Total N = 134
HIV RNA < 50 c/mL	21/44 (47.7)	19/39 (48.7)	28/48 (58.3)	1/2 (50.0)	69/134 (51.5)
Baseline viral load					
< 100,000 c/mL	8/14 (57.1)	6/16 (37.5)	22/32 (68.8)	0/1	36/63 (57.1)
≥ 100,000 c/mL	13/30 (43.3)	13/23 (56.5)	6/16 (37.5)	1/1 (100)	33/71 (46.5)
Baseline NRTI					
ABC/3TC	21/35 (60.0)	11/17 (64.7)	17/25 (68.0)	0/0	49/78 (62.8)
AZT/3TC	0/5	2/4 (50.0)	3/10 (30.0)	0/1	5/20 (25.0)
ABC/AZT	0/2	1/8 (12.5)	4/8 (50.0)	0/0	5/18 (27.8)
Other[a]	0/2	5/10 (50.0)	4/5 (80.0)	1/1 (100)	10/18 (55.6)
HIV RNA < 400 c/mL	28/44 (63.6)	28/39 (71.8)	34/48 (70..8)	1/2 (50.0)	92/134 (68.7)
Baseline viral load					
< 100,000 c/mL	9/14 (64.3)	11/16 (68.6)	26/32 (81.3)	0/1	46/63 (73.0)
≥ 100,000 c/mL	19/30 (63.3)	17/23 (73.9)	8/16 (50.0)	1/1 (100)	46/71 (64.8)
Baseline NRTI					
ABC/3TC	26/35 (74.3)	15/17 (88.2)	20/25 (80.0)	0/0	62/78 (79.5)
AZT/3TC	0/5	3/4 (75.0)	5/10 (50.0)	0/1	8/20 (40.0)
ABC/AZT	1/2 (50.0)	4/8 (50.0)	5/8 (62.5)	0/0	10/18 (55.6)
Other[a]	1/2 (50.0)	6/10 (60.0)	4/5 (80.0)	1/1 (100)	12/18 (66.7)

a Other NRTI regimens include ABC+stavuidine (n = 2), 3TC + didonasine (n = 1); ABC+AST+stavudine (n = 1), and AZT+ABC+3TC (n = 2)

Additional subgroup analyses were provided in an attempt to better interpret efficacy results depending on age, treatment experience, baseline viral load.

Analysis by weight groups

Table 25: Antiviral Response at Week 48 by Weight - Snapshot and Observed Analyses (PRINCE I and PRINCE II)

	Number of Subjects (%)							
	5-<10 kg ATV 150 mg		5-<10 kg ATV 200 mg	10-<15 kg		15-<25 kg		25-<35 kg
	Prince 1 N = 21	Prince II N = 23	Prince II[a] N = 12	Prince I N = 19	Prince II N = 20	Prince I N = 14	Prince II N = 34	Prince II N =2
Snapshot								
HIV RNA <50 c/mL	10 (47.6)	11 (47.8)	2 (16.7)	13 (68.4)	6 (30.0)	10 (71.4)	18 (52.9)	1 (50.0)
HIV RNA< 400 c/mL	14 (66.7)	14 (60.9)	5 (41.7)	14 (73.7)	14 (70.0)	12 (85.7)	22 (64.7)	1 (50.0)
Observed								
HIV RNA <50 c/mL	10/17 (58.8)	11/16 (68.8)	2/7 (28.6)	13/15 (86.7)	6/15 (40.0)	10/13 (76.9)	18/25 (72.0)	1/1 (100)
HIV RNA< 400 c/mL	14 /17 (82.4)	14/16 (87.5)	5/7 (71.4)	14/15 (93.3)	14/15 (93.3)	12/13 (92.3)	22/25 (88.0)	1/1 (100)

a Week 24 results are shown for the 200 mg weight group

Table 26: Virologic Outcome at Week 48 - Eligible Week 48 ATV Powder Cohort (Integrated Analysis PRINCE I and PRINCE II)

	Number of Subjects (%)				
	5-<10 kg (ATV 150 mg) N = 44	10-<15 kg N = 39	15-<25 kg N = 48	25-<35 kg N = 2	Total N = 134
HIV RNA < 50 c/mL	21/44 (47.7)	19/39 (48.7)	28/48 (58.3)	1/2 (50.0)	69/134 (51.5)
Baseline viral load					
< 100,000 c/mL	8/14 (57.1)	6/16 (37.5)	22/32 (68.8)	0/1	36/63 (57.1)
≥ 100,000 c/mL	13/30 (43.3)	13/23 (56.5)	6/16 (37.5)	1/1 (100)	33/71 (46.5)
Baseline NRTI					
ABC/3TC	21/35 (60.0)	11/17 (64.7)	17/25 (68.0)	0/0	49/78 (62.8)
AZT/3TC	0/5	2/4 (50.0)	3/10 (30.0)	0/1	5/20 (25.0)
ABC/AZT	0/2	1/8 (12.5)	4/8 (50.0)	0/0	5/18 (27.8)
Other[a]	0/2	5/10 (50.0)	4/5 (80.0)	1/1 (100)	10/18 (55.6)
HIV RNA < 400 c/mL	28/44 (63.6)	28/39 (71.8)	34/48 (70..8)	1/2 (50.0)	92/134 (68.7)
Baseline viral load					
< 100,000 c/mL	9/14 (64.3)	11/16 (68.6)	26/32 (81.3)	0/1	46/63 (73.0)
≥ 100,000 c/mL	19/30 (63.3)	17/23 (73.9)	8/16 (50.0)	1/1 (100)	46/71 (64.8)
Baseline NRTI					
ABC/3TC	26/35 (74.3)	15/17 (88.2)	20/25 (80.0)	0/0	62/78 (79.5)
AZT/3TC	0/5	3/4 (75.0)	5/10 (50.0)	0/1	8/20 (40.0)
ABC/AZT	1/2 (50.0)	4/8 (50.0)	5/8 (62.5)	0/0	10/18 (55.6)
Other[a]	1/2 (50.0)	6/10 (60.0)	4/5 (80.0)	1/1 (100)	12/18 (66.7)

a Other NRTI regimens include ABC+stavuidine (n = 2), 3TC + didonasine (n = 1); ABC+AST+stavudine (n = 1), and AZT+ABC+3TC (n = 2)

5-<10 kg weight group

Table 27: Virologic Outcome at Week 24 - 5-<10 kg group - Week 24 ATV Powder Cohort (PRINCE I, PRINCE II, and Integrated)

	Number of Subjects (%)			
	PRINCE I	PRINCE II	PRINCE I/II	PRINCE II
	5-<10 kg (ATV 150 mg) N = 21	5-<10 kg (ATV 150 mg) N = 23	5-<10 kg (ATV 150 mg) N = 44)	5-<10 kg (ATV 200 mg) N = 12
HIV RNA < 50 c/mL	7/21 (33.3)	10/23 (43.5)	17/44 (38.6)	2/12 (16.7)
Baseline viral load				
< 100,000 c/mL	0/3	7/11 (63.6)	7/14 (50.0)	0/2
≥ 100,000 c/mL	7/18 (38.9)	3/12 (25.0)	10/30 (33.3)	2/10 (20.0)
Baseline NRTI				
ABC/3TC	7/16 (43.8)	10/19 (52.6)	17/35 (48.6)	1/10 (10.0)
AZT/3TC	0/3	0/2	0/5	1/1 (100)
ABC/AZT	0/1	0/1	0/2	0/1
Other	0/1	0/1	0/2	0/1
HIV RNA < 400 c/mL	12/21 (57.1)	15/32 (65.2)	27/44 (61.4)	5/12 (41.7)
Baseline viral load				
< 100,000 c/mL	2/3 (66.7)	8/11 (72.7)	10/14 (71.4)	0/2
≥ 100,000 c/mL	10/18 (55.6)	7/12 (58.3)	17/30 (56.7)	5/10 (50.0)
Baseline NRTI				
ABC/3TC	10/16 (62.5)	13/19 (68.4)	23/35 (65.7)	4/10 (40.0)
AZT/3TC	0/3	1/2 (50.0)	1/5 (20.0)	1/1 (100)
ABC/AZT	1/1 (100)	0/1	1/2 (50.0)	0/1
Other	1/1 (100)	1/1 (100)	2/2 (100)	0/0

Although exposures were generally higher in the 5-<10 kg ATV 200 mg cohort compared to the 5-<10 kg ATV 150 mg cohort, the virologic response as analysed by mITT was not improved overall in the ATV 200 mg cohort. A possible explanation for the low rate of success in the 200 mg ATV group was the rate of discontinuation before Week 24. Five (5/12) subjects in the 5-<10 kg 200 mg ATV cohort discontinued prior to Week 24 and were counted as virologic failures in the mITT analysis. In the observed analysis, where subjects who discontinued early are counted as missing, the differences between the 150 and 200 mg groups in virologic success rates (HIV RNA < 50 c/mL) analysis are less marked (38.9% and 47.6% in 150 mg ATV groups in PRINCE I and PRINCE II, and 28.6% in the 200 mg ATV group in PRINCE II), while the rates of virologic suppression to HIV RNA < 400 c/mL were similar (66.7% and 71.4% for subjects receiving 150 mg ATV in PRINCE I and PRINCE II, and 71.4% for subjects receiving 200 mg ATV in PRINCE II).

In addition, the median baseline viral load was notably higher in the 200 mg ATV cohort (5.43 log10; range 4.4 to 5.9) in PRINCE II compared with the 150 mg ATV cohorts from PRINCE I (5.0 log10; range 2.8 to 5.9) and PRINCE II (5.0 log10 (range 2.0 to 5.9). Furthermore, the mean log10 drop in viral load at Week 24 was slightly higher in the 200 mg ATV cohort (-3.07) in PRINCE II compared with the 150 mg cohorts in PRINCE I (-2.41) and PRINCE II (-2.10).

Overall, in the 5- 10kg weight group, viral success was similar for the 150mg dose cohorts in PRINCE 1 and 2, while the 200mg dose cohort had a considerably lower success rate. While there were some differences in baseline viral load and treatment experience, an effect on results cannot be concluded based on the available data in this very small group.

There is no reason to assume that efficacy in this weight group, when given a dose of 200/80 mg, would be considerably lower than in other groups based on the C24 levels. The concern is if at this

dose level safety or tolerability problems may contribute to non- adherence or lead to adverse events and/ or treatment discontinuation. In this regards, the high number or dropouts in this group is of concern, however it appears that drop- outs were mostly not due to safety or tolerability issues.

10-<15 kg weight group

Comparison of individual study data showed a notably lower virologic response rate in the 10-<15 kg weight group in PRINCE II (30.0%) than PRINCE I (68.4%), and the lower response rate in PRINCE II appeared to be driving the lower rate of response in the 10-<15 kg group in the integrated analysis.

The most likely explanation for the lower efficacy observed in the 10-<15 kg weight band in PRINCE II is viral blips that occurred in the Week 48 analysis window. A total of 15 subjects in PRINCE II had virologic failure at < 50 c/mL within the Week 48 analysis window. Of these, 7 subjects demonstrated virologic suppression to < 400 c/mL at this time point. These 7 patients recovered a viral load < 50 c/ml after their virologic failure. This is further supported by the similar efficacy observed at Week 48 using a virologic cut-off of < 400 c/mL of 73.7% for subjects in PRINCE I and 70.0% for subjects in PRINCE II.

15-<25 kg weight group

There do not appear to be significant differences in baseline characteristics between the subjects in the 15-<25 kg weight band from PRINCE I and PRINCE II to account for decreased antiviral response in subjects in PRINCE II. However, the similarity of antiviral response (HIV RNA < 50 c/mL and HIV RNA < 400 c/mL) evaluated using an observed analysis suggests that the difference in response by the snapshot analysis is likely due to the number of subjects who discontinued the study or did not provide data during the Week 48 window. Seven subjects in this weight band in PRINCE II were counted as failures due to discontinuation for reasons unrelated to study drug. These subjects were included in the denominator for the snapshot analysis and excluded in the observed analysis.

25-<35 kg weight group

Only 2 subjects in the 25-<35 kg weight group had reached the Week 48 at the time of data cutoff, including one subject with VL < 50 c/ml.

In summary, the exploration of the data did not show evidence that higher viral load, pre-existing PI mutations or the type of OBR affected results. The small numbers of subjects in the respective subgroups are the most likely reason for the inability to identify relevant associations.

Supportive study

Study AI424466

A taste assessment study (AI424466) was performed to compare the sweetness and palatability of 2 new ATV powders formulations (4.2% aspartame +/- sucralose) to the current ATV powder (10% aspartame) in 12 healthy subjects, and to select one ATV powder that has the sweetness most similar to the current ATV powder.

Methods

This is a Phase 1 double-blind, randomized, 3-treatment, 3-period, 3-sequence crossover study in healthy adult subjects. Twelve subjects were randomized to 1 of 3 treatment sequences. Three treatments were assessed:

- Treatment A (15 mg/5 mL ATV powder current formulation [10% aspartame]; Reference),

- Treatment B (15 mg/5 mL ATV in New powder 1 [4.2% aspartame]),

- Treatment C (15 mg/5 mL ATV in New powder 2 [4.2% aspartame + sucralose]).

On Day 1, subjects tasted 5 mL each of treatments in a double-blind, randomized sequence. Treatment tastings were separated by a washout period of at least 45 minutes, and after each tasting, subjects rinsed their mouths with water and ate 2 saltine crackers.

					Period 1		Period 2		Period 3		
Study Day	-14	-3 to -2	-1		1		1		1		1
				Dosing Sequence	TRT		TRT		TRT		
	S, E	Taste Screen	Check-In, R	1	A	W	B	W	C	W	SD
				2	B	W	C	W	A	W	
				3	C	W	A	W	B	W	

S= screening; E = Enrollment; R = Randomization; TRT = Treatment; W = ≥ 45 minutes; SD = Study Discharge; ATV = atazanavir; POU = powder for oral use.
Treatment A = 15 mg/5 mL ATV POU current formulation (10% aspartame; Reference)
Treatment B = 15 mg/5 mL ATV in New POU 1 (4.2% aspartame)
Treatment C = 15 mg/5 mL ATV in New POU 2 (4.2% aspartame + sucralose)

The primary objectives were to compare the sweetness of 2 new ATV powders formulations to the current ATV powder in healthy subjects, and to select one ATV powder that has the sweetness most similar to the current ATV powder. The secondary objective was to compare the overall palatability of the 2 new ATV powders to the current ATV powder in healthy subjects.

Subjects immediately scored the respective treatments for sweetness (during Taste Screening and Treatment Tasting) and overall palatability (during Treatment Tasting only) using the following scales:

- Sweetness was assessed using a subjective sweet intensity scoring system: 0 = no sweet taste, 1 = mildly sweet, 2 = moderately sweet, 3 = very sweet. Subjects were permitted to select a whole or half score number (eg, 1.5) between the minimum score of 0 and the maximum score of 3.0.

- Overall palatability was scored using a scale of 1 through 5, with 1 being least palatable and 5 being most palatable. Only whole score numbers were accepted.

Results

Baseline data

All 12 subjects who were enrolled received medication in this study. Eighty three percent (83.3%) of subjects were male, and 16.7% were female. The mean age was 30.7 years. The race distribution was 83.3% white and 16.7% black/African American. None of the subjects were of Hispanic or Latino ethnicity.

Outcomes and estimation

Sweetness

The median score for all 3 treatment blends was mildly sweet. Treatments A and B had similar median and mean sweetness scores. One subject scored Treatment B as “no sweet taste;” a different subject scored Treatment C as “no sweet taste” and commented “it tastes bitter.” No subject scored Very Sweet for any treatment blend.

Table 28: Sweetness Score Descriptive Statistics by Treatment

Treatment	n	Median (min, max)	Mean (SD)
Treatment A (Reference)	12	1.5 (0.5, 2)	1.3 (0.66)
Treatment B	12	1.5 (0, 2)	1.4 (0.70)
Treatment C	12	1.0 (0, 2.5)	1.0 (0.62)

n = number of observations; min = minimum; max = maximum;
SD = standard deviation; ATV = atazanavir; POU = powder for oral use.
Treatment A = 15 mg/5 mL ATV POU current formulation (10% aspartame)
Treatment B = 15 mg/5 mL ATV in New POU 1 (4.2% aspartame)
Treatment C = 15 mg/5 mL ATV in New POU 2 (4.2% aspartame + 0.53% sucralose)

Table 29: Sweetness Score Frequency by Treatment

		No Sweet Taste		Mildly Sweet		Moderately Sweet		Very Sweet
Treatment	n	0 n (%)	0.5 n (%)	1 n (%)	1.5 n (%)	2 n (%)	2.5 n (%)	3 n (%)
Treatment A	12	0	4 (33.3)	1 (8.33)	3 (25.0)	4 (33.3)	0	0
Treatment B	12	1 (8.33)	2 (16.7)	0	4 (33.3)	5 (41.7)	0	0
Treatment C	12	1 (8.33)	2 (16.7)	6 (50.0)	2 (16.7)	0	1 (8.33)	0

n = number of observations; n (%) = number (percent) of observations; ATV = atazanavir; POU = powder for oral use.
Treatment A = 15 mg/5 mL ATV POU current formulation (10% aspartame); Reference
Treatment B = 15 mg/5 mL ATV in New POU 1 (4.2% aspartame)
Treatment C = 15 mg/5 mL ATV in New POU 2 (4.2% aspartame + 0.53% sucralose)

Palatability

All 3 treatment blends were moderately palatable with median scores of 2 and 3. Treatments A and B had similar median and mean palatability scores.

Table 30: Palatability Score Descriptive Statistics by Treatment

Treatment	n	Median (min, max)	Mean (SD)
Treatment A (Reference)	12	3 (2, 4)	3.0 (0.85)
Treatment B	12	3 (1, 4)	2.8 (1.11)
Treatment C	12	2 (1, 5)	2.3 (1.07)

n = number of observations; min = minimum; max = maximum;
SD = standard deviation; ATV = atazanavir; POU = powder for oral use.
Treatment A = 15 mg/5 mL ATV POU current formulation (10% aspartame)
Treatment B = 15 mg/5 mL ATV in New POU 1 (4.2% aspartame)
Treatment C = 15 mg/5 mL ATV in New POU 2 (4.2% aspartame +0.53% sucralose)

Table 31: Palatability Score Frequency by Treatment

		Least Palatable				Most Palatable
Treatment	n	1 n (%)	2 n (%)	3 n (%)	4 n (%)	5 n (%)
Treatment A	12	0	4 (33.3)	4 (33.3)	4 (33.3)	0
Treatment B	12	2 (16.7)	2 (16.7)	4 (33.3)	4 (33.3)	0
Treatment C	12	1 (8.33)	9 (75.0)	0	1 (8.33)	1 (8.33)

n = number of observations; n (%) = number (percent) of observations; ATV = atazanavir; POU = powder for oral use.
Treatment A = 15 mg/5 mL ATV POU current formulation (10% aspartame); Reference
Treatment B = 15 mg/5 mL ATV in New POU 1 (4.2% aspartame)
Treatment C = 15 mg/5 mL ATV in New POU 2 (4.2% aspartame + 0.53% sucralose)

The sweetness of the 2 new ATV powder formulations was comparable to the current ATV powder formulation. The median sweetness scores and overall score variability suggest that 4.2% aspartame (Treatment B) tasted similar in sweetness to the 10% aspartame formulation (Treatment A).

The median palatability score and overall score variability suggest that 4.2% aspartame (Treatment B) was more palatable than 4.2% aspartame plus sucralose (Treatment C).

The median sweetness score from the 4.2% aspartame test formulation (Treatment B) was equal to the 10% aspartame reference formulation (Treatment A) score with similar minimum to maximum range; therefore, the 4.2% aspartame formulation (Treatment B) can be recommended as the new ATV powder formulation.

2.5.2. Discussion on clinical efficacy

Design and conduct of clinical studies

Two studies, PRINCE I and II, were performed in order to describe safety, efficacy and PK of the new formulation ATV powder in children, boosted with RTV and in combination with 2 NRTIs. Both are relatively small studies enrolling HIV experienced and naïve paediatric subjects, which will affect interpretation of efficacy data, while in adults at least, there was no difference in PK between these groups. Subjects had to harbour virus susceptible to ATV and at least 2 NRTI. Subjects with a history of ≥ 2 PI failures were not eligible. Apart from subjects with any major PI mutations, those with combinations of minor resistance mutations were ineligible, with some differences between the studies in exclusion criteria, so that subjects harbouring virus with relevantly reduced susceptibility were not likely enrolled.

These studies differ by the enrolled subjects: from 3 months to <6 years for PRINCE I and from 3 months to <11 years for PRINCE II. Although in both studies the subjects were initially distributed into 3 weight groups at the inclusion (5-<10 kg [ATV 150 mg], 10-<15 kg [ATV 200 mg] and 15-<25 kg [ATV 250 mg]), the PRINCE II study was afterward amended to enrolled subjects into 2 additional weight groups: 5-<10 kg (ATV 200 mg) and 25-<35 kg (ATV 300 mg). For these two weight groups, only Week 24 results are relevant.

No specific guidance was given on the choice of the optimal background therapy (OBT), except that tenofovir, which is not recommended in children < 2 years of age, was not allowed. OBT may differ

between different age (and hence weight) groups, with potential impact on PK and efficacy/ safety results.

While PRINCE II was still ongoing (but PRINCE I was over), the level of aspartame in the tested ATV powder formulation had to be reduced from 10% to 4.2% in accordance to the PDCO request and the acceptable daily intake of aspartame determined by the EFSA. The CHMP has concluded that no bridge study was required and it is not expected that ATV exposure was affected. Palatability results, issued from the PRINCE studies and from the taste study AI424466, did not highlighted specific concerns with this new formulation.

The HIV RNA assay had to be changed during the trials to Abbott Real Time HIV RNA-1 assay as the Roche Amplicor assay was discontinued. Although it is disputable to change the HIV RNA assay during study, based on the response to the D120 LOQ, the change of the HIV RNA assay did not significantly impact the efficacy results from PRINCE I (all subjects had already reached the 48 time point before the change occurred) and II studies (only small number of subjects involved).

The majority of subjects enrolled in both PRINCE studies come from Africa, especially the youngest strata, have high viral load (HIV RNA > 100,000 c/ml, especially the youngest strata). There are more ARV experienced subjects in PRINCE II than in PRINCE I, especially in subjects weighing 5-<10 kg (10 of the 12 subjects with the recommended 200/80 mg ATV/RTV dose), which could have a significant impact on the antiviral response.

Efficacy data and additional analyses

The studies were not designed or powered to evaluate efficacy. Due to the inclusion and exclusion criteria applied, the population enrolled in the clinical study may have been less likely to harbour virus with reduced susceptibility.

The efficacy results of PRINCE I show a lower virologic suppression at Week 48 and a slower decrease of viral load are observed in subjects weighing 5-<10 kg, suggesting that 150 mg is suboptimal in this subgroup. This is in accordance with the PK results showing a lower ATV exposure in this subgroup.

Overall, virologic suppression of HIV RNA < 50 c/mL was observed in 50% of ARV-experienced subjects vs. 54% of ARV-naïve subjects, and 62% of ARV-experienced subjects achieved HIV RNA < 400 c/mL vs. 79% of ARV-naïve subjects. The greater rate of response in ARV-naive subjects in the paediatric studies is consistent with observations in adult and paediatric studies. It is increasingly recognised that dividing subjects by treatment history into naïve and experienced no longer appropriately defines the relevant treatment populations. It is more relevant do differentiate between subject harbouring HIV that is predicted to be fully susceptible to antiretroviral drugs (i.e. without mutations conferring drug resistance in their major viral populations, as determined by standard genotypic assays) and those that harbour virus not fully susceptible. It may be more informative to provide efficacy data for the different weight/ dose cohorts separated along those lines.

Additional subgroup analyses were provided in an attempt to better interpret efficacy results depending on age, treatment experience, viral load.

When combined the results of PRINCE I and II studies, the antiviral efficacy seems slightly higher in subjects with baseline viral load < 100,000 c/ml compared to ≥ 100,000 c/ml. As regards the baseline NRTI background, the best response rates were observed with Kivexa compared to AZT-based NRTI backgrounds.

When focused on the group 5-<10 kg, the number of subjects treated with the endorsed ATV dose (200 mg) is very low, with only 12 subjects at week 24 and 1 subject at week 48. Therefore, only week 24 results can be interpreted. The percentage of subjects with HIV RNA < 50 c/ml and < 400 c/ml is low (16.7% and 41.7%, respectively) and inferior to the results obtained with the lower ATV dose of 150 mg (38.6% and 61.4%, respectively). This could be due to a high rate of discontinuation before week 24 (5/12 subjects), considered as virologic failure in the mITT analysis. However, none of these subjects discontinued due to lack of efficacy or treatment-related toxicity. In addition, 10/12 subjects had high baseline viral load ⩾ 100,000 c/ml, versus 30/44 subjects.

Overall, in the 5- 10kg weight group, viral success was similar for the 150mg dose cohorts in PRINCE 1 and 2, while the 200mg dose cohort had a considerably lower success rate. While there were some differences in baseline viral load and treatment experience, an effect on results cannot be concluded based on the available data in this very small group.

There is no reason to assume that efficacy in this weight group, when given a dose of 200/80 mg, would be considerably lower than in other groups based on the C_{24} levels. The concern is if at this dose level safety or tolerability problems may contribute to non- adherence or lead to adverse events and/ or treatment discontinuation. In this regards, the high number or dropouts in this group is of concern, however it appears that drop- outs were mostly not due to safety or tolerability issues.

As regards the group 10-<15 kg, the rate of subjects at week 48 is low when considered the primary efficacy endpoint of HIV RNA < 50 c/ml (48.7%), but with a less sensitive criteria of HIV RNA < 400 c/ml the overall virological response (68.7%) of combined PRINCE I and II studies better meets expectations. Of note, 7 patients reported blips < 400 c/ml within week 48. All of them recovered HIV RNA < 50 c/ml.

In conclusion, the applicant has made some attempts to better understand efficacy results in the paediatric population. However, the limited size of the population challenges the interpretation of subgroup analyses.

2.5.3. Conclusions on the clinical efficacy

It is accepted that dose considerations for the paediatric population should mainly be based on PK and PK/PD data, aiming to achieve exposures similar to the adult population. Efficacy data may be considered supportive. The results as provided are quite difficult to interpret as the studies were uncontrolled, weight cohorts were small and included both naïve and experienced patients and results are inconsistent between studies.

With these caveats in mind, the efficacy results, while less favourable than seen with comparable treatment regimens, may not give reasons for major concerns in themselves provided PK and PK/PD data allow concluding that exposures in the paediatric age brackets are sufficiently similar to those in adults. Data are however also only of limited value in supporting the proposed doses, with particular uncertainties in the 5- 10kg weight band. Indeed, while the PK data are limited to substantiate the adequacy of the dose in children from 5 to 10 kg, the poor response rate observed at the recommended dose <20% of patients with undetectable viral load at week 24 can only call for further reservations.

2.6. Clinical safety

The clinical development plan for ATV in paediatric patients was initially based on findings from Study AI424020 that exhibited comparable safety of the combination of ATV/ritonavir to those in the adult

studies. The data from Study AI424020 were previously submitted and reviewed to support the currently approved ATV capsule dosing in paediatric patients 6 years and older. In this study, the safety profile of ATV/RTV in paediatric patients was consistent with that observed in adults, with predicted exposures to ATV that were comparable to adult exposures.

As regards the powder formulation of ATV and the extension of indication in children <6 years of age, this document provides cumulative safety data from studies PRINCE I and PRINCE II in subjects using ATV oral powder boosted with RTV. The results of the Week 48 and cumulative safety analyses are included in this submission, as well as pooled data on subjects from both studies.

Patient exposure

The analysis population consists of enrolled and treated subjects in Studies AI424397 and AI424451 grouped according to baseline weight bands.

Overall, a total of 155 subjects were treated with ATV powder:

Weight group	Patients exposed with ATV powder	Patients with ≥24 Weeks safety data	Patients with ≥48 Weeks safety data
5-<10 kg (ATV 150 mg)	44	38	32
5-<10 kg (ATV 200 mg)	12	7	1
10-<15 kg (ATV 200 mg)	40	36	29
15-<25 kg (ATV 250 mg)	51	46	37
25-<35 kg (ATV 300 mg)	8	6	1
Total	155	133	100

The median time on study therapy was 72 weeks (range: 1 - 192 weeks) for ATV powder and 72 weeks (range: 1 - 192 weeks) for RTV oral solution.

The numbers of subjects exposed to the 4.2% aspartame ATV powder formulation were 61 through 12 weeks, 50 through 24 weeks, 42 through 36 weeks, and 30 through 48 weeks.

Grade 3 or 4 results were reported for some subjects. (Note: In general, these test results were obtained at the randomization visit, not at the visit where subject eligibility was determined.):

- Haematology: Grade 4 platelets (2 subjects [3%]) and Grade 4 absolute neutrophils (1 subject)

- Serum chemistry: Grade 3 amylase (28 subjects [18%]), Grade 3 ALT (3 subjects [2%]), Grade 4 amylase (3 subjects [2%]), Grade 3 lipase, low calcium, low chloride, and low sodium (1 subject each), and Grade 4 alkaline phosphatase, ALT, and AST (1 subject each).

At baseline, 52 subjects (34%) had abnormal ECG findings, and 3 subjects (2%) had CDC Class C AIDS event (oral candidiasis, *pneumocystis jirovecii* pneumonia, and pulmonary tuberculosis in 1 subject each).

Overall, 88% of subjects had used prior medications. Prior medications used by ≥ 20% of subjects were sulfamethoxazole/trimethoprim (60%), multivitamins (34%), nevirapine (36%), 3TC (33%), and lopinavir/RTV (22%).

Adverse events

While on ATV powder, 91% of subjects had AE. The most common AEs were upper respiratory tract infection (36%), gastroenteritis (28%), and vomiting (27%).

Table 32: Most Common Adverse Events (at Least 10% in Any Group) - All Grades on ATV Powder – Treated Subjects

System Organ Class (%) Preferred Term (%)	B/L Weight 5 - < 10 kg (ATV 150mg) N = 44	B/L Weight 5 - < 10 kg (ATV 200mg) N = 12	Combined B/L Weight 5 - < 10 kg N = 56	B/L Weight 10 - < 15 kg N = 40	B/L Weight 15 - < 25 kg N = 51	B/L Weight 25 - < 35 kg N = 8	Total N = 155
TOTAL SUBJECTS WITH AN EVENT	42(95.5)	10(83.3)	52(92.9)	38(95.0)	46(90.2)	5(62.5)	141(91.0)
INFECTIONS AND INFESTATIONS	39(88.6)	8(66.7)	47(83.9)	36(90.0)	41(80.4)	3(37.5)	127(81.9)
UPPER RESPIRATORY TRACT INFECTION	27(61.4)	4(33.3)	31(55.4)	10(25.0)	14(27.5)	1(12.5)	56(36.1)
GASTROENTERITIS	20(45.5)	3(25.0)	23(41.1)	12(30.0)	8(15.7)	0	43(27.7)
NASOPHARYNGITIS	6(13.6)	0	6(10.7)	10(25.0)	12(23.5)	0	28(18.1)
OTITIS MEDIA	14(31.8)	3(25.0)	17(30.4)	5(12.5)	4(7.8)	0	26(16.8)
ORAL CANDIDIASIS	16(36.4)	4(33.3)	20(35.7)	1(2.5)	0	0	21(13.5)
LOWER RESPIRATORY TRACT INFECTION	8(18.2)	4(33.3)	12(21.4)	4(10.0)	2(3.9)	0	18(11.6)
PHARYNGITIS	3(6.8)	0	3(5.4)	8(20.0)	6(11.8)	0	17(11.0)
CANDIDA NAPPY RASH	13(29.5)	2(16.7)	15(26.8)	1(2.5)	0	0	16(10.3)
IMPETIGO	8(18.2)	0	8(14.3)	4(10.0)	4(7.8)	0	16(10.3)
OTITIS MEDIA ACUTE	10(22.7)	0	10(17.9)	1(2.5)	5(9.8)	0	16(10.3)
TINEA CAPITIS	6(13.6)	0	6(10.7)	4(10.0)	6(11.8)	0	16(10.3)
ACARODERMATITIS	10(22.7)	0	10(17.9)	1(2.5)	4(7.8)	0	15(9.7)
TONSILLITIS	8(18.2)	0	8(14.3)	3(7.5)	3(5.9)	0	14(9.0)
VIRAL UPPER RESPIRATORY TRACT INFECTION	5(11.4)	1(8.3)	6(10.7)	6(15.0)	1(2.0)	0	13(8.4)
PNEUMONIA	6(13.6)	0	6(10.7)	3(7.5)	1(2.0)	0	10(6.5)
HELMINTHIC INFECTION	8(18.2)	0	8(14.3)	1(2.5)	0	0	9(5.8)
URINARY TRACT INFECTION	7(15.9)	0	7(12.5)	0	0	0	7(4.5)
VARICELLA	1(2.3)	0	1(1.8)	4(10.0)	0	0	5(3.2)
BODY TINEA	0	1(8.3)	1(1.8)	0	2(3.9)	1(12.5)	4(2.6)
GASTROINTESTINAL DISORDERS	26(59.1)	2(16.7)	28(50.0)	22(55.0)	21(41.2)	2(25.0)	73(47.1)
VOMITING	15(34.1)	1(8.3)	16(28.6)	12(30.0)	12(23.5)	1(12.5)	41(26.5)
DIARRHOEA	17(38.6)	0	17(30.4)	9(22.5)	7(13.7)	1(12.5)	34(21.9)
DENTAL CARIES	3(6.8)	1(8.3)	4(7.1)	4(10.0)	3(5.9)	0	11(7.1)
NAUSEA	0	0	0	0	1(2.0)	1(12.5)	2(1.3)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	23(52.3)	6(50.0)	29(51.8)	16(40.0)	18(35.3)	1(12.5)	64(41.3)
COUGH	10(22.7)	2(16.7)	12(21.4)	5(12.5)	13(25.5)	1(12.5)	31(20.0)
RHINORRHOEA	10(22.7)	0	10(17.9)	2(5.0)	4(7.8)	0	16(10.3)
RHINITIS ALLERGIC	4(9.1)	1(8.3)	5(8.9)	5(12.5)	2(3.9)	0	12(7.7)
NASAL OBSTRUCTION	6(13.6)	3(25.0)	9(16.1)	0	2(3.9)	0	11(7.1)
ASTHMA	1(2.3)	0	1(1.8)	5(12.5)	2(3.9)	0	8(5.2)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	26(59.1)	7(58.3)	33(58.9)	14(35.0)	15(29.4)	1(12.5)	63(40.6)
ECZEMA	12(27.3)	2(16.7)	14(25.0)	4(10.0)	3(5.9)	0	21(13.5)
DERMATITIS DIAPER	11(25.0)	3(25.0)	14(25.0)	1(2.5)	0	0	15(9.7)
SEBORRHOEIC DERMATITIS	6(13.6)	1(8.3)	7(12.5)	0	0	0	7(4.5)
URTICARIA	0	0	0	1(2.5)	0	1(12.5)	2(1.3)
URTICARIA CHRONIC	0	0	0	0	0	1(12.5)	1(0.6)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	23(52.3)	4(33.3)	27(48.2)	11(27.5)	14(27.5)	0	52(33.5)
ANAEMIA	13(29.5)	4(33.3)	17(30.4)	2(5.0)	4(7.8)	0	23(14.8)
LYMPHADENOPATHY	4(9.1)	1(8.3)	5(8.9)	7(17.5)	4(7.8)	0	16(10.3)
NEUTROPENIA	8(18.2)	0	8(14.3)	5(12.5)	3(5.9)	0	16(10.3)
INVESTIGATIONS	17(38.6)	3(25.0)	20(35.7)	10(25.0)	14(27.5)	3(37.5)	47(30.3)
LIPASE INCREASED	4(9.1)	1(8.3)	5(8.9)	2(5.0)	2(3.9)	1(12.5)	10(6.5)
ALANINE AMINOTRANSFERASE INCREASED	3(6.8)	0	3(5.4)	1(2.5)	4(7.8)	1(12.5)	9(5.8)
TRANSAMINASES INCREASED	5(11.4)	0	5(8.9)	0	1(2.0)	0	6(3.9)
HEPATOBILIARY DISORDERS	10(22.7)	0	10(17.9)	14(35.0)	12(23.5)	0	36(23.2)
HYPERBILIRUBINAEMIA	5(11.4)	0	5(8.9)	11(27.5)	8(15.7)	0	24(15.5)
JAUNDICE	0	0	0	4(10.0)	5(9.8)	0	9(5.8)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	17(38.6)	0	17(30.4)	6(15.0)	10(19.6)	1(12.5)	34(21.9)
ARTHROPOD BITE	9(20.5)	0	9(16.1)	0	2(3.9)	0	11(7.1)
METABOLISM AND NUTRITION DISORDERS	15(34.1)	1(8.3)	16(28.6)	7(17.5)	6(11.8)	0	29(18.7)
HYPERCHOLESTEROLAEMIA	10(22.7)	0	10(17.9)	3(7.5)	2(3.9)	0	15(9.7)

GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	5(11.4)	0	5(8.9)	13(32.5)	7(13.7)	3(37.5)	28(18.1)
PYREXIA	5(11.4)	0	5(8.9)	13(32.5)	5(9.8)	2(25.0)	25(16.1)
ASTHENIA	0	0	0	0	1(2.0)	1(12.5)	2(1.3)
CHEST PAIN	0	0	0	0	0	1(12.5)	1(0.6)
PRODUCT TASTE ABNORMAL	0	0	0	0	0	1(12.5)	1(0.6)
EYE DISORDERS	2(4.5)	1(8.3)	3(5.4)	5(12.5)	6(11.8)	1(12.5)	15(9.7)
IRITIS	0	0	0	0	0	1(12.5)	1(0.6)
MYOPIA	0	0	0	0	0	1(12.5)	1(0.6)
NERVOUS SYSTEM DISORDERS	4(9.1)	0	4(7.1)	2(5.0)	6(11.8)	1(12.5)	13(8.4)
HEADACHE	0	0	0	1(2.5)	3(5.9)	1(12.5)	5(3.2)
ENDOCRINE DISORDERS	0	0	0	0	0	1(12.5)	1(0.6)
GOITRE	0	0	0	0	0	1(12.5)	1(0.6)

63% of subjects had Grade 2 - 4 AEs (mainly hyperbilirubinemia [8%], gastroenteritis [7%], lipase increased [7%] and otitis media, and 23% of subjects had Grade 2 - 4 related AEs (mainly hyperbilirubinemia [8%]).

Table 33: Grade 2 - 4 Related Adverse Events on ATV Powder - Treated Subjects

System Organ Class (%) Preferred Term (%)	B/L Weight 5 - < 10 kg (ATV 150mg) N = 44	B/L Weight 5 - < 10 kg (ATV 200mg) N = 12	Combined B/L Weight 5 - < 10 kg N = 56	B/L Weight 10 - < 15 kg N = 40	B/L Weight 15 - < 25 kg N = 51	B/L Weight 25 - < 35 kg N = 8	Total N = 155
TOTAL SUBJECTS WITH AN EVENT	8(18.2)	1(8.3)	9(16.1)	13(32.5)	11(21.6)	3(37.5)	36(23.2)
INVESTIGATIONS	4(9.1)	1(8.3)	5(8.9)	3(7.5)	7(13.7)	3(37.5)	18(11.6)
BLOOD BILIRUBIN INCREASED	0	0	0	2(5.0)	4(7.8)	0	6(3.9)
LIPASE INCREASED	1(2.3)	1(8.3)	2(3.6)	1(2.5)	1(2.0)	1(12.5)	5(3.2)
ALANINE AMINOTRANSFERASE INCREASED	1(2.3)	0	1(1.8)	0	2(3.9)	1(12.5)	4(2.6)
AMYLASE INCREASED	1(2.3)	0	1(1.8)	0	0	1(12.5)	2(1.3)
ASPARTATE AMINOTRANSFERASE INCREASED	1(2.3)	0	1(1.8)	0	1(2.0)	0	2(1.3)
BLOOD BILIRUBIN ABNORMAL	0	0	0	0	0	1(12.5)	1(0.6)
HEPATIC ENZYME INCREASED	0	0	0	0	1(2.0)	0	1(0.6)
TRANSAMINASES INCREASED	1(2.3)	0	1(1.8)	0	0	0	1(0.6)
HEPATOBILIARY DISORDERS	2(4.5)	0	2(3.6)	7(17.5)	5(9.8)	0	14(9.0)
HYPERBILIRUBINAEMIA	2(4.5)	0	2(3.6)	7(17.5)	4(7.8)	0	13(8.4)
JAUNDICE	0	0	0	0	1(2.0)	0	1(0.6)
METABOLISM AND NUTRITION DISORDERS	2(4.5)	0	2(3.6)	2(5.0)	0	0	4(2.6)
HYPERCHOLESTEROLAEMIA	1(2.3)	0	1(1.8)	2(5.0)	0	0	3(1.9)
HYPERLIPASAEMIA	1(2.3)	0	1(1.8)	0	0	0	1(0.6)
GASTROINTESTINAL DISORDERS	0	0	0	3(7.5)	0	0	3(1.9)
GASTRITIS	0	0	0	2(5.0)	0	0	2(1.3)
VOMITING	0	0	0	1(2.5)	0	0	1(0.6)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	1(2.3)	0	1(1.8)	1(2.5)	0	0	2(1.3)
LEUKOPENIA	0	0	0	1(2.5)	0	0	1(0.6)
BLOOD AND LYMPHATIC SYSTEM DISORDERS							
LYMPHADENITIS	1(2.3)	0	1(1.8)	0	0	0	1(0.6)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	0	0	0	0	0	1(12.5)	1(0.6)
PRODUCT TASTE ABNORMAL	0	0	0	0	0	1(12.5)	1(0.6)
IMMUNE SYSTEM DISORDERS	0	0	0	0	1(2.0)	0	1(0.6)
IMMUNODEFICIENCY	0	0	0	0	1(2.0)	0	1(0.6)

Serious adverse events and deaths

No fatal events were reported.

Overall, 36 subjects (23%) had SAEs while on ATV powder. The only SAEs reported in ⩾ 2 subjects were ALT increased (4 subjects [3%]), gastroenteritis (3 subjects [2%]), and herpes zoster, overdose, and transaminases increased (2 subjects [2%] each). Nine subjects had related SAEs on treatment (ALT increased in 3 subjects and acute pancreatitis, blood bilirubin increased, drug-induced liver injury, ECG QT prolonged, hyperbilirubinemia, and vomiting in 1 subject each).

Adverse events of special interest

Hyperbilirubinemia-related AEs

Overall, 33 subjects (21%) had hyperbilirubinemia-related AEs while on ATV powder, including 21 subjects (14%) with Grade 2 - 4 drug-related hyperbilirubinemia AEs.

Table 34: Hyperbilirubinemia related adverse events – All Grades on ATV powder – Treated subjects

System Organ Class (%) Preferred Term (%)	B/L Weight 5 - < 10 kg (ATV 150mg) N = 44	B/L Weight 5 - < 10 kg (ATV 200mg) N = 12	Combined B/L Weight 5 - < 10 kg N = 56	B/L Weight 10 - < 15 kg N = 40	B/L Weight 15 - < 25 kg N = 51	B/L Weight 25 - < 35 kg N = 8	Total N = 155
TOTAL SUBJECTS WITH AN EVENT	5(11.4)	0	5(8.9)	14(35.0)	13(25.5)	1(12.5)	33(21.3)
HEPATOBILIARY DISORDERS	5(11.4)	0	5(8.9)	14(35.0)	11(21.6)	0	30(19.4)
HYPERBILIRUBINAEMIA	5(11.4)	0	5(8.9)	11(27.5)	8(15.7)	0	24(15.5)
JAUNDICE	0	0	0	4(10.0)	5(9.8)	0	9(5.8)
INVESTIGATIONS	0	0	0	3(7.5)	4(7.8)	1(12.5)	8(5.2)
BLOOD BILIRUBIN INCREASED	0	0	0	3(7.5)	4(7.8)	0	7(4.5)
BLOOD BILIRUBIN ABNORMAL	0	0	0	0	0	1(12.5)	1(0.6)
EYE DISORDERS	0	0	0	3(7.5)	1(2.0)	0	4(2.6)
OCULAR ICTERUS	0	0	0	3(7.5)	1(2.0)	0	4(2.6)

Cardiac disorders

Five subjects (3%) had cardiac disorder AEs while on ATV powder:

- 3 subjects (8%) in the 10-<15 kg group had cardiac disorder AEs (Grade 1 ECG abnormal, ECG QT prolonged, and tachycardia in 1 subject each). Only the ECG QT prolonged was considered related to the study drug by the investigators.

- 2 subjects (4%) in the 15-<25 kg group had cardiac disorder AEs (Grade 1 first-degree AV block) considered related to the study drug by the investigators.

Rash

Overall, 24 subjects (16%) had rash events while on ATV powder, including 3 subjects with related rashes. One Grade 2 - 4 related rash event (prurigo in 1 subject in the 10-<15 kg group) was reported.

AIDS-related AEs

Overall, 8 subjects (5%) had CDC Class C AIDS events while on ATV powder: 4 subjects in the 5-<10 kg (ATV 150 mg) group, 2 subjects in the 10-<15 kg group and 2 subjects in the 15-<25 kg group.

The most common event was pulmonary tuberculosis (3 subjects [1%]). None of these CDC Class C AIDS events was considered drug related by the investigators.

Renal toxicity AEs

Overall, 4 subjects (3%) had renal toxicity AEs while on ATV powder (1 subject each in the 5-<10 kg [ATV 150 mg] group had hematuria and proteinuria, 1 subject in the 5-<10 kg [ATV 200 mg] group had hematuria, and 1 subject in the 10-<15 kg group had dysuria). Only the hematuria in the subject in the 5-<10 kg [ATV 200 mg] group was considered drug related by the investigators.

Lactic Acidosis

Overall, 7 treated subjects (5%) had lactic acidosis syndrome/symptomatic hyperlactatemia (LAS/SHL) events (6 Grade 1 hepatomegaly, 1 Grade 2 hepatitis). None of these events was considered related to the study therapy by the investigators.

Lipodystrophy

None of the subjects on ATV powder had lipodystrophy-related events.

Cholelithiasis and nephrolithiasis

No subjects had cholelithiasis or nephrolithiasis.

Laboratory findings

Haematology

Grade 1 - 4 hematologic abnormalities were haemoglobin (50%), absolute neutrophils (41%), haematocrit (20%), platelets (7%), and white blood cells (2%). Grade 3 - 4 hematologic abnormalities were absolute neutrophils (9%) and haemoglobin and platelets (1 subject each).

Liver function tests

Grade 1 - 4 LFTs were total bilirubin (54%), ALT (38%), AST (14%), alkaline phosphatase (13%), and albumin (4%). Grade 3 - 4 LFT abnormalities were total bilirubin (16%), ALT (9%), alkaline phosphatase (3%), and AST (2%). Percent change from baseline in total bilirubin was consistent over time in all weight bands. These rates were higher compared to the adult population as represented in Study AI424138:

Table 35: Abnormal Liver Function Tests - Adults Subjects (AI424138) and Paediatric Subjects (Integrated PRINCE I and PRINCE II)

	Number of subjects/Number with Measurements (%)		
	AI424138 (Adult Data) Week 48		AI424397 and AI424451 Integrated (Pediatric Data) Through Data cutoff
	ATV/RTV N = 441	LPV/RTV N = 437	ATV Powder N = 155
Increased ALT			
Grade 1-4	74/435 (17)	48/431 (11)	58/151 (38)
Grade 3-4	8/435 (2)	6/431 (1)	13/151 (9)
Increased AST			
Grade 1-4	80/435 (18)	56/430 (13)	21/151 (14)
Grade 3-4	9/435 (2)	2/430 (< 1)	3/151 (2)
Increased amylase			
Grade 1-4	NA	NA	112/151 (74)
Grade 3-4	NA	NA	49/151 (33)
Increased lipase			
Grade 1-4	37/435 (9)	44/430 (10)	66/151 (44)
Grade 3-4	6/435 (1)	6/430 (1)	12/151 (8)

Abbreviations: ALT = alnanine aminotransferase; ATV = atanzanavir; LPV = lopinavir; RTV = ritonavir

Potential drug-induced liver injury (DILI) was defined as transaminases (ALT or AST) > 3 x upper limit of normal (ULN) concurrent with total bilirubin > 2 x ULN at the same sampling time point. One case of DILI was reported in study AI424397, and one potential case of DILI was reported in study AI424451.

Other serum chemistries

The majority of subjects had normal serum chemistries, except for low bicarbonate (92%), high amylase (74%), and low sodium (50%). Other Grade 1 – 4 serum chemistry abnormalities were lipase (44%), fasting total cholesterol (45%), fasting low-density lipoprotein cholesterol (35%), high calcium (24%), high potassium (17%), low non-fasting glucose and high non-fasting glucose (16% each), fasting low glucose (14%), blood urea nitrogen/urea (12%), high fasting glucose (10%), low potassium (9%), low calcium (5%), high sodium and uric acid (2% each), and low chloride (1 subject).

While 92% of subjects had low bicarbonate levels, the majority were Grade 1 - 2. Many of the subjects exhibited low serum bicarbonate levels during the pretreatment period, likely due to a variety of causes. Some likely causes include concurrent dehydration due to diarrhea, vomiting, and poor nutritional status.

In all subjects who had normal amylase/lipase levels at baseline and who had abnormal levels reported during the study period were on nucleoside backbone therapy of either ZDV/3TC or ABC/3TC. None of these subjects appeared to have clinical pancreatitis based on clinical symptoms and signs. In 2 subjects, the abnormalities resolved on continued therapy, in 4 subjects, study therapy was discontinued, and in 3 subjects, the abnormalities resolved.

Grade 3 - 4 serum chemistry abnormalities were amylase (33%), lipase (8%), low bicarbonate (1%), and fasting low-density lipoprotein cholesterol, fasting total cholesterol, high potassium, and uric acid (1 subject each).

All of the Grade 3 low serum bicarbonate levels, 60% of the Grade 3 - 4 elevations, and 50% of the Grade 3 pancreatic amylase elevations occurred in subjects in the 5-<10 kg weight bands irrespective of dose (150 mg or 200 mg dose of ATV powder).

Table 36: Serum chemistry teat results - summary of worst toxicity grading – Grade 3 and 4 on ATV powder – treated subjects

Lab Test Description Toxicity Grade	B/L Weight 5 - < 10 kg (ATV 150mg) N = 44	B/L Weight 5 - < 10 kg (ATV 200mg) N = 12	Combined B/L Weight 5 - < 10 kg N = 56	B/L Weight 10 - < 15 kg N = 40	B/L Weight 15 - < 25 kg N = 51	B/L Weight 25 - < 35 kg N = 8	Total N = 155
LIVER FUNCTION TESTS							
ALT/SGPT	N = 43	N = 12	N = 55	N = 39	N = 49	N = 8	N = 151
GRADE 3-4	8 (18.6)	1 (8.3)	9 (16.4)	1 (2.6)	3 (6.1)	0	13 (8.6)
AST/SGOT	N = 43	N = 12	N = 55	N = 39	N = 49	N = 8	N = 151
GRADE 3-4	2 (4.7)	0	2 (3.6)	1 (2.6)	0	0	3 (2.0)
ALKALINE PHOSPHATASE	N = 43	N = 12	N = 55	N = 39	N = 49	N = 8	N = 151
GRADE 3-4	1 (2.3)	1 (8.3)	2 (3.6)	2 (5.1)	0	0	4 (2.6)
TOTAL BILIRUBIN	N = 43	N = 12	N = 55	N = 39	N = 49	N = 8	N = 151
GRADE 3-4	4 (9.3)	0	4 (7.3)	9 (23.1)	9 (18.4)	2 (25.0)	24 (15.9)
OTHER SERUM CHEMISTRIES							
AMYLASE	N = 43	N = 12	N = 55	N = 39	N = 49	N = 8	N = 151
GRADE 3-4	23 (53.5)	7 (58.3)	30 (54.5)	10 (25.6)	8 (16.3)	1 (12.5)	49 (32.5)
LIPASE	N = 43	N = 12	N = 55	N = 39	N = 49	N = 8	N = 151
GRADE 3-4	5 (11.6)	2 (16.7)	7 (12.7)	1 (2.6)	3 (6.1)	1 (12.5)	12 (7.9)
URIC ACID	N = 43	N = 12	N = 55	N = 39	N = 49	N = 8	N = 151
GRADE 3-4	0	0	0	0	1 (2.0)	0	1 (0.7)
BICARBONATE, LOW	N = 43	N = 12	N = 55	N = 39	N = 49	N = 8	N = 151
GRADE 3-4	2 (4.7)	0	2 (3.6)	0	0	0	2 (1.3)
POTASSIUM, HIGH	N = 43	N = 12	N = 55	N = 39	N = 49	N = 8	N = 151
GRADE 3-4	1 (2.3)	0	1 (1.8)	0	0	0	1 (0.7)
TOTAL CHOLESTEROL, FASTING	N = 19	N = 5	N = 24	N = 27	N = 37	N = 6	N = 94
GRADE 3-4	0	0	0	1 (3.7)	0	0	1 (1.1)
LDL CHOLESTEROL, FASTING	N = 15	N = 2	N = 17	N = 27	N = 37	N = 6	N = 87
GRADE 3-4	0	0	0	1 (3.7)	0	0	1 (1.1)

ECG findings

At Week 48, all but 1 subject (in the 10-<15 kg group, QTc > 500 msec) had QTc intervals (Fridericia) ≤ 450 msec, and 3 subjects (2%) had borderline values of PR interval (> 450 - 480 msec).

At Week 48, the overall mean change from baseline in heart rate was -16.3 bpm (range: -66 to 28 bpm), the overall mean change from baseline in PR interval was 5.7 msec (range: -38 to 50 msec) and the overall mean change from baseline in QTc interval (Fridericia) was 6.6 msec (range: -44 to 51 msec).

Safety in special populations

Adverse events by geographic region

While on ATV powder, 92% of subjects in Africa, 89% of subjects in North America, 88% of subjects in South America, all 9 subjects in Europe, and the 1 subject in Asia had AEs. Although baseline regional differences in AEs may exist due to varying living conditions, due to the small sample sizes, no conclusions can be drawn regarding these data.

Discontinuation due to AEs

Overall, 13 subjects (8%) had AEs leading to discontinuation of study therapy while on ATV powder. The only AEs leading to discontinuation of study therapy reported in ≥ 2 subjects were ALT increased, pulmonary tuberculosis, and vomiting (2 subjects [1%] each).

Overdose and dosing errors

There were 2 cases of ATV overdose in study AI424451 who received ATV 250 mg twice daily instead of 250 mg once daily, one subject during 7 days and one subject during 14 days. Some AEs (left ventricular hypertrophy at ECG and mild hyperbilirubinemia with total bilirubin at 1.5 mg/dl) were

reported in the subject overdosed during 7 days. Both subjects did not receive treatment for these events, and no action was taken with regard to the study drug.

Overall, 23.9% (37/155) subjects had 54 dosing interruptions > 3 consecutive days, and more than half (32 vs. 22 interruptions) occurred after Week 48. Three of these 37 subjects were receiving the ATV capsule at the time of a dose interruption. Causes of interruptions > 3 days were as follows:

- Dosing error/missed patient dose, and missed dose due to absent caregiver or other reason was the most common reason for dose interruption across dose groups (17.4% [27/155]) and occurred more often in the 5-<10 kg weight group (30.4% [17/56]), compared with the 10-<15 kg group (10.0% [4/40]), and the 15-<25 kg group (11.8% [6/51]).
- Adverse events leading to dose interruptions > 3 days were reported for 5.8% (9/155) of subjects: 3.6% (2/56) in the 5-<10 kg group; 7.5% (3/40) in the 10-<15 kg group, and 7.8% (4/51) in the 15-<25 kg weight group. One subject had a dose interruption > 3 day due to an adverse event (AE) and a missed dose. Adverse events leading to dose interruptions were primarily laboratory abnormalities (alanine aminotransferase [ALT] elevations [3], alkaline phosphatase elevation [1]), or vomiting (1), rotavirus infection (1) or unspecified AE (3).
- Dosing error (unspecified) led to dose interruptions for 2 additional subjects.

The dosing interruptions in PRINCE 1 and PRINCE II were not due to product design, errors in prescribing, difficulties with understanding how to administer the dose, or improper dose administered, but were omission errors (missed doses) or temporary interruption within the context of an AE. There is no evidence that these dose interruptions led to therapeutic failure, and overall, drug compliance was good in these studies. However, a significantly higher proportion of subjects with dose interruptions > 3 days was noted at one investigational site in South Africa. This was Site 1 in PRINCE I and Site 10 in PRINCE II, which was the same site participating in each study. This site accounted for 22 of the 37 subjects with dose interruptions > 3 days.

Post marketing experience

A literature search performed by the MAH covering the period from 01-Sep-2013 through 31-Dec-2014 confirmed that the safety profile of ATV in real-world clinical use in paediatric patients continues to be consistent with the safety profile that was established in clinical trials.

2.6.1. Discussion on clinical safety

Previously, ATV powder was administered as part of the study AI424020 in 66 paediatric subjects from 3 months to 13 years of age, but at different doses (310 mg/m² in combination with ritonavir). It was concluded that study AI424020 did not highlight new or unexpected safety findings related to ATV in this paediatric population, and there were no clinically relevant differences in the safety profiles of the ATV capsule and powder formulations.

The safety database presented consists of 155 subjects, paediatric subjects above 3 months of age, weighing between 5 kg and 35 kg and treated by RTV-boosted ATV powder in combination with 2 NRTIs (excluding TDF), who had a median exposure time of around 72 weeks to ATV/RTV. There were however considerable differences in median exposure between the weight cohorts, making interpretations of the safety profile considerably more difficult. In particular, the 5-<10kg (200/80 mg) group and the 25-35kg group had less than half the exposure duration of the remaining groups, and were also smaller (respectively 12 subjects weighing 5-<10kg received ATV dose of 200 mg and only

one has week 48 data available and 8 subjects in the highest weight group). Only 100 patients have been treated with ATV powder during at least 48 weeks (and 133 patients reached Week 24);

AEs in these groups may underestimate the prevalence in general and compared to other groups. The relative lack of safety data in the higher dose 5-<10kg cohort is particularly problematic. Over a quarter of the 155 subjects enrolled did not complete phase one of the study. Discontinuations were most common in the 5-<10kg 200/80mg group, but this observation is based on very small numbers.

The vast majority of subjects were recruited in Africa, and this percentage was higher in the 5-<10kg weight groups than in the older groups, which may affect comparison of AEs between cohorts and may not be entirely representative of the situation in the EU.

The safety data are essentially based on exposure to the ATV powder formulation containing 10% aspartame, but it is not expected that the decrease in aspartame to 4.2% in the formulation proposed for marketing is associated detrimental effects on safety.

Consequently, it seems difficult to fully interpret the safety profile of the weight-band doses of ATV powder in these paediatric subjects. Keeping in mind these limitations, the following issues could be raised:

- PK data suggest that for safety events related to C_{max}, if any, the safety profile of ATV in paediatric patients may be expected to be similar to that in adults.

- The main ATV-related AEs were related to hyperbilirubinemia. This AE is dose-dependent and therefore reflect the ATV exposure. The frequencies of other ATV-related AEs (notably gastrointestinal disorders and ALT/AST increase) are low (<2%). There is no appreciable difference with adult data issued from pivotal study AI424138, where hyperbilirubinemia-related AEs, rash and gastrointestinal disorders were observed with a similar or higher frequency than in the PRINCE studies.

- Abnormal chemistry laboratory (mainly hyperamylasemia) and ECG disorders were reported in some subjects at baseline.

- The frequency of AEs seems consistent across the weight groups.

- The profile of adverse events reported is in line with what can be expected in the study population, with some differences between age groups which seem in line with expectations.

- ECG findings are coherent with the known cardiac safety profile of ATV, but could be biased by the increase of age in young subjects. QTc and PR interval prolongations may occurred with the use of ATV. It is unclear to what extent the level of cardiac toxicity in both studies could be regarded as expected based on knowledge in adults. In addition, the observed rate of adverse cardiac events, specifically PR prolongation, in the submitted paediatric studies is considerably less than previously reported in the paediatric population. As part of the D120 LOQ, the applicant was asked to further discuss this finding. It was argued that this may be due to the non-inclusion in the PRINCE studies of subjects with baseline cardiac abnormalities, including AV block. However, as no paediatric subjects with cardiac abnormalities were included, the cardiac risk of ATV observed in the PRINCE studies may be underestimated compared to real life. The exclusion criteria should be stated in the description of the PRINCE studies.

- Low bicarbonate (92%), high amylase (74%), and low sodium (50%) were the most common abnormalities and are likely associated with GI adverse events, which in turn may or may not be drug related. The observed abnormalities have generally been observed previously as reflected in the SPC of the Reyataz capsule formulation. As part of the D120 the applicant was notably asked to further discuss those findings. It is agreed that these elevated rates compared to historical data in adults

seems to be related to the dehydration and poor nutritional status of these paediatric subjects, which were mainly from South Africa. The great majority of subjects had abnormal biological values already at baseline. No increased risk of pancreatitis was observed in these studies.

- The rates of function test (LFT) abnormalities (Grade 1-4 and Grade 3-4) were higher in the paediatric population as represented in PRINCE I and PRINCE II compared to the adult population as represented in Study AI424138. The attitude of the applicant to assign the higher rate of transaminase elevations in children as compared to adults to the effect of infectious diseases is more disputable when considering that transaminases elevations is an expected finding with ATV/rtv as for other protease inhibitors with primary hepatic metabolism. Moreover, transaminases elevations accounted for a significant part of the treatment discontinuations. Consequently, the more frequent elevation of transaminases in children than in adults should be stated in section 4.8.

On the 37 patients with dosing interruptions > 3 consecutive days due to dosing error or missed doses, 22 occurred in the same site investigation (Site 1 PRINCE I corresponding to Site 10 for PRINCE II of South Africa) and were mainly due to social or family reasons, such as the absence of caregiver. This finding indeed makes unlikely the causality of the product design.

2.6.2. Conclusions on the clinical safety

In conclusion, based on the original submission and the applicant's response to the D120 LOQ, the safety profile of ATV powder can be regarded as being overall similar to that of ATV capsules in adults, and no new safety signal was detected. Some issues nevertheless to be highlighted in the SmPC (trend for higher rate of transaminase elevation, exclusion of children with cardiac abnormalities in the PRINCE studies).

2.7. Risk Management Plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 10.0 is acceptable.

The CHMP endorsed the Risk Management Plan version 10.0 with the following content:

Safety concerns

Table 37: Summary of Safety Concerns

Important identified risks	PR interval prolongation (both paediatric and adult populations)
	Nephrolithiasis with or without alteration of the renal function
	Hyperbilirubinemia
	Severe skin reactions
	Cholelithiasis
Important potential risks	QT prolongation

Table 37: Summary of Safety Concerns

	Kernicterus
	Acute renal failure (adults)
	Angioedema
	Interstitial Nephritis
	Immune reconstitution inflammatory syndrome (IRIS)
	Lack of efficacy due to unboosted ATV “off-label use”
Missing information	
	Hepatic impairment
	Pregnancy
	Paediatric patients <3 months of age
	Geriatrics
	Women who are breastfeeding

Pharmacovigilance plan

Table 38: Ongoing and Planned Additional PhV Studies/Activities in the Pharmacovigilance Plan

Study/ Activity Type Title and Category (1-3)	Objectives	Safety Concerns Addressed	Status	Date for Submission of Interim or Final Reports
D:A:D study is a prospective multi-cohort study of HIV-infected persons under active follow up	To understand the association between exposure to ARV drugs and the risk of cardiovascular disease (CVD), chronic liver disease (CLD) (liver failure, liver transplantation, or liver-related death), end-stage renal disease (ESRD) (need for permanent dialysis	Myocardial infarction, CVD, CLD, and ESRD	Data mergers for the collaborative epidemiologic D:A:D study happen every year, and submission of a report to the EMA follows in the second quarter of each year. The HAART-OC has agreed to continue funding the D:A:D study for a further 4 years until 2017 (17th data merger). Funding will not continue past	Second Quarter of each year up to 2017

Table 38: Ongoing and Planned Additional PhV Studies/Activities in the Pharmacovigilance Plan

Study/ Activity Type Title and Category (1-3)	Objectives	Safety Concerns Addressed	Status	Date for Submission of Interim or Final Reports
	or kidney transplantation) or death caused by chronic kidney failure, and non-AIDS-related malignancies		this point. EMA questions (which the HAART OC funds the D:A:D study to answer) are endpoint driven, and in 2017, should have been answered with reasonable statistical power, and thus, regulatory closure will have been met.	
Antiretroviral Pregnancy Registry (APR)	To detect any major teratogenic effects involving any of the Registry drugs, including ATV, to which pregnant women are exposed.	Teratogenicity of Registry drugs, including ATV	The APR, a observational, exposure registration and follow-up study was established in January 1989 to monitor major teratogenic effects of any ARV drug exposure during pregnancy. Interim reports are issued twice a year; the most recent report is for data through 31-Jul-2014.	Last interim report issued December 2014; interim reports are issued every 6 months. Reports to be provided along with PSUR submission.
Study AI424397 is a prospective multicenter safety, PK, and efficacy study in HIV-infected pediatric subjects	To describe the safety of ATV powder and RTV-optimized HAART regimens in pediatric subjects ≥ 3 months to < 5 years and 6 months of age	Safety in pediatric patients	Week 48 report and Addend01 and Addend02 reports have been submitted.	Every 36 months upon approval of the oral powder along with PSUR
Study AI424451 is a prospective, 2-stage, multicenter	To describe the safety of ATV powder and RTV-optimized HAART	Safety in pediatric patients	Interim and Week 48 reports have been submitted.	Every 36 months upon approval of the oral powder

Table 38: Ongoing and Planned Additional PhV Studies/Activities in the Pharmacovigilance Plan

Study/ Activity Type Title and Category (1-3)	Objectives	Safety Concerns Addressed	Status	Date for Submission of Interim or Final Reports
safety, PK, and efficacy study in HIV-infected pediatric subjects	regimens in pediatric subjects ≥ 3 months to < 11 years and weighing ≥ 5 to< 35 kg			along with PSUR

Risk minimisation measures

Table 39: Risk Minimization Measures by Safety Concern

Safety Concern: PR Interval Prolongation	
Objective(s) of the risk minimization measure	To minimize the occurrence and to mitigate the impact of PR interval prolongation if it occurs by providing adequate warnings in the label.
Routine risk minimization measures	CCDS: 5.2 Product specific warnings and precautions PR interval prolongation Atazanavir has the potential to prolong the PR interval of the electrocardiogram in some patients. TRADENAME should be used with caution in patients with preexisting conduction system diseaseCaution should be used when coadministering TRADENAME with medicinal products known to induce PR interval prolongation (see 6 INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION). SmPC: 4.4 Special warnings and precautions for use Paediatric population Safety Asymptomatic PR interval prolongation was more frequent in pediatric patients than adults. Asymptomatic first- and second-degree AV block was reported in pediatric patients (see section 4.8). Caution should be used with medicinal products known to induce PR prolongations. In pediatric patients with pre-existing conduction problems (second degree or higher atrioventricular or complex bundle-branch

Table 39: Risk Minimization Measures by Safety Concern

	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 (eg, bradycardia). 4.8 Undesirable effects *Cardiac disorders:* uncommon: torsades de pointes rare: QTc prolongation, oedema, palpitation
Additional risk minimization measure(s)	None
Effectiveness of Risk Minimization Measures	
How effectiveness of risk minimization measures for the safety concern will be measured	Monitoring in the PSUR
Criteria for judging the success of the proposed risk minimization measures	No increase in frequency or characterization including assessments of presentations, severity, treatments, risk factors, and outcomes, of the cases seen.
Planned date of assessment	August 2015
Results of effectiveness measurement	No increase in frequency or characterization of the cases has been seen in previous PSURs.
Impact of risk minimization	Sufficient
Comment	None
Safety Concern: Nephrolithiasis with or without Alteration of the Renal Function	
Objective(s) of the risk minimization measure	To minimize the occurrence and to mitigate the impact of nephrolithiasis if it occurs by providing adequate warnings in the label.
Routine risk minimization measures	CCDS: 5.2 Product specific warnings and precautions Nephrolithiasis Cases of nephrolithiasis have been reported during postmarketing surveillance in HIV-infected patients receiving TRADENAME therapy If signs or symptoms of nephrolithiasis occur, temporary interruption or discontinuation of therapy may be considered. SmPC: 4.4 Special warnings and precautions for use Nephrolithiasis with or without alteration of the renal

Table 39: Risk Minimization Measures by Safety Concern

	function 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: nephrolithiasisa, hematuria, proteinuria, pollakiuria; rare: kidney pain Routine Risk Minimization Measures: The MAH will monitor and assess all nephrolithiasis, urolithiasis and related events through clinical trials and its safety database on an ongoing basis as a part of routine safety surveillance Continuous review nephrolithiasis and related events in the MAH safety database MAH will continue to review published literature
Additional risk minimization measure(s)	
Effectiveness of Risk Minimization Measures	
How effectiveness of risk minimization measures for the safety concern will be measured	Monitoring in the PSURs
Criteria for judging the success of the proposed risk minimization measures	No increase in frequency or characterization including assessments of presentations, severity, treatments, risk factors, and outcomes, of the cases seen.
Planned date of assessment	August 2015
Results of effectiveness measurement	No increase in frequency or characterization of the cases has been seen in previous PSURs.
Impact of risk minimization	Sufficient
Comment	None
Safety Concern: Hyperbilirubinemia	
Objective(s) of the risk minimization measure	To minimize the occurrence and to mitigate the impact of hyperbilirubinemia if it occurs by providing adequate warnings in the label.
Routine risk minimization measures	CCDS: 5.2 Product specific warnings and precautions

Table 39: Risk Minimization Measures by Safety Concern

	Hyperbilirubinemia Reversible elevations in indirect (unconjugated) bilirubin related to inhibition of UDP-glucuronosyl transferase (UGT) have occurred in patients receiving TRADENAME. Hepatic transaminase elevations that occur with elevated bilirubin in patients receiving TRADENAME should be evaluated for alternative etiologies. No long-term safety data are available for patients experiencing persistent elevations in bilirubin >5 times the upper limit of normal (ULN). Alternative antiretroviral therapy to TRADENAME may be considered if jaundice or scleral icterus associated with bilirubin elevations presents cosmetic concerns for patients. Dose reduction of TRADENAME is not recommended since long-term efficacy of reduced doses has not been established. SmPC: 4.4 Special warnings and precautions for use Hyperbilirubinaemia Reversible elevations in indirect (unconjugated) bilirubin related to inhibition of UDP-glucuronosyltransferase (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) hyperbilirubinaemia due to inhibition of UGT. Combinations of REYATAZ and indinavir have not been studied and co administration of these medicinal products is not recommended (see section 4.5). RISK MINIMZATION MEASURES: BMS will monitor and assess hyperbilirubinemia and related disorders through clinical trials and its safety database on an ongoing basis as a part of routine safety surveillance in the PSURs Monitor frequency of hyperbilirubinemia and related events in the MAH's safety database Continue ongoing routine surveillance of hyperbilirubinemia

Table 39: Risk Minimization Measures by Safety Concern

	and related events reported by consumers and health professionals.
Effectiveness of Risk Minimization Measures	
How effectiveness of risk minimization measures for the safety concern will be measured	Monitoring in the PSURs
Criteria for judging the success of the proposed risk minimization measures	No increase in frequency or characterization including assessments of presentations, severity, treatments, risk factors, and outcomes, of the cases seen.
Planned date of assessment	August 2015
Results of effectiveness measurement	No increase in frequency or characterization of the cases has been seen in previous PSURs.
Impact of risk minimization	Sufficient
Comment	None
Safety Concern: Severe Skin Reactions	
Objective(s) of the risk minimization measures	To minimize the occurrence and to mitigate the impact of severe skin reactions if they occur by providing adequate warnings in the label.
Routine risk minimization measures	CCDS: 5.3 Product specific warnings and precautions Rashes are usually mild-to-moderate maculopapular skin eruptions that occur within the first 3 weeks of initiating therapy with TRADENAME. In most patients, rash resolves within 2 weeks while continuing TRADENAME therapy. TRADENAME should be discontinued if severe rash develops. Cases of SJS, erythema multiforme, and toxic skin eruptions including DRESS syndrome have been reported in patients receiving TRADENAME. SmPC: 4.4 Special warnings and precautions for use Rash and associated syndromes Rashes are usually mild-to-moderate maculopapular skin eruptions that occur within the first 3 weeks of starting therapy with REYATAZ. Stevens-Johnson syndrome, erythema multiforme, toxic skin eruptions and DRESS syndrome have been reported in patients receiving REYATAZ. Patients should be advised of the signs and symptoms and monitored closely for skin reactions. REYATAZ should be discontinued if severe rash

Table 39: Risk Minimization Measures by Safety Concern

	develops.The best results in managing these events come from early diagnosis and immediate interruption of any suspect medicines. If the patient has developed SJS or DRESS associated with the use of REYATAZ, REYATAZ may not be restarted. BMS will monitor and assess severe skin reactions and related disorders through clinical trials and its safety database on an ongoing basis as a part of routine safety surveillance in the PSURs Monitor frequency of severe skin reactions and related events in the MAH's safety database Continue ongoing routine surveillance of severe skin reactions and related events reported by consumers and health professionals.
Additional risk minimization measure(s)	None
Effectiveness of Risk Minimization Measures	
How effectiveness of risk minimization measures for the safety concern will be measured	Monitoring in the PSUR
Criteria for judging the success of the proposed risk minimization measures	No increase in frequency or characterization including assessments of presentations, severity, treatments, risk factors, and outcomes, of the cases seen.
Planned date of assessment	August 2015
Results of effectiveness measurement	No increase in frequency or characterization of the cases has been seen in previous PSURs.
Impact of risk minimization	Sufficient
Comment	None
Safety Concern: Cholelithiasis	
Objective(s) of the risk minimization measure	To minimize the occurrence and to mitigate the impact of cholelithiasis if it occurs by providing adequate warnings in the label.
Routine risk minimization measures	CCDS has been updated to include cholelithiasis in Section 7.2: Postmarketing experience SmPC: 4.4 Special warnings and precautions for use Cholelithiasis has been reported in patients receiving

Table 39: Risk Minimization Measures by Safety Concern

	REYATAZ (see section 4.8). Some patientsrequired hospitalization for additional management and some had complications. If signs or symptomsof cholelithiasis occur, temporary interruption or discontinuation of treatment may be considered. 4.8 Undesirable effects *Hepatobiliary disorders:* common: jaundice; uncommon: hepatitis, cholelithiasis; cholestasis; rare: hepatosplenomegaly, cholecystitis
Additional risk minimization measure(s)	None
Effectiveness of Risk Minimization Measures	
How effectiveness of risk minimization measures for the safety concern will be measured	Monitoring in the PSURs
Criteria for judging the success of the proposed risk minimization measures	No increase in frequency or characterization including assessments of presentations, severity, treatments, risk factors, and outcomes of the cases seen.
Planned date of assessment	August 2015
Results of effectiveness measurement	No increase in frequency or characterization of the cases has been seen in previous PSURs.
Impact of risk minimization	Sufficient
Comment	None
Safety Concern: QT prolongation	
Objective(s) of the risk minimization measure	To minimize the occurrence and to mitigate the impact of QT prolongation, if it occurs by providing adequate warnings in the label.
Routine risk minimization measures	CCDS: 5.7 Postmarketing experience *Cardiac disorders and vascular disorders:* second-degree AV block, third-degree AV block, QTc prolongation, Torsades de Pointes. SmPC: 4.4 Special warnings and precautions for use QT prolongation: Dose related asymptomatic prolongations in PR interval with REYATAZ have been observed in clinical studies. Caution should be used with medicinal products

Table 39: Risk Minimization Measures by Safety Concern

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). Particular caution should be used when prescribing REYATAZ in association with 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).

4.8 Undesirable effects

Cardiac disorders: uncommon: torsades de pointesa; rare: QTc prolongationa, oedema, palpitation

5.3 Preclinical safety data

During in vitro studies, cloned human cardiac potassium channel (hERG), was inhibited by 15% at a concentration (30 µM) of atazanavir corresponding to 30 fold the free drug concentration at Cmax in humans. Similar concentrations of atazanavir increased by 13% the action potential duration (APD90) in rabbit Purkinje fibres study. Electrocardiographic changes (sinus bradycardia, prolongation of PR interval, prolongation of QT interval, and prolongation of QRS complex) were observed only in an initial 2-week oral toxicity study performed in dogs. Subsequent 9-month oral toxicity studies in dogs showed no drug-related electrocardiographic changes. The clinical relevance of these non-clinical data is unknown. Potential cardiac effects of this product in humans cannot be ruled out (see sections 4.4 and 4.8). The potential for PR prolongation should be considered in cases of overdose (see section 4.9).

Other Routine Risk Minimization Measures:

The MAH will monitor and assess all PR interval prolongations, deaths due to cardiac events and sudden deaths through clinical trials and its safety database on an ongoing basis as a part of routine safety surveillance in the PSURs

Continuous review of all deaths (including sudden death), PR interval prolongations, and cardiac system events in the MAH safety database

Closely follow-up on individual cases in the BMS safety database.

Table 39: Risk Minimization Measures by Safety Concern

	MAH will continue to review published literature
Additional risk minimization measure(s)	None
Effectiveness of Risk Minimization Measures	
How effectiveness of risk minimization measures for the safety concern will be measured	Monitoring in the PSURs
Criteria for judging the success of the proposed risk minimization measures	No increase in frequency or characterization including assessments of presentations, severity, treatments, risk factors, and outcomes, of the cases seen.
Planned date of assessment	August 2015
Results of effectiveness measurement	No increase in frequency or characterization of the cases has been seen in previous PSURs.
Impact of risk minimization	Sufficient
Comment	None
Safety Concern: Kernicterus	
Objective(s) of the risk minimization measure	To minimize the occurrence and to mitigate the impact of kernicterus if it occurs by providing adequate warnings in the label.
Routine risk minimization measures	CCDS: 4.2 Posology and method of administration TRADENAME should not be administered to pediatric patients below the age of 3 months due to the risk of kernicterus. SmPC: REYATAZ should not be used in children less than 3 months because of safety concerns especially taking into account the potential risk of kernicterus. Other Routine Risk Minimization Measures: BMS will monitor and assess kernicterus and related disorders through clinical trials and its safety database on an ongoing basis as a part of routine safety surveillance in the PSURs Monitor frequency of kernicterus and related events in the MAH's safety database Continue ongoing routine surveillance of kernicterus and

Table 39: Risk Minimization Measures by Safety Concern

	related events reported by consumers and health professionals.
Additional risk minimization measure(s)	None
Effectiveness of Risk Minimization Measures	
How effectiveness of risk minimization measures for the safety concern will be measured	Monitoring in the PSURs
Criteria for judging the success of the proposed risk minimization measures	No increase in frequency or characterization including assessments of presentations, severity, treatments, risk factors, and outcomes, of the cases seen.
Planned date of assessment	August 2015
Results of effectiveness measurement	No increase in frequency or characterization of the cases has been seen in previous PSURs.
Impact of risk minimization	Sufficient
Safety Concern: Acute Renal Failure	
Objective(s) of the risk minimization measures	To minimize the occurrence and to mitigate the impact of acute renal failure if it occurs by providing adequate warnings in the label.
Routine risk minimization measures	Acute renal failure has not been added to the CCDS or SmPC. After careful evaluation as described in Section 2.8.1, BMS considers that acute renal failure in HIV patients is confounded by concomitant administration of TDF, an aging population, and HIV nephropathy. This association is also seen with other PIs such as LPV and DRV. Other Routine Risk Minimization Measures: BMS will monitor and assess acute renal failure and related disorders through clinical trials and its safety database on an ongoing basis as a part of routine safety surveillance in the PSURs Monitor frequency of acute renal failure and related events in the MAH's safety database Continue ongoing routine surveillance of acute renal failure and related events reported by consumers and health professionals.
Additional risk minimization measure(s):	None

Table 39: Risk Minimization Measures by Safety Concern

Effectiveness of Risk Minimization Measures	
How effectiveness of risk minimization measures for the safety concern will be measured	Monitoring in the PSURs
Criteria for judging the success of the proposed risk minimization measures	No increase in frequency or characterization including assessments of presentations, severity, treatments, risk factors, and outcomes, of the cases seen.
Planned date of assessment	August 2015
Results of effectiveness measurement	No increase in frequency or characterization of the cases has been seen in previous PSURs.
Impact of risk minimization	Sufficient
Safety Concern: Angioedema	
Objective(s) of the risk minimization measures	To minimize the occurrence and to mitigate the impact of angioedema if it occurs by providing adequate warnings in the label.
Routine risk minimization measures	CCDS has been updated to include angioedema in Section 7.2: Post marketing experience. SmPC section 4.4 Special warnings and precautions for use: Rash and associated syndromes Rashes are usually mild -to-moderate maculopapular skin eruptions that occur within the first 3 weeks of starting therapy with REYATAZ. Stevens-Johnson syndrome, erythema multiform, toxic skin eruptions and DRESS syndrome have been reported in patients receiving REYATAZ. Patients should be advised of the signs and symptoms and monitored closely for skin reactions. REYATAZ should be discontinued if severe rash develops. The best results in managing these events come from early diagnosis and immediate interruption of any suspect medicines. If the patient has developed SJS or DRESS associated with the use of REYATAZ, REYATAZ may not be restarted. *Skin and subcutaneous tissue disorders:*common: rash; uncommon: erythema multiform, toxic skin eruptions, DRESS syndrome, angioedema, urticaria, alopecia, pruritus; rare: Stevens Johnson syndrome, vesiculobullous rash, eczema, vasodilatation.

Table 39: Risk Minimization Measures by Safety Concern

	Other Routine Risk Minimization Measures: BMS will monitor and assess angioedema and related disorders through clinical trials and its safety database on an ongoing basis as a part of routine safety surveillance in the PSURs Monitor frequency of angioedema and related events in the MAH's safety database Continue ongoing routine surveillance of angioedema and related events reported by consumers and health professionals.
Additional risk minimization measure(s)	None
Effectiveness of Risk Minimization Measures	
How effectiveness of risk minimization measures for the safety concern will be measured	Monitoring in the PSURs
Criteria for judging the success of the proposed risk minimization measures	No increase in frequency or characterization including assessments of presentations, severity, treatments, risk factors, and outcomes, of the cases seen.
Planned date of assessment	August 2015
Results of effectiveness measurement	No increase in frequency or characterization of the cases has been seen in previous PSURs.
Impact of risk minimization	Sufficient
Safety Concern: Interstitial Nephritis	
Objective(s) of the risk minimization measure	To minimize the occurrence and to mitigate the impact of interstitial nephritis if it occurs by providing adequate warnings in the label.
Routine risk minimization measures	CCDS has been updated to include interstitial nephritis in Section 7.2: Post marketing experience.
Additional risk minimization measure(s)	None
Effectiveness of Risk Minimization Measures	
How effectiveness of risk minimization measures for the safety concern will be measured	Monitoring in the PSURs
Criteria for judging the success of the proposed risk minimization measures	No increase in frequency or characterization including assessments of presentations, severity, treatments, risk

Table 39: Risk Minimization Measures by Safety Concern

	factors, and outcomes of the cases seen.
Planned date of assessment	August 2015
Results of effectiveness measurement	No increase in frequency or characterization of the cases has been seen in previous PSURs.
Impact of risk minimization	Sufficient
Comment	None
Safety Concern: Immune Reconstitution Inflammatory Syndrome (IRIS)	
Objective(s) of the risk minimization measures	To minimize the occurrence and to mitigate the impact of IRIS if it occurs by providing adequate warnings in the label.
Routine risk minimization measures	CCDS: Section 5.1 Drug-class–specific warnings and precautions Immune reconstitution syndrome Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy, including TRADENAME. During the initial phase of combination antiretroviral treatment, patients whose immune system responds may develop an inflammatory response to indolent or residual opportunistic infections (such as *Mycobacterium avium* infection, cytomegalovirus, *Pneumocystis jiroveci* pneumonia [PCP], or tuberculosis), which may necessitate further evaluation and treatment. Autoimmune disorders (such as Graves' disease) have also been reported to occur in the setting of immune reactivation; however, the reported time to onset is more variable and these events can occur many months after initiation of treatment. SmPC: Section 4.4: Autoimmune disorders (such as Graves' disease) have also been reported to occur in the setting of immune reactivation; however, the reported time to onset is more variable and these events can occur many months after initiation of treatment. section 4.8: In HIV-infected patients with severe immune deficiency at the time of initiation of combination antiretroviral therapy (CART), an inflammatory reaction to asymptomatic or residual opportunistic infections may arise, Autoimmune disorders (such as Graves' disease) have also been reported: however, the reported time to onset is more variable and these events can occur many months after

Table 39: Risk Minimization Measures by Safety Concern

	initiation of treatment (see section 4.4). Other routine risk minimization measures: BMS will monitor and assess IRIS and related disorders through clinical trials and its safety database on an ongoing basis as a part of routine safety surveillance in the PSURs Monitor frequency of IRIS and related events in the MAH's safety database Continue ongoing routine surveillance of IRIS and related events reported by consumers and health professionals.
Additional risk minimization measure(s)	None
Effectiveness of Risk Minimization Measures	
How effectiveness of risk minimization measures for the safety concern will be measured	Monitoring in the PSURs
Criteria for judging the success of the proposed risk minimization measures	No increase in frequency or characterization, including assessments of presentations, severity, treatments, risk factors, and outcomes, of the cases seen.
Planned date of assessment	August 2015
Results of effectiveness measurement	No increase in frequency or characterization of the cases has been seen in previous PSURs.
Impact of risk minimization	Sufficient
Safety Concern: Lack of efficacy due to unboosted ATV "off-label use"	
Objective(s) of the risk minimization measures	To minimize the occurrence and to mitigate the impact of lack of efficacy due to unboosted ATV "off-label use" by providing adequate warnings in the label.
Routine risk minimization measures	SmPC: 4.2 Posology and method of administration <u>Posology</u> *Adults:* The recommended dose of REYATAZ capsules is 300 mg once daily taken with ritonavir 100 mg once daily and with food. Ritonavir is used as a booster of atazanavir pharmacokinetics (see sections 4.5 and 5.1). (See also section 4.4 Withdrawal of ritonavir only under restrictive conditions). *Patients with hepatic impairment:* In case of withdrawal of ritonavir from the initial recommended ritonavir boosted

regimen (see section 4.4), unboosted REYATAZ could be maintained in patients with mild hepatic impairment at a dose of 400 mg, and in patients with moderate hepatic impairment with a reduced dose of 300 mg once daily with food (see section 5.2). Unboosted REYATAZ must not be used in patients with severe hepatic impairment.

4.4 Special warnings and precautions for use

Withdrawal of ritonavir only under restrictive conditions

The recommended standard treatment is REYATAZ boosted with ritonavir, ensuring optimal pharmacokinetic parameters and level of virologic suppression.

The withdrawal of ritonavir from the boosted regimen of REYATAZ is not recommended, but may be considered in adults patients at the dose of 400 mg once daily with food only under the following combined restrictive conditions:

Absence of prior virologic failure

Undetectable viral load during the last 6 months under current regimen

Viral strains not harbouring HIV resistance associated mutations (RAMs) to current regimen.

REYATAZ given without ritonavir should not be considered in patients treated with a backbone regimen containing tenofovir disoproxil fumarate and with other concomitant medications that reduce atazanavir bioavailability (see section 4.5 In case of withdrawal of ritonavir from the recommended atazanavir boosted regimen) or in case of perceived challenging compliance.

REYATAZ given without ritonavir should not be used in pregnant patients given that it could result of suboptimal exposure of particular concern for the mother infection and vertical transmission.

4.5 Interaction with other medicinal products and other forms of interaction

Other Interactions: If withdrawal of ritonavir is medically warranted under restrictive conditions (see section 4.4), special attention should be given to atazanavir interactions that may differ in the absence of ritonavir (see information below in Table 2).

In case of withdrawal of ritonavir from the recommended

Table 39: Risk Minimization Measures by Safety Concern

	atazanavir boosted regimen (see section 4.4) The same recommendations for drug drug interactions would apply except: that co-administration is not recommended with tenofovir, boceprevir, carbamazepine, phenytoin, phenobarbital, proton pump inhibitors, and buprenorphine. that co-administration with famotidine is not recommended but if required, atazanavir without ritonavir should be administered either 2 hours after famotidine or 12 hours before. No single dose of famotidine should exceed 20 mg, and the total daily dose of famotidine should not exceed 40 mg. the need to consider that: ▪ co-administration of voriconazole and REYATAZ without ritonavir may affect atazanavir concentrations ▪ co-administration of fluticasone and REYATAZ without ritonavir may increase fluticasone concentrations relative to fluticasone given alone ▪ if an oral contraceptive is administered with REYATAZ without ritonavir, it is recommended that the oral contraceptive contain no more than 30 µg of ethinyloestradiol ▪ No dose adjustment of lamotrigine is required. 5.1 Pharmacodynamic properties *Data on withdrawal of ritonavir from atazanavir boosted regimen (see also section 4.4)* *Study 136 (INDUMA)* Eleven subjects (13%) in the unboosted REYATAZ group and 6 (7%) in the REYATAZ + ritonavir group, had virologic rebound. Four subjects in the unboosted REYATAZ group and 2 in the REYATAZ + ritonavir group had HIV RNA > 500 copies/ml during the maintenance phase. No subject in either group showed emergence of protease inhibitor resistance. The M184V substitution in reverse transcriptase, which confers resistance to lamivudine and emtricitabine, was detected in 2 subjects in the unboosted REYATAZ and 1 subject in the REYATAZ + ritonavir group.
Additional risk minimization measure(s)	None

Table 39: Risk Minimization Measures by Safety Concern

Effectiveness of Risk Minimization Measures	
How effectiveness of risk minimization measures for the safety concern will be measured	Monitoring in the PSUR
Criteria for judging the success of the proposed risk minimization measures	No increase in frequency or characterization including assessments of presentations, severity, treatments, risk factors, and outcomes of the cases seen.
Planned date of assessment	August 2018
Results of effectiveness measurement	No increase in frequency or characterization of the cases has been seen in previous PSURs.
Impact of risk minimization	Sufficient
Comment	None

2.8. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

3. Benefit-Risk Balance

Benefits

So far, Reyataz is approved for use in the treatment of HIV infection for adults and children from 6 years of age either in first line or in treatment experienced patients but with restriction in terms of PI resistance (<4 PI mutations).

A new formulation for extending the use of Reyataz in younger children from 3 months of age is proposed. As a matter of fact, the Applicant has in the past (2009) already claimed an indication in this young population based on PK and clinical data derived from a clinical study AI424020, but the application was withdrawn in view of major objections raised by the CHMP on the critical deficiencies to substantiate the adequacy of the dose in children from 3 months of age.

The clinical development in support of this new application is derived from two clinical studies: PRINCE I and PRINCE II. These two similarly designed studies enrolled a mix population of children with or without ARV experience, with different backbone regimen (excluding tenofovir, without active NRTI backbone and no ATV resistance) and with level of viremia exceeding 1000 copies/ml, with high level of viremia >100 000 copies/ml observed in very young children. These studies were multicentric, mainly performed in Africa especially for the younger children.

From PRINCE I to PRINCE II, significant changes occurred that were addressed through specific amendments:

- Based on PK analysis from PRINCE I, the dose to be tested in very young children from 5-10 kg was adjusted after the PRINCE II started, from 150/80 mg ATV/RTV dose to 200/80 mg dose. Overall, only 10 patients in the 5-10 kg strata received the recommended dose.

- The to-be-marketed formulation with aspartame 4.2% was only introduced in PRINCE II but no children from 5-10 kg could receive it

- An additional age strata from 25-35 kg was lately introduced in the PRINCE II, with only 8 patients being treated

While in PRINCE I all patients have completed the 48 weeks visit, this is not the case for PRINCE II with 24 weeks visit being completed but 48 weeks not yet completed (only one patient achieved week 48 in the 5-10 kg weigh strata and 2 children from the 25 to 35 kg).

Beneficial effects

Reyataz (atazanavir), given together with ritonavir as a PK booster, in combination with other antiretroviral medicinal products, is currently only indicated in HIV infected adults and children aged 6 years and older either in first line or in treatment experienced patients but with restriction in terms of PI resistance (<4 PI mutations).

A new formulation for extending the use of Reyataz in younger children from 3 months of age has been developed. This would be the first boosted Protease Inhibitor to be validated in such a young population. The new formulation intended to be marketed is an aspartame containing oral powder. The content of aspartame has been reduced over time from 10% to the 4.2% in the to-be marketed formulation.

Atazanavir has pharmacokinetics that allow once daily dosing in adults and children ≥ 6 years old, which makes development of a formulation suitable for smaller children desirable as adherence could be expected to improve with such a regimen in this population.

Limited clinical data indicate overall viral success rates which seem in a similar order of magnitude to those seen with other antiretroviral treatments in this population, albeit less favourable at the 50 c/ml level.

Such a virological impact is observed while, as compared to other boosted PIs, this medicinal compound tends to have a lower potential to induce dyslipidemia.

This medicinal product is a suitable formulation for paediatric use that could de added to the therapeutic armamentarium.

Uncertainty in the knowledge about the beneficial effects

The clinical development of antiretrovirals in children focuses on the identification of the appropriate dose for children of all relevant age groups. The selected dose should achieve comparable exposures in children as those observed in adults, and it is expected that this will lead to a comparable efficacy and safety profile of the medicine.

The dose selection was previously substantiated by a one compartment PPK model. The model was then revised to a two compartment model thanks to PK data derived from the PRINCE studies. During the procedure, the PPK model was further revised updated to include a modified maturation function for the characterization of the age-related impact of RTV co-administration on ATV apparent oral clearance (CLT/F), as well as a new maturation function describing the impact of age on ATV

bioavailability, resulting in an improvement in the characterization of the time-course of ATV concentrations in paediatric subjects. The final dosing recommendation for the oral powder and capsule formulation have been set as to take into account the PPKPOP, the need to minimize the gap between oral and capsule formulation and the need to minimize the deviation from the original capsule dosing recommendation. It is acknowledged that these dosing recommendations mainly rely on PPKPOP and clinical relevance.

Risks

Unfavourable effects

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 a significant proportion of adverse events observed in children.

Uncertainty in the knowledge about the unfavourable effects

The paediatric safety database is not extensive, and in particular in the lowest weight group (5- 10 kg BW) receiving the higher (200 mg) dose, there is very little data available. Exposure time was short, and a disproportionately high proportion of subjects were discontinued from the study in this weight group, if mostly for AEs not considered treatment related.

Effects Table for REYATAZ

Effect	Short Description	Unit	Treatment	Uncertainties / Strength of evidence	References
Favourable Effects					
Subjects with HIV-1 RNA <400 c/mL at W48 (%)	ITT Time point: Week 48	%	66.7 in 5-<10 kg (ATV 150 mg) 73.7 in 10-<15 kg (ATV 200 mg) 85.7 in 15-<25 kg (ATV 250 mg)	Dose selection of ATV boosted with ritonavir has not been adequately substantiated especially in children 5-<10Kg Poor response rates observed, from studies of limited sample size and mixing treatment naïve and experienced children, at the recommended dose, notably <20% of patients with undetectable viral load at W24, in the subgroup of children 5-10 kg	AI424397 – PRINCE I Study N=56
	ITT Time point: Week 48	%	60.9 in 5-<10 kg (ATV 150 mg) 100 in 5-<10 kg (ATV 200 mg) 70 in 10-<15 kg (ATV 200 mg) 64.7 in 15-<25 kg (ATV 250 mg) 50 in 25-<35 kg (ATV 300 mg)		AI424451 – PRINCE II Study N=99
Subjects with HIV-1 RNA <50 c/mL at W24 (%)	ITT Time point: Week 24	%	43.5 in 5-<10 kg (ATV 150 mg) 16.7 in 5-<10 kg (ATV 200 mg) 47.6 in 10-<15 kg (ATV 200 mg) 54.3 in 15-<25 kg (ATV 250 mg) 62.5 in 25-<35 kg (ATV 300 mg)		
Unfavourable Effects					
Overall grade 2-4 drug-related AEs		%	23%	Studies of limited sample size, notably few children of 5-10 kg exposed at the recommended dose	Pooled Studies AI424397 – PRINCE I and AI424451 –

Effect	Short Description	Unit	Treatment	Uncertainties / Strength of evidence	References
					PRINCE II (n=155)
Hyperbilirubinaemia-related AEs		%	21%	14% with grade 2-4 drug-related hyperbilirubinemia AE No definite conclusion (Open-label study)	
Other AEs - gastro-intestinal drug-related AEs (Grade 2-4) -rash disorders drug related (grade 2-4)		%	47.1% (1.9%) 16% (<1%)		

Abbreviations: ATV: Atazanavir, HIV: human immunodeficiency virus, RNA: ribonucleic acid, ITT: intend-to-treat population,

Benefit-risk balance

Discussion on the benefit-risk assessment

The PPK model has been significantly improved from the original application, with updated PK data from the PRINCE studies as well as through the inclusion of additional covariates for notably covering modified maturation function for the characterization of the age-related impact of RTV co-administration on ATV apparent oral clearance (CLT/F), as well as a new maturation function describing the impact of age on ATV bioavailability. This overall result in a good fit to data in all age groups.

The final dosing recommendation for the oral powder and capsule formulation have been set as to take into account the PPKPOP, the need to minimize the gap between oral and capsule formulation and the need to minimize the deviation from the original capsule dosing recommendation. It is acknowledged that these dosing recommendations mainly rely on PPKPOP and clinical.

3.1. Conclusions

The CHMP considered the overall risk/benefit of REYATAZ in children weighing at least 5 kg is considered positive.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of Reyataz co-administered with low dose ritonavir, is indicated in combination with other antiretroviral medicinal products for the treatment of HIV-1 infected paediatric patients at least 3 months of age and weighing at least 5 kg is favourable and therefore recommends the granting of the extension marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product

Characteristics, section 4.2).

Conditions and requirements of the Marketing Authorisation

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Paediatric Data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0098/2014and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.