25 July 2013
EMA/759171/2014
Human Medicines Evaluation Division

Assessment report for paediatric studies submitted in accordance with article 46 of regulation (EC) No 1901/2006

Reyataz

International non-proprietary name: atazanavir sulfate

Procedure no.: EMA/H/C/00494/P46/0078

Note

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

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Introduction

On April 2013, the MAH submitted a completed paediatric study for Reyataz (AI424397 – PRINCE 1 study), in accordance with Article 46 of Regulation (EC) No1901/2006, as amended. It could be noted that PK data will be analysed in a separate pharmacokinetic (PK) report after completion of the other paediatric study (AI424451 - PRINCE 2 study).

These data are planned to be submitted as part of the submission of the type II variation for the paediatric extension of indication and the oral powder line extension.

A short critical expert overview has also been provided.

Scientific discussion

Information on the development program

The MAH stated that PRINCE 1 study is part of a clinical development program. The extension application consisting of the full relevant data package (*i.e* containing several studies) is expected to be submitted **by July 2015**. A line listing of all the concerned studies is annexed.

Information on the pharmaceutical formulation used in the study

Reyataz is currently available in hard capsule of 100 mg, 150 mg, 200 mg and 300 mg. Additionally, a more convenient age-appropriate **oral powder formulation was developed**. Safety, PK and optimal dose of atazanavir (ATV) powder was assessed in the dose-finding study PACTG 1020-A (AI424020) in 182 paediatric subjects aged 91 days to 21 years. A population modelling and simulation study based upon the observed data from study PACTG 1020-A resulted in proposed recommended doses that are expected to achieve exposures considered close to that of adults, and therefore, to be sufficient for efficacy.

Clinical aspects

1. Introduction

The MAH submitted a final report for study AI424397 (PRINCE 1). However, as previously stated PK data were not provided in this report and will be analysed in combination with PRINCE 1I study PK data in a separate report.

2. Clinical study

Title: AI424397 – PRINCE 1 is 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.**

Description

The primary purpose of study AI424397 is to confirm that the proposed dose of ATV powder formulation with RTV in optimized regimens given in infants and children 3 months to < 6 years of age

are safe and well tolerated and produce systemic exposures comparable to those seen in adults treated with the once daily (QD) dose of ATV 300 mg boosted with RTV 100 mg.

This study was conducted in 18 sites in Brazil (1), Chile (2), Mexico (6), Peru (2), South Africa (5) and Thailand (2).

This clinical study report summarizes the results of the Week 48 analyses, and includes cumulative safety data through the database lock date of 03-Dec-2012.

Methods

- Objectives

Primary objective: 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), including deaths, serious adverse events (SAEs), and discontinuations due to adverse events (AEs).

Secondary objectives:

- to describe efficacy as measured by proportion of subjects with a virologic response as defined by an undetectable HIV RNA levels < 50 copies/mL and < 400 copies/mL by Roche Amplicor HIV-1 RNA Assay (version 1.5) through Week 48 of ATV powder formulation.

- to describe the PK profile of ATV powder formulation with RTV in pediatric subjects in terms of ATV maximum concentration (Cmax), minimum concentration (Cmin), and area under the concentration-time curve (AUC).

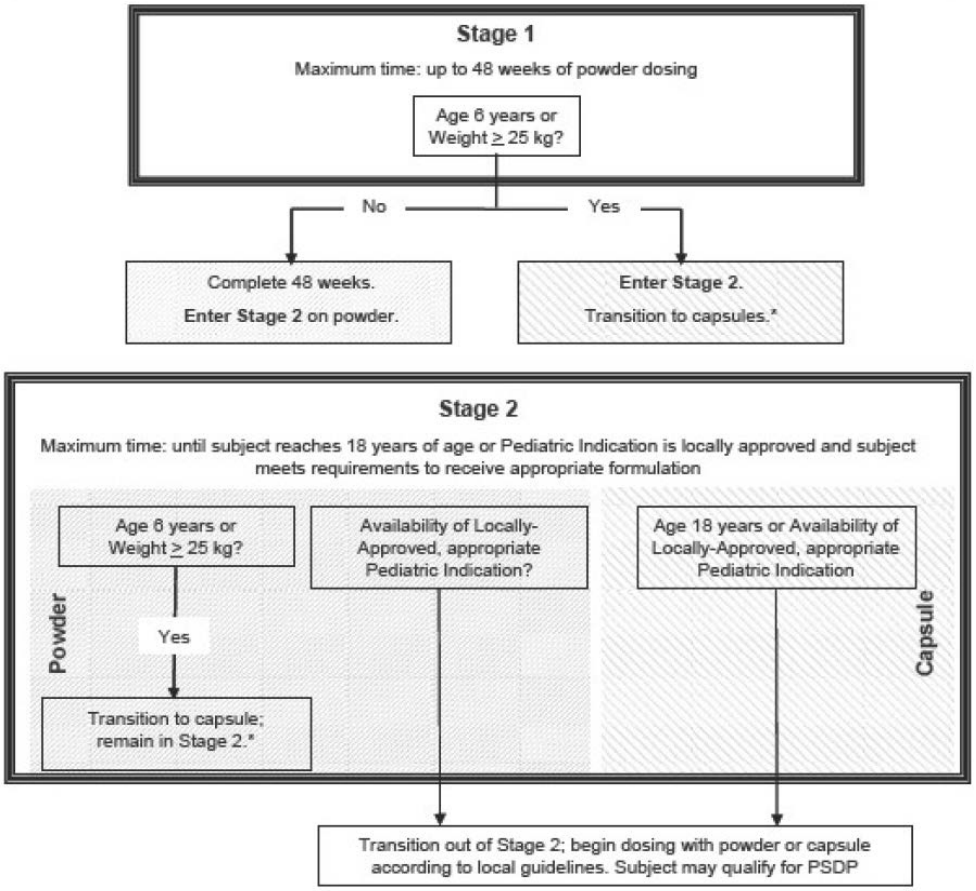
In addition, a non-protocol exploratory objective of this report was to evaluate the PK profile of a subset of subjects ≥ 3 months to < 6 months of age administered 150 mg ATV powder + 80 mg RTV oral solution.

- Study design

This study is a Phase 3b prospective, international, multicenter, **open-label, non randomized**, **2-stage** study of a cohort of HIV-infected pediatric **subjects ≥ 3 months to < 5 years and 6 months of age**, treated with ATV powder and RTV optimized regimens. Subjects can be **ARV naive or experienced** (without prior exposure to ATV). Subjects exposed to ARVs in utero or intra-partum may be included in the study but will be considered “treatment naïve”.

ATV/RTV is combined with a **nucleoside backbone therapy** selected by the investigator and consisted in 2 nucleoside reverse transcriptase inhibitor (NRTIs) approved for pediatric use and dosed as per the local country label (**tenofovir [TDF] is excluded**).

The study was divided into 2 stages. At Stage 1, all subjects received ATV/RTV with ATV powder formulation up to 48 weeks. Subjects completing stage 1 or subjects achieving 6 years old and/or a weight ≥ 25 kg during Stage 1 enter into Stage 2 with the appropriate ATV formulation.



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

- Study population /Sample size

A total of approximately 50 children were to be treated with the ATV powder formulation boosted with RTV oral solution.

Inclusion criteria:

- Informed consent from a parent/legal guardian must have been obtained prior to screening. Minors who were judged to be of an age of reason must also have given their written assent.
- Confirmed HIV-1 infection diagnosed by a positive virologic test result on 2 separate occasions by:
  a) HIV deoxyribonucleic acid polymerase chain reaction (PCR).
  b) HIV RNA with values ≥ 1,000 copies/mL was considered evidence of infection.
  c) Positive HIV enzyme-linked immunosorbent assay (ELISA) at ≥ 18 months of age, with confirmatory Western blot or indirect immunoflourescence antibody.
  Note: At least 1 diagnostic result may have been prior to the Screening visit.
- Infants and children of either gender, ≥ 3 months to < 5 years 6 months of age at the time of first treatment.
- Screening plasma viral load ≥ 1,000 copies/mL by Roche AmplicorR HIV RNA Assay (version 1.5).
- Antiretroviral-naive subjects must have had genotypic sensitivity at screening to ATV and at least 2 NRTIs (excluding TDF); NRTIs must have been approved for pediatric use at the local country level.

- Antiretroviral-experienced subjects (treatment-experienced subjects were defined by a previous exposure to ARVs through either prior treatment for their HIV disease or through a post-natal treatment with ≥ 1 ARVs for PMTCT. For the purposes of this study, subjects exposed to ARVs in utero or intra-partum may have been included in the study but were considered "treatment naïve") must have had documented genotypic and phenotypic sensitivity at screening to ATV (fold change in susceptibility < 2.2) and to both components of the local NRTI backbone. The NRTIs must have been approved for pediatric use at the local country level.

Main exclusion criteria:

- Experienced subjects who received ATV or ATV/RTV at any time prior to study enrolment or who had a prior history of 2 or more PI failures.
- Subjects with genotypic resistance at screening to ATV or either component of the local NRTI backbone based upon the following criteria: i) any major mutations I50L, I84V, N88S; or ii) ≥ 2 of the minor or cross resistant mutations M46I/L, G48V, I54L/V/M/T/A, V82A/T/FI, L90M, V32I; or iii) ≥ 3 of the minor mutations L10I/F/V/C, L24I, L33I/F/V, F53L/Y, A71V/I/T/L, G73C/S/T/A.
- History of psychiatric or cognitive/developmental impairment that could have compromised subject safety or the ability of the subject to comply with the protocol.
- Premature infants (< 37 weeks gestation at birth) until 6 months of age.
- The need for TDF.
- Any active CDC Category C clinical condition.
- Maternal history of hepatitis B virus (HBV) or hepatitis C virus (HCV) infection, or coinfection with either HBV or HCV.
- Cardiac conduction or rhythm abnormalities, cardiac dysfunction, history of syncope, or family history of some QTc interval abnormalities.
- History of pancreatitis, peripheral neuropathy, malignancy that requires systemic therapy.
- Malabsorption syndrome.
- Weight < 5 or ≥ 25 kg at Day 1.
- Grade 2 or more transaminase abnormalities.

• Treatments

Subjects received ATV dispersible powder (ATV 50 mg/sachet) for oral administration and RTV oral solution (80 mg/mL). ATV doses were stratified by body weight.

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.				

The ATV powder was to be mixed with a small amount of food or beverage (if water was used, the mixture must have been taken with food). The entire contents of the mixture must have been consumed to obtain the full dose.

Subjects achieving 6 years old or 25 kg switched to ATV capsules.

- Outcomes/endpoints

Safety: Frequency and severity of adverse events (AEs), serious adverse events (clinical and laboratory) and discontinuations from study due to AEs through Week 48. AEs, laboratory abnormalities and ECG parameters were notified.
Efficacy: Proportion of subjects with HIV RNA < 50 c/mL and < 400 c/mL through Week 48; HIV RNA log10, CD4 cell counts and percents observed values and changes from baseline through Week 48; Viral genotypic and phenotypic resistance profiles.
PK: Cmax, AUC(TAU), Cmin, CLT/F, and CLT/F/kg of both ATV and RTV at Week 2.

- Statistical Methods

Sample size/Power: Sample size was not based on power calculations. Approximately 50 subjects distributed among the 3 weight bands were planned for this study, with a minimum number of 4, 10 and 10 subjects respectively in the weight groups 5-<10 kg, 10-<15 kg and 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%.

Efficacy: Response rates were assessed with the Snapshot algorithm using an intention-to-treat (ITT) analysis set. HIV RNA log10, CD4 cell counts and percents observed values and changes from baseline were summarized at baseline and each analysis week on ATV powder through Week 48. CD4 cell counts and changes from baseline were also summarized using last observation carried forward (LOCF) and baseline observation carried forward (BOCF) methods on ATV powder through Week 48. For LOCF, missing values were replaced with the last on-treatment value in the previous visit window; if a subject did not have any on-treatment value, then the baseline value was carried forward. For BOCF, missing values were replaced with the baseline value. For both analyses, missing baseline values were replaced with the first on-treatment value.

Resistance: Viral genotypic and phenotypic resistance profiles were assessed for virologic failures who meet the criteria for resistance testing: less than a 1 log10 drop from baseline in HIV RNA level by Week 16, confirmed by a second HIV RNA level; or a HIV RNA level > 200 copies/mL after Week 24, confirmed by a second HIV RNA level; or repeated HIV RNA level ≥ 50 copies/mL after Week 48; or a HIV RNA level ≥ 400 copies/mL confirmed by a second HIV RNA level of ≥ 400 copies/mL at any time in a subject who had previously achieved a plasma HIV RNA level < 50 copies/mL; or discontinued due to "lack of efficacy".

Rapporteur's comment:
The selection of ATV dose regimen was based on a population modelling and simulation study based upon the observed data from study AI424020. These doses are expected to achieve exposures considered close to that of adults.

Although considered as secondary endpoints, PK data are deemed critical besides safety data and should be comparable to historical adults PK values to conclude on the adequacy of selected ATV/RTV doses.

As the primary endpoint concerns safety issue, the sample size was determined as such enabling detection of common AEs.

The backbone consisted in two approved NRTIs for paediatric use (excepted tenofovir), i.e. zidovudine, lamivudine, stavudine, abacavir and didanosine.

Of note in parallel of PRINCE 1 study, the PRINCE 2 study is currently ongoing, with similar objectives, endpoints, investigational product (IP) formulations, background therapy and study population, excepted that children from 3 months to < 7 years 6 months of age were included.

Results

- Recruitment/ Number analysed

Eighty-two subjects were enrolled, and 56 subjects (68%) were treated: 21 in the group 5-<10 kg, 19 in the group 10-<15 kg, and 16 in the group 15-<25 kg. Reasons for not being treated were that the subject no longer met study criteria (23 subjects [28%]), other reason (2 subjects [2%]), and subject withdrew consent (1 subject [1%]).

Among the 56 treated subjects, 46 subjects (82%) completed the Stage 1, and 9 subjects (16%) discontinued ATV powder before Week 48. The causes of premature discontinuation were AEs (n = 5), lack of efficacy (n = 2), withdrew consent (n = 1) and subject no longer meets study criteria (n = 1). Additionally, one subject discontinued ATV powder after Stage 1 due to poor/non-compliance.

Among the 45 subjects entered Stage 2, 4 subjects were switched to ATV capsules prior to Week 48.

	B/L Weight 5 - < 10 kg	B/L Weight 10 - < 15 kg	B/L Weight 15 - < 25 kg	Combined 10 - < 25 kg	TOTAL
TREATED	21	19	16	35	56
COMPLETED STAGE 1 TREATMENT PERIOD	17 (81.0)	14 (73.7)	15 (93.8)	29 (82.9)	46 (82.1)
DID NOT COMPLETE STAGE 1 TREATMENT PERIOD	4 (19.0)	5 (26.3)	1 (6.3)	6 (17.1)	10 (17.9)
DISCONTINUED ATV POWDER BEFORE WEEK 48	4 (19.0)	4 (21.1)	1 (6.3)	5 (14.3)	9 (16.1)
ADVERSE EVENT	4 (19.0)	1 (5.3)	0	1 (2.9)	5 (8.9)
SUBJECT WITHDREW CONSENT	0	0	1 (6.3)	1 (2.9)	1 (1.8)
PREGNANCY	0	0	0	0	0
LOST TO FOLLOW-UP	0	0	0	0	0
ADMINISTRATIVE REASON BY SPONSOR	0	0	0	0	0
DEATH	0	0	0	0	0
SUBJ REQUEST TO DISCONTINUE STUDY TRT	0	0	0	0	0
SUBJECT NO LONGER MEETS STUDY CRITERIA	0	0	0	0	0
LACK OF EFFICACY	0	2 (10.5)	0	2 (5.7)	2 (3.6)
POOR/NON-COMPLIANCE	0	1 (5.3)	0	1 (2.9)	1 (1.8)
OTHER	0	0	0	0	0
DISCONTINUED ATV POWDER AT OR AFTER WEEK 48	0	1 (5.3)	0	1 (2.9)	1 (1.8)
ADVERSE EVENT	0	0	0	0	0
SUBJECT WITHDREW CONSENT	0	0	0	0	0
PREGNANCY	0	0	0	0	0
LOST TO FOLLOW-UP	0	0	0	0	0
ADMINISTRATIVE REASON BY SPONSOR	0	0	0	0	0
DEATH	0	0	0	0	0
SUBJ REQUEST TO DISCONTINUE STUDY TRT	0	0	0	0	0
SUBJECT NO LONGER MEETS STUDY CRITERIA	0	0	0	0	0
LACK OF EFFICACY	0	0	0	0	0
POOR/NON-COMPLIANCE	0	1 (5.3)	0	1 (2.9)	1 (1.8)
OTHER	0	0	0	0	0
SUBJECTS CONTINUING IN THE STUDY (%)	16 (76.2)	14 (73.7)	15 (93.8)	29 (82.9)	45 (80.4)
NEXT PHASE ENTERED: STAGE 2	16 (76.2)	14 (73.7)	11 (68.8)	25 (71.4)	41 (73.2)
TRANSITION TO CAPSULE STAGE 2	0	0	4 (25.0)	4 (11.4)	4 (7.1)
OFF-TREATMENT FOLLOW UP	0	0	0	0	0
SUBJECTS NOT CONTINUING IN THE STUDY* (%)	5 (23.8)	5 (26.3)	1 (6.3)	6 (17.1)	11 (19.6)

Rapporteur's comment:
The rate of discontinuation at Week 48 is low (16%), especially for a paediatric population, which suggest a good tolerance of ATV powder.

- Baseline data

  - *Demographic characteristics*

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 from South Africa (68%).

- *Disease characteristics*

Thirty-four subjects (61%) were ARV naïve. The overall median HIV RNA was 5 log10 c/mL and the majority of subjects had HIV RNA > 100,000 c/mL (57%). Overall median CD4 count was 1,004 cells/mm^3.

	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
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)

At baseline, 23 subjects (41%) had abnormal ECG findings. Overall, the most common abnormal findings were sinus tachycardia (10 subjects [18%]), other rhythm abnormalities (8 subjects [14%]), left axis deviation (7 subjects [13%]), and right axis deviation (3 subjects [5%]).

***Rapporteur's comment**:*
The study's population is rather heterogeneous with 61% ARV naïve and 39% ARV experienced subjects.
It could be noted that unlike the two other doses groups, subjects weighing 15-<25 kg had lower baseline HIV-1 RNA level and CD4+ cells count. As expected more children in the lowest weight band had high level of viremia.

- *NRTI background therapy*

Among the 56 subjects receiving ATV powder + RTV, the NRTIs co-administered were abacavir (n = 46), lamivudine (n = 41), zidovudine (n = 21), stavudine (n = 4) and didanosine (n = 2).

- *Compliance*

According to exposure data, most subjects were compliant with the dosing schedule.

Table 6.1-2: Average Daily Dose by Drug - Treated Subjects

Drug (mg)	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
ATAZANAVIR POWDER					
N	21	19	16	35	56
MEAN	162.61	210.70	247.43	227.49	203.16
MEDIAN	163.58	202.23	250.00	231.75	200.00
MIN , MAX	146.0, 183.6	196.8, 246.9	223.5, 250.0	196.8, 250.0	146.0, 250.0
Q1 , Q3	150.00, 175.15	200.00, 221.26	249.23, 250.00	200.00, 250.00	169.49, 246.96
STANDARD DEVIATION	13.598	15.654	6.871	22.254	37.122
ATAZANAVIR CAPSULES					
N	0	0	7	7	7
MEAN			176.66	176.66	176.66
MEDIAN			186.36	186.36	186.36
MIN , MAX			150.0, 200.0	150.0, 200.0	150.0, 200.0
Q1 , Q3			150.00, 200.00	150.00, 200.00	150.00, 200.00
STANDARD DEVIATION			25.321	25.321	25.321
RITONAVIR ORAL SOLUTION					
N	21	19	16	35	56
MEAN	79.46	77.17	78.94	77.98	78.54
MEDIAN	80.00	80.00	80.00	80.00	80.00
MIN , MAX	74.7, 80.0	40.0, 80.0	68.9, 86.6	40.0, 86.6	40.0, 86.6
Q1 , Q3	79.62, 80.00	78.10, 80.00	78.96, 80.00	78.29, 80.00	79.01, 80.00
STANDARD DEVIATION	1.200	9.087	3.878	7.152	5.715
RITONAVIR CAPSULES					
N	0	0	7	7	7
MEAN			100.00	100.00	100.00
MEDIAN			100.00	100.00	100.00
MIN , MAX			100.0, 100.0	100.0, 100.0	100.0, 100.0
Q1 , Q3			100.00, 100.00	100.00, 100.00	100.00, 100.00
STANDARD DEVIATION			0.000	0.000	0.000

Rapporteur's comment:
It is difficult to interpret the compliance data with mean/median value of average daily dose. An expression of results including percentage of subjects achieving 90% to 100%, 80% to 90%, etc… of ATV therapy would be preferable to assess compliance of this paediatric population and would better compare the compliance of subjects in each group. Moreover, the reasons of non-compliance should be explored in order to detect potential inconveniences with powder formulation.

- Efficacy results

  - *Virologic response*

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**, based on Snapshot algorithm.

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

In ARV-experienced and ARV-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.

Treatment Outcomes	ARV Experienced N=20	ARV Naive N=34	Total N=54
HIV RNA < 50 c/mL			
VIROLOGIC SUCCESS	12 (60.0)	21 (61.8)	33 (61.1)
VIROLOGIC FAILURE	5 (25.0)	11 (32.4)	16 (29.6)
HIV RNA >= 50c/mL	4 (20.0)	8 (23.5)	12 (22.2)
DISCONTINUED DUE TO VIROLOGIC FAILURE	1 (5.0)	1 (2.9)	2 (3.7)
DISCONTINUED DUE TO OTHER REASONS AND HIV >= 50 c/mL AT TIME OF DISCONTINUATION	0	2 (5.9)	2 (3.7)
OBT CHANGED	0	0	0
NO VIROLOGIC DATA IN ANALYSIS WEEK WINDOW	3 (15.0)	2 (5.9)	5 (9.3)
DISCONTINUED DUE TO AE OR DEATH	3 (15.0)	2 (5.9)	5 (9.3)
DISCONTINUED DUE TO OTHER REASONS AND HIV RNA < 50c/mL AT TIME OF DISCONTINUATION	0	0	0
MISSING DATA IN WINDOW BUT ON TREATMENT	0	0	0
HIV RNA < 400 c/mL			
VIROLOGIC SUCCESS	15 (75.0)	25 (73.5)	40 (74.1)
VIROLOGIC FAILURE	2 (10.0)	7 (20.6)	9 (16.7)
HIV RNA >= 400c/mL	1 (5.0)	4 (11.8)	5 (9.3)
DISCONTINUED DUE TO VIROLOGIC FAILURE	1 (5.0)	1 (2.9)	2 (3.7)
DISCONTINUED DUE TO OTHER REASONS AND HIV >= 400 c/mL AT TIME OF DISCONTINUATION	0	2 (5.9)	2 (3.7)
OBT CHANGED	0	0	0
NO VIROLOGIC DATA IN ANALYSIS WEEK WINDOW	3 (15.0)	2 (5.9)	5 (9.3)
DISCONTINUED DUE TO AE OR DEATH	3 (15.0)	2 (5.9)	5 (9.3)
DISCONTINUED DUE TO OTHER REASONS AND HIV RNA < 400c/mL AT TIME OF DISCONTINUATION	0	0	0
MISSING DATA IN WINDOW BUT ON TREATMENT	0	0	0

Based on observed values analysis, 89% of subjects had HIV RNA < 400 c/mL and 73% of subjects had HIV RNA < 50 c/mL at Week 48. As observed with Snapshot algorithm, the proportion of subjects with HIV RNA < 400 c/mL (94% and 86%, respectively) and < 50 c/mL (75% and 72%, respectively) was similar in ARV-experienced and -naive subjects.

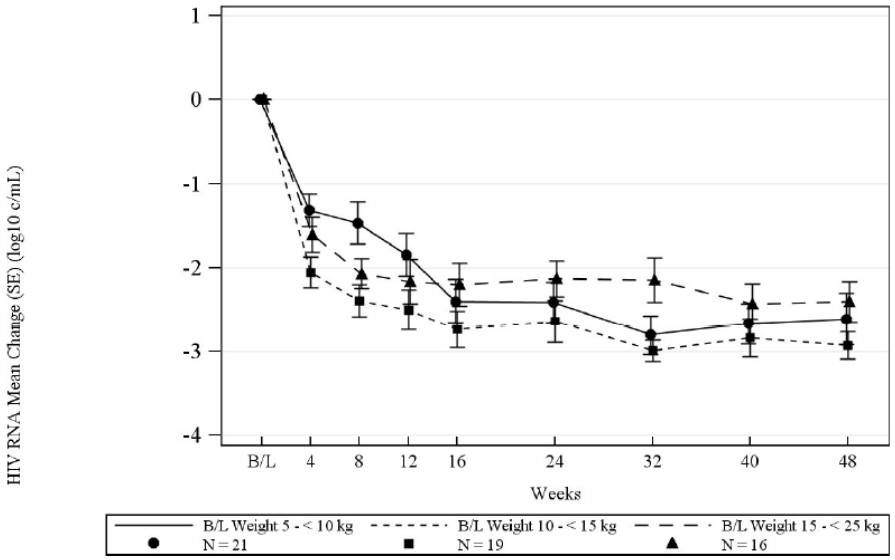
***Rapporteur's comment**:*
Efficacy results of PRINCE 1 study could be compared to the two pivotal studies (AI424-138, AI424-045) in adults and a prior study in older children (PACTG 1020A):

Study	AI424-138	AI424-045	PACTG 1020A		PRINCE I	
Population	ARV naïve adults	ARV experienced adults	ARV naïve children	ARV experienced children	ARV naïve children	ARV experienced children
Age	≥ 18 years	≥ 18 years	6 years to 18 years	6 years to 18 years	3 months to 6 years	3 months to 6 years
N	440	120	16	25	20	34
HIV RNA < 50 c/mL at Week 48	78%	36%	81%	24%	60%	62%
HIV RNA < 400 c/mL at Week 48	86%	53%	88%	32%	75%	74%

Results in PACTG were very low in ARV experienced children 6 to 18 years of age (but finally close to those in adults). In the present study similar level of virologic suppression is observed be the children naïve or experienced, however the level of treatment experience is likely very limited in this young population not including adolescents.
When all subjects were considered a lower rate of virologic success is observed in subjects weighing 5 to 10 kg (48% and 67% had a viral load < 50 c/mL and < 400 c/mL, respectively, versus 70% and 79% in subjects weighing 10 to 25 kg), however, the 5-10 kg weight group (youngest children) had (as expected) higher level of viremia (85%>100 000 copies/ml). Overall, these results will have to be put in perspective with the to-be-submitted PK study report.

- *HIV RNA changes from baseline*

At Week 48, the overall mean (median) change from baseline in HIV RNA was -2.66 (-3.06) log10 c/mL. This value was -2.61 (-3.31), -2.93 (-3.31), and -2.40 (-2.59) log10 c/mL in the 5-<10 kg, 10-<15 kg, and 15-<25 kg groups, respectively, and was -2.90 (-3.25) log10 c/mL and -2.52 (-2.89) log10 c/mL in ARV-experienced and -naive subjects, respectively.



Rapporteur's comment:
The HIV RNA mean change from baseline is similar between the 3 weight groups.

- *CD4 cell count changes from baseline*

At Week 48, the overall mean (median) change from baseline in CD4 cell count was 397 (363) cells/mm3. This value was 550 (491), 225 (274), and 374 (363) cells/mm3 in the 5-<10 kg, 10-<15 kg, and 15-<25 kg groups, respectively, and was 182 (213) cells/mm3 and 493 (520) cells/mm3 in ARV-experienced and -naive subjects, respectively.

- *Resistance*

Through Week 48, 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 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-<20 kg weight band developed I72I/V substitution, and 1 ARV-naive subject in the 5-<10 kg weight band developed L19I/R.

- Safety results

- *Adverse events*

Through Week 48, the majority of subjects (93%) had AEs. The most common AEs were upper respiratory tract infection, diarrhea, and vomiting. Twenty-one subjects (38%) on ATV powder had related AEs, and the most common AEs were hyperbilirubinemia and vomiting.

Adverse Event Summary
All Grades Related on ATV Powder through Week 48
Treated Subjects

System Organ Class (%) Preferred Term (%)	B/L Weight 5 - < 10 kg N = 21	B/L Weight 10 - < 15 kg N = 19	B/L Weight 15 - < 25 kg N = 16
TOTAL SUBJECTS WITH AN EVENT	10 (47.6)	6 (31.6)	5 (31.3)
GASTROINTESTINAL DISORDERS	4 (19.0)	3 (15.8)	2 (12.5)
VOMITING	3 (14.3)	2 (10.5)	0
DIARRHOEA	2 (9.5)	0	1 (6.3)
ABDOMINAL PAIN	0	0	1 (6.3)
GASTRITIS	0	1 (5.3)	0
HEPATOBILIARY DISORDERS	3 (14.3)	2 (10.5)	2 (12.5)
HYPERBILIRUBINAEMIA	3 (14.3)	2 (10.5)	1 (6.3)
JAUNDICE	0	0	2 (12.5)
INVESTIGATIONS	1 (4.8)	2 (10.5)	1 (6.3)
BLOOD BILIRUBIN INCREASED	0	0	1 (6.3)
ELECTROCARDIOGRAM QT PROLONGED	0	1 (5.3)	0
LIPASE INCREASED	0	1 (5.3)	0
TRANSAMINASES INCREASED	1 (4.8)	0	0
METABOLISM AND NUTRITION DISORDERS	3 (14.3)	0	1 (6.3)
HYPERCHOLESTEROLAEMIA	2 (9.5)	0	0
DECREASED APPETITE	1 (4.8)	0	0
HYPERTRIGLYCERIDAEMIA	0	0	1 (6.3)

Eight subjects (14%) had Grade 2 - 4 related AEs, of whom 4 subjects with hyperbilirubinaemia.

Rapporteur's comment:
The most common AEs related to ATV (hyperbilirubinemia and vomiting) are similar than those reported in pivotal studies. No new AE is reported.

- *Serious adverse events and deaths*

Through Week 48, eleven subjects (20%) had SAEs while on ATV powder.

System Organ Class (%) Preferred Term (%)	B/L Weight 5 - < 10 kg N = 21	B/L Weight 10 - < 15 kg N = 19	B/L Weight 15 - < 25 kg N = 16
TOTAL SUBJECTS WITH AN EVENT	5 (23.8)	2 (10.5)	4 (25.0)
INFECTIONS AND INFESTATIONS	4 (19.0)	0	2 (12.5)
HERPES ZOSTER	0	0	2 (12.5)
BRONCHOPNEUMONIA	1 (4.8)	0	0
GASTROENTERITIS	1 (4.8)	0	0
LYMPHADENITIS BACTERIAL	1 (4.8)	0	0
MENINGITIS	1 (4.8)	0	0
PNEUMONIA	1 (4.8)	0	0
BLOOD AND LYMPHATIC SYSTEM DISORDERS	1 (4.8)	0	1 (6.3)
NEUTROPENIA	1 (4.8)	0	0
THROMBOCYTOPENIA	0	0	1 (6.3)
INVESTIGATIONS	0	1 (5.3)	1 (6.3)
ELECTROCARDIOGRAM QT PROLONGED	0	1 (5.3)	0
TRANSAMINASES INCREASED	0	0	1 (6.3)
NERVOUS SYSTEM DISORDERS	0	0	1 (6.3)
FEBRILE CONVULSION	0	0	1 (6.3)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	0	1 (5.3)	0
BRONCHIECTASIS	0	1 (5.3)	0

The only SAE considered related to the study therapy by the investigators was ECG QT prolonged. No deaths were reported.

- *Adverse events leading to discontinuation*

Five subjects (9%) had AEs leading to discontinuation of study therapy while on ATV powder: 4 subjects in the 5-<10 kg group (respectively meningitis, pulmonary tuberculosis, increased transaminases and lymphadenitis) and one subject in the 10-<15 kg group (ECG QT prolonged). These discontinuations were considered related to the study therapy by the investigators for 3 subjects (increased transaminases, lymphadenitis and ECG QT prolonged).

Rapporteur's comment:
The higher rate of discontinuation in the 5-<10 kg group is driven by infection in this more vulnerable strata.

- *Adverse events of special interest*

Hyperbilirubinemia and jaundice: Seven subjects (13%) on ATV powder had hyperbilirubinemia-related events (3 subjects in the 5-<10 kg group and 2 subjects each in the 10-<15 kg and 15-<25 kg groups). All of these events were considered related to the study therapy by the investigators.

Cardiac abnormalities: Three subjects (5%) on ATV powder had cardiac disorders (ECG abnormal and ECG QT prolonged in 1 subject each in the 10-<15 kg group and first degree AV block in 1 subject in the 15-<25 kg group). Two of these cardiac events were considered related to the study therapy by the investigators.

Rash: Eight subjects (14%) on ATV powder had rash events of special interest (4, 1, and 3 subjects in the 5-<10 kg, 10-<15 kg and 15-<25 kg groups, respectively). None of these events was considered related to the study therapy by the investigators.

Renal toxicity: Two subjects (4%) on ATV powder had renal toxicity events (proteinuria in 1 subject in the 5-<10 kg group and dysuria in 1 subject in the 10-<15 kg group). 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.

Lactic acidosis: Seven subjects (13%) had potential lactic acidosis syndrome or symptomatic hyperlactatemia events (6 in the 5-<10 kg and 1 in the 10-<15 kg group). None of these events was considered related to the study therapy by the investigators.

- *Laboratory evaluations*

Lab Test Description Toxicity Grade	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
HEMATOLOGY					
HEMOGLOBIN	N=20	N=17	N=15	N=32	N=52
GRADE 3-4	2 (10.0)	3 (17.6)	0	3 (9.4)	5 (9.6)
NEUTROPHILS (ABSOLUTE)	N=20	N=17	N=15	N=32	N=52
GRADE 3-4	3 (15.0)	2 (11.8)	0	2 (6.3)	5 (9.6)
LIVER FUNCTION TESTS					
ALT/SGPT	N=20	N=18	N=15	N=33	N=53
GRADE 3-4	5 (25.0)	0	1 (6.7)	1 (3.0)	6 (11.3)
AST/SGOT	N=20	N=18	N=15	N=33	N=53
GRADE 3-4	1 (5.0)	0	0	0	1 (1.9)
ALKALINE PHOSPHATASE	N=20	N=18	N=15	N=33	N=53
GRADE 3-4	0	1 (5.6)	0	1 (3.0)	1 (1.9)
TOTAL BILIRUBIN	N=20	N=18	N=15	N=33	N=53
GRADE 3-4	2 (10.0)	0	3 (20.0)	3 (9.1)	5 (9.4)
SERUM CHEMISTRIES					
AMYLASE	N=20	N=18	N=15	N=33	N=53
GRADE 3-4	8 (40.0)	5 (27.8)	1 (6.7)	6 (18.2)	14 (26.4)
LIPASE	N=20	N=18	N=15	N=33	N=53
GRADE 3-4	0	1 (5.6)	1 (6.7)	2 (6.1)	2 (3.8)
URIC ACID	N=20	N=18	N=15	N=33	N=53
GRADE 3-4	0	0	1 (6.7)	1 (3.0)	1 (1.9)

- *ECG*

Through Week 48, mean heart rate decreased, PR interval increased, and QTC (Fredericia) increased in all weight bands on ATV powder. The mean changes were observed at later time points in the 5 - < 10 kg group than in the other 2 weight bands.

Rapporteur's comment:
The safety profile of ATV powder is comparable to that seen with current ATV hard capsules.

- Pharmacokinetic results

PK data will be analysed in a separate pharmacokinetic (PK) report after completion of the other paediatric study (AI424451 - PRINCE 2 study).

Rapporteur's overall conclusion and recommendation

Overall conclusion

AI424397 – PRINCE 1 is a Phase IIIb open-label study to evaluate the safety, efficacy and PK of ATV powder associated to RTV liquid and in combination to 2 NRTIs. Subjects were ARV-naïve or –experienced children **3 months to < 6 years of age** and were divided into three weight groups: from 5 to <10 kg, from 10 to <15 kg and from 15 to <25 kg. Each group received a different dose of ATV powder (150 mg, 200 mg or 250 mg, respectively) plus RTV 80 mg and two NRTIs during 48 weeks.

The study's population is rather heterogeneous with 61% ARV-naïve and 39% ARV-experienced subjects, similar number of males and females, 57% of Black/African American subjects, and a wide range of children age (3 to 65 months).

It is difficult to interpret the compliance data as presented in average daily dose with mean/median values. An expression of results including percentage of subjects achieving 90% to 100%, 80% to 90%, etc… of ATV therapy would be preferable to assess compliance of this paediatric population and would better compare the compliance of subjects in each group. Moreover, the reasons of non-compliance should be explored in order to detect potential inconveniences with powder formulation.

Safety data derived from this study in this young population did not raise signal towards a differential safety profile in this population as compared to adults and older children. Hyperbilirubinemia and gastrointestinal disorders are the most frequently reported AEs. Weight subgroup analyses provide higher rate of discontinuation due to AE in subjects weighing 5 to 10 kg, but partly driven by infection in this more vulnerable weight strata.

As regards efficacy data, 74% of subjects had HIV RNA < 400 c/mL and 61% of subjects had HIV RNA < 50 c/mL at Week 48. While results from a prior study in children (PACTG1020A) show very low virologic suppression in ARV experienced children 6 to 18 years of age, in the present study, similar level of virologic suppression (around 60% <50 copies/ml) is observed be the children ARV naïve or experienced, likely translating the limited level of treatment experience in this young population not including adolescents.

When all subjects were considered, a lower rate of virologic success is observed in subjects weighing 5 to 10 kg (48% and 67% had a viral load < 50 c/mL and < 400 c/mL, respectively, versus 70% and 79% in subjects weighing 10 to 25 kg), however, the 5-10 kg weight group (youngest children) had (as expected) higher level of viremia (85%>100 000 copies/ml).

Overall, efficacy and safety results will have to be put in perspective with the to-be-submitted PK study report. PK data are expected in order to assess PK profile of the new formulation ATV powder, and to compare results with adults historical values.

Recommendation

☒ **Fulfilled** (clarification on compliance data could be submitted in parallel to forthcoming submissions)

In the forthcoming submission of the PK report of PRINCE 1 and PRINCE 2 study results the MAH will have to provide the presentation of the PRINCE 1 compliance data by expressing the results in percentage of subjects achieving 90% to 100%, 80% to 90%, etc… of ATV therapy received during the study. If available, the reasons of non-compliance should be provided. PK data will be put in perspective with the compliance data.

☐ Not fulfilled

Annex I. Line listing of all the studies included in the development program

Clinical studies

Product Name: Reyataz Active substance: atazanavir

Study title	Study number	Date of completion	Date of submission of final study report
PRINCE 1	AI424397	Stage 1: 04/10/2012 Stage 2: ongoing (cut-off 03/12/2012)	12/03/2013
PRINCE 2	AI424451	ongoing	Planned July 2015