London, 9 November 2017
EMA/779741/2017
Committee for Medicinal Products for Human Use (CHMP)

Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

Reyataz

atazanavir / atazanavir sulfate

Procedure no: EMEA/H/C/000494/P46/086

Note

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

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1. Introduction

The MAH submitted the completed paediatric study AI424452 for Reyataz hard capsules, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

Study AI424452 started in November 2012 and completed on 20-Feb-2017. Study AI424452 was a post-approval commitment safety study for the US FDA to assess the safety of ATV capsules boosted with RTV (ATV/RTV) administered with an optimized nucleoside reverse transcriptase inhibitor (NRTI) background therapy in patients ≥ 6 to < 18 years of age and weighing ≥ 15 kg. The study was to provide confirmatory safety data through 24 weeks of study treatment for ATV/RTV at the recommended doses approved in the United States (US) in 2008 and the European Union (EU) in 2010 (ATV 150, 200 and 300 mg, each with RTV 100 mg, for 15 to < 20 kg, 20 to < 40 kg, and ≥ 40 kg weight groups, respectively). Atazanavir paediatric dosing recommendations were later revised in the EU in 2016 and in the US in 2017. The approved dosing recommendations used in Study AI424452 were those in effect at the time of the study and therefore are not consistent with the current posology of Reyataz in US and EU (see below the current approved posology).

Reyataz hard capsules:

Table 1. Dose for paediatric patients (6 years to less than 18 years of age and weighing at least 15 kg) for REYATAZ capsules with ritonavir

Body Weight (kg)	REYATAZ once daily dose	ritonavir once daily dose[a]
15 to less than 35	200 mg	100 mg
at least 35	300 mg	100 mg

a Ritonavir capsules, tablets or oral solution.

Reyataz oral powder:

Table 2. Dose of REYATAZ oral powder with ritonavir for paediatric patients (at least 3 months of age and weighing at least 5 kg)

Body weight (kg)	REYATAZ once daily dose	ritonavir once daily dose
at least 5 to less than 15	200 mg (4 sachets[b])	80 mg[c]
at least 15 to less than 35	250 mg (5 sachets[b])	80 mg[c]
at least 35	300 mg (6 sachets[b])	100 mg[d]

a The same recommendations regarding the timing and maximum doses of concomitant proton pump inhibitors and H2- receptor antagonists in adults also apply to paediatric patients (see section 4.5).

b Each sachet contains 50 mg of atazanavir.

c Ritonavir oral solution.

d Ritonavir oral solution or capsule/tablet.

2.2. Information on the pharmaceutical formulation used in the study

In this study, all subjects received ATV capsules boosted with RTV tablets or capsules administered according approved paediatric dosing recommendations at the time of the study (ATV/RTV 150/100, 200/100 and 300/100 mg for 15 to < 20 kg, 20 to < 40 kg, and ≥ 40 kg weight groups, respectively).

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for study AI424452. This is a prospective, single-arm, open-label study evaluating the safety of ATV capsules boosted with RTV capsules or tablets administered once daily (QD) with an optimized background therapy of 2 NRTIs in HIV-infected antiretroviral (ARV)-naive or –experienced paediatric subjects ≥ 6 to < 18 years of age. Subjects were enrolled from South Africa, South America countries, US and Russia.

2.3.2. Clinical study

Study AI424452

Methods

Objective

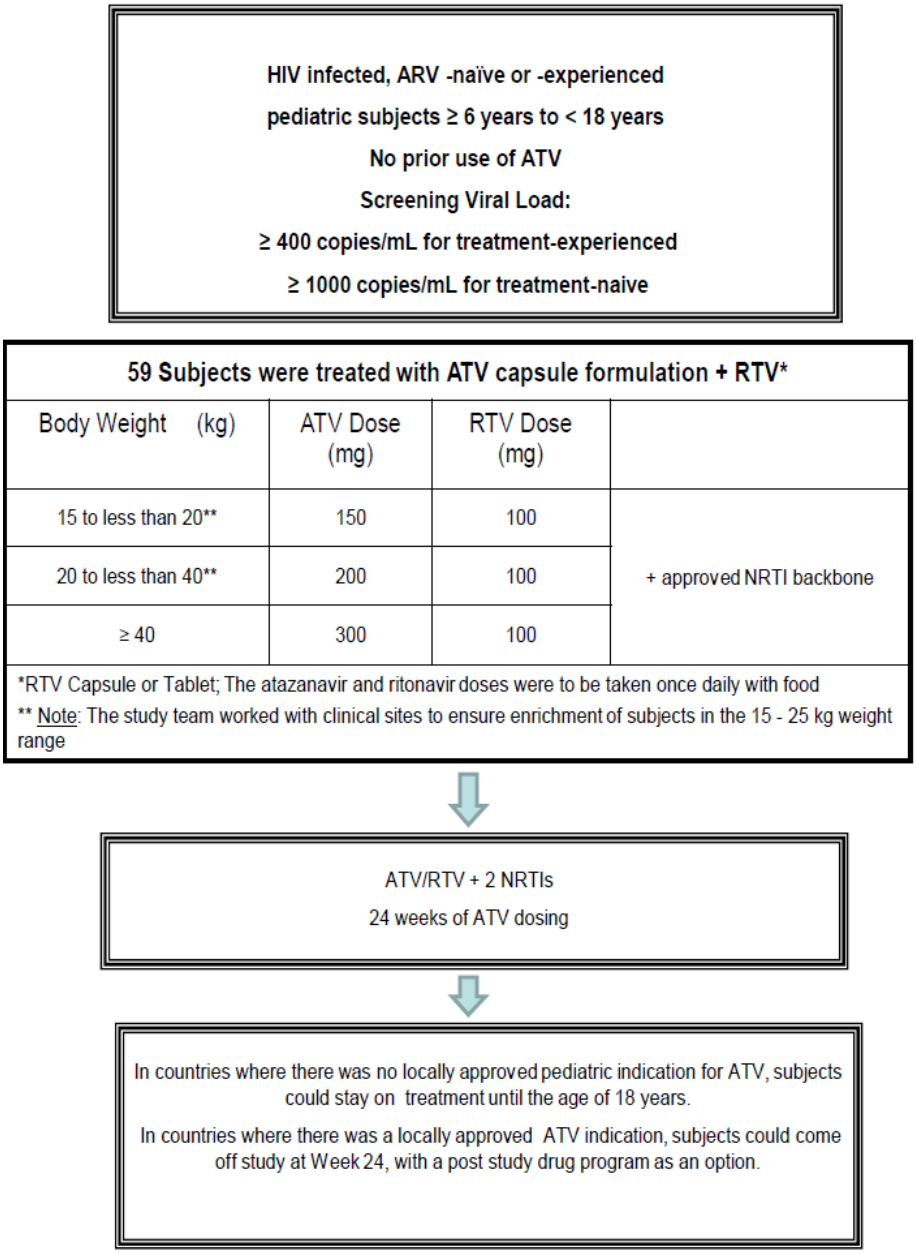
Primary objective was to assess the safety and tolerability of ATV capsule boosted with RTV-based regimens in paediatric subjects ≥ 6 years to < 18 years of age dosed for 24 weeks.

Study design

This is a Phase 4 ongoing prospective single-arm, open-label, multicenter study to evaluate the safety of ATV capsule boosted with RTV capsules or tablets QD with an optimized background therapy of 2 NRTIs in HIV-infected, ARV-naive and -experienced pediatric subjects ≥ 6 years to < 18 years of age, and ≥ 15 kg.

Treatment-experienced subjects were defined by previous exposure to ARV drugs through either prior treatment for their HIV infection, or through post-natal treatment with ≥ 1 ARV as part of the prevention of mother-to-child transmission. For the purposes of this study, subjects exposed to ARVs in utero or intra-partum were eligible for the study, but were considered treatment naive. Eligible subjects were required to have a screening HIV viral load of ≥ 1000 copies/mL (ARV-naive) or ≥ 400 copies/mL (ARV-experienced). Subjects at screening were to have genotypic sensitivity (ARV-naïve subjects) or genotypic and phenotypic sensitivity (ARV-experienced subjects) to ATV and at least 2 NRTIs approved for pediatric use per the local country label.

All subjects received ATV capsules boosted with RTV tablets or capsules administered according approved pediatric dosing recommendations at the time of the study (ATV/RTV 150/100, 200/100 and 300/100 mg for 15 to < 20 kg, 20 to < 40 kg, and ≥ 40 kg weight groups, respectively). The NRTI backbone consisted of 2 NRTIs locally approved for pediatric use at doses specified in the country's label(s). Subjects were dosed for a minimum of 24 weeks. However, in countries where there is no locally approved pediatric indication for ATV capsule, subjects may continue on study treatment and have regular 12-week study visits.



Outcomes/endpoints

Safety variables included deaths, adverse events (AEs) (serious and nonserious), including Other Significant Adverse Events and Centers for Disease Control and Prevention (CDC) Class C acquired immunodeficiency syndrome (AIDS) events, concomitant medication use, laboratory measurements, and electrocardiogram (ECG) results. Class C AIDS events were assessed only through Week 24.

Statistical Methods

No statistical comparisons between weight bands were conducted, and only summary statistics are presented. Categorical variables are summarized with counts and percents or with proportions (number with event divided by number evaluable) and percents. Continuous variables are summarized with univariate statistics.

Results

Recruitment/Number analysed

Fifty-nine subjects were treated. Fifty-three (89.8%) subjects completed 24 weeks of study treatment. Forty-seven (79.7%) subjects continued in the study after Week 24, and 30 of them completed the study.

Table 3. Summary of End of Study Subject Status - Treated Subjects

	Baseline Weight			
	15 - < 20 kg	20 -< 40 kg	>=40 kg	Total
TREATED	3	33	23	59
PHASE 1 (Week 24)				
COMPLETED PHASE 1 (WEEK 24) TREATMENT PERIOD	3 (100.0)	30 (90.9)	20 (87.0)	53 (89.8)
DID NOT COMPLETE PHASE 1 TREATMENT PERIOD	0	3 (9.1)	3 (13.0)	6 (10.2)
REASONS FOR NOT COMPLETING PHASE 1	0	3 (9.1)	3 (13.0)	6 (10.2)
ADVERSE EVENT	0	0	1 (4.3)	1 (1.7)
SUBJECT NO LONGER MEETS STUDY CRITERIA	0	2 (6.1)	0	2 (3.4)
LACK OF EFFICACY	0	1 (3.0)	1 (4.3)	2 (3.4)
POOR/NON-COMPLIANCE	0	0	1 (4.3)	1 (1.7)
CONTINUING IN THE STUDY AFTER PHASE 1	3 (100.0)	27 (81.8)	17 (73.9)	47 (79.7)
NOT CONTINUING THE STUDY [1]	0	6 (18.2)	6 (26.1)	12 (20.3)
END OF STUDY				
COMPLETED THE STUDY	2 (66.7)	15 (45.5)	13 (56.5)	30 (50.8)
DID NOT COMPLETE THE STUDY	1 (33.3)	13 (39.4)	4 (17.4)	18 (30.5) [2]
REASONS FOR NOT COMPLETING THE STUDY	1 (33.3)	13 (39.4)	4 (17.4)	18 (30.5)
ADVERSE EVENT	0	1 (3.0)	1 (4.3)	2 (3.4)
DEATH	0	0	1 (4.3)	1 (1.7)
SUBJ REQUEST TO DISCONTINUE STUDY TRT	0	1 (3.0)	0	1 (1.7)
LACK OF EFFICACY	0	7 (21.2)	1 (4.3)	8 (13.6)
POOR/NON-COMPLIANCE	1 (33.3)	4 (12.1)	1 (4.3)	6 (10.2)

[1] Can include subjects who either completed or discontinued phase 1

[2] Note that Table 1 reports incorrectly that 18 subjects (30.5%) did not complete the study. However, 1 subject is counted in error in the end of study analysis as continuing after Week 24 and discontinuing due to lack of efficacy This subject completed Week 24 but did not continue after Week 24 due to lack of efficacy

Baseline data

Most subjects (50.8%) were female; 59.3% were Black/African American, and 57.6% were from South Africa. Of the 59 treated subjects, 32 (54.2%) were ARV-naive and 27 (45.8%) were ARV-experienced. The overall median baseline HIV RNA was 4.05 log10 c/mL; 15% of subjects had HIV RNA > 100,000 c/mL. The overall median CD4 count was 390 cells/mm3, and the median CD4% was 19%.

Table 4. Demographic Characteristics Summary - Treated Subjects

	B/L Weight 15 - < 20 kg N = 3	B/L Weight 20 - < 40 kg N = 33	B/L Weigh >=40 kg N = 23	Total N = 59
AGE AT BASELINE (YEARS)				
N	3	33	23	59
MEAN	6.0	10.7	14.7	12.0
MEDIAN	6.0	11.0	15.0	12.0
MIN, MAX	6, 6	6, 16	11, 17	6, 17
Q1, Q3	6.0, 6.0	9.0, 13.0	13.0, 16.0	10.0, 15.0
STANDARD DEVIATION	0.00	2.67	1.72	3.26
GENDER (%)				
MALE	1 (33.3)	16 (48.5)	12 (52.2)	29 (49.2)
FEMALE	2 (66.7)	17 (51.5)	11 (47.8)	30 (50.8)
RACE (%)				
WHITE	1 (33.3)	5 (15.2)	4 (17.4)	10 (16.9)
BLACK/AFRICAN AMERICAN	2 (66.7)	24 (72.7)	9 (39.1)	35 (59.3)
OTHER	0	4 (12.1)	10 (43.5)	14 (23.7)
ETHNICITY (%)				
HISPANIC/LATINO	0	1 (3.0)	2 (8.7)	3 (5.1)
NOT HISPANIC/LATINO	1 (33.3)	2 (6.1)	2 (8.7)	5 (8.5)
NOT REPORTED	2 (66.7)	30 (90.9)	19 (82.6)	51 (86.4)
GEOGRAPHIC REGION (%)				
AFRICA	2 (66.7)	24 (72.7)	8 (34.8)	34 (57.6)
EUROPE	0	1 (3.0)	0	1 (1.7)
NORTH AMERICA	1 (33.3)	0	3 (13.0)	4 (6.8)
SOUTH AMERICA	0	8 (24.2)	12 (52.2)	20 (33.9)
COUNTRY (%)				
ARGENTINA	0	3 (9.1)	0	3 (5.1)
BRAZIL	0	3 (9.1)	4 (17.4)	7 (11.9)
CHILE	0	1 (3.0)	2 (8.7)	3 (5.1)
MEXICO	1 (33.3)	0	1 (4.3)	2 (3.4)
PERU	0	1 (3.0)	6 (26.1)	7 (11.9)
RUSSIA	0	1 (3.0)	0	1 (1.7)
SOUTH AFRICA	2 (66.7)	24 (72.7)	8 (34.8)	34 (57.6)
UNITED STATES OF AMERICA	0	0	2 (8.7)	2 (3.4)

Table 5. HIV Disease Characteristics Summary at Baseline - Treated Subject

	B/L Weight 15 - < 20 kg N = 3	B/L Weight 20 - < 40 kg N = 33	B/L Weight >=40 kg N = 23	Total N = 59
HIV RNA (LOG10 C/ML)				
N	3	33	23	59
MEAN	3.94	4.05	4.04	4.04
MEDIAN	4.03	4.22	3.75	4.05
MIN, MAX	3.5, 4.2	1.6, 5.5	2.8, 5.8	1.6, 5.8
STANDARD DEVIATION	0.360	1.004	0.847	0.913
HIV RNA CATEGORIES (C/ML) (%)				
<30,000	3(100.0)	19(57.6)	17(73.9)	39(66.1)
30,000 - 100,000	0	8(24.2)	3(13.0)	11(18.6)
> 100,000	0	6(18.2)	3(13.0)	9(15.3)
CD4 COUNT (CELLS/MM^3)				
N	3	33	23	59
MEAN	848.7	373.4	372.1	397.1
MEDIAN	743.0	360.0	411.0	390.0
MIN, MAX	616, 1187	9, 806	16, 621	9, 1187
STANDARD DEVIATION	299.81	210.87	169.65	222.86
CD4 COUNT CATEGORIES (CELLS/MM^3)				
<50	0	1(3.0)	1(4.3)	2(3.4)
50 - < 200	0	7(21.2)	3(13.0)	10(16.9)
200 - < 350	0	8(24.2)	6(26.1)	14(23.7)
350 - < 500	0	9(27.3)	6(26.1)	15(25.4)
500 - < 750	2(66.7)	6(18.2)	7(30.4)	15(25.4)
750 - < 1000	0	2(6.1)	0	2(3.4)
1000 - < 1500	1(33.3)	0	0	1(1.7)
CD4 PERCENT (%)				
N	3	33	23	59
MEAN	25.7	19.1	20.8	20.1
MEDIAN	27.0	19.0	19.0	19.0
MIN, MAX	14, 36	1, 40	3, 41	1, 41
STANDARD DEVIATION	11.06	8.70	8.60	8.74
CD4 PERCENT CATEGORIES (%)				
< 15	1(33.3)	10(30.3)	4(17.4)	15(25.4)
15 - < 25	0	15(45.5)	12(52.2)	27(45.8)
>= 25	2(66.7)	8(24.2)	7(30.4)	17(28.8)
PRIOR ARV USE (%)				
ARV NAIVE	2(66.7)	17(51.5)	13(56.5)	32(54.2)
ARV EXPERIENCED	1(33.3)	16(48.5)	10(43.5)	27(45.8)

PK results

This was a safety study and no PK analyses were provided.

Efficacy results

This was a safety study and no efficacy data were provided.

Safety results

Exposure

The mean time on ATV/RTV treatment at the time of the Week 24 primary analysis was 37, 47, and 38 weeks in the 15 to < 20 kg, 20 to < 40 kg, and ≥ 40 kg weight groups, respectively. By the end of the study, the mean time on ATV/RTV therapy was 109, 102, and 65 weeks in the 15 to < 20 kg, 20 to < 40 kg, and ≥ 40 kg weight groups, respectively. The shorter exposure in the ≥ 40 kg weight group in the end-of-study analysis reflects the fact that subjects in this weight group were older at baseline than the other 2 groups (11 of the 23 subjects in the ≥ 40 kg weight group were at least 16 years of age at baseline) and reached 18 years of age and completed earlier than subjects in the lower (and younger) baseline weight groups.

Lamivudine tablet was the most common medication in the NRTI backbone both at Week 24 (31 subjects) and at the end of the study (33 subjects). Other common medications in the NRTI backbone were abacavir tablets, tenofovir tablets, and zidovudine tablets. The mean daily doses of NRTI medications were consistent with pediatric dose recommendations in the respective product labels.

Overall safety summary

The overall safety profile at Week 24 of ATV capsules boosted with RTV in pediatric subjects ≥ 6 and < 18 years of age was similar to that observed in previous ATV pediatric and adult studies. No safety finding was identified in this pediatric population that had not been reported previously in other pediatric and adult studies of ATV.

Table 6. Summary of On-treatment Safety

	Number of Subjects (%)				
	Week 24				Cumulative through End of Study
	Baseline Weight				
	15- < 20 kg N = 3	20 - < 40 kg N = 33	≥ 40 kg N = 23	Total N = 59	Total N = 59
Adverse events					
AEs Grade 1-4[a]	3 (100.0)	28 (84.8)	21 (91.3)	52 (88.1)	56 (94.9)
AEs Grade 3-4[a]	0	3 (9.1)	5 (21.7)	8 (13.6)	8 (13.6)
Deaths[a]	0	0	0	0	1 (1.7)
SAEs[a]	0	1 (3.0)	3 (13.0)	4 (6.8)	8 (13.6)
Discontinuations due to AEs[a]	0	1 (3.0)	1 (4.3)	2 (3.4)	3 (5.1)
Other Significant AEs[b]					
Hyperbilirubinemia AEs	0	3 (9.1)	10 (43.5)	13 (22.0)	15 (25.4)
Renal toxicity AEs	0	1 (3.0)	0	1 (1.7)	1 (1.7)
Cardiac disorders	0	4 (12.1)	2 (9.7)	6 (10.2)	7 (11.9)
Rash	0	4 (12.1)	3 (13.0)	7 (11.9)	7 (11.9)
CDC Class C AIDS events	0	1 (3.0)	0	1 (1.7)	NA
Lipodystrophy-related AEs	0	0	0	0	0
Lactic acidosis syndrome or symptomatic hyperlactatemia	0	0	0	0	0
Cholelithiasis	0	0	0	0	0
Nephrolithiasis	0	0	0	0	0
Clinical laboratory tests Grade 3-4[a]					
Total bilirubin	0	3 (9.1)	7 (30.4)	10 (16.9)	19 (32.2)
Amylase (total, pancreatic, salivary)	2 (66.7)	9 (27.3)	4 (17.4)	15 (25.4)	17 (28.8)
Albumin	0	0	0	0	3 (5.1)
Neutrophils	0	1 (3.0)	0	1 (1.7)	2 (3.4)
ALT	0	0	1 (4.3)	1 (1.7)	1 (1.7)
Alkaline phosphatase	0	1 (3.0)	0	1 (1.7)	1 (1.7)
Potassium	0	0	0	0	1 (1.7)
Potential DILI[b]	0	0	2 (8.7)	2 (3.4)	2 (3.4)
EKG AEs treatment related Grade 2-4[a]					
Atrioventricular block (Grade 2)	0	1 (3.0)	0	1 (1.7)	1 (1.7)

a Week 24 results are through Week 24; EOS results are cumulative from Day 1 to the end of the study

b Week 24 results are through database lock for the Week 24 CSR; EOS results are cumulative from Day 1 to the end of the study

ALT = alanine aminotransferase, DILI=drug induced liver injury

The most common AEs (≥ 10% across weight groups) through Week 24 were nasopharyngitis (16.9%), upper respiratory tract infection (16.9%), vomiting (16.9%), cough (13.6%), abdominal pain (11.9%), hyperbilirubinemia (11.9%), and influenza, nausea, and jaundice (each 10.2%).

Hyperbilirubinemia was the most common Grade 3 to 4 AE, occurring in 3 (5.1%) subjects, 2 (6.1%) in the 20 to < 40 kg weight group and 1 (4.3%) in the ≥ 40 kg weight group, all with Grade 3 events. All other Grade 3 to 4 AEs occurred in only 1 subject per AE term (neutropenia, overdose, and post

procedural haemorrhage in the 20 to < 40 kg weight group; and abdominal pain, ALT increased, appendicitis, blood bilirubin increased, hyperbilirubinemia, and hypersensitivity in the ≥ 40 kg weight group). No Grade 3 to 4 rash and no Grade 3 to 4 cardiac events were reported.

Deaths and SAEs

One subject died during Year 2 (bacterial meningitis not considered related to the study therapy).

Overall, the cumulative incidence of SAEs was 8 (13.6%) subjects (0, 1, 3, and 4 subjects in the 15 to < 20 kg, 20 to < 40 kg, and ≥ 40 kg weight groups, respectively). Other than overdose, which was reported as an SAE in 2 subjects as accidental overdose and overdose, respectively, none of the on-treatment SAEs occurring in this study was reported for more than 1 subject per AE term; no SAE was considered by the investigators to be related to study treatment; and none led to treatment discontinuation.

AEs leading to discontinuation

The cumulative incidence of AEs leading to discontinuation was 3 (5.1%) subjects: 1 in the 20 to < 40 kg weight group (Grade 1 pulmonary tuberculosis) and 2 in ≥ 40 kg weight group (Grade 3 acute allergic systemic reaction considered related to study drug and resolved off treatment, and one Grade 2 tuberculosis of the eye).

AEs of interest

- Hyperbilirubinemia: Through Week 24 database lock, 13 (22.0%) subjects had hyperbilirubinemia-related AEs (0, 3 [9.1%] and 10 [43.5%] in the 15 to < 20 kg, 20 to < 40 kg, and ≥ 40 kg weight groups, respectively). Most hyperbilirubinemia AEs were Grade 2 to 4 (9 of the 13 subjects). Four additional subjects had hyperbilirubinemia events (Grade 1 to 3) after the Week 24 database lock. All except 1 were considered related to study drug.

- Renal toxicity: One subject (20 to < 40 kg weight group) had a Grade 1 hematuria on Day 421 that was considered not related to the study drug by the investigator. This subject subsequently experienced 3 renal SAEs (hematuria on Day 665, post-streptococcal glomerulonephritis on Day 695, and glomerulonephritis on Day 865), a non-serious AEs of nephrotic syndrome (Day 787) and proteinuria on Day 1177. None of these AEs or SAE was considered related to the study drug by the investigator.

- Cardiac disorders: Through the Week 24 database lock, 6 (10.2%) subjects had cardiac disorders. Four subjects (20 to < 40 kg group) had, respectively, first degree atrioventricular (AV) block (2 subjects, and one of the two also had sinus bradycardia), AV block (1 subject), and sinus bradycardia (1 subject). The first degree AV block in 1 of the 2 subjects with this event, and the AV block in 1 subject were each considered related to the study drug by the investigators. Two subjects (≥ 40 kg group) had AEs of sinus bradycardia that were considered unrelated to the study drug by the investigators, and the subjects continued on treatment. After Week 24, through the end of the study, a cardiac AE (Grade 1 sinus tachycardia) was reported for 1 additional subject (≥ 40 kg group), which was considered unrelated to study drug by the investigator.

- Rash: Seven (11.9%) subjects had rash events (4 in the 20 to <40 kg group and 3 in the ≥ 40 kg group). None of these events was considered related to the study drug by the investigators. No Grade 3 or Grade 4 AE was reported in the SOC of Skin and Subcutaneous Tissue Disorders.

- AIDS events: 1 subject (20 to < 40 kg group) had Grade 1 pulmonary tuberculosis that was considered not related to the study drug by the investigator.

No on-treatment events of lipodystrophy, lactic acidosis syndrome or symptomatic hyperlactatemia, cholelithiasis, or nephrolithiasis were reported at any time during the study.

Laboratory AEs

The majority of subjects had normal serum chemistries, except for amylase (72.9%), low bicarbonate (71.2%) and total bilirubin (62.7%), which were abnormal at any grade level across all weight groups. Grade 3 to 4 abnormalities were infrequent except for total bilirubin and amylase:

Table 7. Summary of Grade 3 to 4 Laboratory Test Results - Worst Toxicity Grade on Treatment – Treated Subjects

Lab Test Description Toxicity Grade	B/L Weight 15 - < 20 kg N = 3	B/L Weight 20 - < 40 kg N = 33	B/L Weight >=40 kg N = 23	Total N = 59
		WEEK 24		
NEUTROPHILS+BANDS(ABSOLUTE)	N = 3	N = 33	N = 23	N = 59
GRADE 3-4	0	1 (3.0)	0	1 (1.7)
ALT	N = 3	N = 33	N = 23	N = 59
GRADE 3-4	0	0	1 (4.3)	1 (1.7)
ALKALINE PHOSPHATASE	N = 3	N = 33	N = 23	N = 59
GRADE 3-4	0	1 (3.0)	0	1 (1.7)
TOTAL BILIRUBIN	N = 3	N = 33	N = 23	N = 59
GRADE 3-4	0	3 (9.1)	7 (30.4)	10 (16.9)
AMYLASE(TOTAL;TOTAL PANCREATIC OR TOTAL SALIVARY)	N = 3	N = 33	N = 23	N = 59
GRADE 3-4	2 (66.7)	9 (27.3)	4 (17.4)	15 (25.4)
		END OF STUDY		
NEUTROPHILS+BANDS(ABSOLUTE)	N = 3	N = 33	N = 23	N = 59
GRADE 3-4	0	2 (6.1)	0	2 (3.4)
ALT	N = 3	N = 33	N = 23	N = 59
GRADE 3-4	0	0	1 (4.3)	1 (1.7)
ALKALINE PHOSPHATASE	N = 3	N = 33	N = 23	N = 59
GRADE 3-4	0	1 (3.0)	0	1 (1.7)
TOTAL BILIRUBIN	N = 3	N = 33	N = 23	N = 59
GRADE 3-4	2 (66.7)	9 (27.3)	8 (34.8)	19 (32.2)
ALBUMIN	N = 3	N = 33	N = 23	N = 59
GRADE 3-4	1 (33.3)	2 (6.1)	0	3 (5.1)
AMYLASE(TOTAL;TOTAL PANCREATIC OR TOTAL SALIVARY)	N = 3	N = 33	N = 23	N = 59
GRADE 3-4	2 (66.7)	10 (30.3)	5 (21.7)	17 (28.8)
POTASSIUM, HIGH	N = 3	N = 33	N = 23	N = 59
GRADE 3-4	0	0	1 (4.3)	1 (1.7)

Two subjects, both in the ≥ 40 kg weight group, had ALT and total bilirubin measurements that met laboratory criteria for potential DILI (ALT or AST > 3x ULN with concurrent total bilirubin > 2x ULN) during the first 24 weeks of the study.

2.3.3. MAH's discussion

The benefit-risk profile for ATV paediatric capsules has not changed. In the post-approval commitment safety study AI424452, ATV capsules, boosted with RTV capsules or tablets, administered with 2 NRTIs using the approved dosing recommendations, were generally safe and well tolerated across all 3 weight bands through 24 weeks of treatment (the primary endpoint) and through the end of the study. There were no unexpected or novel safety events. No safety findings were identified in this pediatric population that had not been reported previously in other ATV pediatric and adult studies, or that merit an update to the product information.

3. Overall conclusion and recommendation

In 2010, an extension of indication for atazanavir (Reyataz hard capsules) was accepted (variation II-57) to include HIV-1 infected paediatric patients 6 years of age. Study AI424452 was a Post-Assessment Measure (PAM) initiated in 2012 in order to consolidate the safety data of Reyataz in the paediatric subjects. Therefore, the posology and the formulations of Reyataz in this study were those adopted at the time of its initiation.

In 2016 through the procedure EMEA/H/C/494/X/94/G, the posology of Reyataz hard capsules in paediatric subjects (≥ 6 years and weighing at least 15 kg) was modified, and a new formulation (Reyataz oral powder) was authorised for younger paediatric subjects (≥ 3 months of age).

Old paediatric dosage of Reyataz capsules (+RTV)	**Current paediatric dosage of Reyataz capsules (+RTV)**
≥15 kg to <20 kg: 150/100 mg QD	≥15 kg to <35 kg: 200/100 mg QD
≥20 kg to <40 kg: 200/100 mg QD	≥35 kg: 300/100 mg QD
≥40 kg: 300/100 mg QD	

For a similar weight, the ATV exposure may be higher with the current dosage of Reyataz in comparison to the dosage in study AI424452. Therefore, the final results of study AI424452 have become outdated. However, it is noted that no new safety signal was highlighted within this study. We agree with the MAH that the safety profile in this paediatric study is overall similar with those in adults.

In conclusion, no additional recommendation or variation could be issued from this final report of study AI424452.

☒ **Fulfilled:** No regulatory action required.