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Procedure Management and Committees Support Division

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/P46/082

Note

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

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

Reyataz

International non-proprietary name: Atazanavir

Procedure no.: EMA/H/C/494/P46/082

Marketing authorisation holder (MAH): BMS

Rapporteur:	Joseph Emmerich
Start of the procedure:	10 March 2015
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Date of the Rapporteur's final report:	
Need for plenary discussion	No

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1. Introduction

On March 2015, the MAH submitted a completed paediatric study for Reyataz, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

These data are also submitted as part of the paediatric extension of indication and the oral powder line extension.

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that AI424020 (Phase 1/2, open-label, pharmacokinetic and safety study of atazanavir in combination regimens in antiretroviral therapy-naïve and experienced HIV-infected infants, children, and adolescents) is a stand-alone study.

Of note, Reyataz is currently approved in EU for adults and paediatric patients ≥ 6 years of age. This paediatric indication was the outcome of the Week 48 interim results of study AI424020 submitted by the MAH in 2008.

2.2. Information on the pharmaceutical formulation used in the study

Two formulations of atazanavir (ATV) were administered in this study: the current marketed ATV capsules and the new formulation ATV powder.

Depending on the group, ATV was administered alone or boosted with ritonavir (RTV) liquid or capsule formulation, in combination with 2 NRTIs.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for study AI424020. This is a Phase 1/2 multicenter, open-label study conducted in the United States and South Africa to determine the safety, PK, and optimal dose of ATV powder and capsules, administered with or without RTV, in ART-naive and experienced pediatric subjects with HIV aged 91 days to 21 years.

2.3.2. Clinical study

AI424020: Phase 1/2, open-label, pharmacokinetic and safety study of atazanavir in combination regimens in antiretroviral therapy-naïve and experienced HIV-infected infants, children, and adolescents.

Methods

Objectives

Primary objectives were:

- To determine the PK profile and dosing schedule of the capsule formulation for ATV and ATV/RTV in combination with 2 NRTIs in HIV-infected pediatric subjects;

- To determine the PK profile and dosing schedule for the powder formulation of ATV and ATV/RTV in combination with 2 NRTIs in HIV-infected pediatric subjects;

- To determine the safety and tolerability of ATV and ATV/RTV in combination with 2 NRTIs in HIV-infected pediatric subjects.

Key Secondary objectives include the antiretroviral activity and the development of virologic resistance during treatment with ATV and ATV/RTV.

Study design

The study was conducted in two steps:

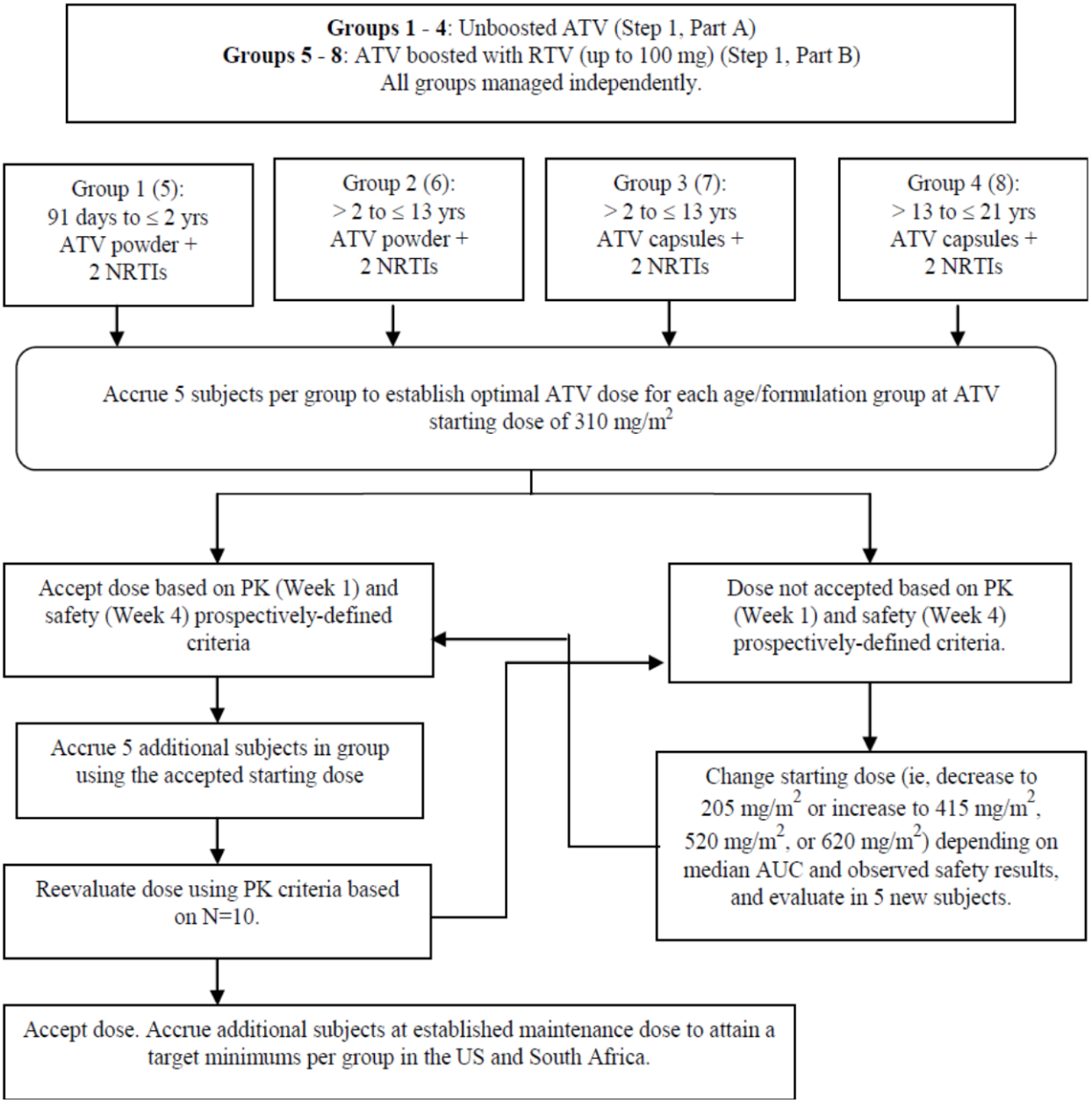
- Step 1: a dose finding PK and safety study, conducted in US and South Africa, divided in two Parts:

- Part A: ATV dose-finding where subjects received ATV without RTV plus 2 NRTIs (excluding ABC and TDF).
- Part B: ATV/RTV dose finding where subjects received ATV plus RTV plus 2 NRTIs (excluding ABC and TDF).

Eligible subjects were assigned to treatment groups, stratified by age, ATV formulation, and concomitant administration of RTV:

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

First, 5 subjects were enrolled in each group to receive the starting dose of ATV at 310 mg/m² QD, +/- RTV 100 mg/m² QD (up to 100 mg QD). If the dose acceptance criteria were not met, the ATV dose was either decreased or increased. If dose acceptance criteria were met, an additional 5 subjects were enrolled at the same dose and the regimen evaluated once more with 10 total subjects. The design of this Step 1 is as follows:



- Step 2: a long-term safety extension that was initiated for the sole purpose of continuing treatment for subjects in South Africa who had achieved virologic response, would benefit from continued treatment in the opinion of the investigator and protocol team, or had reached Week 96 of treatment and could not otherwise obtain the therapy as it was not yet marketed/approved.

Study population /Sample size

Enrolled subjects were ART-naive or experienced HIV infants, children and adolescents from 3 months to 21 years of age, with HIV RNA ≥ 5000 c/ml. This study was to enrol a minimum of 152 subjects (including at least 60 subjects from South Africa).

Outcomes/endpoints

Virologic response (HIV RNA measurements) was assessed using response rates for:

- Virologic one log suppression (VOLS) in the Treated Subjects population

- Virologic response (VR) and virologic response in observed cases (VR-OC)

- Time to loss of virologic response (TLOVR)

Resistance was assessed using phenotypic and genotypic resistance samples collected at the screening visit and at the time of premature discontinuation or the end of the study.

Subjects had intensive, 24-hour PK sampling at Week 1, and again at Week 56 for those who continued on study. Intensive, 24-hour PK sampling was performed 2 weeks after a new dose of ATV had been initiated.

Statistical Methods

The analysis of efficacy parameters incorporated 2 methods of handling missing data: Non-Completer = Failure (NC = F, "modified intention-to-treat [ITT]"), where subjects with missing measurements are treated as failures; and Non-Completer = Missing (NC = M, "Observed Cases"), where subjects with missing measurements are excluded from the analysis.

Results

Recruitment/ Number analysed

The first patient first visit occurred on 16-Nov-2000, and the study was initially closed to accrual on 24-Jan-2007, with 183 subjects enrolled and 182 subjects treated. The age distribution was as follows:

	NUMBER OF SUBJECTS (%)		
	TREATMENT REGIMEN		
	ATV N = 85	ATV/RTV N = 97	TOTAL N = 182
Age Distribution			
Infants			
3 m to < 6 m	0	2 (2)	2 (1)
6 m to < 2 yr	8 (9)	19 (20)	27 (15)
Children			
2 yr to < 6 yr	6 (7)	24 (25)	30 (16)
6 yr to < 12 yr	33 (39)	29 (30)	62 (34)
Adolescents			
12 yr to < 18 yr	35 (41)	17 (18)	52 (29)
Adults			
>= 18 yr	3 (4)	6 (6)	9 (5)

Percentages are based on subjects with measurements

In the 6 month to < 2 year age bracket there were 6 subjects <= 10 months of age at the time of the first dosing (1 at 7 months, 2 at 9 months, and 3 at 10 months)

Subsequently, accrual was reopened to add the Group 5A (3 months – 2 years of age). Study was closed for the last time in March 2010, with a total of 193 treated subjects treated. The age distribution data are not available for the final enrolled population.

	NUMBER OF SUBJECTS (%)		
	TREATMENT REGIMEN		
	ATV N = 85	ATV/RTV N = 108	TOTAL N = 193
TREATED	85 (100)	108 (100)	193 (100)
DISCONTINUED WHILE ON INITIAL FORMULATION	82 (96)	75 (69)	157 (81)
DISCONTINUED PRIOR TO OR ON WEEK 48 VISIT WHILE ON INITIAL FORMULATION	27 (32)	26 (24)	53 (27)
Clinical Events or Progression	9 (11)	4 (4)	13 (7)
Death	0	2 (2)	2 (1)
Disallowed Medications	1 (1)	1 (<1)	2 (1)
Other Reasons	2 (2)	0	2 (1)
Protocol Compliance	4 (5)	9 (8)	13 (7)
Requests Treatment Discontinuation	2 (2)	5 (5)	7 (4)
Toxicity	9 (11)	5 (5)	14 (7)
DISCONTINUED AFTER WEEK 48 VISIT AND PRIOR TO OR ON WEEK 96 VISIT WHILE ON INITIAL FORMULATION	11 (13)	10 (9)	21 (11)
Clinical Events or Progression	3 (4)	0	3 (2)
Disallowed Medications	1 (1)	0	1 (<1)
Other Reasons	1 (1)	0	1 (<1)
Protocol Compliance	4 (5)	7 (6)	11 (6)
Requests Treatment Discontinuation	0	3 (3)	3 (2)
Toxicity	2 (2)	0	2 (1)
DISCONTINUED AFTER WEEK 96 VISIT WHILE ON INITIAL FORMULATION	44 (52)	39 (36)	83 (43)
Clinical Events or Progression	7 (8)	4 (4)	11 (6)
Completion of Treatment	14 (16)	18 (17)	32 (17)
Disallowed Medications	2 (2)	3 (3)	5 (3)
Other Reasons	2 (2)	0	2 (1)
Protocol Compliance	10 (12)	11 (10)	21 (11)
Requests Treatment Discontinuation	8 (9)	1 (<1)	9 (5)
Toxicity	1 (1)	2 (2)	3 (2)
SWITCHED FROM ATV POWDER TO ATV CAPSULE	3 (4)	33 (31)	36 (19)
DISCONTINUED AFTER SWITCH FROM ATV POWDER TO CAPSULE	3 (4)	33 (31)	36 (19)
Clinical Events or Progression	1 (1)	0	1 (<1)
Completion of Treatment	2 (2)	31 (29)	33 (17)

Baseline data

	TREATMENT REGIMEN		
	ATV N = 85	ATV/RTV N = 108	TOTAL N = 193
Age (Years)			
MEAN (SE)	10.45 (0.544)	7.13 (0.571)	8.59 (0.416)
MEDIAN	10.75	5.74	8.53
MIN, MAX	0.54, 20.65	0.29, 21.02	0.29, 21.02
MISSING	0	0	0
Gender: N (%)			
FEMALE	45 (53)	51 (47)	96 (50)
MALE	40 (47)	57 (53)	97 (50)
Race Group: N (%)			
BLACK/MIXED	49 (58)	81 (75)	130 (67)
WHITE	23 (27)	20 (19)	43 (22)
OTHER	13 (15)	6 (6)	19 (10)
ASIAN	0	1 (<1)	1 (<1)
Region: N (%)			
NORTH AMERICA	63 (74)	60 (56)	123 (64)
AFRICA	22 (26)	48 (44)	70 (36)
HIV RNA Level (log10 c/mL)			
MEAN (SE)	4.55 (0.051)	4.62 (0.046)	4.59 (0.034)
MEDIAN	4.66	4.84	4.76
MIN, MAX	3.31, 5.00	3.28, 5.00	3.28, 5.00
MISSING	0	0	0
HIV RNA Distribution (c/mL): N (%)			
< 30000	32 (38)	35 (32)	67 (35)
30000 - < 100000	28 (33)	32 (30)	60 (31)
>= 100000	25 (29)	41 (38)	66 (34)
CD4 Cell Count (cells/mm3)			
MEAN (SE)	456 (37.3)	865 (79.4)	687 (49.9)
MEDIAN	376	510	466
MIN, MAX	0, 1511	2, 4582	0, 4582
MISSING	2	0	2
CD4%			
MEAN (SE)	18 (1.1)	21 (1.1)	20 (0.8)
MEDIAN	18	19	18
MIN, MAX	0, 48	1, 54	0, 54
MISSING	2	0	2

More subjects treated with ATV were treatment experienced (64%) than subjects treated with ATV/RTV (50%). Prior ARV therapies used by ≥ 25% of all subjects were zidovudine (47%), lamivudine (39%), didanosine (35%), stavudine (32%), and nelfinavir (26%).

PK results

ATV without RTV:

No acceptable dose was found for ATV oral powder without RTV in Groups 1 and 2 due to relatively high oral clearance in pediatric subjects and increased variability. In order to maintain the protocol-specified Cmin (no child < 60 ng/mL, and ≤ 2 of 10 children < 120 ng/mL), the ATV dose had to be increased such that ATV AUC and Cmax values for Group 3 at 520 mg/m^2 and Group 4 at 620 mg/m^2 were 1.5 to 2.5-fold greater than those previously observed in adults receiving ATV 400 mg QD (231 mg/m2 for average adult). ATV AUC(TAU) values were similar to but ATV Cmax values were higher than and Cmin values lower than HIV-positive adults receiving ATV/RTV 300/100 mg QD. On average, subjects less than 13 years of age (Group 3) had higher peak to trough concentration ratios, suggesting that they may not be able to maintain adequate Cmin values without RTV at adult equivalent doses of ATV based on body surface area (BSA) or body weight.

ATV with RTV:

For pediatric subjects from 3 months to 13 years of age (Groups 5 and 6), ATV powder at a dose of 310 mg/m^2 + 100 mg/m^2 RTV once daily produced AUC and Cmin values that were comparable to adults receiving ATV/RTV 300/100 mg once daily. There was a trend toward lower Cmin values in subjects younger than 2 years of age (Group 5), but these values were within the range of those observed in adults receiving ATV/RTV 300/100 mg once daily. All subjects in Group 5 received total daily doses of 100 to 150 mg of ATV.

For pediatric subjects from 6 years of age to adulthood (Groups 7 and 8), a capsule regimen of ATV 205 mg/m^2 + RTV 100 mg/m^2 once daily produced AUC and Cmin values that were comparable to adults receiving ATV/RTV 300/100 mg once daily. Pediatric subjects in Group 7 have somewhat higher Cmax and lower Cmin values than those in Group 8, but are still within the range of adults receiving ATV/RTV 300/100 QD.

Efficacy results

Efficacy for the ATV powder Cohort was not analyzed after Week 48 in this study for several reasons. First, a decision had been made that the powder formulation should be administered only boosted with RTV. Second, individual dose adjustments in the boosted arm (ATV/RTV) of the study based on body surface area were such that efficacy information was no longer useful. Finally, the pediatric development plan included two BMS dose finding studies dedicated to an assessment of boosted ATV powder (AI424397 and AI424451).

In conclusion, Week 48 efficacy results for both ATV formulations and Week 96 efficacy results for ATV capsule are provided:

At Week 48:

	ATV[a] N = 85		ATV/RTV[a] N = 97		Overall[a] N = 182	
	n/N	%	n/N	%	n/N	%
Virologic One Log Suppression (VOLS)						
All responders	41/85	48	65/97	67	106/182	58
Age category						
Infant	3/8	38	15/21	71	18/29	62
Children	27/42	64	44/56	79	71/98	72
Adolescents	10/32	31	5/14	36	15/46	33
Adults	1/3	33	1/6	17	2/9	22
Formulation						
Powder	9/19	47	39/47	83	48/66	73
Capsule	32/66	48	26/50	52	58/116	50
Prior Treatment Status						
Naive	18/31	58	39/50	78	57/81	70
Experienced	16/54	30	20/47	43	36/101	36
Region						
US	27/63	43	32/57	56	59/120	49
South Africa	14/22	64	33/40	83	47/62	76
Virologic Response HIV RNA < 400 c/mL) (VR)						
All responders	34/85	40	59/97	61	93/182	51
Age category						
Infant	3/8	38	15/21	71	18/29	62
Children	22/42	52	39/56	70	61/98	62
Adolescents	8/32	25	5/14	36	13/46	28
Adults	1/3	33	0/6	0	1/9	11
Formulation						
Powder	5/19	26	26/47	55	31/66	47
Capsule	17/66	26	19/50	38	36/116	31
Prior Treatment Status						
Naive	14/31	45	33/50	66	47/81	58
Experienced	8/54	15	12/47	26	20/101	20
Region						
US	20/63	32	27/57	47	47/120	39
South Africa	14/22	64	32/40	80	46/62	74

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

The median increase from baseline in CD4 cell count at Week 48 was 188 cells/mm^3 overall (ATV 135 cells/mm^3; ATV/RTV 214 cells/mm^3).

At Week 96:

Table 4.2-1 Virologic Response at Weeks 48 and 96: ATV Capsule Cohort - AI424020

	Responder / Evaluable (%)					
	ARV-naive Subjects			ARV-experienced Subjects		
Method LOQ	ATV N = 26	ATV/RTV N = 17	Total N = 43	ATV N = 37	ATV/RTV N = 25	Total N = 62
VR at Week 48						
400 c/mL	13/26 (50)	14/17 (82)	27/43 (63)	12/37 (32)	8/25 (32)	20/62 (32)
50 c/mL	11/26 (42)	13/17 (76)	24/43 (56)	6/37 (16)	6/25 (24)	12/62 (19)
VR at Week 96						
400 c/mL	10/26 (38)	11/17 (65)	21/43 (49)	11/37 (30)	10/25 (40)	21/62 (34)
50 c/mL	10/26 (38)	10/17 (59)	20/43 (47)	7/37 (19)	8/25 (32)	15/62 (24)
VR-OC at Week 48						
400 c/mL	13/17 (76)	14/16 (88)	27/33 (82)	12/27 (44)	8/16 (50)	20/43 (47)
50 c/mL	11/17 (65)	13/16 (81)	24/33 (73)	6/27 (22)	6/16 (38)	12/43 (28)
VR-OC at Week 96						
400 c/mL	10/15 (67)	11/12 (92)	21/27 (78)	11/20 (55)	10/12 (83)	21/32 (66)
50 c/mL	10/15 (67)	10/12 (83)	20/27 (74)	7/20 (35)	8/12 (67)	15/32 (47)

For the VR algorithm, subjects with missing measurements are treated as failures

For the VR-OC algorithm, subjects with missing measurements are excluded from the analysis.

Between Week 48 and Week 96, VR response was durable in both the ARV-naïve and ARV-experienced groups.

Table 4.2-2: CD4 Cell Count Change from Baseline at Weeks 48 and 96: ATV Capsule Cohort - AI424020

	CD4 Cell Count (cells/mm^3)					
	ARV-naive Subjects			ARV-experienced Subjects		
	ATV N = 26	ATV/RTV N = 17	Total N = 43	ATV N = 37	ATV/RTV N = 25	Total N = 62
Week 48						
N[a]	11	15	26	26	15	41
Mean (SE)	203 (31.4)	268 (84.9)	241 (50.4)	154 (31.0)	239 (52.4)	185 (27.8)
Median	214	173	196	99	240	119
Week 96						
N[a]	16	12	28	19	12	31
Mean (SE)	431 (68.9)	343 (103.2)	394 (58.6)	201 (45.5)	335 (68.1)	252 (39,5)
Median	403	275	335	153	278	220

Overall, virologic and immunologic efficacy was observed with ATV and ATV/RTV across all age groups, with ATV capsule and powder, in treatment-naive subjects and treatment-experienced subjects.

Safety results

A total of 193 subjects were treated in this study (85 with ATV and 108 with ATV/RTV), and 182 subjects had completed at least 48 weeks of therapy.

27% of subjects (53/193) discontinued prior to or on the Week 48 visit while on their initial formulation of study drug. The most common reasons for discontinuation were clinical events or progression and toxicity (7% [14/193] each).

43% of subjects (83/193) discontinued after the Week 96 visit while on their initial formulation of study drug. The most common reasons for discontinuation were completion of treatment (17% [32/193]) and protocol non-compliance (11% [21/193]).

37/193 treated subjects (19%) discontinued study therapy due to AEs.

Deaths and SAEs:

Through study, there were 4 deaths reported; all were not considered related to the study drug by the investigators. The most common SAEs were blood bilirubin increased (33%), blood bilirubin unconjugated increased (47/193 [24%]), and hyperbilirubinemia (15%). At Week 48, SAEs were more frequent in adolescents (63%) and adults (60%) than in infants (34%) and children (44%).

Table 5.2.2-2: Summary of Serious Adverse Events in Subgroups at Week 48: Treated Subjects - AI424020

	Number of Subjects n/N (%)		
Parameter	**ATV[a]**	**ATV/RTV[a]**	**Overall[a]**
SAEs	**44/85 (52)**	**44/98 (45)**	**88/183 (48)**
Age			
Infant	4/8 (50)	6/21 (29)	10/29 (34)
Children	19/42 (45)	24/56 (43)	43/98 (44)
Adolescents	20/32 (63)	9/14 (64)	29/46 (63)
Adults	1/3 (33)	5/7 (71)	6/10 (60)
Formulation			
Powder	11/19 (58)	15/47 (32)	26/66 (39)
Capsule	33/66 (50)	29/51 (57)	62/117 (53)

Grade 3 to 4 AEs:

At Week 48, 64% of the subjects (69% ATV; 60% ATV/RTV) reported Grade 3 to 4 AEs. The most common Grade 3 to 4 AEs were laboratory abnormalities: blood bilirubin unconjugated increased (46%) and blood bilirubin increased (42%). Grade 3 to 4 AEs (excluding laboratory AEs) reported in ≥ 2% of subjects overall were pyrexia (3%) and AV block (2%).

Hyperbilirubinemia, jaundice and ocular icterus:

At Week 48, Grade 2 to 4 total bilirubin levels were reported in 65% of subjects (ATV 55% ATV/RTV 73%). Jaundice and ocular icterus were reported for 10% and 23% of subjects, respectively.

Cardiac abnormalities:

At Week 48, Grade 2 to 4 cardiac AEs were reported for 8 subjects, all of whom received ATV (9%). One subject had an SAE of cardiomyopathy (Grade 3) and congestive heart failure that led to death. This death occurred 136 days after the last dose of study therapy, and was not considered related to the study drug by the investigator.

Six subjects from the ATV group discontinued due to a cardiac disorder, and 44 subjects (24%) had AV block (ATV 31%, ATV/RTV 19%), including 2 subjects with a second degree AV block.

Rash:

Overall rash was reported for 45% of subjects (ATV 37%, ATV/RTV 49%), and generalized rash was reported for 14% of subjects (ATV 11%, ATV/RTV 15%).

AEs within cohorts:

Among the pediatric cohorts, older subjects reported more Grade 3 to 4 AEs (adolescents 70%, children 62%, infants 59%), more Grade 2-4 hyperbilirubinemia (young adults 89%, adolescents 74%, children 78%, infants 66%) and more Grade 2-4 cardiac events (adolescents 9%, children 4%, infants 0%). Conversely, rash was reported for 48% of Infants, 43% of Children, 33% of Adolescents, and 22% of young Adults.

AEs within formulations:

Among subjects who received ATV capsule or powder formulation (Week 48 analysis), more subjects who received capsules had Grade 3 to 4 AEs (68%) compared with subjects who received powder (58%). Frequency of Grade 2-4 hyperbilirubinemia was similar (78% and 70%, respectively, in ATV capsule and powder formulations). Grade 2-4 cardiac abnormalities were reported for 7 (6%) subjects receiving the capsule formulation and 1 (2%) subject who received powder. Grade 2-4 Rash was reported for 14% of subjects receiving either the capsule or powder formulation.

2.3.3. Discussion

As expected based on adult data, PK results are not in favour of unboosted ATV in infants and children. Additionally, efficacy results show lower rate of virologic response (< 400 c/ml) with unboosted ATV (40%) than boosted ATV (61%). With ATV/RTV, the selected doses (ATV powder 310 mg/m^2 and ATV capsule 205 mg/m^2, both boosted with RTV 100 mg/m^2) are associated with comparable ATV exposure (AUC and Cmin) in paediatric subjects compared to adults. Of note, a trend towards lower Cmin in subjects < 2 years of age was highlighted.

Safety results did not highlight new or unexpected safety findings related to ATV in this paediatric population. Overall, there were no clinically relevant differences in the safety profiles of the ATV Capsule and Powder formulations. However, a trend to higher AEs in older subjects (and therefore in more subjects treated by ATV Capsule) could be noted.

3. Rapporteur's overall conclusion and recommendation

Study AI424020 was initiated in 2000 with several interim reports. In 2008, the interim Week 48 clinical study report was submitted (type II variation 494/II/57) in order to extend the use of Reyataz for children ≥ 6 years of age with the current formulation (Reyataz capsules) and for children from 3 months to 6 years of age with a new formulation (Reyataz oral powder). However, the CHMP has concluded in 2010 after several RSI (EMA/CHMP/288775/2015) that data were too limited and the study suffered from critical deficiencies to support an indication under 6 year of age with the new formulation. In conclusion, on the basis of this study, the indication of Reyataz was only extended to children ≥ 6 years of age with the current marketed capsules.

Recently, the MAH has submitted a new paediatric extension (procedure EMEA/H/C/494/X/94/G) with the Reyataz oral powder formulation for extending the indication to children from 3 months of age. The results of additional paediatric studies (the Phase 3 studies PRINCE I and PRINCE II) have been submitted as part of this procedure, as well this currently discussed study AI424020. Although this study was not judged solely appropriate to support the use in young children, it is admitted that it could bring supportive data (mainly safety) in addition to the pivotal PRINCE I and PRINCE II.

In conclusion, no additional recommendation or variation could be issued from this final report of study AI424020. The use of Reyataz in children from 3 months of age is now the subject of a specific Application.

☒ **Fulfilled:**

No regulatory action required.

☐ **Not fulfilled:**