RESEARCH AND DEVELOPMENT

ATAZANAVIR

EU RISK MANAGEMENT PLAN

Version Number: 16.1

Data-lock Point for this RMP: 20-Mar-2025

Date of final sign off: 25-Feb-2026

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LIST OF ABBREVIATIONS

Term	Definition
3TC	lamivudine
ABC	abacavir
AE	adverse event
AERS	FDA adverse event reporting system
AIDS	acquired immunodeficiency syndrome
ALT	alanine aminotransferase
APR	Antiretroviral Pregnancy Registry
aPVA(s)	additional pharmacovigilance activity(ies)
ART	antiretroviral therapy
ARV	antiretroviral
AST	aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical (drug classification system)
ATV	atazanavir (BMS-232632; REYATAZ®)
AUC	area under the concentration-time curve
AUC0-24	area under the concentration-time curve in 24 hours
$AUC_{(0\text{-}INF)}$	area under the concentration-time-curve from time zero to infinity
AUC24avg	24-hour average area under the concentration-time curve
AUC(TAU)	area under the concentration-time curve in 1 dosing interval
AV	atrioventricular
AWAREs	Analytic and Worldwide Adverse Event Reporting and Evaluation (Bristol-Myers Squibb's internal safety database)
BID	twice daily
BMS	Bristol-Myers Squibb Company
cART	combination antiretroviral therapy
CCDS	Company Core Data Sheet
CCR5	CC chemokine receptor 5
CH	Switzerland
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
CL/*F*	total body clearance divided by bioavailability
Cmax	maximum observed concentration
CSR	clinical study report
CYP	cytochrome P450
D:A:D	Data Collection on Adverse Events of Anti-HIV Drugs

Term	Definition
DAIDS	Division of AIDS
ddI	didanosine
DRESS	drug rash with eosinophilia and systemic symptoms
EC	European Commission
ECG	electrocardiogram
EEA	European Economic Area
EFV	efavirenz
eGFR	estimated glomerular filtration rate
EMA	European Medicines Agency
EPAR	European Public Assessment Reports
EU	European Union
FTC	emtricitabine
HAART	Highly Active Antiretroviral Therapy
hERG	human ether-a-go-go-related gene
HIV-1	Human Immunodeficiency Virus-type 1
HLGT	high level group term
HCP	healthcare professional
HR	hazard ratio
IC50	concentration at which 50% inhibition observed
IDV	indinavir
IKr or IKs	rapid (r) or slow (s) cardiac potassium current
IRIS	immune reconstitution inflammatory syndrome
LPV	lopinavir
MAH	marketing authorisation holder
MedDRA	Medical Dictionary for Regulatory Activities
MRV	maraviroc
MTCT	mother-to-child transmission
NFV	nelfinavir
NRTI	nucleoside reverse transcriptase inhibitors
NVP	nevirapine
PACTG	Pediatric AIDS Clinical Trials Group
PI	protease inhibitor
PK	pharmacokinetic(s)
PSUR	periodic safety update report
PT	preferred term

Term	Definition
PY	patient-years
QD	once daily
QPPV	Qualified Person Responsible for Pharmacovigilance
RMP	Risk Management Plan
RNA	ribonucleic acid
RTV	ritonavir
SLE	Systemic Lupus Erythematosus
SmPC	Summary of Product Characteristics
SMQ	Standardized MedDRA Queries
SQV	saquinavir
TDF	tenofovir
UGT	UDP-glucuronosyl transferase
UGT1A1	UDP-glucuronosyl transferase 1A1
US	United States
ZDV	zidovudine

EU RISK MANAGEMENT PLAN (RMP) FOR ATAZANAVIR

RMP version to be assessed as part of this application:

Version Number: 16.1

Data-lock Point for this RMP: 20-Mar-2025

Date of Final Sign-off: 25-Feb-2026

Rationale for submitting an updated RMP:

- Updated to remove the additional pharmacovigilance activity (aPVA) for Antiretroviral Pregnancy Registry (APR)
- Updated the APR Registry exposure numbers for Pregnant women
- Updated the post-authorisation exposure
- Updated to remove all safety concerns, including important identified risks, important potential risks, and missing information, to ensure alignment with the GVP Module V (Rev 2) definition of the list of safety concerns.
- Updated EU QPPV Contact Person.

Summary of Significant Changes in this RMP

Part/Module	Summary of Major Changes	Version # / Date of Positive Opinion for Module Update
Part I Product Overview		
Product Details: Indication and Dosage	N/A	V15.0 / 29-Nov-2018
Part II Safety Specification		
SI Epidemiology of the indication(s) and target population(s)	N/A	V11.0 / 15-Dec-2016
SII Non-clinical part of the safety specification	N/A	V11.0 / 15-Dec-2016
SIII Clinical trial exposure	N/A	V15.0 / 29-Nov-2018
SIV Populations not studied in clinical trials	Updated the APR Registry exposure numbers for Pregnant women	V16.1 / Pending
SV Post-authorisation experience	Updated post-authorisation experience and exposure	V16.1 / Pending
SVI Additional EU requirements for the safety specification	N/A	V11.0 / 15-Dec-2016
SVII Identified and potential risks	Updated to remove all safety concerns, including important identified risks, important potential risks, and missing information	V16.1 / Pending

Summary of Significant Changes in this RMP

Part/Module	Summary of Major Changes	Version # / Date of Positive Opinion for Module Update
SVIII Summary of the safety concerns	Updated to remove all safety concerns, including important identified risks, important potential risks, and missing information	V16.1 / Pending
Part III Pharmacovigilance Plan	Updated to remove the aPVA for APR	V16.1 / Pending
Part IV Plan for post-authorisation efficacy studies	Updated to Not Applicable	V16.1 / Pending
Part V Risk Minimisation Measures	Updated to remove all safety concerns, including important identified risks, important potential risks, and missing information Minor update of routine Risk Minimisation Measures for PR interval and QT prolongation aligned with the SmPC	V16.1 / Pending
Part VI Summary of the Risk Management Plan	Updated to align with changes in the body of the RMP	V16.1 / Pending
Part VII Annexes		
ANNEX 2 Tabulated summary of planned, ongoing, and completed pharmacovigilance study programme	Updated APR from ongoing to completed	V16.1 / Pending
ANNEX 3 Protocols for proposed, ongoing, and completed studies in the pharmacovigilance plan	N/A	V15.0 / 29-Nov-2018
ANNEX 4 Specific adverse drug reaction follow-up forms	N/A	V6.1/30-May-2013
ANNEX 5 Protocols for proposed and on-going studies in RMP Part IV	Updated to Not Applicable	V16.1 / Pending
ANNEX 6 Details of proposed additional risk minimisation activities	N/A	V6.1/30-May-2013
ANNEX 7 Other supporting data	N/A	V6.1/30-May-2013
ANNEX 8 Summary of changes to the risk management plan over time	Updated to include V16.1	V16.1 / Pending

Other RMP versions under evaluation:

None

Details of the currently approved RMP:

Version number: 15.0

Approved with procedure: EMEA/H/C/000494/II/0117

Date of approval: 29-Nov-2018

EU RMP Contact Person: PharmD Roberta Di Menno Di Bucchianico, EU QPPV

QPPV oversight declaration: The content of this RMP has been reviewed and approved by the marketing authorisation holder´s QPPV. The electronic signature is available on file.

1 PART 1: PRODUCT OVERVIEW

Table 1-1: Product Details

Active substance(s) (INN or common name)	atazanavir
Pharmacotherapeutic group(s) (ATC Code)	Protease Inhibitor (PI), ATC code: J05A E08
Marketing Authorisation	Bristol-Myers Squibb Pharma EEIG
Medicinal products to which this RMP refers	1
Invented name(s) in the European Economic Area (EEA)	REYATAZ®
Marketing authorisation procedure	EMEA/H/C/000494
Brief description of the product	ATV is an azapeptide human immunodeficiency virus-type 1 (HIV-1) PI. ATV 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.
Hyperlink to the Product Information	Refer to proposed PI
Indication(s) in the EEA	**Current:** REYATAZ hard capsules REYATAZ capsules, co-administered with low dose ritonavir, are indicated for the treatment of HIV1 infected adults and pediatric patients 6 years of age and older in combination with other antiretroviral medicinal products. Based on available virological and clinical data from adult patients, no benefit is expected in patients with strains resistant to multiple protease inhibitors (≥ 4 PI mutations). The choice of REYATAZ in treatment experienced adult and pediatric patients should be based on individual viral resistance testing and the patient's treatment history. REYATAZ 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-1 infected pediatric patients at least 3 months of age and weighing at least 5 kg. Based on available virological and clinical data from adult patients, no benefit is expected in patients with strains resistant to multiple protease inhibitors (≥ 4 PI 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. **Proposed:** None

Table 1-1: Product Details

Dosage in the EEA

Current:

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 ATV pharmacokinetics.

Pediatric patients (6 years to less than 18 years of age and weighing at least 15 kg)

The dose of ATV capsules for pediatric patients is based on body weight as shown in Table 1 and should not exceed the recommended adult dose. REYATAZ capsules must be taken with ritonavir and have to be taken with food.

Table 1: Dose for pediatric 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.

Pediatric patients (at least 3 months of age and weighing at least 5 kg): REYATAZ oral powder is available for pediatric patients at least 3 months of age and weighing at least 5 kg (see Summary of Product Characteristics for REYATAZ oral powder). Switching to REYATAZ capsules from REYATAZ oral powder is encouraged as soon as patients are able to consistently swallow capsules.

When transitioning between formulations, a change in dose may be needed. Consult the dosing table for the specific formulation (see Summary of Product Characteristics for REYATAZ oral powder).

REYATAZ oral powder; SmPC: section 4.2: The doses of ATV oral powder and ritonavir for pediatric patients are based on body weight as shown in Table 2. REYATAZ oral powder must be taken with ritonavir and has to be taken with food.

Table 2: Dose of REYATAZ oral powder with ritonavir for pediatric patients[a] (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 H_2-receptor antagonists in adults also apply to pediatric patients (see section 4.5 of the SmPC).
[b] Each sachet contains 50 mg of ATV.

Proposed:
None

Table 1-1: Product Details

Pharmaceutical form (s) and strength(s)	**Current:** 100, 150, 200, and 300 mg hard capsules, 50 mg oral powder **Proposed:** None
Is/will the product be subject to additional monitoring in the EU?	No

2 PART II: SAFETY SPECIFICATION

2.1 Epidemiology of the Indication(s) and Target Population(s)

Table 2.1-1: Epidemiologic Characteristics of HIV Infection

HIV-infected patients	
Incidence	HIV-infected patients: An estimated 2.1 million people were newly infected with HIV in 2015.[1] This is a reduction in prevalence compared to the 2.2[1] to 2.7 million[2] new HIV infections estimated for 2010.[1,2] Adults: An estimated 1.9 million adults were newly infected with HIV in 2015, slightly less than the number infected in 2010.[1,2] Sub-Saharan Africa remains the region most heavily affected by HIV.[3] In 2015, 960,000 adults in Eastern and southern Africa, 410,000 in Western and central Africa, 300,000 in Asia and the Pacific, and 190,000 in Eastern Europe and central Asia were newly infected by HIV.[1] Children/Adolescents: Most pediatric HIV infections are acquired through mother-to-child transmission during pregnancy, birth, or breastfeeding. Adolescents frequently acquire HIV through sexual contact or sharing infected needles. Globally, an estimated 0.15 million children < 15 years were newly infected with HIV in 2015, down from 0.29 million children in 2010.[1] Estimated number of children (< 15 years of age) newly infected with HIV in 2015 and categorized by region include:[1] • Western and central Africa: 66,000 • Eastern and southern Africa: 56,000 • Asia and the Pacific: 19,000 • Middle East and North Africa: 2,100 • Latin America and the Caribbean: 2,100 • Eastern Europe and central Asia: <1,000

Table 2.1-1: Epidemiologic Characteristics of HIV Infection

HIV-infected patients	
Prevalence	About 36.7 million people were living with HIV worldwide in 2015.[1] Prevalence varies across regions and countries; estimates of adult (age 15-49) prevalence of HIV infection range from 0.1% in the Western Pacific and eastern Mediterranean, 0.3% in southeast Asia, 0.4% in Europe, 0.5% in the Americas, and 4.4% in Africa.[4] Antiretroviral therapy (ART) coverage varies across countries, largely due to income levels, from as low as < 1% to as high as 100%. In 2015, 17 million patients worldwide were being treated with anti-retrovirals, an increase from 7.5 million in 2010.[1]
Demographics of the population: age, gender, racial and/or ethnic origin	In 2015, women accounted for more than half of all people living with HIV in eastern and southern Africa, and about 60% of people living with HIV in western and central Africa.[1] Women aged 15-24 years accounted for about 48% of new cases in Middle East and northern Africa, 46% of new cases in Eastern Europe and Central Asia, 46% of new adult cases in the Caribbean, 36% of new cases in Latin America, 41% of new cases in Asia and the Pacific, and 26% of new cases in Western and central Europe and North America.[5] Globally, in 2015 there were an estimated 2.3 million adolescent girls and young women (age 15-24) living with HIV that constituted 60% of all young people living with HIV. Fifty-eight percent of new HIV infections among young persons occurred among adolescent girls and young women.[5] Eastern and southern Africa continue to bear the highest proportion of the global burden of HIV, as 46% of new HIV infections and 43% of acquired immunodeficiency syndrome (AIDS) deaths in 2015 occurred in this region.[1]
Risk factors for the disease	HIV infection is related to life-threatening complications, including opportunistic infections, nephropathy, and liver disease.[6,7,8]
Main treatment options	Co-administration of ATV is recommended with ritonavir (RTV); other treatment options for HIV infection include: PIs - darunavir, fosamprenavir, indinavir (IDV), nelfinavir (NFV), saquinavir (SQV), tipranavir, lopinavir (LPV) and COBI as boosting agents; nucleoside **r**everse transcriptase inhibitors - abacavir (ABC), didanosine (ddI), emtricitabine (FTC), lamivudine (3TC), tenofovir disoproxyl fumarate (TDF), tenofovir alafenamide (TAF), zidovudine (ZDV), non-nucleoside reverse transcriptase inhibitors - efavirenz (EFV), delavirdine, etravirine, nevirapine (NVP), rilpivarine, and other classes such as fusion inhibitors (enfuvirtide), CC chemokine receptor 5 (CCR5) antagonists (maraviroc [MRV]), and integrase inhibitors (raltegravir, dolutegravir and elvitegravir).
Mortality and morbidity (natural history)	An estimated 1.1 million people died of AIDS worldwide in 2015.[1] About 470,000 in eastern and southern Africa, 330,000 in western and central Africa, 180,000 in Asia and the Pacific, 50,000 in Latin America and the Caribbean, 47,000 in Eastern Europe and Central

Table 2.1-1: Epidemiologic Characteristics of HIV Infection

HIV-infected patients	
	Asia, and 22,000 in North America, western and central Europe, died of AIDS-related causes in 2015.[1]
Important co-morbidities	Immunosuppression is a complication of HIV infection leading to many opportunistic infections like pneumocystis carinii pneumonia, fungal infections, tuberculosis, and viral hepatitis, and kidney disease as co-morbidities.

2.2 Nonclinical Part of the Safety Specification

The nonclinical pharmacology, pharmacokinetics (PK), and safety evaluations performed with ATV support its continued use in the treatment of HIV infection. Moreover, the nonclinical safety data demonstrated no special hazard for humans based on conventional studies of safety pharmacology, repeat-dose toxicity, genotoxicity, carcinogenicity, and reproduction.[9,10]

The liver was identified as the target organ in mice, rats, and dogs. However, microscopic evidence of hepatic cytotoxicity was noted only in mice at plasma ATV exposures (area under the concentration-time curve [AUC]) 3 times those observed in humans given ATV 300 mg/RTV 100 mg once daily (QD) or 4 times those observed in humans given 400 mg ATV QD. Liver-related effects included increased serum bilirubin and liver enzymes (alanine aminotransferase [ALT], aspartate aminotransferase [AST], alkaline phosphatase, gamma-glutamyltransferase); alterations in serum glucose, cholesterol, and triglycerides; increased liver weight; and hepatocellular hypertrophy, vacuolation, and single-cell necrosis. Additionally, ATV increased the incidence of benign hepatocellular adenomas in female mice in the 2-year carcinogenicity study at exposures (AUC) 5 times those observed in humans given ATV 300 mg/RTV 100 mg QD or 7 times those observed in humans given 400 mg ATV QD. The increased incidence of this benign tumor was considered the result of increased hepatocellular proliferation secondary to single-cell hepatocellular necrosis and is considered to have limited clinical relevance at therapeutic exposures. Based on the results of a full battery of standard genotoxicity tests, ATV was not genotoxic.

In vitro cardiac electrophysiology assessments, including human ether-a-go-go-related gene and Purkinje fiber studies, showed that ATV has a weak in vitro effect on electrophysiologic signals suggestive of a potential for ATV-related cardiac conduction alterations.[10,11] However, in the in vivo dog studies up to 9 months duration, no corroborative electrocardiogram (ECG) changes were observed. Moreover, there were no effects on other cardiovascular parameters evaluated in dogs, and no effects on the function of the respiratory or central nervous system in rats and/or dogs.[10,11]

In a fertility and early embryonic development study in rats, ATV altered estrus cycling with no effect on mating or fertility.[12] No teratogenic effects were observed in rats or rabbits at maternally

toxic doses. In the pre- and postnatal development assessment in rats, ATV produced a transient reduction in body weight in the offspring at a maternally toxic dose. Systemic exposure to ATV at doses that resulted in maternal toxicity was at least equal to or slightly greater than that observed in humans given 400 mg QD.

Safety concerns from nonclinical studies are summarized in Table 2.2-1.

Table 2.2-1: Summary of Significant Non-clinical Safety Findings

Key Safety findings	Relevance to human usage
Hepatotoxicity	
Generally common liver findings were observed in mice (≤ 640 mg/kg/day for 3 months), rats (≤ 1,200 mg/kg/day for ≤ 6 months), and dogs (≤ 360 mg/kg/day for ≤ 9 months), and included increased serum total bilirubin, AST, ALT, and alkaline phosphatase; increased liver weights; and hepatocellular hypertrophy, vacuolation, and single-cell necrosis (mice only) at 3 or 4× maximum freedrug plasma concentration in humans given ATV 300 mg/RTV 100 mg or ATV 400 mg QD, respectively.	Clinical use of ATV has been associated with elevated liver enzymes and hyperbilirubinemia.
Benign hepatocellular adenoma	
Increased incidence in benign hepatocellular adenomas observed in female mice at a hepatic cytotoxic dose of 360 mg/kg/day (5× human exposure at ATV 300 mg/RTV 100 mg or 7× human exposure at ATV 400 mg QD). The highest non-tumorigenic AUC in female mice was 3× the human AUC at ATV 300 mg/RTV 100 mg QD or 4× the human AUC at ATV 400 mg QD.	Not observed in humans, limited clinical relevance.
Cardiac conduction/ion currents	
In the in vitro Purkinje-fiber assay, ATV minimally increased APD_{90} at concentrations up to 30 μM (35 or 30× maximum free-drug plasma concentration in humans given ATV 300 mg/RTV 100 mg or ATV 400 mg QD, respectively). In the in vitro assays (hERG and Purkinje fiber), ATV weakly inhibited sodium and potassium (IKs and IKr) currents (IC50 > 30μM) and moderately inhibited calcium currents (IC50 of 10.4 μM).	Relevance to clinical use is unclear. ATV has been shown to prolong the PR interval and there have been reports of QT interval prolongation in the post-marketing period. However, in a definitive ECG study, ATV did not prolong the QT interval.[13]

2.2.1 Conclusions on Nonclinical Data

There were no nonclinical findings that would preclude the administration of ATV to humans for the treatment of HIV infection (Table 2.2.1-1).

Table 2.2.1-1: Nonclinical Safety Concerns

Important Identified Risks	• PR interval prolongation • Hyperbilirubinemia
Important Potential Risks	None
Missing Information	None

2.3 Clinical Trial Exposure

Clinical investigation of ATV has been ongoing since 02-Oct-1998. Through the end of data-lock for this section of the EU RMP (19-Jun-2016), approximately 8,208 subjects have been assigned to treatment (ie, assigned to treatment with the investigational medicinal product, active comparator, and/or placebo control) in Company-sponsored clinical trials, with approximately 6,714 subjects exposed to ATV. In addition, approximately 8,100 subjects have been exposed to ATV in the AI424900 Expanded Access Program. Cumulatively, for all completed investigator-sponsored research/trials for which BMS has received a final CSR, an estimated 2,435 subjects were exposed to ATV. In total, approximately 17,249 subjects have been exposed to ATV in BMS-sponsored clinical trials and investigator-sponsored research since 1998.

In Phase 2 and 3 studies, ATV, either as the sole PI or pharmacologically enhanced with RTV, was shown to be an effective component of cART for patients who have not been previously treated with cART or for patients who have failed previous cART. The efficacy of ATV-containing regimens has been demonstrated in a diverse population of HIV-infected adults across a wide spectrum of CD4 cell counts, baseline HIV ribonucleic acid (RNA) levels, and prior treatment regimens, as well as across gender, geographic regions, races, and ethnicities.

To highlight key clinical trials, Study AI424034, completed in 2002, showed similar efficacy and safety of ATV 400 mg without RTV boosting to an EFV-based regimen that was considered standard of care at the time. Subsequently Study AI424089 demonstrated the safety and efficacy of ATV/RTV 300 mg/100 mg compared with ATV 400 mg in treatment-naive subjects. Study AI424138 (CASTLE) demonstrated non-inferiority of ATV/RTV 300 mg/100 mg QD versus LPV/RTV 400 mg/100 mg twice daily (BID) (standard of care PI), both given in combination with 2 NRTIs in 883 randomized ARV-naïve HIV-1-infected subjects from 28 countries. Study AI424077 had subjects previously enrolled in BMS clinical studies AI42034, AI424041, AI424043, AI424044, AI424089, AI424138, and AI424182.

Overall exposure to ATV in clinical trials is presented in the following tables.

Table 2.3-1: Duration of ATV Exposure - Adults - Randomized, Blinded Trial Population

ATV Exposure by Duration - Randomized, Blinded Trial Population

Duration of Exposure	Persons	Person Time (Year)
Cumulative Up to 4 Weeks	419	31.7
Cumulative Up to 8 Weeks	407	62.7
Cumulative Up to 12 Weeks	397	92.6
Cumulative Up to 16 Weeks	383	121.8
Cumulative Up to 20 Weeks	377	150.7
Cumulative Up to 24 Weeks	372	179.3
Cumulative Up to 28 Weeks	366	207.1
Cumulative Up to 32 Weeks	360	234.5
Cumulative Up to 36 Weeks	353	261.5
Cumulative Up to 40 Weeks	349	288.4
Cumulative Up to 44 Weeks	345	314.5
Cumulative Up to 48 Weeks	339	340.6
Cumulative Up to 52 Weeks	335	366.1
Cumulative Up to 56 Weeks	327	390.8
Cumulative Up to 60 Weeks	317	415.1
Cumulative Up to 64 Weeks	316	439.4
Cumulative Up to 68 Weeks	312	463.4
Cumulative Up to 72 Weeks	311	487.1
Cumulative Up to 76 Weeks	305	510.6
Cumulative Up to 80 Weeks	301	533.3
Cumulative Up to 84 Weeks	280	552.1
Cumulative Up to 88 Weeks	200	564.1
Cumulative Up to 92 Weeks	100	569.2
Cumulative Up to 96 Weeks	44	571.4
Cumulative Up to 100 Weeks	17	572.2
Cumulative Up to 104 Weeks	2	572.3

Double Blinded studies: AI424-034, -037

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Table 2.3-2: Duration of ATV Exposure - Adults - Clinical Trial Population

ATV Exposure by Duration - Clinical Trial Population

Duration of Exposure	Persons	Person Time (Year)
Cumulative Up to 4 Weeks	3318	252.4
Cumulative Up to 8 Weeks	3242	499.4
Cumulative Up to 12 Weeks	3190	743.0
Cumulative Up to 16 Weeks	3142	983.0
Cumulative Up to 20 Weeks	3097	1219.8
Cumulative Up to 24 Weeks	3057	1453.5
Cumulative Up to 28 Weeks	2949	1676.7
Cumulative Up to 32 Weeks	2875	1895.9
Cumulative Up to 36 Weeks	2825	2111.0
Cumulative Up to 40 Weeks	2771	2322.9
Cumulative Up to 44 Weeks	2733	2531.5
Cumulative Up to 48 Weeks	2700	2736.4
Cumulative Up to 52 Weeks	2478	2914.0
Cumulative Up to 56 Weeks	2233	3083.2
Cumulative Up to 60 Weeks	2173	3249.0
Cumulative Up to 64 Weeks	2133	3411.9
Cumulative Up to 68 Weeks	2093	3571.6
Cumulative Up to 72 Weeks	2061	3729.5
Cumulative Up to 76 Weeks	2033	3882.7
Cumulative Up to 80 Weeks	1919	4025.4
Cumulative Up to 84 Weeks	1813	4163.1
Cumulative Up to 88 Weeks	1762	4296.7
Cumulative Up to 92 Weeks	1722	4428.2
Cumulative Up to 96 Weeks	1696	4555.8
Cumulative Up to 100 Weeks	1359	4648.2

Studies include: AI424-007,008,009,034,037,041,043,044,045,
067,077,089,097,121,131,136,138,182,227,376

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Table 2.3-2: Duration of ATV Exposure - Adults - Clinical Trial Population (cont)

Duration of Exposure	Persons	Person Time (Year)
Cumulative Up to 104 Weeks	1140	4734.7
Cumulative Up to 108 Weeks	1115	4819.9
Cumulative Up to 112 Weeks	1101	4903.9
Cumulative Up to 116 Weeks	1083	4986.3
Cumulative Up to 120 Weeks	1057	5066.7
Cumulative Up to 124 Weeks	1035	5145.7
Cumulative Up to 128 Weeks	1018	5223.9
Cumulative Up to 132 Weeks	1013	5301.6
Cumulative Up to 136 Weeks	1005	5378.3
Cumulative Up to 140 Weeks	986	5453.4
Cumulative Up to 144 Weeks	968	5527.2
Cumulative Up to 148 Weeks	949	5599.5
Cumulative Up to 152 Weeks	929	5670.1
Cumulative Up to 156 Weeks	902	5738.7
Cumulative Up to 160 Weeks	878	5804.7
Cumulative Up to 164 Weeks	843	5868.5
Cumulative Up to 168 Weeks	807	5929.2
Cumulative Up to 172 Weeks	779	5988.8
Cumulative Up to 176 Weeks	771	6046.7
Cumulative Up to 180 Weeks	733	6102.4
Cumulative Up to 184 Weeks	713	6156.0
Cumulative Up to 188 Weeks	679	6207.3
Cumulative Up to 192 Weeks	659	6257.3
Cumulative Up to 196 Weeks	611	6302.1
Cumulative Up to 200 Weeks	562	6344.9

Studies include: AI424-007,008,009,034,037,041,043,044,045,
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Table 2.3-2: Duration of ATV Exposure - Adults - Clinical Trial Population (cont)

Duration of Exposure	Persons	Person Time (Year)
Cumulative Up to 204 Weeks	549	6386.9
Cumulative Up to 208 Weeks	544	6428.2
Cumulative Up to 212 Weeks	529	6468.5
Cumulative Up to 216 Weeks	520	6508.2
Cumulative Up to 220 Weeks	510	6547.2
Cumulative Up to 224 Weeks	503	6585.5
Cumulative Up to 228 Weeks	489	6622.6
Cumulative Up to 232 Weeks	476	6659.1
Cumulative Up to 236 Weeks	466	6693.6
Cumulative Up to 240 Weeks	427	6724.0
Cumulative Up to 244 Weeks	353	6749.2
Cumulative Up to 248 Weeks	308	6771.8
Cumulative Up to 252 Weeks	281	6792.9
Cumulative Up to 256 Weeks	269	6813.1
Cumulative Up to 260 Weeks	256	6832.6
Cumulative Up to 264 Weeks	249	6851.5
Cumulative Up to 268 Weeks	244	6870.3
Cumulative Up to 272 Weeks	241	6888.2
Cumulative Up to 276 Weeks	226	6905.2
Cumulative Up to 280 Weeks	218	6921.4
Cumulative Up to 284 Weeks	207	6937.3
Cumulative Up to 288 Weeks	206	6953.0
Cumulative Up to 292 Weeks	201	6968.4
Cumulative Up to 296 Weeks	201	6983.9
Cumulative Up to 300 Weeks	199	6999.1

Studies include: AI424-007,008,009,034,037,041,043,044,045,
067,077,089,097,121,131,136,138,182,227,376

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Table 2.3-2: Duration of ATV Exposure - Adults - Clinical Trial Population (cont)

Duration of Exposure	Persons	Person Time (Year)
Cumulative Up to 304 Weeks	194	7013.9
Cumulative Up to 308 Weeks	192	7028.5
Cumulative Up to 312 Weeks	189	7042.9
Cumulative Up to 316 Weeks	184	7056.7
Cumulative Up to 320 Weeks	176	7069.9
Cumulative Up to 324 Weeks	169	7082.5
Cumulative Up to 328 Weeks	159	7094.7
Cumulative Up to 332 Weeks	158	7106.7
Cumulative Up to 336 Weeks	155	7118.6
Cumulative Up to 340 Weeks	155	7130.6
Cumulative Up to 344 Weeks	153	7142.3
Cumulative Up to 348 Weeks	151	7153.8
Cumulative Up to 352 Weeks	149	7165.1
Cumulative Up to 356 Weeks	146	7176.3
Cumulative Up to 360 Weeks	145	7187.5
Cumulative Up to 364 Weeks	144	7198.4
Cumulative Up to 368 Weeks	139	7209.1
Cumulative Up to 372 Weeks	137	7219.4
Cumulative Up to 376 Weeks	132	7229.2
Cumulative Up to 380 Weeks	125	7238.6
Cumulative Up to 384 Weeks	114	7247.0
Cumulative Up to 388 Weeks	103	7254.6
Cumulative Up to 392 Weeks	98	7262.0
Cumulative Up to 396 Weeks	97	7269.4
Cumulative Up to 400 Weeks	93	7276.4

Studies include: AI424-007,008,009,034,037,041,043,044,045,
067,077,089,097,121,131,136,138,182,227,376

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Table 2.3-2: Duration of ATV Exposure - Adults - Clinical Trial Population (cont)

Duration of Exposure	Persons	Person Time (Year)
Cumulative Up to 404 Weeks	90	7283.1
Cumulative Up to 408 Weeks	83	7289.4
Cumulative Up to 412 Weeks	79	7295.5
Cumulative Up to 416 Weeks	78	7301.5
Cumulative Up to 420 Weeks	76	7307.2
Cumulative Up to 424 Weeks	74	7312.9
Cumulative Up to 428 Weeks	73	7318.4
Cumulative Up to 432 Weeks	70	7323.7
Cumulative Up to 436 Weeks	69	7328.9
Cumulative Up to 440 Weeks	67	7334.0
Cumulative Up to 444 Weeks	64	7338.9
Cumulative Up to 448 Weeks	64	7343.8
Cumulative Up to 452 Weeks	64	7348.7
Cumulative Up to 456 Weeks	64	7353.6
Cumulative Up to 460 Weeks	63	7358.5
Cumulative Up to 464 Weeks	63	7363.3
Cumulative Up to 468 Weeks	63	7368.2
Cumulative Up to 472 Weeks	62	7372.9
Cumulative Up to 476 Weeks	62	7377.7
Cumulative Up to 480 Weeks	62	7382.5
Cumulative Up to 484 Weeks	62	7387.2
Cumulative Up to 488 Weeks	59	7391.6
Cumulative Up to 492 Weeks	57	7395.9
Cumulative Up to 496 Weeks	45	7399.0
Cumulative Up to 500 Weeks	34	7401.0

Studies include: AI424-007,008,009,034,037,041,043,044,045,
067,077,089,097,121,131,136,138,182,227,376

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Table 2.3-2: Duration of ATV Exposure - Adults - Clinical Trial Population (cont)

Duration of Exposure	Persons	Person Time (Year)
Cumulative Up to 504 Weeks	18	7402.1
Cumulative Up to 508 Weeks	11	7402.8
Cumulative Up to 512 Weeks	8	7403.3
Cumulative Up to 516 Weeks	7	7403.9
Cumulative Up to 520 Weeks	7	7404.4
Cumulative Up to 524 Weeks	7	7404.9
Cumulative Up to 528 Weeks	7	7405.5
Cumulative Up to 532 Weeks	7	7406.0
Cumulative Up to 536 Weeks	7	7406.6
Cumulative Up to 540 Weeks	7	7407.1
Cumulative Up to 544 Weeks	7	7407.6
Cumulative Up to 548 Weeks	7	7408.2
Cumulative Up to 552 Weeks	7	7408.7
Cumulative Up to 556 Weeks	7	7409.3
Cumulative Up to 560 Weeks	7	7409.8
Cumulative Up to 564 Weeks	7	7410.3
Cumulative Up to 568 Weeks	7	7410.9
Cumulative Up to 572 Weeks	7	7411.4
Cumulative Up to 576 Weeks	7	7411.9
Cumulative Up to 580 Weeks	7	7412.5
Cumulative Up to 584 Weeks	7	7413.0
Cumulative Up to 588 Weeks	7	7413.6
Cumulative Up to 592 Weeks	7	7414.1
Cumulative Up to 596 Weeks	7	7414.6
Cumulative Up to 600 Weeks	7	7415.2

Studies include: AI424-007,008,009,034,037,041,043,044,045,
067,077,089,097,121,131,136,138,182,227,376

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Table 2.3-2: Duration of ATV Exposure - Adults - Clinical Trial Population (cont)

Duration of Exposure	Persons	Person Time (Year)
Cumulative Up to 604 Weeks	7	7415.7
Cumulative Up to 608 Weeks	7	7416.3
Cumulative Up to 612 Weeks	7	7416.8
Cumulative Up to 616 Weeks	7	7417.3
Cumulative Up to 620 Weeks	7	7417.9
Cumulative Up to 624 Weeks	7	7418.4
Cumulative Up to 628 Weeks	7	7418.9
Cumulative Up to 632 Weeks	7	7419.5
Cumulative Up to 636 Weeks	7	7420.0
Cumulative Up to 640 Weeks	7	7420.6
Cumulative Up to 644 Weeks	7	7421.0
Cumulative Up to 648 Weeks	6	7421.5
Cumulative Up to 652 Weeks	6	7422.0
Cumulative Up to 656 Weeks	6	7422.4
Cumulative Up to 660 Weeks	6	7422.9
Cumulative Up to 664 Weeks	6	7423.3
Cumulative Up to 668 Weeks	6	7423.8
Cumulative Up to 672 Weeks	6	7424.3
Cumulative Up to 676 Weeks	6	7424.7
Cumulative Up to 680 Weeks	6	7425.2
Cumulative Up to 684 Weeks	6	7425.7
Cumulative Up to 688 Weeks	6	7426.1
Cumulative Up to 692 Weeks	6	7426.6
Cumulative Up to 696 Weeks	6	7427.0
Cumulative Up to 700 Weeks	6	7427.5

Studies include: AI424-007,008,009,034,037,041,043,044,045,
067,077,089,097,121,131,136,138,182,227,376

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Table 2.3-2: Duration of ATV Exposure - Adults - Clinical Trial Population (cont)

Duration of Exposure	Persons	Person Time (Year)
Cumulative Up to 704 Weeks	6	7428.0
Cumulative Up to 708 Weeks	6	7428.4
Cumulative Up to 712 Weeks	6	7428.9
Cumulative Up to 716 Weeks	6	7429.3
Cumulative Up to 720 Weeks	6	7429.8
Cumulative Up to 724 Weeks	6	7430.3
Cumulative Up to 728 Weeks	6	7430.7
Cumulative Up to 732 Weeks	6	7431.2
Cumulative Up to 736 Weeks	6	7431.7
Cumulative Up to 740 Weeks	6	7432.1
Cumulative Up to 744 Weeks	6	7432.6
Cumulative Up to 748 Weeks	6	7433.0
Cumulative Up to 752 Weeks	6	7433.5
Cumulative Up to 756 Weeks	6	7433.9
Cumulative Up to 760 Weeks	5	7434.3
Cumulative Up to 764 Weeks	2	7434.4

Studies include: AI424-007,008,009,034,037,041,043,044,045,
067,077,089,097,121,131,136,138,182,227,376

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PROGRAM SOURCE: /wwbdm/clin/proj/av/424/iss01/val/cpp/output/rmp_2016/sfty_rmp_int.sas RUN DATE: 02-SEP-2016 16:29

Table 2.3-3: Clinical Exposure by Dose - Adults - Randomized, Blinded Trial Population

ATV Exposure by Dose Level - Randomized, Blinded Trial Population

Dose of Exposure	Persons	Person Time (Year)
ATV 400 mg	419	572.3

Double Blinded studies: AI424-034, -037

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PROGRAM SOURCE: /wwbdm/clin/proj/av/424/iss01/val/cpp/output/rmp_2016/sfty_rmp_int.sas RUN DATE: 02-SEP-2016 16:29

Table 2.3-4: Clinical Exposure by Dose - Adults - Clinical Trial Population

ATV Exposure by Dose Level - Clinical Trial Population

Dose of Exposure	Persons	Person Time (Year)
ATV 200 mg	102	154.2
ATV 300 mg	1217	2646.9
ATV 400 mg	1808	3786.4
ATV 500 mg	107	170.0
ATV 600 mg	222	676.9

Studies include: AI424-007,008,009,034,037,041,043,044,045,
067,077,089,097,121,131,136,138,182,227,376
Subject may be counted under multiple Dose of Exposure categories

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Table 2.3-5: Clinical Exposure by Age Group and Gender - Randomized, Blinded Trial Population

ATV Exposure by Age Group and Gender - Randomized, Blinded Trial Population

	Persons		Person Time (Year)	
Age Group	Male	Female	Male	Female
< 16	0	0	0	0
16 - 20	6	6	8.4	9.5
21 - 64	257	148	355.3	195.7
>= 65	1	1	1.9	1.6

Double Blinded studies: AI424-034, -037

LIBRARY: /wwbdm/clin/proj/av/424/iss01/sasds/sasds_mar2013_rmp EXTRACT DATE: 26-MAR-2013
PROGRAM SOURCE: /wwbdm/clin/proj/av/424/iss01/val/cpp/output/rmp_2016/sfty_rmp_int.sas RUN DATE: 02-SEP-2016 16:29

Table 2.3-6: ATV Exposure by Age Group and Gender - Clinical Trial Population

ATV Exposure by Age Group and Gender - Clinical Trial Population

	Persons		Person Time (Year)	
Age Group	Male	Female	Male	Female
< 16	0	0	0	0
16 - 20	23	22	53.3	45.2
21 - 64	2283	949	5019.9	2252.4
>= 65	34	7	52.5	11.1

Studies include: AI424-007,008,009,034,037,041,043,044,045,
067,077,089,097,121,131,136,138,182,227,376

LIBRARY: /wwbdm/clin/proj/av/424/iss01/sasds/sasds_mar2013_rmp EXTRACT DATE: 26-MAR-2013
PROGRAM SOURCE: /wwbdm/clin/proj/av/424/iss01/val/cpp/output/rmp_2016/sfty_rmp_int.sas RUN DATE: 02-SEP-2016 16:29

Table 2.3-7: Clinical Exposure by Ethnic or Racial Origin - Randomized, Blinded Trial Population

ATV Exposure by Race - Randomized, Blinded Trial Population

Race	Persons	Person Time (Year)
WHITE	145	182.4
BLACK/MIXED	63	83.6
ASIAN/PACIFIC ISLANDERS	58	89.2
HISPANIC/LATINO	153	217.0

Double Blinded studies: AI424-034,-037

LIBRARY: /wwbdm/clin/proj/av/424/iss01/sasds/sasds_mar2013_rmp EXTRACT DATE: 26-MAR-2013
PROGRAM SOURCE: /wwbdm/clin/proj/av/424/iss01/val/cpp/output/rmp_2016/sfty_rmp_int.sas RUN DATE: 02-SEP-2016 16:29

Table 2.3-8: Clinical Exposure by Ethnic or Racial Origin - Clinical Trial Population

ATV Exposure by Race - Clinical Trial Population

Race	Persons	Person Time (Year)
WHITE	1938	3645.8
BLACK/MIXED	660	1587.5
ASIAN/PACIFIC ISLANDERS	173	605.7
HISPANIC/LATINO	325	860.7
OTHER	222	734.7

Studies include: AI424-007,008,009,034,037,041,043,044,045,
067,077,089,097,121,131,136,138,182,227,376
Hispanic/Latino is not a race category in studies AI424-067, 097, 089 and 138.

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PROGRAM SOURCE: /wwbdm/clin/proj/av/424/iss01/val/cpp/output/rmp_2016/sfty_rmp_int.sas RUN DATE: 02-SEP-2016 16:29

Table 2.3-9: Clinical Exposure by Special Populations - AI424020 Pediatric Trial

AI424020 Pediatric Trial Population

Special Population	Persons	Person Time (Year)
Pediatric Subjects	193	737.7

Study: AI424-020

LIBRARY: /wwbdm/clin/proj/av/424/020/sasds/finalcsr_20141212
PROGRAM SOURCE: /wwbdm/clin/proj/av/424/iss01/dev/cpp/output/rmp_2014/rt-rmp-v01.sas

EXTRACT DATE: 12-DEC-2014
RUN DATE: 26-JAN-2015 15:13

Table 2.3-10: Clinical Exposure by Special Populations - AI424397 and AI424451 Pediatric Trials

ATV Exposure by Special Population - AI424397 and AI424451 Pediatric Trial Population

Special Population	Persons	Person Time (Year)
Pediatric Subjects	155	344.1

Study: AI424-397[19] and AI424-451[20]

Table 2.3-11: Clinical Exposure by Special Population - AI424452 Pediatric Trials

AI424452 Pediatric Trial Population

Special Population	Persons	Person Time (Year)
Pediatric Subjects	59	49.0

Study: AI424-452

LIBRARY: /gbs/prod/clin/data/ai/424/452/ia01/unblinded/level1
PROGRAM SOURCE: /wwbdm/clin/proj/av/424/iss01/dev/cpp/output/rmp_2014/rt-rmp-v01.sas

EXTRACT DATE: 04-DEC-2014
RUN DATE: 26-JAN-2015 15:13

Table 2.3-12: Clinical Exposure by Region - Randomized, Blinded Trial Population

ATV Exposure by Region - Randomized, Blinded Trial Population

Region	Persons	Person Time (Year)
ASIA	57	86.5
EUROPE	111	149.8
NORTH AMERICA	67	75.2
SOUTH AMERICA	144	204.0
AFRICA	40	56.8

Double Blinded studies: AI424-034,-037

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PROGRAM SOURCE: /wwbdm/clin/proj/av/424/iss01/val/cpp/output/rmp_2016/sfty_rmp_int.sas RUN DATE: 02-SEP-2016 16:29

Table 2.3-13: Clinical Exposure by Region - Clinical Trial Population

ATV Exposure by Region - Clinical Trial Population

Region	Persons	Person Time (Year)
ASIA	156	553.1
EUROPE	1256	2039.5
NORTH AMERICA	658	1084.0
SOUTH AMERICA	864	2556.4
AFRICA	384	1201.4

Studies include: AI424-007,008,009,034,037,041,043,044,045,
067,077,089,097,121,131,136,138,182,227,376
Europe includes Australia

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Table 2.3-14: Clinical Exposure by Special Populations - Treated Mothers in Study AI424182

ATV Exposure by Special Populations - Treated Mothers in Study AI424182

	Time on Study Therapy							
	Treatment Regimen							
	ATV300/RTV N = 20				ATV400/RTV N = 21			
Interval (Weeks) (a)	N at Risk (b)	N Events (c)	N Censored (c)	Prop (d)	N at Risk (b)	N Events (c)	N Censored (c)	Prop (d)
0 - 2	20	0	0	1.0000	21	1	0	0.9524
2 - 4	20	0	0	1.0000	20	1	0	0.9524
4 - 6	20	0	0	1.0000	20	1	0	0.9524
6 - 8	20	0	0	1.0000	20	1	0	0.9524
8 - 10	20	2	0	0.9000	20	2	0	0.9048
10 - 12	18	3	0	0.8500	19	2	0	0.9048
12 - 14	17	4	0	0.8000	19	3	0	0.8571
14 - 16	16	7	0	0.6500	18	4	0	0.8095
16 - 18	13	9	0	0.5500	17	4	0	0.8095
18 - 20	11	12	0	0.4000	17	7	0	0.6667
20 - 22	8	14	0	0.3000	14	10	0	0.5238
22 - 24	6	16	0	0.2000	11	12	0	0.4286
24 - 26	4	17	0	0.1500	9	14	0	0.3333
26 - 28	3	19	0	0.0500	7	15	0	0.2857
28 - 30	1	20	0	0.0000	6	19	0	0.0952
30 - 32	0	20	0	0.0000	2	21	0	0.0000

(a) Intervals include right endpoint
(b) At risk entering interval
(c) Cumulative
(d) Kaplan-Meier cumulative proportion without events at end of interval

LIBRARY: /wwbdm/data/ai/424/182/fa01/blinded/analysis EXTRACT DATE: 11-SEP-2009
PROGRAM SOURCE: /wwbdm/clin/proj/av/424/182/val/stats/fa01/dse_tmtherapy.sas RUN DATE: 29-OCT-2009 09:19

2.4 Populations Not Studied in Clinical Trials

The efficacy of ATV-containing regimens has been demonstrated in a diverse population of HIV-infected adults across a wide spectrum of CD4 cell counts, baseline HIV RNA levels, and prior treatment regimens, as well as across genders, geographic regions, races, and ethnicities.

Subjects < 3 months of age have not been included in ATV pediatric clinical trials, because ATV is associated with a reversible elevation in indirect (unconjugated) bilirubin related to inhibition of the hepatic enzyme, UGT1A1. Indirect (unconjugated) hyperbilirubinemia can potentially produce brain damage, either acutely ("acute bilirubin encephalopathy") or chronically with permanent sequelae ("kernicterus") in pre-term and term infants.

2.4.1 Exclusion Criteria in Pivotal Clinical Studies within the Development Programme

Table 2.4.1-1: Important Exclusion Criteria in Pivotal Clinical Studies

Criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale (if not included as missing information)
Moderate or severe hepatic insufficiency	ATV is metabolized and excreted by the liver and levels could be increased with significant liver impairment.	No	Use of ATV is contraindicated for patients with moderate to severe hepatic impairment
Known Hypersensitivity to ATV or any components	May be potentially life threatening. Alternative therapy should be considered for patients who are hypersensitive to ATV.	No	Hypersensitivity to ATV or any of its components is a contraindication.
Cardiac disease	Important risk of PR prolongation and the potential risk of QT prolongation	No	Included as important risk of PR prolongation and the potential risk of QT prolongation (see Section 2.7.3)
Cardiac conduction abnormalities	Important risk of PR prolongation and the potential risk of QT prolongation	No	Included as important risk of PR prolongation and the potential risk of QT prolongation (see Section 2.7.3)

2.4.2 Limitations to Detect Adverse Reactions in Clinical Trial Development Programmes

The clinical development programme is unlikely to detect certain types of adverse reactions such as rare adverse reactions and adverse reactions (ARs) with long latency. Continuing post-marketing safety monitoring support the identification of new AR related to ATV that are either rare or that have a long latency.

2.4.3 Limitations in Respect to Populations Typically Under-represented in Clinical Trial Development Programmes

Table 2.4.3-1: Exposure of Special Populations Included or Not in Clinical Trial Development Programmes

Type of special population	Exposure
Pregnant women: Study AI424182 serves as the basis for the recommendations for dosing of ATV during pregnancy in the Summary of Product Characteristics (SmPC). The Antiretroviral Pregnancy Registry (APR) has sufficient numbers of first trimester exposures to ATV to detect at least a 1.5-fold increase in risk of overall birth defects. No such increases have been detected to date, although these data represent a limited number of pregnancies among HIV-infected women. The current ART guidelines from the National Institutes of Health (NIH) and International AIDS Society support the use of ATV during pregnancy.	Study AI424182:[14] 41 subjects APR Registry: As of 31-Jul-2024, a total of 1,493 live births were reported among pregnancies with exposure to any ATV-containing regimen in the first trimester exposure; 797 live births were reported among pregnancies with exposure to any ATV-containing regimen in the second/third trimester.[15]
Breastfeeding women: ATV has been detected in human milk in HIV+ women receiving highly active antiretroviral therapy.[16] No data are available regarding ATV effects on milk production in humans. A study in lactating rats demonstrated that ATV is secreted in milk. [17] Because of both the potential for HIV transmission and the potential for serious ARs in nursing infants, mothers should be instructed not to breastfeed if they are receiving ATV.	No formal clinical studies conducted
Pediatrics: Pediatric studies have included subjects from ≥ 3 months to 21 years.	Study AI424020 (PACTG 1020A):[18] 193 subjects StudyAI424397:[19] 56 subjects Study AI424451:[20] 99 subjects Study AI424452:[21] 59 subjects Study AI424450:[22] 372 subjects
Patients with relevant comorbidities:	
Patients with hepatic impairment: Increased concentrations of ATV are expected in patients with moderately or severely impaired hepatic function. The PK of ATV in combination with RTV has not been studied in subjects with hepatic impairment.	Study AI424015:[23] 33 subjects
Patients with renal impairment	Study AI424105:[24] 20 subjects
Patients with cardiovascular impairment	No formal clinical studies conducted
Immunocompromised patients	No formal clinical studies conducted

Table 2.4.3-1: Exposure of Special Populations Included or Not in Clinical Trial Development Programmes

Type of special population	Exposure
Patients with a disease severity different from inclusion criteria in clinical trials	No formal clinical studies conducted , other than those listed for hepatic and renal impairment
Population with relevant different ethnic ethnicity	ATV has been studied in different races (Blacks, Caucasians, Asians, Hispanics, and Mestizos) and geographic regions (Europe, Asia, Africa, and North and South America).
Subpopulations carrying relevant genetic polymorphisms:	
UGT1A1	AI424007:[25] 29 subjects AI424008:[25] 206 subjects
Other	
Pediatrics < 3 months old: ATV should not be used in children < 3 months of age because of the potential risk of kernicterus.	No formal clinical studies conducted
Elderly Patients	AI424014:[26] 30 subjects

2.5 Post-Authorisation Experience

Atazanavir has been on the market in the United States (US) since 2003, and in the EU since 2004, and it is marketed in many other countries and regions.

2.5.1 Post-authorisation Exposure

2.5.1.1 Method Used to Calculate Exposure

There is no readily available information on the number of patients treated with marketed ATV. However, an estimate of the number of treated patients can be derived from available sales figures.

Vendors provide sales figures to the Company for ATV on a quarterly basis that are generally available 3 months after the close of a calendar quarter. Although these data represent the bulk (80% - 85%) of the Company's worldwide sales of ATV, they are only an estimation of the total quantity of product sold based on the total amount of product distributed in all countries worldwide. Additionally, the sales data from vendors may vary from one reporting period to another because of changes in subscription agreements and changes to the number of data channels available within a given country (eg, direct-to-consumer sales, hospital sales, and home care sales).

2.5.1.2 Exposure

ATV has a well-characterized safety profile that is consistent across approved indications (see Section 2.7.3). Taking into account the available sales data and the assumptions the cumulative number of patients treated from 20-Jun-2003 through 31-Mar-2025 is estimated to be:

Capsules - 2,636,768 patients

Oral powder - 107 patients

The numbers above are estimates and should be interpreted with caution, taking into account all of the above mentioned limitations.

2.6 Additional EU Requirements for the Safety Specification

2.6.1 Potential for Misuse for Illegal Purposes

The risk of misuse for illegal purposes is low, as the drug is not a controlled substance, and has no addictive potential.

2.7 Identified and Potential Risks

2.7.1 Identification of Safety Concerns in the Initial RMP Submission

Safety concerns identified in the initial submission of the RMP[27] from 2008 are summarized in Table 2.7.1-1.

Table 2.7.1-1: Safety Concerns in the Initial RMP

Important identified risks	Cardiac conduction abnormalities (PR interval prolongation)
	Nephrolithiasis
	Hyperbilirubinemia
Important potential risks	QT prolongation
Missing information	Pregnancy and lactation
	Renal impairment
	Hepatic impairment
	Pediatric population

Source: REYATAZ EU RMP V1.0[27]

2.7.1.1 Risks Not Considered Important for Inclusion in the List of Safety Concerns in the RMP

At the time of the initial RMP submission, safety risks that were not included in the RMP did not meet the criteria to be designated as an important identified or potential risk. ATV's well characterized safety profile has been consistent across approved indications and reflected in the SmPC under Sections 4.4 and 4.8.

2.7.1.2 Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

Risks considered important for inclusion in the list of safety concerns for the initial RMP[27] from 2008 are provided in Table 2.7.1.2-1.

Table 2.7.1.2-1: Risks Considered Important for Inclusion in the List of Safety Concerns in the Initial RMP

Risk Type	Risk-Benefit Impact
Important identified risks	
Cardiac conduction abnormalities (PR interval prolongation)	Dose related asymptomatic prolongations in PR interval with ATV have been observed in clinical studies. Caution should be used with medicinal products known to induce PR prolongations. In patients with pre-existing conduction problems (second degree or higher atrioventricular or complex bundle-branch block), ATV should be used with caution and only if the benefits exceed the risk.
Nephrolithiasis	ATV is metabolized and excreted mainly through the liver, and only 13% of a single radiolabeled 400 mg dose was recovered in the urine, of which 7% constituted unchanged drug. The mechanism of development of kidney stones containing ATV or ATV metabolites is not known.
Hyperbilirubinemia	Reversible elevations in indirect (unconjugated) bilirubin related to inhibition of UDP-glucuronosyl transferase (UGT) have occurred in patients receiving ATV. Hepatic transaminase elevations that occur with elevated bilirubin in patients receiving ATV should be evaluated for alternative etiologies. Alternative ARV therapy to ATV may be considered if jaundice or scleral icterus is unacceptable to a patient. Dose reduction of ATV is not recommended because it may result in a loss of therapeutic effect and development of resistance. Indinavir is also associated with indirect (unconjugated) hyperbilirubinemia due to inhibition of UGT. Combinations of ATV and indinavir have not been studied and co-administration of these medicinal products is not recommended.
Important potential risks	
QT prolongation	Particular caution should be used when prescribing ATV concomitantly 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, and electrolyte imbalances etc.)
Missing Information	
Pregnancy and lactation	There are no adequate data from the use of ATV in pregnant women. Studies in animals have not shown evidence of selective developmental toxicity or effects on reproductive function and fertility. ATV should be used during pregnancy only if the potential benefit justifies the potential risk. It is not known whether ATV administered to the mother during pregnancy will exacerbate physiological hyperbilirubinemia and lead to kernicterus in neonates and infants. In the pre-partum period, additional monitoring and alternative therapy to ATV should be considered. It is not known whether ATV is excreted in human milk. Studies in rats have demonstrated that ATV is excreted in the milk. It is therefore recommended that mothers being treated with ATV do not breast-feed their infants. As a general rule, it is recommended that HIV infected women not breast-feed their infants in order to avoid transmission of HIV.
Renal impairment	In healthy subjects, the renal elimination of unchanged ATV was approximately 7% of the administered dose. There are no PK data

Table 2.7.1.2-1: Risks Considered Important for Inclusion in the List of Safety Concerns in the Initial RMP

Risk Type	Risk-Benefit Impact
	available on patients with renal insufficiency; however, the impact of renal impairment on ATV's elimination is anticipated to be minimal.
Hepatic impairment	ATV with RTV should be used with caution in patients with mild hepatic insufficiency. ATV should not be used in patients with moderate to severe hepatic insufficiency. ATV with RTV has not been studied in patients with hepatic insufficiency.
Pediatric population	The experience in children is limited.

2.7.2 New Safety Concerns and Reclassification with a Submission of an Updated RMP

Table 2.7.2-1: New Safety Concerns and Reclassification with a Submission of an Updated RMP

Safety Concern	
Reclassification	
Important Identified Risks	
PR interval prolongation (both pediatric and adult populations) removed from list of important identified risk	Background: To ensure alignment with the GVP Module V (Rev 2) definition of the list of safety concerns. Action Taken: In response to the revisions in GVP Module V, the MAH has removed PR interval prolongation (both pediatric and adult populations) from the list of safety concerns. Rationale: There are no additional pharmacovigilance activities and/or risk minimization activities in relation to the important identified risk of PR interval prolongation (both pediatric and adult populations). Risk minimisation communication in the product label appropriately addresses this risk. As this product has been on the market for a long time (more than 20 years), the SmPC routine risk minimisation measures are expected to be fully integrated into standard clinical practice. The MAH will continue to monitor PR interval prolongation as part of routine pharmacovigilance.
Nephrolithiasis removed from list of important identified risk	Background: To ensure alignment with the GVP Module V (Rev 2) definition of the list of safety concerns. Action Taken: In response to the revisions in GVP Module V, the MAH has removed Nephrolithiasis from the list of safety concerns. Rationale: There are no additional pharmacovigilance activities and/or risk minimization activities in relation to the important identified risk of Nephrolithiasis. Risk minimisation communication in the product label appropriately addresses this risk. As this product has been on the market for a long time (more than 20 years), the SmPC routine risk minimisation measures are expected to be fully integrated into standard clinical practice. The MAH will continue to monitor Nephrolithiasis as part of routine pharmacovigilance.

Table 2.7.2-1: New Safety Concerns and Reclassification with a Submission of an Updated RMP

Safety Concern	
Hyperbilirubinemia removed from list of important identified risk	Background: To ensure alignment with the GVP Module V (Rev 2) definition of the list of safety concerns. Action Taken: In response to the revisions in GVP Module V, the MAH has removed Hyperbilirubinemia from the list of safety concerns. Rationale: There are no additional pharmacovigilance activities and/or risk minimization activities in relation to the important identified risk of Hyperbilirubinemia. Risk minimisation communication in the product label appropriately addresses this risk. As this product has been on the market for a long time (more than 20 years), the SmPC routine risk minimisation measures are expected to be fully integrated into standard clinical practice. The MAH will continue to monitor Hyperbilirubinemia as part of routine pharmacovigilance.
Severe skin reactions removed from list of important identified risk	Background: To ensure alignment with the GVP Module V (Rev 2) definition of the list of safety concerns. Action Taken: In response to the revisions in GVP Module V, the MAH has removed Severe skin reactions from the list of safety concerns. Rationale: There are no additional pharmacovigilance activities and/or risk minimization activities in relation to the important identified risk of Severe skin reactions. Risk minimisation communication in the product label appropriately addresses this risk. As this product has been on the market for a long time (more than 20 years), the SmPC routine risk minimisation measures are expected to be fully integrated into standard clinical practice. The MAH will continue to monitor Severe skin reactions as part of routine pharmacovigilance.
Cholelithiasis removed from list of important identified risk	Background: To ensure alignment with the GVP Module V (Rev 2) definition of the list of safety concerns. Action Taken: In response to the revisions in GVP Module V, the MAH has removed Cholelithiasis from the list of safety concerns. Rationale: There are no additional pharmacovigilance activities and/or risk minimization activities in relation to the important identified risk of Cholelithiasis. Risk minimisation communication in the product label appropriately addresses this risk. As this product has been on the market for a long time (more than 20 years), the SmPC routine risk minimisation measures are expected to be fully integrated into standard clinical practice. The MAH will continue to monitor Cholelithiasis as part of routine pharmacovigilance.
Angioedema removed from list of important identified risk	Background: To ensure alignment with the GVP Module V (Rev 2) definition of the list of safety concerns. Action Taken: In response to the revisions in GVP Module V, the MAH has removed Angioedema from the list of safety concerns. Rationale: There are no additional pharmacovigilance activities and/or risk minimization activities in relation to the important identified risk of Angioedema. Risk minimisation communication in the product label appropriately addresses this risk. As this product has been on the market for a long time (more than 20 years), the SmPC routine risk minimisation measures are expected to be fully integrated into standard clinical practice. The MAH will continue to monitor Angioedema as part of routine pharmacovigilance.

Table 2.7.2-1: New Safety Concerns and Reclassification with a Submission of an Updated RMP

Safety Concern	
IRIS removed from list of important identified risk	Background: To ensure alignment with the GVP Module V (Rev 2) definition of the list of safety concerns. Action Taken: In response to the revisions in GVP Module V, the MAH has removed IRIS from the list of safety concerns. Rationale: There are no additional pharmacovigilance activities and/or risk minimization activities in relation to the important identified risk of IRIS. Risk minimisation communication in the product label appropriately addresses this risk. As this product has been in the market for a long time (more than 20 years), the SmPC routine risk minimisation measures are expected to be fully integrated into standard clinical practice. The MAH will continue to monitor IRIS as part of routine pharmacovigilance.
CKD removed from list of important identified risk	Background: To ensure alignment with the GVP Module V (Rev 2) definition of the list of safety concerns. Action Taken: In response to the revisions in GVP Module V, the MAH has removed CKD from the list of safety concerns. Rationale: There are no additional pharmacovigilance activities and/or risk minimization activities in relation to the important identified risk of CKD. Risk minimisation communication in the product label appropriately addresses this risk. As this product has been in the market for a long time (more than 20 years), the SmPC routine risk minimisation measures are expected to be fully integrated into standard clinical practice. The MAH will continue to monitor CKD as part of routine pharmacovigilance.
Important Potential Risk	
QT prolongation removed from list of important potential risk	Background: To ensure alignment with the GVP Module V (Rev 2) definition of the list of safety concerns. Action Taken: In response to the revisions in GVP Module V, the MAH has removed QT prolongation from the list of safety concerns. Rationale: There are no additional pharmacovigilance activities and/or risk minimization activities in relation to the important potential risk of QT prolongation. Risk minimisation communication in the product label appropriately addresses this important potential risk. As this product has been on the market for a long time (more than 20 years), the SmPC routine risk minimisation measures are expected to be fully integrated into standard clinical practice. The MAH will continue to monitor QT prolongation as part of routine pharmacovigilance.
Kernicterus removed from list of important potential risk	Background: To ensure alignment with the GVP Module V (Rev 2) definition of the list of safety concerns. Action Taken: In response to the revisions in GVP Module V, the MAH has removed Kernicterus from the list of safety concerns. Rationale: There are no additional pharmacovigilance activities and/or risk minimization activities in relation to this important potential risk of Kernicterus. Risk minimisation communication in the product label appropriately addresses this important potential risk. As this product has been on the market for a long time (more than 20 years), the SmPC routine risk minimisation measures are

Table 2.7.2-1: New Safety Concerns and Reclassification with a Submission of an Updated RMP

Safety Concern	
	expected to be fully integrated into standard clinical practice. The MAH will continue to monitor Kernicterus as part of routine pharmacovigilance.
Acute renal failure (adults) removed from list of important potential risk	Background: To ensure alignment with the GVP Module V (Rev 2) definition of the list of safety concerns. Action Taken: In response to the revisions in GVP Module V, the MAH has removed Acute renal failure (adults) from the list of safety concerns. Rationale: There are no additional pharmacovigilance activities and/or risk minimization activities in relation to the important potential risk of Acute renal failure. Risk minimisation communication in the product label appropriately addresses this important potential risk. As this product has been on the market for a long time (more than 20 years), the SmPC routine risk minimisation measures are expected to be fully integrated into standard clinical practice. The MAH will continue to monitor Acute renal failure (adults) as part of routine pharmacovigilance.
Interstitial nephritis removed from list of important potential risk	Background: To ensure alignment with the GVP Module V (Rev 2) definition of the list of safety concerns. Action Taken: In response to the revisions in GVP Module V, the MAH has removed Interstitial nephritis from the list of safety concerns. Rationale: There are no additional pharmacovigilance activities and/or risk minimization activities in relation to the important potential risk of Interstitial nephritis. Risk minimisation communication in the product label appropriately addresses this important potential risk. As this product has been on the market for a long time (more than 20 years), the SmPC routine risk minimisation measures are expected to be fully integrated into standard clinical practice. The MAH will continue to monitor Interstitial nephritis as part of routine pharmacovigilance.
Lack of efficacy due to unboosted ATV “off-label use” removed from list of important potential risk	Background: To ensure alignment with the GVP Module V (Rev 2) definition of the list of safety concerns. Action Taken: In response to the revisions in GVP Module V, the MAH has removed Lack of efficacy due to unboosted ATV “off-label use” from the list of safety concerns. Rationale: There are no additional pharmacovigilance activities and/or risk minimization activities in relation to the important potential risk of Lack of efficacy due to unboosted ATV “off-label use”. Risk minimisation communication in the product label appropriately addresses this important potential risks. As this product has been on the market for a long time (more than 20 years), the SmPC routine risk minimisation measures are expected to be fully integrated into standard clinical practice. The MAH will continue to monitor Lack of efficacy due to unboosted ATV “off-label use” as part of routine pharmacovigilance.
Missing Information	
Pregnancy previously classified as missing information removed from the list of safety concerns.	Rationale to justify removal of missing information “pregnancy”: The data within the Antiretroviral Pregnancy Registry (APR) is considered sufficient enough to detect any potential increase in the risk of birth defects with respect to atazanavir. There are also no increased risks when comparing pregnancies exposed in the first trimester to those exposed in the second or third

Table 2.7.2-1: New Safety Concerns and Reclassification with a Submission of an Updated RMP

Safety Concern	
	trimesters. The APR data are substantial enough to rule out a 1.5-fold increase in the risk of overall birth defects and a 2-fold increase in risk for birth defects in the most common defect classes. Additionally, there is no consistent pattern among the types of reported birth defects. A review of the Company Safety Database has not identified any new safety signals or concerns beyond those already captured through the APR. The prevalence of birth defects among infants born to individuals with HIV is comparable to the general population (2%–6%).
Geriatric patients previously classified as missing information removed from the list of safety concerns.	Background: To ensure alignment with the GVP Module V (Rev 2) definition of the list of safety concerns. Action Taken: In response to the revisions in GVP Module V, the MAH removed geriatric patients from the list of safety concerns. Rationale: A cumulative search of the events (359 cases with 703 events) reported in patients aged 65 years and above did not identify any new safety information than is previously known. Based on the available data, no apparent differences were observed in the types of events reported in this subgroup compared with the general population. Atazanavir has been on the market for a long time (20 years) it is determined that no existing or future PV activities could further characterize the safety profile of the product with respect to the use in geriatrics. The MAH will continue to monitor Geriatric patients as part of routine pharmacovigilance.

2.7.3 Details of Important Identified Risks, Important Potential Risks, and Missing Information

There are no important identified risks, important potential risks, or missing information for ATV.

2.8 Summary of the Safety Concerns

There are no safety concerns for ATV.

3 PART III: PHARMACOVIGILANCE PLAN

3.1 Routine Pharmacovigilance Activities

There are no routine pharmacovigilance activities beyond signal detection and adverse events reporting.

3.2 Additional Pharmacovigilance Activities

There are no aPVAs proposed at this time.

3.3 Summary Table of Additional Pharmacovigilance Activities

Not Applicable.

4 PART IV: PLANS FOR POST-AUTHORISATION EFFICACY STUDIES

Not Applicable.

5 PART V: RISK MINIMISATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMISATION ACTIVITIES)

5.1 Routine Risk Minimisation Measures

Not applicable; there are no safety concerns.

5.2 Additional Risk Minimisation Measures

Not applicable; there are no safety concerns.

5.3 Summary Table of Risk Minimisation Measures

Not applicable.

6 SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of risk management plan for REYATAZ (atazanavir)

This is a summary of the risk management plan (RMP) for REYATAZ. The RMP details important risks of REYATAZ, how these risks can be minimised, and how more information will be obtained about REYATAZ's risks and uncertainties (missing information).

REYATAZ's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how REYATAZ should be used.

This summary of the RMP for REYATAZ should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of REYATAZ's RMP.

I. The medicine and what it is used for

REYATAZ is used together with low-dose ritonavir (RTV) and other antiviral medicines to treat adults and children aged 3 months and over and weighing at least 5 kg who are infected with human immunodeficiency virus type 1 (HIV-1), a virus that causes acquired immune deficiency syndrome (AIDS). It contains atazanavir sulphate as the active substance and it is given by oral route.

Further information about the evaluation of REYATAZ's benefits can be found in REYATAZ's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage.

https://www.ema.europa.eu/en/medicines/human/EPAR/reyataz

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of REYATAZ, together with measures to minimise such risks and the proposed studies for learning more about REYATAZ's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals
- Important advice on the medicine's packaging
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly
- The medicine's legal status — the way a medicine is supplied to the patient (eg, with or without prescription) can help to minimise its risks

Together, these measures constitute *routine risk minimisation* measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment, so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of REYATAZ is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of REYATAZ are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of REYATAZ. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (eg, on the long-term use of the medicine). There are no important risks or missing information for REYATAZ.

II.B Summary of important risks

Not applicable; there are no safety concerns.

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of REYATAZ.

II.C.2 Other studies in post-authorisation development plan

There are no ongoing or planned studies in the post-authorisation development.

ANNEX 4 SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

None

ANNEX 6 DETAILS OF PROPOSED ADDITIONAL RISK MINIMISATION ACTIVITIES (IF APPLICABLE)

Not applicable