ASSESSMENT REPORT
FOR
REYATAZ

International Nonproprietary Name:
atazanavir sulphate

Procedure No. EMEA/H/C/494/II/39

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

1.1 Introduction

Reyataz (atazanavir/ATV), in combination with low dose ritonavir (RTV), is indicated for the treatment of HIV-1 in antiretroviral (ARV) treatment-experienced patients. The recommended dose for ATV/RTV is 300/100 mg once daily with food.

The Marketing Authorisation (MA) of this protease inhibitor was granted on 2 March 2004 on the basis of a pivotal study (AI424045 or 045) in ARV-experienced patients where RTV-boosted ATV was compared to the fixed combination of lopinavir and ritonavir (Kaletra, LPV/RTV). Given the limited efficacy/safety data derived from study 045 (circa 100 treated patients per arm) the MA was granted under exceptional circumstances.

As part of the post approval commitments, the MAH was requested "to provide clinical data from the use of atazanavir boosted with ritonavir within triple once daily combination expected to be increasingly used in clinical practice with the arrival of the once daily ATV/RTV association" (specific obligation clinical number 3).

The MAH had provided within the initial MA application (MAA) the results of a study performed in antiretroviral naïve patients with atazanavir unboosted (400 mg once daily, QD) compared to efavirenz (EFV). Due to the fact that this study was flawed by methodological problems, no MA could be granted in antiretroviral naïve patients at the time of the original approval. In the USA, contrarily to Europe, Reyataz was approved in ARV-naïve and in ARV-experienced patients with the following dose recommendation: 400 mg QD with food and 300 mg QD with RTV 100 mg QD with food, respectively.

Within this procedure, the MAH applies for an extension of the therapeutic indication of ATV/RTV 300/100 mg QD to include ARV-naïve patients. This indication is supported by the 48-week data from a randomised open-label study (AI424138 or 138) conducted in ARV-naïve patients to assess the efficacy of ATV/RTV compared to LPV/RTV, in combination with a NRTI fixed-association [i.e. Tenofovir DF (TDF) + Emtricitabine (FTC)].

In support of the ATV/RTV 300/100 mg QD regimen safety profile in ARV-naïve patients, the MAH also included in this submission data obtained from a previous study (AI424089 or 089).

The 96-week data of study 089 were previously assessed by the CHMP (Reyataz FUM 057). The study was judged open to criticism as regards the efficacy demonstration given that it consisted in the comparison of two non validated arms in antiretroviral naïve patients. This study confirmed the CHMP's concern that the unboosted regimen of Reyataz (400 mg QD) might not offer an optimal therapeutic management to antiretroviral naïve patients as compared to the boosted regimen (substantiated by the efficacy as well as by the pharmacokinetics (PK) sub analysis). Within this submission, however, this study is rather aimed at completing the safety database.

Moreover, to support proposed changes in the SPC regarding the interaction of ATV/RTV with TDF, the MAH has performed a PK substudy within study 138 and a combined statistical analyses of ATV PK available data from patients in the current (138) and previous studies (074, 089 and 137). It was previously observed that TDF decreases the ATV plasma concentrations through an unknown mechanism. Therefore, this issue was further explored by the MAH within this submission.

In addition, the food effect on ATV PK was assessed in study 172, with ATV co-administered with RTV. So far, only food effect on unboosted ATV had been assessed. Subsequent to results of study 172, an updated wording is proposed for the SPC.

The MAH also submitted updated versions of the Environmental Risk Assessment (ERA) and of the Pharmacovigilance System. Version 1.0 the Risk Management Plan (RMP) had already been submitted and assessed in the framework of the Annex II application EMEA/H/C/494/X/33.

The MAH proposed to update sections 4.1, 4.2, 4.3, 4.4, 4.5, 4.8, 5.1 and 5.2 of the SPC. The PL was updated accordingly; in addition, the MAH took this opportunity to update the contact details for their local representatives in Denmark and Romania.

1.2 Toxico-pharmacological aspects – Environmental Risk Analysis

Within this extension of indication variation, the potential environmental risks from the use and excretion of the active substance ATV were evaluated to support the addition of naïve patients to the treatment population.

This assessment has been conducted under the EMEA 2006 *Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use*.

Conclusion

The Phase I Predicted Environmental Concentration of ATV in surface water ($PEC_{surface\ water}$) was calculated to be = 0.0015 mg/L or 1.5 µg/L. The estimated PEC exceeded the proposed action limit of 0.01 µg/L. Therefore a Phase II assessment was needed. Regarding the phase II-Tier A, the evaluation of PEC/PNEC (Predicted No Effect Concentration in surface water) ratios for surface water and groundwater all gave ratios below 1 and for microorganisms well below 0.1, indicating that there are no specific concerns for the environment.

However ATV appears to be very slowly transformed in aerobic and anaerobic sediments. A complementary Chironomid emergence study (OECD 218) will be undertaken by the MAH and results will be provided as soon as possible in order to give a final conclusion on the environmental risk assessment for ATV.

The log K_{ow}[1] (between 3.47 and 3.17 depending of pH) did not exceed the limit value (4.5). However, it showed that ATV was moderately lipophilic. In addition, ATV was stable in the environment. This could have triggered a study to evaluate bio-concentration factor in fish, but as the elimination half-life of ATV was short (7 hours) and as it is not requested by the guideline, the lack of this study is acceptable.

1.3 Clinical aspects – Pharmacology

PK substudy 138

Study Design

This study was designed as a Week 4 Intensive PK Sub-Study of the 96 week Study Comparing the Antiviral Efficacy and Safety of ATV/RTV with LPV/RTV, Each in Combination with Fixed Dose TDF-FTC in HIV-1 Infected Treatment Naïve Subjects. Its objectives were the assessment of the steady state pharmacokinetics of ATV/RTV and LPV/RTV in the presence of an ARV regimen including TDF at week 4 and to compare the differential effect of ATV/RTV and LPV/RTV on the pharmacokinetics of TDF at week 4. In addition the comparison of the differential effect of ATV and LPV on the pharmacokinetics of RTV at week 4 was done as well as the assessment of the inhibitory quotients (IQ) of ATV and LPV at week 4 (when dosed with RTV).

For this intensive PK substudy, at the week 4 visit, blood for plasma was to be drawn at predose, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24 h post dosing with ATV/RTV and TDF all given once daily and at predose, 1, 2, 3, 4, 6, 8, 12 h post dosing with LPV/RTV given twice daily and TDF given once daily. Plasma samples were analysed for ATV, LPV, RTV, and TDF (according to treatment regimen) concentrations by validated assay methods. 40 subjects were planned of which 39 were analysed. The treatment groups were as follows:

[1] Octanol-water partition coefficient (K_{ow}): A measurement of how a chemical is distributed at equilibrium between octanol and water. It is an important parameter and is used often in the assessment of environmental fate and transport for organic chemicals. Additionally, K_{ow} is a key variable used in the estimation of other properties.

Treatment Group A (test product):
ATV: 2 x 150 mg capsules once daily (QD) with food (meal or snack)
RTV: 1 x 100 mg capsule once daily with food (meal or snack)
TDF/FTC: 1 x 300/200 mg fixed dose combination tablet once daily (meal or snack)

Treatment Group B (reference therapy):
LPV/RTV: 3 x 133/33.3 mg capsules twice daily (BID) (meal or snack)
TDF/FTC: 1 x 300/200 mg fixed dose combination tablet once daily (meal or snack)

The following PK parameters were evaluated for ATV, LPV, RTV and TDF:

- Cmax: Maximum observed concentration at week 4
- Tmax: Time to reach Cmax at week 4
- Cmin: Plasma concentration at the end of the intensive PK dosing interval at week 4
- AUC(TAU): Area under the concentration-time curve, in one dosing interval [AUC(TAU)] from time
    - 0 to 12 hours for LPV and RTV in the LPV/RPV regimen,
    - 0-24 hours for ATV and RTV in the ATV/RTV regimen, and
    - 0-24 hours for tenofovir in both regimens at week 4.
- T-HALF: Dosing interval terminal half-life at week 4.

For RTV in the LPV/RTV regimen, the following parameter was also estimated:

- AUC(0-24): Estimated as 2 times the AUC(TAU) based on 12-hour PK.

Inhibitory quotient (IQ) was determined, calculated as the concentration at plasma trough concentration (Cmin) divided by the protein binding adjusted EC90 for each individual subject HIV-1 strain for either ATV or LPV. The IQ of ATV was compared to the IQ of LPV using analyses of variance performed on log (IQ).

Outcome

Pharmacokinetic Population
Among the 883 subjects randomised in study 138, a total of 39 subjects were enrolled in the intensive PK substudy (18 patients in the ATV/RTV arm and 21 patients in the LPV/RTV arm).

Because of extremely high values of AUC(TAU), Cmax and Cmin of TDF for one subject in the LPV/RTV group (pneumonia, dehydration, transient decrease in renal function), summary and statistical analysis with and without this subject were performed.

Pharmacokinetic Results for ATV and LPV
The PK parameters obtained for ATV and LPV are given in the following tables.

Table 1 Summary statistics for ATV PK parameters after administration of ATV/RTV 300/100 mg QD + TDF/FTC 300/200 mg QD (Treatment A)

Cmax (ng/mL) Geo. Mean (C. V. %) (95% CI)	AUC(TAU)[a] (ng*h/mL) Geo. Mean (C. V. %) (95% CI)	Tmax (h) Median (min,max)	T-Half (h) Mean (S. D.)	Cmin[b] (ng/mL) Geo. Mean (C. V. %) (95% CI)
N = 18	N = 18	N = 18	N = 17[c]	N = 18
2897 (46) (2200, 3816)	28605 (46) (22315, 36669)	3.0 (1.5, 24.0)	10.3 (3.3)	526.4 (57) (385, 720)

[a] TAU=24 hours
[b] Cmin defined as concentration at 24 hours post-dose
[c] T-Half for one subject cannot be determined

Table 2 Summary statistics for LPV PK parameters after administration of LPV/RTV 400/100 mg BID + TDF/FTC 300/200 mg QD (Treatment B)

Cmax (ng/mL) Geo. Mean (C. V. %) (95% CI)	AUC(TAU)[a] (ng*h/mL) Geo. Mean (C. V. %) (95% CI)	Tmax (h) Median (min,max)	T-Half (h) Mean (S. D.)	Cmin[b] (ng/mL) Geo. Mean (C. V. %) (95% CI)
N = 21	N = 21	N = 21	N = 12[c]	N = 21
10655 (51) (8818, 12873)	90946 (59) (73891, 111938)	4.0 (0.0, 12.0)	13.9 (14.5)	5944 (68) (4518, 7821)

[a] TAU=12 hours
[b] Cmin defined as concentration at 12 hours post -dose
[c] T-Half for 9 subjects cannot be determined

Pharmacodynamic Results for ATV and LPV

Summary statistics of ATV and LPV Cmin, EC_{90}, and IQ, as well as the ratios of geometric means and the corresponding 90% CI for the ATV IQ to LPV IQ ratio, at week 4 are presented in the following table.

Table 3 Summary of Statistical Analysis on ATV and LPV IQ and Summary of ATV and LPV Cmin and EC_{90}

Pharmacokinetic Parameter	Summary Statistics		Ratio of Geometric Means (A/B) Pt. Estimate (90% C.I.)
	A: ATV/RTV 300mg/100mg QD+ TDF/FTC 300/200mg QD	B: LPV/RTV 400mg/100mg BID+ TDF/FTC 300/200mg QD	
Cmin (ng/mL)	N=18	N=21	
Geometric Mean (CV%)	526 (57)	5944 (68)	
Median (Range)	596 (130, 1350)	5527 (1556, 22739)	
Protein binding adjusted EC_{90} (ng/mL) at Baseline[a]	N=36	N=36	
Geometric Mean (CV%)	16 (44)	173 (44)	
Median (Range)	15 (8, 35)	170 (76, 472)	
IQ at Week 4	N=17	N=19	
Geometric Mean (CV%)	27 (60)	36 (68)	0.76 (0.51, 1.14)
Median (Range)	35 (4, 77)	34 (11, 129)	

Results from table 3 suggest an approximately 24% difference between ATV IQ and LPV IQ when co-administered with RTV and TDF.

Except for one subject in the LPV/RTV treatment group with a considerably higher IQ (IQ = 129), there was considerable overlap in individual IQ values and distribution between ATV/RTV and LPV/RTV groups. Fifteen (15) of 17 (88%) patients in the ATV group and all patients in the LPV group achieved IQ > 10. There were no subjects from either group with an IQ < 4. The lowest two IQ values in the ATV group were 4 and 7; the lowest IQ in the LPV group was 11.

Pharmacokinetic results for TDF

Table 4 Summary Statistics for TDF PK parameters

Lopinvair Dose and Regimen	Cmax (ng/mL) Geom. Mean (C. V. %) (95% CI)	AUC(TAU) (ng.h/mL) Geom. Mean (C. V. %) (95% CI)	Cmin[a] (ng/mL) Geometric Mean (C.V. %) (95% CI)	Tmax (h) Median (min, max)	T-half (h) Mean (S. D.)
A: ATV /RTV 300mg/100mg QD+ TDF/FTC 300/200 mg QD N=17	352 (32) (293, 423)	3272 (30) (2822, 3794)	72.5 (36) (58.8, 89.4)	1.5 (0.0,6.0)	13.5[b] (3.2)
B: LPV /RTV 400mg/100mg BID+ TDF/FTC 300/200 mg QD N=19	351 (41) (285, 432)	3320 (38) (2866, 3846)	75.7 (45) (63.8, 89.9)	1.5 (0.5,4.0)	13.5[c] (2.9)

[a]Cmin defined as concentration at 24 hours post-dose.
[b]N=15, T-Half for 2 subjects are non-determinable
[c]N=17, T-Half for 2 subjects are non-determinable.
One Subject is excluded from the summary and analysis of tenofovir.

Conclusions regarding PK substudy 138

The intensive PK assessment at week 4 indicated that when both ATV and LPV were co-administered with RTV and TDF, both regimens achieved a comparable IQ. The geometric mean IQ was estimated to be 27 for ATV and 36 for LPV, suggesting similar *in vivo* activity for the two regimens in these HIV-treatment naïve patients; no individual subject had an IQ <4.

Although the difference between the ATV and LPV IQ was calculated to be approximately 24%, the 90% CI for the ratio of the geometric mean values for ATV vs. LPV included 1.00 (with a wide CI). The median IQ (interquantile range) was also similar between both regimens (ATV 35 [20, 50]; LPV 34 [21, 60]). The lowest IQ in the ATV regimen was 4 (vs. 11 with LPV). Therefore these differences were not considered to be relevant.

TDF exposures were similar in both regimens, suggesting ATV/RTV and LPV/RTV increase TDF exposures to a similar extent.

As expected, this study showed that ATV concentrations were somewhat lower when combined with TDF. Nevertheless, as demonstrated by the efficacy results (discussed below), no detrimental clinical effect of this lower exposure in combination with TDF was observed.

Study 172 – Effect of food

Study Design

This was an open-label, randomized, three-period, three-treatment, crossover study in healthy subjects. Subjects underwent screening evaluations to determine eligibility within 21 days prior to first study dose. Subjects were admitted to the clinical facility the evening prior to dosing (Day -1) for each period. Prior to Period 1, 42 subjects were randomized to receive 1 of 6 sequences of 3 treatments including:

Treatment A
A single oral dose of ATV 300 mg (2 x 150 mg capsules) with RTV 100 mg (1 x 100 mg capsule) in a fasted condition,

Treatment B
A single oral dose of ATV 300 mg with RTV 100 mg after consuming a standard light breakfast

Treatment C
A single oral dose of ATV 300 mg with RTV 100 mg after consuming a standard high fat breakfast.

There was a ≥ 7 day washout period between each dose. For each treatment period, subjects were confined to the clinical facility until at least 72 hours post-dose. Blood samples were collected for PK analysis up to 72 hours post-dose. Physical examinations, vital sign measurements, 12-lead electrocardiograms (ECG), and clinical laboratory evaluations were performed at selected times throughout the study. Subjects were closely monitored for adverse events (AEs) throughout the study.

A total of 60 subjects were enrolled and 42 were treated in this study. Thirty-nine (39) subjects completed the study.

Pharmacokinetic Results
Study AI424172 showed that a standard light meal intake (Treatment B) improved ATV exposure after ATV/RTV dosing, as indicated by 40%, 33%, and 40% increases in Cmax, AUC(INF), and C24, respectively. A standard light meal is more representative of patients' typical daily meals than a high-fat, high-calorie meal being used in a standard food-effect assessment, thus is more relevant to the clinical setting. The increased bioavailability of ATV administered after a light meal was observed in the majority of the subjects (67%), and especially in all 10 subjects who had relatively low ATV exposures (defined as AUC[INF] below 20,000 ng*h/ml, and C24 below 200 ng/ml) when dosed under fasted condition.

When ATV/RTV was administered with a high-fat meal (Treatment C), C24 increased by about 33%, even though the Cmax and AUC were similar to the fasted condition.

Table 5 Statistical Analyses for ATV PK parameters fasted vs. light or high fat meal

Pharmacokinetic Parameter	Adjusted Geometric Means		Ratios of Adjusted Geometric Means Point Estimate (90% CI)
	A: ATV/RTV 300/100 mg fasted	B: ATV/RTV 300/100 mg Light Meal	
Cmax (ng/mL)	2386	3335	1.3976 (1.1740, 1.6637)
AUC(INF) (ng•h/mL)	22148	29507	1.3323 (1.1696, 1.5175)
AUC(0-T) (ng•h/mL)	21937	29356	1.3382 (1.1729, 1.5267)
C24 (ng/mL)	270	377	1.3954 (1.2414, 1.5685)
	A: ATV/RTV 300/100 mg fasted	C: ATV/RTV 300/100 mg High Fat Meal	
Cmax (ng/mL)	2386	2120	0.8883 (0.7478, 1.0553)
AUC(INF) (ng•h/mL)	22148	22430	1.0127 (0.8904, 1.1519)
AUC(0-T) (ng•h/mL)	21937	22261	1.0147 (0.8907, 1.1561)
C24 (ng/mL)	270	358	1.3258 (1.1809, 1.4885)

As the observed difference could have been driven by two outlier results, the analysis was redone, excluding the 2 patients who had substantially higher C24. This re-analysis showed a positive

geometric mean ratio of 1.28 (90% CI = [1.14, 1.44]) with a high-fat meals vs. fasted condition, confirming an improvement for C24 in the majority of subjects when ATV/RTV was administered with food (see also table 6).

Table 6 Statistical Re-Analyses for ATV PK parameters fasted vs. light or high fat meal

Statistical Analysis for Atazanavir C24 (ng/mL)

INDIVIDUAL TREATMENT SUMMARIES

	LOG-TRANSFORMED SCALE			ORIGINAL (UNTRANSFORMED) SCALE		
TREATMENT	ADJ'D MEAN	S. E.	90% C. I.: (LCL, UCL)	ADJ'D MEAN		90% C. I.: (LCL, UCL)
A	5.578	0.088	(5.430, 5.725)	264.445	(228.203,	306.444)
B	5.902	0.088	(5.754, 6.049)	365.662	(315.557,	423.722)
C	5.827	0.087	(5.682, 5.973)	339.506	(293.495,	392.731)

TREATMENT COMPARISON

	DIFFERENCES ON THE LOG-TRANSFORMED SCALE					RATIO ON THE ORIGINAL SCALE		
TREATMENT COMPARISON	PT. EST.	S. E.	T	P	90% C.I. (LCL, UCL)	PT. EST.		90% C.I. (LCL, UCL)
B vs. A	0.3241	0.0704	4.6043	0.0000	(0.2068, 0.4414)	1.3827	(1.2297,	1.5548)
C vs. A	0.2499	0.0697	3.5852	0.0006	(0.1337, 0.3660)	1.2838	(1.1431,	1.4419)

Subjects AI424172-1-9 and AI424172-1-27 excluded from analyses

Treatment Code: A=ATV/RTV 300/100 mg Fasted
B=ATV/RTV 300/100 mg Light Meal
C=ATV/RTV 300/100 mg High Fat Meal

C24 was defined as 24h post-dose concentration

Conclusions regarding study 172

When considering the mean PK results but also the individual data, food intake improves the ATV exposure after ATV/RTV dosing, especially in the area of lower AUC and Cmin values. Whereas food does not reduce the variability of ATV PK parameters when co-administered with RTV, it favourably impacts the ATV critical C24 values.

Higher values of Cmin and AUC seemed to be driven by two outlier individuals. The re-analysis for the high fat meal showed that, even when excluding the two outlier patients with higher C24 values, food still increases the mean C24 value by 28%.

Taking these results into consideration, the fact that ATV/RTV was administered with food in study 138, that taking ATV/RTV in fasted state might expose some patients to sub-optimal ATV concentrations, and that the poor gastro-intestinal tolerance of RTV generally drives an intake with food, the recommendation to take ATV/RTV with food should be maintained.

1.4 Clinical aspects – Efficacy

Main study - AI424138

Design

Study 138 is an ongoing open-label, randomised, multicentre study comparing ATV/RTV vs. LPV/RTV at weeks 48 and 96. The primary objective was to determine the proportion of patients who achieved HIV RNA < 50 c/ml at week 48. Important secondary efficacy objectives were to assess the proportion of patients who achieved HIV RNA < 50 c/ml at week 96, the proportion of patients with HIV RNA < 400 copies/ml (c/ml), the change from baseline in HIV RNA, and the change from baseline in CD4 cell count, all at weeks 48 and 96. The resistance profiles of patients experiencing virologic failure were also assessed.

The study population comprised 883 antiretroviral-naïve patients with screening HIV RNA ≥ 5000 c/ml. Patients who received any antiretroviral therapy within 30 days prior to screening, or prior antiretroviral therapy ≥ 1 week were excluded, with exceptions granted for prior antiretroviral exposure in specific settings, as described by the protocol. Patients were randomised in a 1:1 ratio to receive ATV/RTV or LPV/RTV, each co-administered with TDF/FTC. Randomisation was stratified by qualifying HIV RNA (< 100,000 or ≥ 100,000 c/ml) and geographic region. Treatment continued through week 96.

Statistics

Study 138 was designed as a non-inferiority study. The primary efficacy endpoint was the proportion of patients with HIV RNA < 50 c/ml at week 48. The principal analysis of the primary endpoint was based on the Confirmed Virologic Response (CVR) Non-Completer = Failure (NC = F) response definition.

Supportive analyses used CVR Non-Completer = Missing (NC = M), time to loss of virologic response (TLOVR), and Virologic Response - Observed Cases (VR-OC) definitions. The efficacy endpoints HIV RNA < 50 c/ml and HIV RNA < 400 c/ml at week 48 were both analysed using the CVR definition.

Efficacy analyses were stratified as randomised by qualifying HIV RNA and region. Treatments were compared using the difference in proportions (ATV/RTV - comparator) and 95% confidence intervals (CI) based on a stratified normal approximation. ATV/RTV was determined to be similar (non-inferior) to the comparator if the lower confidence limit (CL) for the difference in proportions was greater than -10%.

Outcome Definitions for HIV RNA < 50 c/ml

Confirmed Virologic Response (CVR)

CVR defines response as confirmed HIV RNA < 50 c/ml at week 48 for NC = F. CVR uses the TLOVR definition of response and failure but allows for re-suppression (i.e., patients could have confirmed HIV RNA < 50 c/ml at week 48 having previously experienced virologic rebound).

The supportive analysis CVR Non-Completers = Missing (NC = M) excludes patients who do not have minimum follow-up (i.e., who discontinued prior to obtaining week 48 HIV RNA). Minimum follow-up was based on the lower boundary of the week 48 visit window, and was defined as at least 42 weeks of study therapy with HIV RNA on or after 42 weeks.

Time to loss of virologic response (TLOVR)

TLOVR defines response at week 48 as confirmed HIV RNA < 50 c/ml through week 48 without intervening virologic rebound or treatment discontinuation. Virologic rebound was defined as confirmed on-treatment HIV RNA ≥ 50 c/ml or last on-treatment HIV RNA ≥ 50 c/ml followed by discontinuation. Patients were considered failures if they experienced virologic rebound at or before week 48, discontinued before week 48, never responded by week 48, never received study therapy, or had missing HIV RNA at week 48 and beyond. Patients were classified as completers if they had minimum follow-up, as defined above. Completers could fail based only on their HIV RNA results without regard to discontinuation.

Virologic Response - Observed Cases (VR-OC)

VR-OC classifies patients who remained on study therapy as responders according to a single HIV RNA measurement < 50 c/ml closest to the planned week 48 visit and within a pre-defined visit window. The denominator was based on patients who remained on study therapy through week 48. Patients with HIV RNA ≥ 50 c/ml were considered failures. Patients who remain on study therapy and were missing their week 48 measurement were responders only if the previous and subsequent measurements were < 50 c/ml.

Treatment Outcomes

Treatment outcomes at week 48 for HIV RNA < 50 c/ml were tabulated by treatment based on CVR (NC = F). Outcome categories were responder (responder without rebound, or re-suppressed after

rebound), virologic failure (virologic rebound, never suppressed through week 48 and on study at week 48, or discontinued due to insufficient viral load response [as determined by the investigator]), discontinued before achieving confirmed suppression, discontinued while suppressed, and never treated. Tabulations also included reasons for discontinuation before achieving confirmed suppression, and reasons for discontinuation while suppressed. Treatment outcomes were based on the primary reason for failure through week 48.

HIV RNA < 400 c/ml at week 48

The proportion of patients with HIV RNA < 400 c/ml at week 48 was assessed using methods analogous to those used for analysis of HIV RNA < 50 c/ml, including treatment outcomes.

CD4 Cell Count Changes

Regimens were compared using the difference (ATV/RTV - LPV/RTV) in mean CD4 changes from baseline at Weeks 24 and 48.

Comparisons used difference estimates and 95% CIs based on normal approximations stratified as randomised by qualifying HIV RNA level (< 100,000 and ≥ 100,000 c/ml) and geographic region (Africa, Asia, Europe, North America, South America). The difference estimate and standard error were computed within the 10 randomisation strata and combined using a weighted average with weights proportional to stratum size (CMH weighting).

Principal analyses used observed values, while sensitivity analyses used LOCF to address missing values due to missed visits or discontinuation. Missing values were replaced with the last available measurement in the previous visit window. Baseline was carried forward for randomised subjects who had no on-treatment measurements.

HIV RNA Changes

HIV RNA levels and changes from baseline were summarised through week 48 using observed values. Treatment regimens were compared using the difference between ATV/RTV and LPV/RTV in mean HIV RNA changes from baseline (log10 c/ml) at weeks 24 and 48, using the methodology described above for CD4 changes.

Efficacy Subgroup Analyses and Subpopulation Analyses

The following key efficacy endpoints at week 48 were tabulated by efficacy subgroups:

- Proportions of patients with HIV RNA < 50 c/ml using CVR (NC = F and NC = M)
- Proportions of patients with HIV RNA < 400 c/ml using CVR (NC = F and NC = M)
- CD4 cell count change from baseline.

The efficacy subgroups were defined by categories of HIV RNA and CD4 cell count:

- Qualifying HIV RNA < 100,000 and ≥ 100,000 c/ml
- Baseline HIV RNA < 100,000, 100,000 to < 500,000 and ≥ 500,000 c/ml
- Baseline CD4 cell count < 50, 50 to < 100, 100 to < 200, and ≥ 200 cells/mm^3
- Baseline HIV RNA (c/ml) and CD4 cell count (cells/mm^3): < 100,000 and < 100; < 100,000 and ≥ 100; ≥ 100,000 and < 100; ≥ 100,000 and ≥ 100

Patient disposition, demographics, baseline characteristics and the 3 key efficacy endpoints at week 48 were tabulated by the subpopulations of gender, race, region, and baseline HBV/HCV co-infection. In addition, proportions with HIV RNA < 50 c/ml and HIV RNA < 400 c/ml were tabulated by baseline HIV subtype. Subpopulations were gender, race, region, baseline HBV/HCV co-infection, and baseline HIV subtype.

Resistance Profiles

Genotypic and phenotypic resistance profiles were tabulated for patients who met criteria for virologic failure through week 48 for HIV RNA ≥ 400 c/ml. Virologic failure was defined using CVR (NC = F) as virologic rebound without re-suppression, never suppressed and on study through week 48, or discontinued due to insufficient viral load response before week 48.

Outcomes

Patient Disposition

A total of 883 patients were randomised (440 ATV/RTV, 443 LPV/RTV); 878 were treated (438 ATV/RTV, 440 LPV/RTV); 753 (385 ATV/RTV, 368 LPV/RTV) were continuing on treatment at data cut-off (48 weeks) for this analysis (11 June 2007). Three patients were randomised to the LPV/RTV regimen but received ATV/RTV during the entire treatment period. These were grouped as-randomised to LPV/RTV in all efficacy analyses, including VR-OC. Ninety-seven patients discontinued through week 48 (39 ATV/RTV, 58 LPV/RTV). As of data cut-off for this analysis, 28 discontinued on or after week 48 (14 on each regimen). The most common (≥ 2% total) reasons for discontinuation through week 48 were adverse event, poor/non-compliance, and withdrawal of consent.

Demographics and Baseline Disease Characteristics

Overall, demographic characteristics were balanced between regimens. The median baseline HIV RNA and the proportions with baseline HIV RNA ≥ 100,000 c/ml and the proportions with CD4 < 50 cells/mm^3 at baseline were balanced. Most patients had baseline CD4 cell counts in the range of 100 to < 350 cells/mm^3. Across treatment groups, 66% of patients had subtype B, including 80% of patients in Europe, 100% in North America, and 78% in South America. Subtype C was more frequent in Africa (89%) but infrequent (< 5%) in all other regions. The rates of hepatitis B and C co infection were balanced, though only very few cases were present.

Results

Summary

ATV/RTV was non-inferior to LPV/RTV, as assessed by the primary efficacy endpoint at week 48 using CVR (NC = F). The lower CL of the difference estimate was greater than the boundary of -10%, supporting non-inferiority. Non-inferiority was confirmed by supportive analyses for the primary endpoint (CVR NC = M, VR-OC, and TLOVR) and by analyses of the secondary efficacy endpoint. The mean changes from baseline at week 48 in CD4 cell count were comparable.

Table 7 Summary of Efficacy at week 48: As Randomised Patients

	ATV/RTV N = 440	LPV/RTV N = 443	Difference (95% CI)	Estimate
Baseline				
HIV RNA mean (SE), log_{10} c/ml	4.95 (0.029)	4.94 (0.027)	--	
CD4 mean (SE), cells/mm^3	211 (6.5)	218 (6.3)	--	
Primary Endpoint				
HIV RNA < 50 c/ml, responder/evaluable (%)				
CVR (NC = F)[a]	343/440 (78)	338/443 (76)	1.7 (-3.8, 7.1)	
CVR (NC = M)	343/398 (86)	338/379 (89)	-2.9 (-7.5, 1.6)	
TLOVR[b]	343/440 (78)	337/443 (76)	1.9 (-3.6, 7.4)	
VR-OC	335/399 (84)	333/382 (87)	-3.5 (-8.7, 1.8)	
Secondary Endpoints				
HIV RNA < 400 c/ml, responder/evaluable (%)				
CVR (NC = F)	377/440 (86)	365/443 (82)	3.3 (-1.5, 8.1)	
CVR (NC = M)	377/398 (95)	365/379 (96)	-1.8 (-5.1, 1.5)	
TLOVR[b]	377/440 (86)	363/443 (82)	3.8 (-1.1, 8.6)	
VR-OC	374/399 (94)	364/382 (95)	-1.7 (-5.2, 1.8)	
HIV RNA mean (SE) change from baseline, log_{10} c/ml	(N = 397) -3.09 (0.042)	(N = 379) -3.13 (0.037)	--	
CD4 mean (SE) change from baseline, cells/mm^3	(N = 370) 203.3 (7.1)	(N = 363) 219.4 (7.2)	-16.4 (-35.9, 3.1)	

[a] Principal analysis of the primary endpoint

[b] Hazard ratio estimates (ATV/RTV:LPV/RTV) and 95% CIs are 0.93 (0.71, 1.23) for HIV RNA < 50 c/ml, and 0.78 (0.56, 1.09) for HIV RNA < 400 c/ml

Primary Endpoint

HIV RNA < 50 c/ml

Most subjects achieved HIV RNA < 50 c/ml by Week 24. Response rates at Week 48 ranged from 76% to 89% across regimens, depending on the analysis (see table 7 above). The response rates were similar in both groups and the pre-specified definition for non-inferiority was achieved, with the lower bound of the CI being 3.8%. (for CVR (NC=F)).

When the results were stratified by baseline subgroups, it became evident that for both treatment arms the response rates were lower (10%) in patients with a higher viral load (above 100 000 c/ml) as compared to those with a viral load below 100 000 c/ml (see table 8). The effect of ATV/RTV compared to LPV/RTV was consistent across sub-groups.

Table 8 CVR (NC=F) at week 48 by baseline subgroups (HIV RNA <50 c/ml) – As Randomised Patients

	Responder/Evaluable (%)	
Subgroup	**ATV/RTV N = 440**	**LPV/RTV N = 443**
Overall	343/440 (78)	338/443 (76)
Qualifying HIV RNA		
< 100,000 c/mL	179/217 (82)	177/218 (81)
≥ 100,000 c/mL	164/223 (74)	161/225 (72)
Baseline CD4		
< 50 cells/mm^3	45/58 (78)	30/48 (63)
50 - < 100 cells/mm^3	34/45 (76)	20/29 (69)
100 - < 200 cells/mm^3	80/106 (75)	104/134 (78)
≥ 200 cells/mm^3	178/222 (80)	182/228 (80)
Baseline HIV RNA ≥ 100,000 c/mL and CD4 < 100 cells/mm^3	60/83 (72)	40/64 (63)
Region		
Africa	47/67 (70)	52/65 (80)
Asia	32/39 (82)	36/40 (90)
Europe	53/65 (82)	49/66 (74)
North America	46/67 (69)	50/69 (72)
South America	165/202 (82)	151/203 (74)
HIV Subtype		
AE	23/28 (82)	25/28 (89)
B	219/280 (78)	205/276 (74)
C	51/73 (70)	52/65 (80)

The primary efficacy endpoint (HIV RNA <50 c/ml at Week 48) was reassessed using CVR on the evaluable per protocol cohort that excluded non-completers and patients with major protocol deviations. The conclusion of non-inferiority of ATV/RTV to LPV/RTV was maintained in this analysis. Response rates were 338/392 (86%) on ATV/RTV and 332/372 (89%) on LPV/RTV, with a difference estimate (95% CI 3.0 (-7.6, 1.5) (Table 9).

Table 9 CVR Per-Protocol Analysis at Week 48 (HIV RNA < 50 c/ml) by Baseline Subgroups – As-Randomised Subjects in Per-Protocol Analysis

		HIV RNA < 50 c/mL at Week 48	
		Responder/Evaluable (%)	
		Treatment Regimen	
Subgroup	Level	ATV/RTV N = 392	LPV/RTV N = 372
QUALIFYING HIV RNA	< 100,000 C/ML	176/192 (92)	173/183 (95)
	>= 100,000 C/ML	162/200 (81)	159/189 (84)
B/L HIV RNA	< 100,000 C/ML	175/191 (92)	185/195 (95)
	100,000 - < 500,000 C/ML	129/155 (83)	120/139 (86)
	>= 500,000 C/ML	34/46 (74)	27/38 (71)
B/L CD4	< 50 CELLS/MM^3	44/51 (86)	29/34 (85)
	50 - < 100 CELLS/MM^3	34/40 (85)	20/25 (80)
	100 - < 200 CELLS/MM^3	80/94 (85)	104/114 (91)
	>= 200 CELLS/MM^3	174/198 (88)	178/196 (91)
B/L HIV RNA AND CD4	< 100,000 C/ML AND < 100 CELLS/MM^3	18/18 (100)	9/9 (100)
	< 100,000 C/ML AND >= 100 CELLS/MM^3	156/170 (92)	176/185 (95)
	>= 100,000 C/ML AND < 100 CELLS/MM^3	60/73 (82)	40/50 (80)
	>= 100,000 C/ML AND >= 100 CELLS/MM^3	98/122 (80)	106/125 (85)

Treatment outcomes

Treatment outcomes were based on the primary reason for failure through week 48. Virologic failure for HIV RNA < 50 c/ml using CVR (NC = F) was the most frequent reason for not being a responder on both regimens. Most patients with virologic failure were never suppressed through week 48, while 4% on each regimen experienced rebound. Few patients on either regimen discontinued due to death or adverse events. Fewer patients on ATV/RTV discontinued before achieving confirmed virologic suppression or discontinued while suppressed, primarily due to patients' withdrawal of consent.

Table 10 CVR Treatment Outcomes at week 48 (HIV RNA < 50 c/ml): As Randomised Patients

Outcome	**ATV/RTV N = 440**	**LPV/RTV N = 443**
Responder	343 (78)	338 (76)
Virologic failure	55 (13)	45 (10)
Rebound	16 (4)	19 (4)
Never suppressed through week 48	39 (9)	26 (6)
Death	5 (1)	4 (< 1)
Discontinued due to adverse event	10 (2)	14 (3)
Discontinued for other reasons[a]	25 (6)	39 (9)
Never treated	2 (< 1)	3 (< 1)

[a] Includes discontinued due to insufficient viral load response, lost to follow-up, other, poor/non compliance, pregnancy, patient no longer meets study criteria, patient withdrew consent, and other.

Secondary Endpoints

HIV RNA < 400 c/ml

Most subjects achieved HIV RNA < 400 c/ml by Week 12. Response rates at week 48 ranged from 82% to 96% across regimens, depending on the analysis (see table 7 above). Difference estimates were ≤ 3.8% in magnitude. The treatment outcome of virologic failure using CVR (NC = F) was 6% on both regimens. The 3 subjects who were randomised to LPV/RTV but actually received ATV/RTV were all responders. Two subjects on LPV/RTV achieved re-suppression after rebound. More subjects on LPV/RTV had treatment outcomes of discontinued before achieving confirmed suppression and discontinued while suppressed, which was primarily due to subject's withdrawal of consent. Treatment outcomes were consistent using TLOVR.

As was the case for the primary endpoint, the non-inferiority margin of 10% was satisfied. The trend favoured the LPV/RTV group.

Reduction in log_{10} HIV RNA from Baseline

Both regimens resulted in HIV RNA mean decreases from baseline of ≥ 2.0 log10 c/ml at weeks 4 and 12, and ≥ 3.0 log10 c/ml at week 24, and this was sustained through week 48. At week 48, the mean decreases in HIV RNA were 3.09 and 3.13 log10 c/ml for ATV/RTV and LPV/RTV, respectively. The proportion of patients with HIV RNA < 50 c/ml across regimens was 86% (VR-OC); the limit of quantification (LOQ) of the HIV RNA assay censored the measurement of the actual decline in viral load.

Table 11 Reduction in HIV RNA (log_{10} c/ml)

	ATV/RTV		LPV/RTV	
	n	**Mean (se)**	**n**	**Mean (se)**
Baseline	440	4.95 (0.029)	443	4.94 (0.027)
Change from baseline				
Week 4	428	-2.28 (0.029)	426	-2.22 (0.028)
Week 12	419	-2.95 (0.033)	420	-2.87 (0.034)
Week 24	415	-3.08 (0.040)	414	-3.06 (0.039)
Week 36	405	-3.06 (0.043)	398	-3.10 (0.039)
Week 48	397	-3.09 (0.042)	379	-3.13 (0.037)

The trend seemed to favour the LPV/RTV group. However, as this was an observed case analysis, it is likely to be biased against ATV/RTV, as there were fewer drop-outs in that group. The primary analysis of responders, where all patients are included, was less likely to be biased, and there the trend favoured ATV/RTV.

The statistical analysis of the change from baseline at weeks 24 and 48, providing both observed case and ITT analysis is given in table 12. All of the 95% CIs contained 0, supporting the comparable effect of the regimens.[2]

Table 12 HIV RNA Changes from Baseline at Weeks 24 and 48 - As-Randomised Subjects

	HIV RNA Mean Changes (SE) from Baseline (log10 c/mL)							
	Treatment Regimen							
	ATV/RTV N = 440			LPV/RTV N = 443			Difference Estimate (95% CI) ATV/RTV - LPV/RTV	
WEEK 24								
OBSERVED VALUES	-3.08	(0.040)	[N = 415]	-3.06	(0.039)	[N = 414]	-0.01	(-0.11, 0.09)
LAST OBSERVATION CARRIED FORWARD	-2.99	(0.045)	[N = 440]	-2.93	(0.047)	[N = 443]	-0.06	(-0.18, 0.06)
WEEK 48								
OBSERVED VALUES	-3.09	(0.042)	[N = 397]	-3.13	(0.037)	[N = 379]	0.05	(-0.05, 0.15)
LAST OBSERVATION CARRIED FORWARD	-2.95	(0.048)	[N = 440]	-2.91	(0.049)	[N = 443]	-0.04	(-0.16, 0.09)

Difference estimates are stratified by qualifying HIV RNA and region.

[2] Note that statistical comparisons of HIV RNA changes from baseline were not pre-planned for Study 138.

1. Unlike CD4 cell count increases, the limit of quantification of the HIV RNA assay censors the measurement of the actual decline in viral load. This "floor effect" biases results towards patients with higher baseline values.
2. HIV RNA change from baseline is a less clinically relevant endpoint for treatment-naive patients, 70% of whom achieved HIV RNA <50 c/ml by Week 24.
3. The study is overpowered to assess HIV RNA changes, and may identify statistically significant differences between regimens that are not clinically relevant

CD4 Cell Count Changes from Baseline

The change from baseline was calculated for each treatment group at each time-point. Statistical analysis was carried out on the change from baseline at weeks 24 and 48 using both the observed data only as well as using LOCF to impute data to replace missing values. No formal test for non-inferiority was carried out and so no non-inferiority margin was defined.

Table 13 CD4 Mean Changes from Baseline

	ATV/RTV		LPV/RTV	
	n	**Mean (se)**	**n**	**Mean (se)**
Baseline	431	211 (6.5)	439	218 (6.3)
Change from baseline				
Week 4	392	85 (4.1)	405	82 (4.5)
Week 12	386	119 (4.7)	402	120 (5.0)
Week 24	388	142 (5.7)	386	147 (5.6)
Week 36	383	175 (6.0)	380	190 (8.6)
Week 48	370	203 (7.1)	363	219 (7.2)

Analysis of change from baseline	**Treatment difference (95% CI)**
Week 24	
Observed data	-4.2 (-19.5, 11.2)
LOCF	-0.3 (-14.7, 14.2)
Week 48	
Observed data	-16.4 (-35.9, 3.1)
LOCF	-7.2 (-25.7, 11.3)

Difference estimates are stratified by qualifying HIV RNA and region

The trend did not favour ATV/RTV when considering change from baseline in CD4 count. The analysis of observed data shows the larger differences, but this is likely to be biased as patients withdrawing before week 48, many due to virologic failure, were not included. The analysis using LOCF which accounts for all patients shows smaller differences. The differences in CD4 counts were not considered to be of an important magnitude.

Resistance

No patient on ATV/RTV who had wild-type virus at baseline and who subsequently experienced virologic failure developed resistance. Among patients with virologic failure on ATV/RTV, emerging PI substitutions were observed only in those who entered the study with pre-existing PI substitutions.

Genotypic and phenotypic resistance profiles were determined for patients who had virologic failure through week 48 for HIV RNA ≥ 400 c/ml. Virologic failure was defined using CVR (NC = F) as virologic rebound without re-suppression, never suppressed and on study through week 48, or discontinuation due to insufficient viral load response before week 48.

Six percent of patients had virologic failure through 48 weeks on both regimens (27/440 on ATV/RTV, 26/443 on LPV/RTV). Baseline genotypes were available for 25/27 ATV/RTV patients and 22/26 LPV/RTV patients. International AIDS Society (IAS)-defined minor substitutions were present in 25/25 and 22/22 baseline isolates of ATV/RTV and LPV/RTV virologic failure patients, respectively.

IAS-defined major PI substitutions M46I, V82A, I84V, and L90M were observed in baseline isolates of only 2 patients with virologic failure. Both were randomised to ATV/RTV. One of these had 2 major PI substitutions at baseline, V82A and L90M; the other had 3 major PI substitutions at baseline, M46I, I84V and L90M. Both had ≥ 5 additional minor substitutions associated with ATV/RTV resistance, and phenotypic resistance to multiple PIs, including ATV/RTV and LPV/RTV, plus phenotypic resistance to FTC, and in one case, TDF.

No patient on either regimen with virologic failure who had a wild-type isolate at baseline developed resistance. The ATV-related major PI resistance substitution, I50L, emerged in 1 patient on

ATV/RTV. This patient had a baseline isolate that was phenotypically resistant to ATV/RTV (fold change [FC] = 19), LPV/RTV (FC = 39), FTC (FC > 43.75) and TDF (FC = 1.74). The baseline isolate had 2 major and 6 minor PI substitutions, 2 thymidine analogue mutations (TAMs), and the M184V substitution.

Table 14 Baseline Resistance in Isolates: As Randomised Patients with Virologic Failure

		ATV/RTV N = 440	LPV/RTV N = 443
Virologic failure through week 48 (HIV RNA ≥ 400 c/ml)		27/440	26/443
Baseline genotypes		25/27	22/26
Baseline phenotypes		18/27	17/26
IAS-defined major PI substitutions[a]		2/25	0/22
IAS-defined minor PI substitutions[b]		25/25	22/22
PI phenotypic resistance	ATV/RTV FC >5.2	2/18	0/17
	LPV/RTV FC > 9	2/18	0/17
RT substitutions[c]	TAMS	3/25	0/22
	M184V	2/25	1/22
RTI phenotypic resistance	Emtricitabine FC >3.5	2/18	1/17
	Tenofovir FC > 1.4	1/18	0/17

[a] IAS-defined major PI substitutions are D30N, V32I, L33F, M46IL, I47VA, G48V, I50LV, I54ML, L76V, V82AFLTS, I84V, N88S, and L90M

[b] Includes all IAS defined PI substitutions except those listed in footnote "a"

[c] Substitutions searched for were: thymidine analogue mutation (TAMS), 151-complex, 69 insertion complex, and IAS-defined substitutions associated with tenofovir and/or emtricitabine resistance

Table 15 Treatment-emergent Resistance: As Randomised Patients with Virologic Failure

		ATV/RTV N = 440	LPV/RTV N = 443
Virologic failure through week 48 (HIV RNA ≥ 400 c/ml)		27/440	26/443
Paired genotypes		17/27	15/26
Paired phenotypes		18/27	16/26
IAS-defined major PI substitutions[a]		1/17[b]	0/15
All other IAS-defined PI substitutions		6/17[c]	2/15[d]
PI phenotypic resistance	ATV/RTV FC >5.2	1/18	0/16
	LPV/RTV FC > 9	0/18	0/16
	Other PIs	4/18	4/16
RT substitutions[e]	TAMs	1/17	1/15
	M184V	3/17	3/15
RTI phenotypic resistance	Emtricitabine FC >3.5	4/18	3/16
	Tenofovir FC > 1.4	0/18	1/16
	Other NRTIs	5/18	5/16

[a] IAS-defined major substitutions associated with resistance to ATV/RTV are I50L, I84V, and N88S; for LPV/RTV, the major substitutions are V32I, I47V/A, V82A/F/T/S.

[b] The PI resistance substitution, I50L, emerged in one patient on ATV/RTV whose baseline isolate had 2 major and 6 minor PI substitutions, and was phenotypically resistant to ATV/RTV, LPV/RTV, FTC and TDF.

[c] Includes all IAS-defined PI substitutions except I50L, I84V, and N88S

[d] Includes all IAS-defined PI substitutions except V321, I47V/A, V82A/F/T/S

[e] Substitutions searched for were: TAMS, 151-complex, 69 insertion complex, and IAS-defined substitutions associated with tenofovir and/or emtricitabine resistance

Phenotypic resistance to ATV/RTV emerged in an isolate from 1 patient treated with ATV/RTV. This isolate had 5 minor PI substitutions at baseline, including 4 associated with ATV/RTV resistance (M36I, I62V, A71A/T, and I93L), plus 4 other polymorphisms. Phenotypic resistance to LPV/RTV did not emerge in isolates from any ATV/RTV patient with virologic failure; however resistance to other PIs emerged in isolates from 4/18 patients. Phenotypic resistance to LPV/RTV or ATV/RTV

was not observed in the on-study isolates from patients with virologic failure on LPV/RTV; however, resistance to other PIs did emerge in isolates from 4/16 LPV/RTV virologic failure patients.

Conclusion and Discussion on Clinical Efficacy

This study was an open label study because a double blind, double dummy design would have imposed a high pill burden that might have altered the study enrolment. A stringent 10% non inferiority margin (in terms of percentage of patients with undetectable viral load (<50 copies/ml) was used, which is appropriate. The chosen endpoint of proportions of patients with HIV RNA levels < 50 c/ml is the currently recommended endpoint in HIV-1 trials evaluating compounds for the treatment of treatment-naïve patients infected with HIV-1. In addition, this study will provide long term data at 96 weeks as recommended in the guideline. The MAH has committed to submit the 96 weeks study report in the first quarter of 2009.

In line with the pivotal study 45 in antiretroviral experienced patients, TDF was part of the backbone therapy. As tenofovir has been shown to reduce ATV AUC (25%) and Cmin (40%), the choice of backbone could mitigate the efficacy of ATV. Nevertheless, this backbone is attractive in clinical practice as a once daily combination for combination ARV treatment.

The per protocol population (PPP) analysis taking into account protocol deviations, in underlined the demonstrated non inferiority result in the "as randomised" population.

The results for the MAH's selected populations were compatible with the predefined non inferiority margin (-10%). The most borderline situation is observed with the VR-OC, which is expected to be a close to a per protocol population (patients truly receiving the randomised treatment during 48 weeks).

It is noteworthy that 2 antiretroviral naïve patients in the ATV/RTV arm were apparently infected with circulating resistant strains. These patients had major PI substitutions at baseline, including M46I, V82A, I84V, and L90M. Both also had baseline phenotypic resistance to the study PIs and FTC, and in one case TDF. Both of these patients were randomised to ATV/RTV.

1.5 Clinical aspects – Safety

The safety information presented by the MAH to support the use of ATV/RTV as part of HAART regimens in a patient population with no or minimal exposure to prior antiretroviral treatment was based primarily on 2 studies:

- **AI424138** (138): Study 138 compared safety of ATV/RTV to a standard-of-care boosted PI, LPV/RTV in treatment-naïve patients through 48 weeks.
- **AI424089** (089): Study 089 was a supportive study that compared safety of ATV/RTV to unboosted ATV and provided long-term safety data on the use of ATV/RTV in treatment-naïve patients through 96 weeks.

Different backbone drugs were used in these 2 studies, a fixed-dose combination of tenofovir and emtricitabine in 138, and stavudine-extended release (XR) and lamivudine in 089.

Patient exposure

In 138, a total of 878 patients were treated; 441 in ATV/RTV and 437 in LPV/RTV. In 138, 97 patients discontinued through week 48 (39 ATV/RTV, 58 LPV/RTV). Adverse Events (AEs) were the most common reason for discontinuation on both treatment regimens (10 ATV/RTV, 14 LPV/RTV). More patients on ATV/RTV discontinued due to jaundice/hyperbilirubinemia (3 [<1%] vs. 0), while more patients on LPV/RTV discontinued due to diarrhoea (4 [<1%] vs. 0).

In 089, 200 patients were randomised; 199 patients were treated (95 ATV/RTV, 104 ATV400). Twenty-one (21) patients discontinued through week 48, in addition, 14 patients discontinued on or

after week 48 visit and prior to week 96 visit. Discontinuation due to AEs through week 96 was more common for patients in the ATV/RTV than ATV400 regimen (8 patients vs. 3 patients); 5 of these discontinuations in ATV/RTV regimen were protocol mandated (for persistent Grade 4 hyperbilirubinemia and abnormal blood bilirubin).

Characteristics of study population

In the pooled ATV/RTV population, median age of all randomised patients was 34 years, and majority of patients were males (69%). The most common race was white (48%), and the most common region was South America (43%). Patients' gender, age, race, and region were consistent between studies.

Co-infection: In 138, 60 (14%) patients in ATV/RTV and 51 (12%) in LPV/RTV and in 089, 17 (18%) in ATV/RTV and 20 (19%) in ATV400 regimen were HBV and/or HCV positive at baseline.

Most patients in both studies had normal liver function tests at baseline. In the ATV/RTV regimen, Grade 1 to 2 elevations in ALT were observed in 14% (138) and 16% (089) of patients and AST elevations were observed in 18% (138) and 12% (089) of patients at baseline. In 138, < 1% patients and in 089 no patients had Grade 3 to 4 ALT/AST abnormalities at baseline. In 089, 100% and in 138, > 99% patients had normal total bilirubin at baseline.

In both studies, fasting lipids at baseline were categorised by NCEP (National Cholesterol Education Program) guidelines as desirable or optimal.

Table 16 Baseline Fasting Lipids (NCEP Categories) : As-Treated Patients

	138		**089**	
	ATV/RTV N = 441	LPV/RTV N = 437	ATV/RTV N = 95	ATV400 N = 104
Fasting total cholesterol < 200 mg/dL	92%	93%	86%	84%
Fasting high-density lipoprotein (HDL) cholesterol ≥ 60 mg/dL	4%	3%	5%	7%
Fasting non-HDL cholesterol < 130 mg/dL	71%	73%	65%	62%,
Fasting LDL cholesterol < 100 mg/dL	62%	61%	60%	52%
Fasting triglycerides < 150 mg/dL	76%	72%	61%	65%

The median fasting glucose values at baseline in both studies were consistent between regimens (138: 84 mg/dl, ATV/RTV; 86 mg/dl, LPV/RTV and in 089, 86 mg/dl ATV/RTV; 86 mg/dl, ATV400).

Adverse events

All adverse events

In 138, the overall incidence of AEs of any grade through week 48 was 91% on both ATV/RTV and LPV/RTV regimens. The majority of AEs of any grade occurred in < 1% of patients in either regimen. Treatment-related AEs through week 48 were 61% and 70% in ATV/RTV and LPV/RTV, respectively. Treatment-related AEs that were reported with a higher frequency (≥ 5% difference) on the ATV/RTV than LPV/RTV regimen were jaundice (15% vs. < 1%), hyperbilirubinemia (10% vs. 0), and ocular icterus (8% vs. 0).

Treatment-related AEs that occurred with a lower frequency on the ATV/RTV than LPV/RTV regimen included diarrhoea (11% vs. 46%), nausea (15% vs. 22%), and hypertriglyceridaemia (2% vs. 8%). Renal toxicity was 2% on each regimen.

In the pooled ATV/RTV population from 138 and 089 (N = 536), through week 48, most (91%) patients reported at least 1 AE regardless of relationship to ATV/RTV or the comparator regimens. The most frequently reported (≥ 10%) treatment-related AEs (all grades) were jaundice (16%), nausea (15%), diarrhoea (12%), ocular icterus (11%), and hyperbilirubinemia (10%).

Grade 2 to Grade 4 adverse events

In 138, through week 48, the overall incidence of Grade 2 to 4 AEs was 57% for ATV/RTV, and 59% for LPV/RTV, and 26% and 30%, respectively for Grade 2 to 4 treatment-related AEs.

- Hepatobiliary AEs: Hyperbilirubinemia was the only Grade 2 to 4 treatment-related AE (6% and 0%) that occurred with a higher frequency (≥ 5 % difference) on the ATV/RTV than LPV/RTV regimen,
- Gastrointestinal AEs: Diarrhoea was the only Grade 2 to 4 treatment-related AE (2% and 11%) that occurred with a lower frequency (≥ 5 % difference) on the ATV/RTV than LPV/RTV regimen,
- Metabolism and nutrition AEs: Grade 2 to 4 treatment-related hypertriglyceridaemia was higher in the LPV/RTV (4% vs. < 1%),
- Rash AEs: The incidence of these Grade 2 to 4 AEs was consistent in the ATV/RTV and LPV/RTV regimens (3% and 2%, respectively).

Table 17 Grade 2 to 4 Adverse Events (Treatment-Related) of Clinical Interest through week 48 As-Treated Patients in 138:

	Number of Subjects (%)	
	Treatment Regimen	
System Organ Class Preferred Term	ATV/RTV N = 441	LPV/RTV N = 437
ANY ADVERSE EVENT	115 (26)	129 (30)
GASTROINTESTINAL DISORDERS	39 (9)	82 (19)
NAUSEA	17 (4)	33 (8)
DIARRHOEA	10 (2)	50 (11)
VOMITING	4 (< 1)	6 (1)
HEPATOBILIARY DISORDERS	39 (9)	1 (< 1)
HYPERBILIRUBINAEMIA	26 (6)	0
JAUNDICE	16 (4)	0
NERVOUS SYSTEM DISORDERS	18 (4)	13 (3)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS*	14 (3)	9 (2)
DERMATITIS ALLERGIC	1 (< 1)	1 (< 1)
PRURIGO	0	1 (< 1)
PSORIASIS	1 (< 1)	0
RASH	10 (2)	3 (< 1)
RASH ERYTHEMATOUS	0	1 (< 1)
RASH GENERALISED	2 (< 1)	0
RASH MACULO-PAPULAR	1 (< 1)	0
RASH PAPULAR	0	1 (< 1)
ROSACEA	0	1 (< 1)
URTICARIA LOCALISED	0	1 (< 1)
URTICARIA PAPULAR	0	0
INVESTIGATIONS	14 (3)	11 (3)
BLOOD BILIRUBIN INCREASED	4 (< 1)	1 (< 1)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	5 (1)	8 (2)
EYE DISORDERS	4 (< 1)	0
OCULAR ICTERUS	4 (< 1)	0
METABOLISM AND NUTRITION DISORDERS	4 (< 1)	33 (8)
HYPERTRIGLYCERIDAEMIA	3 (< 1)	18 (4)
DYSLIPIDAEMIA	0	1 (< 1)
HYPERLIPIDAEMIA	0	5 (1)

In 089, the overall incidence of treatment-related Grade 2 to 4 AEs through week 48 for the ATV/RTV regimen, was 43% versus 36% for the ATV400 regimen. Treatment-related Grade 2 to 4 AEs reported with higher frequency (≥ 5% difference) in the ATV/RTV than ATV400 regimen were hyperbilirubinemia and increased blood bilirubin. Through week 96 in 089, the incidence rate of

treatment-related Grade 2 to 4 AEs for the ATV/RTV regimen was 48% and for ATV400 was 39%. Hyperbilirubinemia was the only Grade 2 to 4 AE and treatment-related AE (15% vs. 7%) reported more frequently in the ATV/RTV than ATV400 regimen.

Overall, the pattern of AEs seen in 138 and 089 was as expected and consistent with the known safety profile of ATV/RTV. No unexpected Grade 2 to 4 AEs, regardless of relationship to study drug, were apparent from the two studies submitted by the MAH.

Deaths and Discontinuations due to adverse events

Deaths
In 138, 13 deaths were reported: 6 on ATV/RTV; 6 on LPV/RTV; 1 additional enrolled patient was hospitalised prior to randomisation and subsequently died. One (1) death on LPV/RTV (case of mesenteric thrombosis) was considered "possibly related" to study drug; all others were considered "unrelated" or "not likely" related to study drug.
There were 2 deaths in 089, both in patients on the ATV400 regimen and were judged by the investigators to be not related to study drug. One (1) patient died of head injuries sustained in a motor vehicle accident and the other patient died of metastatic lung cancer after discontinuation from the study prior to week 96.

Discontinuations due to adverse events
In 138 through week 48, 11 (2%) patients in ATV/RTV and 15 (3%) in LPV/RTV discontinued therapy because of AEs. All individual AEs leading to discontinuation occurred with an incidence of < 1%. Events leading to discontinuation in both regimens were consistent with the known side effect profiles of the study drugs and comparison/backbone treatments. More patients on ATV/RTV discontinued due to jaundice/hyperbilirubinemia (3 [<1%] vs. 0), while more patients on LPV/RTV discontinued due to diarrhoea (4 [<1%] vs. 0). The proportion of patients who discontinued due to rash (< 1% and < 1%) and rash generalised (< 1% and 0) was consistent between the treatment regimens.

In 089, 8 (8%) patients discontinued in ATV/RTV and 3 (3%) discontinued in the ATV400 regimen because of AEs. Five (5) of these discontinuations from the ATV/RTV regimen were protocol mandated due to persistent bilirubin elevations.

Analysis of Safety by Organ System

Hyperbilirubinemia and jaundice

In 138 through week 48, AEs of ocular icterus, hyperbilirubinemia, and jaundice (all grades) were more common on ATV/RTV than LPV/RTV (31% vs. 1%) ; the most frequently reported Grade 2 to 4 treatment-related AEs that were higher in ATV/RTV than LPV/RTV were hyperbilirubinemia (7% vs. < 1%) and jaundice (4% vs. 0%).

Similar to 138, in 089 through week 48, more patients in ATV/RTV than in ATV400 (52% vs. 31%, respectively) experienced 1 or more AEs (all grades) of ocular icterus, hyperbilirubinemia, and jaundice. In 138, mean total bilirubin levels at week 48 in ATV/RTV were 1.9 mg/dl and in LPV/RTV were 0.5 mg/dl. Mean changes from baseline in total bilirubin levels through week 48 were higher in ATV/RTV than in LPV/RTV (1.5 mg/dl and 0.1 mg/dl, respectively).

For all cohorts and for all grades (i.e. Grade 3 to 4 and Grade 4), the majority of cases of bilirubin elevation were total bilirubin measures (predominantly unconjugated bilirubin). This observation, in combination with the lack of reported clinical sequelae (i.e., liver failure) for those patients with concurrent bilirubin and transaminase elevations are consistent with previous safety analyses of ATV.

Adverse Events by Hepatitis B or C Co-infection

In 138, 60 (14%) patients in ATV/RTV and 51 (12%) in LPV/RTV and in 089, 17 (18%) in ATV/RTV and 20 (19%) in ATV400 regimen were HBV and/or HCV positive at baseline.

The Grade 3 to 4 AST/ALT and total bilirubin abnormalities in both 138 and 089 through week 48 are summarised in the table below:

Table 18 AST/ALT and Total Bilirubin (Grade 3 to 4) Abnormalities in Patients Co-infected with Hepatitis B and/or C Through week 48 in 138 and 089

	138				**089**			
	ATV/RTV		**LPV/RTV**		**ATV/RTV**		**ATV400**	
Abnormalities	Co-infected N = 60	Not co-infected N = 380	Co-infected N = 51	Not co-infected N = 385	Co-infected N = 17	Not co-infected N = 78	Co-infected N = 20	Not co-infected N = 84
ALT	8%	< 1%	6%	< 1%	29%	1%	15%	0%
AST	8%	1%	0%	< 1%	12%	1%	10%	1%
Total Bilirubin	38%	33%	0%	< 1%	53%	60%	25%	19%

As expected, co-infected patients experienced higher baseline and on-treatment hepatic transaminase levels than those not co-infected. In 138, patients on both ATV/RTV and LPV/RTV who had HBV and/or HCV co-infection had higher rates of liver enzyme elevations than the not co-infected patients.

Higher rates of Grade 3-4 ALT and AST elevations were observed in the ATV/RTV arm compared to the LPV/RTV one in the combined group. Randomisation was not stratified by HBV/HCV status in the study, making results within these subgroups susceptible to bias.

To determine whether a specific co-infection subgroup might provide further insight into the clinical relevance of the observed differences, Grade 3-4 liver function elevations through Week 48 were determined by regimen separately for baseline HBV and HCV co infected patients:

- Grade 3-4 AST elevations were higher on ATV/RTV than LPV/RTV for both HBV and HCV patients. On ATV/RTV, rates were 3/24 (13%) for HBV patients and 3/39 (8%) for HCV patients. Rates were 0% on LPV/RTV for both subgroups.
- Grade 3-4 ALT elevations were higher on ATV/RTV than LPV/RTV for HBV patients: 4/24 (17%) versus 1/19 (5%). Rates were consistent between regimens for HCV patients: 2/39 (5%) versus 2/33 (6%).

This variety of potential causes (inflammation as a result of immune reconstitution and inflammatory syndrome, drug-induced hepatocellular toxicity, or “flares” due to the antiviral effect of tenofovir and emtricitabine), in addition to the susceptibility to bias noted above, makes it difficult to assess, in the small numbers of co-infected patients seen in study 138, if the differences observed between the regimens, particularly for AST, are of any clinical relevance.

Lipodystrophy related adverse events

In 138, few (< 1% in both regimens) lipodystrophy-related AEs were reported through week 48. Only acquired lipodystrophy was reported in the ATV/RTV regimens (1 patient); acquired lipodystrophy, lipoatrophy and lipohypertrophy were reported in the LPV/RTV regimen (1 patient for each event). All lipodystrophy-related AEs were non-serious AEs. One (1) AE of acquired lipodystrophy in the LPV/RTV regimen resulted in discontinuation after 333 days of dosing; this Grade 2 AE was considered certainly related to study drug by the investigator.

In 089, 2% and 3% of patients on ATV/RTV and ATV400, respectively had lipodystrophy-acquired reported as an AE; 3% and 2% respectively had lipoatrophy reported through week 48. The most common lipodystrophy-related AEs through both week 48 and week 96 were lipoatrophy (3% to 6%

and 2% to 4%, respectively) and acquired lipodystrophy (2% to 3% and 3% to 5%, respectively). All lipodystrophy-related AEs were non-serious AEs and none resulted in treatment discontinuation.

A lipodystrophy substudy was planned in study 138 to compare the changes in body fat redistribution between ATV/RTV and LPV/RTV treatment regimens, as assessed by the change from baseline in trunk-to-limb fat ratio measured by Dual Energy Xray Absorptiometry (DEXA) at week 96. This substudy report will be submitted 3rd quarter 2009.

Immune reconstitution syndrome adverse events

In 138, immune reconstitution syndrome AEs were uncommon (27/878), fourteen (14) events (3%) were reported in the ATV/RTV and 13 (3%) in the LPV/RTV regimen. The most frequently reported events were hepatitis flare (6 events), Kaposi Sarcoma (5 events) and *Mycobacterium tuberculosis* infection (3 events). Among the 27 patients with an immune reconstitution syndrome event, 5 patients discontinued therapy on or before week 48 and 3 patients discontinued after week 48. Six (6) of the 8 discontinuations occurred among patients on the LPV/RTV regimen and the remaining 2 occurred in the ATV/RTV regimen. In 138, there was only 1 spontaneous investigator reported serious adverse event (SAE) of immune reconstitution syndrome. This SAE was reported for 1 patient in the LPV/RTV regimen.

In 089, immune reconstitution syndrome was not reported as an AE for any patients.

Renal toxicity adverse events

Renal toxicity AEs were uncommon (≤ 2%) and consistent between ATV/RTV and LPV/RTV regimen. All renal toxicity AEs occurred with an incidence of < 1%. One (1) patient on each regimen discontinued due to a renal AE, Fanconi syndrome on ATV/RTV and proteinuria on LPV/RTV. There were 2 cases (< 1%) of nephrolithiasis on ATV/RTV and 1 (< 1%) on LPV/RTV; all 3 were considered non-serious AEs.

Grade 3 to Grade 4 creatinine was reported in only 1 subject on each regimen. Only 1 subject on ATV/RTV and 3 subjects on LPV/RTV required substitution using alternative NRTIs for TDF-FTC through Week 48. Renal function was stable overall with no change from baseline in the mean serum creatinine at Week 48 on either regimen. The overall calculated creatinine clearance appeared to fluctuate over time: the median percent changes were -6% and -7% at Week 4 on the ATV/RTV and LPV/RTV regimens, respectively, and returned toward baseline values by Week 48, at -1% for both regimens.

Currently, the ATV SPC mentions that when TDF 300mg is co-administered with ATV 300mg and ritonavir 100mg, an increase in concentrations of TDF was observed (increase in AUC of 37% with 90% confidence interval (30-45%)). Higher TDF concentrations could potentiate TDF-associated adverse events, including renal disorders. Patients receiving ATV and TDF should be monitored for TDF associated adverse events.

Fasting lipid abnormalities

In clinical studies, ATV (with or without RTV), has been shown to induce dyslipidaemia to a lesser extent than LPV/RTV. The data available from study 138 on the lipid profile (mean change from baseline) are described in treatment-naïve subjects (Table 19); historical data for treatment-experienced subjects (study 045) are reflected in Table 20.

Table 19 Fasting Lipid Values, Mean Change from Baseline, Study AI424-138

	ATV/RTV[a,b]			**LPV/RTV[b,c]**		
	Baseline mmol/L (n=428[e])	**Week 48 mmol/L (n=372[e])**	**Week 48 Change[d] (n=372[e])**	**Baseline mmol/L (n=424[e])**	**Week 48 mmol/L (n=335[e])**	**Week 48 Change[d] (n=335[e])**
LDL-cholesterol	2.38	2.7	14%	2.4	2.87	19%
HDL-cholesterol	0.95	1.2	29%	0.93	1.24	37%
Total cholesterol	3.86	4.36	13%f	3.88	4.84	25%
Triglycerides	1.42	1.63	15% [f]	1.46	2.2	52%

[a] ATV 300 mg plus RTV 100 mg once daily with the fixed-dose combination: 300 mg TDF, 200 mg FTC twice daily.

[b] Values obtained after initiation of serum lipid-reducing agents were not included in these analyses. Use of serum lipid-reducing agents was more common in the lopinavir treatment arm (8%) than in the REYATAZ arm (2%).

[c] LPV 400 mg plus RTV 100mg once daily with the fixed-dose combination 300 mg TDF, 200 mg FTC twice daily.

[d] The change from baseline is the mean of within-patient changes from baseline for patients with both baseline and Week 48 values

[e] Number of patients with LDL-cholesterol measured.

[f] $p < 0.0001$; ATV/RTV vs. LPV/RTV

Table 20 Lipid Values, Mean Change from Baseline, Study AI424-045

ATV/RTV[a]						**LPV/RTV[a]**					
	Baseline mmol/L (n=111[d])	**Week 48 mmol/L (n=76[d])**	**Week 48 Change[b] (n=75[d])**	**Week 96 mmol/L (n=52[d])**	**Week 96 Change[c] (n=52[d])**	**Baseline mmol/L (n=108[d])**	**Week 48 mmol/L (n=76[d])**	**Week 48 Change[b] (n=73[d])**	**Week 96 mmol/L (n=44[d])**	**Week 96 Change[c] (n=43[d])**
Total Cholesterol	**4.9**	**4.4**	**-8%**	**4.5**	**-7%**	**4.7**	**4.8**	**6%**	**4.9**	**9%**
LDL Cholesterol[e]	**2.8**	**2.5**	**-11%**	**2.6**	**-11%**	**2.7**	**2.7**	**1%**	**2.6**	**1%**
HDL Cholesterol	**1.0**	**1.0**	**-7%**	**1.1**	**-5%**	**1.0**	**1.1**	**2%**	**1.1**	**7%**
Triglycerides[e]	**2.4**	**1.8**	**-3%**	**1.9**	**-2%**	**2.2**	**2.5**	**30%**	**2.5**	**30%**

a Values obtained after initiation of serum lipid-reducing agents were not included in these analyses

b The change from baseline is the mean of within-patient changes from baseline for patients with both baseline and Week 48 values

c The change from baseline is the mean of within-patient changes from baseline for patients with both baseline and Week 96 values

d Number of patients with LDL-cholesterol measured

e Fasting

Overall, these data suggest that ATV/RTV is associated with a less negative lipid profile than LPV/RTV. However, a clinical study to prove the benefit of these laboratory parameter findings in a cardiovascular outcome was found to be too extensive to perform (forecasted duration ca. 8 years, enrolment ca. 8,000 patients). As such, the potential clinical benefit remains unproven.

Fasting glucose abnormalities

In both studies, through week 48, Grade 3 to 4 fasting glucose abnormalities were infrequent (≤ 1%) among treatment regimens. week 96 results in 089 were consistent with those for week 48.

Other observations related to safety

Collection of ECGs was not required in either 138 or 089; however, there were no episodes of PR interval or QT prolongation reported as AEs. Patients with known cardiac abnormalities were excluded from both studies.

Conclusion on safety:

The safety profile with the addition of data for treatment-naïve patients available from 138 and 089 to the integrated safety database for the proposed SPC is consistent with the current SPC. No new safety signals were identified for ATV/RTV than previously observed. The pattern of adverse events was consistent with the known safety profile of ATV/RTV, LPV/RTV and the backbone medicines, TDF/FTC. The overall discontinuation numbers and reasons for discontinuation were consistent with previous studies.

Overall, discontinuations due to adverse events prior to week 48 were 2% and 3% on ATV/RTV and LPV/RTV, respectively. The majority of liver function test abnormalities were mild to moderate, with an incidence of 2% and 1% Grade 3 to Grade 4 ALT for ATV/RTV and LPV/RTV, respectively. As expected, the incidence of abnormal bilirubin was greater on ATV/RTV than LPV/RTV (Grade 1 to Grade 4: 84% and 4%; Grade 3 to Grade 4: 34% and <1%).

The higher frequency of liver enzyme elevations for co-infected patients in the ATV/RTV arm vs. LPV/RTV: 8% vs. 6% for ALT elevation and 8% vs. 0% for AST elevation was most likely due to the small number of co-infected patients in the study, which do not allow for a relevant statistical comparison between both arms for this population.

Renal toxicity AEs were uncommon (≤ 2%) and consistent between ATV/RTV and LPV/RTV regimen. All renal toxicity AEs occurred with an incidence of < 1%. One (1) patient on each regimen discontinued due to a renal AE, Fanconi syndrome on ATV/RTV and proteinuria on LPV/RTV. There were 2 cases (< 1%) of nephrolithiasis on ATV/RTV and 1 (< 1%) on LPV/RTV; all 3 were considered non-serious AEs.

The use of PI-based highly active ARV treatment has been associated with dyslipidaemia. Clinical data suggest that ATV/RTV is associated with a less negative lipid profile than LPV/RTV. However, a clinical study to prove the benefit of these laboratory parameter findings in a cardiovascular outcome was found to be too extensive to perform (forecasted duration ca. 8 years, enrolment ca. 8,000 patients). As such, the potential clinical benefit remains unproven.

1.6 Risk Management Plan

The CHMP considered that the Pharmacovigilance system as described by the MAH fulfils the legislative requirements.

The CHMP did not require the MAH to submit an updated risk management plan because it had recently been assessed in the framework of the line extension for ATV 300 mg hard capsule (EMEA/H/C/494/X/33) and was judged acceptable. No further changes were deemed necessary.

1.7 Changes to the Product Information

Summary of Product Characteristics

Section 4.1, 4.2 and 4.3
Changes to reflect the new patient populations were introduced in sections 4.1 and 4.2. In section 4.3 "should" was exchanged for "must" in order to avoid translation ambiguity.

Section 4.4 "Special warnings and precautions for use"
A statement underling the risk of developing dyslipidaemia under HAART, including ATV was added.

Section 4.5 "Interaction with other medicinal products and other forms of interaction"
This section was updated with data from study 138 in relation to the co-administration of both RTV and TDF with ATV.

Section 4.8 "Undesirable Effects"
This section was updated in the light of safety finding from study 138 and 089, which led to some changes in frequency categories for listed ADRs.

Section 5.1 Pharmacodynamic properties
This section was extensively updated in order to reflect both the findings relating to clinical outcome as well as resistance in treatment naïve patients. In addition, the section on lipid parameters was taken out, as the clinical benefit in terms of cardiovascular outcome for patients cannot be proven. Therefore, these data might be falsely reassuring.

Section 5.2 Pharmacokinetic properties
The paragraphs on absorption, food effect and elimination were updated in order to include the findings in the treatment naïve population.

Package Leaflet
The section on possible side effects was updated in line with the update in section 4.8.

Generally, the Product Information was revised in an effort to consistently use British spelling.

1.8 Discussion and Benefit Risk Assessment

Given the once daily dosing possibility of ATV, the extension of indication to include the treatment of antiretroviral naïve patients is of interest, especially in view of potential benefit in terms of adherence to long-term treatment.

ATV was originally (2004) developed as an unboosted regimen (400 mg QD) in antiretroviral naïve patients in a study where it was compared to efavirenz. Due to methodological problems this study failed to provide a convincing non inferiority demonstration of ATV unboosted to efavirenz (with an ultra-sensitive test of 50 copies/ml (secondary endpoint in the study) it was even shown as being inferior). From the beginning of the assessment it was identified that an unboosted regimen might provide suboptimal PK exposure in some patients. The MAH has performed a study AI424 089 that consisted of a comparison between the unboosted and boosted regimen of ATV (two non validated arms in the target population for an EU perspective). This study confirmed the CHMP concerns that, from a clinical and PK point of view, the unboosted regimen might be suboptimal.

The MAH subsequently performed study 138 to support the extension of indication in antiretroviral naïve patients in the EU with ATV boosted with ritonavir 300/100 mg QD, this treatment is currently recommended for treatment experienced patients.

This study was an open label study, which is regretful. However, it has to be recognised that a double blind, double dummy would have imposed a high pill burden (5 BID) that might have altered the study enrolment. The stringent 10% non inferiority margin in terms of percentage of patients with undetectable viral load (<50 copies/ml) was used, which is appreciated. Its long term data at 96 weeks will be submitted in the first quarter of 2009.

In line with the pivotal study 45 in antiretroviral experienced patients, TDF was part of the backbone therapy. To some extent this might somewhat mitigate the efficacy of ATV. Indeed, TDF has been shown to reduce the ATV AUC (25%) and Cmin (40%) whereas no significant influence has been observed on lopinavir exposure. Nevertheless this backbone is attractive in clinical practice and allows the MAH to fulfil the specific obligation consisting of exploring the use of ATV in a once daily HAART combination.

As a main finding, the results observed are well in accordance with the predefined non inferiority margin for this study.

For both treatment arms the response rate was lower (10%) in patients with a higher viral load (>100 000 copies/ml) as compared to patients with viral load <100 000 copies/ml. A similar 3 log copies/ml viral load decrease was observed in both treatment arms. No major concern was raised as regards the emergence of resistance.

No major safety issue was raised in this population of patients as compared to the antiretroviral experienced patients. A trend for a lower rate of dyslipidaemia was observed, however the translation of this laboratory parameter effect into a clinical benefit (i.e. cardiovascular outcome) will remain unproven, as a study in support of such an outcome would be unrealistically long and large.

Hyperbilirubinemia was observed but not perceived as a significant limiting factor of the use of the medicinal product (accounts for <1 % of adverse events leading discontinuation). A higher rate of hyperbilirubinemia and a lower rate of diarrhoea as compared to lopinavir/ritonavir were observed.

CONCLUSION

On 24 April 2008 the CHMP considered this Type II variation to be acceptable and agreed on the amendments to be introduced in the Summary of Product Characteristics and Package Leaflet.