Clinical Study Synopsis for Public Disclosure

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The synopsis - which is part of the clinical study report - had been prepared in accordance with best practice and applicable legal and regulatory requirements at the time of study completion.

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A synopsis is not intended to provide a comprehensive analysis of all data currently available regarding a particular drug. More current information regarding a drug is available in the approved labeling information which may vary from country to country.

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Title of study:	The pharmacodynamic/pharmacokinetic interaction of tipranavir and ritonavir with loperamide in healthy volunteers
Investigator:	[redacted]
Study center:	[redacted] (cf. Appendix 16.1.4)
Publication (reference):	Data from this study have not been published.
Clinical phase:	I
Objectives:	The objective of the study was to determine if the co-administration of loperamide (LOP) with tipranavir (TPV), ritonavir (RTV), or TPV plus RTV (TPV/r) caused a clinically significant change in the respiratory response to carbon dioxide (CO_2), defined as a 10% decrease in the area under the pharmacodynamic effect/time curve or at least a 25% decrease in at least one pharmacodynamic time point.
Methodology:	Open-label, randomized, parallel-group Phase I study.
No. of subjects:	
planned:	Enrolled: 40, entered: 20
actual:	Enrolled: 128, entered: 24 Group I: Entered: 12, treated: 12, analyzed (for primary endpoint): 10 Group II: Entered: 12, treated: 12, analyzed (for primary endpoint): 10
Diagnosis and main criteria for inclusion:	Healthy HIV-1-negative males or females 18 to 60 years of age inclusive.
Test product:	Tipranavir, 250 mg, Soft Elastic Capsules, Self-Emulsifying Drug Delivery System (SEDDS) formulation
dose:	750 mg BID
mode of admin.:	Oral
batch no.:	PD-2101
Test product:	Ritonavir (Norvir®), 100 mg Soft Elastic Capsules
dose:	200 mg BID
mode of admin.:	Oral
batch no.:	817772E21

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Test product:	Loperamide, Imodium®, 2 mg
dose:	16 mg QD
mode of admin.:	Oral
batch no.:	FDA 008, FCA 081, FCA 156
Duration of treatment:	Subjects received LOP on Days 1, 9, and 22; TPV or RTV for 5.5 consecutive days (Days 4-9), TPV/r for 10.5 days (Days 12-22). On Days 2 and 3 and Days 10 and 11, no study drugs were administered.
Criteria for evaluation:	
Efficacy:	This study was not designed to determine efficacy.
Safety:	Safety was assessed by adverse events (AEs), vital signs, electrocardiograms (ECGs), and laboratory test measurements.
Pharmacodynamic:	The following primary endpoints were analyzed: • The maximum decrease in the percentage baseline CO_2 response slope (observed at one of the examination time points during the 6-hour rebreathing test); • The 0-to-6 hour area under the plasma concentration time curve (AUC_{0-6h}) for the percentage baseline CO_2 response slope profile. The secondary pharmacodynamic endpoint was the pupillary response to LOP after administration of TPV, RTV or TPV/r, as measured by the ratio between the diameter of the pupil and iris. (A decrease in the ratio would be of clinical significance.) The primary comparison of the pharmacodynamic response focused on the difference in response on Day 22 (combined effect of TPV/r with LOP) compared with the response on Day 1 (effect of LOP alone).

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Pharmacokinetic:	The following pharmacokinetic (PK) parameters were evaluated: • Loperamide and N-demethyl-loperamide (with and without TPV and/or RTV): C_{max}, $t_{max,}$ and $AUC_{0-\infty}$. • Tipranavir and/or RTV (with and without LOP): C_{max}, Cp_{12h}, t_{max}, $t_{1/2,}$ Cl/F, and AUC_{0-12h} (Day 21).
Statistical methods: (Pharmacodynamic)	The primary comparison of the pharmacodynamic response focused on the difference in response on Day 22 compared with the Day 1 response. The Day 22 response reflects the combined effect of LOP and TPV/r, and the Day 1 response reflects the effect of LOP alone. The secondary comparison of the pharmacodynamic response focused on the difference in response on Day 9 compared with the Day 1 response. The Day 9 response reflects the combined effect of LOP and TPV or LOP and RTV, and the Day 1 response reflects the effect of LOP alone. The Wilcoxon signed rank test was used for the comparison of LOP alone with LOP+TPV or LOP+RTV or LOP alone with LOP+TPV/r for the respiratory response, as measured by the maximum decrease in the percentage baseline CO_2 response slope. An analysis of variance (ANOVA) was used for the AUC_{0-6h} for the percentage baseline CO_2 response slope profile. The individual pharmacodynamic observations used to construct the AUC were derived from the rebreathing test. The rebreathing test data (ventilation per minute of end tidal CO_2 [V_E-$P_{ET}CO_2$]) at each time point were summarized by fitting to a linear regression model that relates the ventilation rate (L/minute) to the end-tidal partial pressure of CO_2 (P_{CO2}) (mm Hg). The slope of this regression was expressed relative to the baseline slope, the baseline slope being determined just before administration of LOP for the same subject on the same day. Because duplicate measures were taken, the baseline slope was determined by using the average of the duplicate values on the same day. The results of the rebreathing tests for the first 6 hours after LOP administration were summarized by the area under the pharmacodynamic effect time curve using the trapezoidal rule. The data for the secondary pharmacodynamic endpoint of pupillary response, as measured using the ratio of the diameter of the pupil and the iris, were analyzed using descriptive statistics.

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Statistical methods:

(Pharmacokinetic)

The PK parameters C_{max}, t_{max}, and $AUC_{0-\infty}$ were calculated for LOP and N-demethyl-loperamide (with and without TPV/r, TPV and RTV). The PK parameters C_{max}, Cp_{12h}, t_{max}, AUC_{0-12h} (Day 21), Cl/F and $t_{1/2}$ were calculated for TPV and RTV (with and without LOP). Descriptive statistics and tabular and graphic summaries of these PK parameters are presented; formal statistical analyses were performed for C_{max}, Cp_{12h}, $AUC_{0-\infty}$, and AUC_{0-12h} (Day 21).

Drug-drug interactions were assessed, on the basis of 90% confidence intervals for the geometric mean ratios of selected PK parameters (i.e., LOP and N-demethyl-loperamide: $AUC_{0-\infty}$ and C_{max}; TPV/r: AUC $_{0-12h}$, C_{max}, and Cp_{12h}).

(Safety)

The onset of AEs was classified according to Type 1 and Type 2 treatment definitions: Type 1 = non-overlapping treatment phases and Type 2 = overall exposure to LOP, TPV, RTV, and the combination of TPV/r. The focus of safety results uses Type 2 definitions. Tabulations of AEs, by frequency, intensity, relationship to study drug, seriousness, and outcome were presented. Laboratory test data were analyzed by treatment group and each laboratory test using descriptive statistics; data for vital signs were analyzed by treatment group and study visit using descriptive statistics. For ECG data, descriptive statistics were calculated for heart rate, QT interval, PR and QRS intervals, QTcB and QTcF intervals; the incidence of ECG abnormalities and relevant changes in the QT interval were tabulated, and the magnitude of the QTc change from baseline compared with Day 24 was calculated.

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SUMMARY – CONCLUSIONS:

Efficacy results: No efficacy analyses were performed.

Pharmacodynamic results:

The primary comparison of the pharmacodynamic response focused on the difference in response on Day 22 (combined effect of TPV/r with LOP) compared with the response on Day 1 (effect of LOP alone). The respiratory response, as measured by the mean $AUC_{0\text{-}6h}$ for the percentage baseline V_E-$P_{ET}CO_2$ response slope profile, for the coadministration of LOP+TPV/r was not statistically significantly different from that observed for LOP alone (P=0.844). No evidence of a clinically relevant decline in the respiratory response (defined as a 10% decrease in $AUC_{0\text{-}6h}$) was observed. There was a mean increase of 1.6% in the respiratory response ($AUC_{0\text{-}6h}$) between Day 1 (LOP alone) and Day 22, when TPV/r was added to LOP treatment. However, the possibility cannot be excluded that the respiratory response (defined as $AUC_{0\text{-}6h}$ for the percentage baseline CO_2 slope profile) could be reduced by as much as 12.9% (lower 90% confidence limit) when TPV/r is administered with LOP. The respiratory response profile (percentage V_E-$P_{ET}CO_2$ response slope, expressed as a percentage of the baseline slope) over the 6 hours after receiving study drugs was similar between the LOP alone and the LOP+TPV/r treatments. No significant differences in the mean percentage baseline slope were seen over the 6 hours of testing (LOP alone compared with LOP+TPV/r). The difference between the LOP alone response profile and the LOP+TPV/r response profile was considerably less than the 25% decrease at any examination timepoint that was defined in the protocol as being clinically relevant.

The secondary comparison of the pharmacodynamic response focused on the difference in response on Day 9 (the combined effect of LOP with TPV or RTV) compared with the response on Day 1 (LOP alone). The respiratory response, as measured by the $AUC_{0\text{-}6h}$ for the percentage V_E-$P_{ET}CO_2$ response slope profile, for the coadministration of LOP with either TPV (P=0.838) or with RTV (P=0.207) was not statistically significantly different from that observed for LOP alone. On Day 9, there was a mean 1% decrease in the respiratory response ($AUC_{0\text{-}6h}$) when TPV was added to LOP treatment. The possibility cannot be excluded that the respiratory response ($AUC_{0\text{-}6h}$) could be reduced by as much as 17.6% (lower 90% confidence limit) when TPV is administered with LOP. On Day 9, there was a mean 12% increase in the respiratory response ($AUC_{0\text{-}6h}$) when RTV was added to LOP treatment. However, as noted above, the possibility also cannot be excluded that the respiratory response ($AUC_{0\text{-}6h}$) could be reduced by as much as 5.3% (lower 90% confidence limit) when RTV is administered with LOP.

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	For the secondary pharmacodynamic endpoint of pupillary response, the mean pupil-to-iris ratio was unaffected by administration of LOP alone or of LOP+TPV/r, LOP+TPV or LOP+RTV. The pupil-to-iris ratio on Day 22 was virtually identical to that on Day 1 (P=0.927). No trend in the pupil-to-iris ratio was apparent with time after drug treatment. There was no significant difference in the mean pupillary response, as measured by the ratio between the diameter of the pupil and iris, for LOP + TPV/r compared to LOP alone over the 6 hours of testing.
Pharmacokinetic results:	Coadministration of single-dose LOP with steady-state TPV and RTV, as the combination TPV/r, resulted in a decrease of plasma LOP AUC of 51% and C_{max} of 61% and a decrease in the plasma N-demethyl-loperamide AUC of 77% and C_{max} of 79%. Since the dose of LOP used in this study was the maximum recommended daily dose, the decrease in plasma AUC and C_{max} for LOP are of unknown clinical relevance. The interaction of LOP with TPV and RTV (coadministered as the combination TPV/r) resulted in a decrease in plasma TPV Cp_{12h} of 26% with relatively no change in C_{max} and $AUC_{0\text{-}12h}$. This decrease in TPV Cp_{12h} is of unknown clinical relevance. The effect of this interaction on RTV pharmacokinetics was greater and resulted in a 30% decrease in RTV Cp_{12h}, a 28% decrease in RTV C_{max} and a 22% decrease in RTV $AUC_{0\text{-}12h}$.
Safety results:	There were no deaths or SAEs observed during the study. None of the subjects experienced any severe AEs, nor did any of the subjects have AEs leading to discontinuation of study treatment. Overall, the most frequently observed AEs ($\geq$2 subjects or >8.0%), regardless of causality, were observed in the following percentages of subjects: loose stools (37.5%); nausea (33.3%); abdominal pain NOS (29.2%); headache NOS (25.0%); vomiting NOS (16.7%); dyspepsia, maculopapular rash (each in 12.5%); and dizziness (excluding vertigo), flatulence, pruritus NOS (each in 8.3%), all in the TPV+RTV group, and headache NOS (12.5%) and constipation (8.3%) in the LOP alone group. The nature of the most frequently observed AEs that were considered related to study treatment and the percentages of subjects experiencing them were almost identical to those for AEs, regardless of causality. For both Type 1 and Type 2 definition analyses, all subjects recovered from all AEs that were experienced during the study and regardless of treatment relationship.

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Nine subjects had clinically significant laboratory abnormalities (defined as DAIDS Grade 3 or 4 values). One subject had a decreased hematocrit while receiving TPV/r+LOP treatment. Eight subjects had clinically significant increases in ALT values (4 in each treatment group). Four of the 8 subjects with clinically significant ALT elevations also had clinically significant increases in AST values. Of the eight subjects with clinically significant increases in ALT and the 4 subjects with increases in AST values, their baseline AST and ALT values were within the normal range. In all eight subjects, most of these elevations in AST/ALT occurred on Study Day 24 and were the last values on treatment. Follow-up testing was performed after Day 24 in subjects who had clinically significant increases in ALT/AST until the values returned to within the normal range or were considered stabilized. None of the clinically significant laboratory abnormalities were considered to be AEs. No clinically significant laboratory abnormalities were observed for any lipid tests (total cholesterol, HDL, LDL, or triglycerides) or any of the other clinical chemistry or hematology tests.

For vital signs, there were no clinically relevant changes observed for systolic or diastolic blood pressure and pulse rate in either treatment group. The only clinically relevant change in ECG findings (defined as heart rate >100 beats per minute [bpm]) consisted of an increase in one subject in heart rate (108 bpm) on Day 24, which fell below 100 bpm on subsequent evaluations on Day 24.

Conclusions:

None of the primary or secondary pharmacodynamic endpoints of this study demonstrated clinically relevant pharmacodynamic interactions of the combination of TPV/r with LOP or of TPV or RTV with LOP in healthy HIV-1-negative subjects. However, the possibility of some interaction cannot be excluded based on the lower 90% CI observed for the primary pharmacodynamic endpoint, $AUC_{0\text{-}6h}$ for the percentage baseline CO_2 slope profile. There were substantial changes in the PK of both LOP (decreases of 51% in the AUC and 61% in the C_{max}) and of TPV (a decrease of 26% in the Cp_{12h}); these changes are of unknown clinical relevance. Evaluation of data for safety in Trial 1182.55 demonstrated no new or unexpected safety issues based on the body of data already obtained in other Phase I and Phase II studies of HIV-1-positive patients or healthy HIV-1-negative volunteers receiving TPV. In addition, data from this trial indicated that coadministration of TPV and RTV (TPV/r) with LOP posed no safety concerns.