

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

205395Orig1s000

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA: 205395	Original Submission Date: March 31, 2014
Brand Name	Prezcobix
Generic Name	Darunavir/cobicistat
Reviewer	Stanley Au, Pharm.D., BCPS
Pharmacometrics Reviewer	Jeffrey Florian, Ph.D.
Clinical Pharmacology Team Leader	Kellie Reynolds, Pharm.D. (acting)
OCP Division	Division of Clinical Pharmacology 4
OND Division	Division of Antiviral Products (DAVP)
Applicant	Janssen Research and Development
Formulation; strength(s)	Fixed dose combination tablet: Darunavir 800 mg/cobicistat 150 mg
Indication	Treatment of HIV-1 infection
Review Type	505 (b)(1) New Drug Application, standard review

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1 Executive Summary

The applicant, Janssen Research and Development, submitted a New Drug Application (NDA) for a fixed dose combination tablet consisting of darunavir 800 mg and cobicistat 150 mg (formulation G006). Another applicant, Gilead Sciences, submitted the cobicistat NDA (203094) and cobicistat in combination with darunavir as single entities was evaluated as part of the cobicistat NDA. Cobicistat was approved for U.S. marketing in September 2014. The pivotal trial for the current NDA compared the relative bioavailability for darunavir and cobicistat as part of a fixed dose combination tablet compared to single entity formulations. The TMC114IFD1003 trial evaluated the relative bioavailability of the fixed dose combination tablet consisting of darunavir 800 mg and cobicistat 150 mg that is proposed for U.S. marketing (formulation G006) compared to single entity formulations of darunavir (two 400 mg tablets, formulation F030) and cobicistat (150 mg tablets). The food effect of the darunavir and cobicistat fixed dose combination tablets (formulation G006) was also evaluated as part of the TMC114IFD1003 trial.

The Clinical Pharmacology review evaluated the food effect data for the fixed dose combination tablet consisting of darunavir and cobicistat (formulation G006). Additional pertinent review issues for the TMC114IFD1003 trial include evaluating the relative bioavailability data and reviewing the inspection findings from the Office of Scientific Investigations, as well as the relevant bioanalytical information. The biopharmaceutics reviewers within the Office of New Drug Quality Assessment (ONDQA) will assess these regulatory issues. Additionally, the Division of Pharmacometrics evaluated the darunavir population pharmacokinetic data from the GS-US-216-130 trial (with darunavir and cobicistat administered as single entities) that the applicant proposes to include in the U.S. prescribing information for the darunavir/cobicistat fixed dose combination tablets (see section 4 for the Pharmacometrics review and the clinical pharmacology review for NDA 203094 for further information regarding the GS-US-216-130 trial).

The TMC114IFD1001 trial that was also included as part of NDA 205395 was not reviewed by the Office of Clinical Pharmacology. The TMC114IFD1001 trial was not conducted with the G006 formulation and instead compared two formulations of a fixed dose combination tablet consisting of darunavir 800 mg and cobicistat 150 mg (formulation G003 and formulation G004) to darunavir 800 mg and ritonavir 100 mg as single entities. The review of this trial was not necessary since cobicistat in combination with darunavir as single entities is an approved regimen in the United States for the treatment of HIV-1 infection.

1.1 Recommendation

The clinical pharmacology information submitted in the NDA supports the approval of the application.

1.2 Postmarketing Commitments or Requirements

There are no postmarketing commitments or requirements for this NDA.

1.3 Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

A) Evaluation of the food effect data from the TMC114IFD1003 trial

A food effect was observed for darunavir when administered as a fixed dose combination tablet in combination with cobicistat. When compared to fasted conditions, with high fat meals, a 70% increase in $AUC_{[0-\text{inf}]}$ and a 127% increase in C_{max} were observed when darunavir is administered as part of a fixed dose combination tablet with cobicistat. The changes in darunavir exposure when administered with cobicistat as part of a fixed dose combination tablet exceeds the magnitude of the increase in C_{max} and $AUC_{(0-\text{inf})}$ for darunavir when coadministered with ritonavir as single entity formulations with a high fat meal when compared to fasted conditions (48% increase in $AUC_{[0-\text{inf}]}$ and 59% increase in C_{max}). There was no food effect trial that was conducted for darunavir when coadministered with cobicistat as single entities.

The single entity darunavir U.S. prescribing information recommends that darunavir in combination with ritonavir should be administered with food. The same recommendation also applies for darunavir and cobicistat when coadministered as single entities. No specific darunavir exposure-safety issues have been identified for the range of darunavir exposures associated with the dosage regimens that are included in the darunavir U.S. prescribing information. A food effect was not observed for cobicistat when administered as part of a fixed dose combination tablet with darunavir. Therefore, for darunavir and cobicistat, the applicant's recommendation to administer the darunavir/cobicistat fixed dose combination tablet with food is acceptable.

B) Clinical Pharmacology revisions to the proposed U.S prescribing information for the darunavir/cobicistat fixed dose combination tablets

The Clinical Pharmacology revisions to the proposed U.S prescribing information for the darunavir/cobicistat fixed dose combination tablets that are outlined in section 2 (Labeling Recommendations) were primarily based on the information in the cobicistat U.S. prescribing information that is relevant to administration with darunavir. Please see the Clinical Pharmacology review for NDA 203094 for further information regarding the extrapolation of drug-drug interaction information for darunavir coadministered with ritonavir to darunavir coadministered with cobicistat. For drug-drug interactions that are not currently included in the darunavir or cobicistat U.S. prescribing information, the proposed recommendations in section 7 were based on a determination regarding the most appropriate recommendation in the absence of drug-drug interaction data for concomitant use with darunavir coadministered with cobicistat.

C) Review of the bioanalytical data for the GS-US-216-130 trial

The bioanalytical information to support the darunavir concentration data for the GS-US-216-130 trial was reviewed as part of the Clinical Pharmacology review for NDA 209094. At the time the review was finalized, the long term stability data for darunavir that was necessary for the darunavir plasma samples from the GS-US-216-130 trial was not available. The information was requested from Janssen. Based on the information that was provided, stability for darunavir was demonstrated for up to 588 days at both -20°C and -70°C in K₂EDTA anticoagulated plasma.

D) Evaluation of the relative bioavailability data from the TMC114IFD1003 trial (based on the ONDQA Biopharmaceutics review)

The applicant demonstrated that the 90% confidence were within 80-125% for the darunavir/cobicistat fixed dose combination tablets compared with the single entity darunavir and cobicistat tablets under both fed (non high fat) and fasting conditions in the TMC114IFD1003 trial.

2 Labeling Recommendations

The applicant’s proposed revisions and the clinical pharmacology reviewer’s proposed modifications for the darunavir and cobicistat fixed dose combination tablets U.S. prescribing information are displayed below. Changes are highlighted in yellow where applicable. The proposed changes below are supported by the review, where applicable. The darunavir and cobicistat fixed dose combination tablets U.S. prescribing information was not finalized at the time the review was completed.

Highlights

Applicant proposed language	Proposed reviewer changes
<p>Contraindications</p> <p>Coadministration with (b) (4) (b) (4) (b) (4) (4)</p>	<p>Contraindications</p> <ul style="list-style-type: none"> Coadministration with certain drugs for which altered plasma concentrations are associated with serious and/or life-threatening events or loss of therapeutic effect. (4)
<p>Drug Interactions</p> <p>Co-administration of TRADENAME with other drugs can alter the concentration of other drugs and other drugs may alter the concentrations of darunavir or cobicistat. (b) (4) (4, (b) (4) 7, 12.3).</p>	<p>Drug Interactions</p> <p>Co-administration of TRADENAME with other drugs can alter the concentration of other drugs and other drugs may alter the concentrations of darunavir or cobicistat. (b) (4) (4, (b) (4) 7, 12.3).</p>

Section 4-Contraindications

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Applicant proposed language	Proposed reviewer changes
None	(b) (4)

Section 5-Warnings and Precautions

Applicant proposed language	Proposed reviewer changes
(b) (4)	

Section 7-Drug Interactions

Applicant proposed language	Proposed reviewer changes
	<p data-bbox="1050 381 2028 495">(b) (4) No drug interaction trials have been performed using TRADENAME and drug interaction trials have (b) (4) been conducted with darunavir (b) (4) with ritonavir.</p>

Applicant proposed language	Proposed reviewer changes
<p data-bbox="79 354 789 391">7.1 Potential for TRADENAME to Affect Other Drugs</p> <div data-bbox="33 415 1052 837" style="background-color: #cccccc; width: 100%; height: 100%; position: relative;"> (b) (4) </div>	<p data-bbox="1062 354 1766 391">7.1 Potential for TRADENAME to Affect Other Drugs</p> <p data-bbox="1062 428 2024 716">When evaluated separately, darunavir and cobicistat both inhibited CYP3A and CYP2D6. Cobicistat inhibits the following transporters: p-glycoprotein (P-gp), BCRP, OATP1B1 and OATP1B3. Therefore, co-administration of TRADENAME with drugs that are primarily metabolized by CYP3A and/or CYP2D6 or are substrates of P-gp, BCRP, OATP1B1 or OATP1B3 may result in increased plasma concentrations of such drugs, which could increase or prolong their therapeutic effect and can be associated with adverse events (see Table (b) (4)).</p>

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<p data-bbox="65 310 1045 375">Table ^(b)₍₄₎ Potentially Significant Drug Interactions: Alterations in Dose or Regimen May Be Recommended Based on Drug Interaction Trials or Predicted Interaction</p> <table border="1" data-bbox="65 407 1045 626"> <thead> <tr> <th data-bbox="65 407 472 440">Concomitant Drug</th> <th data-bbox="472 407 1045 440">Effect on Concentration</th> <th data-bbox="472 440 1045 472">Clinical Comment</th> </tr> </thead> <tbody> <tr> <td data-bbox="65 472 472 505">Class: Drug Name</td> <td data-bbox="472 472 1045 505">of Darunavir, Cobicistat, or Concomitant Drug</td> <td data-bbox="472 472 1045 505"></td> </tr> </tbody> </table> <p data-bbox="65 626 1045 659">HIV-1 Antiviral Agents: Nucleoside Reverse Transcriptase Inhibitors (NRTIs)</p> <p data-bbox="65 659 1045 846">[Redacted]</p>	Concomitant Drug	Effect on Concentration	Clinical Comment	Class: Drug Name	of Darunavir, Cobicistat, or Concomitant Drug		<p data-bbox="1045 310 2053 350"><i>Clinical pharmacology reviewer note:</i> [Redacted] ^(b)₍₄₎</p> <p data-bbox="1045 350 2053 496">[Redacted] ^(b)₍₄₎</p>
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	(b) (4)		<p><i>Initiation of TRADENAME in patients taking tadalafil:</i> Avoid use of tadalafil during the initiation of TRADENAME. Stop tadalafil at least 24 hours prior to starting TRADENAME. After at least one week following the initiation of TRADENAME, resume tadalafil at 20 mg once daily. Increase to 40 mg once daily based upon individual tolerability.</p> <p>Patients switching from darunavir/ritonavir to TRADENAME: Maintain tadalafil dose.</p> <p><i>Use of PDE-5 inhibitors for erectile dysfunction:</i> Sildenafil at a single dose not exceeding 25 mg in 48 hours, vardenafil at a single dose not exceeding 2.5 mg dose in 72 hours, or tadalafil at a single dose not exceeding 10 mg dose in 72 hours can be used with increased monitoring for PDE-5 inhibitor-associated adverse (b) (4)</p>
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Applicant proposed language	Proposed reviewer changes (modifications are highlighted)								
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<div style="background-color: #cccccc; height: 100%; width: 100%;"></div>	<p>(b)(4)</p> <p>Sedatives/Hypnotics metabolized by CYP3A: e.g. buspirone, diazepam, estazolam, parenterally administered midazolam, zoldipem</p>	<p>↑ sedatives/hypnotics</p>	<p>With concomitant use, titration is recommended with sedatives/hypnotics metabolized by CYP3A and a lower dose of the sedatives/hypnotics should be considered with monitoring for adverse events.</p> <p>Coadministration of parenteral midazolam should be done in a setting that ensures close clinical monitoring and appropriate medical management in case of respiratory depression and/or prolonged sedation. Dose reduction for parenteral midazolam should be considered, especially if more than a single dose of midazolam is administered.</p> <p>Coadministration of TRADENAME with oral midazolam or triazolam is CONTRAINDICATED [see <i>Contraindications</i>].</p>						





Section 8-Use in Specific Populations

Applicant proposed language	Proposed reviewer changes (modifications are highlighted)
(b) (4)	<p>8.6 Hepatic Impairment</p> <p>No clinical trials were conducted with darunavir in combination with cobicistat in hepatically impaired subjects and the effect of hepatic impairment on darunavir exposure when coadministered with cobicistat has not been evaluated. Based on the recommendation for darunavir in combination with ritonavir, a dose adjustment for patients with mild or moderate hepatic impairment is not necessary. No pharmacokinetic or safety data are available regarding the use of darunavir in subjects with severe hepatic impairment. Therefore, TRADENAME is not recommended for use in patients with severe hepatic impairment [<i>see Clinical Pharmacology (12.3)</i>].</p>

Applicant proposed language	Proposed reviewer changes (modifications are highlighted)
(b) (4)	<p>8.7 Renal Impairment</p> <p>A renal impairment trial was not conducted for darunavir administered in combination with cobicistat [<i>see Clinical Pharmacology (12.3)</i>]. Cobicistat has been shown to decrease estimated creatinine clearance without affecting actual renal glomerular function. Dosing recommendations are not available for drugs that require dosage adjustment for renal impairment when used in combination with TRADENAME [<i>see Warnings and Precautions (5.3) and Clinical Pharmacology (12.2)</i>].</p>

(b) (4)



Section 12-Clinical Pharmacology

Applicant proposed language	Proposed reviewer changes (modifications are highlighted)
 (b) (4)	<p>Section 12.1-Mechanism of Action</p> <p>TRADENAME is a fixed-dose combination of the HIV-1 antiviral drug darunavir and a CYP3A inhibitor, cobicistat [<i>see Microbiology (12.4)</i>].</p>

Applicant proposed language	Proposed reviewer changes (modifications are highlighted)
Section 12.2-Pharmacodynamics	Section 12.2-Pharmacodynamics
<div style="background-color: #cccccc; width: 100%; height: 100%; position: relative;"> (b) (4) </div>	<p>Separate thorough QT trials have been conducted for darunavir/ritonavir and for cobicistat. The effect of the combination of darunavir and cobicistat on the QT interval has not been evaluated.</p>
	<p>Cardiac Electrophysiology</p> <p><i>Darunavir:</i> In an open-label, randomized, placebo-and active-controlled, four-way crossover trial, 40 healthy subjects were administered suprathertapeutic doses of darunavir/ritonavir 1600/100 mg once daily and 800/100 mg twice daily for seven days. At the mean maximum darunavir concentration of 6599 ng/mL observed in this trial, the mean increase in QTcF was 2.2 ms with a 90% two-sided confidence interval (CI) of -2.0 to 6.3 ms. When evaluating the 2-sided 90% CI on the time-matched mean changes in QTcF versus placebo control, the upper bounds of both darunavir/ritonavir groups never exceeded the 10 ms boundary. In the setting of this trial, darunavir/ritonavir did not appear to prolong the QTc interval.</p>
	<p><i>Cobicistat:</i> The effect of a single dose of cobicistat 250 mg and 400 mg (approximately 1.7 and 2.7 times the recommended dose) on QTc interval was evaluated in a randomized, placebo-and active-controlled (moxifloxacin 400 mg) four-period crossover thorough QT trial in 48 healthy subjects. In this trial, no significant QTc prolongation effect of cobicistat was detected. The dose of 400 mg cobicistat is expected to provide information on a high exposure clinical scenario. Prolongation of the PR interval was noted in subjects receiving cobicistat in the same trial. The maximum mean (95% upper confidence bound) difference in PR from placebo after baseline-correction was 9.5 (12.1) msec for 250 mg and 20.2</p>

(b) (4)

(22.8) msec for 400 mg of cobicistat.

Effects on Serum Creatinine

Cobicistat: The effect of cobicistat on serum creatinine was investigated in a trial in subjects with normal renal function (eGFR \geq 80 mL/min, N=12) and mild-to-moderate renal impairment (eGFR 50-79 mL/min, N=18). A statistically significant decrease in the estimated glomerular filtration rate, calculated by Cockcroft-Gault method (eGFR_{CG}) from baseline, was observed after 7 days of treatment with cobicistat 150 mg among subjects with normal renal function (-9.9 ± 13.1 mL/min) and mild-to-moderate renal impairment (-11.9 ± 7.0 mL/min). No statistically significant changes in eGFR_{CG} were observed compared to baseline for subjects with normal renal function or mild-to-moderate renal impairment 7 days after cobicistat was discontinued. The actual glomerular filtration rate, as determined by the clearance of probe drug iohexol, was not altered from baseline following treatment of cobicistat among subjects with normal renal function and mild-to-moderate renal impairment, indicating that cobicistat inhibits tubular secretion of creatinine, reflected as a reduction in eGFR_{CG}, without affecting the actual glomerular filtration rate.

Applicant proposed language	Proposed reviewer changes (modifications are highlighted)
<p data-bbox="79 318 485 350">Section 12.3-Pharmacokinetics</p> <div data-bbox="33 375 1045 1174" style="background-color: #cccccc; width: 100%; height: 492px; position: relative;"> (b) (4) </div>	<p data-bbox="1062 318 1461 350">Section 12.3-Pharmacokinetics</p> <p data-bbox="1062 386 2011 565">Under fed (533 total kcal, 171 kcal from fat, 268 kcal from carbohydrates, 96 kcal from protein) and fasted conditions in healthy subjects the 90% confidence intervals when comparing darunavir exposure between TRADENAME and darunavir/cobicistat 800/150 mg co-administered as single entities were within 80-125%.</p> <p data-bbox="1062 605 1923 675">Darunavir is primarily metabolized by CYP3A. Cobicistat inhibits CYP3A, thereby increasing the plasma concentrations of darunavir.</p> <p data-bbox="1062 716 2011 1036">The pharmacokinetics of darunavir, co-administered with cobicistat (150 mg), has been evaluated in healthy adult subjects and in HIV-1 infected subjects. Table 5 displays the population pharmacokinetic estimates of darunavir after oral administration of darunavir/ritonavir 800/100 mg once daily (based on sparse sampling in 335 subjects in Trial TMC114-C211 and 280 subjects in Trial TMC114-C229) and darunavir/cobicistat 800/150 mg once daily administered as single entities (based on sparse sampling in 298 subjects in Trial GS-US-216-0130) to HIV-1 infected subjects.</p>

Applicant proposed language	Proposed reviewer changes (modifications are highlighted)
<p data-bbox="71 318 485 350">Section 12.3-Pharmacokinetics</p> <p data-bbox="71 391 485 423"><i>Absorption and Bioavailability</i></p> <div data-bbox="44 443 1045 717" style="background-color: #cccccc; height: 150px; width: 100%; position: relative;"> (b) (4) </div>	<p data-bbox="1054 318 1461 350">Section 12.3-Pharmacokinetics</p> <p data-bbox="1054 386 1465 418"><i>Absorption and Bioavailability</i></p> <p data-bbox="1054 459 2011 597">In healthy subjects, under fed conditions, when single doses of the darunavir/cobicistat fixed dose combination tablet were administered, the maximum plasma concentration is achieved within approximately 4 to 4.5 hours for darunavir and approximately 4 to 5 hours for cobicistat.</p>

Applicant proposed language	Proposed reviewer changes (modifications are highlighted)
<p data-bbox="71 870 485 902">Section 12.3-Pharmacokinetics</p> <p data-bbox="71 943 552 976"><i>Effects of Food on Oral Absorption</i></p> <div data-bbox="33 995 1045 1325" style="background-color: #cccccc; height: 180px; width: 100%; position: relative;"> (b) (4) </div>	<p data-bbox="1054 870 1461 902">Section 12.3-Pharmacokinetics</p> <p data-bbox="1054 938 1528 971"><i>Effects of Food on Oral Absorption</i></p> <p data-bbox="1054 1011 2032 1222">When compared to fasted conditions, administration of TRADENAME to healthy adult subjects with a high-fat meal (965 total kcal; 129 kcal from protein, 236 kcal from carbohydrates and 600 kcal from fat) resulted in a 70% increase in AUC_(0-inf) and a 127% increase in C_{max} for darunavir. Cobicistat exposures were not affected by food. TRADENAME should be taken with food.</p>

Applicant proposed language	Proposed reviewer changes (modifications are highlighted)
<p>Section 12.3-Pharmacokinetics</p> <p>Elimination</p> <p><i>Darunavir:</i> A mass balance study in healthy volunteers showed that after single dose administration of 400 mg ¹⁴C-darunavir, co-administered with 100 mg ritonavir, approximately 79.5% and 13.9% of the administered dose of ¹⁴C-darunavir was recovered in the feces and urine, respectively. Unchanged darunavir accounted for approximately 41.2% and 7.7% of the administered dose in feces and urine, respectively. (b) (4)</p> <p>(b) (4)</p>	<p>Section 12.3-Pharmacokinetics</p> <p>Elimination</p> <p><i>Darunavir:</i> A mass balance trial in healthy subjects showed that after single dose administration of 400 mg ¹⁴C-darunavir, co-administered with 100 mg ritonavir, approximately 79.5% and 13.9% of the administered dose of ¹⁴C-darunavir was recovered in the feces and urine, respectively. Unchanged darunavir accounted for approximately 41.2% and 7.7% of the administered dose in feces and urine, respectively.</p> <p>When single doses of the darunavir/cobicistat fixed dose combination tablet were administered, the terminal elimination half-life of darunavir was approximately 7 hours under fed conditions.</p> <p><i>Cobicistat:</i> When single doses of the darunavir/cobicistat fixed dose combination tablet were administered, the terminal elimination half-life of cobicistat was approximately 4 hours under fed conditions.</p> <p>With single dose administration of ¹⁴C-cobicistat after multiple dosing of cobicistat for six days, the mean percent of the administered dose excreted in feces and urine was 86.2% and 8.2%, respectively.</p>

Applicant proposed language	Proposed reviewer changes (modifications are highlighted)
<p data-bbox="71 318 485 350">Section 12.3-Pharmacokinetics</p> <p data-bbox="71 391 352 423"><i>Hepatic impairment</i></p> <div data-bbox="44 451 1045 1044" style="background-color: #cccccc; height: 365px; width: 100%;"></div>	<p data-bbox="1054 318 1461 350">Section 12.3-Pharmacokinetics</p> <p data-bbox="1054 383 1329 415"><i>Hepatic impairment</i></p> <p data-bbox="1054 456 2028 748">^{(b) (4)} <i>Darunavir:</i> Darunavir is primarily metabolized by the liver. The steady-state pharmacokinetic parameters of darunavir were similar after multiple dose co-administration of darunavir/ritonavir 600/100 mg twice daily to subjects with normal hepatic function (n=16), mild hepatic impairment (Child-Pugh Class A, n=8), and moderate hepatic impairment (Child-Pugh Class B, n=8). The effect of severe hepatic impairment on the pharmacokinetics of darunavir has not been evaluated[see <i>Use in Specific Populations (8.6)</i>].</p> <p data-bbox="1054 789 2028 1044"><i>Cobicistat:</i> Cobicistat is primarily metabolized by the liver. A trial evaluating the pharmacokinetics of cobicistat was performed in non-HIV-1 infected subjects with moderate hepatic impairment. No clinically relevant differences in cobicistat pharmacokinetics were observed between subjects with moderate hepatic impairment (Child-Pugh Class B) and healthy subjects. The effect of severe hepatic impairment on the pharmacokinetics of cobicistat has not been evaluated [see <i>Use in Specific Populations (8.6)</i>].</p>

Applicant proposed language	Proposed reviewer changes (modifications are highlighted)
<p>Section 12.3-Pharmacokinetics</p> <p><i>Hepatitis B or Hepatitis C Virus Co-infection</i></p> <p>(b) (4)</p>	<p>Section 12.3-Pharmacokinetics</p> <p><i>Hepatitis B or Hepatitis C Virus Co-infection</i></p> <p><i>Darunavir:</i> In HIV-infected subjects taking darunavir/ritonavir, the 48 week analysis of the data from clinical studies in HIV-1 infected subjects indicated that hepatitis B and/or hepatitis C virus co-infection status had no apparent effect on the exposure of darunavir.</p> <p>The effect of hepatitis B and/or C virus infection on the pharmacokinetics of TRADENAME have not been evaluated.</p>

Applicant proposed language	Proposed reviewer changes (modifications are highlighted)
<p data-bbox="73 316 483 349">Section 12.3-Pharmacokinetics</p> <p data-bbox="73 389 325 422"><i>Renal Impairment</i></p> <div data-bbox="37 451 1045 894" style="background-color: #cccccc; width: 100%; height: 273px; position: relative;"> (b) (4) </div>	<p data-bbox="1054 316 1459 349">Section 12.3-Pharmacokinetics</p> <p data-bbox="1054 381 1312 414"><i>Renal Impairment</i></p> <p data-bbox="1054 454 2026 706"><i>Darunavir</i>: Population pharmacokinetic analysis showed that the pharmacokinetics of darunavir were not significantly affected in HIV-1 infected subjects with moderate renal impairment taking darunavir/ritonavir (CrCL between 30-60 mL/min, n=20). There are no pharmacokinetic data available in HIV-1 infected patients with severe renal impairment or end stage renal disease taking darunavir coadministered with either ritonavir or cobicistat [see Use in Specific Populations (8.7)].</p>

Applicant proposed language	Proposed reviewer changes (modifications are highlighted)
<p data-bbox="71 318 485 350">Section 12.3-Pharmacokinetics</p> <p data-bbox="71 391 184 423">Gender</p> <div data-bbox="16 431 1058 781" style="background-color: #cccccc; height: 215px; width: 100%; position: relative;"> (b) (4) </div>	<p data-bbox="1054 318 1461 350">Section 12.3-Pharmacokinetics</p> <p data-bbox="1054 386 1163 418">Gender</p> <p data-bbox="1054 459 2028 597"><i>Darunavir:</i> In HIV-infected subjects taking darunavir/ritonavir, population pharmacokinetic analysis showed higher mean darunavir exposure in HIV-1 infected females compared to males. This difference is not clinically relevant.</p> <p data-bbox="1054 643 1997 708"><i>Cobicistat:</i> No clinically relevant pharmacokinetic differences have been observed between men and women for cobicistat.</p>

Applicant proposed language	Proposed reviewer changes (modifications are highlighted)
<p data-bbox="71 899 485 932">Section 12.3-Pharmacokinetics</p> <p data-bbox="71 976 153 1008">Race</p> <div data-bbox="33 1024 1045 1364" style="background-color: #cccccc; height: 209px; width: 100%; position: relative;"> (b) (4) </div>	<p data-bbox="1054 899 1461 932">Section 12.3-Pharmacokinetics</p> <p data-bbox="1054 967 1129 1000">Race</p> <p data-bbox="1054 1040 1976 1138"><i>Darunavir:</i> Population pharmacokinetic analysis of darunavir in HIV-1 infected subjects taking darunavir/ritonavir indicated that race had no apparent effect on the exposure to darunavir.</p> <p data-bbox="1054 1183 2018 1281"><i>Cobicistat:</i> Population pharmacokinetic analysis of cobicistat in HIV-1 infected subjects indicated that race had no clinically relevant effect on the exposure of cobicistat.</p>

Applicant proposed language	Proposed reviewer changes (modifications are highlighted)
<p>Section 12.3-Pharmacokinetics</p> <p><i>Geriatric Patients</i></p> <div style="background-color: #cccccc; width: 100%; height: 150px; margin-top: 10px;"> (b) (4) </div>	<p><i>Clinical pharmacology reviewer note: the information regarding geriatric subjects and darunavir was reworded by the clinical reviewer based on the information from the darunavir U.S. prescribing information.</i></p> <p>Section 12.3-Pharmacokinetics</p> <p><i>Geriatric Patients</i></p> <p><i>Darunavir:</i> In HIV-infected subjects taking darunavir/ritonavir, population pharmacokinetic analysis showed no considerable differences in darunavir pharmacokinetics for ages 18 to 75 years compared to ages greater than or equal to 65 years (n=12). [see <i>Use in Specific Populations</i> (8.5)].</p> <p><i>Cobicistat:</i> Insufficient data are available to determine whether potential differences exist in the pharmacokinetics of cobicistat in geriatric (65 years of age and older) subjects compared to younger subjects.</p>

5 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

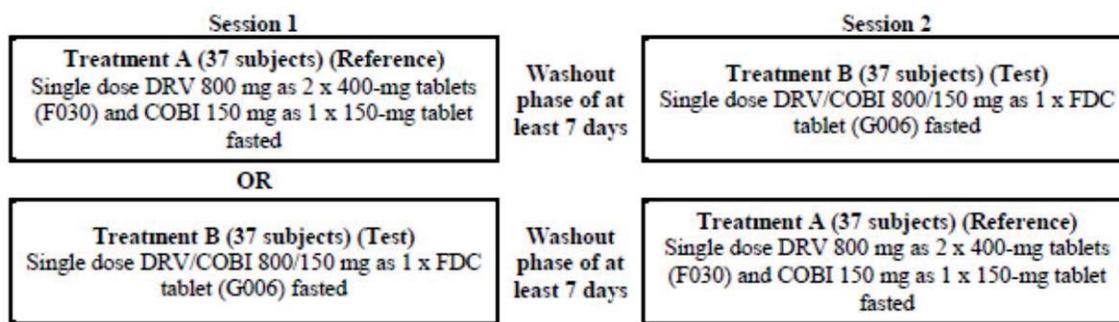
3 Individual Trial Reviews

TMC114IFD1003

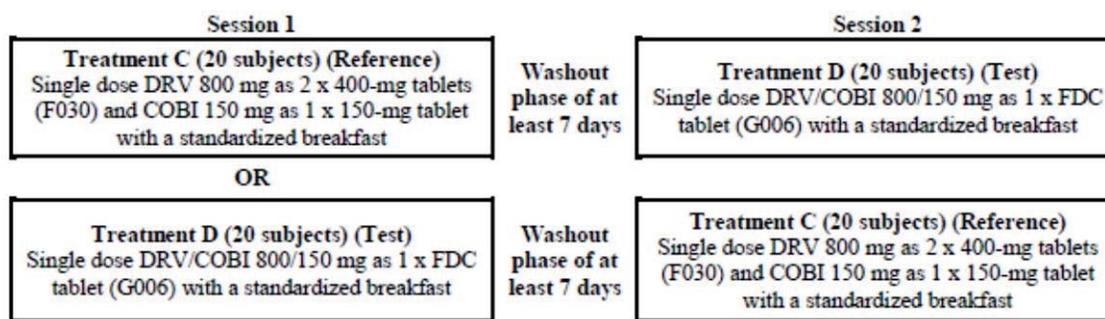
TMC114IFD1003 was an open label clinical trial that enrolled healthy male and female subjects 18 to 60 years old. The relative bioavailability for darunavir and cobicistat when administered as part of a fixed dose combination (FDC) tablet compared to darunavir and cobicistat when administered as single entity formulations was determined as displayed in Figure 1 below. The relative bioavailability of the two formulations was determined under fed (21 grams of fat, 533 kcal) and fasted conditions. The relative bioavailability information will not be discussed as part of the Clinical Pharmacology review; please see the biopharmaceutics review for further information regarding the relative bioavailability comparisons.

Figure 1-TMC114IFD1003 relative bioavailability trial design (fasted and fed)

A) Fasted conditions

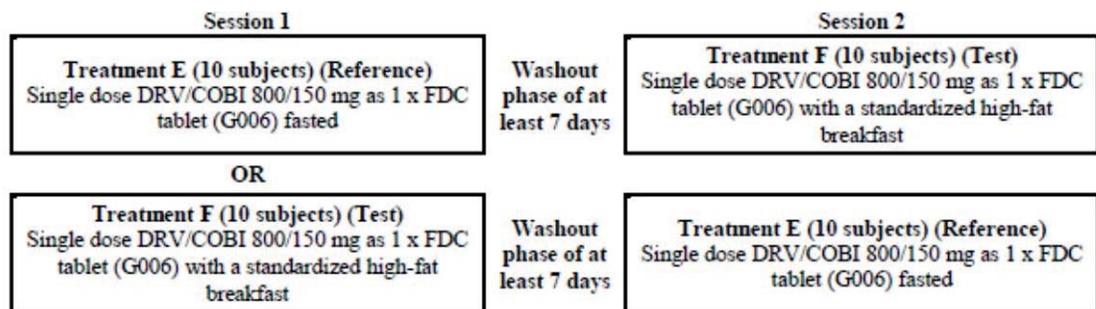


B) Fed conditions (21 grams of fat, 533 kcal)



The second part of the trial evaluated the effect of a high fat meal on the single dose pharmacokinetics of a fixed dose combination tablet consisting of darunavir 800 mg and cobicistat 150 mg. The trial design for the food effect comparison is displayed in Figure 2 below.

Figure 2- TMC114IFD1003 food effect evaluation for the darunavir/cobicistat fixed dose combination tablets



For the food effect evaluation, a high fat meal was administered. In response to an information request, the specific breakdown of the number of calories for the high fat meal was 965 total kcal with 129 kcal from protein, 236 kcal from carbohydrates and 600 kcal from fat. Subjects were fasted overnight for a minimum of ten hours and were administered trial medication between 25 and 30 minutes after the initiation of a high fat meal.

For the food effect evaluation, the administered fixed dose combination tablet formulation consisting of darunavir 800 mg and cobicistat 150 mg was labeled as G006. Based on the information provided in the NDA submission, the G006 tablets are the proposed fixed dose combination formulation for U.S. marketing.

According to the trial report, all medications were to be stopped a minimum of fourteen days prior to the first dose of trial medication with the restrictions continuing up to seven days after the last dose of trial medication with the following exceptions: acetaminophen, ibuprofen, contraceptives, hormone replacement treatment (in postmenopausal women), and vitamins. The trial permitted the use of acetaminophen or ibuprofen during the trial (maximum limits of 1500 mg/day or 3 grams/week and 200 mg/dose and 400 mg/day, respectively). Natural medicines were to be stopped from twenty eight days prior to the first dose of trial medication and continuing up to seven days after the last dose of trial medication.

In the event of an adverse event, the following medications were permitted:

- A) Rash or an allergic reaction: (levo)cetirizine, topical corticosteroids, topical A and D ointment or antipruritics (specific medications were not included in the trial report)
- B) Nausea (grade 1 and 2): domperidone and metoclopramide
- C) Diarrhea (grade 1 and 2): loperamide

During the trial, for each concomitant medication, the majority were used by no more than two subjects with the exception of acetaminophen which was used by fourteen subjects. The conclusions of the trial are not expected to be significantly altered by the concomitant medications that were administered in the trial.

Table 1 through Table 4 below displays the darunavir and cobicistat exposure data under fed (high fat) and fasted conditions when administered as a fixed dose combination tablet.

Table 1-Pharmacokinetic parameters for darunavir with single doses of a FDC tablet containing darunavir 800 mg and cobicistat 150 mg under fed (high fat) and fasted conditions

Pharmacokinetics of Darunavir (Mean ± SD, t_{max} and t_{last} : Median [Range])	DRV/COBI 800/150 mg as Fixed Dose Combination (G006), Fasted		DRV/COBI 800/150 mg as Fixed Dose Combination (G006), Fed (High-fat Breakfast)		
	Treatment E (Reference)		Treatment F (Test)		
n	18 ^a		18 ^b		
C_{max} , ng/mL	3173	± 859	7053	± 1057	
t_{max} , h	3.00 (1.00-5.07)		4.50 (1.50-6.00)		
C_{last} , ng/mL	16.9	± 18.4	10.4	± 5.46	
t_{last} , h	60.00 (36.00-72.00)		60.00 (36.03-72.02)		
AUC_{last} , ng.h/mL	47356	± 17723	75258	± 21632	
AUC_{∞} , ng.h/mL	43985	± 13548	76165	± 22090	
λ_z , 1/h	0.116	± 0.0380	0.128	± 0.0552	
$t_{1/2term}$, h	6.8	± 3.1	6.6	± 3.2	

^a n=16 for AUC_{∞} , λ_z and $t_{1/2term}$

^b n=17 for AUC_{∞} , λ_z and $t_{1/2term}$

Table 2-Pharmacokinetic parameters for cobicistat with single doses of a FDC tablet containing darunavir 800 mg and cobicistat 150 mg under fed (high fat) and fasted conditions

Pharmacokinetics of Cobicistat (Mean ± SD, t_{max} and t_{last} : Median [Range])	DRV/COBI 800/150 mg as Fixed Dose Combination (G006), Fasted		DRV/COBI 800/150 mg as Fixed Dose Combination (G006), Fed (High-fat Breakfast)		
	Treatment E (Reference)		Treatment F (Test)		
n	18		18 ^a		
C_{max} , ng/mL	741	± 222	769	± 174	
t_{max} , h	2.00 (0.98-4.00)		4.98 (1.00-6.00)		
C_{last} , ng/mL	12.7	± 6.63	15.3	± 11.5	
t_{last} , h	24.00 (20.00-36.00)		24.00 (20.00-48.00)		
AUC_{last} , ng.h/mL	5459	± 1959	5491	± 1425	
AUC_{∞} , ng.h/mL	5532	± 1967	5526	± 1478	
λ_z , 1/h	0.181	± 0.0361	0.184	± 0.0375	
$t_{1/2term}$, h	3.9	± 0.7	3.9	± 0.7	

^a n=17 for AUC_{∞} , λ_z and $t_{1/2term}$

Table 3-Statistical analyses for darunavir with single doses of a FDC tablet containing darunavir 800 mg and cobicistat 150 mg under fed (high fat) and fasted conditions

Parameter	LS Means ^a			90% CI ^c	p-Value	
	DRV/COBI 800/150 mg as Fixed Dose Combination (G006), Fasted (Reference)	DRV/COBI 800/150 mg as Fixed Dose Combination (G006), Fed (High-fat Breakfast) (Test)	LS Means Ratio, %		Session	Sequence
C _{max} , ng/mL	3073	6978	227.09	205.75 - 250.63	0.4077	0.9562
AUC _{last} , ng.h/mL	44487	72597	163.18	144.90 - 183.78	0.1041	0.8506
AUC _∞ , ng.h/mL ^b	43549	74119	170.20	148.50 - 195.06	0.3563	0.8178

^a n=18 for reference and test

^b n=16 for reference and n=17 for test

^c 90% confidence intervals

Table 4-Statistical analyses for cobicistat with single doses of a FDC tablet containing darunavir 800 mg and cobicistat 150 mg under fed (high fat) and fasted conditions

Parameter	LS Means ^a			90% CI ^c	p-Value	
	DRV/COBI 800/150 mg as Fixed Dose Combination (G006), Fasted (Reference)	DRV/COBI 800/150 mg as Fixed Dose Combination (G006), Fed (High-fat Breakfast) (Test)	LS Means Ratio, %		Session	Sequence
C _{max} , ng/mL	708	751	106.02	98.34 - 114.29	0.0590	0.3395
AUC _{last} , ng.h/mL	5117	5313	103.83	96.32 - 111.93	0.5570	0.4669
AUC _∞ , ng.h/mL ^b	5189	5413	104.31	96.45 - 112.82	0.6587	0.4455

^a n=18 for reference and test

^b n=18 for reference and n=17 for test

^c 90% confidence intervals

A food effect was observed for darunavir when administered as a fixed dose combination tablet in combination with cobicistat with darunavir AUC_(0-∞) and C_{max} increased by 70% and 127%, respectively with a high fat meal compared to fasted conditions. Based on the information provided in the original darunavir Clinical Pharmacology NDA review (see NDA 21976), when single entity darunavir was coadministered with ritonavir as single entity formulations under high fat conditions, the darunavir AUC_(0-∞) and C_{max} were increased by 48% and 59%, respectively when compared to fasted conditions. According to the report for the single entity darunavir food effect trial, the high fat meal provided 928 kcal and the specific breakdown of the number of calories for the high fat meal was 164 kcal from protein, 260 kcal from carbohydrates, and 504 kcal from fat. The

darunavir U.S prescribing information states that darunavir should be administered with food.

The observed increase in darunavir exposure when darunavir is administered as part of a fixed dose combination tablet with cobicistat exceeded the magnitude of the increase in C_{\max} and $AUC_{(0-\infty)}$ for darunavir when administered as a single entity tablet. As part of the original darunavir Clinical Pharmacology NDA review, exposure-safety analyses were conducted evaluating the relationship between darunavir $AUC_{(0-24h)}$ and the maximum change in cholesterol, lipids and liver function parameters that included the two recommended darunavir/ritonavir dosage regimens: 600 mg/100 mg twice daily and 800 mg/100 mg once daily. There was no discernable relationship that was observed. Therefore, no specific darunavir safety issues are anticipated with the fixed dose combination tablets and the applicant's recommendation to administer the fixed dose combination tablet with food with respect to darunavir is acceptable.

A food effect was not observed for cobicistat when administered as part of a fixed dose combination tablet with darunavir. Therefore, the applicant's recommendation to administer the fixed dose combination tablet with food when administered with respect to cobicistat is acceptable.

4 Pharmacometrics Review

APPEARS THIS WAY ON
ORIGINAL

PHARMACOMETRIC REVIEW

1. SUMMARY OF FINDINGS

The population pharmacokinetic (PK) model developed by the Applicant is capable of characterizing the pharmacokinetics of darunavir based on a single dataset consisting of 1 clinical trial in adult HIV-1 infected subjects (GS-US-216-0130) where darunavir was co-administered with cobicistat as single entities.

The model was developed using a subset of richly sampled PK data (n=53). Model parameters were then re-estimated using an enriched dataset that was collected through week 24 weeks (n=55). The final model was used for the Bayesian feedback analysis with the whole dataset (n=298).

The structural model that best described the pharmacokinetics of darunavir was a 2-compartment disposition model with a sequential zero-order-first-order absorption. Alpha1-acid glycoprotein concentration (AAG) and total daily dose (TDD) were two significant covariates on apparent clearance (CL/F). The population PK estimates (%RSE) of darunavir were: CL/F 51.6 L/h (3.4%); apparent central volume of distribution (Vc/F) 35.6 L (19.9%); inter-compartmental clearance (CLp/F) 24.0 L/h (19.4%); peripheral volume of distribution (Vp/F) 90.0 L (10.4%); absorption rate constant (KA) 0.393 h⁻¹ (18.5%) and zero-order duration of input (D1) 1.49 h (11.1%). The inter-subject variability was 24.9% (18.3%) for CL/F; 15.6% (210%) for Vc/F; 51.0% (34.3%) for CLp/F and 88.4% (27.4%) for D1.

The apparent central volume of distribution was lower than that previously estimated by Applicant in the original NDA submission for darunavir (112 L (8.2%)). The Applicant claims the reason may be the modeling data in GS-US-216-0130 was obtained at steady-state in contrast to data used in the original analysis that originated from five Phase I and two Phase IIb trials that included both single dose and multiple dose administration. Other population PK parameters were similar to the previous analysis.

1.1 Key Review Questions

The purpose of this review is to address the following key question:

1.1.1 Are the PK parameters reported in the label supported by the population PK analysis submitted by the Applicant?

Yes. The PK parameters for darunavir/cobicistat 800/150 mg once daily in adult patients reported in section 12.3 (Pharmacokinetics) of the proposed darunavir label are supported by the population PK analysis as shown in Table 1. The means, standard deviations, medians, and ranges of AUC_{24h} and C_{0h} were in good agreement with the Applicant's results. The difference of means and standard deviations is due to rounding and the differences in the listed values are not clinically meaningful.

In addition, the Applicant stated that age, body weight, height, body surface area and race have no impact on the darunavir exposure. As there were only 3 female subjects included in the dataset, sex

was not evaluated in a model based analysis despite trends suggesting sex might be able to describe variability in CL/F, CLp/F, Vc/F and D1.

Table 1: Population PK estimates of darunavir as darunavir/cobicistat 800/150 mg once daily (Study GS-US-216-0130, 24 week analysis), n=298 (Comparison of Applicant's Label Claims and Reviewer Analyses)		
Parameter	Applicant*	Reviewer
AUC _{24h} (ng·h/mL)		
Mean ± Standard Deviation	100152 ± 32042	100030 ± 32078
Median (Range)	96900 (34500-224000)	96905 (34290-223900)
C _{0h} (ng/mL)		
Mean ± Standard Deviation	2043 ± 1257	2041 ± 1259
Median (Range)	1875 (70-6890)	1875 (70-6887)

*Applicant's draft-labeling-text.pdf, (section 12.3 [Pharmacokinetics])

1.2 Recommendations

The Division of Pharmacometrics (Office of Clinical Pharmacology) has reviewed this application and recommends approval of 800/150 mg darunavir/cobicistat administered once daily. The reviewer agrees with the Applicant's conclusion from the population PK analysis that no dose adjustments are necessary for darunavir based on age, body weight, height, body surface area and race in adult patients.

2 PERTINENT REGULATORY BACKGROUND

The darunavir/cobicistat fixed dose combination (FDC) tablet is a combination of 2 single agents. Darunavir is approved for the treatment of HIV-1 infected adults who are anti-retroviral treatment (ART) naïve or ART-experienced with no darunavir resistance association mutations (RAMs) at a dose of 800 mg once daily. For anti-retroviral treatment-experienced adult patients with 1 or more darunavir RAMs, the dose of darunavir is 600 mg twice daily. Darunavir must always be dosed with ritonavir or cobicistat which acts as a CYP450 3A inhibitor to increase systemic darunavir exposure. Use of cobicistat in combination with darunavir as single entities was approved for U.S. marketing in September 2014.

3 RESULTS OF APPLICANT'S ANALYSIS

The pharmacometric analysis covered in this review is the Applicant's population PK analysis.

3.1 Population PK analysis

3.1.1 Objectives:

1. To describe darunavir concentration-time data from trial GS-US-216-0130 by updating a previously developed darunavir population PK model
2. To identify and quantify covariate effects which describe inter-subject variability for selected PK parameters
3. To determine the individual empirical Bayes PK parameter estimates for darunavir at Week 24 for subject recruited in trial GS-US-216-0130
4. To perform a further graphical analysis on the Week 24 Bayesian estimates to determine if any covariates could explain the inter-subject variability for selected PK parameters.

3.1.2 Trial included in the population PK model

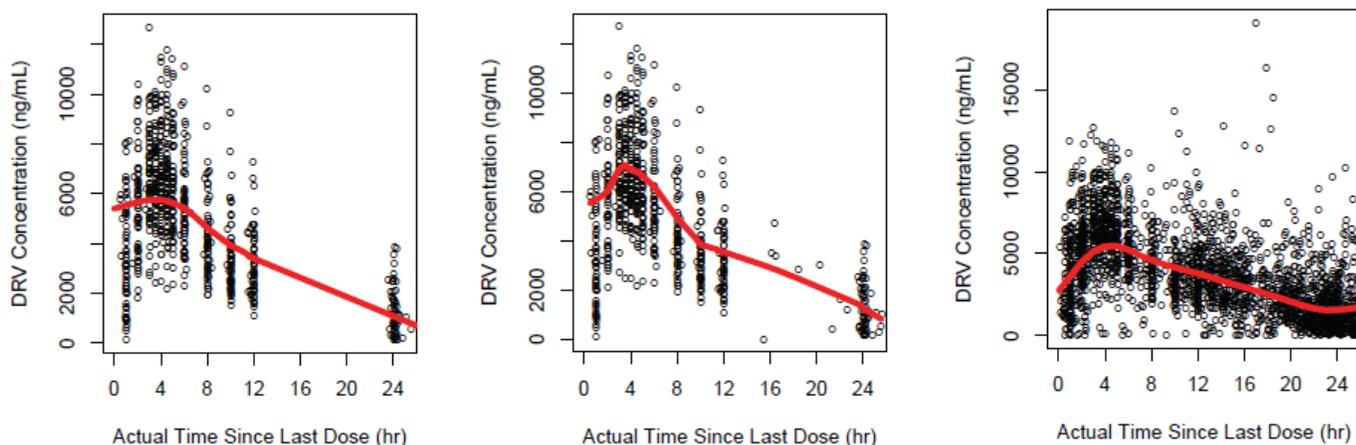
The data used to develop the population PK model were obtained from trial GS-US-216-0130. A subset of richly sampled PK data with 53 subjects was included in the initial model building. Then an enriched dataset collected through week 24 with 55 subjects was included in the parameter re-estimation. Finally, the whole dataset were used in the 24 week Bayesian feedback analyses. A summary of the data is presented in Table 2.

Table 2 Summary of available data

Item	Details
Trial code	GS-US-216-0130
No. and type of subjects	60 HIV-1 infected adults for model development, 53 of which had evaluable PK sampling 60 HIV-1 infected adults for parameter re-estimation, 55 of which had evaluable PK sampling 303 HIV-1 infected adults for the Bayesian feedback, 298 of which had evaluable PK sampling
Treatment duration	48 Weeks
Darunavir dose	800 mg QD
Cobicistat dose	150 mg QD
Single/multiple dose	Multiple dose
No. of PK observations available for analysis	~12 samples per subject in 53 subjects used for model development ~12 samples per subject in 55 subjects used for parameter re-estimation ~18 samples per subject in 55 subjects with rich sampling used for the Bayesian feedback ~6 samples per subject in 243 subjects without rich sampling used for the Bayesian feedback
Darunavir assay (LLOQ)	5.00 ng/mL

Adopted from Applicant's pharmacometrics report of darunavir from trial GS-US-216-0130, Table 1.

The observed darunavir concentrations are plotted over time in Figure 1. Summaries of demographic information for model building dataset, 24 week parameter re-estimation dataset and 24 week Bayesian feedback dataset are shown in Table 3-5, respectively.



Adopted from Applicant’s pharmacometrics report of darunavir from trial GS-US-216-0130, Figure 1-3.

Figure 1 Observed plasma darunavir concentration for model building dataset, 24 week parameter re-estimation dataset and 24 week Bayesian feedback dataset, respectively.

The solid red line shows the trend of the data with the black circles representing the observed data. Darker coloring indicates multiple/overlapping observations.

Table 3 Summary Demographics – model building dataset

	AGE (yr)	WT (kg)	BSA (m ²)	BMI (kg/m ²)	CRCL mL/min	AAG (mg/dL)	RACE	SEX
N	53	53	53	53	53	53	39 (73.6%) White	3 (5.66%) F
Mean	35.1	80.7	1.97	26	117	90.5	1 (1.89%) Asian	50 (94.3%) M
SD	9.33	15	0.187	4.47	23.6	24	12 (22.6%) Black	-
CV	26.6	18.6	9.49	17.2	20.2	26.5	1 (1.89%) Other	-
Median	35	79.4	1.94	25.4	119	87	-	-
Min	18	59.7	1.64	19.8	67.1	44	-	-
Max	58	132	2.49	39.3	183	186	-	-

Adopted from Applicant’s pharmacometrics report of darunavir from trial GS-US-216-0130, Table 8.

Table 4 Summary Demographics – 24 week parameter re-estimation dataset

	AGE (yr)	WT (kg)	BSA (m ²)	BMI (kg/m ²)	CRCL mL/min	AAG (mg/dL)	RACE	SEX
N	55	55	55	55	55	55	40 (72.7%) White	4 (7.27%) F
Mean	35	80	1.95	25.9	116	90.1	1 (1.82%) Asian	51 (92.7%) M
SD	9.24	15.2	0.193	4.51	23.4	23.1	12 (21.8%) Black	-
CV	26.4	19	9.86	17.4	20.1	25.7	1 (1.82%) Am.Ind.	-
Median	35	78.5	1.93	25.4	119	87	1 (1.82%) Other	-
Min	18	55.8	1.64	19	67.1	44	-	-
Max	58	132	2.49	39.3	183	178	-	-

Adopted from Applicant’s pharmacometrics report of darunavir from trial GS-US-216-0130, Table 9.

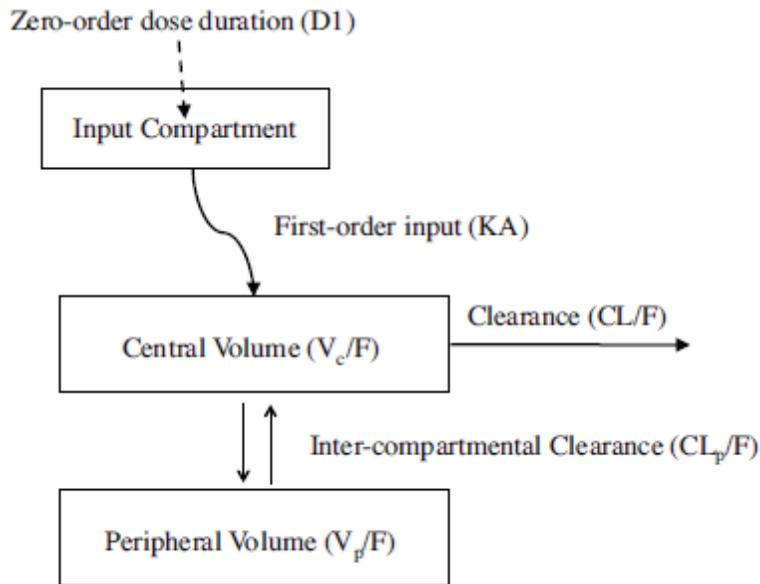
Table 5 Summary Demographics – 24 Bayesian feedback dataset

	AGE (yr)	WT (kg)	BSA (m ²)	BMI (kg/m ²)	CRCL mL/min	AAG (mg/dL)	RACE	SEX
N	298	298	298	298	298	298	177 (59.4%) White	32 (10.7%) F
Mean	36.5	80.5	1.96	26.1	118	96.7	4 (1.34%) Asian	266 (89.3%) M
SD	10.4	14.9	0.192	4.4	29.7	28.8	103 (34.6%) Black	-
CV	28.6	18.5	9.81	16.8	25.1	29.8	4 (1.34%) Am.Ind.	-
Median	35	80.1	1.96	25.6	114	93	8 (2.68%) Other	-
Min	18	41.7	1.34	16.5	67.1	41	2 (0.671%) Haw.Is	-
Max	69	147	2.66	45.3	321	274	-	-

Adopted from Applicant’s pharmacometrics report of darunavir from trial GS-US-216-0130, Table 10.

3.1.3 Base model:

The base model incorporated a sequential zero-order-first-order input to describe absorption, together with a 2-compartment disposition model as shown in Figure 2. TDD and AAG were significant covariates on CL/F and the effects were retained from the previously developed population PK model by Applicant in the original NDA submission for darunavir (equation 1). The parameter estimates for the base model are presented in Table 6.



Adopted from Applicant’s pharmacometrics report of darunavir from trial GS-US-216-0130, Figure 7.

Figure 2 Model schematic of the final model

$$CL/F = (\theta_1 \cdot \frac{1}{1+\theta_3 \cdot AAG}) \cdot e^{\eta_1} \cdot (\frac{TDD}{1200})^{\theta_2} \tag{1}$$

Adopted from Applicant’s pharmacometrics report of darunavir from trial GS-US-216-0130, Equation 8.

Table 6 Parameter estimates for the base model

Parameter		Parameter Estimate	Parameter SE (CV%)	BSV Estimate (CV%)	BSV SE (CV%)
CL_{INT}/F (L/hr)	θ_1	51.9	3.4	25.1	18.6
Effect of TDD on CL_{INT}/F	θ_2	0.388*			
Effect of AAG on CL_{INT}/F (dL/mg)	θ_3	0.0304*			
V_c/F (L)	θ_4	29.8	12.8	14.6	86.8
CL_p/F (L/hr)	θ_5	21.9	12.6	53.3	29.0
V_p/F (L)	θ_6	86.4	12.7	55.7 FIX	
KA (/hr)	θ_7	0.34	9.7		
F_{REL}	θ_8	1.18*			
D1 (hr)	θ_9	1.48 [#]	13.7	85.1	27.7
R (V_c/F , D1)		0.634			
RUV (CV%)		15.4	17.8		

Adopted from Applicant’s pharmacometrics report of darunavir from trial GS-US-216-0130, Table 12.

3.1.4 Covariate model development

To evaluate if any of the covariates impact on darunavir exposure, univariate covariate analysis was performed. The results are summarized in Table 7. None of the covariates were statistically significant at $P < 0.05$, which required a drop in objective function value (OBJ) > 7.9 points. As such, no additional covariate was included in the model.

Table 7 Summary of univariate analysis for single forward entry

Model	Covariate	Parameter	OBJ	Δ OBJ	Min	\$COV	Covariate Parameter
023 (BASE Model)			9476.017				
023heightcl	HT	CL/F	9470.794	-5.223	SUCCESSFUL	OK	1.74
023raceD1	RACE	D1	9471.64	-4.377	SUCCESSFUL	OK	1.78
023weightcl	WT	CL/F	9474.847	-1.17	SUCCESSFUL	OK	0.213
023weightD1	WT	D1	9474.892	-1.125	SUCCESSFUL	OK	0.766
023agevp	AGE	V_p/F	9475.239	-0.778	SUCCESSFUL	OK	0.283
023bsavc	BSA	V_c/F	9475.977	-0.04	SUCCESSFUL	OK	0.136
023racevc	RACE	V_c/F	9475.988	-0.029	SUCCESSFUL	OK	1.02
023weightvc	WT	V_c/F	9476.028	0.011	SUCCESSFUL	ABORTED	0.01
023agecl	AGE	CL/F	9476.243	0.226	SUCCESSFUL	OK	0.01

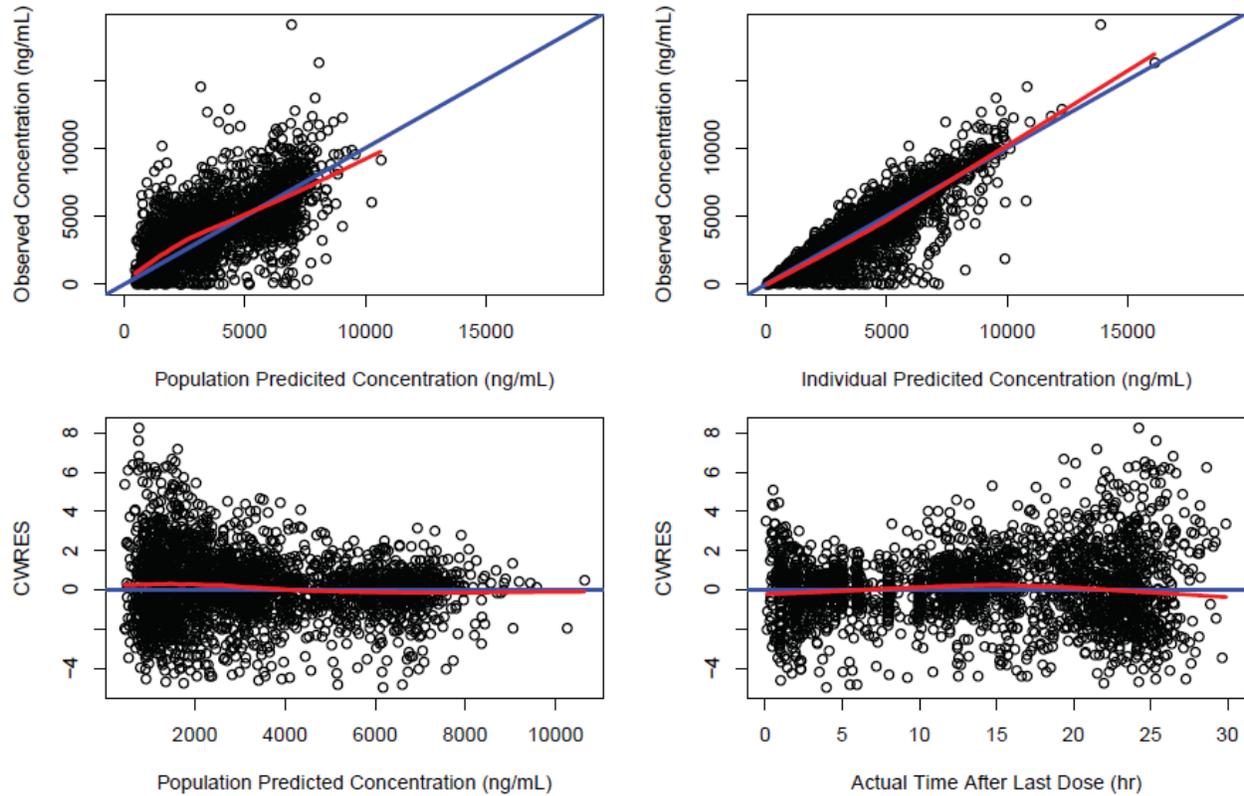
Adopted from Applicant’s pharmacometrics report of darunavir from study GS-US-216-0130, Table 13.

3.1.5 Parameter re-estimation at 24 weeks

When fitting the model to the revised dataset, the correlation term between V_c/F and D1 was removed. There was no significant increase in the OBJ. The updated model provided a good description of the revised data.

3.1.6 Bayesian feedback at 24 weeks

The final updated model was then fit to the 24 week Bayesian feedback dataset with parameters fixed to those obtained during the estimation process. The goodness-of-fit is presented in Figure 3 with no noticeable bias.

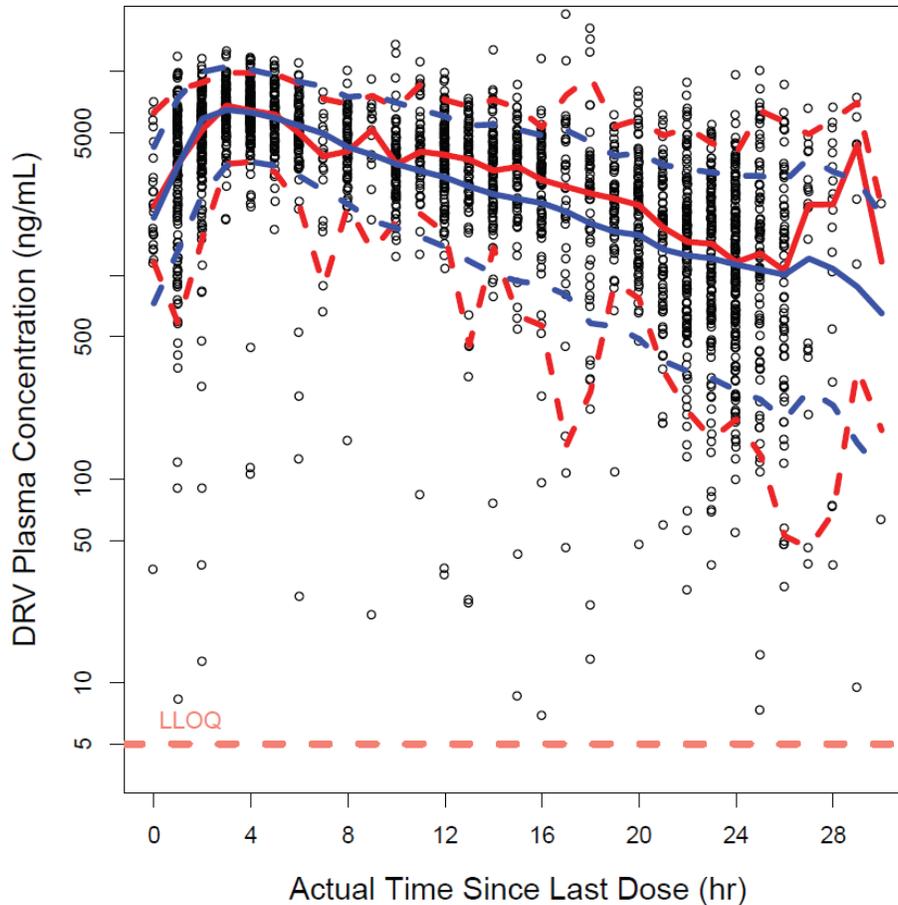


Adopted from Applicant's pharmacometrics report of darunavir from study GS-US-216-0130, Figure 15.

Figure 3 Goodness-of-fit plots for the Bayesian feedback at 24 weeks

The blue solid line in the top panel represents the line of unity with the solid red line representing a smoother of the data.

A visual predictive check is shown in Figure 4 showing that the model adequately describes the data. Some observed concentrations are lower than expected; the potential reasons for this discrepancy could be non-adherence to one or both mediations or improper dosing.



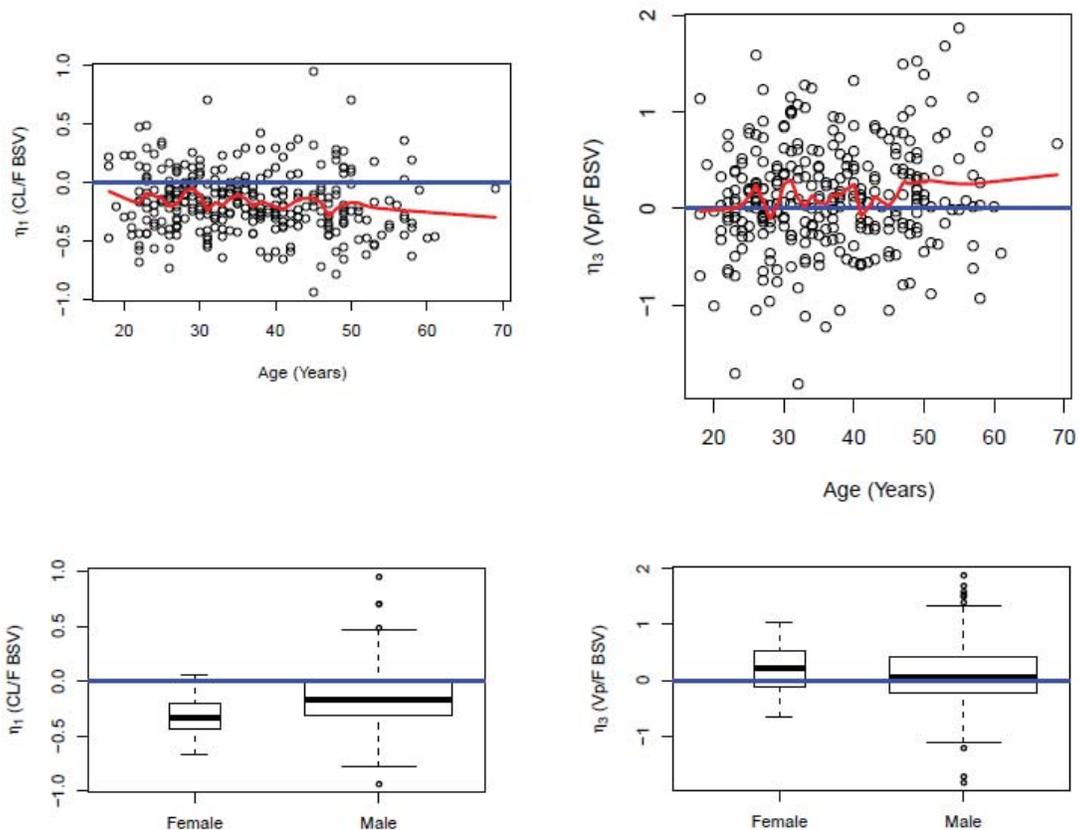
Adopted from Applicant's pharmacometrics report of darunavir from study GS-US-216-0130, Figure 17.

Figure 4 Visual predictive check for the Bayesian feedback at 24 weeks

The black circles represent the observed data. The lower and upper red dashed lines represent the 5th and 95th percentiles for the observed data. The red solid line represents the 50th percentile for the observed data. The lower and upper blue dashed lines represent the 5th and 95th percentiles for the simulated data. The blue solid line represents the 50th percentile for the simulated data. The dashed horizontal line represents the LLOQ.

3.1.7 Graphical covariate analysis for 24 week Bayesian feedback

To determine if any additional covariates could further describe the data, a graphical analysis was performed to relate parameter ETA values to covariates of interest. It can be seen that age and sex had a weak relationship with CL/F and Vp/F (Figure 5), with no covariates potentially describing variability in the data. Given the high shrinkage estimates for CLp/F and Vc/F, plots of these parameters should be viewed with caution as it is not possible to visually identify a covariate relationship.



Adopted from Applicant's pharmacometrics report of darunavir from trial GS-US-216-0130, Figure 34, 36 and 39.

Figure 5 Relationship between ETA on CL/F, Vp/F and age or sex

The blue solid line represents the line of unity with the solid red line representing the trend of the data. The solid black horizontal lines and box heights represent the median, and 25th to 75th percentiles, respectively. The whiskers represent 1.5 times the interquartile range, with outliers shown as open circles. The blue solid lines represent values of zero.

3.1.8 Applicant's conclusion

A 2-compartment disposition model with a sequential zero-order-first-order absorption was able to describe the PK of darunavir with good precision and no bias following oral administration of darunavir/cobicistat at a dose of 800/150 mg QD. The effects of TDD and AAG on CL/F were retained from the original model as shown in Equation 1. None of the other covariates that were investigated were significant and therefore were not added to the model. Parameter estimates for the updated model in this analysis, together with the previously developed model using data with darunavir boosted with ritonavir, are shown below in Table 8. It can be seen that all fixed effects parameters were similar, excluding Vc/F, which was estimated to be 35.6 L in this analysis compared to 122 L in the previous analysis. The difference may be explained by modelling data obtained at steady-state for current study

while the data used to develop the original PK model included contained both single dose and multiple dose trials.

Table 8 Comparison of Parameter Estimates between Prior and Current Models

Parameter	Updated Model		Prior Model ^[1]	
	Parameter Estimate SE (CV%)	BSV Estimate (CV%) SE (CV%)	Parameter Estimate SE (CV%)	BSV Estimate (CV%) SE (CV%)
CL _{INT} /F (L/hr)	51.6 (3.4)	24.9 (18.3)	41.9 (13)	26 (8)
Effect of TDD on CL _{INT} /F	0.388*		0.388 (8.8)	
K _{AFF} of AAG (dL/mg)	0.0304*		0.0304 (18)	
V _c /F (L)	35.6 (19.9)	15.6 (210)	122 (8.2)	88 (23)
CL _p /F (L/hr)	24.0 (19.4)	51.0 (34.3)	15.0 (11)	65 (30)
V _p /F (L)	90.0 (10.4)	55.7 FIX	84.3 (11)	56 (36)
KA (/hr)	0.393 (18.5)		0.455 (8.1)	74 (17)
F _{REL}	1.18*		1.18 (1.6)	
D1(hr)	1.49 (11.1)	88.4 (27.4)		
R (V _c /F, KA)			0.61	
RUV (CV%)	18.2 (20.5)		34.9 (4.2)	

Adopted from Applicant's pharmacometrics report of darunavir from trial GS-US-216-0130, Table 19.

Reviewer's comment: The reviewer verified the Applicant's population PK analyses for darunavir. The goodness-of-fit plots indicate that the model reasonably describes the data. The model structure was developed based on the previous population PK model from the original NDA submission for darunavir. The parameter estimates had a good agreement with previous estimates except the lower estimate for the volume of distribution for the central compartment. The reviewer agrees that no clinically significant impact of age, body weight, height, body surface area and race were identified from the available data. However, it is worth noting that there were only a few females that were included in the model building dataset (3 females vs 50 males), therefore, gender was not considered as potential covariate. Afterwards, using a graphical analysis to determine if any additional covariates could further describe the 24 week Bayesian feedback data, gender was identified to have a weak relationship with CL/F (32 females vs 266 males) (Figure 5). The result is consistent with the reviewer's evaluation of covariates (Figure 6).

The reviewer verified that the AUC_{24h} and C_{0h} calculations for darunavir are appropriate. The difference in comparing means and standard deviations between Applicant's and reviewer's results is due to rounding (Table 1). The predictions of AUC_{24h} and C_{0h} based on population PK model are acceptable from a pharmacometric perspective.

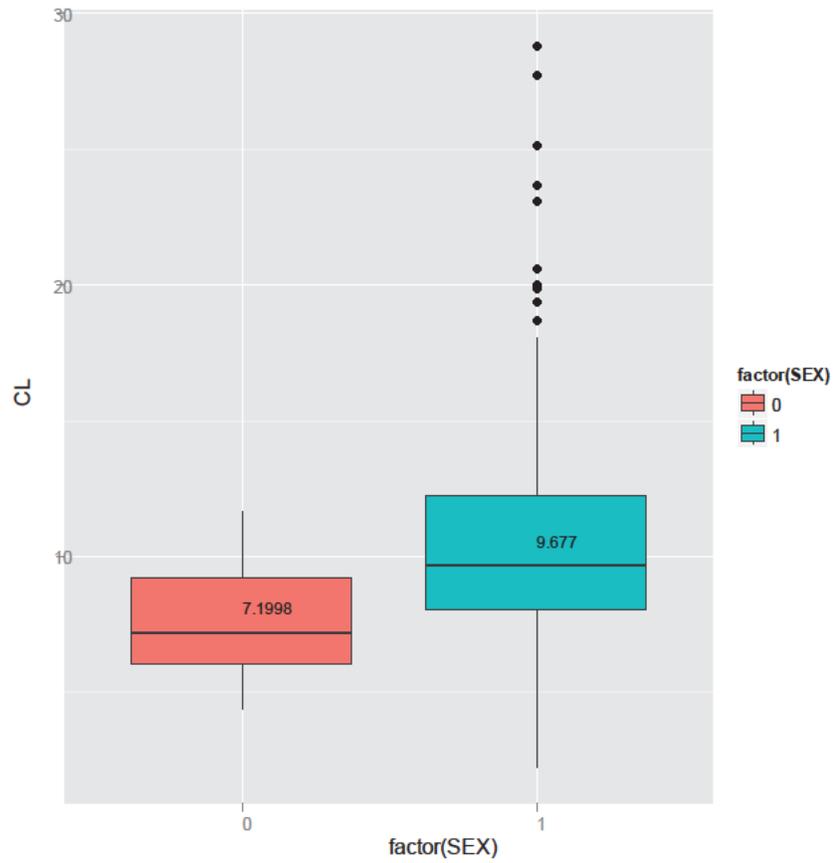


Figure 6 Relationship between CL/F and sex

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/s/

STANLEY AU
12/19/2014

JEFFRY FLORIAN
12/19/2014

KELLIE S REYNOLDS
12/23/2014

BIOPHARMACEUTICS REVIEW
Office of New Drug Quality Assessment

Application No.:	NDA 205395	Reviewer: Minerva Hughes	
Submission Date:	31 March 2014		
Division:	DAVP	Team Leader: Angelica Dorantes	
		Acting Supervisor: Paul Seo	
Sponsor:	Janssen Products	Secondary Reviewer: Team Leader	
Trade Name:	Prezcobix Tablets	Date Assigned:	31 March 2014
		GRMP:	26 December 2014
		PDUFA Date:	31 January 2015
Generic Name:	Darunavir/Cobicistat	Date of Review:	5 December 2014
Indication:	HIV	Type of Submission: 505(b)(1)	
Dosage Form/Strengths	Fixed dose tablet DRV/COBI (800/150 mg)		
Route of Administration	Oral		

Biopharmaceutics Review Focus:

- Pivotal BE Study Review (TMC114IFD1003)
- Drug product dissolution method development and acceptance criteria.
- Drug product formulation development and dissolution quality risks.

SYNOPSIS - SUMMARY OF IMPORTANT BIOPHARMACEUTICS FINDINGS

General

NDA 205395 was submitted in accordance with Section 505(b)(1) of the FDC act for the use of darunavir/cobicistat (DRV/COBI) for the treatment of HIV-1 infection in adult patients. DRV is an HIV-1 protease inhibitor approved as a single entity tablet and in combination with the pharmacokinetic enhancer ritonavir (rtv) (DRV/rtv) (PREZISTA, NDA 21976). The proposed drug product under this NDA is a fixed dose combination (FDC) tablet containing 800 mg of DRV and 150 mg of COBI. COBI is used in the FDC similarly to rtv, which is to boost systemic DRV exposure through inhibition of CYP3A mediated metabolism. COBI is an approved drug substance as part of the FDC tablet STRIBILD (elvitegravir, cobicistat, emtricitabine, and tenofovir disoproxil fumarate) (NDA 203100), which is also indicated for antiretroviral therapy.

Bioequivalence Study

This Biopharmaceutics review is focused on the acceptability of the pivotal bioequivalence study, Study 1003, supporting NDA approval. Study 1003 was a single-dose, open-label, 3-panel, randomized, pivotal crossover study to assess the bioequivalence of DRV when co-administrated with COBI as either a FDC tablet (G006) or as single agents under fed and fasted conditions in healthy subjects. Panels 1 and 2 evaluated bioequivalence under fasting

and fed conditions. Panel 3 evaluated the food effect and is not covered in this review*.

- *Bioequivalence under fasting conditions*
 - Bioequivalence was satisfactorily demonstrated for the DRV/COBI FDC tablet compared with the single entity tablets under fasting conditions.
- *Bioequivalence under fed conditions*
 - Bioequivalence was satisfactorily demonstrated for the DRV/COBI FDC tablet compared with the single entity tablets under fed conditions.

*NOTE: OCP is reviewing Panel 3 as per MOU

Dissolution Testing

The following dissolution methods and acceptance criteria are acceptable for product quality control.

Dissolution Method - DRV	
Apparatus	USP 2
Medium	0.05 M sodium phosphate buffer, pH 3.0, 2% Tween 20,900 mL
Agitation speed	75 rpm
Temperature	37°C
Analytical Method	HPLC w/UV at ^(b) (4) nm
Acceptance Criterion	Q = ^(b) (4) % in 30 minutes
Dissolution Method - COBI	
Apparatus	USP 2
Medium	0.05 M citrate phosphate buffer, pH 4.2, 900 mL
Agitation speed	75 rpm
Temperature	37°C
Analytical Method	HPLC w/UV at ^(b) (4) nm
Acceptance Criterion	Q = ^(b) (4) % in 15 minutes

CONSULTS

The Office of Scientific Investigations (OSI) was consulted on 2 May 2014 to inspect the clinical and bioanalytical sites used for the fed/fasted BE study No. TMC114IFD1003. All clinical and analytical study data were deemed acceptable for review.

PHASE 4 COMMITMENTS

None.

RISK ASSESSMENT EVALUATION

Refer to the CMC review for the overall quality risk assessment table of this product and conclusions regarding the proposed drug product quality control strategy. From the Biopharmaceutics perspective, dissolution is rate limiting for DRV bioavailability. As such, product and process attributes that significantly impact DRV dissolution are potentially high risk factors with respect to drug exposure and should be appropriately mitigated.¹

¹ Reference is made to the DRV NDA 21976 for more details on how changes in DRV formulation (e.g., solution, tablet, etc.) impact bioavailability.

RECOMMENDATION

NDA 205395 for the use of darunivir/cobicistat (800/150 mg) fixed dose tablets to treat HIV infections in adults is recommended for *APPROVAL* from the Biopharmaceutics perspective.

Signature Block:

**Minerva A.
Hughes -S**
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Date: 2014.12.05 14:38:21 -05'00'

Minerva Hughes, Ph.D.

Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

**Angelica
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Date: 2014.12.05 15:02:25 -05'00'

Angelica Dorantes, Ph.D.

Biopharmaceutics Team Leader
Office of New Drug Quality Assessment

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BIOPHARMACEUTICS REVIEW

1 GENERAL ATTRIBUTES

1.1 *What are the highlights of the chemistry and physico-chemical properties of the drug substance (e.g. solubility) and formulation of the drug product?*

The proposed drug product is a fixed dose combination (FDC) tablet comprised of the HIV protease inhibitor darunavir (DRV) and the pharmaco-enhancer cobicistat (COBI), along with other excipients.

Reference is made to DMF 18825 for full DRV drug substance information. However, it is noted that DRV is prepared as a (b) (4) (see structure below).

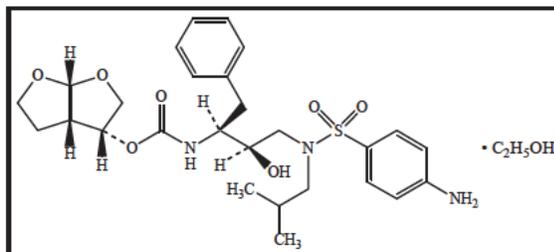


Figure 1. Structure of DRV, with a molecular formula of $C_{27}H_{37}N_3O_7S \cdot C_2H_5OH$ and molecular weight of 593.73 g/mol.

DRV is known to exhibit (b) (4)
(b) (4)
 Under the proposed drug substance manufacturing conditions, however, (b) (4)
(b) (4) The results of a relative bioavailability study (Study TMC114-C148) showed that the presence of DRV (b) (4) has no impact on bioavailability (reference to Prezista NDA 21976).

DRV is only (b) (4)

Reference is made to DMF 25188 for full COBI drug substance information. COBI is a structural analog of the known pharmaco-enhancer ritonavir (Norvir NDAs 22417, 20945, and 20659), as illustrated below.

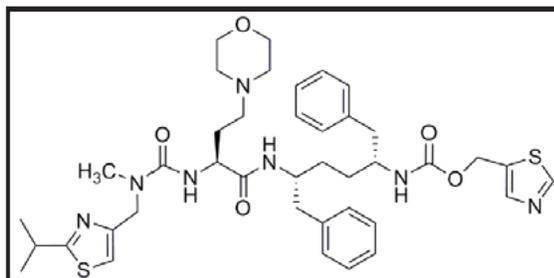


Figure 2. Structure of COBI, with a molecular formula of $C_{40}H_{53}N_7O_5S_2$ and a molecular weight of 776.0 g/mol.

The drug substance is an (b) (4). It is relatively (b) (4).
 COBI is used in an adsorbed form (i.e., on silica) (b) (4).

A single tablet strength is proposed for marketing. The quantitative and qualitative formulation is summarized in the following table.

Table 1: Quantitative and Qualitative Composition of the Drug Product

Component	Quality Reference ^a	Function	Quantity per Tablet (mg)
(b) (4) Tablet			
Darunavir	Company standard	Active	(b) (4)
Hypromellose (b) (4)	Ph. Eur., USP	(b) (4)	(b) (4)
(b) (4)	Ph. Eur., USP	(b) (4)	(b) (4)
Cobicistat ^e	Company standard		
Cobicistat (b) (4)		Active	150.00 ^f
Colloidal Silicon Dioxide		(b) (4)	(b) (4)
Silicified Microcrystalline Cellulose	NF	(b) (4)	(b) (4)
Crospovidone	Ph. Eur., NF	(b) (4)	(b) (4)
Magnesium Stearate ^e	Ph. Eur., NF	(b) (4)	(b) (4)
(b) (4)			
Film Coating			(b) (4)
(b) (4)	Noncompendial ^d	Film-coat (b) (4)	(b) (4)
	Ph. Eur., USP		
Total Tablet Weight			(b) (4)

1.2 What are the proposed mechanism(s) of action and therapeutic indication(s)?

The proposed indication is for the treatment of HIV-1 infection in adults. DRV is the active agent, selectively inhibiting the cleavage of HIV 1 encoded Gag-Pol polyproteins in infected cells, thereby preventing the formation of mature virus particles. COBI inhibits cytochromes P450 of the CYP3A subfamily. Inhibition of CYP3A-mediated metabolism enhances the systemic exposure of CYP3A substrates such as DRV.

1.3 What are the proposed dosage(s) and route(s) of administration?

The recommended dose is one oral tablet (800 mg DRV and 150 mg COBI) take daily with food.

1.4 Is there any information on BCS classification? What claim does the applicant make based on BCS classification? What data are available to support this claim?

No information was provided.

2 GENERAL BIOPHARMACEUTICS (IN VIVO)

2.1 CLINICAL STUDIES

2.1.1 *What are the design features of the biopharmaceutics studies used to support the proposed to-be-marketed formulation? Summary of individual study reviews provided.*

There are two biopharmaceutics studies submitted in support of marketing approval.

- Relative bioavailability Study TMC114IFD1001 comparing DRV/COBI 800/150 mg FDC tablets with DRV/ritonavir 800/100 mg tablets, administered as single entities.
 - *This study is not covered in this review. Reference is made to the Clinical Pharmacology Review.*
- Pivotal bioequivalence (BE) Study TMC114IFD1003 comparing DRV/COBI FD800/150-mg with DRV (800 mg) and COBI (150 mg) single entity tablets under fed and fasted conditions.
 - *Study 1003 was a 3-panel study and only the BE assessments are included in this review (i.e., Panel 1 and Panel 2). The food effect portion is referred to the Clinical Pharmacology Review.*

Study 1003 (Pivotal Bioequivalence)	
STUDY DESIGN	A single-dose, open-label, 3-panel, randomized, pivotal crossover study to assess the bioequivalence of DRV when coadministered with COBI as either a fixed dose combination tablet (G006) or as single agents under fed and fasted conditions in healthy subjects.
METHODOLOGY	<p>A 3 panel/phase study: a screening phase of approximately 3 weeks (Days - 21 to -1; before the first study drug administration of the first treatment session) followed by an open-label treatment phase consisting of 3 panels with 2 single-dose treatment sessions of 5 days each (Days -1 to 4) separated by a washout phase of at least 7 days, and a follow-up phase 7 to 10 days after the last intake of study drugs. Subjects were confined to the study site from Day -1 of each treatment session, at least 10 hours before each study drug administration, until completion of the 72-hour pharmacokinetic blood sample collection on Day 4.</p> <p>Panel 1 – Fasting bioequivalence Panel 2 – Fed bioequivalence (standard breakfast) Panel 3 - Food effect portion (see Clinical Pharmacology Review)</p> <p>Treatments: DRV: Commercial tablet formulation F030, administered as 2 x 400-mg oral tablets. Batch number: BDZ0600. COBI: Administered as 1 x 150-mg oral tablet (investigational formulation, intended for commercialization). Batch number: BB1004B2.</p>
NUMBER OF SUBJECTS/DEMO	Analyzed (randomized and treated): 133 healthy subjects; Panel 1: 74 subjects, Panel 2: 40 subjects, and Panel 3: 19 subjects.

Study 1003 (Pivotal Bioequivalence)						
GRAPHICS						
Study Population:						
Demographic Parameters		Panel 1	Panel 2	Panel 3	Total	
Subjects treated (F/M)		74 (34/40)	40 (17/23)	19 (8/11)	133 (59/74)	
Age (Years)						
Median (Range)		46.0 (19; 60)	43.0 (19; 60)	46.0 (22; 59)	46.0 (19; 60)	
Weight (kg)						
Median (Range)		73.6 (53; 116)	75.3 (58; 102)	75.0 (57; 103)	74.2 (53; 116)	
BMI (kg/m²)						
Median (Range)		25.1 (19; 30)	25.2 (20; 30)	25.3 (19; 30)	25.2 (19; 30)	
Race, n (%)						
Black or African American		1 (1.4)	0	1 (5.3)	2 (1.5)	
White		73 (98.6)	40 (100.0)	18 (94.7)	131 (98.5)	
Discontinuations		1	2	0	3	
Reason:						
Protocol Violation		1	0	0	1	
Withdrawal by Subject		0	2	0	2	
n= number of observations						
SUMMARY OF RESULTS	Major protocol deviations were reported for 5 subjects, all in Panel 1 (fasting BE). These subjects were enrolled despite not satisfying exclusion criteria for drug use (1 subject) and laboratory tests (abnormal hemoglobin and LDL). Major blood sampling deviations occurred in three subjects are a single, early sampling time point. These data were excluded from descriptive statistics, but included in the PK analyses. PK data were excluded for one subject who experienced emesis within two hours of taking treatment.					
DRV	Fasting BE					
	LS Means ^a				p-Value	
Parameter	DRV/COBI 800/150 mg as Single Agents, Fasted (Reference)	DRV/COBI 800/150 mg as Fixed Dose Combination (G006), Fasted (Test)	LS Means Ratio, %	90% CI ^c	Session	Sequence
C _{max} , ng/mL	2992	2950	98.59	93.72 - 103.73	0.6767	0.8887
AUC _{last} , ng.h/mL	44525	42831	96.20	90.98 - 101.71	0.1186	0.5153
AUC _∞ , ng.h/mL ^b	44851	43058	96.00	90.30 - 102.07	0.0217*	0.6235
^a n=72 for reference and n=74 for test						
^b n=66 for reference and test						
^c 90% confidence intervals						
* Statistically significant difference						
	Fed BE					
	LS Means ^a				p-Value	
Parameter	DRV/COBI 800/150 mg as Single Agents, Fed (Reference)	DRV/COBI 800/150 mg as Fixed Dose Combination (G006), Fed (Test)	LS Means Ratio, %	90% CI ^c	Session	Sequence
C _{max} , ng/mL	6873	6650	96.76	93.06 - 100.60	0.8095	0.7228
AUC _{last} , ng.h/mL	76499	74744	97.71	93.08 - 102.57	0.8611	0.9025
AUC _∞ , ng.h/mL ^b	75962	74302	97.81	92.85 - 103.05	0.7272	0.8799
^a n=38 for reference and n=40 for test						
^b n=35 for reference and n=37 for test						
^c 90% confidence intervals						

Study 1003 (Pivotal Bioequivalence)

Cobicistat

Fasting BE

Parameter	LS Means ^a		LS Means Ratio, %	90% CI ^c	p-Value	
	DRV/COBI 800/150 mg as Single Agents, Fasted (Reference)	DRV/COBI 800/150 mg as Fixed Dose Combination (G006), Fasted (Test)			Session	Sequence
C _{max} , ng/mL	572	591	103.40	94.25 - 113.44	0.2581	0.5453
AUC _{last} , ng·h/mL	4175	4226	101.20	91.77 - 111.61	0.0720	0.4548
AUC _∞ , ng·h/mL ^b	4390	4580	104.33	94.85 - 114.77	0.0374*	0.6248

^a n=72 for reference and n=73 for test

^b n=71 for reference and test

^c 90% confidence intervals

* Statistically significant difference

Fed BE

Parameter	LS Means ^a		LS Means Ratio, %	90% CI ^b	p-Value	
	DRV/COBI 800/150 mg as Single Agents, Fed (Reference)	DRV/COBI 800/150 mg as Fixed Dose Combination (G006), Fed (Test)			Session	Sequence
C _{max} , ng/mL	808	789	97.65	93.77 - 101.70	0.2100	0.3216
AUC _{last} , ng·h/mL	5879	5751	97.82	94.65 - 101.10	0.4427	0.4078
AUC _∞ , ng·h/mL	5975	5842	97.77	94.60 - 101.05	0.4906	0.4396

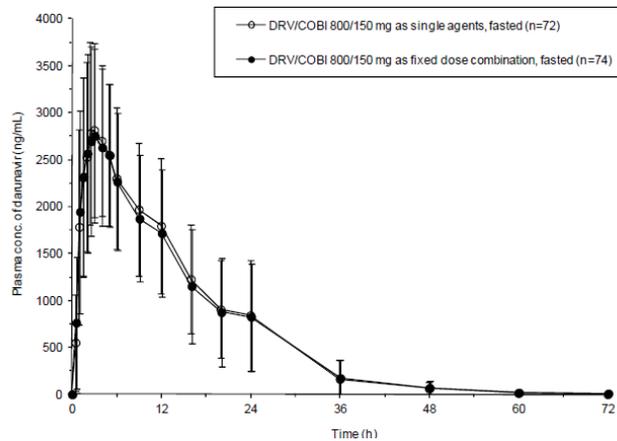
^a n=38 for reference and n=40 for test

^b 90% confidence intervals

Mean Plasma Concentration Profiles (Fasting)

Mean Plasma Concentration Profile (DRV)

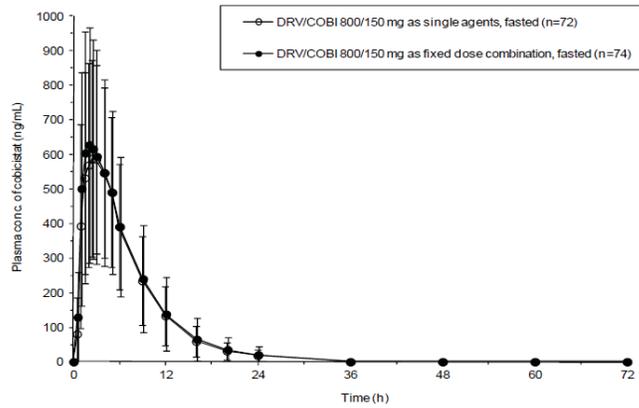
Figure 3: Mean Plasma Concentration-Time Curves of DRV (Including SD Bars) After Administration of DRV/COBI 800/150 mg as Single Agents (Treatment A), and as Fixed Dose Combination (Treatment B) Under Fasted Conditions



Study 1003 (Pivotal Bioequivalence)

Mean Plasma Concentration Profile (Cobicistat)

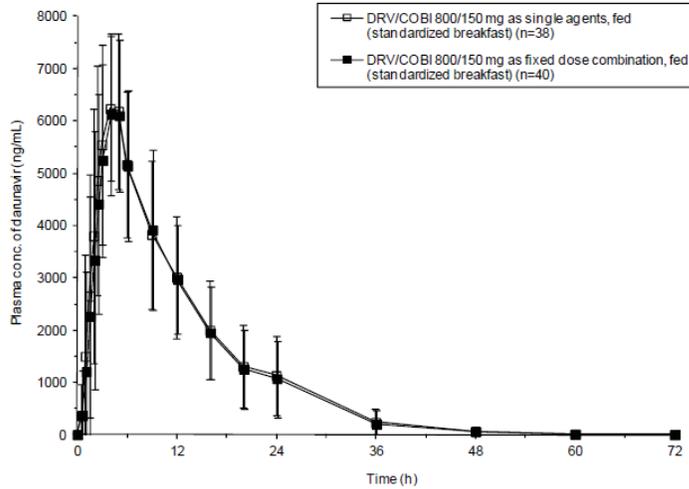
Figure 4: Mean Plasma Concentration-Time Curves of COBI (Including SD Bars) After Administration of DRV/COBI 800/150 mg as Single Agents (Treatment A), and as Fixed Dose Combination (Treatment B) Under Fasted Conditions



Mean Plasma Concentration Profiles (Fed)

Mean Plasma Concentration Profile (DRV)

Figure 5: Mean Plasma Concentration-Time Curves of DRV (Including SD Bars) After Administration of DRV/COBI 800/150 mg as Single Agents (Treatment C), and as Fixed Dose Combination (Treatment D) Under Fed Conditions



Mean Plasma Concentration Profile (Cobicistat)

Study 1003 (Pivotal Bioequivalence)	
	<p>Figure 6: Mean Plasma Concentration-Time Curves of COBI (Including SD Bars) After Administration of DRV/COBI 800/150 mg as Single Agents (Treatment C), and as Fixed Dose Combination (Treatment D) Under Fed Conditions</p>
SUMMARY OF SAFETY	There were no deaths or SAEs reported in the study. See Clinical review for an evaluation of drug safety.

Reviewer’s Evaluation: SATISFACTORY

The pharmacokinetic parameters for DRV and COBI administered using the proposed FDC tablet were comparable to the commercial DRV and COBI tablets using the standard 80 - 125% bioequivalence criteria under both fasting and fed conditions. In addition, there were no significant differences in the concentration-time plasma profiles. A statistically significant session effect for AUCI was observed; however, a washout period of 7 days is considered adequate to mitigate carryover issues for DRV (half-life ~ 7 h) and COBI (half-life ~4 h). Further, additional information was provided in the June 30, 2014, NDA amendment to confirm the acceptability of the DRV and COBI single entities used in the study.

2.1.2 If the formulations do not meet the standard criteria for bioequivalence, what clinical pharmacology and/or clinical safety and efficacy data support the approval of the to-be-marketed product?

Bioequivalence was demonstrated using the standard criteria.

2.1.3 What is the effect of food on the bioavailability (BA) of the drug from the dosage form? What dosing recommendation should be made, if any, regarding administration of the product in relation to meals or meal types?

Refer to the Clinical Pharmacology review.

2.2 BIOANALYTICAL METHOD SECTION

2.2.1 *How are the active moieties and/or metabolites identified and measured in the plasma in the biopharmaceutics studies?*

Blood samples were collected in Li-heparin and K₂EDTA (4 mLs each) to determine the plasma concentrations of DRV and COBI.

2.2.2 *What bioanalytical methods are used to assess concentrations?*

An LC/MS-MS bioanalysis method, (b) (4) 60-0949, was developed to evaluate the concentration of COBI in plasma. Another LC/MS-MS method, BA10396, was used for the DRV analysis.

2.2.2.1 *What is the range of the standard curve? How does it relate to the requirements for the clinical studies? What curve fitting techniques are used? What are the lower and upper limits of quantification (LLOQ/ULOQ), and assay validation parameter: accuracy, precision, selectivity, sample stability, etc.?*

A summary of the validation results is provided below.

Method	LC-MS/MS
Study Location	Module 5.3.1.4/TMC114-BA10396
	BA10396, Full Validation
Analyte	DRV
Matrix	Plasma
Validated concentration range	5 to 10,000 ng/mL
Inter-run accuracy (%RE)	-4.0 to 0.4
Inter-run precision (%CV)	0.0 to 2.5
Intra-run accuracy (%)	-5.4 to 4.3
Intra-run precision (%CV)	3.0 to 7.3
Intra-run accuracy (dilution) (%)	0.8 (10× dilution)
Intra-run precision (dilution) (%CV)	3.3 (10× dilution)
Incurred sample reproducibility	Study TMC114IFD1003: 305/308 samples within 20%
Selectivity	No relevant interferences
Stability in blood	2 hours at 0°C and room temperature
Stability in plasma	4 freeze-thaw cycles 26 hours at room temperature
Processed sample stability	119 hours at 10°C
Stability in frozen matrix	232 days at -20°C and -70°C 1,597 days at -20°C (BA502)

Table 8 Validation Summary for GS-9350

Information Requested	Data
Bioanalytical method validation report location	Validation of a Method for the Determination of GS-9137 and GS-9350 in K ₂ EDTA Human Plasma by LC-MS/MS (b) (4) (60-0949)
Study Number	(b) (4) 50-0949
Analyte Name	GS-9350
Internal Standard (IS)	(b) (4)
Analytical Method Type	LC-MS/MS
Extraction Method	Solid Phase
Sample Volume	50 µL
QC Concentrations	5, 15, 200, and 2000 ng/mL
Standard Curve Concentrations	5, 15, 45, 125, 375, 1250, 2250, and 2500 ng/mL
Lower Limit Of Quantitation	5 ng/mL
Upper Limit Of Quantitation	2500 ng/mL
Average Recovery of Drug (%)	63.9
QC Intraday Precision Range (%CV)	2.5 to 7.2
QC Intraday Accuracy Range (%RE)	-6.6 to 11.8
QC Interday Precision Range (%CV)	3.9 to 8.3
QC Interday Accuracy Range (%RE)	-0.3 to 9.7
Stock Solution Solvent	Acetonitrile:Water (50:50/v:v)
Master Stock Solution Stability in Acetonitrile:Water (50:50/v:v)	183 Days at -70°C
Master Stock Solution Stability in Acetonitrile:Water (50:50/v:v)	6 Hours at Room Temperature
Reinjection Reproducibility in Processed Samples	124 Hours at 4°C
Benchtop Stability in Human Plasma	20 Hours at Room Temperature
Freeze/Thaw Stability in Human Plasma	6 Cycles at -70°C
Long-term Storage Stability in Human Plasma	121 Days at -10°C to -30°C ^a 365 Days at -60°C to -80°C ^a
Dilution Integrity	7500 ng/mL diluted 10-fold
Selectivity	≤ 20.0% LLOQ for analyte; ≤ 5.0% for IS
Interference Tests for Midazolam (MDZ), 1-OH Midazolam (1-OH MDZ), 4-OH Midazolam (4-OH MDZ), Emtricitabine (FTC), and Tenofovir (TFV)	No interference from co-administered drugs to GS-9350 (b) (4)

^a Refer to V_GS9350_HUMAN_PLASMA_V2

^b Performed under (b) (4) 50-0949B

Method	LC-MS/MS
Study Location	Module 5.3.1.4/QPS 60-0949 (b) (4) 60-0949, Full Validation
Analyte	COBI
Matrix	Plasma
Validated concentration range	5 to 2,500 ng/ml
Inter-run accuracy (%RE)	-0.3 to 9.7
Inter-run precision (%CV)	3.9 to 8.3
Intra-run accuracy (%)	-6.6 to 11.8
Intra-run precision (%CV)	2.5 to 7.2
Intra-run accuracy (dilution) (%)	-0.7 (10× dilution)
Intra-run precision (dilution) (%CV)	2.7 (10× dilution)
Incurred sample reproducibility	Study TMC114IFD1003: 292/303 samples within 20%
Selectivity	No relevant interferences
Stability in blood	-
Stability in plasma	6 freeze-thaw cycles 20 hours at room temperature
Processed sample stability	124 hours at 4°C
Stability in frozen matrix	121 days at -10°C to -30°C 365 days at -60°C to -80°C

CV = coefficient of variation; LC-MS/MS = liquid chromatography coupled to tandem mass spectrometry; RE = relative error.

2.2.2.2 Are the Inspection reports of the BE study acceptable?

Yes. The following clinical and analytical sites were inspected by the Office of Scientific Investigations as part of this application’s review.

Clinical

- Laboratorium AZ Jan Palfijn
Lange Bremstraat 70, B-2170, Merksem, Belgium

Analytical – analysis of darunavir

- (b) (4)

Analytical – analysis of COBI

- (b) (4)

At the time of this review, the Establishment Inspection Report was completed for the (b) (4) facility (see DARRTS review dated 4 December 2014 by Kara Scheibner); however the reports were pending for the clinical and (b) (4) site audits. However, per the email communication with OSI (attached) all site data were found acceptable for review. A 483 was issued for (b) (4) concerning issues with method validations for studies unrelated to this NDA. Nevertheless, these issues have been satisfactorily addressed. There were no observations at the clinical and (b) (4) sites.

3 GENERAL BIOPHARMACEUTICS (IN VITRO)

3.1 DISSOLUTION INFORMATION

3.2 DISSOLUTION METHOD

3.2.1 What is the proposed dissolution method?

The proposed dissolution methods are:

DRV:

Table 6: Dissolution Method Parameters for Darunavir in the Drug Product

Dissolution Apparatus	2 (Paddle)
Medium	2.0% Tween [®] 20 in 0.05 M sodium phosphate buffer, pH 3.0
Medium Volume	900 mL
Medium Temperature	37 °C
Rotation Speed	75 rpm
(b) (4)	
Analytical Method	(b) (4) with UV detection at (b) (4) nm

COBI

Table 41: Dissolution Method Parameters for Cobicistat in the Drug Product

Dissolution Apparatus	2 (Paddle)
Medium	0.05 M Citrate phosphate buffer, pH 4.2
Medium Volume	900 mL
Medium Temperature	37 °C
Rotation Speed	75 rpm
(b) (4)	
Analytical Method	HPLC with UV detection at (b) (4) nm

3.2.2 What data are provided to support the adequacy of the proposed dissolution method (e.g. medium, apparatus selection, etc.)?

A single dissolution method was not deemed appropriate (b) (4)
(b) (4)
administered at a high dose (800 mg) in the drug product. (b) (4)

In contrast, the COBI solubility varies from (b) (4)
(b) (4)
(b) (4)
(b) (4)

(b) (4)

(b) (4)

(b) (4)

3.2.6 *Is the proposed method acceptable? If not, what are the deficiencies?*

Yes, the proposed dissolution methods for DRV and COBI are acceptable.

3.3 **ACCEPTANCE CRITERIA**

3.3.1 *What are the proposed dissolution acceptance criteria for this product?*

The proposed dissolution acceptance criteria are summarized below.

Darunavir: $Q = \frac{(b)}{(4)}\%$ in $\frac{(b)}{(4)}$ minutes

COBI: $Q = \frac{(b)}{(4)}\%$ in 15 minutes

3.3.2 *What data are available to support the criteria?*

(b) (4)

(b) (4)

A summary

of the key dissolution data are tabulated below.

(b) (4)

3.3.3 *Is the setting of the dissolution acceptance criteria based on data from clinical and registration batches?*

The clinical and registration batches were used to define the dissolution acceptance criteria; (b) (4)

3.3.4 *Are mean (n =12) dissolution profile data used for the setting of the acceptance criteria?*

Yes.

3.3.5 *Are the acceptance criteria acceptable? If not, what are the recommended criteria?*

The proposed acceptance criterion of $Q = \frac{(b)}{(4)}\%$ at 15 minutes for COBI is acceptable.

The proposed acceptance criterion of $Q = \frac{(b)}{(4)}\%$ at $\frac{(b)}{(4)}$ minutes for DRV is not acceptable and a criterion of $Q = \frac{(b)}{(4)}\%$ at 30 minutes is recommended. (b) (4)

(b) (4)

The Applicant agreed with FDA's recommended changes to the dissolution acceptance criterion. A revised drug product specification was submitted to the NDA on October 17, 2014. The final proposed acceptance criterion of $Q = \frac{(b)}{(4)}\%$ in 30 minutes for DRV is acceptable.

4 DISSOLUTION APPLICATIONS

4.1 FORMULATION CHANGES

4.1.1 *Is the to-be-marketed formulation the same as the formulation used in the pivotal clinical or bioequivalence studies? If not, is dissolution used to bridge the data?*

The DRV/COBI FDC tablet (G006) used in the bioequivalence study is the proposed commercial formulation. (b) (4)

(b) (4)

Is the finished tablet scored? Do the dissolution data comparing the split versus whole tablet support tablet splitting?

No.

4.2 BIOWAIVERS

4.2.1 Is there a waiver request for in vivo BA or BE data (Biowaiver)? If yes, what is/are the purpose/s of the biowaiver request/s? What data support the biowaiver request/s? Is the biowaiver request acceptable?

No.

4.2.2 Is there any IVIVR or IVIVC information submitted? What is the regulatory application of the IVIVR/IVIVC in the submission? What data are provided to support the acceptability of the IVIVR or IVIVC model?

Not applicable.

4.3 SURROGATES IN LIEU OF DISSOLUTION

4.3.1 Are there any manufacturing parameters (e.g. disintegration, drug substance particle size, etc.) being proposed as surrogates in lieu of dissolution testing? What data are available to support the approval of the proposed surrogate test?

No.

4.4 DISSOLUTION AND QBD

4.4.1 Does the application contain QbD elements? If yes, is dissolution identified as a CQA for defining design space?

The application includes a manufacturing process design of experiment to establish a PAR, but not a design space per se.

4.4.2 Was dissolution included in the DoE? What raw materials and process variables are identified as having an impact on dissolution? What is the risk assessment been performed to evaluate the criticality of dissolution?

Dissolution was used in the manufacturing process DOE, and a shift toward slower dissolution for DRV was observed at the extremes of the PAR. The DRV dissolution acceptance criterion was revised to $Q = \frac{(b)}{(4)}\%$ in 30 minutes for better quality control. The revised tolerance, however, does not invalidate the proposed PAR.

Aside from the process DOE study, other studies show an impact on DRV dissolution with respect to (b) (4) and an impact on COBI dissolution with respect to (b) (4).

Reference is made to the Chemistry Quality review for an evaluation of the manufacturing process and acceptability of proposed process ranges and controls.

4.4.3 What biopharmaceutics information is available to support the clinical relevance of the proposed design space?

A design space is not proposed.

4.4.4 Is there any dissolution model information submitted as part of QbD implementation? What is the regulatory application of the dissolution model in the submission? What data are provided to support the acceptability of the dissolution model?

No.

5 LABELING

Comments on the proposed labeling were communicated to the review team as part of labeling negotiations and are not captured in this review.

6 INFORMATION REQUESTS DURING THE REVIEW

The following information requests were issued during the NDA review cycle. Responses are incorporated into the QBR above. There are no outstanding review issues.

June 12, 2014 – responses received on June 30, 2014.

1. Please submit the SAS transport files for the plasma concentration (pc.xpt) and PK parameters (pp.xpt) from the pivotal bioequivalence study TMC114IFD1003 as separate files in column format, as illustrated below:
 - i. *SUBJ SEQ PER TRT C1 C2 C3...Cn KE_FIRST KE_LAST T1 T2 T3...Tn, etc.*
 - ii. *SUBJ SEQ PER TRT AUCT AUCI CMAX TMAX KE Thalf, etc.*
2. Provide the formulation composition and batch analysis data for the drug products used in clinical study GS-US-216-013; specifically, the following drug product lots:
 - i. *COBI: BB1006B1, BB1006B1-A, BB1102D1*
 - ii. *DRV: BEZ0S00, BGZ0E00*

August 27, 2014 – responses received on September 12, 2014.

1. Your proposed dissolution acceptance criterion of $Q = \frac{(b)}{(4)}\%$ in $\frac{(b)}{(4)}$ minutes for DRV in the FDC tablet is not adequately supported by your data, and is therefore not acceptable. Based on the mean dissolution performance of the clinical and primary stability batches, an acceptance criterion of $Q = \frac{(b)}{(4)}\%$ in 30 minutes is recommended for optimal quality control. Further, a final sampling time of 30 minutes is most sensitive to manufacturing variations and dissolution stability changes as summarized in Section 3.2.P.2 of your NDA.
2. Using the clinical batch 2CG7515-X as a reference, provide the results of similarity f1/f2 testing for each $\frac{(b)}{(4)}$ evaluated in the manufacturing DOE and development studies to support the proposed PAR for the commercial process. $\frac{(b)}{(4)}$

October 8, 2014, (email) and October 10, 2014, teleconference.

1. The Agency maintains its recommendation regarding the dissolution acceptance criterion and seeks to (1) have a better understanding of expected product performance ^{(b) (4)} [REDACTED] ^{(b) (4)} [REDACTED] and (2) reach an agreement on a mutually acceptable dissolution acceptance criterion to support the pending NDA.

Attachment – OSI Email Communication Regarding Clinical Site Audit

Hughes, Minerva

From: Hughes, Minerva
Sent: Friday, December 05, 2014 2:23 PM
To: Hughes, Minerva
Subject: FW: Follow-up Regarding BE Inspections for NDA 205395

From: Chen, Xikui
Sent: Friday, December 05, 2014 9:50 AM
To: Scheibner, Kara; Hughes, Minerva
Cc: Mani, Nina
Subject: RE: Follow-up Regarding BE Inspections for NDA 205395

Hi Minerva,

There was no form FDA-483 issued at (b) (4) or the Belgium clinical facilities, and no significant finding. Both facilities will be classified as NAI. The review memo is pending. Thanks!

Xikui

**CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS
FILING FORM/CHECKLIST FOR NDA/BLA or Supplement**

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA/BLA Number	205395	Brand Name	TBD
OCP Division (I, II, III, IV, V)	DCP4	Generic Name	Darunavir and cobicistat
Medical Division	DAVP	Drug Class	Darunavir: HIV-1 protease inhibitor Cobicistat: CYP3A inhibitor
OCP Reviewer	Stanley Au	Indication(s)	HIV-1 infection
OCP Team Leader	Shirley Seo	Dosage Form	Tablets
Pharmacometrics Reviewer		Dosing Regimen	Once daily fixed dose combination regimen: darunavir (800 mg), cobicistat (150 mg)
Date of Submission	March 31, 2014	Route of Administration	Oral
Estimated Due Date of OCP Review	December 27, 2014	Sponsor	Janssen
Medical Division Due Date	January 3, 2015	Priority Classification	Standard
PDUFA Due Date	January 31, 2015		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.				
Tabular Listing of All Human Studies				
HPK Summary	X (section 2.7.2)			
Labeling	X			
Reference Bioanalytical and Analytical Methods				
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				

File name: 5_Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for NDA_BLA or Supplement 090808

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD -				
Phase 2:				
Phase 3:				
PK/PD -				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:	X (TMC114IFD1001)	1	None	This trial will not be reviewed.
Bioequivalence studies -				
traditional design; single / multi dose:	X (TMC114IFD1003)	1	None	The bioequivalence component of the trial will be reviewed by biopharmaceutics.
replicate design; single / multi dose:				
Food-drug interaction studies	X (TMC114IFD1003)	1	1	The food effect component of the trial will be reviewed by clinical pharmacology.
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies				

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	X Note: this will be not be reviewed by clinical pharmacology			The adequacy of the bioequivalence assessment will be made by the biopharmaceutics reviewer.
2	Has the applicant provided metabolism and drug-drug interaction information?			X	
3	Has the sponsor submitted			X	

File name: 5_Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for NDA_BLA or Supplement 090808

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

	bioavailability data satisfying the CFR requirements?				
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	X (for the TMC114IFD1003 trial) Note: this will be not be reviewed by clinical pharmacology			The adequacy of the bioanalytical information will be made by the biopharmaceutics reviewer.
5	Has a rationale for dose selection been submitted?			X	
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	X			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	X			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	X			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
Data					
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?			X	
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			X	
Studies and Analyses					
11	Is the appropriate pharmacokinetic information submitted?	X			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?			X	
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?			X	
14	Is there an adequate attempt by the applicant to use exposure-response			X	

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**CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS
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	relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?				
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			X	
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			X	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?			X	
General					
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	X			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			X	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?

 Yes

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

See signature page

Reviewing Clinical Pharmacologist

Date

See signature page

Team Leader/Supervisor

Date

File name: 5_Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for NDA_BLA or Supplement 090808

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

STANLEY AU
05/02/2014

SHIRLEY K SEO
05/02/2014