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APPLICATION NUMBER:

205395Orig1s000

MEDICAL REVIEW(S)

Clinical Review

Date	December 19, 2014
From	Sarita Boyd, Pharm.D.
Subject	Clinical Review
NDA/BLA #	NDA 205395
Supplement#	
Applicant	Janssen
Date of Submission	March 28, 2014
PDUFA Goal Date	January 31, 2015
Proprietary Name / Established (USAN) names	Prezcobix (Darunavir/cobicistat)
Dosage forms / Strength	Tablet / 800 mg of darunavir and 150 mg of cobicistat
Proposed Indication(s)	Fixed dose combination indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection in adults
Recommended:	Approval

1. Introduction

This review summarizes the main issues for NDA 205395, which includes Week 24 safety and efficacy data from Protocol GS-US-216-0130: *A Phase 3b, Open-Label, Single Arm Study to Evaluate the Safety and Efficacy of Cobicistat-boosted Darunavir Plus Two Fully Active Nucleoside Reverse Transcriptase Inhibitors in HIV-1 Infected, Antiretroviral Treatment-Naïve and -Experienced Adults with No Darunavir Resistance-associated Mutations*. Additionally, the review considers data from the bioavailability (BA) and pivotal bioequivalence (BE) studies, TMC114IFD1001 and TMC114IFD1003, respectively.

2. Background

Darunavir (DRV) is an HIV protease inhibitor (PI) approved in combination with low-dose ritonavir (RTV), a cytochrome P450 3A (CYP3A) inhibitor that increases DRV exposure. Darunavir coadministered with ritonavir (DRV/r) and other antiretroviral agents is indicated for treatment of HIV-1 infection with two different dosage recommendations based on past treatment experience. Once daily DRV 800 mg with RTV 100 mg is recommended for treatment-naïve and -experienced adults with no DRV resistance-associated substitutions. DRV/r is not available as a fixed-dose combination (FDC) tablet.

Cobicistat (COBI) received approval on September 24, 2014 as a CYP3A inhibitor indicated to increase systemic exposure of DRV (once daily dosing regimen) or atazanavir (ATV) in combination with other antiretroviral agents for treatment of HIV-1 infection. The Applicant

is proposing approval of a FDC product containing DRV and COBI, two currently approved drugs.

The Applicant has developed darunavir/cobicistat (DRV/co) as a FDC product in collaboration with Gilead Sciences, Inc. The bioequivalence (BE) study results are considered pivotal for approval of this application of DRV/co 800/150 mg as a FDC tablet indicated in combination with other antiretroviral agents for treatment of HIV-1 infection in adults. A clinical trial with DRV/co was not required because DRV and COBI are approved as individual drugs, and pharmacokinetic studies demonstrating bioequivalence of the FDC tablet to the approved, individual components are adequate. Efficacy and safety of DRV/co is extrapolated from DRV/r clinical trials; the link between DRV and COBI as single drugs and DRV/r was established during the COBI NDA review. This NDA includes safety and efficacy results for Protocol GS-US-216-0130 as a supportive clinical trial.

3. CMC/Device

DRV/co FDC tablets contain 800 mg of DRV (b) (4) and 150 mg of COBI (b) (4)

(b) (4)
The tablets are (b) (4)-shaped and film-coated with the color pink. The core tablet contains the following inactive ingredients: hypromellose, colloidal silicon dioxide, silicified microcrystalline cellulose, crospovidone, and magnesium stearate. The film coating is composed of (b) (4) Pink, which contains polyvinyl alcohol-partially hydrolyzed, titanium dioxide, (b) (4), (b) (4) iron oxide red, and iron oxide black. The proposed shelf life is 24 months in all climatic zones. Please refer to the CMC Reviews by Drs. Fuqiang Liu and Krishnakali Gosh for complete details.

4. Nonclinical Pharmacology/Toxicology

Nonclinical studies were not conducted with DRV in combination with COBI. The combined use of DRV and COBI is not expected to produce clinically relevant additive or synergistic effects. Additionally, DRV and COBI are approved as single agents to use in combination for the same indication proposed in this NDA. Comprehensive nonclinical programs for single agents DRV and COBI have been conducted by the Applicant and Gilead Sciences, respectively. The nonclinical program for COBI included safety pharmacology, nonclinical pharmacokinetics, and toxicology of COBI as a single agent and in combination with ATV or elvitegravir (EVG). Please refer to the original NDA reviews for DRV and COBI as single agents for complete details.

5. Clinical Pharmacology/Biopharmaceutics

The development program for DRV/co FDC is based on comprehensive development and approval of DRV and COBI as single agents and pharmacokinetic (PK) bridging of DRV/co FDC to the single agents. Study TMC114IFD1001 evaluated relative BA of DRV with two

different DRV/co 800/150 mg FDC formulations compared to DRV/r 800/100 mg in 36 healthy subjects following repeated once daily dosing under fed conditions. Results from this study led to selection of one of these formulations, with use of a different color coating, to move forward in development. Study TMC114IFD1003 evaluated BE of DRV with the selected DRV/co 800/150 mg FDC formulation compared to DRV 800 mg and COBI 150 mg administered as single agents in 133 subjects following single doses under fasted and fed (standard meal) conditions. Additionally, Study TMC114IFD1003 assessed the effect of a high-fat breakfast on the BA of the selected DRV/COBI FDC formulation (food effect).

Overall, Study TMC114IFD1003 showed acceptable BE of DRV/co FDC compared to the single agents under fasted and fed (standard meal) conditions. Although the study formulation (white) differs from the commercial formulation (pink) in its color coating, the change does not impact the BE study results per the Biopharmaceutics Reviewer, Dr. Minerva Hughes, because the film coating is nonfunctional.

A high-fat meal (vs. fasting) increased the area under the concentration time curve (AUC) and maximum plasma concentration (C_{max}) for DRV by 70% and 127%, respectively, with the FDC. However, absolute DRV C_{max} values overlap for DRV/co FDC administered with either a standard meal (i.e., recommended administration) or a high fat meal. DRV AUCs observed or estimated in the original DRV NDA (with RTV) were comparable or higher than those observed in the DRV/co FDC food effect study. In the original NDA for DRV/r once daily dosing, there were no apparent relationships between DRV exposures and maximum changes in laboratory parameters or occurrence of adverse events (AEs). Therefore, the increased DRV exposures occurring when DRV/co is coadministered with a high fat meal are not expected to be clinically relevant.

Please refer to the Biopharmaceutics Review by Dr. Minerva Hughes and the Clinical Pharmacology Review by Dr. Stanley Au for complete details.

6. Clinical Microbiology

Study GS-US-216-0130 provides supportive virology data for the use of DRV and COBI as single agents in treatment-naïve and -experienced subjects with no DRV resistance-associated substitutions, which are bridged to the FDC via the pivotal, BE study. In the Week 24 analysis of Study GS-US-216-0130, 10 of 313 subjects who received at least 1 dose of study drug (DRV/co) met the criteria for resistance test analysis. One treatment-experienced subject developed a DRV resistance-associated substitution, I84I/V, and one treatment-naïve subject developed a secondary PI substitution, I93I/L. Phenotypic resistance to DRV or other PIs was not seen in either of these subjects or in any other subjects. One treatment-experienced subject developed 2 reverse transcriptase (RT) substitutions, L74I/L and P225H/P, which are associated with resistance to abacavir and didanosine and to efavirenz, respectively. M184I/V was present at baseline and on treatment in this subject. Of note, the subject's background regimen in the study included emtricitabine, tenofovir, and zidovudine. Although interpretation of results is relatively limited in an open-label, single arm trial with Week 24

results, the low rate of resistance development with DRV/co is consistent with that observed for DRV/r in the same population. Please refer to the Clinical Virology review by Dr. Takashi Komatsu for complete details.

7. Clinical Efficacy

Efficacy Summary

Study GS-US-216-0130 is an ongoing Phase 3b, open-label, single arm, multicenter study evaluating the safety and efficacy of DRV/co (as single agents) coadministered with 2 fully active NRTIs in HIV-1 infected, antiretroviral treatment-naïve (n=295) and treatment-experienced (n=18) adults with no DRV resistance-associated mutations. At baseline, the median age of subjects was 35 years, 11% were female, 40% were non-white, 42% had HIV-1 RNA >100,000 copies/mL, and 19% had CD4+ cell count <200 cells/mm³. At 24 weeks, 82% of subjects treated with darunavir and cobicistat plus two nucleoside reverse transcriptase inhibitors achieved HIV RNA <50 copies/mL. Although interpretation of clinical efficacy in a single-arm trial is somewhat limited, the results provide support that DRV and COBI have adequate antiviral activity.

7.1 Indication

The proposed indication for DRV/co 800/150 mg FDC is for use in combination with other antiretroviral agents for the treatment of HIV-1 infection in adults. The recommended patient population includes treatment-naïve and -experienced patients with no DRV resistance-associated substitutions, which is the same for DRV/co administered as single agents (see approved prescribing information for TYBOST [cobicistat]) and DRV/r 800/100 mg once daily regimen (see approved prescribing information for PREZISTA [darunavir]).

7.1.1 Methods

The indication is based on clinical pharmacology data from Studies TMC114IFD1001 and TMC114IFD1003, which compared BA and BE of DRV/co FDC to DRV/r and DRV/co as single agents, respectively. See Section 5 for discussion of these studies.

There are no clinical efficacy data with the DRV/co administered as the FDC formulation. Study GS-US-216-0130 provides supportive clinical data for DRV/co administered as single agents. (b) (4).

The efficacy review includes Week 24 data analysis of GS-US-216-0130 using JReview.

7.1.2 Demographics

The full analysis set includes 313 HIV-infected subjects who received at least 1 dose of DRV/co. The majority of subjects were treatment-naïve (n=295) vs. treatment-experienced

(n=18). All subjects were enrolled at 56 U.S. sites. The majority of subjects were male (90%) and white (60%) or black (35%). Five subjects (1.6%) were hepatitis B surface antigen positive, and 8 subjects (2.6%) were HCV seropositive. Select demographic and baseline characteristics are displayed in Table 1 and match the Applicant’s analysis.

Table 1. GS-US-216-0130: Demographic and Baseline Characteristics

Characteristic	Treatment-naïve (n=295)	Treatment-experienced (n=18)	Total (n=313)
Age			
Median (Min, Max)	34 (18, 72)	48 (22, 69)	35 (18, 72)
Sex			
Male	266 (90%)	13 (72%)	279 (89%)
Female	29 (10%)	5 (28%)	34 (11%)
Race			
White	176 (60%)	11 (61%)	187 (60%)
Black or African	101 (34%)	7 (39%)	108 (35%)
American Indian	4 (1%)	0	4 (1%)
Asian	4 (1%)	0	4 (1%)
Other	10 (3%)	0	10 (3%)
Ethnicity			
Hispanic or Latino	64 (22%)	4 (22%)	68 (22%)
Not Hispanic or Latino	231 (78%)	14 (78%)	245 (78%)
Baseline HIV-1 RNA			
Median (Min, Max)	4.8 (2.6, 7.0)	5.0 (2.7, 6.8)	4.8 (2.6, 7.0)
≤ 100,000 copies/mL	173 (59%)	9 (50%)	182 (58%)
> 100,000 copies/mL	122 (41%)	9 (50%)	131 (42%)
Baseline CD4 Cell Count			
Median (Min, Max)	370 (6, 1473)	107 (5, 643)	361 (5, 1473)
≤ 200 cells/mm ³	47 (16%)	12 (67%)	59 (19%)
> 200 cells/mm ³	248 (84%)	6 (33%)	254 (81%)

Source: ADSL and ADLB datasets

7.1.3 Subject Disposition

Of 313 subjects in the full analysis set, 39 subjects (12.5%) discontinued study drug before the Week 24 data cutoff date. The most common reason for premature discontinuation was adverse events (15 subjects, 4.8%) followed by lost to follow-up (11 subjects, 3.5%). Table 2 displays subject disposition, which matches the Applicant’s analysis.

Table 2. GS-US-216-0130: Subject Disposition

Subject Disposition	Treatment-naïve	Treatment-experienced	Total
Full Analysis Set (Received ≥ 1 Dose)	295	18	313
Discontinued Study Drug Before W24	36	3	39
Adverse event	15	0	15

Table 2. GS-US-216-0130: Subject Disposition

Subject Disposition	Treatment-naïve	Treatment-experienced	Total
Investigator's discretion	1	0	1
Lack of efficacy	0	0	0
Lost to follow-up	9	2	11
Pregnancy	0	0	0
Protocol violation	1	0	1
Subject non-compliance	6	0	6
Withdrew consent	4	1	5
Taking Study Drug at W24 Data Cut-off	259	15	274

Source: ADSL dataset

7.1.4 Analysis of Primary Efficacy Endpoint

Study GS-US-216-0130 had no pre-specified primary efficacy endpoint.

7.1.5 Analysis of Secondary Efficacy Endpoints

Secondary efficacy endpoints include the proportion of subjects achieving HIV RNA <50 copies/mL as determined by the FDA-defined snapshot analysis at Weeks 24 and 48. This reviewer's analysis of Week 24 efficacy results are displayed in Table 3 and match the Applicant's analysis. As previously mentioned, the study is supportive but not pivotal, and efficacy in this single arm trial was a secondary endpoint.

Table 3. GS-US-216-0130: Week 24 Efficacy Analysis (Snapshot Analysis, Full Analysis Set)

HIV RNA Category	Treatment-naïve (n=295)	Treatment-experienced (n=18)	Total (n=313)
Virologic Success at W24			
HIV RNA < 50 c/mL	247 (84%)	11 (61%)	258 (82%)
95% Confidence Interval	79-88%	36-83%	78-87%
Virologic Failure at W24	29 (10%)	7 (39%)	36 (12%)
HIV RNA ≥ 50 c/mL	17 (6%)	5 (28%)	22 (7%)
Discontinued Study Drug and Last HIV RNA ≥ 50 c/mL	12 (4%)	2 (11%)	14 (5%)
No Virologic Data at W24 Window	19 (6%)	0	19 (6%)
Discontinued Due to AE	14 (5%)	0	14 (5%)
Discontinued Due to Other Reasons and Last HIV RNA < 50 c/mL	3 (1%)	0	3 (1%)
Missing Data on Study Drug	2 (<1%)	0	2 (<1%)

Source: ADEFFOUT dataset (Reviewer's analysis)

Overall, the results demonstrate reasonable ability of DRV/co plus 2 NRTIs to suppress HIV RNA at Week 24. Although full interpretation of efficacy is challenging without a comparator

group, the results raise no general concerns about 24-week efficacy of DRV/co in treatment-naïve subjects. The treatment-experienced group is too small to interpret separately.

Historically, the proportion of subjects with HIV RNA <50 copies/mL at Week 48 in treatment-naïve subjects randomized to DRV/r 800/100 mg once daily vs. lopinavir/ritonavir was 84% vs. 78%, respectively (Trial TMC114-C211). In Trial TMC114-C229 which enrolled treatment-experienced subjects with no DRV resistance-associated substitutions and randomized subjects to DRV/r 800/100 mg once daily or DRV/r 600/100 mg twice daily, 69% of subjects in both groups achieved HIV RNA <50 copies/mL at Week 48. Study GS-US-216-0130 results cannot be directly compared to historical controls given different time points of measure of virologic suppression (Week 24 vs. 48) and different trial designs (open-label, single arm vs. randomized, double-blind). Nonetheless, Study GS-US-216-0130 provides supportive data for DRV/co efficacy.

7.1.6 Other Endpoints

Subjects experienced considerable increases in CD4 cell count from baseline through Week 24 with DRV/co plus 2 NRTIs. The mean (SD) increases from baseline CD4 cell count in treatment-naïve and -experienced subjects were 145 (132) cells/ μ L and 99 (162) cells/ μ L, respectively, at Week 24, based on observed data. The mean (SD) increases from baseline CD4% in treatment-naïve and -experienced subjects were 7.2% (4.5%) and 4.1% (3.3%), respectively.

8. Safety

Safety Summary

Overall, there are no new safety concerns for DRV/co that were not previously assessed during the NDA reviews for DRV and COBI as single agents and included in the DRV or COBI labels. Safety information for DRV/co is available for 313 subjects (295 treatment-naïve and 18 treatment-experienced) who received at least 1 dose of study drug in Study GS-US-216-0130. The most common AEs with DRV/co are generally consistent with either DRV/r once daily dosing or cobicistat-containing regimens, but the incidence of individual AEs cannot be directly compared across clinical trials because of the different trial designs. Interpretation of the incidence of AEs with DRV/co itself is also limited in an open-label, single-arm study. However, this trial supports safety of DRV/co.

8.1 Methods

The main source of data for the safety review is Study GS-US-216-0130, the ongoing Phase 3b, open-label, single arm study. The treatment-naïve and -experienced groups were combined for the safety review because the treatment-experienced group was too small to

evaluate separately and the safety results are expected to be similar across both groups. The study results were reviewed as follows:

- Week 24 data analysis using JReview (data cut date August 16, 2012)
- Week 48 narrative review of available reports for deaths, nonfatal SAEs, and AEs leading to treatment discontinuation (data cut date July 1, 2013)
- Safety update for new deaths and nonfatal SAEs (data cut date April 30, 2014)

The Applicant also submitted results from Study GS-US-236-0118, a Phase 3 single-arm, open-label safety study in patients with mild to moderate renal impairment. In this trial subjects with eGFR calculated by the Cockcroft-Gault equation (eGFR_{CG}) 50 to <90 mL/min enrolled in one of two cohorts to receive 96 weeks of treatment with Stribild (Cohort 1) or with DRV/co or ATV/co (Cohort 2). Subjects in Cohort 2 were virologically suppressed on DRV/r or ATV/r plus 2 NRTIs and had RTV replaced with COBI at baseline. In the Safety Update Report, the Applicant provided Week 48 interim analysis for subjects in Cohort 2; subjects who received DRV/co (n=21) are discussed in Section 8.4. For more details pertaining to the DRV/co group, please see the clinical review for NDA 203094 resubmission.

8.2 Major Safety Results

8.2.1 Deaths

No deaths occurred in Study GS-US-216-0130.

8.2.2 Nonfatal Serious Adverse Events (SAEs)

A total of 15 (4.8%) subjects experienced a treatment-emergent SAE through Week 24. The most common SAE by System Organ Class (SOC) was “Infection and Infestation” occurring in 3 (1.0%) subjects. SAEs by preferred term (PT) reported in more than one subject were pyrexia and rash, which occurred in two subjects each. Investigators considered 3 (1.0%) SAEs related or possibly related to study drug: immune reconstitution syndrome, rash, and maculopapular rash. Table 4 lists all SAEs by PT.

Table 4. All Treatment-Emergent SAEs Occurring in Study GS-US-216-0130

Preferred Term	Number of subjects (%) DRV/co (n=313)
Number of subjects experiencing any treatment-emergent SAE	15 (4.8%)
PYREXIA	2 (0.6%)
ANAEMIA	1 (0.3%)
IDIOPATHIC THROMBOCYTOPENIC PURPURA	1 (0.3%)
RETINAL DETACHMENT	1 (0.3%)
GASTRITIS	1 (0.3%)
BILE DUCT STONE	1 (0.3%)
BILIARY DYSKINESIA	1 (0.3%)
CHOLECYSTITIS ACUTE	1 (0.3%)

Table 4. All Treatment-Emergent SAEs Occurring in Study GS-US-216-0130

Preferred Term	Number of subjects (%) DRV/co (n=313)
HYPERSENSITIVITY	1 (0.3%)
IMMUNE RECONSTITUTION SYNDROME	1 (0.3%)
FURUNCLE	1 (0.3%)
PELVIC INFLAMMATORY DISEASE	1 (0.3%)
PILONIDAL CYST	1 (0.3%)
LACERATION	1 (0.3%)
CASTLEMAN'S DISEASE	1 (0.3%)
KAPOSI'S SARCOMA	1 (0.3%)
ALCOHOL ABUSE	1 (0.3%)
DRUG DEPENDENCE	1 (0.3%)
RASH	1 (0.3%)
RASH MACULO-PAPULAR	1 (0.3%)

Source: ADAE dataset using JReview (Reviewer's Analysis)

Subject 1541-4147 experienced immune reconstitution inflammatory syndrome (IRIS) that manifested as left eye zoster ophthalmicus and led to hospitalization approximately two months after initiating DRV/co and TDF/FTC. The event resolved with acyclovir treatment and continuation of study drug. Association of IRIS with initiation of ART is well known and labeled as a Warning and Precaution in the current DRV label.

The serious, drug-related rash events are reviewed with the rash events that led to treatment discontinuation in Section 8.2.3 due to the similar nature of the reports.

From Week 24 through the Safety Update Report, 25 additional subjects experienced any treatment-emergent SAE for a total of 40 (12.8%) subjects. No additional serious pyrexia or rash events occurred after Week 24. SAEs reported in more than one subject since the Week 24 safety report were pneumonia, suicide attempt, and abdominal pain, all of which occurred in two subjects each and none of which were related to study drug according to the investigator. Overall, SAEs in 35 of 40 subjects were considered not related to study drug by the investigator; based on a review of all narratives, these assessments are reasonable.

Since the safety report at Week 24, one subject (Subject 1780-4245) experienced ectopic pregnancy, which the investigator reported as having an unknown relationship to study drug exposure. The Applicant assessed the patient's ectopic pregnancy as likely a background event, which is a reasonable assessment at this time. One subject (Subject 0729-4313) experienced myocardial infarction, which the investigator assessed as having an unknown relationship to study drug. The event occurred almost two years after initiation of DRV/co and TDF/FTC in a 52-year-old male of African descent with hyperlipidemia and hypertension. Causality assessment is difficult, particularly with underlying cardiac risk factors.

Two SAEs of suicide attempt prompted a review of all SAEs reported for the SOC Psychiatric Disorders. Table 5 describes the psychiatric-related SAEs, all of which had plausible alternate causes.

Table 5: SAEs of Interest – Psychiatric Disorders Occurring in Study GS-US-216-0130

Subject ID	Event(s)	Treat-ment d/c	Related (Investigator/Reviewer)	Possible Alternate Cause/Confounders	Proposed Labeling
0754-4070	Suicide attempt	N	No / Unlikely	Recent discontinuation of bipolar medications	None
1534-4305	Suicide attempt	N	No / Unlikely	Unspecified traumatic life events; under the influence of marijuana and ethanol at time of event	None
1236-4291	Suicidal ideation Depression	N	No / Unlikely	Recent discontinuation of multiple psychiatric medications	None
0754-4216	Anxiety	Y	No / Unlikely	Pre-existing anxiety and depression; switched to Stribild	None

d/c = discontinuation

Source: Narrative review of SAEs through Week 48 (Reviewer’s Analysis)

8.2.3 Dropouts and/or Discontinuations

A total of 15 (4.8%) subjects experienced an AE leading to discontinuation of study drug through Week 24. The most common AE leading to discontinuation of study drug by System Organ Class (SOC) was “Skin and Subcutaneous Disorders” occurring in 7 (2.2%) subjects. Additional AEs resulting in treatment discontinuation and occurring in more than one subject were hypersensitivity and nausea. Table 4 lists all AEs leading to study drug discontinuation by SOC and PT.

Table 6. AEs Leading to Study Drug Discontinuation in Study GS-US-216-0130

Dictionary-Derived Term	Number of subjects (%)
<i>SYSTEM ORGAN CLASS</i>	<i>DRV/co</i>
<i>PREFERRED TERM</i>	<i>(N=313)</i>
Any AE Leading to Study Drug Discontinuation	15 (4.8%)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	7 (2.2%)
DERMATITIS ALLERGIC	1 (0.3%)
RASH	3 (1.0%)
RASH MACULAR	1 (0.3%)
RASH MACULO-PAPULAR	3 (1.0%)
RASH VESICULAR	1 (0.3%)
IMMUNE SYSTEM DISORDERS	2 (0.6%)
HYPERSENSITIVITY	2 (0.6%)

Table 6. AEs Leading to Study Drug Discontinuation in Study GS-US-216-0130

Dictionary-Derived Term	Number of subjects (%)
<i>SYSTEM ORGAN CLASS</i>	<i>DRV/co (N=313)</i>
<i>PREFERRED TERM</i>	
GASTROINTESTINAL DISORDERS	2 (0.6%)
DYSPEPSIA	1 (0.3%)
NAUSEA	2 (0.6%)
VOMITING	1 (0.3%)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	1 (0.3%)
IDIOPATHIC THROMBOCYTOPENIC PURPURA	1 (0.3%)
INFECTIONS AND INFESTATIONS	1 (0.3%)
MYCOBACTERIUM AVIUM COMPLEX INFECTION	1 (0.3%)
NERVOUS SYSTEM DISORDERS	2 (0.6%)
DYSGEUSIA	1 (0.3%)
HEADACHE	1 (0.3%)

Source: ADAE dataset using JReview (Reviewer's Analysis)

Narratives for treatment discontinuations due to rash and hypersensitivity were very similar in nature and are discussed together (Subjects 2154-4111, 2843-4190, 0121-4113, 0407-4100, 0589-4316, 0991-4067, 1950-4269, 1978-4069, 2157-4130). All subjects were also taking TDF/FTC. The investigator assessed these AEs as serious (medically significant) in two subjects, severe (Grade 3) in three subjects, and mild or moderate (Grade 1-2) in four subjects. Rash and hypersensitivity events assessed as serious or Grade 3 are described below.

Subject 2843-4190

A 33-year-old male developed a maculopapular rash on his thorax, arms, and legs on Day 11 after initiating DRV/co and TDF/FTC. He was not taking any other medications. He stopped the study drugs and received diphenhydramine for 10 days until the rash resolved. The investigator assessed the rash as serious (medically significant), most likely related to DRV, and possibly related to FTC.

Subject 0121-4113

A 36-year-old male developed a diffuse rash that spread to the face on Day 7 after initiating DRV/co and TDF/FTC. He was not taking any other medications. He received diphenhydramine, but the rash worsened from Grade 2 to Grade 3. He discontinued study drugs, and the rash resolved on Day 11. The investigator assessed the rash as related to DRV/co.

Subject 0589-4316

A 49-year-old female developed pruritus on her hands and feet on Day 24 after initiating DRV/co and TDF/FTC. On Day 25 the reaction progressed to a diffuse erythematous rash, some angioedema, and pruritus at which time study drugs were discontinued. Liver enzymes, white blood cell count, and eosinophil count were normal. The next day, the subject had no oral lesions, blistering, or noticeable angioedema. The subject received antihistamines and prednisone, and the event

resolved over a few days. The investigator assessed the event as Grade 3 and related to study medications.

Subject 2157-4130

A 24-year-old male developed a Grade 2 non-pruritic rash without oropharynx involvement on Day 10 after initiating DRV/co and TDF/FTC. Liver enzymes, white blood cell count, and eosinophil count were normal. He received antihistamines and continued study drugs. On Day 80 the subject experienced Grade 3 allergic dermatitis with unchanged laboratory results. He received methylprednisolone and discontinued study drugs, and the rash resolved on Day 86.

There were no cases of Stevens-Johnson syndrome or toxic epidermal necrolysis. All nine events were related to study drug, most likely DRV and possibly COBI, and all resolved with discontinuation of DRV/co and treatment with antihistamines and/or corticosteroids. The events are consistent with the current labels for DRV and COBI as single agents.

Since Week 24, two additional subjects discontinued study drug due to an AE, one of which was the aforementioned anxiety event listed in Table 5 in Section 8.2.2. The second AE resulting in treatment discontinuation was proximal renal tubulopathy in a subject (Subject 1236-4051) also taking TDF/FTC. The event is consistent with the proximal renal tubulopathy events seen with COBI and TDF (in combination with either EVG or ATV) and labeled for COBI.

8.3 Supportive Safety Results

8.3.1 Common Adverse Events

All tables in this section were produced in JReview using the ADAE dataset and represent this reviewer’s analyses.

Table 7 provides an overview of treatment-emergent clinical AEs by severity and relatedness. Four of the five subjects with Grade 3-4 study drug-related AEs experienced rash (2) or hypersensitivity (2).

Table 7. Overview of Treatment-Emergent AEs Occurring in Study GS-US-216-0130

Treatment-Emergent AE	Number of subjects (%) DRV/co (n=313)
Any AE	275 (87.9%)
Any AE Grade 2-4	139 (44.4%)
Any AE Grade 3-4	18 (5.8%)
Any Study Drug-Related AE	123 (39.3%)
Any Study Drug-Related AE Grade 2-4	42 (13.4%)
Any Study Drug-Related AE Grade 3-4	5 (1.6%)

The most common AEs by SOC irrespective of grade or causality were Gastrointestinal Disorders (52%), Infections and Infestations (49%), and Skin and Subcutaneous Tissue Disorders (28%). The most common AEs by PT irrespective of grade or causality reported in $\geq 5\%$ of DRV/co-treated subjects included diarrhea, nausea, upper respiratory tract infection, headache, rash, vomiting, fatigue, flatulence, nasopharyngitis, and sinusitis.

Table 8 lists Grade 2-4 AEs by PT regardless of causality and occurring in at least 2% of subjects. The Applicant's grouped terms for rash did not include dermatitis, dermatitis allergic, drug eruption, rash vesicular, or urticaria. Addition of these rash terms resulted in a slightly higher percentage of rash events.

Table 8. Treatment-Emergent AEs by Preferred Term Regardless of Causality Occurring in At Least 2% of Subjects in Study GS-US-216-0130

Preferred Term	Number of subjects (%) DRV/co (n=313)
RASH (Reviewer's Grouped Terms ¹)	21 (6.7%)
RASH (Applicant's Grouped Terms ²)	18 (5.8%)
DIARRHEA (Applicant's Grouped Terms ³)	16 (5.1%)
UPPER RESPIRATORY TRACT INFECTION	11 (3.5%)
NAUSEA	10 (3.2%)
BRONCHITIS	6 (1.9%)
DEPRESSION	6 (1.9%)
SINUSITIS	6 (1.9%)
HEADACHE	5 (1.6%)
HYPERSENSITIVITY (Applicant's Grouped Terms ⁴)	5 (1.6%)
VOMITING	5 (1.6%)

- 1 Dermatitis, Dermatitis allergic, Drug eruption, Generalized erythema, Rash, Rash erythematous, Rash generalized, Rash macular, Rash maculo-papular, Rash morbilliform, Rash papular, Rash pruritic, Rash vesicular, Urticaria
- 2 Generalized erythema, Rash, Rash erythematous, Rash generalized, Rash macular, Rash maculo-papular, Rash morbilliform, Rash papular, Rash pruritic
- 3 Diarrhea, Frequent bowel movements
- 4 Hypersensitivity, Drug hypersensitivity

Table 9 lists Grade 2-4 AEs by PT at least possibly attributed to study drug by the investigator and occurring in at least 2% of subjects. Both versions of grouped terms for rash resulted in an equal number of events. The terms are consistent with drug-related AEs in the DRV and COBI labels.

Table 9. Treatment-Emergent Drug-Related AEs by Preferred Term Occurring in At Least 2% of Subjects in Study GS-US-216-0130

Preferred Term	Number of subjects (%) DRV/co (n=313)
RASH (Reviewer’s Grouped Terms ¹)	27 (4.5%)
RASH (Applicant’s Grouped Terms ²)	27 (4.5%)
NAUSEA	7 (2.2%)
DIARRHEA (Applicant’s Grouped Terms ³)	5 (1.6%)

- 1 Dermatitis, Dermatitis allergic, Drug eruption, Generalized erythema, Rash, Rash erythematous, Rash generalized, Rash macular, Rash maculo-papular, Rash morbilliform, Rash papular, Rash pruritic, Rash vesicular, Urticaria
- 2 Generalized erythema, Rash, Rash erythematous, Rash generalized, Rash macular, Rash maculo-papular, Rash morbilliform, Rash papular, Rash pruritic
- 3 Diarrhea, Frequent bowel movements

8.3.2 Laboratory Findings

The laboratory analysis in Table 10 reflects treatment-emergent laboratory abnormalities that increased at least one toxicity grade from baseline. Individual subjects are counted once for each laboratory abnormality, with the maximum toxicity grade reported. Missing baseline values are assumed to be Grade 0.

Interpretation of the incidence of laboratory abnormalities with DRV/co is limited in an open-label, single-arm study, but no new safety concerns emerged through Week 24 in this study. Grade 3-4 liver or pancreatic enzyme abnormalities were not associated with clinical AEs, including pancreatitis, in any subject. No subject had concurrent ALT and bilirubin elevations consistent with Hy’s law criteria; and Grade 3 triglyceride elevations were not associated with pancreatitis.

The percentage of subjects who experienced Grade 1 serum creatinine elevations is consistent with the known safety profile of cobicistat. A similar percentage of Grade 1 serum creatinine elevations occurred in clinical trials with cobicistat and atazanavir (see Dr. Peter Miele’s Clinical Review for the original cobicistat NDA).

Grade 3-4 neutropenia was not associated with any clinically significant or related AEs, including infections. One subject experienced Grade 4 thrombocytopenia, which was associated with the SAE idiopathic thrombocytopenic purpura noted in Section 8.2.2 and was considered unlikely related to study drug. One subject experienced Grade 3 anemia along with pelvic inflammatory disease, both of which are noted as SAEs in Section 8.2.2 and were considered not related to study drug. Both events resolved with a blood transfusion and antibiotics.

Table 10. Treatment-Emergent Laboratory Abnormalities in Study GS-US-216-0130

Laboratory Parameter	Limit	DRV/co (n=313)	
		n	%
Chemistry Laboratory Values			
Alkaline Phosphatase			
Grade 1	1.25 – 2.50 x ULN	4	1
Grade 2	>2.50 – 5.00 x ULN	3	1
Grade 3	>5.00 – 10.00 x ULN	0	0
Grade 4	>10.00 x ULN	0	0
ALT			
Grade 1	1.25 – 2.50 x ULN	20	6
Grade 2	>2.50 – 5.00 x ULN	7	2
Grade 3	>5.00 – 10.00 x ULN	5	2
Grade 4	>10.00 x ULN	2	1
AST			
Grade 1	1.25 – 2.50 x ULN	20	7
Grade 2	>2.50 – 5.00 x ULN	18	6
Grade 3	>5.00 – 10.00 x ULN	4	1
Grade 4	>10.00 x ULN	2	1
Total Bilirubin			
Grade 1	>1.0 – 1.5 x ULN	10	3
Grade 2	>1.5 – 2.5 x ULN	4	1
Grade 3	>2.5 – 5.0 x ULN	1	<1
Grade 4	>5.0 x ULN	0	0
Serum Creatinine (mg/dL)			
Grade 1	>1.5 – 2.0	22	7
Grade 2	>2.0 – 3.0	1	<1
Grade 3	>3.0 – 6.0	0	0
Grade 4	>6.0	0	0
Amylase			
Grade 1	>1.0 – 1.5 x ULN	47	15
Grade 2	>1.5 – 2.0 x ULN	17	6
Grade 3	>2.0 – 5.0 x ULN	6	2
Grade 4	>5.0 x ULN	0	0
Lipase			
Grade 1	>1.0 – 1.5 x ULN	14	5
Grade 2	>1.5 – 2.0 x ULN	18	3
Grade 3	>2.0 – 5.0 x ULN	2	1
Grade 4	>5.0 x ULN	3	1
Non-fasting Serum Glucose, Hyperglycemia (mg/dL)			
Grade 1	>ULN – 160	69	22
Grade 2	>160 – 250	16	5
Grade 3	>250 – 500	0	0
Grade 4	>500	1	<1

Table 10. Treatment-Emergent Laboratory Abnormalities in Study GS-US-216-0130

Laboratory Parameter	Limit	DRV/co (n=313)	
		n	%
Lipid Laboratory Values			
Total Cholesterol, Fasting (mg/dL)			
Grade 1	200 – 239	47	16
Grade 2	>239 – 300	21	7
Grade 3	>300	3	1
Triglycerides, Fasting (mg/dL)			
Grade 2	500 – 750	3	1
Grade 3	>750 – 1,200	4	1
Grade 4	>1,200	0	0
Hematologic Laboratory Values			
Leukocytes (cells/mm ³)			
Grade 1	2,000 – 2,500	3	1
Grade 2	1,500 – <2,000	1	<1
Grade 3	1,000 – <2,500	0	0
Grade 4	<1,000	0	0
Absolute Neutrophil Count (cells/mm ³)			
Grade 1	1,000 – 1,300	15	5
Grade 2	750 – <1,000	7	2
Grade 3	500 – <750	2	1
Grade 4	<500	2	1
Platelets (cells/mm ³)			
Grade 1	100,000 – <125,000	6	2
Grade 2	50,000 – <100,000	1	<1
Grade 3	25,000 – 50,000	0	0
Grade 4	<25,000	1	<1
Hemoglobin (g/dL)			
Grade 1	8.5 – 10.0	4	1
Grade 2	7.5 – <8.5	0	0
Grade 3	6.5 – <7.5	1	<1
Grade 4	<6.5	0	0

Source: ADLB dataset using JReview

8.4 Additional Submissions

Renal Impairment Study: GS-US-236-0118

Study 118 is an ongoing Phase 3 open-label safety study evaluating cobicistat in HIV-1-infected patients with mild to moderate renal impairment. The submission contains Week 48 analysis in which subjects on stable ART switched from ritonavir to cobicistat and received at least 1 dose of DRV/co (n=21).

There were no deaths or kidney-related SAEs. Two cardiac-related SAEs occurred in subjects (6259-2060 and 1560-2005) greater than 60 years of age with a history of cigarette smoking and hypercholesterolemia, respectively; both subjects also had mild-to-moderate renal impairment per study inclusion criteria. Significant confounders provide a plausible alternate explanation for each event. This study did not raise any new safety concerns for DRV/co.

9. Pediatrics

The NDA does not contain pediatric data. The Applicant submitted the Agreed Initial Pediatric Study Plan for DRV/co FDC; the Agency previously agreed with the Applicant's planned waiver and deferral requests. The Applicant submitted a partial waiver request for children < 3 years of age and ≥ 3 years of age weighing < 15 kg and a deferral request for children ≥ 3 to < 18 years of age weighing ≥ 15 kg. A partial waiver for children < 3 years of age is necessary because of toxicology concerns with DRV as a single agent in this patient population. The deferral request is reasonable because different DRV/co FDC oral formulations are necessary for weight-based dosing and cannot be developed until there is an identified pediatric dose recommendation for COBI as a single agent in combination with DRV. Determination of pediatric dosing with DRV and COBI as single agents is ongoing through another sponsor (Gilead). The deferral and waiver requests was reviewed by the Pediatric Review Committee (PeRC) on December 3, 2014.

10. Labeling

COBI as a single agent received approval during this NDA review cycle. Overall, the following edits were made throughout the DRV/co label:

- Updated to maintain consistency with the COBI label as it pertains to DRV/co.

(b) (4)

Additional major revisions proposed to the Applicant are as follows:

U.S. Package Insert (USPI)

INDICATIONS AND USAGE

Clarified and simplified as follows: “PREZCOBIX is indicated in combination with other antiretroviral agents for the treatment of human immunodeficiency virus (HIV-1) infection in treatment-naïve and treatment-experienced adults with no darunavir resistance-associated substitutions (V11I, V32I, L33F, I47V, I50V, I54L, I54M, T74P, L76V, I84V, L89V).”

DOSAGE AND ADMINISTRATION



CONTRAINDICATIONS

- Added colchicine in patients with renal and hepatic impairment based on a pending labeling supplement for Prezista (i.e., colchicine in patients with renal and hepatic impairment)
- Added lurasidone based on recommendations from the Division of Psychiatry Products in response to a consult request.

WARNINGS AND PRECAUTIONS

Added “Antiretrovirals Not Recommended” which include other antiretroviral drugs that require pharmacokinetic boosting (i.e., another PI or EVG) and products containing DRV, COBI, or RTV

ADVERSE REACTIONS

The Applicant agreed to (b) (4) (b) (4) retain a general statement to convey to prescribers that clinical experience was gained with DRV/co. In response, the following statement was added, “One single arm clinical trial was conducted with darunavir and cobicistat administered as single entities in 313 HIV-infected subjects. Adverse reactions evaluated through Week 24 did not differ substantially from those reported in clinical trials with darunavir/ritonavir.”

DRUG INTERACTIONS

Table 4

Added interaction recommendations for newer oral anticoagulants, anticancer drugs, and immunosuppressants with darunavir based on a pending labeling supplement for Prezista

U.S. Patient Package Insert (USPPI)

- Added information regarding COBI-related kidney effects

(b) (4)

11. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action

I recommend approval of darunavir/cobicistat 800/150 mg tablet, a fixed-dose HIV protease inhibitor and CYP3A inhibitor that increases systemic DRV exposures, in combination with other antiretroviral agents for the treatment of HIV-1 infection in adults. The recommendation is based on the BE of the DRV/co FDC tablet compared to the approved single-agent products DRV and COBI for the same indication and is supported by clinical efficacy and safety data with DRV and COBI single agents in HIV-infected subjects.

- Risk Benefit Assessment

Efficacy and safety data in the supportive clinical trial do not alter the risk-benefit assessments made during the original NDA reviews for DRV and for COBI. Although interpretation of safety data is limited by the single-arm, open-label trial design, no new safety concerns arise from the clinical trial. Safety of DRV/co is consistent with current labeling for DRV and COBI single agents.

- Recommendation for Postmarketing Risk Evaluation and Management Strategies

The NDA contains no safety information necessitating a REMS.

- Recommendation for other Postmarketing Requirements and Commitments

A PMR will be issued for pediatric studies under the Pediatric Research Equity Act (PREA) and consistent with the Agreed Initial Pediatric Study Plan. No additional PMRs are recommended.

Of note, PMRs are in place for DRV and COBI as single agents for pediatric studies and

(b) (4)

[Redacted]

Clinical Review
 Sarita Boyd
 NDA 205395
 Prezcobix (darunavir/cobicistat)

APPENDIX

Clinical Investigator Financial Disclosure

Application Number: 205395
 Submission Date(s): March 31, 2014
 Applicant: Janssen
 Product: darunavir/cobicistat

Reviewer: Sarita Boyd, Pharm.D.
 Date of Review: December 3, 2014
 Covered Clinical Study (Name and/or Number): TMC114IFD1003

Was a list of clinical investigators provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request list from applicant)
Total number of investigators identified: <u>5</u>		
Number of investigators who are sponsor employees (including both full-time and part-time employees): <u>0</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>0</u>		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes <input type="checkbox"/>	No <input type="checkbox"/> (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes <input type="checkbox"/>	No <input type="checkbox"/> (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>1</u>		
Is an attachment provided with the reason:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request explanation from applicant)

Four of the five investigators reported having no disclosed financial interests/arrangements. The sponsor stated that its parent company, Johnson & Johnson, was not able to obtain financial disclosure for one clinical investigator who participated in support of this application because no response was received or no forwarding address was available. The Office of Regulatory Affairs' inspection for the clinical site for Trial TMC114IFD1003 did not result in any 483 observations to suggest any evidence of submission of false data. Therefore, lack of

Clinical Review
Sarita Boyd
NDA 205395
Prezcobix (darunavir/cobicistat)

disclosure despite due diligence for one investigator should not affect the approvability of the application.

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

/s/

SARITA D BOYD
12/22/2014

MARY E SINGER
12/22/2014

I concur with Dr. Boyd's review and recommendations as amended with financial disclosure information.

Clinical Review

Date	December 19, 2014
From	Sarita Boyd, Pharm.D.
Subject	Clinical Review
NDA/BLA # Supplement#	NDA 205395
Applicant	Janssen
Date of Submission	March 28, 2014
PDUFA Goal Date	January 31, 2015
Proprietary Name / Established (USAN) names	Prezcobix (Darunavir/cobicistat)
Dosage forms / Strength	Tablet / 800 mg of darunavir and 150 mg of cobicistat
Proposed Indication(s)	Fixed dose combination indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection in adults
Recommended:	Approval

1. Introduction

This review summarizes the main issues for NDA 205395, which includes Week 24 safety and efficacy data from Protocol GS-US-216-0130: *A Phase 3b, Open-Label, Single Arm Study to Evaluate the Safety and Efficacy of Cobicistat-boosted Darunavir Plus Two Fully Active Nucleoside Reverse Transcriptase Inhibitors in HIV-1 Infected, Antiretroviral Treatment-Naïve and -Experienced Adults with No Darunavir Resistance-associated Mutations*. Additionally, the review considers data from the bioavailability (BA) and pivotal bioequivalence (BE) studies, TMC114IFD1001 and TMC114IFD1003, respectively.

2. Background

Darunavir (DRV) is an HIV protease inhibitor (PI) approved in combination with low-dose ritonavir (RTV), a cytochrome P450 3A (CYP3A) inhibitor that increases DRV exposure. Darunavir coadministered with ritonavir (DRV/r) and other antiretroviral agents is indicated for treatment of HIV-1 infection with two different dosage recommendations based on past treatment experience. Once daily DRV 800 mg with RTV 100 mg is recommended for treatment-naïve and -experienced adults with no DRV resistance-associated substitutions. DRV/r is not available as a fixed-dose combination (FDC) tablet.

Cobicistat (COBI) received approval on September 24, 2014 as a CYP3A inhibitor indicated to increase systemic exposure of DRV (once daily dosing regimen) or atazanavir (ATV) in combination with other antiretroviral agents for treatment of HIV-1 infection. The Applicant

is proposing approval of a FDC product containing DRV and COBI, two currently approved drugs.

The Applicant has developed darunavir/cobicistat (DRV/co) as a FDC product in collaboration with Gilead Sciences, Inc. The bioequivalence (BE) study results are considered pivotal for approval of this application of DRV/co 800/150 mg as a FDC tablet indicated in combination with other antiretroviral agents for treatment of HIV-1 infection in adults. A clinical trial with DRV/co was not required because DRV and COBI are approved as individual drugs, and pharmacokinetic studies demonstrating bioequivalence of the FDC tablet to the approved, individual components are adequate. Efficacy and safety of DRV/co is extrapolated from DRV/r clinical trials; the link between DRV and COBI as single drugs and DRV/r was established during the COBI NDA review. This NDA includes safety and efficacy results for Protocol GS-US-216-0130 as a supportive clinical trial.

3. CMC/Device

DRV/co FDC tablets contain 800 mg of DRV (b)(4) and 150 mg of COBI (b)(4). Development of the FDC is based on formulation of the DRV 800 mg tablet. (b)(4)

The tablets are (b)(4)-shaped and film-coated with the color pink. The core tablet contains the following inactive ingredients: hypromellose, colloidal silicon dioxide, silicified microcrystalline cellulose, crospovidone, and magnesium stearate. The film coating is composed of (b)(4) Pink, which contains polyvinyl alcohol-partially hydrolyzed, titanium dioxide, (b)(4), tac, iron oxide red, and iron oxide black. The proposed shelf life is 24 months in all climatic zones. Please refer to the CMC Reviews by Drs. Fuqiang Liu and Krishnakali Gosh for complete details.

4. Nonclinical Pharmacology/Toxicology

Nonclinical studies were not conducted with DRV in combination with COBI. The combined use of DRV and COBI is not expected to produce clinically relevant additive or synergistic effects. Additionally, DRV and COBI are approved as single agents to use in combination for the same indication proposed in this NDA. Comprehensive nonclinical programs for single agents DRV and COBI have been conducted by the Applicant and Gilead Sciences, respectively. The nonclinical program for COBI included safety pharmacology, nonclinical pharmacokinetics, and toxicology of COBI as a single agent and in combination with ATV or elvitegravir (EVG). Please refer to the original NDA reviews for DRV and COBI as single agents for complete details.

5. Clinical Pharmacology/Biopharmaceutics

The development program for DRV/co FDC is based on comprehensive development and approval of DRV and COBI as single agents and pharmacokinetic (PK) bridging of DRV/co FDC to the single agents. Study TMC114IFD1001 evaluated relative BA of DRV with two

different DRV/co 800/150 mg FDC formulations compared to DRV/r 800/100 mg in 36 healthy subjects following repeated once daily dosing under fed conditions. Results from this study led to selection of one of these formulations, with use of a different color coating, to move forward in development. Study TMC114IFD1003 evaluated BE of DRV with the selected DRV/co 800/150 mg FDC formulation compared to DRV 800 mg and COBI 150 mg administered as single agents in 133 subjects following single doses under fasted and fed (standard meal) conditions. Additionally, Study TMC114IFD1003 assessed the effect of a high-fat breakfast on the BA of the selected DRV/COBI FDC formulation (food effect).

Overall, Study TMC114IFD1003 showed acceptable BE of DRV/co FDC compared to the single agents under fasted and fed (standard meal) conditions. Although the study formulation (white) differs from the commercial formulation (pink) in its color coating, the change does not impact the BE study results per the Biopharmaceutics Reviewer, Dr. Minerva Hughes, because the film coating is nonfunctional.

A high-fat meal (vs. fasting) increased the area under the concentration time curve (AUC) and maximum plasma concentration (C_{max}) for DRV by 70% and 127%, respectively, with the FDC. However, absolute DRV C_{max} values overlap for DRV/co FDC administered with either a standard meal (i.e., recommended administration) or a high fat meal. DRV AUCs observed or estimated in the original DRV NDA (with RTV) were comparable or higher than those observed in the DRV/co FDC food effect study. In the original NDA for DRV/r once daily dosing, there were no apparent relationships between DRV exposures and maximum changes in laboratory parameters or occurrence of adverse events (AEs). Therefore, the increased DRV exposures occurring when DRV/co is coadministered with a high fat meal are not expected to be clinically relevant.

Please refer to the Biopharmaceutics Review by Dr. Minerva Hughes and the Clinical Pharmacology Review by Dr. Stanley Au for complete details.

6. Clinical Microbiology

Study GS-US-216-0130 provides supportive virology data for the use of DRV and COBI as single agents in treatment-naïve and -experienced subjects with no DRV resistance-associated substitutions, which are bridged to the FDC via the pivotal, BE study. In the Week 24 analysis of Study GS-US-216-0130, 10 of 313 subjects who received at least 1 dose of study drug (DRV/co) met the criteria for resistance test analysis. One treatment-experienced subject developed a DRV resistance-associated substitution, I84I/V, and one treatment-naïve subject developed a secondary PI substitution, I93I/L. Phenotypic resistance to DRV or other PIs was not seen in either of these subjects or in any other subjects. One treatment-experienced subject developed 2 reverse transcriptase (RT) substitutions, L74I/L and P225H/P, which are associated with resistance to abacavir and didanosine and to efavirenz, respectively. M184I/V was present at baseline and on treatment in this subject. Of note, the subject's background regimen in the study included emtricitabine, tenofovir, and zidovudine. Although interpretation of results is relatively limited in an open-label, single arm trial with Week 24

results, the low rate of resistance development with DRV/co is consistent with that observed for DRV/r in the same population. Please refer to the Clinical Virology review by Dr. Takashi Komatsu for complete details.

7. Clinical Efficacy

Efficacy Summary

Study GS-US-216-0130 is an ongoing Phase 3b, open-label, single arm, multicenter study evaluating the safety and efficacy of DRV/co (as single agents) coadministered with 2 fully active NRTIs in HIV-1 infected, antiretroviral treatment-naïve (n=295) and treatment-experienced (n=18) adults with no DRV resistance-associated mutations. At baseline, the median age of subjects was 35 years, 11% were female, 40% were non-white, 42% had HIV-1 RNA >100,000 copies/mL, and 19% had CD4+ cell count <200 cells/mm³. At 24 weeks, 82% of subjects treated with darunavir and cobicistat plus two nucleoside reverse transcriptase inhibitors achieved HIV RNA <50 copies/mL. Although interpretation of clinical efficacy in a single-arm trial is somewhat limited, the results provide support that DRV and COBI have adequate antiviral activity.

7.1 Indication

The proposed indication for DRV/co 800/150 mg FDC is for use in combination with other antiretroviral agents for the treatment of HIV-1 infection in adults. The recommended patient population includes treatment-naïve and -experienced patients with no DRV resistance-associated substitutions, which is the same for DRV/co administered as single agents (see approved prescribing information for TYBOST [cobicistat]) and DRV/r 800/100 mg once daily regimen (see approved prescribing information for PREZISTA [darunavir]).

7.1.1 Methods

The indication is based on clinical pharmacology data from Studies TMC114IFD1001 and TMC114IFD1003, which compared BA and BE of DRV/co FDC to DRV/r and DRV/co as single agents, respectively. See Section 5 for discussion of these studies.

There are no clinical efficacy data with the DRV/co administered as the FDC formulation. Study GS-US-216-0130 provides supportive clinical data for DRV/co administered as single agents, (b) (4).

The efficacy review includes Week 24 data analysis of GS-US-216-0130 using JReview.

7.1.2 Demographics

The full analysis set includes 313 HIV-infected subjects who received at least 1 dose of DRV/co. The majority of subjects were treatment-naïve (n=295) vs. treatment-experienced

(n=18). All subjects were enrolled at 56 U.S. sites. The majority of subjects were male (90%) and white (60%) or black (35%). Five subjects (1.6%) were hepatitis B surface antigen positive, and 8 subjects (2.6%) were HCV seropositive. Select demographic and baseline characteristics are displayed in Table 1 and match the Applicant's analysis.

Table 1. GS-US-216-0130: Demographic and Baseline Characteristics

Characteristic	Treatment-naïve (n=295)	Treatment-experienced (n=18)	Total (n=313)
Age			
Median (Min, Max)	34 (18, 72)	48 (22, 69)	35 (18, 72)
Sex			
Male	266 (90%)	13 (72%)	279 (89%)
Female	29 (10%)	5 (28%)	34 (11%)
Race			
White	176 (60%)	11 (61%)	187 (60%)
Black or African	101 (34%)	7 (39%)	108 (35%)
American Indian	4 (1%)	0	4 (1%)
Asian	4 (1%)	0	4 (1%)
Other	10 (3%)	0	10 (3%)
Ethnicity			
Hispanic or Latino	64 (22%)	4 (22%)	68 (22%)
Not Hispanic or Latino	231 (78%)	14 (78%)	245 (78%)
Baseline HIV-1 RNA			
Median (Min, Max)	4.8 (2.6, 7.0)	5.0 (2.7, 6.8)	4.8 (2.6, 7.0)
≤ 100,000 copies/mL	173 (59%)	9 (50%)	182 (58%)
> 100,000 copies/mL	122 (41%)	9 (50%)	131 (42%)
Baseline CD4 Cell Count			
Median (Min, Max)	370 (6, 1473)	107 (5, 643)	361 (5, 1473)
≤ 200 cells/mm ³	47 (16%)	12 (67%)	59 (19%)
> 200 cells/mm ³	248 (84%)	6 (33%)	254 (81%)

Source: ADSL and ADLB datasets

7.1.3 Subject Disposition

Of 313 subjects in the full analysis set, 39 subjects (12.5%) discontinued study drug before the Week 24 data cutoff date. The most common reason for premature discontinuation was adverse events (15 subjects, 4.8%) followed by lost to follow-up (11 subjects, 3.5%). Table 2 displays subject disposition, which matches the Applicant's analysis.

Table 2. GS-US-216-0130: Subject Disposition

Subject Disposition	Treatment-naïve	Treatment-experienced	Total
Full Analysis Set (Received ≥ 1 Dose)	295	18	313
Discontinued Study Drug Before W24	36	3	39
Adverse event	15	0	15

Table 2. GS-US-216-0130: Subject Disposition

Subject Disposition	Treatment-naïve	Treatment-experienced	Total
Investigator's discretion	1	0	1
Lack of efficacy	0	0	0
Lost to follow-up	9	2	11
Pregnancy	0	0	0
Protocol violation	1	0	1
Subject non-compliance	6	0	6
Withdrew consent	4	1	5
Taking Study Drug at W24 Data Cut-off	259	15	274

Source: ADSL dataset

7.1.4 Analysis of Primary Efficacy Endpoint

Study GS-US-216-0130 had no pre-specified primary efficacy endpoint.

7.1.5 Analysis of Secondary Efficacy Endpoints

Secondary efficacy endpoints include the proportion of subjects achieving HIV RNA <50 copies/mL as determined by the FDA-defined snapshot analysis at Weeks 24 and 48. This reviewer's analysis of Week 24 efficacy results are displayed in Table 3 and match the Applicant's analysis. As previously mentioned, the study is supportive but not pivotal, and efficacy in this single arm trial was a secondary endpoint.

Table 3. GS-US-216-0130: Week 24 Efficacy Analysis (Snapshot Analysis, Full Analysis Set)

HIV RNA Category	Treatment-naïve (n=295)	Treatment-experienced (n=18)	Total (n=313)
Virologic Success at W24			
HIV RNA < 50 c/mL	247 (84%)	11 (61%)	258 (82%)
95% Confidence Interval	79-88%	36-83%	78-87%
Virologic Failure at W24	29 (10%)	7 (39%)	36 (12%)
HIV RNA ≥ 50 c/mL	17 (6%)	5 (28%)	22 (7%)
Discontinued Study Drug and Last HIV RNA ≥ 50 c/mL	12 (4%)	2 (11%)	14 (5%)
No Virologic Data at W24 Window	19 (6%)	0	19 (6%)
Discontinued Due to AE	14 (5%)	0	14 (5%)
Discontinued Due to Other Reasons and Last HIV RNA < 50 c/mL	3 (1%)	0	3 (1%)
Missing Data on Study Drug	2 (<1%)	0	2 (<1%)

Source: ADEFFOUT dataset (Reviewer's analysis)

Overall, the results demonstrate reasonable ability of DRV/co plus 2 NRTIs to suppress HIV RNA at Week 24. Although full interpretation of efficacy is challenging without a comparator

group, the results raise no general concerns about 24-week efficacy of DRV/co in treatment-naïve subjects. The treatment-experienced group is too small to interpret separately.

Historically, the proportion of subjects with HIV RNA <50 copies/mL at Week 48 in treatment-naïve subjects randomized to DRV/r 800/100 mg once daily vs. lopinavir/ritonavir was 84% vs. 78%, respectively (Trial TMC114-C211). In Trial TMC114-C229 which enrolled treatment-experienced subjects with no DRV resistance-associated substitutions and randomized subjects to DRV/r 800/100 mg once daily or DRV/r 600/100 mg twice daily, 69% of subjects in both groups achieved HIV RNA <50 copies/mL at Week 48. Study GS-US-216-0130 results cannot be directly compared to historical controls given different time points of measure of virologic suppression (Week 24 vs. 48) and different trial designs (open-label, single arm vs. randomized, double-blind). Nonetheless, Study GS-US-216-0130 provides supportive data for DRV/co efficacy.

7.1.6 Other Endpoints

Subjects experienced considerable increases in CD4 cell count from baseline through Week 24 with DRV/co plus 2 NRTIs. The mean (SD) increases from baseline CD4 cell count in treatment-naïve and -experienced subjects were 145 (132) cells/ μ L and 99 (162) cells/ μ L, respectively, at Week 24, based on observed data. The mean (SD) increases from baseline CD4% in treatment-naïve and -experienced subjects were 7.2% (4.5%) and 4.1% (3.3%), respectively.

8. Safety

Safety Summary

Overall, there are no new safety concerns for DRV/co that were not previously assessed during the NDA reviews for DRV and COBI as single agents and included in the DRV or COBI labels. Safety information for DRV/co is available for 313 subjects (295 treatment-naïve and 18 treatment-experienced) who received at least 1 dose of study drug in Study GS-US-216-0130. The most common AEs with DRV/co are generally consistent with either DRV/r once daily dosing or cobicistat-containing regimens, but the incidence of individual AEs cannot be directly compared across clinical trials because of the different trial designs. Interpretation of the incidence of AEs with DRV/co itself is also limited in an open-label, single-arm study. However, this trial supports safety of DRV/co.

8.1 Methods

The main source of data for the safety review is Study GS-US-216-0130, the ongoing Phase 3b, open-label, single arm study. The treatment-naïve and -experienced groups were combined for the safety review because the treatment-experienced group was too small to

evaluate separately and the safety results are expected to be similar across both groups. The study results were reviewed as follows:

- Week 24 data analysis using JReview (data cut date August 16, 2012)
- Week 48 narrative review of available reports for deaths, nonfatal SAEs, and AEs leading to treatment discontinuation (data cut date July 1, 2013)
- Safety update for new deaths and nonfatal SAEs (data cut date April 30, 2014)

The Applicant also submitted results from Study GS-US-236-0118, a Phase 3 single-arm, open-label safety study in patients with mild to moderate renal impairment. In this trial subjects with eGFR calculated by the Cockcroft-Gault equation (eGFR_{CG}) 50 to <90 mL/min enrolled in one of two cohorts to receive 96 weeks of treatment with Stribild (Cohort 1) or with DRV/co or ATV/co (Cohort 2). Subjects in Cohort 2 were virologically suppressed on DRV/r or ATV/r plus 2 NRTIs and had RTV replaced with COBI at baseline. In the Safety Update Report, the Applicant provided Week 48 interim analysis for subjects in Cohort 2; subjects who received DRV/co (n=21) are discussed in Section 8.4. For more details pertaining to the DRV/co group, please see the clinical review for NDA 203094 resubmission.

8.2 Major Safety Results

8.2.1 Deaths

No deaths occurred in Study GS-US-216-0130.

8.2.2 Nonfatal Serious Adverse Events (SAEs)

A total of 15 (4.8%) subjects experienced a treatment-emergent SAE through Week 24. The most common SAE by System Organ Class (SOC) was “Infection and Infestation” occurring in 3 (1.0%) subjects. SAEs by preferred term (PT) reported in more than one subject were pyrexia and rash, which occurred in two subjects each. Investigators considered 3 (1.0%) SAEs related or possibly related to study drug: immune reconstitution syndrome, rash, and maculopapular rash. Table 4 lists all SAEs by PT.

Table 4. All Treatment-Emergent SAEs Occurring in Study GS-US-216-0130

Preferred Term	Number of subjects (%) DRV/co (n=313)
Number of subjects experiencing any treatment-emergent SAE	15 (4.8%)
PYREXIA	2 (0.6%)
ANAEMIA	1 (0.3%)
IDIOPATHIC THROMBOCYTOPENIC PURPURA	1 (0.3%)
RETINAL DETACHMENT	1 (0.3%)
GASTRITIS	1 (0.3%)
BILE DUCT STONE	1 (0.3%)
BILIARY DYSKINESIA	1 (0.3%)
CHOLECYSTITIS ACUTE	1 (0.3%)

Table 4. All Treatment-Emergent SAEs Occurring in Study GS-US-216-0130

Preferred Term	Number of subjects (%) DRV/co (n=313)
HYPERSENSITIVITY	1 (0.3%)
IMMUNE RECONSTITUTION SYNDROME	1 (0.3%)
FURUNCLE	1 (0.3%)
PELVIC INFLAMMATORY DISEASE	1 (0.3%)
PILONIDAL CYST	1 (0.3%)
LACERATION	1 (0.3%)
CASTLEMAN'S DISEASE	1 (0.3%)
KAPOSI'S SARCOMA	1 (0.3%)
ALCOHOL ABUSE	1 (0.3%)
DRUG DEPENDENCE	1 (0.3%)
RASH	1 (0.3%)
RASH MACULO-PAPULAR	1 (0.3%)

Source: ADAE dataset using JReview (Reviewer's Analysis)

Subject 1541-4147 experienced immune reconstitution inflammatory syndrome (IRIS) that manifested as left eye zoster ophthalmicus and led to hospitalization approximately two months after initiating DRV/co and TDF/FTC. The event resolved with acyclovir treatment and continuation of study drug. Association of IRIS with initiation of ART is well known and labeled as a Warning and Precaution in the current DRV label.

The serious, drug-related rash events are reviewed with the rash events that led to treatment discontinuation in Section 8.2.3 due to the similar nature of the reports.

From Week 24 through the Safety Update Report, 25 additional subjects experienced any treatment-emergent SAE for a total of 40 (12.8%) subjects. No additional serious pyrexia or rash events occurred after Week 24. SAEs reported in more than one subject since the Week 24 safety report were pneumonia, suicide attempt, and abdominal pain, all of which occurred in two subjects each and none of which were related to study drug according to the investigator. Overall, SAEs in 35 of 40 subjects were considered not related to study drug by the investigator; based on a review of all narratives, these assessments are reasonable.

Since the safety report at Week 24, one subject (Subject 1780-4245) experienced ectopic pregnancy, which the investigator reported as having an unknown relationship to study drug exposure. The Applicant assessed the patient's ectopic pregnancy as likely a background event, which is a reasonable assessment at this time. One subject (Subject 0729-4313) experienced myocardial infarction, which the investigator assessed as having an unknown relationship to study drug. The event occurred almost two years after initiation of DRV/co and TDF/FTC in a 52-year-old male of African descent with hyperlipidemia and hypertension. Causality assessment is difficult, particularly with underlying cardiac risk factors.

Two SAEs of suicide attempt prompted a review of all SAEs reported for the SOC Psychiatric Disorders. Table 5 describes the psychiatric-related SAEs, all of which had plausible alternate causes.

Table 5: SAEs of Interest – Psychiatric Disorders Occurring in Study GS-US-216-0130

Subject ID	Event(s)	Treat-ment d/c	Related (Investigator/Reviewer)	Possible Alternate Cause/Confounders	Proposed Labeling
0754-4070	Suicide attempt	N	No / Unlikely	Recent discontinuation of bipolar medications	None
1534-4305	Suicide attempt	N	No / Unlikely	Unspecified traumatic life events; under the influence of marijuana and ethanol at time of event	None
1236-4291	Suicidal ideation Depression	N	No / Unlikely	Recent discontinuation of multiple psychiatric medications	None
0754-4216	Anxiety	Y	No / Unlikely	Pre-existing anxiety and depression; switched to Stribild	None

d/c = discontinuation

Source: Narrative review of SAEs through Week 48 (Reviewer’s Analysis)

8.2.3 Dropouts and/or Discontinuations

A total of 15 (4.8%) subjects experienced an AE leading to discontinuation of study drug through Week 24. The most common AE leading to discontinuation of study drug by System Organ Class (SOC) was “Skin and Subcutaneous Disorders” occurring in 7 (2.2%) subjects. Additional AEs resulting in treatment discontinuation and occurring in more than one subject were hypersensitivity and nausea. Table 4 lists all AEs leading to study drug discontinuation by SOC and PT.

Table 6. AEs Leading to Study Drug Discontinuation in Study GS-US-216-0130

Dictionary-Derived Term	Number of subjects (%)
SYSTEM ORGAN CLASS	DRV/co
PREFERRED TERM	(N=313)
Any AE Leading to Study Drug Discontinuation	15 (4.8%)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	7 (2.2%)
DERMATITIS ALLERGIC	1 (0.3%)
RASH	3 (1.0%)
RASH MACULAR	1 (0.3%)
RASH MACULO-PAPULAR	3 (1.0%)
RASH VESICULAR	1 (0.3%)
IMMUNE SYSTEM DISORDERS	2 (0.6%)
HYPERSENSITIVITY	2 (0.6%)

Table 6. AEs Leading to Study Drug Discontinuation in Study GS-US-216-0130

Dictionary-Derived Term	Number of subjects (%)
<i>SYSTEM ORGAN CLASS</i>	<i>DRV/co (N=313)</i>
<i>PREFERRED TERM</i>	
GASTROINTESTINAL DISORDERS	2 (0.6%)
DYSPEPSIA	1 (0.3%)
NAUSEA	2 (0.6%)
VOMITING	1 (0.3%)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	1 (0.3%)
IDIOPATHIC THROMBOCYTOPENIC PURPURA	1 (0.3%)
INFECTIONS AND INFESTATIONS	1 (0.3%)
MYCOBACTERIUM AVIUM COMPLEX INFECTION	1 (0.3%)
NERVOUS SYSTEM DISORDERS	2 (0.6%)
DYSGEUSIA	1 (0.3%)
HEADACHE	1 (0.3%)

Source: ADAE dataset using JReview (Reviewer's Analysis)

Narratives for treatment discontinuations due to rash and hypersensitivity were very similar in nature and are discussed together (Subjects 2154-4111, 2843-4190, 0121-4113, 0407-4100, 0589-4316, 0991-4067, 1950-4269, 1978-4069, 2157-4130). All subjects were also taking TDF/FTC. The investigator assessed these AEs as serious (medically significant) in two subjects, severe (Grade 3) in three subjects, and mild or moderate (Grade 1-2) in four subjects. Rash and hypersensitivity events assessed as serious or Grade 3 are described below.

Subject 2843-4190

A 33-year-old male developed a maculopapular rash on his thorax, arms, and legs on Day 11 after initiating DRV/co and TDF/FTC. He was not taking any other medications. He stopped the study drugs and received diphenhydramine for 10 days until the rash resolved. The investigator assessed the rash as serious (medically significant), most likely related to DRV, and possibly related to FTC.

Subject 0121-4113

A 36-year-old male developed a diffuse rash that spread to the face on Day 7 after initiating DRV/co and TDF/FTC. He was not taking any other medications. He received diphenhydramine, but the rash worsened from Grade 2 to Grade 3. He discontinued study drugs, and the rash resolved on Day 11. The investigator assessed the rash as related to DRV/co.

Subject 0589-4316

A 49-year-old female developed pruritus on her hands and feet on Day 24 after initiating DRV/co and TDF/FTC. On Day 25 the reaction progressed to a diffuse erythematous rash, some angioedema, and pruritus at which time study drugs were discontinued. Liver enzymes, white blood cell count, and eosinophil count were normal. The next day, the subject had no oral lesions, blistering, or noticeable angioedema. The subject received antihistamines and prednisone, and the event

resolved over a few days. The investigator assessed the event as Grade 3 and related to study medications.

Subject 2157-4130

A 24-year-old male developed a Grade 2 non-pruritic rash without oropharynx involvement on Day 10 after initiating DRV/co and TDF/FTC. Liver enzymes, white blood cell count, and eosinophil count were normal. He received antihistamines and continued study drugs. On Day 80 the subject experienced Grade 3 allergic dermatitis with unchanged laboratory results. He received methylprednisolone and discontinued study drugs, and the rash resolved on Day 86.

There were no cases of Stevens-Johnson syndrome or toxic epidermal necrolysis. All nine events were related to study drug, most likely DRV and possibly COBI, and all resolved with discontinuation of DRV/co and treatment with antihistamines and/or corticosteroids. The events are consistent with the current labels for DRV and COBI as single agents.

Since Week 24, two additional subjects discontinued study drug due to an AE, one of which was the aforementioned anxiety event listed in Table 5 in Section 8.2.2. The second AE resulting in treatment discontinuation was proximal renal tubulopathy in a subject (Subject 1236-4051) also taking TDF/FTC. The event is consistent with the proximal renal tubulopathy events seen with COBI and TDF (in combination with either EVG or ATV) and labeled for COBI.

8.3 Supportive Safety Results

8.3.1 Common Adverse Events

All tables in this section were produced in JReview using the ADAE dataset and represent this reviewer's analyses.

Table 7 provides an overview of treatment-emergent clinical AEs by severity and relatedness. Four of the five subjects with Grade 3-4 study drug-related AEs experienced rash (2) or hypersensitivity (2).

Table 7. Overview of Treatment-Emergent AEs Occurring in Study GS-US-216-0130

Treatment-Emergent AE	Number of subjects (%) DRV/co (n=313)
Any AE	275 (87.9%)
Any AE Grade 2-4	139 (44.4%)
Any AE Grade 3-4	18 (5.8%)
Any Study Drug-Related AE	123 (39.3%)
Any Study Drug-Related AE Grade 2-4	42 (13.4%)
Any Study Drug-Related AE Grade 3-4	5 (1.6%)

The most common AEs by SOC irrespective of grade or causality were Gastrointestinal Disorders (52%), Infections and Infestations (49%), and Skin and Subcutaneous Tissue Disorders (28%). The most common AEs by PT irrespective of grade or causality reported in $\geq 5\%$ of DRV/co-treated subjects included diarrhea, nausea, upper respiratory tract infection, headache, rash, vomiting, fatigue, flatulence, nasopharyngitis, and sinusitis.

Table 8 lists Grade 2-4 AEs by PT regardless of causality and occurring in at least 2% of subjects. The Applicant's grouped terms for rash did not include dermatitis, dermatitis allergic, drug eruption, rash vesicular, or urticaria. Addition of these rash terms resulted in a slightly higher percentage of rash events.

Table 8. Treatment-Emergent AEs by Preferred Term Regardless of Causality Occurring in At Least 2% of Subjects in Study GS-US-216-0130

Preferred Term	Number of subjects (%) DRV/co (n=313)
RASH (Reviewer's Grouped Terms ¹)	21 (6.7%)
RASH (Applicant's Grouped Terms ²)	18 (5.8%)
DIARRHEA (Applicant's Grouped Terms ³)	16 (5.1%)
UPPER RESPIRATORY TRACT INFECTION	11 (3.5%)
NAUSEA	10 (3.2%)
BRONCHITIS	6 (1.9%)
DEPRESSION	6 (1.9%)
SINUSITIS	6 (1.9%)
HEADACHE	5 (1.6%)
HYPERSENSITIVITY (Applicant's Grouped Terms ⁴)	5 (1.6%)
VOMITING	5 (1.6%)

- 1 Dermatitis, Dermatitis allergic, Drug eruption, Generalized erythema, Rash, Rash erythematous, Rash generalized, Rash macular, Rash maculo-papular, Rash morbilliform, Rash papular, Rash pruritic, Rash vesicular, Urticaria
- 2 Generalized erythema, Rash, Rash erythematous, Rash generalized, Rash macular, Rash maculo-papular, Rash morbilliform, Rash papular, Rash pruritic
- 3 Diarrhea, Frequent bowel movements
- 4 Hypersensitivity, Drug hypersensitivity

Table 9 lists Grade 2-4 AEs by PT at least possibly attributed to study drug by the investigator and occurring in at least 2% of subjects. Both versions of grouped terms for rash resulted in an equal number of events. The terms are consistent with drug-related AEs in the DRV and COBI labels.

Table 9. Treatment-Emergent Drug-Related AEs by Preferred Term Occurring in At Least 2% of Subjects in Study GS-US-216-0130

Preferred Term	Number of subjects (%) DRV/co (n=313)
RASH (Reviewer’s Grouped Terms ¹)	27 (4.5%)
RASH (Applicant’s Grouped Terms ²)	27 (4.5%)
NAUSEA	7 (2.2%)
DIARRHEA (Applicant’s Grouped Terms ³)	5 (1.6%)

- 1 Dermatitis, Dermatitis allergic, Drug eruption, Generalized erythema, Rash, Rash erythematous, Rash generalized, Rash macular, Rash maculo-papular, Rash morbilliform, Rash papular, Rash pruritic, Rash vesicular, Urticaria
- 2 Generalized erythema, Rash, Rash erythematous, Rash generalized, Rash macular, Rash maculo-papular, Rash morbilliform, Rash papular, Rash pruritic
- 3 Diarrhea, Frequent bowel movements

8.3.2 Laboratory Findings

The laboratory analysis in Table 10 reflects treatment-emergent laboratory abnormalities that increased at least one toxicity grade from baseline. Individual subjects are counted once for each laboratory abnormality, with the maximum toxicity grade reported. Missing baseline values are assumed to be Grade 0.

Interpretation of the incidence of laboratory abnormalities with DRV/co is limited in an open-label, single-arm study, but no new safety concerns emerged through Week 24 in this study. Grade 3-4 liver or pancreatic enzyme abnormalities were not associated with clinical AEs, including pancreatitis, in any subject. No subject had concurrent ALT and bilirubin elevations consistent with Hy’s law criteria; and Grade 3 triglyceride elevations were not associated with pancreatitis.

The percentage of subjects who experienced Grade 1 serum creatinine elevations is consistent with the known safety profile of cobicistat. A similar percentage of Grade 1 serum creatinine elevations occurred in clinical trials with cobicistat and atazanavir (see Dr. Peter Miele’s Clinical Review for the original cobicistat NDA).

Grade 3-4 neutropenia was not associated with any clinically significant or related AEs, including infections. One subject experienced Grade 4 thrombocytopenia, which was associated with the SAE idiopathic thrombocytopenic purpura noted in Section 8.2.2 and was considered unlikely related to study drug. One subject experienced Grade 3 anemia along with pelvic inflammatory disease, both of which are noted as SAEs in Section 8.2.2 and were considered not related to study drug. Both events resolved with a blood transfusion and antibiotics.

Table 10. Treatment-Emergent Laboratory Abnormalities in Study GS-US-216-0130

Laboratory Parameter	Limit	DRV/co (n=313)	
		n	%
Chemistry Laboratory Values			
Alkaline Phosphatase			
Grade 1	1.25 – 2.50 x ULN	4	1
Grade 2	>2.50 – 5.00 x ULN	3	1
Grade 3	>5.00 – 10.00 x ULN	0	0
Grade 4	>10.00 x ULN	0	0
ALT			
Grade 1	1.25 – 2.50 x ULN	20	6
Grade 2	>2.50 – 5.00 x ULN	7	2
Grade 3	>5.00 – 10.00 x ULN	5	2
Grade 4	>10.00 x ULN	2	1
AST			
Grade 1	1.25 – 2.50 x ULN	20	7
Grade 2	>2.50 – 5.00 x ULN	18	6
Grade 3	>5.00 – 10.00 x ULN	4	1
Grade 4	>10.00 x ULN	2	1
Total Bilirubin			
Grade 1	>1.0 – 1.5 x ULN	10	3
Grade 2	>1.5 – 2.5 x ULN	4	1
Grade 3	>2.5 – 5.0 x ULN	1	<1
Grade 4	>5.0 x ULN	0	0
Serum Creatinine (mg/dL)			
Grade 1	>1.5 – 2.0	22	7
Grade 2	>2.0 – 3.0	1	<1
Grade 3	>3.0 – 6.0	0	0
Grade 4	>6.0	0	0
Amylase			
Grade 1	>1.0 – 1.5 x ULN	47	15
Grade 2	>1.5 – 2.0 x ULN	17	6
Grade 3	>2.0 – 5.0 x ULN	6	2
Grade 4	>5.0 x ULN	0	0
Lipase			
Grade 1	>1.0 – 1.5 x ULN	14	5
Grade 2	>1.5 – 2.0 x ULN	18	3
Grade 3	>2.0 – 5.0 x ULN	2	1
Grade 4	>5.0 x ULN	3	1
Non-fasting Serum Glucose, Hyperglycemia (mg/dL)			
Grade 1	>ULN – 160	69	22
Grade 2	>160 – 250	16	5
Grade 3	>250 – 500	0	0
Grade 4	>500	1	<1

Table 10. Treatment-Emergent Laboratory Abnormalities in Study GS-US-216-0130

Laboratory Parameter	Limit	DRV/co (n=313)	
		n	%
Lipid Laboratory Values			
Total Cholesterol, Fasting (mg/dL)			
Grade 1	200 – 239	47	16
Grade 2	>239 – 300	21	7
Grade 3	>300	3	1
Triglycerides, Fasting (mg/dL)			
Grade 2	500 – 750	3	1
Grade 3	>750 – 1,200	4	1
Grade 4	>1,200	0	0
Hematologic Laboratory Values			
Leukocytes (cells/mm ³)			
Grade 1	2,000 – 2,500	3	1
Grade 2	1,500 – <2,000	1	<1
Grade 3	1,000 – <2,500	0	0
Grade 4	<1,000	0	0
Absolute Neutrophil Count (cells/mm ³)			
Grade 1	1,000 – 1,300	15	5
Grade 2	750 – <1,000	7	2
Grade 3	500 – <750	2	1
Grade 4	<500	2	1
Platelets (cells/mm ³)			
Grade 1	100,000 – <125,000	6	2
Grade 2	50,000 – <100,000	1	<1
Grade 3	25,000 – 50,000	0	0
Grade 4	<25,000	1	<1
Hemoglobin (g/dL)			
Grade 1	8.5 – 10.0	4	1
Grade 2	7.5 – <8.5	0	0
Grade 3	6.5 – <7.5	1	<1
Grade 4	<6.5	0	0

Source: ADLB dataset using JReview

8.4 Additional Submissions

Renal Impairment Study: GS-US-236-0118

Study 118 is an ongoing Phase 3 open-label safety study evaluating cobicistat in HIV-1-infected patients with mild to moderate renal impairment. The submission contains Week 48 analysis in which subjects on stable ART switched from ritonavir to cobicistat and received at least 1 dose of DRV/co (n=21).

There were no deaths or kidney-related SAEs. Two cardiac-related SAEs occurred in subjects (6259-2060 and 1560-2005) greater than 60 years of age with a history of cigarette smoking and hypercholesterolemia, respectively; both subjects also had mild-to-moderate renal impairment per study inclusion criteria. Significant confounders provide a plausible alternate explanation for each event. This study did not raise any new safety concerns for DRV/co.

9. Pediatrics

The NDA does not contain pediatric data. The Applicant submitted the Agreed Initial Pediatric Study Plan for DRV/co FDC; the Agency previously agreed with the Applicant's planned waiver and deferral requests. The Applicant submitted a partial waiver request for children < 3 years of age and \geq 3 years of age weighing < 15 kg and a deferral request for children \geq 3 to < 18 years of age weighing \geq 15 kg. A partial waiver for children < 3 years of age is necessary because of toxicology concerns with DRV as a single agent in this patient population. The deferral request is reasonable because different DRV/co FDC oral formulations are necessary for weight-based dosing and cannot be developed until there is an identified pediatric dose recommendation for COBI as a single agent in combination with DRV. Determination of pediatric dosing with DRV and COBI as single agents is ongoing through another sponsor (Gilead). The deferral and waiver requests was reviewed by the Pediatric Review Committee (PeRC) on December 3, 2014.

10. Labeling

COBI as a single agent received approval during this NDA review cycle. Overall, the following edits were made throughout the DRV/co label:

- Updated to maintain consistency with the COBI label as it pertains to DRV/co.

(b) (4)

Additional major revisions proposed to the Applicant are as follows:

U.S. Package Insert (USPI)

INDICATIONS AND USAGE

Clarified and simplified as follows: “PREZCOBIX is indicated in combination with other antiretroviral agents for the treatment of human immunodeficiency virus (HIV-1) infection in treatment-naïve and treatment-experienced adults with no darunavir resistance-associated substitutions (V11I, V32I, L33F, I47V, I50V, I54L, I54M, T74P, L76V, I84V, L89V).”

DOSAGE AND ADMINISTRATION



CONTRAINDICATIONS

- Added colchicine in patients with renal and hepatic impairment based on a pending labeling supplement for Prezista (i.e., colchicine in patients with renal and hepatic impairment)
- Added lurasidone based on recommendations from the Division of Psychiatry Products in response to a consult request.

WARNINGS AND PRECAUTIONS

Added “Antiretrovirals Not Recommended” which include other antiretroviral drugs that require pharmacokinetic boosting (i.e., another PI or EVG) and products containing DRV, COBI, or RTV

ADVERSE REACTIONS

The Applicant agreed [redacted] (b) (4) [redacted] (b) (4) a general statement to convey to prescribers that clinical experience was gained with DRV/co. In response, the following statement was added, “One single arm clinical trial was conducted with darunavir and cobicistat administered as single entities in 313 HIV-infected subjects. Adverse reactions evaluated through Week 24 did not differ substantially from those reported in clinical trials with darunavir/ritonavir.”

DRUG INTERACTIONS

Table 4

Added interaction recommendations for newer oral anticoagulants, anticancer drugs, and immunosuppressants with darunavir based on a pending labeling supplement for Prezista

U.S. Patient Package Insert (USPPI)

- Added information regarding COBI-related kidney effects

(b) (4)

11. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action

I recommend approval of darunavir/cobicistat 800/150 mg tablet, a fixed-dose HIV protease inhibitor and CYP3A inhibitor that increases systemic DRV exposures, in combination with other antiretroviral agents for the treatment of HIV-1 infection in adults. The recommendation is based on the BE of the DRV/co FDC tablet compared to the approved single-agent products DRV and COBI for the same indication and is supported by clinical efficacy and safety data with DRV and COBI single agents in HIV-infected subjects.

- Risk Benefit Assessment

Efficacy and safety data in the supportive clinical trial do not alter the risk-benefit assessments made during the original NDA reviews for DRV and for COBI. Although interpretation of safety data is limited by the single-arm, open-label trial design, no new safety concerns arise from the clinical trial. Safety of DRV/co is consistent with current labeling for DRV and COBI single agents.

- Recommendation for Postmarketing Risk Evaluation and Management Strategies

The NDA contains no safety information necessitating a REMS.

- Recommendation for other Postmarketing Requirements and Commitments

A PMR will be issued for pediatric studies under the Pediatric Research Equity Act (PREA) and consistent with the Agreed Initial Pediatric Study Plan. No additional PMRs are recommended.

Of note, PMRs are in place for DRV and COBI as single agents for pediatric studies

(b) (4)

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/s/

SARITA D BOYD
12/19/2014

MARY E SINGER
12/19/2014

I concur with Dr. Boyd's review and recommendations.

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 205395

Applicant: Janssen

Stamp Date: 03/31/14

**Drug Name: Darunavir/cobicistat NDA/BLA Type: NDA
505(b)(1)**

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	X			
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (e.g., are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?	X			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	X			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (i.e., Module 2 summaries)?	X			
9.	Has the applicant submitted the integrated summary of safety (ISS)?			X	Single study
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?			X	Single study
11.	Has the applicant submitted a benefit-risk analysis for the product?	X			
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2).	X			505(b)(1)
505(b)(2) Applications					
13.	If appropriate, what is the reference drug?			X	
14.	Did the applicant provide a scientific bridge demonstrating the relationship between the proposed product and the referenced product(s)/published literature?			X	
15.	Describe the scientific bridge (e.g., BA/BE studies)			X	
DOSE					
16.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (i.e., appropriately designed dose-ranging studies)?	X			Dosing is based on the development of DRV and cobicistat as single agents.
EFFICACY					
17.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? Pivotal Study #1 TMC114IFD1003: BE study comparing DRV/cobi FDC to	X			PK data for DRV with the proposed DRV/cobi FDC tablet were bridged with the existing data for

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CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	DRV coadministered with cobicistat as single agents Indication: Treatment of HIV-1 infection in adults (same population for which DRV/r 800/100 mg once daily [coadministered as single agents] is approved)				DRV/r administered as single agents. With extrapolation of DRV/r efficacy to DRV/cobi, a comparative Phase 3 efficacy study is not necessary. Cobicistat is currently approved as part of another FDC (Stribild) and is currently under review for approval as a single agent.
18.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X			BA/BE study is pivotal. Approval is contingent upon approval of cobicistat as a single agent.
19.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	X			BA/BE requirements
20.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?			X	Although the BA/BE studies were conducted in Belgium, applicability of foreign data is not a concern for these types of studies. Open-label safety study was conducted in the U.S.
SAFETY					
21.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			Study 130 (open-label, single arm) evaluated safety and efficacy of DRV/cobi FDC coadministered with two fully active NRTIs in subjects with no DRV RAMs through Weeks 24 and 48.
22.	Has the applicant submitted adequate information to assess the arrhythmogenic potential of the product (e.g., QT interval studies, if needed)?	X			ECG parameters from Study 130 are presented. In addition, QT interval studies were conducted for DRV/r and for cobicistat under their respective INDs.
23.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			Summary of most recent PSUR for DRV.
24.	For chronically administered drugs, have an adequate	X			Adequate numbers of

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	Content Parameter	Yes	No	NA	Comment
	number of patients (based on ICH guidelines for exposure ¹) been exposed at the dose (or dose range) believed to be efficacious?				patients have been exposed to DRV and cobicistat separately. Approval is contingent upon approval of cobicistat as a single agent.
25.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			X	
26.	Has the applicant submitted the coding dictionary ² used for mapping investigator verbatim terms to preferred terms?	X			
27.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	X			Safety issues relevant to DRV/r
28.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	X			Deaths, SAEs, AEs leading to discontinuation, AEs of interest, pregnancy (treatment emergent)
OTHER STUDIES					
29.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?			X	
30.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (e.g., label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
31.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			Agreed iPSP which includes request for waiver/deferral
ABUSE LIABILITY					
32.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
FOREIGN STUDIES					
33.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?		X		See comment above
DATASETS					
34.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
35.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			
36.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			Open-label safety study (not pivotal)

¹ For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

² The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

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CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
37.	Are all datasets to support the critical safety analyses available and complete?	X			
38.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	X			
CASE REPORT FORMS					
39.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			
40.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?			X	
FINANCIAL DISCLOSURE					
41.	Has the applicant submitted the required Financial Disclosure information?	X			Not required for open-label safety study
GOOD CLINICAL PRACTICE					
42.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? yes

If the Application is not fileable from the clinical 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.

Please submit narratives for deaths, SAEs, and treatment-related discontinuations for Study GS-US-216-0130 through Week 48 that have not already been submitted with Week 24 analysis.

Sarita Boyd, Pharm.D.

 Reviewing Medical Officer

May 5, 2014

 Date

Mary Singer, M.D.

 Clinical Team Leader

May 5, 2014

 Date

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

/s/

SARITA D BOYD
05/05/2014

MARY E SINGER
05/06/2014