Medical Officer Review

Date	December 19, 2012
From	Yodit Belew, M.D.
Subject	Medical Officer Review
NDA/NDA # **Supplement #**	202895/21976 S-5, 6 and S- 28,29 (to NDAs 202895 and 21976, respectively)
Applicant	Janssen, Inc.
Date of Submission	August 3, 2012
PDUFA Goal Date	February 3, 2012
Proprietary Name / Established (USAN) names	Prezista(darunavir)
Dosage forms / Strength	Approved dosage forms: Oral Suspension: 100mg/mL; tablets: 75 mg, 150 mg, 400 mg, 600 mg, 800 mg
Proposed Indication(s)	Treatment of HIV infection
Recommended:	Approval

1. Introduction

This review summarizes the main issues for Janssen's sNDAs seeking approval for Prezista once daily dosing regimen for pediatric patients 3 to less than 18 years of age. This review highlights the supporting pharmacokinetic, safety and efficacy (antiviral activity) data. Of note, Prezista twice daily, in combination with ritonavir is currently approved for use in HIV infected children 3 to less than 18 years of age and weighing at least 10 kg. This application extends the dosing regimen to include once daily dosing for treatment naïve or treatment experienced pediatric patients with no darunavir resistance associated substitutions. Additionally, the application was granted a priority review as it pertains to pediatric population and provides simpler, once daily dosing regimen for the population.

2. Background

Prezista, originally approved in June 2006, is an important product for adults and pediatric patients receiving antiretroviral treatment for HIV-1 infection. According to DHHS treatment guidelines, Prezista is recommended as a preferred protease inhibitor for initiation of ART in naïve adult patients and is recommended as an alternative regimen for pediatric patients 3 years of age and older. The recommended dose of Prezista in treatment naïve and experienced adult patients with no darunavir resistance associated substitutions is 800 mg of darunavir co-administered with 100 mg of ritonavir once daily. In treatment experienced adult patients with one or more darunavir resistance associated substitutions, the recommended dosage regimen is 600 mg of darunavir co-administered with 100 mg of ritonavir twice daily. The weight based twice daily dosing recommended in pediatric patients 3 years of age and older and weighing at least 10 kg is summarized in tables 1 and 2.

- *Pediatric pateints weighing at least 10 kg but less than 15 kg*

The weight-based dosing in pediatric patients is PREZISTA 20 mg/kg with ritonavir 3 mg/kg twice daily:

Table 1 Recommended Dose for pediatric patients weighing 10 kg to less than 15 kg	
Body weight (kg)	**Formulation: PREZISTA Oral Suspension (100 mg/mL) and Ritonavir Oral Solution***
	Dose: Twice daily with food
Greater than or equal to 10 kg to less than 11 kg	PREZISTA 200 mg (2 mL) with ritonavir 32 mg (0.4 mL)
Greater than or equal to 11 kg to less than 12 kg	PREZISTA 220 mg (2.2 mL) with ritonavir 32 mg (0.4 mL)
Greater than or equal to 12 kg to less than 13 kg	PREZISTA 240 mg (2.4 mL) with ritonavir 40 mg (0.5 mL)
Greater than or equal to 13 kg to less than 14 kg	PREZISTA 260 mg (2.6 mL) with ritonavir 40 mg (0.5 mL)
Greater than or equal to 14 kg to less than 15 kg	PREZISTA 280 mg (2.8 mL) with ritonavir 48 mg (0.6 mL)
*with ritonavir oral solution: 80 mg/mL	

- *Pediatric patients weighing at least 15 kg*

Pediatric patients weighing at least 15 kg can be dosed with Prezista oral tablet or solution using the following table

Table 2 Recommended dose for pediatric patients weighing at least 15 kg		
Body Weight (kg)	**Formulation: PREZISTA oral tablets and ritonavir oral tablets or capsules[£]**	**Formulation: PREZISTA oral suspension and ritonavir oral solution***
	Dose: Twice daily with food	**Dose: Twice daily with food**
Greater than or equal to 15 kg to less than 30 kg	PREZISTA 375 mg with ritonavir* 50 mg (0.6 mL)	PREZISTA 3.8 mL (375 mg[^]) with ritonavir 0.6 mL (50 mg)
Greater than or equal to 30 kg to less than 40 kg	PREZISTA 450 mg with ritonavir* 60 mg (0.75 mL)	PREZISTA 4.6 mL (450 mg[#]) with ritonavir 0.75 mL (60 mg)
Greater than or equal to 40 kg	PREZISTA 600 mg with ritonavir[£] 100 mg	PREZISTA 6 mL (600 mg) with ritonavir 1.25 mL (100 mg)
[£] ritonavir capsules or tablets: 100 mg *ritonavir oral solution: 80 mg/mL ^The 375 mg dose using darunavir tablets for this weight group is rounded off to 3.8 mL for suspension dosing. # The 450 mg dose using darunavir tablets for this weight group is rounded off to 4.6 mL for suspension dosing.		

Once daily dosing is currently not approved for pediatric patients; the current sNDA submissions provide pharmacokinetic, safety and efficacy data to support once daily dosing recommendation. The recommendations are based on the following:

- Results from one trial in treatment-naive pediatric subjects 12 to less than 18 years of age demonstrating similar darunavir plasma exposures, virologic response rate and safety profile compared to treatment-naive adults.
- Results from population pharmacokinetic modeling and simulation in children 3 to less than 12 years of age predicting similar darunavir plasma exposures compared to treatment-naive adults. In addition, although no clinical trial was conducted to collect exposure-safety data, the predicted exposures from the once daily dosing is supported by exposures observed in pediatric clinical trial(s) where twice-daily dosing was administered.

The proposed once daily dosing regimen for treatment-naïve or treatment-experienced pediatric patients with no darunavir resistance associated substitutions is also weight based and is summarized in tables 3 and 4:

- *Pediatric pateints weighing at least 10 kg but less than 15 kg*

The weight-based dose in treatment-naïve or treatment-experienced pediatric patients with no darunavir resistance associated substitutions is PREZISTA 35 mg/kg once daily with ritonavir 7 mg/kg once daily. Dosing can be administered using the following table:

Table 3: Recommended dose for pediatric patients weighing 10 kg to less than 15 kg who are treatment-naïve or treatment-experienced with no darunavir resistance associated substitutions†

Body weight (kg)	Formulation: PREZISTA Oral Suspension (100 mg/mL) and Ritonavir Oral Solution*
	Dose: once daily
Greater than or equal to 10 kg to less than 11 kg	PREZISTA 3.6 mL‡ (350 mg) with ritonavir 0.8 mL (64 mg)
Greater than or equal to 11 kg to less than 12 kg	PREZISTA 4 mL‡ (385 mg) with ritonavir 0.8 mL (64 mg)
Greater than or equal to 12 kg to less than 13 kg	PREZISTA 4.2 mL (420 mg) with ritonavir 1 mL (80 mg)
Greater than or equal to 13 kg to less than 14 kg	PREZISTA 4.6 mL‡ (455 mg) with ritonavir 1 mL (80 mg)
Greater than or equal to 14 kg to less than 15 kg	PREZISTA 5.0 mL‡ (490 mg) with ritonavir 1.2 mL (96 mg)

† darunavir resistance associated substitutions: V11I, V32I, L33F, I47V, I50V, I54M, I54L, T74P, L76V, I84V and L89V
*with ritonavir oral solution: 80 mg/mL
‡ The 350 mg, 385 mg, 455 mg and 490 mg darunavir doses for the specified weight groups were rounded off for suspension dosing to 3.6 mL, 4 mL, 4.6 mL and 5 mL, respectively.

- *Pediatric patients weighing at least 15 kg*

Treatment-naïve or treatment-experienced pediatric patients with no darunavir resistance associated substitutions who weigh at least 15 kg can be dosed with Prezista oral tablet or solution using the following table:

Table 4: Recommended dose for pediatric patients weighing at least 15 kg who are treatment-naïve or treatment-experienced with no darunavir resistance associated substitutions†

Body Weight (kg)	Formulation: PREZISTA oral tablets and oral ritonavir capsules or tablets£	Formulation: PREZISTA oral suspension and ritonavir oral solution*
	Dose: once daily	Dose: Once daily
Greater than or equal to 15 kg to less than 30 kg	PREZISTA 600 mg with ritonavir100 mg	PREZISTA 6 mL with ritonavir 1.25 mL
Greater than or equal to 30 kg to less than 40 kg	PREZISTA 675 mg with ritonavir 100 mg	PREZISTA 6.8 mL§,∫ mL with ritonavir 1.25 mL
Greater than or equal to 40 kg	PREZISTA 800 mg with ritonavir 100 mg	PREZISTA 8 mL# with ritonavir 1.25 mL

†darunavir resistance associated substitutions: V11I, V32I, L33F, I47V, I50V, I54M, I54L, T74P, L76V, I84V and L89V
£ritonavir capsules or tablets: 100 mg
*ritonavir oral solution: 80 mg/mL
§ The 675 mg dose using darunavir tablets for this weight group is rounded off to 6.8 mL for suspension dosing.
∫ An 6.8 mL darunavir dose should be taken as two 3.4 mL administrations with the included oral dosing syringe
Darunavir oral suspension: an 8 mL darunavir dose should be taken as two 4 mL administrations with the included oral dosing syringe

This current application fulfills the following postmarketing requirements under Pediatric Research Equity Act (PREA):

- 'Deferred pediatric study under PREA for the treatment of HIV-1 infection in treatment-naïve pediatric subjects from 12 to <18 years of age. Conduct a pediatric safety and activity study of darunavir, in combination with ritonavir, in the treatment-naïve population with activity based on the results of virologic response over at least 24 weeks of dosing and safety monitored over 48 weeks.'
- 'Deferred pediatric study under PREA for the treatment of HIV-1 infection in treatment-naive pediatric subjects from 3 to <12 years of age. Conduct a pediatric safety and activity study of darunavir, in combination with ritonavir, in the treatment-naive population with activity based on the results of virologic response over at least 24 weeks of dosing and safety over 48 weeks'.

3. CMC

No new CMC information was submitted with the current sNDAs.

4. Nonclinical Pharmacology/Toxicology

No new pre-clinical information was submitted with the current sNDAs.

5. Summary of Pharmacokinetic Data

Prezista/ritonavir, in combination with other antiretroviral agents, has been evaluated in three pediatric, Phase 2 trials.

TMC114-C230 was conducted in treatment naïve pediatric subjects 12 to less than 18 years of age. The trial evaluated the pharmacokinetic profile, safety and efficacy of once daily dosing of darunavir/ritonavir (800/100 mg QD, the adult once daily recommended dose). The results from this 48 week trial are submitted in support of once daily dosing regimen for this age group.

TMC114-C228 was a Phase 2 trial in which the safety, pharmacokinetic and efficacy of twice daily darunavir/ritonavir was evaluated in 21 treatment-experienced HIV-1-infected pediatric subjects 3 to less than 6 years of age and weighing at least 10 kg. A pharmacokinetic sub-study was also conducted within this trial. After 24 weeks of treatment with twice daily darunavir/ritonavir, subjects who had confirmed virologic suppression (<50 copies/mL) were switched to once daily dosing for 2 weeks to collect intensive PK data for the once daily dosing, while their OBR were continued. The targeted dose of darunavir/ritonavir 40/7 mg/kg qd (for subjects weighing 10 to <15 kg) and a dose of 600/100 mg qd for subjects weighing ≥ 15 kg were evaluated. Subjects were then switched back to their twice daily darunavir/ritonavir dosing regimen. In sum, study TCM114-C228 provided long-term PK, safety, and efficacy data for the twice daily regimen and an intensive (2 week) pharmacokinetic data for the once daily regimen in this age group. The results from the twice daily dosing supported BID dosing recommendations/labeling in children 3 to less than 6 years of age. The pharmacokinetic results from the once daily sub-study (population PK modeling and simulation), in combination with other PK, safety and efficacy data are currently submitted to support once daily dosing for this age group.

No clinical trial was conducted evaluating once daily dosing regimen in children 6 to less than 12 years of age. Population PK modeling and simulations utilizing adult and pediatric PK data were used to propose dosing for this age group. Although no direct exposure-safety data is available for the once daily dosing in this age group, the predicted exposures from the proposed once daily dosing are supported by exposures observed in the pediatric clinical trial C212 where twice daily dosing was administered.

TMC114-C212 was a Phase 2 trial in which the safety, pharmacokinetic and efficacy of twice daily darunavir/ritonavir was evaluated in 80 treatment-experienced HIV-1-infected pediatric subjects 6 to less than 18 years of age and weighing at least 20 kg. The results from this study supported twice daily dosing recommendations/labeling in children 6 to less than 18 years of age.

Summary of Important Clinical Pharmacology Finding for the Once Daily Dosing

The overall pharmacokinetics objective was to determine a once daily dosing regimen in pediatric subjects that is comparable to the exposure achieved in HIV-1 infected adults when treated with DRV/rtv 800/100 mg once daily (study C211). Darunavir exposures (AUC and Ct) in adults receiving darunavir/rtv 800/100 mg once daily (studies TMC114-C211 and C229) were:
- TMC114-C211: AUC24h: 87.9 (45.0 - 219.2) µg.h/mL, C0h: 2041 (368 - 7242) ng/mL;
- TMC114-C229: AUC24h: 87.8 (45.4 - 236.9) µg.h/mL, C0h: 1896 (184 - 7881) ng/mL.

In the population PK analyses for C230 (pediatric subjects 12 to < 18 years) and weighing ≥ 40 kg), darunavir 800/100 mg once daily resulted in a geometric mean exposure of 77.8 µg.h/mL, which represents 86.7% of the target adult exposure of 89.7 µg.h/mL. The median (range) C_{0h} was also comparable to the adult median C_{0h}.

In the population PK analyses for the 2-week once daily substudy of C228 (subjects 3 to < 6 years and weighing 10 to < 20 kg), darunavir doses 40/7 mg/kg q.d. for subjects weighing < 15 kg and of 600/100 mg q.d. for subjects weighing ≥ 15 kg resulted in a geometric mean exposure of 115 µg.h/mL, which represents 128% of the target adult exposure of 89.7 µg.h/mL. The median (range) C_{0h} was also comparable to the adult median C_{0h}.

As described by the Applicant, the population pharmacokinetic model for darunavir was updated with the results of the trial TMC114-C228 sub-study and trial TMC114-C230. This model was then used to simulate dosing regimens to recommend a weight-based once daily dose of darunavir in combination with ritonavir for pediatric subjects from 3 to < 18 years of age and weighing > 10 kg. The objective of this model-based simulation was to achieve pharmacokinetic exposures (AUC24h and C0h) in pediatric population that were similar to exposures in adults receiving 800/100 mg of darunavir/ritonavir once daily. A target exposure (AUC24h) of 89.7 µg.h/mL was used, which represents the geometric mean darunavir AUC24h observed in treatment-naïve HIV-1 infected adults.

Based on the population PK modeling and simulation, the Applicant initially proposed the following doses:

Weight Category	Dose	Median C_{0h} (5_{th}-95_{th} percentile) ng/mL	Median AUC_{24h} (5_{th}-95_{th} percentile) µg.h/mL	Median C_{max} (5_{th}-95_{th} percentile) ng/mL
10 to15 kg	(b) (4)			
	20 mg/kg BID	3270 (2035 – 5772)	103 (69.3 – 167)	5557 (4135 – 8234)
15 to 30 kg	**600 mg QD**	**2460 (1325 – 5088)**	**93.3 (60.6 – 163)**	**7004 (5236 – 10388)**
	375 mg BID	3547 (2028 – 6944)	117 (75.7 – 203)	6222 (4335 – 10066)
30 to 40 kg	(b) (4)			
	450 mg BID	3329 (2018 – 6021)	112 (76.8 – 180)	5963 (4397 – 8932)
40 kg onward	**800 mg QD**	**1920 (1031 – 3948)**	**81.1 (53.8 – 137)**	**6066 (4615 – 8785)**
	600 mg BID	3599 (2100 – 6831)	122 (80.7 – 205)	6426 (4559 – 10120)
Adult (TMC114-C211)	800 mg QD	2041 (911 – 4632)	87.9 (60.5 – 143)	6576 (5001 – 9521)

As mentioned previously, with regards to choosing the effective once daily dosing in children, the targeted exposures (AUC, C0) are exposures that are comparable to the exposures observed in the approved once daily dose in adults which have been shown to be effective. Thus it is reasonable for the Applicant to have proposed the above doses as they are predicted to have the desired exposures (i.e. AUC is comparable to 87.9 µg.h/mL and C0 is comparable to 2041 ng/mL).

However, the selected doses and exposures (AUC, Cmax) also need to be shown to be safe when used in the pediatric population. Therefore, supportive exposure-safety data at the predicted exposures (doses) are necessary. The proposed doses for the '15 - <30 kg' and the '40 kg onward' weight bands are supported by PK and exposure-safety data from previous pediatric trials (see Safety section below). But the proposed doses (and predicted exposures) for the '10 -<15 kg' and the '30 -<40 kg' exceed exposures previously observed in children receiving BID regimen. Therefore, the Division conducted further PK and safety analysis to propose alternative dosing regimens for these two weight bands as summarized in the table below (Table 5).

- Weight band10 to <15 kg: 35 mg/kg QD
- Weight band 30 to < 40 kg: 675 mg/kg QD

The Division's proposed doses will provide exposures (AUC, C0) that are expected to be efficacious, as supported by their similarity to the observed exposures from the approved adult doses. Further, the proposed doses also have exposures (AUC, Cmax) that are supported by the exposure-safety data from the pediatric clinical trials where twice daily dosing were administered (see Safety section below for further discussion):

Table 5 FDA proposed dosing regimens and predicted exposures (AUC, C0, Cmax)

Weight band	Dosing	Efficacy (AUC, C0 compared to Adults receiving 800/100 QD dosing)				Safety (AUC, Cmax Compared to children receiving BID dosing)*				
		Median C0h (ng/mL)	% difference from adults	Median AUC(0-24h) [mcg*hr/mL]	% difference from adults	Median AUC(0-24h) [mcg*hr/mL]	% difference from BID exposure (same weight group)	Median Cmax (ng/mL)	% difference from BID exposure (same weight group)	
10 to < 15 kg										
FDA proposal	**35 mg/kg**	**2570**	**126**	**90**	**102**	**90**	**87**	**6641**	**120**	**96^**
Applicant's proposal										
15 to < 30 kg										
	600 mg	***2460***	***121***	***93.3***	***106***	***93.3***	***80***	***7004***	***113***	
30 to< 40 kg										
FDA's proposal	**675 mg**	**2084**	**102**	**83.8**	**95**	**83.8**	**75**	**6347**	**106**	
Applicant's proposal										

* Once-daily exposures compared to the approved twice-daily dosing in children.
^Once-daily exposures compared to the Cmax from the non-approved 25/3 mg/kg BID dose. The Cmax from the 25/3 mg/kg BID dosing is 6946 in the 10-15 kg group.

6. Efficacy Evaluation

The efficacy (antiviral activity) of once daily darunavir/ritonavir in combination with other ARVs was evaluated in one, open label, single arm, 48-week study in pediatric subjects 12 to less than 18 years of age. Although no dedicated once-daily dosing efficacy (antiviral activity) trial was conducted in subjects 3 to less than 12 years of age, the effectiveness of the proposed once daily darunavir dose(s) for this age group can be extrapolated.

Whether the pediatric efficacy data are limited to a small single arm, open label trial (e.g. trial C230) or limited to pharmacokinetic modeling and simulation data (as in the case for pediatric subjects 3 to less than 12 years of age), extrapolation of efficacy for antiretroviral drugs such as darunavir is based on the presumption that the course of HIV disease and the effects of the drug are sufficiently similar in adults and pediatric subjects (21 CFR 201.57 (f)(9)(iv), Sec. 505B 21 USC 355c). Thus, one can rely on the pharmacokinetics data to extrapolate efficacy; that is, the goal would be to target the exposure(s) (AUC) that are similar to the observed exposures (AUC) from the approved adult dose(s). Although AUC is the primary pharmacokinetic parameter targeted when selecting pediatric dose(s), C0 may also be an important pharmacokinetic parameter for some antiretroviral drugs with regards to establishment of exposure-response relationship. In the case of darunavir, both AUC and C0 were considered when

selecting the pediatric once daily dosing. The clinical efficacy (antiviral activity) data obtained from pediatric trials, when available, are used as supportive data.

In pediatric and adult subjects, treatment of HIV disease is monitored by the same two surrogate markers, CD4 count and HIV RNA viral load. Antiretroviral drugs including nucleoside reverse transcriptase inhibitors (NRTIs), nonnucleoside reverse transcriptase inhibitors (NNRTIs) and protease inhibitors (PIs) have been shown to lower HIV RNA, improve CD4 counts (or percentage) and improve general clinical outcome in adult and pediatric subjects and treatment recommendations are very similar across all age groups (see Working Group on Antiretroviral Therapy and Medical Management of HIV-Infected Children. Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection. February 28, 2008 1-134. Available at http://aidsinfo.nih.gov/ContentFiles/PediatricGuidelines.pdf. for a review of studies and references).

Efficacy evaluation for once daily dosing in children less than 12 years of age

As no clinical trial data are available for once daily dosing of darunavir/ritonavir in pediatric subjects less than 12 years of age, efficacy is extrapolated using pharmacokinetic modeling and simulation. As summarized in the table below (Table 6), the proposed doses for the various weight bands are predicted to have similar or higher exposures (AUC, C0) to the approved once daily dosing in adults (800/100 mg QD). For the 10 to <15 kg weight band, although both the 35mg/kg and the 40 mg/kg doses lead to an acceptable effective exposures (AUC, C0), the lower (35mg/kg) dose has been proposed by the Division because supporting safety data are lacking for the higher, 40mg/kg dose. Similarly, for the 30 to <40kg weight band, the 675mg qd dose (instead of 800 mg qd) is proposed by the Division because the predicted exposures (AUC, Cmax), are expected to be effective and are also supported by the available exposure-safety data from the twice-daily dosing pediatric trial (see discussion under the Safety section).

Table 6 Exposures and efficacy extrapolation (compared to adults receiving 800/100 QD dosing)

Weight band	Pediatric Dosing	Median C0h (ng/mL)	% difference from adults	Median AUC (0-24h) [mcg*hr/mL]	% difference from adults
10 to < 15 kg					
	35 mg/kg	2570	**126**	90	**102**
	40 mg/kg	*2937*	***144***	*103*	***117***
15 to < 30 kg					
	600 mg	*2460*	***121***	*93.3*	***106***
30 to< 40 kg					
	675 mg	2084	**102**	83.8	**95**
	800 mg	*2470*	***121***	*99.3*	***113***

Efficacy evaluation for once daily dosing in children 12 to less than 18 years of age

Trial TMC114-C230 was a Phase 2, open-label trial designed to evaluate the pharmacokinetics, safety and efficacy of darunavir with low-dose ritonavir (DRV/rtv) administered at 800/100 mg once daily (q.d.) in combination with an investigator-selected

background regimen [either zidovudine (AZT)/lamivudine (3TC) or abacavir (ABC)/3TC] in antiretroviral (ARV) treatment-naïve HIV-1 infected pediatric subjects 12 to < 18 years of age and weighing ≥ 40 kg. A total of 12 ARV treatment-naïve subjects were included in the study and treated for 48 weeks. The mean duration of treatment was 49.6 weeks.
Majority of the subjects enrolled in the study were female (8 subjects); seven subjects were White and 5 subjects were Black or African American. The median age and weight were 14.4 years (range: 12.6 to 17.3 years) and 50.5 kg (range: 40.0 to 61.6 kg), respectively.

Their baseline disease characteristics were as follows: Five subjects were infected via vertical transmission; others were infected by heterosexual contact (n=3), blood transfusion (n =1), or another cause (n= 3). The median baseline $\log_{10}$ viral load was 4.92 $\log_{10}$ copies/mL and the median CD4+ cell count was 282 cells/mm^3. All subjects were infected with virus susceptible to darunavir. In summary, the main baseline disease characteristics and resistance data of the subjects in study TMC114-C230 were comparable to the treatment-naïve adult subjects enrolled in study TMC114-C211.

The primary efficacy endpoint was plasma viral load < 50 copies/mL at Week 24. The proportion of subjects with plasma viral load < 50 copies/mL at Week 24 (based on FDA snapshot algorithm) was 100% (12/12); at Week 48, 11 of the 12 subjects (92%) continued to have HIV RNA <50 copies/mL (Table 7)

Table 7 Virologic Outcome at Week 24

	DRV/r N = 12
Week 24 Virologic Success (HIV RNA <50 copies/mL), n (%)	12(100)
Week 24 Non-responders, n (%)	0
HIV RNA ≥50 copies/mL (Virologic Failure)*	0
No virologic data week 24-discontinued due to AE/death#	0
Missing data week 24	0
Week 48 Virologic Success (HIV RNA <50 copies/mL), n (%)	11(91.7)
Week 48 Non-responders, n (%)	1(8.3)
HIV RNA ≥50 copies/mL (Virologic Failure)*	1
No virologic data week 48-discontinued due to AE/death#	0
Missing data week 48	0

* Includes a) subjects who had ≥ 50 copies/mL in the Week-24 (or 48) window, b) subjects who discontinued prior to Week 24 (or 48) for lack or loss of efficacy, c) subjects who had a switch in their OBR that was not permitted by the protocol (provided the switch occurred before the earliest onset of an AE leading to permanent stop of trial medication), and d) subjects who discontinued for reasons other than AEs/death, and lack or loss of efficacy (provided their last available viral load was detectable).
#Includes subjects who discontinued due to AE or death at any time point from Day 1 through the Week-24 (or 48) time window if this resulted in no virologic data on treatment during the specified window (provided the earliest AE leading to permanent stop was not preceded by a switch in the OBR that was not permitted by the protocol).

In summary, although the trial did not have a comparative arm, when cross trial comparisons are made, the virologic success rates (HIV RNA <50 copies/mL) observed in this pediatric trial were similar to previously reported in treatment-naïve adults (i.e. 84%). No exposure-response relationship was identified during the pediatric trial.

7. Safety Evaluation

The primary pharmacokinetic parameter routinely used for exposure-safety analysis is AUC. While AUC correlates with overall (and long-term) safety profile of a dose, Cmax can be used for assessment of acute toxicity of a given dose.

As outlined previously, safety data from once-daily dosing are available from clinical C230 for pediatric subjects 12 to less than 18 years of age. Supportive safety data for once-daily dosing in pediatric subjects 3 to less than 12 years of age are available from previously conducted pediatric clinical trials where twice-daily darunavir/ritonavir was administered.

Safety evaluation for once daily dosing in children 12 to less than 18 years of age

Overall, eleven subjects reported at least one AE. The most commonly reported AEs (by preferred term) were vomiting (n=4), nausea (n=3), and anemia (n=3). Most were Grade 1 or 2. There were no deaths during the trial. Serious AEs were reported in four subjects and include: anemia (n=2), neutropenia (n=1), traumatic brain injury (n=1) and cervical dysplasia (n=1). Three subjects experienced Grade 3 or 4 events of interest: one subject had anemia; another subject had anemia, leukopenia/neutropenia, diarrhea, nausea and vomiting. None of the events led to treatment discontinuation. Grade 2 or above, treatment-related adverse events (as assessed by the investigators) were reported in two subjects and include abdominal pain, nausea and diarrhea (all in 1 subject), and dizziness (1 subject). One additional subject experienced nausea that was considered to be treatment-related but the event was Grade 1. One subject experienced rash (Grade 1, doubtfully related to study drug). No liver-related, pancreas-related, or cardiac-related events were reported.

Laboratory toxicity

Summary of hepatic and hematologic laboratory toxicities are presented in the table below:

Table 8 Selected Laboratory Toxicities, Worse Grade

Liver-related toxicities n, (%)	**N=12**
ALT	
G1	2(17)
G2	0
G3	0
G4	0
AST	
G1	1(8)
G2	0
G3	0
G4	0
ALP	
G1	1(8)
G2	0
G3	0
G4	0
Bilirubin (total)	
G1	0
G2	1(8)
G3	0
G4	0
Hematologic-related toxicities n, (%)	**N=12**
Hemoglobin	
G1	2(17)
G2	0
G3	0
G4	2(17)
Neutrophil	
G1	4(33)

G2	2(17)
G3	0
G4	1(8)
WBC	
G1	3(25)
G2	0
G3	1(8)
G4	0

No graded platelet toxicity was reported. No abnormalities for amylase or creatinine were reported. One subject had Grade 1 elevation in lipase. Of note, subjects with hematological events (anemia, neutropenia) that were considered to be Grade 3 or 4 were co-administered Zidovudine as part of their background regimen.

In summary, darunavir when co-administered with ritonavir and other ARTs, was generally safe and tolerated. There were no deaths, non-fatal serious AEs (except laboratory related or non-treatment related) and no subject discontinued due to AE. There were no significant hepatic- or skin- related events. There were no grade 3 or higher liver-related laboratory abnormalities. The Grade 3 or 4 hematological laboratory toxicities occurred in subjects who were co-administered zidovudine, an ART known to cause bone marrow toxicity. No unexpected safety findings were observed.

Safety evaluation for once daily dosing in children less than 12 years of age

No dedicated trial has been conducted using the once-daily dosing in children 3 to less than 12 years of age. Safety data (24-48 weeks) are available from two previous pediatric clinical trials where twice-daily dosing was administered. TMC114-C228 was a Phase 2 trial in which the safety, pharmacokinetic and efficacy of twice daily darunavir/ritonavir was evaluated in 21 treatment-experienced HIV-1-infected pediatric subjects 3 to less than 6 years of age and weighing at least 10 kg. TMC114-C212 was a Phase 2 trial in which the safety, pharmacokinetic and efficacy of twice daily darunavir/ritonavir was evaluated in 80 treatment-experienced HIV-1-infected pediatric subjects 6 to less than 18 years of age and weighing at least 20 kg.

The safety data from the twice-daily dosing were previously reviewed (see below for summary). Based on the overall safety (exposure-safety), tolerability and risk-benefit analysis, the twice daily dosing regimens were recommended and approved.

As summarized in the table below (Table 9), the proposed once daily dosing is expected to have similar exposure (AUC and Cmax) to the twice daily exposures.

- 10 to <15 kg (35 mg/kg QD): the predicted AUC, when compared to the AUC from BID (20/3 mg/kg BID) dosing for the same weight band, is 13% lower; the predicted Cmax, when compared to the Cmax from the BID dosing for the same weight band, is 20% higher. Additional comparison was made to the Cmax observed with a higher BID dose (25/3 mg/kg BID). Although this higher dose is not the approved dose, it provides safety data for the proposed 35 mg/kg qd dose: the predicted Cmax from the once daily dose, when compared to the Cmax from BID (25/3 mg/kg BID) dosing for the same weight band is 4% lower. Of note, an even lower QD dosing (e.g. 30mg/kg) could be considered for dose selection. The 30 mg/kg QD dose is predicted to have AUC and Cmax that is 25% lower and 2% higher, respectively, than the approved 20/3

mg/kg BID. However, the 30 mg/kg QD dose would also lead to exposures (AUC) that may compromise the efficacy (i.e. the 30 mg/kg would lead to an AUC that is 12% lower compared to the AUC observed with the approved adult dose).

- 15 to <30 kg (600 mg QD): the predicted AUC, when compared to the AUC from BID (20/3 mg/kg BID) dosing for the same weight band is 20% lower; the predicted Cmax, when compared to the Cmax from the BID dosing for the same weight band is 13% higher.
- 30 to <40 kg (675 mg QD): the predicted AUC, when compared to the AUC from BID (20/3 mg/kg BID) dosing for the same weight band is 25% lower; the predicted Cmax, when compared to the Cmax from the BID dosing for the same weight band is 6% higher.

In summary, the total daily dose of darunavir is lower for the proposed QD regimens compared to the approved BID regimens. Thus, as expected, all the predicted AUCs from the once daily dosing are lower than what is observed from the BID dosing. Therefore, the predicted AUCs are supported by the exposure-safety data from the pediatric trial where twice daily dosing was administered. Also as expected, the predicted Cmax from the once daily dosing are higher when compared to the BID dosing. However, none of the predicted Cmax from the once daily are significantly higher than what was observed with the BID dosing (i.e. range: 4-13% higher). Such increases may be observed in scenarios such as drug-drug interactions where no dose adjustments would be recommended. Therefore, based on the percent differences calculated between the QD and the BID doses for a given weight band, the once daily dosing is expected to be generally safe and tolerated.

Table 9 Safety
(Comparing the Predicted AUC, Cmax from Once Daily Dosing to the Observed AUC, Cmax from Twice-Daily dosing*: Trials C212 and C228)

Weight band	Pediatric Dosing	Median AUC(0-24h) [mcg*hr/mL]	**% difference from BID exposure (same weight group)**	Median Cmax (ng/mL)	**% difference from BID exposure (same weight group)**	
10 to < 15 kg						
	35 mg/kg	90	**87**	6641	**120**	**96^**
	40 mg/kg	*103*	***100***	*7590*	***137***	***107^***
15 to < 30 kg						
	600 mg	*93.3*	***80***	*7004*	***113***	
30 to< 40 kg						
	675 mg	83.8	**75**	6347	**106**	
	800 mg	*99.3*	***89***	*7522*	***126***	

* Once-daily exposures compared to the approved twice-daily dosing in children.
^Once-daily exposures compared to the Cmax from the non-approved 25/3 mg/kg BID dose. The Cmax from the 25/3 mg/kg BID dosing is 6946 in the 10-15 kg group.

Summary of safety profile from the approved twice-daily dosing in children is provided below. Of note, no exposure-safety relationship was identified during the analysis. Please refer to the clinical and clinical pharmacology reviews of Trial C228 and C212 for additional details.

Safety evaluation in 3 to less than 6 years of age (C228; BID dosing)
During the 24 week treatment period, 1 patient discontinued the trial due to AE (vomiting); the vomiting (Grade 2) was considered to be very likely related to ritonavir, but not darunavir. The event resolved after treatment discontinuation on Day 14. There were no deaths reported during the 24 week treatment period. The most common adverse events (all grades, regardless of causality) reported in at least 3 subjects were (by preferred term) were: upper respiratory tract infection (33%, n=9), diarrhea (30%, n=8), hypokalemia (19%, n=5), alkalosis, cough and nasopharyngitis (15%, n=4 each). No treatment related grade 3 or higher adverse events were reported after the darunavir dosage regimens were adjusted (i.e. after Week 2). Three patients (11%) had liver-related adverse event during the treatment period (AST increased, ALP increased, hepatosplenomegaly). All were grade 2 in severity; AST increased was considered possibly related to DRV. None of the events were reported as an SAE, or led to permanent treatment discontinuation. There were no subjects meeting Hy's Law criteria. Four rash events (regardless of causality, severity) were reported from three subjects. The events included: erythema (1 patient), rash (1 patient), and rash papular and rash pruritic (both in the same patient). One subjects had grade 1 rash (papular) considered possibly treatment-related. No rash-related AEs were reported as serious events, or led to permanent treatment discontinuation. With the exception of the one subject with grade 2 increased AST (referenced above), there were no additional liver-related laboratory parameters reported as abnormal. All except 1 hematology laboratory abnormality were grade 1 in severity. Grade 3 decreased neutrophil was observed in 1 patient at Week 24; this patient had grade 1 decreased neutrophil at screening, and marked fluctuations during treatment period. Refer to the clinical review of study C228 for additional details.

Safety evaluation in 6 to less than 18 years of age (C212; BID dosing)
The types of adverse events reported during this clinical trial were similar to what was observed during the adult clinical trial but the frequency of events was lower in the pediatric trial. There were no deaths reported; no subject (in the age group 6 to 12 years of age) discontinued due to adverse event while one, 17 year old subject discontinued due to 'acute anxiety' (Grade 3, non-serious, not related to study drug). The most common SAE reported (by System Organ Class) was 'Infection and Infestations', which is similar to what was observed during the adult clinical trial. Overall, 18(23%) reported adverse events ≥ Grade 3, which included neutropenia, leukopenia, increase in ALT and anxiety. In addition, 5(6%) reported hepatic related adverse events: increase in liver enzyme, hepatomegaly, and Hepatitis A infection. Five subjects experienced rash (rash, macular rash, maculopapular rash, papular rash, allergic rash, pruritis). Of note, 'Hepatotoxicity' and 'Severe Skin Reactions' are included under the Warnings section of the approved PI. In summary, darunavir co-administered with ritonavir in combination with other antiretroviral drugs was safe and tolerable when administered to pediatric subjects 6 to 18 years of age. Based on efficacy, safety, pharmacokinetic, and overall risk-benefit analysis, study C212 was used to recommend twice daily darunavir dosing in children 6 to less than 18 years of age.

8. Labeling

Package Insert

The following revisions to the Dosing and Administrations section of the USPI were successfully negotiated:

The recommendations for the PREZISTA/ritonavir dosage regimens were based on the following:

- Results from one trial in treatment-naive pediatric subjects 12 to less than 18 years of age demonstrating similar darunavir plasma exposures, virologic response rate and safety profile compared to treatment-naive adults.
- Results from population pharmacokinetic modeling and simulation in children 3 to less than 12 years of age predicting similar darunavir plasma exposures compared to treatment-naive adults. (b) (4) although no clinical trial was conducted to collect exposure-safety data, the predicted exposures from the once daily dosing is supported by exposures observed in pediatric clinical trials where twice-daily dosing was administered.

- *Pediatric pateints weighing at least 10 kg but less than 15 kg*

The weight-based dose in treatment-naïve (b) (4) pediatric patients with no darunavir resistance associated substitutions is PREZISTA 35 mg/kg once daily with ritonavir 7 mg/kg (b) (4) using the following table:

Table 1: Recommended dose for pediatric patients weighing 10 kg to less than 15 kg who are treatment-naïve or treatment-experienced with no darunavir resistance associated substitutions*

Body weight (kg)	**Formulation: PREZISTA Oral Suspension (100 mg/mL) and Ritonavir Oral Solution†**
	Dose: once daily with food
Greater than or equal to 10 kg to less than 11 kg	PREZISTA 3.6 mL‡ (350 mg) with ritonavir 0.8 mL (64 mg)
Greater than or equal to 11 kg to less than 12 kg	PREZISTA 4 mL‡ (385 mg) with ritonavir 0.8 mL (64 mg)
Greater than or equal to 12 kg to less than 13 kg	PREZISTA 4.2 mL (420 mg) with ritonavir 1 mL (80 mg)
Greater than or equal to 13 kg to less than 14 kg	PREZISTA 4.6 mL‡ (455 mg) with ritonavir 1 mL (80 mg)
Greater than or equal to 14 kg to less than 15 kg	PREZISTA 5.0 mL‡ (490 mg) with ritonavir 1.2 mL (96 mg)

* darunavir resistance associated substitutions: V11I, V32I, L33F, I47V, I50V, I54M, I54L, T74P, L76V, I84V and L89V (b) (4)

‡ The 350 mg, 385 mg, 455 mg and 490 mg darunavir doses for the specified weight groups were rounded (b) (4) for suspension dosing to 3.6 mL, 4 mL, 4.6 mL and 5 mL, respectively.

- *Pediatric patients weighing at least 15 kg*

(b) (4) pediatric patients (b) (4) at least 15 kg can be dosed with Prezista oral tablet or solution using the following table:

Table 2: Recommended dose for pediatric patients weighing at least 15 kg who are treatment-naïve or treatment-experienced with no darunavir resistance associated substitutions*		
Body Weight (kg)	**Formulation: PREZISTA tablet(s) and ritonavir capsule or tablet†**	**Formulation: PREZISTA oral suspension and ritonavir oral solution‡**
	Dose: once daily with food	**Dose: once daily with food**
Greater than or equal to 15 kg to less than 30 kg	PREZISTA 600 mg with ritonavir 100 mg	PREZISTA 6 mL with ritonavir 1.25 mL
Greater than or equal to 30 kg to less than 40 kg	PREZISTA 675 mg with ritonavir 100 mg	PREZISTA 6.8 mL§,∫ with ritonavir 1.25 mL
Greater than or equal to 40 kg	PREZISTA 800 mg with ritonavir 100 mg	PREZISTA 8 mL# with ritonavir 1.25 mL
* darunavir resistance associated substitutions: V11I, V32I, L33F, I47V, I50V, I54M, I54L, T74P, L76V, I84V and L89V † with ritonavir capsule or tablet: 100 mg ‡ with ritonavir oral solution: 80 mg/mL § The 675 mg dose using darunavir tablets for this weight group is rounded off to 6.8 mL for suspension dosing. ∫ An 6.8 mL darunavir dose should be taken as two 3.4 mL administrations with the included oral dosing syringe # (b) (4)		

9. Outstanding Issues

None.

10. Recommendations/ Risk Benefit Assessment

I recommend the approval of these sNDAs which provide for once daily dosing regimen in treatment naïve or experienced pediatric patients 3 to less than 18 years of age with no darunavir associated substitutions.

The data from the current submission provides sufficient pharmacokinetic evidence to recommend darunavir once daily dosing, co-administered with ritonavir in combination with other ART for the treatment of HIV-1 infection in pediatric patients 3 to < 12 years of age. The doses selected are predicted to lead to exposures (AUC) that are within 95% to 102% of the target mean adult AUC and the predicted C0 are within 102% to 126% of the target mean adult C0. Results from C230 also demonstrated that darunavir was an effective treatment in suppressing HIV RNA below assay limits of detection. Overall the proportion of subjects with HIV RNA < 50 copies/mL at Week 48 was 92%. No subject discontinued due to virologic failure. Based on pharmacokinetic data, it can be extrapolated that the predicted exposures from the once daily dosing in all pediatric age group should be efficacious.

As no clinical safety data was collected for the once daily dosing in the 6 to less than 12 years of age group, the predicted exposure from the recommended doses were compared to the exposure data from the twice-daily dosing in children 3 to less than 12 years of age. The once daily doses selected are predicted to lead to exposures (AUC) that are within 75% to 87% of the observed AUC in pediatric BID dosing. The predicted Cmax are within 106% to 120% of observed Cmax from the approved pediatric BID dosing; alternatively, the predicted Cmax are within 96% to 113% of the observed Cmax when comparison includes the non-approved 25mg/kg BID dosing for the 10 to less than 15 kg weight band. Specifically, when the

predicted Cmax for the 35mg/kg QD dosing is compared to the non-approved 25/3 mg/kg BID dosing, the difference between the QD vs. BID Cmax is even less- i.e. the predicted Cmax from QD dosing is within 96% of the observed Cmax at the 25/3 mg BID dosing. In addition, no exposure-safety relationship was identified during the clinical trial where twice daily dosing was administered. Safety data submitted from trial C230 supports the proposed once daily dosing in children 12 to less than 18 years of age. There were no deaths or AEs leading to treatment discontinuation.

Recommendation for other Postmarketing Requirements and Commitments

None.

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/s/

YODIT BELEW
01/10/2013