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Poster 509

HIV-1 Attachment Inhibitor Prodrug BMS-663068: Pharmacokinetics, Pharmacodynamics and Model-Based Dose Selection

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BACKGROUND

- BMS-663068 is a prodrug of BMS-626529, a first-in-class attachment inhibitor that binds to HIV-1 gp120, preventing initial viral attachment and entry into the host CD4+ T cell (Figure 1).[1]
  - Active against CCR5-, CXCR4- and dual-tropic strains of HIV-1.[2-5]
  - *In vitro* activity against HIV-1 viruses, except subtype AE and group O.[2]
  - Unique resistance profile with no *in vitro* cross-resistance to other classes of antiretrovirals.[2,5]
- BMS-663068 is delivered as an extended-release formulation, which is metabolized to the active moiety BMS-626529 by alkaline phosphatase in the gastrointestinal lumen (Figure 2).[6]
  - BMS-626529 is rapidly absorbed due to its efficient membrane permeability.[2,6]
  - BMS-626529 is a substrate of the P-glycoprotein transporter and is predominately metabolized by an esterase-mediated hydrolysis pathway with contributions from a CYP3A4-mediated oxidative pathway.

Figure 1: BMS-626529 attachment inhibitor: proposed mechanism of action

Figure 2: Conversion of BMS-663068 to BMS-626529

Figure 1

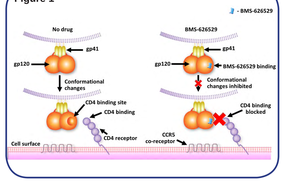
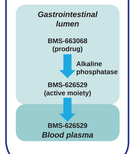


Figure 2



- In a Phase IIa BMS-663068 monotherapy study in treatment-naïve and -experienced subjects (AI438006), maximum median changes in plasma HIV-1 RNA of -1.21 to -1.73 $\log_{10}$ c/mL were observed after 8 days of monotherapy.[7]
  - BMS-663068 doses of 600 mg + 100 mg ritonavir (RTV) every 12 hours (Q12H); 1200 mg + 100 mg RTV every bedtime; 1200 mg + 100 mg RTV Q12H; 1200 mg Q12H + 100 mg RTV every morning, and 1200 mg Q12H were evaluated.
- AI438011 is an ongoing Phase IIb, dose-finding study in HIV-1-infected, treatment-experienced subjects.[8]
  - Seven-day BMS-663068 monotherapy substudy, followed by 96 weeks of combination antiretroviral therapy (cART) with raltegravir (RAL) + tenofovir disoproxil fumarate (TDF) (vs. RTV-boosted atazanavir + RAL + TDF).
  - BMS-663068 doses of 400 mg BID, 800 mg BID, 600 mg QD and 1200 mg QD evaluated.
  - A summary of key efficacy data is shown in Table 1.
- Population pharmacokinetic (PPK) and exposure–response (ER) analyses were performed to help select a Phase III dose, using data from AI438011 and AI438006.
  - As a 600 mg extended-release formulation of BMS-663068 is available, an additional BMS-663068 dose of 600 mg BID (not studied clinically) was evaluated due to clinical interest.

Table 1: Antiviral activity in AI438011

	BMS-663068 400 mg BID	BMS-663068 800 mg BID	BMS-663068 600 mg QD	BMS-663068 1200 mg QD	ATV/r 300/100 mg QD
	Monotherapy substudy				
N	7	5	10	10	-
Mean change in HIV-1 RNA after 7 days, $\log_{10}$ c/mL[§]	-0.7	-1.4	-1.2	-1.5	-
	cART with TDF (300 mg QD) + RAL (400 mg BID) Modified intent-to-treat analysis				
N	50	49	51	50	51
Proportion of subjects achieving HIV-1 RNA <50 c/mL through Week 24, %[¶]	80	69	77	72	75
Proportion of subjects achieving HIV-1 RNA <50 c/mL through Week 48, %[¶]	82	61	69	68	71

[§] See CROI poster 545, Thompson *et al.* (*Session P-J1, Tues Feb 24th, 2:30–4:00 pm PST*).
[¶] ATV/r, ritonavir boosted atazanavir; cART, combination antiretroviral therapy RAL, raltegravir; TDF, tenofovir disoproxil fumarate.

OBJECTIVES

- Population PK analysis
  - Develop a PPK model for BMS-626529 in HIV-1-infected subjects.
  - Explore and quantify the potential influence of covariates that contribute significantly to inter-subject differences in BMS-626529 PK parameters.
  - Determine post hoc estimates of derived systemic exposure metrics (maximum concentration [C_{max}], concentration at the end of a dosing interval [C_{tau}], and average steady-state concentration [$C_{ss,avg}$]) for BMS-626529 with and without normalizing for viral susceptibility.
- Exposure–response analysis
  - Develop models to characterize relationships between BMS-626529 systemic exposures, antiviral response during monotherapy and cART, and key safety parameters.
- Model-based dose simulation
  - Use model-based simulation to predict antiviral response as a function of BMS-626529 exposure for five proposed BMS-663068 dosing regimens.
  - Determine an appropriate BMS-663068 dose for use in the Phase III program.

METHODS

Population PK model development

- Non-linear, mixed-effect modeling approach implemented using NONMEM 7.2.0 (first-order conditional estimation model with interaction [FOCEI]).
- Data from Phase II studies AI438006 and AI438011:
  - BMS-663068 doses ranging from 600 mg QD to 1200 mg Q12H (with food)[7,8]
  - BMS-663068 dosed with or without RTV in AI438006[7]
  - BMS-663068 extended-release formulation; two formulations used, wet granulation (400 and 600 mg formulations used in AI438011) and dry granulation (AI438006).
- Base model developed using data from AI438011 and then applied to combined data from AI438011 and AI438006, allowing for selected covariates to assist with model stability.
  - Bioavailability factor included to convert BMS-663068 dose to BMS-626529 based on the relative molecular weights of BMS-663068 and BMS-626529.
- Covariate–parameter relationships investigated including: age, gender, race, treatment experience, laboratory parameters (creatinine clearance, liver enzyme levels, creatinine levels, total bilirubin), baseline disease characteristics (HIV-1 RNA, BMS-626529 IC_{90}, CD4+ T-cell count/%, CD8+ T-cell count/%).
  - All covariate–parameter relationships entered into base model to create full model.
  - Step-wise backwards deletion carried out at the p<0.001 significance level (increased objective function value <10.83 points, degrees of freedom=1), where the relative influence of each covariate was re-evaluated by deleting it from the full model on an individual basis.
  - Only statistically significant and/or clinically relevant relationships included in the final model.
- Model evaluation
  - A visual predictive check was used to evaluate the ability of the model to describe the central tendency and variability in exposures of BMS-626529.

Exposure–response analysis

- Exploratory graphical ER analyses were used to investigate potential relationships between BMS-626529 systemic exposure and response variables during BMS-663068 monotherapy and cART, including:
  - antiviral response during BMS-663068 monotherapy (decline in HIV-1 RNA [$\log_{10}$ copies/mL] from baseline)
  - antiviral response as part of cART (HIV-1 RNA <50 copies/mL through Weeks 24/48)
  - selected AEs (headache, diarrhea, nausea, vomiting and rash) – most frequently observed AEs in the AI438011 and AI438006 trials (other than infections)
  - changes in select laboratory parameters (serum albumin, liver enzymes, creatine kinase, amylase, total lipase, hematologic parameters).
- Linear models were used to quantify trends observed between BMS-626529 systemic exposure and antiviral response during BMS-663068 monotherapy.
  - With and without normalization for protein binding-adjusted BMS-626529 IC_{50} ($PBAIC_{50}$) and $\log_e$-transformation.
  - Baseline HIV-1 RNA tested as a covariate on the slope of linear models.
- Logistic regression was used to evaluate possible relationships between BMS-626529 systemic exposure and response as part of cART.

Model-based simulations of BMS-663068 doses

- The final PPK and ER models were implemented in Pharsight Trial Simulator and the following BMS-663068 dosing regimens were evaluated: 400, 600 and 800 mg BID; 600 and 1200 mg QD.
  - 600 mg BID dose not studied clinically.
  - Simulations incorporated the expected range in baseline $PBAIC_{50}$ values, resampled at random from baseline IC_{90} values observed in AI438006 and AI438011.
  - Simulations were used to estimate the proportion of patients expected to achieve a decrease in HIV-1 RNA from baseline of >1 and >0.5 $\log_{10}$ c/mL for each proposed dosing regimen.

RESULTS

Subject disposition, demographics and disease characteristics

- The PPK analyses included 244 subjects (50 from AI438006 and 194 from AI438011).
  - A summary of baseline subject demographics and disease characteristics is shown in Table 2.
- The ER analyses performed at the subject level included 209 subjects:
  - 77 subjects who received BMS-663068 monotherapy (48 from AI438006 and 29 from AI438011).
  - 190 subjects who received BMS-663068 as part of cART (AI438011 – modified intent-to-treat population).

Table 2: Baseline demographics and disease characteristics

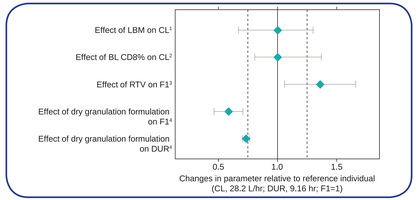
Parameter	Value (N=244)[*]
Median baseline age, years (range)	40.0 (20–70)
Median baseline weight, kg (range)	71.0 (40.0–151.3)
Median baseline LBM, kg (range)	54.0 (32.0–76.0)
Gender, n (%)	
Male	166 (68)
Female	78 (32)
Race, n (%)	
White	122 (50)
Black/African American	59 (24)
Asian	2 (1)
Other*	61 (25)
BMS-663068 formulation, n (%)	
Dry granulation	50 (20)
Wet granulation	194 (80)
Received concomitant ritonavir (AI438006 only), n (%)	40 (16)
Prior therapy experience, n (%)	
Experienced	210 (86)
Naïve	34 (14)
Median baseline HIV-1 RNA, $\log_{10}$ copies/mL (range)	4.8 (1.7–6.8)
Median baseline CD4+ T-cell count, cells/mm^3 (range)	271 (32–921)
Median baseline CD8+ T-cell count, cells/mm^3 (range)	886 (180–3162)
Median baseline CD4+ T-cell count, % (range)	18 (3–40)
Median baseline CD8+ T-cell count, % (range)	57 (32–83)

[*] Majority of subjects within the "other" category reported themselves as multiracial. [†] N=240 for CD4+ and CD8+ T-cell counts.
LBM, lean body mass.

Population PK model

- The PK of BMS-626529, following repeat oral administration of BMS-663068 to subjects with HIV-1 infection, were described as:
  - a two-compartment model with first-order elimination from the central compartment
  - an absorption phase with zero-order release into a hypothetical absorption compartment, and first-order absorption into the central compartment.
- Parameter estimates for the final PPK model are shown in Table 3.
- Final covariates that were statistically significant (p<0.001) on backwards deletion are shown in Figure 3.
  - Although p>0.001, effect of RTV on relative bioavailability was included due to clinical interest and magnitude of effect (~36% increase in relative bioavailability of the dry granulation formulation).

Figure 3: Predicted fold-change in PK parameters due to covariate effects



Categorical covariates (RTV, dry granulation formulation): Diamonds represent the estimated change in parameter due to the covariate and whiskers represent the 95% CI of the estimate. Continuous covariates (LBM, BL CD8%): Diamonds represent the reference and whiskers represent the change in parameter at the minimum and maximum value of the covariate (noted on plot). Dashed lines represent 25% change in parameter relative to reference individual. [1]Exponent for effect of median-normalized baseline LBM on CL. [2]Exponent for effect of median-normalized baseline CD8% on CL. [3]Change relative to reference (BMS-663068 dosed without RTV). [4]Change relative to reference (wet granulation) formulation.
BL, baseline; CL, apparent clearance; DUR, estimated duration of BMS-663068 release from the extended-release formulation; F1, relative bioavailability; LBM, lean body mass; RTV, ritonavir.

Table 3: Parameter estimates for the final PPK model

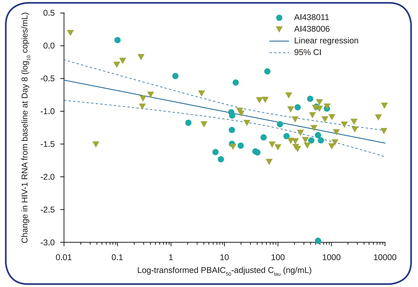
Parameter	Units	Estimate (CV, %)	RSE %	95% CI Lower	95% CI Upper
Fixed effects					
CL (θ1)	L/hr	28.2	3.39	26.3	30.1
V2 (θ2)	L	32.3	16.2	22.1	42.5
KA (θ3)	hr^{-1}	1.22	9.92	0.983	1.46
Q (θ4)	L/hr	14.5	5.17	13.0	16.0
V3 (θ5)	L	85.5	6.32	74.9	96.1
DUR (θ6)	hr	9.16	1.06	8.97	9.35
Effect of dry formulation on F1 (θ7)[‡]	-	0.586	10.6	0.464	0.708
Effect of dry formulation on DUR (θ8)[‡]	-	0.736	2.11	0.706	0.766
Effect of RTV on F1 (θ9)[‡]	-	1.36	11.1	1.06	1.66
Effect of LBM on CL (θ10)[§]	-	0.770	18.8	0.486	1.05
Effect of baseline CD8% on CL (θ11)[¶]	-	-0.548	28.6	-0.856	-2.40
Inter-individual random effects					
CL, variance	-	0.132 (36.3)	10.8	0.104	0.160
V2, variance	-	1.12 (106.0)	18.7	0.710	1.53
V3, variance	-	0.295 (54.3)	18.6	0.187	0.403
Residual error random effects					
Proportional error	-	0.341 (58.4)	2.12	0.327	0.355

1. Change relative to reference (wet granulation) formulation. 2. Change relative to reference (BMS-663068 dosed without RTV). 3. Exponent for effect of median-normalized baseline LBM on CL. 4. Exponent for effect of median-normalized baseline CD8% on CL. $CL = \theta2 \times (LBM/54)^{\theta10} \times (BL\ CD8\%/57)^{\theta11}$; [‡] $F1 = 0.81 \times \theta7^{FORM}$ (if 600 mg dry granulation, FORM = 1, otherwise = 0) x $\theta9^{RTV}$ (if RTV coadministration, RTV = 1, otherwise = 0); 0.81 converts dose of BMS-663068 to BMS-626529 equivalent. DUR = $\theta6 \times \theta8^{FORM}$ (if 600 mg dry granulation, FORM = 1, otherwise = 0).
95% CI, 95% confidence interval; BL CD8%, baseline CD8%; CL, apparent oral clearance; CV, coefficient of variation; DUR, estimated duration of BMS-663068 release from the extended-release formulation; F1, relative bioavailability; FORM, formulation; KA, first-order absorption rate constant; LBM, lean body mass; Q, inter-compartmental clearance; RSE, relative standard error of the estimate; RTV, ritonavir; V2, central volume of distribution; V3, peripheral volume of distribution.

Exposure–response analysis

- For BMS-663086 given as monotherapy:
  - baseline viral drug susceptibility ($PBAIC_{50}$) was the most influential factor in determining the magnitude of decline in HIV-1 RNA levels during BMS-663068 monotherapy
  - the final model used described the relationship between $\log_e$-transformed $PBAIC_{50}$ adjusted $C_{ss,avg}$ and C_{tau} and the change in HIV-1 RNA ($\log_{10}$ copies/mL) from baseline after 7 days of treatment (Figure 4)
  - no trends were noted for any other efficacy or safety variables during monotherapy.

Figure 4: Relationship between $PBAIC_{50}$-adjusted C_{tau} and change from baseline in HIV-1 RNA ($\log_{10}$ c/mL)[§] after 7 days of BMS-663068 monotherapy



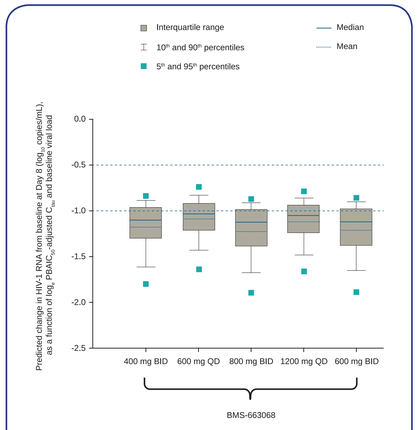
CI, confidence interval; $C_{ss,avg}$, concentration at the end of a dosing interval; $PBAIC_{50}$, protein binding-adjusted half-maximal inhibitory concentration.

- For BMS-663068 given as part of cART: no relationships were observed between BMS-626529 systemic exposure and any efficacy or safety variables during 24 or 48 weeks of combination therapy with RAL + TDF (data not shown).
- As no discernable differences were seen between $C_{ss,avg}$ and C_{tau} in predicting HIV-1 decline during monotherapy, C_{tau} was selected for analysis because it is traditionally considered to be a better predictor of antiviral activity.

Model-based simulation of proposed BMS-663068 doses

- Simulations were used to assess the probability of achieving a >0.5 or >1 $\log_{10}$ c/mL decline in HIV-1 RNA after 7 days of BMS-663068 monotherapy, as a function of BMS-626529 $\log_e$ $PBAIC_{50}$-adjusted C_{tau}, for the five proposed BMS-663068 dosing regimens (Figure 5).
  - Baseline HIV-1 RNA was included as a significant covariate in response.
- The ER modeling predicted:
  - a 99–100% probability of achieving a >0.5 $\log_{10}$ c/mL decline in HIV-1 RNA for all proposed doses
  - a 57–73% probability of achieving a >1 $\log_{10}$ c/mL decline in HIV-1 RNA for BMS-663068 400 mg BID, 600 mg QD, and 800 mg BID
  - a 61% probability of achieving a >1 $\log_{10}$ c/mL decline in HIV-1 RNA for a BMS-663068 1200 mg QD dose
  - a 71% probability of achieving a >1 $\log_{10}$ c/mL decline in HIV-1 RNA for a BMS-663068 600 mg BID dose (not studied clinically).

Figure 5: Probability of achieving a >0.5 and >1 $\log_{10}$ c/mL decline in HIV-1 RNA after 7 days of BMS-663068 monotherapy as a function of $\log_e$ $PBAIC_{50}$-adjusted C_{tau}



	BMS-663068 400 mg BID	BMS-663068 600 mg QD	BMS-663068 800 mg BID	BMS-663068 1200 mg QD	BMS-663068 600 mg BID
Probability of >0.5 $\log_{10}$ c/mL decline, %	100	99.5	99.9	99.8	100
Probability of >1 $\log_{10}$ c/mL decline, %	68.0	57.4	72.6	60.8	71.1

$C_{ss,avg}$, concentration at the end of a dosing interval; $PBAIC_{50}$, protein binding-adjusted half-maximal inhibitory concentration.

CONCLUSIONS

- This modeling and simulation analysis showed that:
  - all proposed BMS-663068 doses had a similar probability (99–100%) of achieving a decline in HIV-1 RNA of >0.5 $\log_{10}$ copies/mL, after 7 days of BMS-663068 monotherapy
  - BID doses had a slightly higher probability of achieving a decline in HIV-1 RNA of >1 $\log_{10}$ copies/mL, compared with QD doses.
- Phase III dose of 600 mg BID was selected based on the following:
  - 600 mg BID dose had a similar or slightly higher probability of achieving a decline in HIV-1 RNA of >1 $\log_{10}$ copies/mL following 7 days of BMS-663068 monotherapy, when compared with the 800 mg BID and 1200 mg QD doses, respectively
    - A total daily dose of 1200 mg (1200 mg QD) showed comparable efficacy and safety to a total daily dose of 1600 mg (800 mg BID) when administered as cART for 24/48 weeks in AI438011 (Table 1)[8,*]
    - 400 mg BID dose excluded as an HIV-1 RNA decline of >1.0 $\log_{10}$ c/mL was not achieved after 7 days of monotherapy in AI438011 (Table 1).[8]
  - The 600 mg BID dose is expected to result in a lower C^{max}, compared with 800 mg BID and 1200 mg QD doses, allowing for a greater margin from supratherapeutic doses associated with QTc interval prolongation.
    - A supratherapeutic dose of BMS-663068 2400 mg BID was associated with QTc interval prolongation; whereas a dose of 1200 mg QD had no clinically meaningful effect on QTc intervals.[9]
    - BMS-663068 may be used in combination with antiretroviral agents, such as RTV-boosted protease inhibitors that may increase BMS-626529 C_{max} by ~50–68%.[10,†]
    - The lower C_{max} estimated for the 600 mg BID dose would minimize the risk of QTc interval prolongation if BMS-663068 was to be coadministered with RTV-boosted protease inhibitors.
  - 600 mg BID dose yielded a higher C_{tau} than the 1200 mg QD dose despite comparable efficacy based on quantitative analysis.
    - C_{tau} is considered to be an important PK-PD determinant with respect to antiviral effect so the 600 mg BID dose would be expected to maximize efficacy.

- Two accompanying posters are presented:
  - *Attachment Inhibitor Prodrug BMS-663068 in Antiretroviral-Experienced Subjects: Week 48 Analysis (*Poster 545, Session P-J1, Tuesday, February 24th 2:30–4:00 pm PST*).
  - [†]HIV-1 Attachment Inhibitor Prodrug BMS-663068: Interactions with DRV/r and/or ETR (*Poster 523, Session P-H3, Tuesday, February 24th 2:30–4:00 pm PST*).

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