Poster 472

Attachment Inhibitor Prodrug BMS-663068 in Antiretroviral-Experienced Subjects: Week 96 Analysis

E DeJesus,[1] M Martins,[2] A Stoehr,[3] JA Villanueva,[4] N Zakharova,[5] DA Stock,[6] C Llamoso,[6] SR Joshi,[6] GJ Hanna,[7] M Lataillade[6]

1. Orlando Immunology Center, Orlando, FL, USA; 2. Instituto Oulton, Córdoba, Argentina; 3. IFI Institute for Interdisciplinary Medicine, Asklepios Klinik St Georg, Hamburg, Germany; 4. HIV Unit, Hospital Civil de Guadalajara "Fray Antonio Alcalde", Guadalajara, Mexico; 5. Saint-Petersburg GUZ Center of AIDS, St Petersburg, Russian Federation; 6. Bristol-Myers Squibb, Research and Development, Wallingford, CT, USA; 7. Bristol-Myers Squibb, Research and Development, Princeton, NJ, USA

Corresponding author:
Edwin DeJesus, MD
Orlando Immunology Center
Orlando, FL 32803
USA
Email: edejesus@oicorlando.com
Phone: +1-(407)-647-3960

BACKGROUND

- BMS-663068 is a prodrug metabolized to the active moiety 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 (Figures 1a & 1b).[1,2]
- Unlike CCR5 antagonists, BMS-626529 binds directly to the virus rather than the host cell[2,3] and therefore:
  - acts prior to co-receptor binding and fusion[2]
  - is active against CCR5-, CXCR4- and dual-tropic (R5X4) strains of HIV-1.[2,4–7]
- BMS-626529 has:
  - *in vitro* activity against HIV-1 viruses (except subtype AE and Group O)[4]
  - a unique resistance profile and no *in vitro* cross-resistance has been observed with other classes of antiretrovirals (ARVs).[4,5]

Figure 1a: Conversion of BMS-663068 to BMS-626529

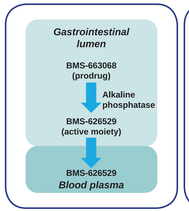
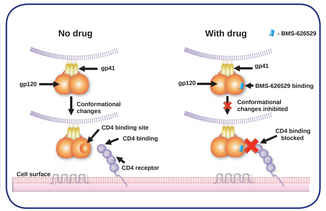


Figure 1b: BMS-626529 attachment inhibitor: proposed mechanism of action



AI438011 efficacy and safety through Week 48[8,9]

- AI438011 is an ongoing Phase IIb study investigating the efficacy, safety and dose response of BMS-663068 versus ritonavir-boosted atazanavir (ATV/r), each with tenofovir disoproxil fumarate (TDF) and raltegravir (RAL), in HIV-1-infected, treatment-experienced subjects.
  - A 7-day lead-in monotherapy substudy showed median decreases in plasma HIV-1 RNA of 0.69–1.44 $\log_{10}$ c/mL.
  - After 24 and 48 weeks, the BMS-663068 arms (doses of 400 and 800 mg BID, and 600 and 1200 mg QD) showed similar efficacy to the ATV/r arm.
    - Modified intent-to-treat (mITT) analysis: 69–80% and 61–82% of subjects achieved HIV-1 RNA <50 c/mL at Week 24 and Week 48, respectively, versus 75% and 71% in the ATV/r arm, respectively.
    - Observed analysis: 78–87% and 69–91%, of subjects achieved HIV-1 RNA <50 c/mL at Week 24 and Week 48, respectively, versus 86% and 88% in the ATV/r arm, respectively.
  - BMS-663068 was generally well tolerated, with no dose-related safety signals.
  - As BMS-663068 1200 mg QD was selected as the open-label continuation dose after Week 48, we present the pooled efficacy and safety results through Week 96.

Endpoints

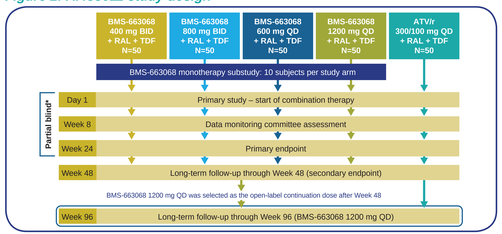
- Week 96 secondary endpoints (presented here for the first time):
  - proportion of subjects achieving HIV-1 RNA <50 c/mL
  - mean change in CD4+ T-cell count from baseline
  - frequency of serious adverse events (SAEs) and AEs leading to discontinuation.

METHODS

AI438011 study design (Figure 2)

- Phase IIb, randomized, active-controlled, blinded-to-BMS-663068 dose trial (NCT01384734).
- Consisted of a 7-day elective monotherapy substudy and the main study.
- Subjects were randomized 1:1:1:1:1 to four experimental arms and a reference arm.
- BMS-663068 1200 mg QD was selected as the open-label continuation dose after Week 48.

Figure 2: AI438011 study design



* Blinded to BMS-663068 dose.
ATV/r, ritonavir-boosted atazanavir; RAL, raltegravir; TDF, tenofovir disoproxil fumarate.

Key entry criteria

- ARV treatment experienced (current or previous exposure to ≥1 ARV for ≥1 week).
- Plasma HIV-1 RNA ≥1000 c/mL.
- CD4+ T-cell count >50 cells/μL.
- Susceptibility to RAL, TDF and ATV.
- BMS-626529 IC_{50} <0.1 μM (100 nM) as determined by screening PhenoSense® Entry assay (Monogram Biosciences, USA).

Statistical analysis

- This was an estimation study and not powered to demonstrate statistical differences between treatment arms.
- mITT analyses consisted of all randomized subjects who received at least one dose of study medication.
- Observed analyses consisted of all treated subjects who received at least one dose of study medication with HIV-1 RNA measurements within the time period of interest.
- For Week 96, presentation of efficacy and safety results is a pooled analysis.

RESULTS

Baseline characteristics

- Baseline demographic and disease characteristics were broadly similar across all treatment groups (Table 1).
  - Median age 39 years; 60% male.
  - 66% HIV-1 subtype B.
  - Median baseline HIV-1 RNA: 4.85 $\log_{10}$ c/mL.
  - Median baseline CD4+ T-cell count: 229.5 cells/μL.
  - ~50% of subjects had ≥1 major protease inhibitor (PI), nucleoside reverse transcriptase inhibitor (NRTI) or non-NRTI resistance-associated mutation at baseline (M184V/I, 31%; K103N, 29%; thymidine analogue mutations, 13%; major PI mutations, 2%).

Table 1: Baseline characteristics

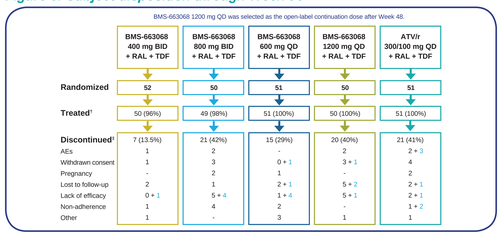
Parameter	BMS-663068 + TDF + RAL					ATV/r + TDF + RAL
	400 mg BID N=50	800 mg BID N=49	600 mg QD N=51	1200 mg QD N=50	Pooled N=200	300 mg/100 mg QD N=51
Median age, years (range)	39 (22–57)	37 (23–60)	40 (26–58)	40 (20–67)	39 (20–67)	39 (20–68)
Male, %	62.0%	57.1%	56.9%	68.0%	61.0%	56.9%
Race, %						
White	40.0%	38.8%	33.3%	32.0%	36.0%	45.1%
Black/African-American	28.0%	30.6%	31.4%	36.0%	31.5%	25.5%
Other*	32.0%	30.6%	35.3%	32.0%	32.5%	29.4%
HIV subtype, %						
B	70.0%	59.2%	68.6%	64.0%	65.5%	66.7%
C	16.0%	24.5%	21.6%	20.0%	20.5%	17.6%
Other	14.0%	16.4%	9.9%	16.0%	14.0%	15.7%
HIV-1 RNA						
Median, $\log_{10}$ c/mL	4.97	5.01	4.88	4.78	4.9	4.78
≥100,000 c/mL, %	46.0%	51.0%	45.1%	36.0%	44.5%	35.3%
CD4+ T-cell count						
Median, cells/μL	214	237	226	224	226	249
<200 cells/μL, %	38.0%	32.6%	41.2%	42.0%	38.5%	37.3%
BMS-626529 IC_{50} median, nM	0.68	0.65	0.43	0.82	0.65	0.73

Majority of subjects within the "other" category reported themselves as multiracial. Previously presented by Lalezari *et al.*[8]
ATV/r, ritonavir-boosted atazanavir; RAL, raltegravir; TDF, tenofovir disoproxil fumarate.

Subject disposition

- 581 subjects were screened, 254 randomized and 251 treated (Figure 3).
- Most common reason for screen failure was a screening plasma HIV-1 RNA <1000 c/mL (29%).
- Of those receiving treatment, 63/200 (31.5%) across the BMS-663068 arms and 21/51 (41%) in the ATV/r arm failed to complete 96 weeks of treatment (Figure 3).
  - Overall, a total of 22 additional subjects discontinued treatment between the Week 48 and Week 96 database locks (Figure 3, additional subjects are shown in blue text).

Figure 3: Subject disposition through Week 96*



* 581 subjects screened. † Two subjects in 400 mg BID arm and one subject in the 800 mg BID arm were randomized but not treated. ‡ Overall, an additional 22 subjects discontinued between the Week 48 and Week 96 database locks; additional subjects are highlighted in blue text.
AE, adverse event; ATV/r, ritonavir-boosted atazanavir; RAL, raltegravir; TDF, tenofovir disoproxil fumarate.

Virologic efficacy

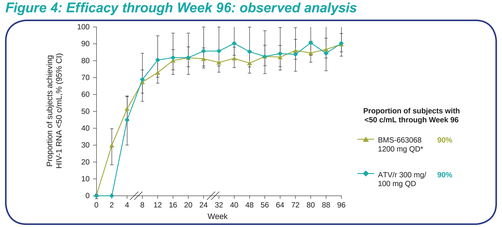
- Week 96 efficacy results are presented in Tables 2 and 3, and in Figures 4 and 5.

Table 2: Proportion of subjects achieving HIV-1 RNA <50 c/mL (Week 96 Snapshot): mITT analysis

Parameter, n (%)	BMS-663068 + TDF + RAL 1200 mg QD* N=200	ATV/r + TDF + RAL 300 mg/100 mg QD N=51
HIV-1 RNA <50 c/mL	122 (61%)	27 (53%)
HIV-1 RNA ≥ 50 c/mL	14 (7%)	3 (6%)
Reasons for not achieving HIV-1 RNA <50 c/mL	64 (32%)	21 (41%)
Discontinued due to lack of efficacy	21 (10.5%)	3 (6%)
Discontinued due to other reasons	24 (12%)	6 (12%)
No virologic data at Week 96		
Discontinued due to AEs	6 (3%)	5 (10%)
Discontinued for other reasons	13 (6.5%)	7 (14%)

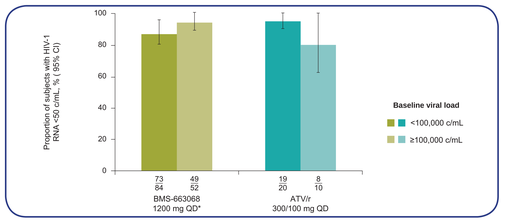
* Pooled data are presented because BMS-663068 1200 mg QD was selected as the open-label continuation dose after Week 48.
ATV/r, ritonavir-boosted atazanavir; mITT, modified intent-to-treat; RAL, raltegravir; TDF, tenofovir disoproxil fumarate.

Figure 4: Efficacy through Week 96: observed analysis



* Pooled data are presented because BMS-663068 1200 mg QD was selected as the open-label continuation dose after Week 48.
ATV/r, ritonavir-boosted atazanavir; CI, confidence interval.

Figure 5: Efficacy through Week 96 by baseline viral load: observed analysis



* Pooled data are presented because BMS-663068 1200 mg QD was selected as the open-label continuation dose after Week 48.
ATV/r, ritonavir-boosted atazanavir; CI, confidence interval

Table 3: Efficacy through Week 96 by baseline BMS-626529 IC_{50} category: observed analysis

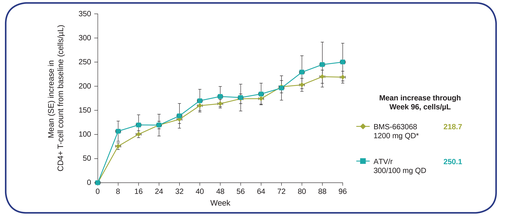
Baseline BMS-626529 IC_{50} category, n (%)	BMS-663068 + TDF + RAL 1200 mg QD* N=136	ATV/r + TDF + RAL 300 mg/100 mg QD N=30
<0.1 nM	5/6 (83%)	0
≥0.1 nM	117/130 (90%)	27/30 (90%)
<1 nM	70/79 (89%)	16/18 (89%)
≥1 nM	52/57 (91%)	11/12 (92%)
<10 nM	107/120 (89%)	24/27 (89%)
≥10 nM	15/16 (94%)	3/3 (100%)

* Pooled data are presented because BMS-663068 1200 mg QD was selected as the open-label continuation dose after Week 48.
ATV/r, ritonavir-boosted atazanavir; RAL, raltegravir; TDF, tenofovir disoproxil fumarate.

Immunologic endpoints

- Mean change in CD4+ T-cell count from baseline through Week 96 is shown in Figure 6.

Figure 6: Mean change in CD4+ T-cell counts from baseline through Week 96: observed analysis



* Pooled data are presented because BMS-663068 1200 mg QD was selected as the open-label continuation dose after Week 48.
ATV/r, ritonavir-boosted atazanavir; SE, standard error.

Safety endpoints from baseline through Week 96

- Safety endpoints from baseline through Week 96 are summarized in Table 4,
  - There were no SAEs or AEs leading to discontinuation that were related to BMS-663068.
  - SAEs related to study drug(s):
    - BMS-663068 arms: TDF-induced acute renal failure and study drug overdose
    - ATV/r: influenza-like symptoms and study drug (RAL) overdose.
  - AEs leading to discontinuation that were related to study drug(s):
    - BMS-663068 arms: TDF-induced acute renal failure
    - ATV/r arm: abdominal distension, flatulence, increased blood bilirubin, hepatic steatosis and hypertransaminasemia.
  - One death occurred, which was unrelated to study drugs (gun shot wound).

Table 4: Safety summary*

Parameter, number of subjects (%)	BMS-663068 + TDF + RAL 1200 mg QD† N=200	ATV/r + TDF + RAL 300 mg/100 mg QD N=51
SAEs‡	24 (12%)	7 (14%)
AEs leading to discontinuation‡	5 (2.5%)	5 (10%)
Grade 2–4-related clinical AEs		
Total subjects with an event	17 (8.5%)	19 (37%)
Present in ≥2 subjects		
Hyperbilirubinemia	0	6 (12%)
Blood bilirubin increased	0	3 (6%)
Abdominal pain	1 (0.5%)	2 (4%)
Jaundice	0	2 (4%)
Nausea	0	2 (4%)
Headache	1 (0.5%)	2 (4%)

* AEs reported by investigators.
† BMS-663068 arms: Death (gun shot wound), anal abscess, herpes encephalitis, overdose (n=5), extrapulmonary tuberculosis (n=2), herpes zoster, abdominal pain, myalgia, spontaneous abortion, acute renal failure, cellulitis (n=2), lymphangitis, chronic cholecystitis, back pain (n=3), deep vein thrombosis, loss of appetite and herpes zoster neuralgia enoral, raised creatinine kinase, suicide attempt, sepsis of unknown origin/lumbar pain (screening) and vertigo/oral candidiasis (on treatment), neutropenia. ATV/r arm: overdose, influenza, pneumonia, pyelonephritis, diarrhea, cholelithiasis, migraine, trimalleolar right foot fracture.
‡ Illegal substance use, extrapulmonary tuberculosis (n=3), acute renal failure, abdominal distension, flatulence, jaundice, hepatic steatosis, hypertransaminasemia, blood bilirubin increase.
§ Pooled data are presented because BMS-663068 1200 mg QD was selected as the open-label continuation dose after Week 48.
AE, adverse event; ATV/r, ritonavir-boosted atazanavir; RAL, raltegravir; SAE, serious AE; TDF, tenofovir disoproxil fumarate.

Select Grade 3–4 laboratory abnormalities (≥2 subjects)

- A summary of Grade 3–4 laboratory abnormalities, present in ≥2 subjects is shown in Table 5.

Table 5: Select Grade 3–4 laboratory abnormalities (≥2 subjects)

Parameter, number of subjects (%)	BMS-663068 + TDF + RAL 1200 mg QD* N=200	ATV/r + TDF + RAL 300 mg/100 mg QD N=51
Neutropenia	6 (3%)	1 (2%)
Alanine aminotransferase	2 (1%)	3 (6%)
Aspartate aminotransferase	4 (2%)	3 (6%)
Total bilirubin	0	31 (62%)
Creatinine kinase	6 (3%)	0
Glucose fasting serum	2 (1%)	0
Uric acid	3 (2%)	0

* Pooled data are presented because BMS-663068 1200 mg QD was selected as the open-label continuation dose after Week 48.
ATV/r, ritonavir-boosted atazanavir; RAL, raltegravir; TDF, tenofovir disoproxil fumarate.

CONCLUSIONS

- Following a switch of all BMS-663068-treated subjects to 1200 mg QD at Week 48, virologic (mITT and observed) and immunologic responses appeared to be generally similar across the BMS-663068 and ATV/r arms through Week 96.
- BMS-663068 was generally well tolerated and there were no BMS-663068-related SAEs or AEs leading to discontinuation.
- These results support the ongoing Phase III trial evaluating BMS-663068 in heavily treatment-experienced adults with limited therapeutic options (≤2 classes of active antiretrovirals remaining) due to resistance, tolerability issues and contraindications (NCT02362503).
- An accompanying poster (460) will be presented on February 25, 2016, 2:45 PM–4:00 PM titled, "HIV-1 Attachment Inhibitor Prodrug BMS-663068: PK Assessment with Rosuvastatin".

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