Melanie Thompson, MD
AIDS Research Consortium of Atlanta,
1512 Piedmont Avenue Northeast,
Atlanta GA 30324 USA
Email: drmt@mindspring.com
Phone: +1 (404) 876 2317

Attachment Inhibitor Prodrug BMS-663068 in Antiretroviral-Experienced Subjects: Week 48 Analysis

Poster 545

M Thompson,[1] J Lalezari,[2] R Kaplan,[3] Y Pinedo,[4] OA Sussmann Pena,[5] P Cahn,[6] D Stock,[7] SR Joshi,[7] GJ Hanna,[8] M Lataillade[7]

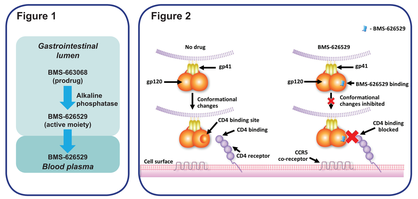
[1]AIDS Research Consortium of Atlanta, Atlanta, GA, USA; [2]Quest Clinical Research, San Francisco, CA, USA; [3]Desmond Tutu HIV Foundation, Cape Town, South Africa; [4]Asociacion Civil Via Libre, Lima, Peru; [5]Asistencia Cientifica de Alta Complejidad SAS, Bogotá, Colombia; [6]Fundacion Huesped, Buenos Aires, Argentina; [7]Bristol-Myers Squibb, Research and Development, Wallingford, CT, USA; [8]Bristol-Myers Squibb, Research and Development, Princeton, NJ, USA

BACKGROUND

- Novel antiretroviral agents are needed for heavily treatment-experienced patients who may have limited treatment options due to drug resistance, drug toxicities and drug interactions.
- 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 (Figure 1 & 2).[1,2]
  - — *In vitro* activity against HIV-1 viruses (except subtype AE and Group O).[3]
  - — Active against CCR5-, CXCR4- and dual-tropic (R5X4) strains of HIV-1.[2–6]
  - — Unique resistance profile with no *in vitro* cross-resistance to other classes of antiretrovirals.[3–4]
- 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 patients.
  - — In a lead-in BMS-663068 monotherapy substudy, mean decreases in plasma HIV-1 RNA of 0.7–1.5 $\log_{10}$ c/mL were observed after 7 days.[7]
  - — Through Week 24, the proportion of subjects achieving HIV-1 RNA <50 c/mL was similar across the BMS-663068 and ATV/r arms and there were no BMS-663068-related serious adverse events (SAEs) or adverse events (AEs) leading to discontinuation.[7]
    - In the modified intent-to-treat (mITT) analysis, 69–80% of patients in the BMS-663068 arms achieved HIV-1 RNA <50 c/mL compared with 75% of patients in the ATV/r arm.[7]
    - In the observed analysis, 78–87% of patients in the BMS-663068 arms achieved HIV-1 RNA <50 c/mL compared with 86% of patients in the ATV/r arm.[7]

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

Figure 2: BMS-626529 attachment inhibitor: proposed mechanism of action



OBJECTIVES

- Week 24 primary endpoints:[7]
  - — proportion of subjects achieving HIV-1 RNA <50 c/mL
  - — frequency of SAEs and AEs leading to discontinuation.
- Week 48 secondary endpoints:
  - — proportion of subjects achieving HIV-1 RNA <50 c/mL
  - — change in CD4+ T-cell count from baseline
  - — frequency of SAEs and AEs leading to discontinuation.

METHODS

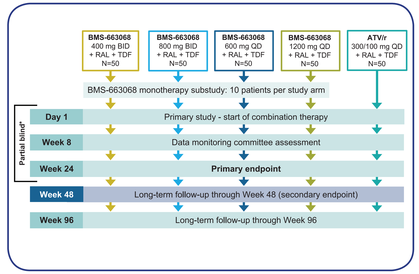
AI438011 study design

- Phase IIb, randomized, active-controlled, blinded-to-BMS-663068 dose trial (NCT01384734).
- Consisted of a 7-day elective monotherapy substudy and the main study (Figure 3).
- Subjects were randomized 1:1:1:1:1 to four experimental arms and a reference arm (Figure 3).

Key entry criteria

- Antiretroviral treatment-experienced (current or previous exposure to ≥1 antiretroviral for ≥1 week).
- Plasma HIV-1 RNA ≥1000 copies/mL.
- CD4+ T-cell count >50 cells/mm^3.
- Susceptibility to RAL, TDF, and ATV.
- BMS-626529 IC_{50} <100 nM as determined by screening PhenoSense® Entry Assay (Monogram Biosciences - LabCorp).

Figure 3: AI438011 study design



* Blinded to BMS-663068 dose. Subjects and investigators blinded to Week 48.

Statistical analysis

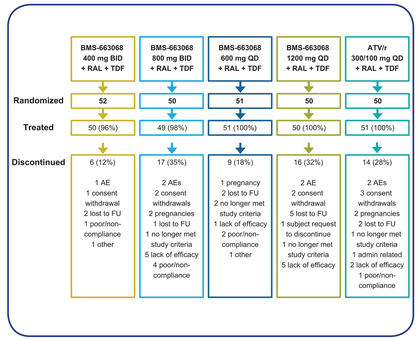
- This was an estimation study and not powered to demonstrate statistical differences between treatment arms.

RESULTS

Subject disposition

- 581 subjects were screened, 254 randomized and 251 treated (Figure 4).
- Most common reason for screen failure was a screening plasma HIV-1 RNA <1000 copies/mL (29%).
- The PhenoSense® Entry Assay, only used in Phase II studies, failed to produce a result in 26% of screening samples in this study.
- Of the samples successfully tested in the PhenoSense® Entry Assay, approximately 6% had a BMS-626529 IC_{50} >100 nM at screening.
- Of those receiving treatment, 48/201 (24%) across the BMS-663068 arms and 14/51 (28%) in the ATV/r arm failed to complete 48 weeks' treatment (Figure 4).

*Figure 4: Subject disposition through Week 48**



* 581 patients screened.
AE, adverse event; FU, follow-up.

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 or non-nucleoside reverse transcriptase inhibitor resistance-associated mutation at baseline (M184V/I, 31%; K103N, 29%; thymidine analogue mutations, 13%; major PI mutations, 2%).

Table 1: Baseline characteristics

Parameter	400 mg BID N=50	800 mg BID N=49	600 mg QD N=51	1200 mg QD N=50	300 mg/100 mg QD N=51
	BMS-663068 + TDF + RAL				ATV/r + TDF + RAL
Median age, years (range)	39 (22–57)	37 (23–60)	40 (26–58)	40 (20–67)	39 (20–68)
Male, %	62.0%	57.1%	56.9%	68.0%	56.9%
Race, %					
White	40.0%	38.8%	33.3%	32.0%	45.1%
Black/African-American	28.0%	30.6%	31.4%	36.0%	25.5%
Other*	32.0%	30.6%	35.3%	32.0%	29.4%
HIV subtype, %					
B	70.0%	59.2%	68.6%	64.0%	66.7%
C	16.0%	24.5%	21.6%	20.0%	17.6%
Other	14.0%	16.2%	9.9%	16.0%	15.6%
HIV-1 RNA					
Median, $\log_{10}$ c/mL	4.97	5.01	4.88	4.78	4.78
≥100,000 c/mL, %	46.0%	51.0%	45.1%	36.0%	35.3%
CD4+ T-cell count					
Median, cells/μL	214	237	226	224	249
<200 cells/μL, %	38.0%	32.6%	41.2%	42.0%	37.3%
BMS-626529 IC_{50} median, nM	0.68	0.65	0.43	0.82	0.73

* Majority of subjects within the "other" category reported themselves as multiracial. Previously presented by Lalezari *et al.*[8]

Virologic endpoints

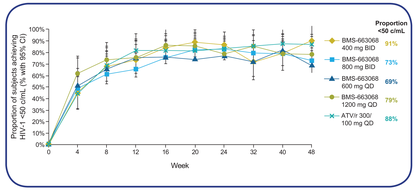
- The proportion of subjects achieving HIV-1 RNA <50 c/mL through Week 48 is shown in:
  - — Table 2: mITT analysis
  - — Figure 5: observed analysis.
- The proportion of subjects achieving HIV-1 RNA <50 c/mL through Week 48 by subgroup is shown in:
  - — Figure 6: baseline viral load
  - — Table 3: baseline BMS-626529 IC_{50} category.

Table 2: Proportion of subjects achieving HIV-1 RNA <50 or <400 c/mL (Week 48 Snapshot): mITT

Parameter	400 mg BID N=50	800 mg BID N=49	600 mg QD N=51	1200 mg QD N=50	300 mg/100 mg QD N=51
	BMS-663068 + TDF + RAL				ATV/r + TDF + RAL
HIV-1 RNA <50 c/mL, %	82.0%	61.2%	68.6%	68.0%	70.6%
HIV-1 RNA ≥50 c/mL, %	4.0%	18.4%	19.6%	16.0%	9.8%
Discontinued (lack of efficacy), %	0%	4.1%	0%	2.0%	0%
Discontinued (other reasons), %	6.0%	2.0%	5.9%	12.0%	5.9%
No virologic data at Week 48					
Discontinued due to AE or death, n (%)	1 (2.0%)	2 (4.1%)	0	1 (2.0%)	2 (3.9%)
Discontinued for other reasons, n (%)	2 (4.0%)	5 (10.2%)	3 (5.9%)	0	5 (9.8%)
Missing data during window but on study, n (%)	1 (2.0%)	0	0	0	0
HIV-1 RNA <400 c/mL, %	86.0%	75.5%	84.3%	80.0%	74.5%

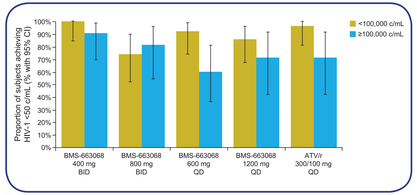
mITT, modified intent-to-treat.

Figure 5: Proportion of subjects achieving HIV-1 RNA <50 c/mL through Week 48 (observed)



CI, confidence interval.

Figure 6: Proportion of subjects achieving HIV-1 RNA <50 c/mL through Week 48 by baseline viral load: observed



CI, confidence interval.

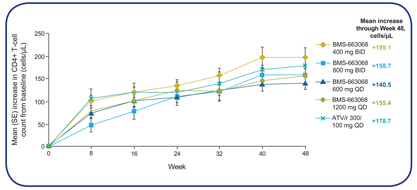
Table 3: Proportion of subjects achieving HIV-1 RNA <50 c/mL through Week 48 by baseline BMS-626529 IC_{50} category: observed

Baseline BMS-626529 IC_{50} category, n (%)	400 mg BID N=43	800 mg BID N=39	600 mg QD N=45	1200 mg QD N=42	300 mg/100 mg QD N=41
	BMS-663068 + TDF + RAL				ATV/r + TDF + RAL
<0.1 nM	2/2 (100%)	1/1 (100%)	2/3 (67%)	2/2 (100%)	0
≥0.1 nM	39/41 (95%)	29/38 (76%)	33/42 (79%)	32/40 (80%)	36/41 (88%)
<1.0 nM	24/26 (92%)	16/19 (84%)	21/30 (70%)	17/21 (81%)	24/26 (92%)
≥1.0 nM	17/17 (100%)	14/20 (70%)	14/15 (93%)	17/21 (81%)	12/15 (80%)
<10 nM	34/36 (94%)	28/33 (85%)	30/39 (77%)	30/37 (81%)	35/38 (92%)
≥10 nM	7/7 (100%)	2/6 (33%)	5/6 (83%)	4/5 (80%)	1/3 (33%)

Immunologic endpoints

- Mean change in CD4+ T-cell count from baseline through Week 48 is shown in Figure 7.

Figure 7: Mean change in CD4+ T-cell counts from baseline through Week 48: observed



SE, standard error.

Safety endpoints

- A summary of safety data through Week 48 is shown in Table 4.
  - — 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, nausea, jaundice
    - None were related to BMS-663068.
  - — SAEs that were related to study drug(s):*
    - BMS-663068 800 mg BID: TDF-induced acute renal failure
    - ATV/r 300/100 mg QD: influenza-like symptoms.

* In the BMS-663068 1200 mg QD arm, one episode of overdose was listed as related to study medications. This was changed to unrelated after the Week 48 database lock.

*Table 4: Safety summary**

Parameter, n (%)	400 mg BID N=50	800 mg BID N=49	600 mg QD N=51	1200 mg QD N=50	300 mg/100 mg QD N=51
	BMS-663068 + TDF + RAL				ATV/r + TDF + RAL
SAEs†	3 (6.0%)	5 (10.2%)	4 (7.8%)	3 (6.0%)	5 (9.8%)
AEs leading to discontinuation‡	1 (2.0%)	2 (4.1%)	0	2 (4.0%)	2 (3.9%)
Grade 2–4-related clinical AEs					
Total subjects with an event	4 (8.0%)	4 (8.2%)	3 (5.9%)	6 (12.0%)	15 (29.4%)
Present in ≥2 subjects					
Abdominal pain	0	0	0	1 (2.0%)	2 (3.9%)
Nausea	0	0	0	0	2 (3.9%)
Hyperbilirubinemia	0	0	0	0	4 (7.8%)
Jaundice	0	0	0	0	2 (3.9%)
Blood bilirubin increased	0	0	0	0	3 (5.9%)
Headache	0	1 (2.0%)	0	0	2 (3.9%)

* As reported by investigators.
† Anal abscess, herpes encephalitis, overdose (3), extrapulmonary tuberculosis (2), herpes zoster, abdominal pain, myalgia, spontaneous abortion, acute renal failure, cellulitis (2), lymphangitis, chronic cholecystitis, back pain, influenza, pneumonia, pyelonephritis, diarrhea, cholelithiasis, migraine.
‡ Illegal substance use; extrapulmonary tuberculosis (3); acute renal failure; abdominal distension, flatulence, nausea; jaundice
AE, adverse event; SAE, serious AE.

- A summary of Grade 3–4 laboratory abnormalities present in ≥2 subjects is shown in Table 5.
  - — Elevations in total bilirubin occurred in 29/51 (58%) of subjects in the ATV/r arm.
  - — No clinically relevant changes in total cholesterol, low-density lipoprotein and triglycerides from baseline were observed across the BMS-663068 arms at Week 48 (mean change from baseline).
    - Total cholesterol, mg/dL: BMS-663068 arms, -7.386 to 0.696; ATV/r, 10.480.
    - Fasting low-density lipoprotein, mg/dL: BMS-663068 arms, -0.503 to -9.745; ATV/r, 6.458.
    - Triglycerides, mg/dL: BMS-663068 arms, -23.029 to 0.531; ATV/r, -1.151.

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

Parameter, n (%)	400 mg BID N=50*	800 mg BID N=49	600 mg QD N=51*	1200 mg QD N=50*	300 mg/100 mg QD N=51*
	BMS-663068 + TDF + RAL				ATV/r + TDF + RAL
Neutrophils (absolute)	1 (2.1%)	1 (2.0%)	2 (3.9%)	1 (2.1%)	1 (2.0%)
Alkaline phosphatase	0	0	0	1 (2.1%)	0
Alanine aminotransferase	0	0	0	2 (4.2%)	1 (2.0%)
Aspartate aminotransferase	1 (2.1%)	1 (2.0%)	0	2 (4.2%)	2 (4.0%)
Total bilirubin	0	0	0	0	29 (58.0%)
Creatine kinase	0	1 (2.0%)	1 (2.0%)	2 (4.2%)	2 (4.0%)
Glucose fasting serum	0	1 (2.0%)	2 (3.9%)	0	0
Uric acid	0	0	0	2 (4.2%)	0

* Data not available for all subjects.

DISCUSSION

Virologic and immunologic efficacy

- Virologic response rates (HIV-1 RNA <50 c/mL) appear to be generally similar across the BMS-663068 and ATV/r arms.
  - — 61–82% on BMS-663068 and 71% on ATV/r (mITT Snapshot algorithm).
  - — 69–91% on BMS-663068 and 88% on ATV/r (observed).
- Virologic response rates appear to be generally similar across the BMS-663068 and ATV/r arms according to:
  - — baseline viral load
  - — BMS-626529 IC_{50} category.
- Immunologic response: mean increase in CD4+ T-cell count from baseline through Week 48 appears to be similar across the BMS-663068 and ATV/r arms.

Safety

- BMS-663068 continues to be generally well tolerated.
  - — No dose-related safety signals.
- No BMS-663068-related AEs led to discontinuation.
- Across the BMS-663068 and ATV/r arms, 17/200 (8.5%) and 15/51 (29.4%) subjects had clinical Grade 2–4-related AEs, respectively.
  - — For the BMS-663068 arm, most occurred in only one subject.
  - — For the ATV/r arm these were mostly gastrointestinal and hepatobiliary disorders.
- Across the BMS-663068 and ATV/r arms, 15/200 (7.5%) and 5/51 (9.8%) subjects had SAEs, respectively.
  - — Most were attributable to infections.
- No notable trends for Grade 3–4 or Grade 2–4-related laboratory abnormalities were observed across the BMS-663068 arms.
- Elevations in total bilirubin observed in the ATV/r arm were consistent with the known safety profile of ATV.[8]
- There were no new or unexpected safety signals for RAL.
- One subject developed TDF-induced acute renal failure on study.

Study strengths

- Baseline characteristics were broadly similar across arms:
  - — females, those with baseline viral loads ≥100,000 c/mL, and those with CD4+ T-cell counts <200 cells/μL were well represented.

Study limitations

- The PhenoSense® Entry Assay did not provide a result for 26% of screening samples in this study:
  - — no assay will be used prospectively for the upcoming Phase III study.
- Exclusion of subjects with an BMS-626529 IC_{50} >100 nM:
  - — no exclusion based on IC_{50} in the upcoming Phase III study.
- Subjects receiving BMS-663068 had a higher pill burden compared to those receiving ATV/r:
  - — potential effect on adherence.

CONCLUSIONS

- Virologic response rates (mITT and observed) and immunologic responses appear to be generally similar across the BMS-663068 and ATV/r arms through Week 48.
- All BMS-663068 doses were generally well tolerated with no dose–response safety signals reported.
- A continuation dose of BMS-663068 1200 mg QD was chosen for the Phase IIb study:
  - — a Phase III dose has been selected*
- A Phase III study in heavily treatment-experienced patients with limited therapeutic options has begun.
  - — Subjects will be enrolled regardless of baseline susceptibility to BMS-626529.
  - — A retrospective analysis will be conducted to determine whether a companion phenotypic assay is necessary in the future.

- Two accompanying posters are presented:
  - — *HIV-1 Attachment Inhibitor Prodrug BMS-663068: Pharmacokinetics, Pharmacodynamics and Model-Based Dose Selection (*Poster 509, Session P-H1, 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*).

ACKNOWLEDGMENTS

- We would like to thank all of the AI438011 clinical trial participants and their families.
- AI438011 Investigators: JD Altclas, G Amaya-Tapia, JF Andrade-Villanueva, V Arama, AI Arango-Duque, K Arastéh, J Arribas, R Bardinas-Rodriguez, CM Benites-Villafane, J Bogner, C Brinson, PE Cahn, WM Casapia-Morales, LI Cassetti, B Clotet, E DeJesus, IG Diaconescu, JI Echevarría, R Elion, J Ernst, J Feinberg, J Fourie, J Galindez, JM Gatell, ER Granados-Reyes, S Hassler, C Hicks, D Johnson, R Kaplan, J Lalezari, JR Lama-Valdivia, AM La Rosa Rodriguez, GH Latiff, MY Leon-Paredes, SH Lupo, F Marquez-Diaz, MD Martins, FC Mendo-Urbina, Y Pinedo-Ramirez, LJ Prisacariu, J Rockstroh, S Rugina, MR Salazar-Castro, AR Scribner, JG Sierra-Madero, LM Sloan, A Stoehr, OA Sussmann Pena, P Tebas, M Thompson, SC Treviño-Pérez, OA Tsybakova, EE Voronin, AA Yakovlev, NG Zakharova.
- Bristol-Myers Squibb: A Rightmire, M DeGrosky, J Coumbis, N Ray, N Cusack, M Krystal, C Hwang and T Correll.
- Other: P Lill and J Reifler (ICON CRO).
- Professional medical writing and editorial assistance was provided by Amanda Gallagher at MediTech Media and was funded by Bristol-Myers Squibb.

REFERENCES

1. Brown J *et al. J Pharm Sci* 2013; 102: 1742–1751.
2. Langley DL *et al. Proteins* 2015; 83: 331–350.
3. Nowicka-Sans B *et al. Antimicrob Agents Chemother* 2012; 56: 3498–3507.
4. Li Z *et al. AAC* 2013; 57: 4172–4180.
5. Ray N *et al. JAIDS* 2013; 64: 7–15.
6. Zhou N *et al. JAC* 2014; 69: 573–581.
7. Lalezari J *et al.* CROI 2014: Oral Abstract 86.
8. Bristol-Myers Squibb. Reyataz prescribing information. 2013. Available at: http://packageinserts.bms.com/pi/pi_reyataz.pdf. Accessed February 2015.