THE LANCET HIV

Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: Lalezari JP, Latiff GH, Brinson C, et al, for the AI438011 study team. Safety and efficacy of the HIV-1 attachment inhibitor prodrug BMS-663068 in treatment-experienced individuals: 24 week results of AI438011, a phase 2b, randomised controlled trial. *Lancet HIV* 2015; published online Sept 2. http://dx.doi.org/10.1016/S2352-3018(15)00177-0.

Supplementary Appendix

Supplement to: Lalezari JP, Latiff G, Brinson C, *et al*. Phase 2b randomized, controlled, partially-blinded trial of the safety and efficacy of BMS-663068, the prodrug of the HIV-1 attachment inhibitor BMS-626529, in treatment-experienced HIV-1-infected subjects: 24-week results.

Supplementary Figures and Tables

Figure S1: Conversion of prodrug BMS-663068 to the active moiety BMS-626529[1]

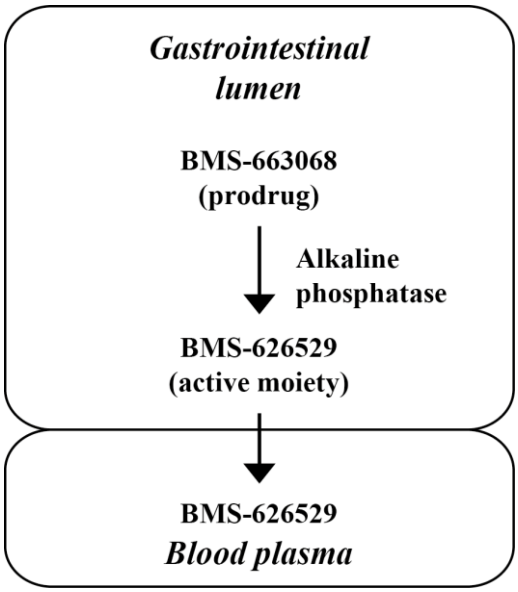
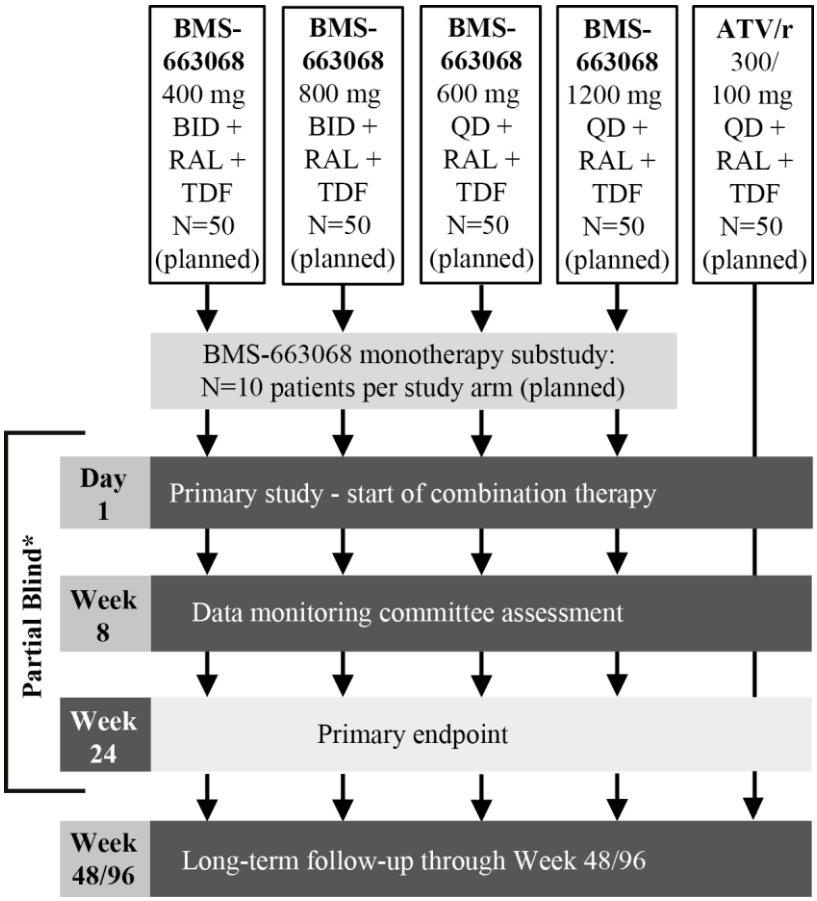


Figure S2: AI438011 Study design



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

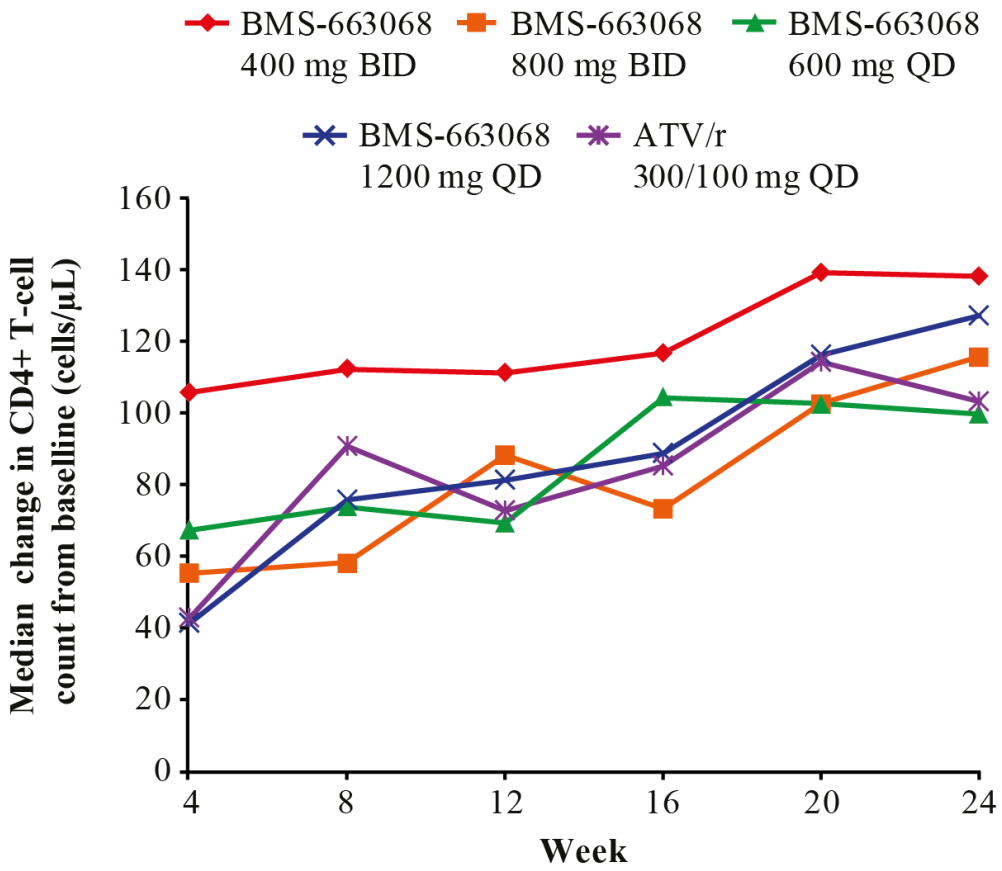
Table S1: Baseline HIV-1 genotypic drug resistance profile for the modified intent-to-treat population: select resistance-associated mutations*

	BMS-663068 + RAL + TDF				ATV/r + RAL + TDF
Number of subjects with baseline resistance-associated mutation, n (%)[†]	**400 mg twice daily N=50**	**800 mg twice daily N=49**	**600 mg once daily N=51**	**1200 mg once daily N=50**	**300 mg/100 mg once daily N=51**
Protease inhibitor substitutions (major)[‡]	2 (4)	1 (2)	0	1 (2)	1 (2)
Nucleos(t)ide reverse transcriptase inhibitor substitutions	22 (44)	17 (35)	14 (28)	13 (26)	16 (31)
Thymidine analogue mutation	7 (14)	8 (16)	4 (8)	8 (16)	6 (12)
M184I	3 (6)	0	0	0	1 (2)
M184V	20 (40)	14 (29)	13 (26)	11 (22)	15 (29)
Non-nucleos(t)ide reverse transcriptase inhibitor substitutions	25 (50)	30 (61)	20 (39)	19 (38)	26 (51)
K103N	14 (28)	19 (39)	13 (26)	10 (20)	16 (31)
G190A/S	6 (12)	8 (16)	2 (4)	4 (8)	1 (2)

* Selected based on clinical interest. [†] 38–61% of subjects had at least one major protease inhibitor, nucleos(t)ide reverse transcriptase inhibitor, or non- nucleos(t)ide reverse transcriptase inhibitor resistance-associated mutation at baseline. [‡] Did not confer phenotypic resistance to ATV/r (in line with exclusion criteria).

ATV/r, ritonavir-boosted atazanavir; RAL, raltegravir; TDF, tenofovir disoproxil fumarate.

Figure S3: Median increase in CD4+ T-cell count from baseline through Week 24 for the observed population



Number contributing data

BMS-663068 400 mg BID	47	46	44	47	45	42
BMS-663068 800 mg BID	49	47	45	45	42	38
BMS-663068 600 mg QD	49	50	49	49	50	48
BMS-663068 1200 mg QD	47	42	43	44	42	42
ATV/r 300/ 100 mg QD	48	44	44	45	44	40

ATV/r, ritonavir-boosted atazanavir; BID, twice daily; QD, once daily.

Table S2: Treatment-emergent genotypic and phenotypic resistance profile through Week 24

	BMS-663068 + RAL + TDF				ATV/r + RAL + TDF
	400 mg twice daily (N=50)	**800 mg twice daily (N=49)**	**600 mg once daily (N=51)**	**1200 mg once daily (N=50)**	**300 mg/100 mg once daily (N=51)**
Met criteria for resistance testing, n*	3	6	6	8	8
Genotype/phenotype determinable using the PhenoSense® GT and Integrase assays, n	2	5	6	8	8
Phenotype determinable using the PhenoSense® Entry assay, n	3	5	6	5	-
Emergent resistance/reduced susceptibility to study drugs					
>3-fold change in BMS-626529 fold-change in IC_{50} from baseline, n	0	2	3	3	–
Raltegravir resistance-associated mutation, n	0	1[a]	1[b]	2[c]	0
TDF resistance-associated mutation, n	0	0	0	0	0
ATV/r resistance associated mutation, n	–	–	–	–	0

* Minimum criteria for resistance testing: (1) Confirmed HIV-1 RNA $\geq$400 copies/mL after achieving viral suppression (HIV-1 RNA <50 copies/mL) (2) Discontinuation from study prior to achieving viral suppression after Week 8, with last plasma HIV-1 RNA $\geq$400 copies/mL. [a]N155H (fold-change in IC_{50}, 5.15). [b]N155H (fold-change in IC_{50}, 12). [c]Y143C/H.R (fold-change in IC_{50},32) and Q148R+N155H (fold-change in IC_{50} 2.21).

ATV/r, ritonavir-boosted atazanavir; RAL, raltegravir; TDF, tenofovir disoproxil fumarate.

Table S3: Summary of adverse events leading to discontinuation through Week 24

	BMS-663068 + RAL + TDF				ATV/r + RAL + TDF
	400 mg twice daily (N=50)	800 mg twice daily (N=49)	600 mg once daily (N=51)	1200 mg once daily (N=50)	300/100 mg once daily (N=51)
Total subjects with adverse events leading to discontinuation, n (%)	1 (2)	2 (4)	0	1 (2)	2 (4)
Gastrointestinal disorders, n (%)	0	0	0	0	2 (4)
Abdominal distention	0	0	0	0	1 (2)
Flatulence	0	0	0	0	1 (2)
Nausea	0	0	0	0	1 (2)
Infections, n (%)	0	1 (2)	0	1 (2)	0
Bone tuberculosis	0	1 (2)	0	0	0
Disseminated tuberculosis	0	0	0	1 (2)	0
Hepatobiliary, n (%)	0	0	0	0	1 (2)
Jaundice	0	0	0	0	1 (2)
Musculoskeletal, n (%)	0	0	0	1 (2)	0
Back pain	0	0	0	1 (2)	0
Renal, n (%)	0	1 (2)	0	0	0
Acute renal failure	0	1 (2)	0	0	0
Vascular, n (%)	1 (2)	0	0	0	0
Ischaemia (likely related to cocaine use)	1 (2)	0	0	0	0

ATV/r, ritonavir-boosted atazanavir; RAL, raltegravir; TDF, tenofovir disoproxil fumarate.

Table S4: Summary of Grade 2–4-related adverse events through Week 24

	BMS-663068 + RAL + TDF				ATV/r + RAL + TDF
	400 mg twice daily (N=50)	**800 mg twice daily (N=49)**	**600 mg once daily (N=51)**	**1200 mg once daily (N=50)**	**300/100 mg once daily (N=51)**
Total subjects with Grade 2–4- related adverse events, n (%)	6 (12)	3 (6)	2 (4)	6 (12)	14 (28)
Gastrointestinal disorders, n (%)	0	1 (2)	0	2 (4)	5 (10)
Abdominal pain	0	0	0	1 (2)	2 (4)
Dyspepia	0	0	0	1 (2)	1 (2)
Gastritis	0	0	0	0	2 (4)
Nausea	0	0	0	0	2 (4)
Abdominal distension	0	0	0	0	1 (2)
Upper abdominal pain	0	0	0	0	1 (2)
Flatulence	0	0	0	0	1 (2)
Vomiting	0	1 (2)	0	0	0
Hepatobiliary disorders, n (%)	0	0	0	0	7 (14)
Hyperbilirubinaemia	0	0	0	0	4 (8)
Jaundice	0	0	0	0	2 (4)
Drug-induced liver injury	0	0	0	0	1 (2)
Investigations, n (%)	2 (4)	0	1 (2)	0	2 (4)
Increased blood bilirubin	0	0	0	0	2 (4)
Increased blood creatine phosphokinase	1 (2)	0	1 (2)	0	0
Increased amylase	1 (2)	0	0	0	0
Increased lipase	1 (2)	0	0	0	0
Decreased weight	1 (2)	0	0	0	0
Nervous system disorders, n (%)	0	1 (2)	0	1 (2)	2 (4)
Headache	0	1 (2)	0	0	2 (4)

Dizziness	0	0	0	0	1 (2)
Peripheral neuropathy	0	0	0	1 (2)	0
Metabolism and nutrition disorders, n (%)	2 (4)	0	0	0	1 (2)
Decreased appetite	1 (2)	0	0	0	0
Hypertriglyceridaemia	0	0	0	0	1 (2)
Increased appetite	1 (2)	0	0	0	0
Eye disorders, n (%)	1 (2)	0	0	0	1 (2)
Ocular icterus	0	0	0	0	1 (2)
Visual impairment	1 (2)	0	0	0	0
Infections and infestations, n (%)	0	0	0	0	2 (4)
Gastroenteritis	0	0	0	0	1 (2)
Influenza	0	0	0	0	1 (2)
Renal and urinary disorders, n (%)	0	1 (2)	1 (2)	0	0
Haematuria	0	0	1 (2)	0	0
Proteinuria	0	0	1 (2)	0	0
Acute renal failure	0	1 (2)*	0	0	0
Blood and lymphatic system disorders, n (%)	0	0	0	1 (2)	0
Neutropenia	0	0	0	1 (2)	0
Injury, poisoning and procedural complications, n (%)	0	0	0	1 (2)	0
Overdose	0	0	0	1 (2)	0
Psychiatric disorders, n (%)	0	0	0	1 (2)	0
Insomnia	0	0	0	1 (2)	0
Reproductive system and breast disorders, n (%)	0	0	0	0	1 (2)
Amenorrhoea	0	0	0	0	1 (2)
Skin and subcutaneous disorders, n (%)	0	1 (2)	0	0	0

Hyperhidrosis	0	1 (2)	0	0	0
Vascular disorders, n (%)	1 (2)	0	0	0	0
Ischaemia (likely related to cocaine use)	1 (2)	0	0	0	0

[*] Tenofovir disoproxil fumarate-induced acute renal failure.

ATV/r, ritonavir-boosted atazanavir; RAL, raltegravir; TDF, tenofovir disoproxil fumarate.

Table S5: Summary of serious adverse events through Week 24

	BMS-663068 + RAL + TDF				ATV/r + RAL + TDF
	400 mg twice daily (N=50)	800 mg twice daily (N=49)	600 mg once daily (N=51)	1200 mg once daily (N=50)	300/100 mg once daily (N=51)
Total subjects with serious adverse events, n (%)	4 (8)	4 (8)	3 (6)	2 (4)	5 (10)
Infections and infestations, n (%)	2 (4)	2 (4)	2 (4)	1 (2)	3 (6)
Anal abscess	1 (2)	0	0	0	0
Bone tuberculosis	0	1 (2)	0	0	0
Disseminated tuberculosis	0	0	0	1 (2)	0
Herpes encephalitis	1 (2)	0	0	0	0
Herpes zoster	0	1 (2)	0	0	0
Influenza	0	0	0	0	1 (2)
Localised infection	0	0	1 (2)	0	0
Lymphangitis	0	0	1 (2)	0	0
Pneumonia	0	0	0	0	1 (2)
Acute pyelonephritis	0	0	0	0	1 (2)
Injury/poisoning, n (%)	1 (2)	0	1 (2)	1 (2)	0
Accidental overdose	1 (2)	0	1 (2)	0	0
Overdose	0	0	0	1 (2)	0
Musculoskeletal disorders, n (%)	0	1 (2)	0	1 (2)	0
Back pain	0	0	0	1 (2)	0
Myalgia	0	1 (2)	0	0	0
Gastrointestinal disorders, n (%)	0	0	0	0	1 (2)
Diarrhoea	0	0	0	0	1 (2)
Hepatobiliary disorders, n (%)	0	0	0	0	1 (2)

Cholelithiasis	0	0	0	0	1 (2)
Nervous system disorders, n (%)	0	0	0	0	1 (2)
Migraine	0	0	0	0	1 (2)
Pregnancy, puerperium and perinatal conditions, n (%)	0	1 (2)	0	0	0
Spontaneous abortion	0	1 (2)	0	0	0
Renal and urinary disorders, n (%)	0	1 (2)	0	0	0
Acute renal failure	0	1 (2)	0	0	0
Respiratory, thoracic and mediastinal disorders, n (%)	1 (2)	0	0	0	0
Sleep apnea syndrome	1 (2)	0	0	0	0

ATV/r, ritonavir-boosted atazanavir; RAL, raltegravir; TDF, tenofovir disoproxil fumarate.

Supplementary References

1. Brown J, Chien C, Timmins P, et al. Compartmental absorption modelling and site of absorption studies to determine feasibility of an extended-release formulation of an HIV-1 attachment inhibitor phosphate ester prodrug. J Pharm Sci 2013;**102:**1742–51.