Data on the Use of *Rukobia* when Dosed Once-Daily

Summary

- The dose of Rukobia (fostemsavir [FTR]) that progressed into a phase 3 study with heavily treatment-experienced patients (BRIGHTE) was 600 mg twice-daily.[1,2] FTR is only recommended at a dose of 600 mg twice-daily; the safety and efficacy of once-daily dosing have not been established.[3]
- A phase 2b study included two arms with FTR at a dosing frequency of once-daily.[4] The virologic efficacy (HIV-1 RNA <50 copies/mL) of all FTR doses tested was numerically similar to that of ritonavir-boosted atazanavir (ATV/r) at Weeks 24, 48, 144, and 192.
    - Baseline temsavir (TMR) IC_{50} was not predictive of virologic efficacy.
    - The most common adverse event in patients treated with FTR was headache.[4]
- Important safety information is found in the attached Prescribing Information.

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DOSE USED IN PHASE 3

Based on pharmacokinetic/pharmacodynamic modelling of data obtained from phase 2 studies, the dose selected for progression into phase 3 in heavily treatment-experienced patients was FTR 600 mg twice-daily.[1,2]

The only recommended dosage of FTR is 600 mg orally twice daily.[3] FTR is not recommended when dosed at a frequency of once daily as the safety and efficacy have not been established.

STUDY 205889 (AI438011)

Design

Study 205889 was a phase 2b randomized, controlled, partially-blinded, multinational trial conducted to assess the safety, efficacy, and dose-response of FTR with the backbone of raltegravir (RAL) and tenofovir disoproxil fumarate (TDF) in treatment-experienced patients with HIV-1.[4,5] A reference arm of ATV/r with RAL and TDF provided an active comparator.

Patients were eligible for inclusion if they were at least 18 years of age or older, treatment-experienced, with a HIV-1 RNA >1000 copies/mL and CD4+ T-cell count >50 cells/µL.[4] Treatment-experienced was defined as having received ≥1 week of at least 1 antiretroviral agent. Susceptibility to ATV/r, RAL, and TDF were required.

Initially, patients were randomized to one of four doses of FTR or ATV/r, each in combination with raltegravir and tenofovir disoproxil fumarate.[4] The doses of FTR investigated were 400 mg twice-daily, 800 mg twice-daily, 600 mg once-daily, or 1200 mg once-daily. Patients were stratified by baseline HIV-1 RNA and baseline TMR IC_{50}.

The primary objectives of the study were to assess the proportion of patients with HIV-1 RNA <50 copies/mL, the frequency of serious adverse events, and adverse events leading to discontinuation through Week 24.[4]

A subset of approximately 10 patients in each of the four FTR groups were given FTR monotherapy for 7 days.[4]

Results

Baseline demographics and characteristics were similar across all treatment groups and are presented below in Table 1.[4]

Table 1. Baseline Demographics and Characteristics of Patients Included in Study 205889[4]

	FTR 400 mg twice-daily group (n=50)	FTR 800 mg twice-daily group (n=49)	FTR 600 mg once-daily group (n=51)	FTR 1200 mg once-daily group (n=50)	ATV/r group (n=51)
Age, median (IQR)	39 (32-44)	37 (31-43)	40 (32-49)	40 (29-46)	39 (32-44)
Male sex, n (%)	31 (62)	28 (57)	29 (57)	34 (68)	29 (57)
Ethnicity, n (%)					
White	20 (40)	19 (39)	17 (33)	16 (32)	23 (45)
Black or African American	14 (28)	15 (31)	16 (31)	18 (36)	12 (25)
American Indian or Alaskan	0	0	16 (31)	18 (36)	13 (25)
Asian	0	2 (4)	0	0	0
Other	16 (32)	13 (27)	17 (33)	15 (30)	14 (27)
HIV-1 RNA, median (IQR)	4.97 (4.24-5.42)	5.01 (4.53-5.32)	4.88 (4.24-5.75)	4.78 (3.89-5.38)	4.78 (4.26-5.25)
HIV-1 RNA >100,000 copies/mL, n (%)	23 (46)	25 (51)	23 (45)	18 (36)	18 (35)
CD4+ T-cell count, median (IQR)	214 (155-308)	237 (156-319)	226 (162-299)	224 (132-344)	249 (139-337)
CD4+ T-cell count <200 cells/µL, n (%)	19 (38)	16 (33)	21 (41)	21 (42)	19 (37)
TMR IC_{50}, median (IQR), nmol/L	0.68 (0.28-2.87)	0.65 (0.27-2.52)	0.43 (0.21-1.94)	0.82 (0.31-2.88)	0.73 (0.28-1.78)
TMR IC_{50} <1.3 nmol/L	34 (68)	32 (65)	37 (73)	34 (68)	36 (71)
TMR IC_{50} ≥1.3 nmol/L	16 (32)	17 (35)	14 (27)	16 (32)	15 (29)

ATV/r = ritonavir-boosted atazanavir; FTR = fostemsavir; IQR = interquartile range; TMR = temsavir

Week 24

7-Day Monotherapy Substudy

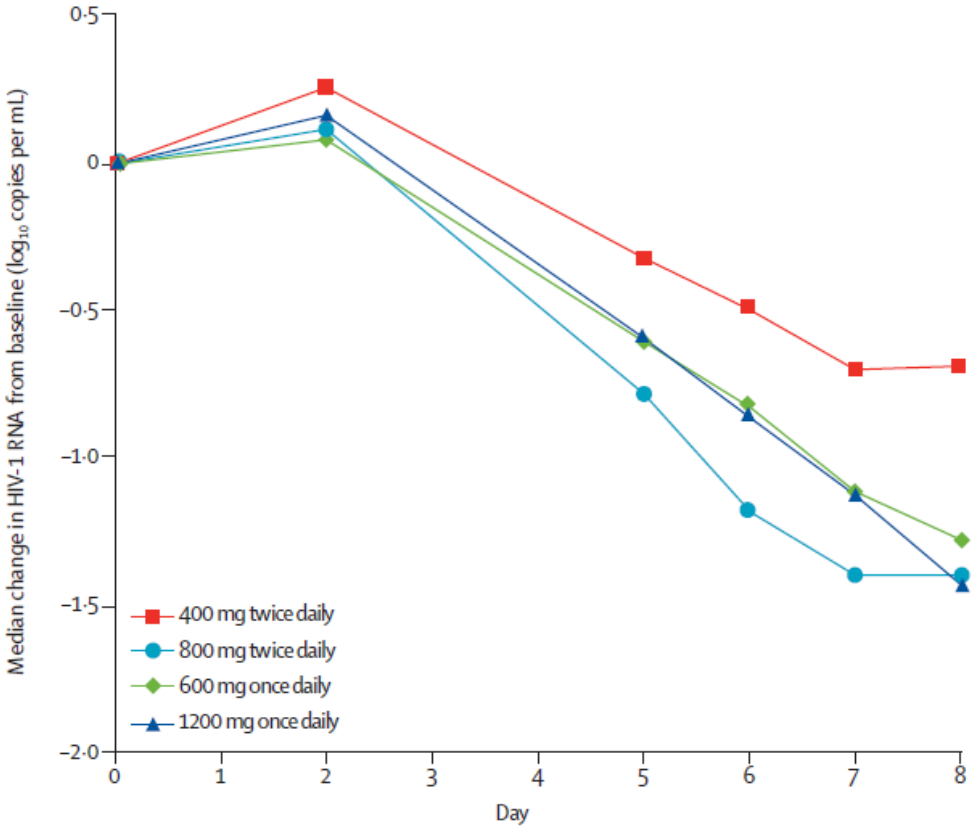
Results of the substudy can be found below in Table 2 and Figure 1.[4]

Table 2. Change from Baseline in HIV-1 RNA at Day 8 in Patients Treated with FTR Monotherapy[4]

	FTR 400 mg twice-daily group	FTR 800 mg twice-daily group	FTR 600 mg once-daily group	FTR 1200 mg once-daily group
Change from baseline in HIV-1 RNA, median (IQR), log_{10} copies/mL	-0.69 (-1.17 to -0.38)	-1.40 (-1.59 to -1.16)	-1.28 (-1.49 to -0.93)	-1.44 (-1.61 to -1.06)

FTR = fostemsavir; IQR = interquartile range

Figure 1. Change from Baseline in HIV-1 RNA through Day 8 in Patients Treated with FTR Monotherapy[4]



Number of patients contributing to data analysis

400 mg twice daily	7	7	7	7	6	6
800 mg twice daily	5	5	4	5	5	4
600 mg once daily	10	9	10	10	10	9
1200 mg once daily	10	9	10	10	10	9

Primary Efficacy Analysis

At Week 24, the proportion of patients with an HIV-1 RNA <50 copies/mL was similar across each of the FTR groups as well as the ATV/r group. Full results can be found in Table 3 below.[4]

Table 3. Proportion of Patients with HIV-1 RNA <400 and <50 copies/mL at Week 24[4]

	FTR 400 mg twice-daily group (n=50)	FTR 800 mg twice-daily group (n=49)	FTR 600 mg once-daily group (n=51)	FTR 1200 mg once-daily group (n=50)	ATV/r group (n=51)
Modified ITT Analysis (FDA Snapshot)					
HIV-1 RNA <50 copies/mL	40 (80)	34 (69)	39 (76)	36 (72)	38 (75)
HIV-1 RNA ≥50 copies/mL	8 (16)	10 (20)	11 (22)	13 (26)	9 (18)
No virologic data in window					
Discontinued due to AE or death	1 (2)	2 (4)	0	1 (2)	2 (4)
Discontinued for other reasons	1 (2)	3 (6)	1 (2)	0	2 (4)
HIV-1 RNA <400 copies/mL	46 (92)	39 (80)	46 (90)	40 (80)	42 (82)
Observed Analysis (patients with data in window)					
Number of patients	46	42	50	43	44
HIV-1 RNA <50 copies/mL	40 (87)	34 (81)	39 (78)	36 (84)	38 (86)
HIV-1 RNA <400 copies/mL	46 (100)	39 (93)	46 (92)	40 (93)	42 (95)

All data are n (%) except number of patients

ATV/r = ritonavir-boosted atazanavir; FTR = fostemsavir.

Virologic efficacy by baseline stratification can be found below in Table 4.[4]

Table 4. Virologic Efficacy by Baseline Stratification at Week 24 (Observed Population)[4]

	FTR 400 mg twice-daily group (n=46)	FTR 800 mg twice-daily group (n=42)	FTR 600 mg once-daily group (n=50)	FTR 1200 mg once-daily group (n=43)	ATV/r group (n=44)
Baseline HIV-1 RNA (copies/mL), %					
<100,000	96	87	85	82	93
≥100,000	77	74	70	87	73
Baseline TMR IC_{50} Category (nmol/L), % (95% CI)					
<1.3	88 (71-97)	92 (74-99)	75 (58-88)	82 (62-94)	90 (74-98)
≥1.3	86 (57-98)	65 (38-86)	86 (57-98)	88 (62-98)	77 (46-95)

ATV/r = ritonavir-boosted atazanavir; FTR = fostemsavir; TMR = temsavir.

Change from baseline in CD4+ T-cell count was similar across the four FTR groups and the ATV/r group.[4]

At Week 24, 23 (12%) patients from across the FTR groups and 8 (16%) patients in the ATV/r group met the on-study criteria for resistance testing.[4] All but 2 patients from the FTR groups had samples that were successfully tested using the PhenoSense GT or Integrase assays.

Eight FTR-treated patients had virus that exhibited >3-fold change in TMR IC_{50} from baseline, and 4 of the 8 had virus exhibiting emergent raltegravir resistance.[4] Of the 8 patients in the ATV/r group who met the criteria for resistance testing, none had virus that exhibited resistance to any of the study drugs.

A summary of adverse events can be found below in Table 5.[4] The most common adverse event reported in FTR-treated patients was headache (14%). Most were Grade 1.

Table 5. Summary of Adverse Events through Week 24[4]

	FTR 400 mg twice-daily group (n=50)	FTR 800 mg twice-daily group (n=49)	FTR 600 mg once-daily group (n=51)	FTR 1200 mg once-daily group (n=50)	ATV/r group (n=51)
Any AE	44 (88)	40 (82)	41 (80)	42 (84)	48 (94)
AE leading to discontinuation	1 (2)	2 (4)	0	1 (2)	2 (4)
Serious AE	4 (8)	4 (8)	3 (6)	2 (4)	5 (10)
AE related to study drugs	17 (34)	13 (27)	13 (25)	18 (36)	25 (49)
Grade 2-4 AE related to study drugs	6 (12)	3 (6)	2 (4)	6 (12)	14 (27)

All data are n (%).

AE = adverse event; ATV/r = ritonavir-boosted atazanavir; FTR = fostemsavir.

Study 205889 was not powered to show a statistical difference between the FTR arms. There was no observable difference in efficacy between the FTR groups.

Week 48

At Week 48, the proportion of patients with HIV-1 RNA <50 copies/mL was between 61-82% for patients in the FTR groups.[5] Full results can be found in Table 6 below.

When stratified by baseline HIV-1 RNA, the proportion of patients with a HIV-1 RNA <50 copies/mL was generally higher in patients with a baseline HIV-1 RNA <100,000 copies/mL.[5] The proportion of patients with HIV-1 RNA <50 copies/mL when stratified by whether the baseline TMR IC_{50} were: <1.3 nmol/L, 72-94% and ≥1.3 nmol/L, 71-100% across the FTR groups.

Table 6. Proportion of Patients with HIV-1 RNA <50 copies/mL at Week 48 (Modified ITT Analysis)[5]

	FTR 400 mg BID (n=50)	FTR 800 mg BID (n=49)	FTR 600 mg QD (n=51)	FTR 1200 mg QD (n=50)	ATV/r (n=51)
HIV-1 RNA <50 copies/mL	41 (82)	30 (61.2)	35 (68.6)	34 (68)	36 (70.6)
HIV-1 RNA ≥50 copies/mL	2 (4)	9 (18.4)	10 (19.6)	8 (16)	5 (9.8)
Discontinued due to lack of efficacy	0	2 (4.1)	0	1 (2)	0
Discontinued for other reasons	3 (6)	1 (2)	3 (5.9)	6 (12)	3 (5.9)
No virologic data in window					
Discontinued due to AE or death	1 (2)	2 (4.1)	0	1 (2)	2 (3.9)
Discontinued for other reasons	2 (4)	5 (10.2)	3 (5.9)	0	5 (9.8)
Missing data but on study	1 (2)	0	0	0	0

All data are n (%). AE = adverse event; ATV/r = ritonavir-boosted atazanavir; FTR = fostemsavir ITT = intention-to-treat.

The increase from baseline in CD4+ T-cell count was similar across the FTR and ATV/r arms.[5]

A summary of adverse events through Week 48 can be found below in Table 7. Like the Week 24 analysis, the most frequent adverse event across the FTR groups was headache (15%).[5] Most were Grade 1. There were no FTR-related adverse events that led to discontinuation.

Table 7. Summary of Adverse Events through Week 48[5]

	FTR 400 mg twice-daily group (n=50)	FTR 800 mg twice-daily group (n=49)	FTR 600 mg once-daily group (n=51)	FTR 1200 mg once-daily group (n=50)	ATV/r group (n=51)
Serious AE	3 (6)	5 (10.2)	4 (7.8)	3 (6)	5 (9.8)
AE leading to discontinuation	1 (2)	2 (4.1)	0	2 (4)	2 (3.9)
Grade 2-4 AE related to study drugs	4 (8)	4 (8.2)	3 (5.9)	6 (12)	15 (29.4)

All data are n (%)

AE = adverse event; ATV/r = ritonavir-boosted atazanavir; FTR = fostemsavir.

Based on these results and the results of pharmacokinetic modelling FTR 1200 mg once-daily was selected for as the continuation dose beyond week 48 in this study.[5]

Beyond Week 48

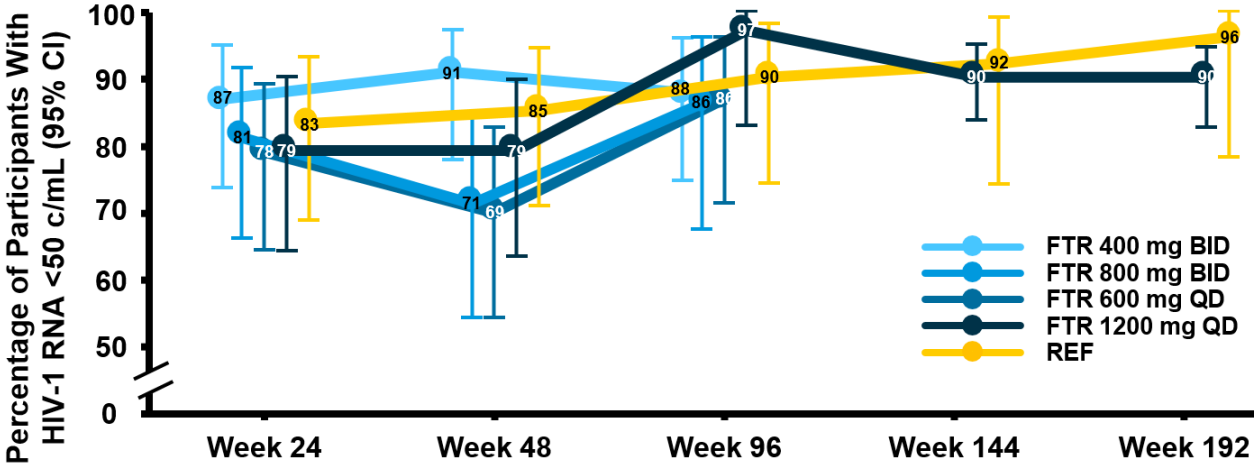
At Week 96, approximately 50% of patients in the original FTR groups had been switched to FTR 1200 mg once-daily.[6] By Week 110, all treated patients had been switched. Snapshot results at Weeks 144 and 192 can be found in Table 8 below. Virologic response rates by Snapshot analysis and Observed analysis (Figure 2) were comparable between the FTR and ATV/r arms.[7] Week 192 marks the latest study visit that all patients had an opportunity to complete prior to study conclusion.

Table 8. Proportion of Patients with HIV-1 RNA <50 copies/mL at Weeks 144 and 192 (Snapshot Analysis, ITT-E Population)[6]

	FTR 1200 mg Once-Daily Group (n=200) n (%) (95% CI)	ATV/r Group (n=51) n (%) (95% CI)
Week 144	116 (58) (50.8, 64.9)	23 (45) (31.1, 59.7)
Week 192	105 (53) (45.3, 59.6)	22 (43) (29.3, 57.8)

ATV/r = ritonavir-boosted atazanavir; CI = confidence interval; FTR = fostemsavir; ITT-E = intention-to-treat-exposed.

Figure 2. Virologic Response Through Week 192, Observed Analysis[7]

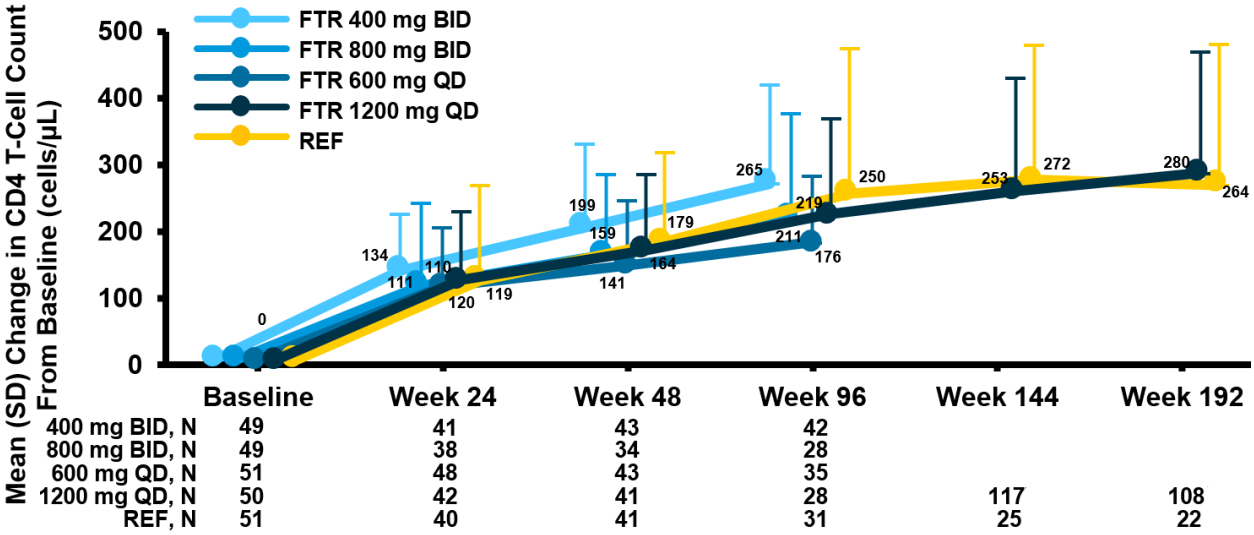


	Week 24	Week 48	Week 96	Week 144	Week 192
400 mg BID, N	46	43	43		
800 mg BID, N	42	38	28		
600 mg QD, N	49	45	36		
1200 mg QD, N	43	42	30	123*	115*
REF, N	42	41	31	25	23

BID = twice daily; CI = confidence interval; FTR = fostemsavir; QD = once daily; REF = ritonavir-boosted atazanavir arm.

Increases from baseline CD4+ T-cell count were observed through Week 144 and were similar between the FTR and ATV/r groups.[6]

Figure 3. Mean Change in CD4 T-Cell Count Through Week 192[7]



BID = twice daily; CI = confidence interval; FTR = fostemsavir; QD = once daily; REF = ritonavir-boosted atazanavir arm.

Through Week 192, the most common FTR-related AEs were headache (6%) and nausea (5%).[7] A higher percentage of patients in the ATV/r arm (12%) experienced AEs leading to discontinuation compared to the FTR arms (4%) and none were considered related to FTR.

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