Safety, Tolerability, and Pharmacokinetics of BRII-778, A Modified-Release Oral Formulation of Rilpivirine in Healthy Adult Subjects

Poster # 1283

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Background

- BRII-778 is a modified release (MR) formulation of rilpivirine (NNRTI) for once-weekly (QW) oral administration, in combination with other QW oral antiretrovirals to treat HIV-1 infection.
- BRII-778 aims to prolong oral absorption, lower C_{max}, relatively, and reduce peak to trough ratio achieved with a MR formulation of rilpivirine.
- Plasma concentration targets coverage within the known efficacy and safety bounds established by once daily oral administration of rilpivirine.
- It is expected that QW dosing will have considerable advantages over once daily dosing regimens in terms of patient convenience, quality of life, and treatment adherence.
- Multiple MR formulations of rilpivirine were evaluated in healthy adult subjects of Phase 1 study.

Study Design

- This was a Phase 1, randomized, double-blinded, placebo-controlled, study consisting of single ascending dose (SAD) and multiple ascending dose (MAD) cohorts to evaluate the safety, tolerability, and PK of BRII-778 in healthy adult subjects with three MR formulations of rilpivirine, BRII-778-A1, -A2, and -A3.
- The primary study objective: to assess the safety and tolerability of BRII-778 MR formulations when administered to healthy adult subjects.
- The secondary study objectives: to assess rilpivirine PK of single and multiple doses of BRII-778 MR formulations (150 mg to 750 mg) under fed state; to assess the effect of food on the BRII-778-A3 formulation at 750 mg; and to evaluate the effect of single and multiple doses of BRII-778 MR formulations on QTc interval and other ECG parameters.
- **Treatment Regimen (Cohorts) Information:**
  - **SAD: Cohorts: 1-6**
    - Objective: SAD PK and safety
    - Dose: 150-750 mg BRII-778-A1, -A2, and -A3
  - **SAD: Cohorts: 5-6**
    - Objective: food effect
    - Dose: 750 mg BRII-778-A3 (Fed/Fasted)
  - **MAD: Cohort: 8**
    - Objective: MAD PK and safety
    - Dose: 750 mg QW x 3BRII-778-A3

Results

BRII-778-001 Safety Data

Table 1. Demographics and Baseline Characteristics (All Subjects Enrolled)

	SAD Total (N = 63)	MAD BRII-778-A3 (Fed) 750 mg QW x 3 (N = 12)
Age (years)		
n	63	12
Mean (SD)	37 (9.2)	36 (7.9)
Median	38	34
Q1, Q3	30, 45	32, 41
Min, Max	19, 55	20, 51
Sex at Birth		
Male	37 (58.7%)	9 (75.0%)
Female	26 (41.3%)	3 (25.0%)
Ethnicity		
Hispanic or Latino	34 (54.0%)	4 (33.3%)
Not Hispanic or Latino	29 (46.0%)	8 (66.7%)
Race		
Asian	2 (3.2%)	
Black or African American	22 (34.9%)	4 (33.3%)
White	38 (60.3%)	8 (66.7%)
Other	1 (1.6%)	
Weight (kg)		
n	61	12
Mean (SD)	73.7 (11.67)	83.0 (11.58)
Median	71.1	81.2
Q1, Q3	65.2, 81.1	73.3, 89.0
Min, Max	48.1, 110.7	69.5, 107.6
Height (cm)		
n	61	12
Mean (SD)	168.9 (10.74)	175.0 (7.02)
Median	168.7	173.8
Q1, Q3	159.7, 176.5	171.6, 177.1
Min, Max	148.3, 192.9	165.4, 191.7
Body Mass Index (kg/m^2)		
n	61	12
Mean (SD)	25.8 (2.87)	27.0 (2.17)
Median	26.4	26.5
Q1, Q3	23.8, 28.2	25.7, 29.2
Min, Max	18.9, 29.7	23.6, 29.5

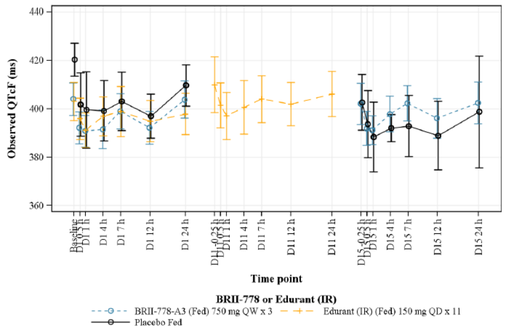
Abbreviations: Min = Minimum; Max = Maximum; N = number of subjects in Randomized/Enrolled population in each Treatment Arm; Q1 = First Quartile; Q3 = Third Quartile; SD = Standard Deviation.

Table 2. Treatment-Emergent Adverse Events Overall Summary (Safety Population)

	SAD Total (N = 61)	MAD BRII-778-A3 (Fed) 750 mg QW x 3 (N = 12)
Any TEAE	13 (21.3%)	5 (41.7%)
Grade 1	10 (16.4%)	4 (33.3%)
Grade 2	3 (4.9%)	1 (8.3%)
Grade 3	0	0
Grade 4	0	0
Grade 5	0	0
Drug-related TEAE	1 (1.6%)	3 (25.0%)
Grade 1	0	2 (16.7%)
Grade 2	1 (1.6%)	1 (8.3%)
Grade 3	0	0
Grade 4	0	0
Grade 5	0	0

TE = Treatment-Emergent; TEAE = Treatment-Emergent Adverse Event

Figure 1 Absolute QTcF across time points with descriptive statistics (QT/QTc analysis population)

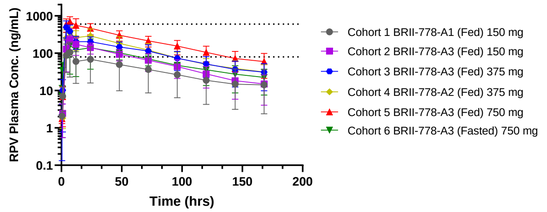


- There were no Grade ≥3 AEs, SAEs or AEs leading to withdrawal in BRII-778 dosing arms.
- A single BRII-778 related TEAE (Grade 2 headache) was observed in SAD
- Three BRII-778 related TEAEs were observed in MAD (Grade 1 GERD; Grade 1 Headache; Grade 2 ALT increase)
- Exploratory C-QTc analysis confirmed a concentration-dependent effect on the QTc interval with escalating doses of BRII-778, but the interpretations are limited by small sample size.
- There were no clinically significant EKG changes and no individual subject met QTc stopping criteria.
- No absolute QTcF values >480 msec or QTc change from baseline >60 msec were observed across all BRII-778 cohorts

Results

BRII-778-001 Pharmacokinetic (PK) Data

Figure 2. Mean (SD) BRII-778 (RPV) Plasma Concentration-Time Profiles Following Single Dose Administration of BRII-778 MR Formulations

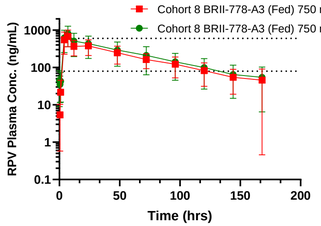


BRII-778 PK Parameter Mean (%CV)[a]	Single Dose of BRII-778 MR Formulations					
	150 mg -A1 Cohort 1, N = 8	150 mg -A3 Cohort 2, N = 8	375 mg -A3 Cohort 3, N = 8	375 mg -A2 Cohort 4, N = 8	750 mg -A3 Cohort 5, N = 8	750 mg -A3 Cohort 6[b], N = 8
C_{max} (ng/mL)	110.6 (49.8%)	261.1 (31.7%)	507.4 (43.8%)	441.5 (31.2%)	774.8 (28.9%)	221.6 (63.2%)
C_{last} (ng/mL)	14.3 (80.4%)	15.1 (73.2%)	31.2 (68.2%)	31.3 (58.5%)	59.9 (64.5%)	22.5 (66.3%)

[b] BRII-778 administered under fasted state in Cohort 6. All other cohorts administered under fed state.

- Rilpivirine PK profiles post BRII-778 dosing was consistent with slower oral absorption with MR formulation with T_{max} at 4-7 hr.
- BRII-778-A3 750 mg under the fed state enhanced bioavailability by improving gastric dissolution and/or subsequent absorption.

Figure 3. Mean (SD) BRII-778 Plasma Concentration-Time Profiles on Day 1 and Day 15 Following Three QW Oral Doses of BRII-778-A3 at 750 mg



- Following 3 QW oral administrations of BRII-778-A3 formulation at 750 mg, the PK absorption profile observed on Day 1 and Day 15 was similar.
- Exposure (AUC and C_{max}) inter-subject variability was moderate for BRII-778-A3 formulation on both Day 1 and Day 15. A mild accumulation in AUC, C_{max}, and C_{last} was observed (≤1.3-fold).

Conclusions

- In the Phase 1 study, SAD and MAD administration of BRII-778 formulations were generally safe and well tolerated.
- BRII-778-A3 750 mg under the fed state enhanced bioavailability by improving solubility and/or absorption.
- BRII-778 demonstrated good cardiac safety up to 750 mg dosed weekly, with concentration dependent QTc effect and no individuals meeting QTc stopping criteria
- Rilpivirine PK and safety profiles post BRII-778 dosing supports further evaluation of BRII-778 for QW regimen to treat HIV-1 infection.