Safety, Tolerability, and Pharmacokinetics of BRII-732, A Medoxomil Carbonate Prodrug of Islatravir in Healthy Adult Subjects

Poster # 1282

David Margolis[1], Ji Ma[1], Michael Watkins[1], Yujin Wang[1], Chetana Trivedi[1], Chi-Chi Peng[1], Xuelian Wei[1], Lijie Zhong[1], Kamlesh Patel[1], Jean-Luc Girardet[1], Michael Wang[1], Annalise VonderEmbse[1], Li Yan[1], Zhi Hong, Lianhong Xu[1]

[1] Brii Biosciences, Limited

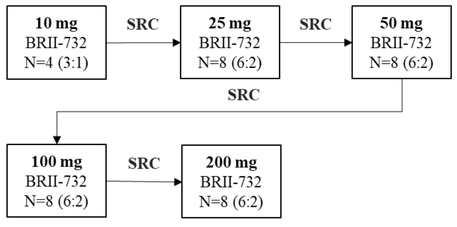
BACKGROUND

- BRII-732, a prodrug of Islatravir (ISL), is a potent HIV-1 nucleotide reverse transcriptase translocation inhibitor.
- Following oral absorption, BRII-732 is rapidly converted to ISL, which is metabolized intracellularly to the active metabolite, ISL triphosphate (ISL-TP).
- Single doses of ISL as low as 0.5 mg significantly suppressed HIV-1 RNA by more than 1.0 log at day 7 in treatment-naive adults with HIV-1 infection*.
- Current development work with BRII-732 is designed to provide optimal drug exposure to enable once weekly (QW) oral dosing, to be part of combination antiretroviral therapy
- Once weekly dosing has the potential to improve patient satisfaction and treatment adherence.

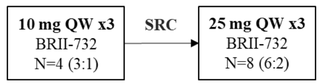
METHODS

- This was a Phase 1, randomized, double-blind, placebo-controlled study
- Healthy adult subjects enrolled in five single ascending dose and two multiple ascending dose cohorts. (36 in SAD and 12 in MAD)
- BRII-732 was orally administered in the fasted state using an oral solution formulation.
- The objectives of the study were to assess the safety, tolerability, and PK profiles of BRII-732 and ISL in plasma; ISL-DP and ISL-TP in human PBMCs.
- Safety-related assessments included physical examinations, ECGs, vital signs, AEs, and standard clinical laboratory tests.

Part A: Single Ascending Dose

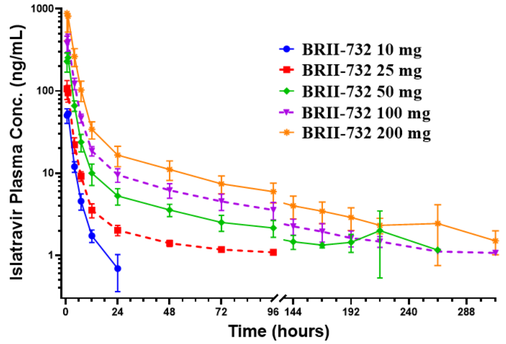


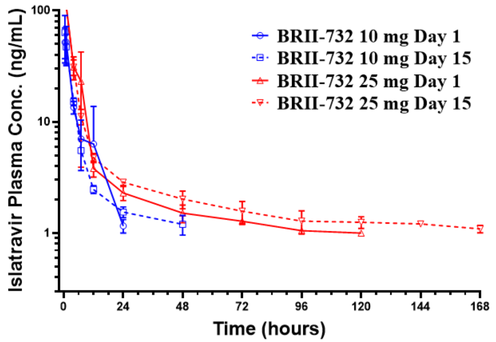
Part B: Multiple Ascending Dose



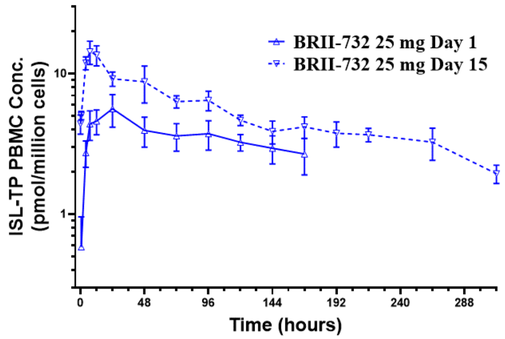
RESULTS

Mean ± SD Islatravir (ISL) Plasma Concentration – Time Profiles Following Single or Multiple Oral Doses of BRII-732 to Healthy Adult Subjects





Mean Islatravir-Triphosphate (ISL-TP) PBMC Concentration – Time Profiles on Day 1 and 15 Following Multiple Oral Doses of BRII-732 to Healthy Adult Subjects



Summary Pharmacokinetics of ISL-TP in PBMCs Following 3 Weekly Oral Doses of 25 mg BRII-732 to Healthy Adult Subjects

	AUC_{last} (h*pmol/10^6 cells)	C_{max} (pmol/10^6 cells)	C_{168h} (pmol/10^6 cells)	T_{max} (h)	Apparent terminal $t_{1/2}$ (h)
Day 1 (N=6)	617 (20.8)	5.70 (23.8)	2.70 (29.5)	24 (12, 24)	NC
Day 15 (N=6)	2210 (21.3)	15.4 (16.5)	4.70 (27.6)	7.0 (7.0, 12)	177 (172, 183)

Note Data reported in mean (%CV) except T_{max} and apparent terminal $t_{1/2}$ in median (Q1, Q3).

Summary Pharmacokinetics of Islatravir in Plasma Following 3 Weekly Oral Doses of 25 mg BRII-732 to Healthy Adult Subjects

	AUC_{last} (h*ng/mL)	C_{max} (ng/mL)	C_{168h} (ng/mL)	T_{max} (h)	Apparent terminal $t_{1/2}$ (h)
Day 1 (N=6)	511 (21.7)	120 (18.8)	NC	0.53 (0.5, 1.0)	45 (33, 52)
Day 15 (N=6)	620 (22.3)	121 (26.0)	1.10 (12.9)	0.5 (0.5, 0.52)	76 (59, 91)

Note Data reported in mean (%CV) except T_{max} and apparent terminal $t_{1/2}$ in median (Q1, Q3).

- **After single or multiple oral administrations of BRII-732 up to 200 mg, no measurable systemic exposure to BRII-732 was detected (LLOQ of 1.0 ng/mL), suggesting fast and efficient release of EFdA from BRII-732**
- **Dose-dependent ISL plasma PK profiles were observed after single or multiple oral doses of BRII-732 over the range of 10 mg to 200 mg. No meaningful EFdA accumulation was observed in plasma.**
- **Efficient intracellular formation of ISL-TP in PBMCs was observed in a dose-dependent manner.**
- **Consistent with the long cellular half-lives, significant ISL-TP accumulations were observed after 3 weekly doses of 25 mg BRII-732.**

Overall Summary of Subjects with Treatment-emergent Adverse Events Following 3 Weekly Oral Doses of 10 mg and 25 mg BRII-732

Number (%) of Subjects with Any	BRII-732 10 mg QW x 3 (N=3)	BRII-732 25 mg QW x3 (N=6)	Pooled Placebo (N=3)
TEAE	2 (66.7%)	2 (33.3%)	3 (100%)
Grade 1	2 (66.7%)	2 (33.3%)	3 (100%)
Grade 2, 3, 4, or 5	0	0	0
TEAE Related to Study Drug	2 (66.7%)	2 (33.3%)	2 (66.7%)
Grade 1	2 (66.7%)	2 (33.3%)	2 (66.7%)
Grade 2, 3, 4, or 5	0	0	0
Treatment-emergent Serious AE	0	0	0
TEAE Leading to Premature Discontinuation of Study Drug	0	0	0
Death	0	0	0

- **TEAEs reported by more than 1 subject in SAD were Gr1 constipation (n = 4 subjects) and headache (n = 3). TEAEs reported by more than 1 subject in MAD were Gr1 nausea (n=4 subjects) constipation (n = 2), headache (n = 2) and diarrhea (n=2).**
- **The majority of laboratory abnormalities were Grade 1. Two BRII-732 subjects had Grade 3 LDL increases (SAD) and no Grade ≥ 3 labs (MAD). No graded lymphocyte decreases were reported. CD4+/CD8+ subsets were not collected**

CONCLUSIONS

- **BRII-732 was generally well tolerated at single doses up to 200mg and repeat doses up to 25mg**
- **PK profiles including ISL in plasma and ISL-TP in PBMC cells after single and multiple oral administrations of BRII-732 demonstrated linear pharmacokinetics and achieved therapeutic targets**
- **BRII-732 is currently on FDA clinical hold pending further evaluation of CD4+ cell decline observed at higher doses in ISL Phase2/3 trials**
- **Safety and PK data supports further development of BRII-732 as part of oral weekly combination antiretroviral therapy.**

REFERENCES

** Dirk Schurmann, et. Al., Safety, pharmacokinetics, and antiretroviral activity of islatravir (ISL, MK-8591), a novel nucleoside reverse transcriptase translocation inhibitor, following single-dose administration to treatment-naive adults infected with HIV-1:an open-label, phase 1b, consecutive-panel trial, LANCET, 2020, S2352-3018 (19) 30408-4*