A Phase 1a/b Dose Escalation Study of the BTK/FLT3 Inhibitor Luxeptinib in Patients with Relapsed or Refractory B-Cell Malignancies

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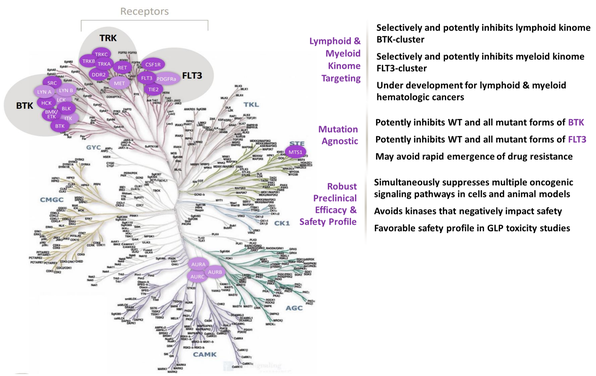
INTRODUCTION

Luxeptinib (CG-806) is an orally active, non-covalent inhibitor of BTK and FLT3 kinases. It suppresses BCR signaling pathways (LYN, SYK, BTK, AKT, ERK), MAP kinases, and other oncogenic pathways in cell lines and primary leukemic cells. Luxeptinib kills malignant B-cells insensitive to ibrutinib at concentrations in the nanomolar range and shows enhanced activity in combination with venetoclax. Described here is an update of the ongoing Phase 1a/b trial in relapsed or refractory B-cell malignancies (NCT03893682) in which a novel and more bioavailable formulation of Luxeptinib (G3) was recently explored.



Luxeptinib is also being evaluated in a Phase 1a/b trial in patients with relapsed or refractory AML (NCT04477291) (ASH 2022 - Abstract #2767)

STUDY DESIGN

Phase 1a/b, open-label, single arm, multi-center, dose escalation study to determine the safety, pharmacokinetics (PK), and pharmacodynamics (PD) and antitumor activity of luxeptinib in ascending 6 dose cohorts of patients with relapsed or refractory CLL/SLL or NHL who failed or are intolerant to prior therapies or for whom no other treatment options are available

- Additional patients may be enrolled (back filling) at dose levels previously declared safe
- Bioavailability sub-study conducted as part of this study and a related luxeptinib Phase 1a/b study (NCT03893682) to establish viability of an optimized G3 formulation
  - Patients receive a single dose of the G3 formulation 72 hours prior to Cycle 1 Day 1 followed by PK sampling
  - Patients then go on to receive continuous BID dosing with the original (G1) formulation on Cycle 1 Day 1.

OBJECTIVES

Primary objectives:

- Assess the safety and tolerability of luxeptinib at escalating dose levels
- Determine the dose and schedule of luxeptinib that maintains a biologically active plasma concentration
- Establish the recommended Phase 2 dose (RP2D) in CLL/SLL or NHL patients

Secondary objectives:

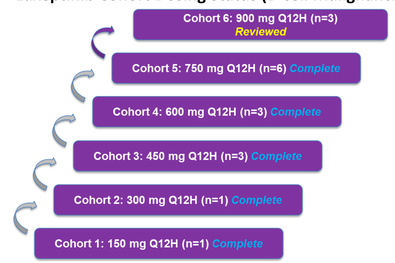
- Evaluate luxeptinib PK profile and impact on expression of PD biomarkers
- Obtain preliminary evidence of antitumor activity

We thank our principal investigators, clinical site staff, and most importantly, our patients and their families for their participation in this clinical trial.

ASH2022 Abstract# 2893

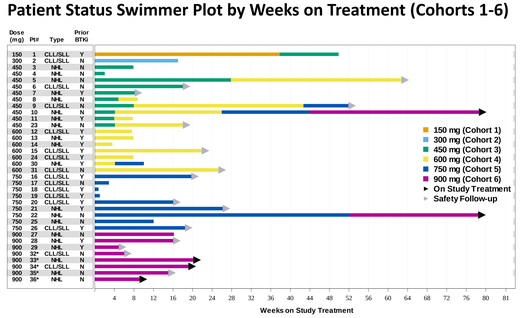
LUXEPTINIB STUDY STATUS

Luxeptinib Cohort Dosing Status (B-cell Malignancies)



n = DLT evaluable patients, not representative of total enrolled at each cohort level (which includes unevaluable and backfill).

Patient Status Swimmer Plot by Weeks on Treatment (Cohorts 1-6)



\# Data-cut date: Sep 30, 2022; 5 patients are on study among 600mg - 900mg Cohort.
* Patients enrolled for G3BA Sub-study.

PATIENT CHARACTERISTICS

Heavily pre-treated CLL / SLL (16; 44.4%) or NHL (20; 55.6%) patient population:

- Most of patient enrolled are White (33; 91.7%) in race and non-Hispanic (28; 77.8%) ethnicity.
- Median 3 lines of prior therapies (range 1-13)

Patient Characteristics	
Patient Demographics	**Cohorts 1 to 6 (N=36)***
Median Age (Range), Years	62 (41, 84)
Sex	
Male	23 (63.9%)
Female	13 (36.1%)
Relapsed or Refractory, N (%)	
Relapsed	15 (41.7%)
Refractory	5 (13.9%)
Both Relapsed and Refractory	13 (36.1%)
None/Neither	3 (8.3%)
Median Number of Lines of Prior Therapy (Range)*	**3 (1, 13)**
Chemotherapy, N(%)	31 (86.1%)
Radiation	7 (19.4%)
Transplant[ł]	1(2.8%)
Targeted and Immunotherapy	
Targeted and Immunotherapy, N (%)	
Antibody	36 (100%)
BTK-Inhibitor (ibrutinib, acalabrutinib, AVL-292)**	17 (47.2%)
Steroid	11 (30.6%)
PI3K-Inhibitor (idelalisib, duvelisib)	10 (27.8%)
Immunomodulatory Agent	10 (27.8%)
BCL2-Inhibitor (venetoclax)	8 (22.2%)
Kinase Inhibitor	6 (16.7%)
Cellular	4 (11.1%)
Other Experimental Agent	3 (8.3%)
Proteasome Inhibitor	2 (5.6%)
EZH2 Inhibitor	1 (2.8%)
Experimental PI3K-Delta Inhibitor	1 (2.8%)
Other Kinase Inhibitor	1 (2.8%)

ł 1 patient had autologous transplant.
* Maintenance and consolidation therapies are not considered prior therapies.
** 17 patients received Btk-inhibitor; 14 received ibrutinib (IBR); 1 received IBR and AVL-292; 1 received IBR and acalabrutinib; and 1 received IBR, obinituzumab, HDMP, and Venetoclax.

SAFETY AND TOLERABILITY

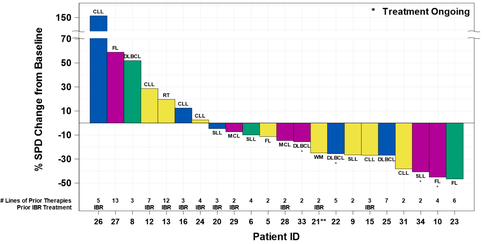
Overall, luxeptinib has been well tolerated at dose levels up to 900 mg BID over multiple cycles. Luxeptinib has been received by 65 patients (N=36 in this study) and the AML study (NCT04477291) (N=29) to treat their disease.

Treatment-emergent AEs (TEAEs) Cohorts 1 to 6 (N=36)	
Patients Experiencing TEAEs:	**N (%)**
Any	34 (94.4%)
Most Common AE	
Diarrhea	17 (47.2%)
Fatigue	15 (41.7%)
Nausea	12 (33.3%)
≥ Grade 3	23 (63.9%)
SAEs	18 (50.0%)
Leading to treatment discontinuation	6 (16.7%)
Patients Experiencing TEAEs Related to Luxeptinib	**N (%)**
Any	30 (83.3)%
≥ Grade 3	14 (38.9%)
Non-hematologic	
Diarrhea	3 (8.3%)
Alanine aminotransferase increased	1 (2.8%)
Headache	1 (2.8%)
Hyperhidrosis	1 (2.8%)
Hypertension	1 (2.8%)
SAEs*	6 (16.7%)
Leading to death	0 (0%)
Dose Limiting Toxicity (DLT)**	1 (2.8%)

*Six patients reported a related SAE of dysarthria, encephalopathy, hypertension and neutropenic sepsis (one patient each).
**One patient at 750 mg BID dose level reported DLT: experienced a new onset grade 2 hypertension during screening (prior to treatment with luxeptinib) that increased to grade 4 after beginning luxeptinib treatment for 5 days. No drug-related hypertension was observed in any other patient treated to date.

ANTITUMOR ACTIVITY

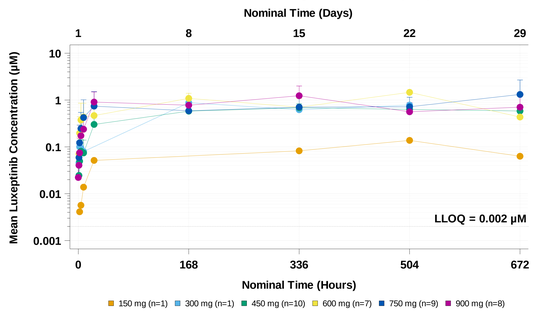
Change in Sum of Product Diameters (SPD)



Note: IBR- Ibrutinib; only patients with post-screening assessments are shown on plot.
** WM patient(s) measuring % IgM
*** Dose level shown from time of disease assessment, if at least 1 cycle of doses received at this level.

G1 PHARMACOKINETIC PROFILE

Mean Plasma concentrations of the generation 1 (G1) formulation



Note: Analysis is based on the PK Exclusion Working Instructions and Cycle 1 Day 15 post dose timepoints are excluded from analysis. Concentrations below LLOQ are excluded from this plot. 900 mg cohort includes five G3BA patients.

To seek improved exposure, a novel generation 3 (G3) was explored as part of relative bioavailability sub-study.

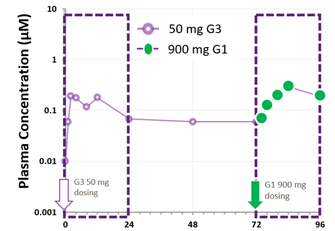
G3 FORMULATION OF LUXEPTINIB

A relative bioavailability sub-study was initiated as part of this study and a luxeptinib Phase 1 AML study (NCT04477291). Three days prior to study Cycle 1 Day 1, sub-study patients received a single dose of the G3 formulation at dose levels of 50 mg, 100 mg, and 200 mg followed by 72 hours of PK sampling. The results of the comparative analysis completed showed:

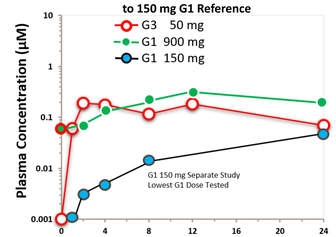
- The novel G3 formulation shows more rapid absorption and higher bioavailability compared with the original G1 formulation of luxeptinib.
- A single 50 mg dose of G3 achieved comparable exposure to a single 900 mg dose of G1, suggesting that G3 may have up to 18-fold better absorption.

PK Comparison of 50 mg G3 to 900 mg G1 Luxeptinib in a Single AML Patient

Sequential Exposure to 50 mg G3 Followed by 900 mg G1



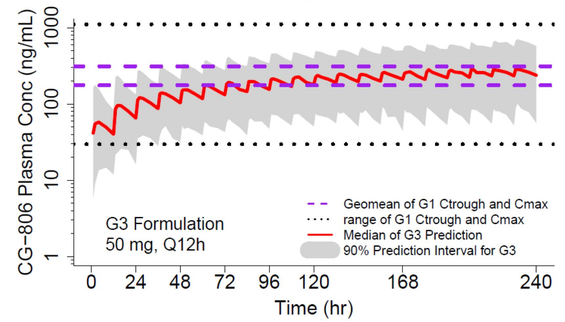
Visualization of Overlapping Exposure with Comparison to 150 mg G1 Reference



PREDICTED PK PROFILE OF G3 FORMULATION

PK profiles of the G3 formulation were simulated using point estimates of PK parameters of G1-treated population PK model. Predications show a sustained exposure level at 50 mg G3, Q12h within the geometric mean of the G1 C_{trough} and C_{max}.

Simulated Plasma Concentration (ng/mL) of Luxeptinib G3 50 mg Q12h



CONCLUSIONS

- **Dose escalation study indicates luxeptinib is well-tolerated at dose levels up to 900 mg BID over multiple cycles with no drug-related deaths.**
- **Anti-tumor activity is observed in multiple B-cell malignancies: FL, WM, CLL/SLL, DLBCL.**
- **PK plasma concentrations at steady state approach ~1µM across 300 mg to 900 mg cohort.**
- **The generation 3 (G3) formulation of luxeptinib achieves higher PK exposure per mg administered.**
- **Modeling predicts 50 mg BID of G3 can produce roughly equivalent to 900 mg BID of the original (G1) formulation.**
- **Continuous dosing with G3 has commenced, and may reduce pill burden, reduce drug substance requirements and deliver greater exposures.**

Disclosures: Current clinical study is sponsored by Aptose Biosciences Inc. The following authors are employees of Aptose Biosciences Inc.: R Sinha, DN Haney, A. Capell, J Hu, N Khan, W Rice, and R Bejar.