A Phase 1 a/b Dose Escalation Study of the FLT3/BTK Inhibitor Luxeptinib (CG-806) in Patients with Relapsed or Refractory Acute Myeloid Leukemia and Higher-Risk Myelodysplastic Syndromes

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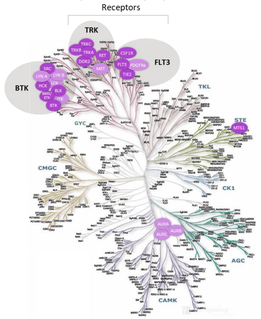
INTRODUCTION

Luxeptinib (CG-806) is a potent oral small molecule inhibitor of the wild type and mutant forms of the FLT3 kinase, including the ITD, TKD, and F691L forms. Luxeptinib suppresses additional signaling pathways in AML cells (CSF1R, PDGFRα, TRK, SYK, BTK, LYN, AKT, ERK, MAPK), kills primary AML cells insensitive to other FLT3 inhibitors at pM and low nM concentrations, and shows enhanced activity in combination with venetoclax. Here we describe the progress of a Phase 1a/b trial of Luxeptinib in patients with relapsed or refractory (R/R) AML (NCT04477291) in which a new formulation of luxeptinib (generation 3 "G3") was explored for greater bioavailability.

Luxeptinib Selectively & Potently Inhibits Myeloid & Lymphoid Kinomes



Robust Preclinical Efficacy Covered Key Mutational Subgroups in AML

FLT3	Lux potently inhibits both the wild type and all mutant forms of FLT3
NPM1	Lux inhibits **SYK** phosphorylation and efficiently suppresses its downstream pathways
IDH1	AML patient samples with IDH1 mutations are more sensitive to Lux than IDH WT
TP53	AML patient samples with wild type and mutant TP53 remain sensitive to Lux
NRAS	AML patient samples with wild type and mutant NRAS remain sensitive to Lux
ASXL1	AML patient samples with wild type and mutant ASXL1 are equally sensitive to Lux
KIT	Lux potently inhibits both the wild type and certain mutant forms of KIT

Luxeptinib is also being evaluated in a Phase 1a/b trial in patients with relapsed or refractory CLL/SLL, and NHL. (NCT03893682) (ASH 2022-Abstract #2893)

STUDY DESIGN

Phase 1a/b, open-label, multi-center, 3+3 dose escalation clinical study in relapsed or refractory AML, higher-risk MDS, or CMML with ≥5% bone marrow blasts who failed or are ineligible for or intolerant of intensive chemotherapy or transplantation.

- At least half of each cohort may have FLT3 mutation
- Oral capsules administered twice daily (after C1D1) on a 28-day cycle
- Study of the safety, pharmacokinetics (PK), and pharmacodynamics (PD) of luxeptinib in ascending cohorts of 3 or 4
- Relative bioavailability (RBA) sub-study conducted as part of this study (and the Phase 1a/b study; NCT03893682) to characterize the PK of optimized G3 luxeptinib formulation
- Patients receive a single dose of the G3 formulation 72 hrs prior to Cycle 1 Day 1 followed by continuous dosing with original formulation (generation 1 "G1") on 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 R/R AML 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.

STUDY STATUS

AS OF SEPTEMBER 22, 2022 DATA-CUT:

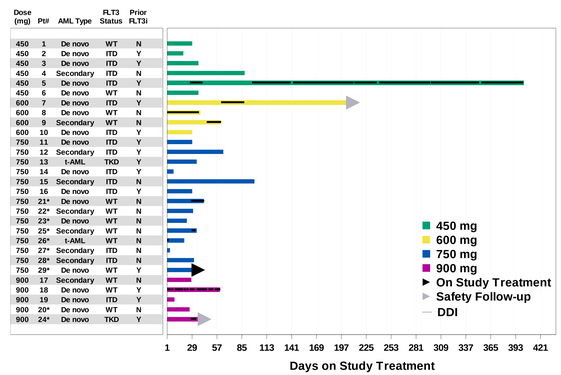
- Twenty-nine (29) patients treated across 4 cohorts:

Cohort Status

Cohort	Dose	Status
1	450 mg BID	Completed
2	600 mg BID	Completed
3	750 mg BID	Completed
4	900 mg BID	Completed

- Single dose G3 formulation for relative bioavailability sub-study was conducted as part of this study and the Phase 1a/b study for patients with R/R B-cell malignancies (NCT03893682).
- Preliminary G3 analysis completed pooling 11 patients across both studies.

Patient Status Swimmer Plot by Days on Treatment (Cohorts 1-4)



* = Patients enrolled for G3BA Sub-study.

PATIENT CHARACTERISTICS

Patient Characteristics	
Patient Demographics	**Cohorts 1 to 4 (N=29)***
Median Age (Range), Years	74 (19, 87)
Sex	
Male	19 (65.5%)
Female	10 (34.5%)
Median Lines of Prior Therapy	**3 (1,10)**
Chemotherapy	18 (62.1%)
Transplant	4 (13.8%)
Radiation	2 (6.9%)
Targeted and Immunotherapy	
Hypomethylating agent	28(96.6%)
BCL-2 inhibitor	26 (89.7%)
FLT3 Inhibitor	14 (48.3%)
Antibody drug conjugate	4 (13.8%)
IDH1-inhibitor	2 (8.0%)
JAK inhibitor	1 (3.4%)
Checkpoint Inhibitor	1 (3.4%)
Other Experimental Agent	5 (17.2%)
RBC Transfusion Dependent	19 (65.5%)
Platelet Transfusion Dependent	18 (62.1%)

*Twelve (12, 41.4%) received giltertinib, 8 also received other FLT3i including midostaurin, AMML-1031, quizartinib or crenolanib; 1 patient received sorafenib.

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SAFETY AND TOLERABILITY

Luxeptinib has generally been well tolerated at dose levels up to 900 mg BID over multiple cycles. The majority of adverse events observed are Grade 1 or Grade 2 with few non-hematologic drug-related adverse events.

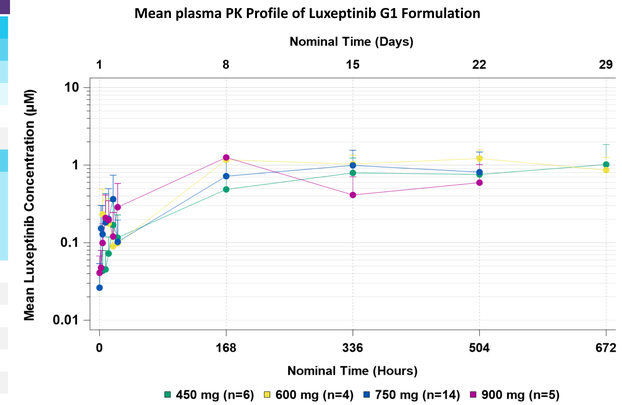
Treatment-emergent AEs (TEAEs) Cohorts 1 to 4 (N=29*)	
Patients Experiencing TEAEs:	**N (%)**
Any	28 (96.6%)
Most Common AE	
Edema Peripheral	11 (37.9%)
Constipation	10 (34.5%)
Hypokalemia	9 (31%)
Hypophosphatemia	9 (31%)
Nausea	9 (31%)
≥ Grade 3	25 (86.2%)
SAEs	25 (86.2%)
Leading to treatment discontinuation	3 (10.3%)
Leading to death	9 (31%)
Patients Experiencing TEAEs Related to Luxeptinib	**N (%)**
Any	15 (51.7%)
≥ Grade 3	5 (17.2%)
Most common Non-hematologic AE	
Encephalopathy	1 (3.4%)
Pericardial effusion	1 (3.4%)
SAEs*	2 (6.9%)
Leading to death	0 (0%)
Dose Limiting Toxicity (DLT)**	2 (6.9%)

*Three treatment-related SAEs of pericardial effusion, pleural effusion, and encephalopathy were reported by 2 patients.
**Two patients in the 450 mg and 750 mg dose cohorts each experienced a single DLT of pericardial effusion and encephalopathy, respectively (each "possibly related" to study drug). No DLTs occurred in the other 5 patients, supporting dose escalation.

G1 PHARMACOKINETIC PROFILE

Plasma concentrations of the generation 1 (G1) formulation of luxeptinib reached steady state (trough levels) within 8 days.

Mean plasma PK Profile of Luxeptinib G1 Formulation



- Analysis is based on PK Exclusion Working Instructions and Cycle 1 Day 15 post dose timepoints are excluded from analysis. Concentrations below LLOQ are excluded from this plot.
- PK data at Cycle 1 Day 1 2 hour timepoint was not collected in Cohort 450 mg and 600 mg. 750 mg cohort includes eight RBA G3 patients; 900 mg cohort includes two RBA G3 patients.

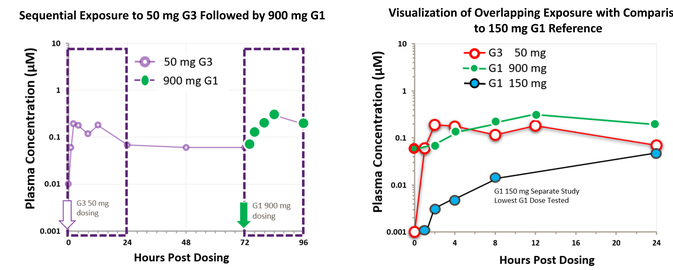
Disclosures: Current clinical study is sponsored by Aptose Biosciences The following authors are employees of Aptose Biosciences: R Sinha, DN Haney, A Capell, J Hu, N Khan, W Rice, and R Bejar

G3 FORMULATION OF LUXEPTINIB

A relative bioavailability sub-study was initiated as part of this study and the CLL/SLL/NHL study (NCT03893682). The results of the comparative analysis completed showed:

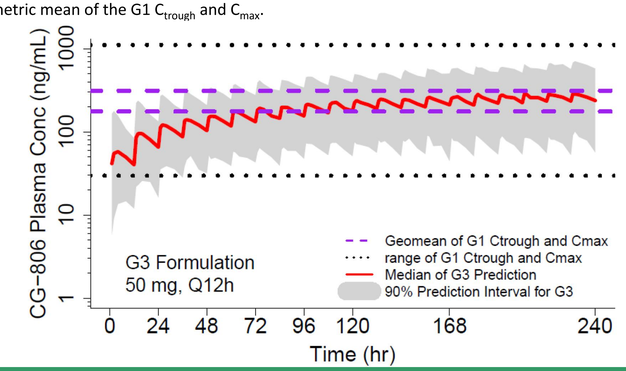
- PK comparison of the G3 and G1 formulations showed higher bioavailability of the G3 formulation of luxeptinib.
- A single 50 mg dose of G3 achieved comparable exposure to a single 900 mg dose of G1, suggesting that G3 may have up to 18-fold better absorption.

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



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}.



CONCLUSIONS

- **Luxeptinib is well tolerated at dose levels of 450, 600, 750, and 900 mg BID over multiple cycles.**
- **PK plasma concentrations at steady state approached ~1µM across the 600 mg to 900 mg cohorts.**
- **The generation 3 (G3) formulation of luxeptinib achieved higher PK exposure per mg administered when given as a single dose.**
- **Modeling of continuous dosing predicts 50 mg BID is 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.**
- **Continuous dosing of G3 will replace G1 for newly enrolled R/R AML patients in this study, starting at 50 mg BID.**