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#1546

Covalent-103: A Phase 1, Open-Label, Dose Escalation, and Dose-Expansion Study of BMF-500, an Oral Covalent *FLT3* Inhibitor, in Adults with Acute Leukemia (AL)

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FLT3 MUTATION IN ACUTE LEUKEMIA

- *FLT3* mutations occur in 25%-35% of patients with AML, and in ~ 5% of ALL patients and are associated with poor prognosis [1, 2]
- *FLT3* abnormalities are most commonly *ITD* and *TKD* mutations

BMF-500 BACKGROUND

- BMF-500 is an orally bioavailable, selective, covalent, small-molecule inhibitor of *FLT3*, including *WT, ITD,* and *TKD* mutants, and retains potency against *FLT3* inhibitor resistance mutations such as the *F691* gatekeeper and *D835* mutations
- BMF-500 has demonstrated high affinity for *FLT3*, lack of cKIT inhibition, and sustained cell-killing capacity that persists even after prolonged drug washout[3]
- BMF-500 has shown sustained tumor regression and improved survival in both subcutaneous and disseminated xenograft models of mutant *FLT3*-driven AML[3]
- BMF-500 is currently supplied as 25 and 100 mg strength tablets for oral administration

COVALENT-103 STUDY OVERVIEW

- COVALENT-103 (NCT05918692) is an open-label, nonrandomized, first-in-human, Phase I study evaluating the safety, tolerability, and activity of escalating doses of twice daily oral BMF-500 in patients with R/R AL, including AML, ALL, or MPAL, with or without *FLT3* mutations
- As of Nov 2023, the study is open for enrollment at 5 sites in the United States; additional sites to open soon
- Enrollment commenced in Sep 2023 and has dosed patients in both Arms with Dose Level 1 complete; escalation continues

OBJECTIVES & ENDPOINTS

	Primary	Secondary	Exploratory
Objectives	• Evaluate the safety and tolerability of BMF-500 • Determine the OBD and RP2D of BMF-500	• Determine the single and multiple dose PK of BMF-500 • Assess the effect of food on the PK exposure of BMF-500 • Evaluate the efficacy of BMF-500 • Assess additional evidence of antitumor activity per investigator assessment as per corresponding response criteria	• Assess MRD • Characterize the PD effects over the course of treatment with BMF-500
Endpoints	• Incidence of TEAEs and SAEs • OBD/RP2D determination based on evaluation of available PK/ PD, safety and tolerability, and efficacy data	• C_{max}, t_{max}, AUC_{last}, AUC_{inf}, $t_{1/2}$ of BMF-500 after a single dose, and C_{max}, t_{max}, C_{min}, t_{min}, AUC_{last}, steady-state AUC_t, $t_{1/2}$, AR after multiple dosing • CRc (CR, CRh, CRp, CRi), ORR: CR, CRh, CRp, CRi, MLFS, or PR as measured by PI using ELN 2017 • DOR , RFS, OS	• Rate of MRD-negativity in patients with AL who achieve CR or CRi • Changes in molecular profiling as well *FLT3* signaling by plasma inhibitory assay

STUDY DESIGN

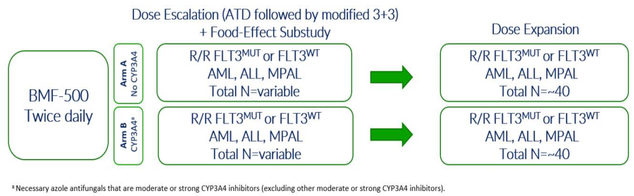

Fig. 1 Study Schema

Dose Escalation Scheme

Dose Levels for Escalation Phase

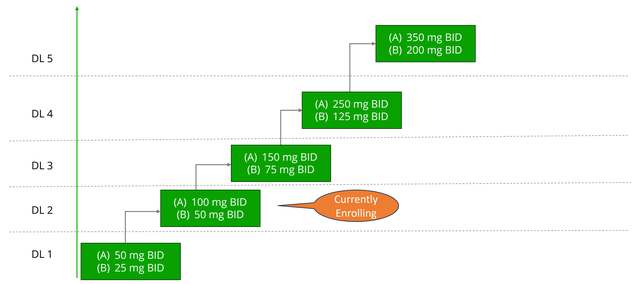

Fig. 2 Accelerated titration design followed by modified 3+3

- BMF-500 doses are escalated in single-subject cohorts independently for each Arm until 1 subject experiences either any ≥ Grade 2 TRAE which does not meet DLT criteria, or a DLT in the first 28-day cycle
- At that point, the dose level for the specific Arm will follow a classical "3 + 3" dose escalation design

STUDY FLOWCHART

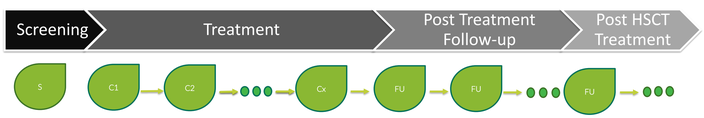

Fig. 3 Study flowchart

Screening	• Up to 28 days from consent
Treatment	• BMF-500 administered BID in 28-day cycles
Post Treatment Follow-up	• Efficacy follow-up assessments for patients who discontinued in absence of progression • Long-term survival follow-up for patients post-progression or after initiation of subsequent anti-cancer therapy
Post HSCT Follow-Up	• BMF-500 treatment post-HSCT may be permitted as part of ongoing study participation

KEY ELIGIBILITY CRITERIA

Inclusion Criteria

- Adults (≥18 years of age) with ECOG performance status of 0-2 and estimated life expectancy of >3 months
- R/R FLT3-mutant AML, ALL, MPAL, and R/R *FLT3*-WT AML, ALL, MPAL (≤33% per Arm)
- Histologically or pathologically confirmed diagnosis of AML, ALL, or MPAL and documentation of *FLT3* status
- Must be R/R or must have progressed on or following discontinuation of the most recent anti-cancer therapy and/or ineligible for any approved standard of care therapies, including HSCT
- Patients with *FLT3*-mutant AML must have received treatment with an approved *FLT3* inhibitor and must have relapsed, progressed and/or discontinued the inhibitor
- Adequate washout from prior therapies (e.g., ≥60 days from TBI; ≥60 days from stem cell infusion; ≥14 days from biologics or steroids, immunotherapy, and chemotherapy)
- Adequate liver function: Bilirubin ≤1.5 x ULN; ALT/AST ≤2.0 x ULN
- Adequate renal function: eCrCl ≥60 mL/min using the Cockcroft-Gault equation

Exclusion Criteria

- Diagnosis of acute promyelocytic leukemia, chronic myeloid leukemia in blast crisis
- WBC count >50,000/µL (uncontrollable with cytoreductive therapy)
- Clinically active CNS leukemia; previously controlled CNS leukemia is acceptable
- Known positive test for HIV, Hep C, Hep B surface antigen
- Active uncontrolled acute or chronic systemic fungal, bacterial, or viral infection
- Clinically significant cardiovascular disease; LVEF <45%
- Mean QTcF or QTcB of >470 millisecond
- Acute or chronic GVHD except disease limited to skin with adequate control using topical steroids
- GI disease that may affect oral absorption
- Concurrent malignancy in the previous 2 years

REFERENCES

1. Bystrom R, Levis MJ. An Update on FLT3 in Acute Myeloid Leukemia: Pathophysiology and Therapeutic Landscape. Curr Oncol Rep. 2023 Apr;25(4):369-378. doi: 10.1007/s11912-023-01389-2. Epub 2023 Feb 18. PMID: 36808557.
2. Zhang, Y., Zhang, Y., Wang, F. *et al.* The mutational spectrum of FLT3 gene in acute lymphoblastic leukemia is different from acute myeloid leukemia. *Cancer Gene Ther* **27**, 81–88 (2020)
3. Law et al., ASH 2022 Abstract 2756