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Covalent FLT3 Inhibitor BMF-500 in Relapsed or Refractory (R/R) Acute Leukemia (AL): Preliminary Phase 1 Data from the COVALENT-103 Study (NCT05918692)

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FLT3 Mutation in Acute Leukemia

- FLT3 mutations occur in up to 37% of patients with acute myeloid leukemia (AML) and are associated with poor prognosis [1, 2]
- Once failing the only approved agent in the R/R setting, gilteritinib, patients have abysmal prognosis and very short survival (mOS ~1.8 months) [3]; for example, no complete remissions (CRs) were reported among the gilteritinib-exposed FLT3-mutant AL patients treated with FF-10101, an investigational covalent FLT3 inhibitor which otherwise demonstrated efficacy in gilteritinib-naïve FLT3-mutant AL[4]
- FLT3 abnormalities are most commonly ITD and TKD mutations; some approved FLT3 inhibitors are effective only for ITD mutations

BMF-500 Background

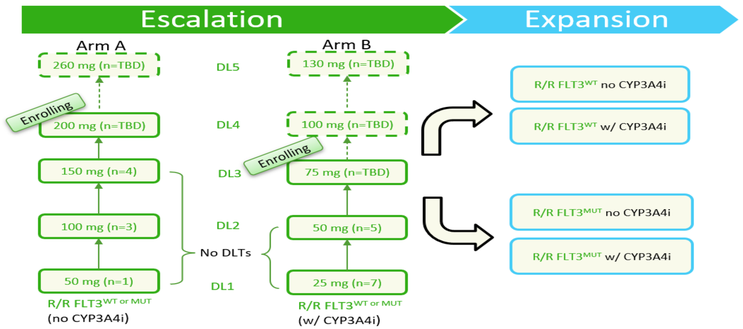
- BMF-500 is an orally bioavailable, selective, covalent small-molecule investigational inhibitor of FLT3, including wild type, ITD, and TKD mutants, that retains potency against FLT3 inhibitor resistance mutations such as the F691 gatekeeper and D835 mutations
- BMF-500 has demonstrated high affinity for FLT3, a lack of cKIT inhibition (thereby avoiding suppression of normal hematopoiesis), and a sustained cell-killing capacity that persists even after prolonged drug washout[5]
- BMF-500, in preclinical studies, has shown sustained tumor regression and improved survival in both subcutaneous and disseminated xenograft models of mutant FLT3-driven AML[5]

COVALENT-103 Study Overview and Objectives

- COVALENT-103 (NCT05918692) is an open-label, first-in-human, Phase I study evaluating the safety, tolerability, and clinical activity of twice-daily oral BMF-500 in patients with R/R acute leukemia, with or without FLT3 mutations
- As of 19 May 2025, the study is open for enrollment at 21 sites in the United States
- Study commenced in Q4 2023 and has dosed 27 patients to date; enrollment is ongoing
- Objectives
  - Evaluate safety and tolerability
  - Determine the optimal biologic dose (OBD) and recommended Phase II dose (RP2D)
  - Evaluate efficacy per ELN2022 as assessed by the Investigator
  - Characterize on-treatment PD effects
  - Evaluate changes in molecular profiling

Study Design

- **Dose Escalation** is conducted using Accelerated Titration Design (ATD) followed by classical "3+3"; Arm A / B (not taking / taking CYP3A4i) enrolled in parallel
- **Dose Expansion** will be initiated to explore at least two dose levels

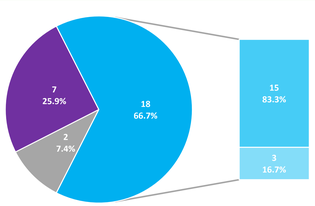


BMF-500 orally twice daily administered in continuous 28-day cycles
N~110

Key Eligibility Criteria

- Adults (≥18 years), ECOG ≤2, life expectancy >3 months
- R/R FLT3-mutant AML and R/R wild type FLT3 AML (≤33% per Arm)
- Must be R/R and progressed after SOC
- FLT3-mutant patients must have failed treatment with approved FLT3 inhibitor(s)
- Adequate organ function: Bilirubin ≤1.5 x ULN; ALT/AST ≤2.0 x ULN, eCrCl ≥60 mL/min
- Absence of significant CV disease (LVEF >45%, mean QTcF or QTcB of <470 ms)

FLT3 Mutational Status at Study Entry



FLT3 mutational status determined by central lab

- As per protocol, at each dose level up to 33% of patients may be wild type FLT3
- 100% (n=18) FLT3-mutant patients had progressed on or after a gilteritinib-containing regimen
- 9 of 18 FLT3-mutant patients had received at least two FLT3 inhibitors prior to study entry

Data extract: 19May2025

Baseline Characteristics

	Arm A (N=10)	Arm B (N=17)	Total (N=27)
Median age, years (range)	57.4 (34, 69)	58.5 (23, 87)	58.1 (23,87)
ECOG Performance Status			
0	1 (10 %)	4 (24%)	5 (19%)
1	6 (60%)	8 (47%)	14 (52%)
2	3 (30%)	5 (29%)	8 (30%)
Gender			
Female, n (%)	3 (30%)	5 (29%)	8 (30%)
Male, n (%)	7 (70%)	12 (71%)	19 (70%)
Prior Therapies			
Median # prior therapies (range)	4.5 (2,10)	4 (1,8)	4 (1,10)
Prior treatment with intensive therapy	5 (50%)	8 (47%)	13 (48%)
Prior Hematopoietic Stem Cell Transplant (HSCT)	5 (50%)	7 (41%)	12 (44%)
Prior Venetoclax-containing regimen	10 (100%)	16 (94%)	26 (96%)

Data extract: 19May2025

BMF-500 Was Generally Well Tolerated

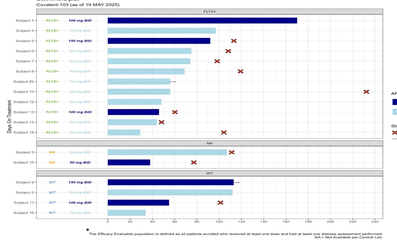
TEAEs with Preferred Term (Incidence ≥ 20%)	Related (N = 27)	Unrelated (N = 27)	All (N = 27)
Participants with at least one TEAE	**10 (37%)**	**25 (93%)**	**25 (93%)**
Hypokalaemia	0	10 (37%)	10 (37%)
Dyspnoea	0	9 (33%)	9 (33%)
Febrile neutropenia	0	9 (33%)	9 (33%)
Alanine aminotransferase increased	3 (11%)	4 (15%)	7 (26%)
Aspartate aminotransferase increase	3 (11%)	4 (15%)	7 (26%)
Fatigue	0	7 (26%)	7 (26%)
Hypocalcaemia	0	7 (26%)	7 (26%)
Hypophosphataemia	0	7 (26%)	7 (26%)
Nausea	2 (7%)	5 (19%)	7 (26%)
Oedema peripheral	0	7 (26%)	7 (26%)
Diarrhoea	2 (7%)	4 (15%)	6 (22%)
Hypotension	1 (4%)	5 (19%)	6 (22%)
Pneumonia	0	6 (22%)	6 (22%)

- BMF-500 has shown a generally well-tolerated safety profile across all dose levels explored
- No DLTs reported
- No drug-related QTc prolongation

Data extract: 19May2025

Early Efficacy Data and Time on Treatment (Efficacy-Evaluable population*)

Dose levels 1, 2 and 3 in Arms A and B (n=18)

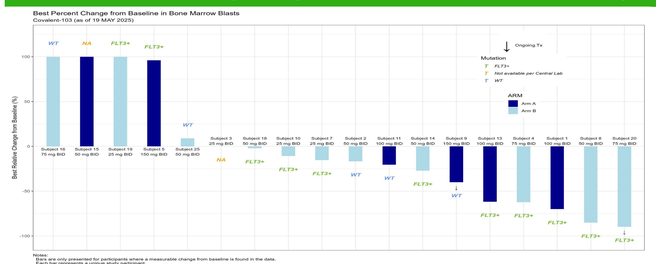


*The Efficacy Evaluable population is defined as all patients enrolled who received at least one dose and had at least one disease assessment performed. NA = Not Available per Central Lab.

- **1 CRi** (1 of 2 FLT3-mutant patients at 100 mg BID/DL2, Arm A; duration of response 104 days [6 cycles])
- **1 MLFS** (1 of 2 FLT3-mutant patients at 75 mg BID/DL3, Arm B; duration of response: ongoing)
- **1 near PR** (1 of 3 FLT3-mutant patients at 50 mg BID/DL2, Arm B; duration of response: 92 days [3 cycles], achieved all PR criteria except minimum platelet count)
- **2 of 4 FLT3 wild-type** efficacy-evaluable patients achieved durable disease control lasting for ≥ 120 days, with treatment ongoing for one patient
- **12 Decreased bone marrow blasts**: 1 patient with normalized blasts, 6 patients with >60% reduction, 1 patient with 25-50% reduction, and 4 patients with ≤25% reduction
- **9 Decreased peripheral blasts:** 5 patients with complete clearance, 2 patients with >90% reduction, 1 patient with >75% reduction and 1 patient with <50% reduction
- **4 patients decreased hydroxyurea use**
- **5 patients experienced a reduction in RBC transfusion dependency**
- **4 patients experienced a reduction in platelet transfusion dependency**

Data extract: 19May2025

Early Efficacy Data: Bone Marrow (BM) Blasts % Change



Notes:
Bars are only presented for participants where a measurable change from baseline is found in the data.
Each bar represents a unique study participant.
Participants with best relative change from baseline >100% are trimmed.

- 9 of 11 FLT3-mutant patients had a reduction in bone marrow blasts; 5 of 11 had a >50% BM blast reduction
- 3 of 4 FLT3 wild-type patients had a modest reduction in bone marrow blasts, with 1 patient showing a 40% decrease

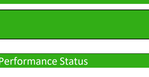
Data extract: 19May2025

REFERENCES

1. Bystrom et al. Curr Oncol Rep. 2023 Apr;25(4):369-378.
2. Zhang et al. Cancer Gene Ther. 27, 81–88 (2020).
3. Corley et al. (P1798) HemaSphere 2024;8(S1), 3339-3340.
4. Levis et al. Blood Adv 2024; 8 (10): 2527–2535.
5. Law et al. ASH 2022 Abstract 2756.

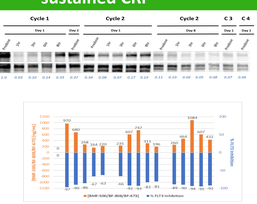
61-year-old male FLT3-mutant patient treated with BMF-500 100 mg BID (Arm A/DL2) achieved sustained CRi

Acute Leukemia	Primary AML
Mutations detected at study entry	**FLT3-ITD**, ASXL1, IDH2, PHF6, RUNX1, SRSF2
# of prior therapies	4 (including venetoclax and gilteritinib-containing regimens)
Prior HSCT	Yes



Timepoint: Screening, C2D1, C3D1, C4D1, C5D1, C6D1, §

Response	-	MLFS	CRi	MRD+	MRD-*	MRD+
BM blasts (%):	10%	5%	3%	5%	5%	14%
Allelic Ratio:	0.1	-	-	-	-	-
MFC MRD:	-	-	-	3.82%#	<0.1%*	13.99%#



#Based on bone marrow assessment
*Based on peripheral blood assessment

§Duration of response 104 days (6 cycles completed)

- **The magnitude of FLT3 inhibition correlated with the plasma concentration of BMF-500**
- **Study treatment was generally well tolerated with no interruptions or dose modifications**
- **Best objective response of CRi, as assessed by Investigator per ELN 2022 criteria**

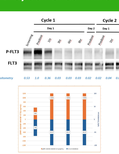
42-year-old male FLT3-mutant patient treated with BMF-500 75 mg BID (Arm B/DL3) achieved MLFS

Acute Leukemia	Secondary AML
Mutations detected at study entry	**FLT3-ITD (3 distinct ITD mutations), FLT3 D835Y, FLT3 D835H,** WT1
# of prior therapies	6 (including azacitidine, venetoclax and gilteritinib-containing regimens)
Prior HSCT	No

Timepoint: Screening, C2D1, C3D1, ¥

Response	-	PR	MLFS
BM blasts (%):	68%	7%	1%
Allelic Ratio:	0.68	-	-
MFC MRD:	-	ND	ND

ND: Not Done ¥ Response ongoing



- Note near-complete FLT3 inhibition as early as C1D1 3hr post-dose
- Near-complete FLT3 inhibition was also achieved on C2D1, both pre-dose and at all post-dose timepoints
- In the bar graph, PK values are shown for C1D1 post-dose at 1, 3, 6 and 8 hrs; PK values were not available for C2D1
- Patient achieved partial response (PR) at Cycle 2 Day 1 (C2D1) with improvement to MLFS by Cycle 3 Day 1 (C3D1); response is ongoing

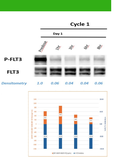
26-year-old male FLT3-mutant AML patient treated with BMF-500 50 mg BID (Arm B/DL2) achieved near PR

Acute Leukemia	Primary AML
Mutations detected at study entry	**FLT3-ITD**, KMT2A-MLLT3
# of prior therapies	8 (including azacitidine, venetoclax and gilteritinib-containing regimens)
Prior HSCT	Yes

Timepoint: Screening, C2D1, C3D1, §

Response	-	PD	spelling
BM blasts (%):	81%	49%	12%
Allelic Ratio:	0.94		
MFC MRD:	-	MRD+ (14.8%)	MRD+ (35.7%)

§ EOT: C3D9

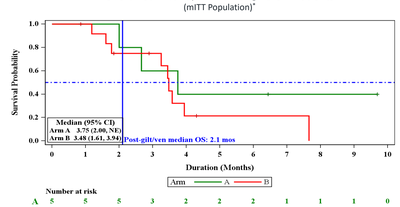


- Near-complete FLT3 inhibition was observed at all timepoints post-dose on C1D1
- In the bar graph, PK values and FLT3 inhibition are shown for C1D1 at 1, 3, 6 and 8 hrs post-dose
- Best response was categorized as progressive disease (PD) per ELN 2022; however, the patient achieved all criteria for PR except platelet recovery

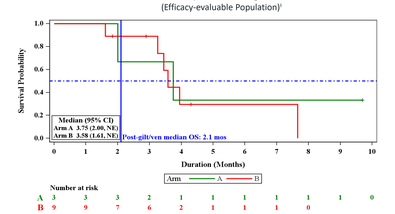
COVALENT-103 KM Survival Plots: FLT3-mutant Patients (n=18)

Key Takeaways:
- **mOS 3.48 to 3.75 mos**
- *Historical mOS ~2.1 mos (post-gilt/ven R/R AL)[3]

Overall Survival by Arm among FLT3m Patients (mITT Population)*



Overall Survival by Arm among FLT3m Patients (Efficacy-evaluable Population)†



*The modified Intent-to-Treat (mITT) Population is defined as Patients who received at least one dose of BMF-500.
NE = Not evaluable

†The efficacy-evaluable population is defined as all patients who received at least one dose of BMF-500 and had at least one efficacy assessment performed.

*** Reference survival parameters[3]:**
- Pts who failed gilteritinib and received no subsequent treatment: mOS 0.28 mos
- The mOS for all R/R AML pts post gilteritinib failure: ~1.8 mos
- Pts who failed both gilteritinib and venetoclax: mOS 2.1 mos

[3]Corley E et al. (P1798) Clinical outcomes of R/R AML after treatment with gilteritinib. HemaSphere 2024;8(S1), 3339-3340.

Data extract: 19May2025

Summary

- **Safety and tolerability data:**
  - No significant safety or tolerability issues observed to date (e.g., no QT prolongations) and no dose-limiting toxicities (DLTs) reported
  - BMF-500 has been generally well tolerated, and the dose escalation continues without safety restrictions
- **Early clinical activity data:**
  - Responses observed as early as the end of Cycle 1 and best overall responses of CRi and MLFS achieved at explored dose levels
  - Reduction of bone marrow blasts in 9 of 18 (50%) of FLT3-mutant patients
  - Other evidence of clinical activity observed (e.g., clearance of peripheral blasts, reduction of transfusion frequency, reduction in use of hydroxyurea)
  - Median overall survival (mOS) for the FLT3 mutant patients (N=18) represents a marked improvement over historical mOS of 2.1-month in a comparable patient population[3]
- **PK/PD markers confirm on-target FLT3 inhibition:**
  - BMF-500 induced dose-proportional FLT3 inhibition
  - Most patients were able to achieve near complete FLT3 inhibition on first day of dosing
  - BMF-500 and its major metabolites have shown similar concentrations in bone marrow compared to plasma suggesting good compartmental penetration

Collectively, these data support the ongoing development of BMF-500

ACKNOWLEDGEMENTS

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