Preliminary Results from a Phase 1 Dose Escalation Study of FHD-286, a Novel BRG1/BRM (SMARCA4/SMARCA2) Inhibitor, Administered as an Oral Monotherapy in Patients with Advanced Hematologic Malignancies

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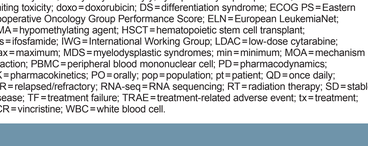
INTRODUCTION

FHD-286 is a first-in-class, orally administered compound that potently and selectively inhibits the ATPase components of the BAF complex, BRG1/BRM (SMARCA4/2).

- BRG1 and BRM are the catalytic core of a subset of chromatin remodeling complexes known as BAF complexes.
- BAF complexes are critical to the regulation of cellular differentiation and proliferation: mutations in BAF are implicated in cancer as well as other diseases.
- AML cells were highly sensitive to BAF inhibition.

BAF Chromatin Remodeling Complex



OBJECTIVES AND METHODS

Endpoints: safety, tolerability, DLTs, PK, PD, preliminary clinical activity

Monotherapy Dose Escalation

FHD-286 Administered PO QD in continuous 28-day cycles → 2.5 mg QD → 5 mg QD → 7.5 mg QD → 10 mg QD

Key Eligibility Criteria:

- R/R AML (must have previously failed all prior therapies known to be active for treatment of their diagnosed hematologic disease)
- R/R MDS (must have previously failed treatment with ≥4 cycles of an HMA known to be active for treatment of their diagnosed hematologic disease)
- Other R/R advanced hematologic malignancy (eg, CMML)

ACKNOWLEDGEMENTS

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Abbreviations: AE = adverse event; ALT = alanine aminotransferase; AML = acute myeloid leukemia; ANC = absolute neutrophil count; ATPase = adenosine triphosphatase; $AUC_{0\text{-}24hr}$ = area under the concentration-time curve from 0 to 24 hours; aza = azacytidine; C_{max} = maximum concentration; CMML = chronic myelomonocytic leukemia; CNS = central nervous system; CxDy = Cycle x Day y; cyclophos = cyclophosphamide; DLT = dose-limiting toxicity; doxo = doxorubicin; DS = differentiation syndrome; ECOG PS = Eastern Cooperative Oncology Group Performance Score; ELN = European LeukemiaNet; HMA = hypomethylating agent; HSCT = hematopoietic stem cell transplant; ifos = ifosfamide; IWG = International Working Group; LDAC = low-dose cytarabine; max = maximum; MDS = myelodysplastic syndromes; min = minimum; MOA = mechanism of action; PBMC = peripheral blood mononuclear cell; PD = pharmacodynamics; PK = pharmacokinetics; PO = orally; pop = population; pt = patient; QD = once daily; R/R = relapsed/refractory; RNA-seq = RNA sequencing; RT = radiation therapy; SD = stable disease; TF = treatment failure; TRAE = treatment-related adverse event; tx = treatment; VCR = vincristine; WBC = white blood cell.

RESULTS

Baseline Demographics and Disease Characteristics

Patient population had advanced, heavily pretreated disease.

Parameter	2.5 mg QD (N = 5)	5 mg QD (N = 16)	7.5 mg QD (N = 13)	10 mg QD (N = 6)	Total (N = 40)
Age (years), median (min, max)	73 (61, 84)	67.5 (43, 80)	66 (25, 75)	45 (27, 79)	65.5 (25, 84)
Gender, n (%)					
Male	1 (20)	8 (50)	8 (61.5)	3 (50)	20 (50)
Female	4 (80)	8 (50)	5 (38.5)	3 (50)	20 (50)
Race, n (%)					
White	4 (80)	13 (81.3)	12 (92.3)	5 (83.3)	34 (85)
Other[a]	1 (20)	3 (18.7)	1 (7.7)	1 (16.7)	6 (15)
ECOG PS, n (%)					
0	0	5 (31.3)	5 (38.5)	3 (50)	13 (32.5)
1	4 (80)	8 (50)	7 (53.8)	3 (50)	22 (55)
2	1 (20)	3 (18.8)	1 (7.7)	0	5 (12.5)
Hematologic malignancy, n (%)					
AML	5 (100)	13 (81.3)	12 (92.3)	6 (100)	36 (90)
MDS	0	3 (18.8)	1 (7.7)	0	4 (10)
Genetic risk stratification[b], n (%)					
Favorable	0	0	2 (15.4)	0	2 (5)
Intermediate	0	1 (6.3)	0	3 (50)	4 (10)
Adverse	4 (80)	10 (62.5)	9 (69.2)	3 (50)	26 (65)
Unknown	0	5 (31.3)	2 (15.4)	0	7 (17.5)
Number of prior lines of systemic anticancer therapy[c], median (min, max)	3 (1, 5)	3 (1, 6)	4 (1, 7)	3 (1, 5)	3 (1, 7)
Prior HSCT, n (%)	1 (20)	7 (43.8)	4 (30.8)	1 (16.7)	13 (32.5)

Data cutoff date 02 Aug 2022. [a]Includes Black or African American, Asian, and Other. [b]Missing: 1 (6.3%) patient at 5 mg QD. Based on ELN 2017 recommendations. [c]Twenty-seven (67.5%) patients overall had received ≥3 prior lines of systemic anticancer therapy for their AML/MDS; 9 (22.5%) had received ≥5 prior lines.

Patient Disposition

Most common reasons for tx discontinuation were AE and disease progression/tx failure.

Parameter, n (%)	2.5 mg QD (N = 5)	5 mg QD (N = 16)	7.5 mg QD (N = 13)	10 mg QD (N = 6)	Total (N = 40)
Patients who discontinued study tx	5 (100)	16 (100)	13 (100)	6 (100)	40 (100)
Reason for discontinuation of study tx					
Adverse event	3 (60)	6 (37.5)	5 (38.5)	3 (50)	17 (42.5)
Disease progression/tx failure	2 (40)	5 (31.3)	7 (53.8)	1 (16.7)	15 (37.5)
Clinical suspicion of disease progression	0	3 (18.8)	1 (7.7)	2 (33.3)	6 (15)
Withdrawal of consent	0	2 (12.5)	0	0	2 (5)

Data cutoff date 02 Aug 2022.

Summary of Treatment-Related AEs and DLTs

Parameter, n (%)	2.5 mg QD (N = 5)	5 mg QD (N = 16)	7.5 mg QD (N = 13)	10 mg QD (N = 6)	Total (N = 40)
Any TRAE	5 (100)	15 (93.8)	10 (76.9)	4 (66.7)	34 (85)
TRAEs occurring in ≥15% of patients					
Dry mouth	0	8 (50)	3 (23.1)	0	11 (27.5)
Increased blood bilirubin[a]	0	4 (25)	3 (23.1)	2 (33.3)	9 (22.5)
ALT increased	1 (20)	4 (25)	2 (15.4)	1 (16.7)	8 (20)
Rash[b]	1 (20)	4 (25)	1 (7.7)	2 (33.3)	8 (20)
Diarrhoea	0	4 (25)	2 (15.4)	1 (16.7)	7 (17.5)
Nausea/vomiting[c]	0	5 (31.3)	0	2 (33.3)	7 (17.5)
Fatigue	1 (20)	5 (31.3)	0	1 (16.7)	7 (17.5)
Dysgeusia	0	4 (25)	0	2 (33.3)	6 (15)
Any Grade ≥3 TRAE[d]	1 (20)	9 (56.3)	8 (61.5)	2 (33.3)	20 (50)
Grade ≥3 TRAEs occurring in ≥2 patients					
Increased blood bilirubin[a]	0	2 (12.5)	2 (15.4)	1 (16.7)	5 (12.5)
Stomatitis	0	2 (12.5)	1 (7.7)	0	3 (7.5)
ALT increased	0	1 (6.3)	2 (15.4)	0	3 (7.5)
Hypocalcaemia	1 (20)	1 (6.3)	0	1 (16.7)	3 (7.5)
Differentiation syndrome	0	1 (6.3)	2 (15.4)	0	3 (7.5)
Diarrhoea	0	2 (12.5)	0	0	2 (5)
Fatigue	0	1 (6.3)	0	1 (16.7)	2 (5)
Mucosal inflammation	0	0	2 (15.4)	0	2 (5)
Rash[b]	0	1 (6.3)	1 (7.7)	0	2 (5)
Overall summary of TRAEs					
Any serious TRAE	1 (20)	4 (25)	5 (38.5)	3 (50)	13 (32.5)
Any TRAE leading to dose reduction	0	0	2 (15.4)	0	2 (5)
Any TRAE leading to dose interruption	1 (20)	4 (25)	6 (46.2)	2 (33.3)	13 (32.5)
Any TRAE leading to tx discontinuation	0	1 (6.3)	0	1 (16.7)	2 (5)
Dose-limiting toxicities					
Muscular weakness	0	0	0	1 (16.7)	1 (2.5)
Hyperbilirubinaemia	0	1 (6.3)	0	0	1 (2.5)

Data cutoff date 02 Aug 2022. [a]Increased blood bilirubin includes Blood bilirubin increased and Hyperbilirubinaemia. [b]Rash includes Acute febrile neutrophilic dermatosis, Drug eruption, Skin erosion, Skin exfoliation, Exfoliative rash, Rash macular, Dermatitis allergic, Dermatitis bullous, Rash erythematous, Rash generalized, Urticaria, Rash maculo-papular, Rash, Rash papular, Rash pruritic, Rash pustular, Rash vesicular, and Butterfly rash. [c]Nausea/vomiting includes Nausea, Vomiting, and Retching. [d]There were no fatal TRAEs.

Differentiation Syndrome

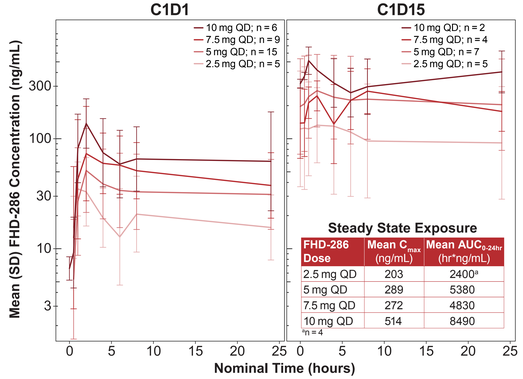
Investigator-reported differentiation syndrome was treated with dexamethasone or other corticosteroid for ≥3 days; other treatments were hydroxyurea, furosemide, oxygen therapy, and hemodynamic monitoring.

Parameter	Per Investigators	Per Retrospective DS Adjudication Committee
Frequency of DS	4 patients	6 patients[a]
Grades of DS	Grade 2 in 1 patient Grade 3 in 3 patients	Grade 3 in 5 patients Grade 4 in 1 patient
Time from first dose of FHD-286 to initial onset of DS	4 to 31 days	4 to 42 days
Signs and symptoms associated with DS	Pleural effusion, pericardial effusion, fluid overload, hypotension, peripheral edema, shortness of breath, hypoxia, fever, leukocytosis, hyperbilirubinemia, elevated creatinine, elevated liver function tests, elevated cardiac troponin	Pleural effusion, pericardial effusion, volume overload, hypotension, weight gain, ground glass opacities/pulmonary infiltrates on imaging without documentation of positive cultures, hypoxia, pyrexia, elevated WBC count, multi-organ involvement (lung, heart, kidneys)

Data cutoff date 02 Aug 2022. [a]Includes 1 patient adjudicated as having definitive DS (Grade 3) and 5 patients adjudicated as indeterminate for DS.

Plasma Pharmacokinetics

- FHD-286 has a long half-life (≥24 hr) and accumulates with QD dosing, with steady state reached by ~C1D15
- Plasma concentrations increased with increasing dose
- Exposure-response analysis showed that concomitant administration of azoles tended to result in higher FHD-286 exposure

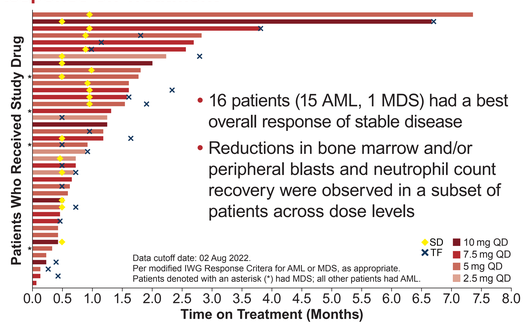


Steady State Exposure

FHD-286 Dose	Mean C_{max} (ng/mL)	Mean $AUC_{0\text{-}24hr}$ (hr*ng/mL)
2.5 mg QD	203	2400[a]
5 mg QD	289	5380
7.5 mg QD	272	4830
10 mg QD	514	8490

[a]n = 4

Response on Treatment

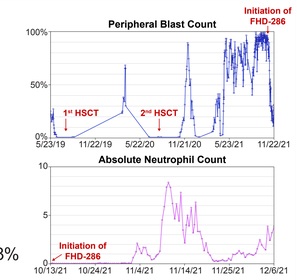


- 16 patients (15 AML, 1 MDS) had a best overall response of stable disease
- Reductions in bone marrow and/or peripheral blasts and neutrophil count recovery were observed in a subset of patients across dose levels

Preliminary Clinical Activity

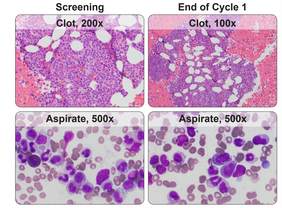
Case 1: 25-year-old male with treatment-related AML with KMT2A rearrangement

- Progressive AML with CNS involvement
- 7 lines prior treatment, 2 HSCTs
- History of Ewing's sarcoma treated with chemo/RT/surgery (VCR, doxo, cyclophos, ifos, etoposide)
- Starting dose: FHD-286 7.5 mg QD
- Peripheral blasts reduced from 97% to 5%
- Bone marrow blasts reduced from 89% to 48%
- ANC recovery



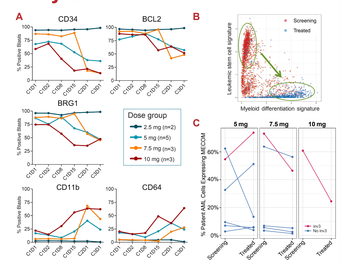
Case 2: 47-year-old male with secondary AML with abnormal karyotype

- Progressive AML
- 4 lines prior treatment, 2 HSCTs
- History of MDS treated with 4 cycles of aza
- Starting dose: FHD-286 10 mg QD
- Bone marrow blasts reduced from 40% to 6%
- Clear evidence of differentiation
- Persistent cytogenetic abnormalities
- ANC recovery



Exploratory PD Analyses – Preliminary Data

- Markers of myeloid differentiation observed in a subset of patients, who had a broad range of cytogenetic backgrounds, including enhancer-driven leukemias such as MECOM and KMT2A
- Exploratory assessment of markers of differentiation, hematopoietic stem cell identity, and apoptosis suggested dose-dependent target engagement (A)
- Exploratory sequencing analysis on bone marrow blasts suggested comprehensive impacts on AML-specific expression pathways and stem cell-likeness genes (B and C)
- Exposure-response analysis showed a trend toward lower blast count with higher FHD-286 exposure[a]



A) PBMCs were analyzed by flow cytometry for indicated markers. Samples were live cell-gated and blasts were identified by CD45 vs side scatter. Pts with MDS, pts who completed < 1 cycle, and samples with < 1000 viable blasts were excluded. Data points represent group median. B) Single-cell RNA-seq performed on paired screening and on-treatment pt bone marrow aspirates. Shown: analysis of screening and C2D1 samples from a single pt at 5 mg QD. Similar effects observed across 5 mg QD, 7.5 mg QD, and 10 mg QD.

[a]Exposure-response analysis conducted using % peripheral blasts (333 samples) and results from popPK model.

CONCLUSIONS

- FHD-286 was evaluated in a Phase 1 dose escalation study in patients with R/R AML or R/R MDS.
- FHD-286 was tolerable and safe at continuous daily dose levels of up to 7.5 mg QD.
- MOA of FHD-286 appears to be via differentiation of leukemic stem cells.
- Differentiation syndrome was identified as a risk for FHD-286.
- Sixteen patients had a best overall response of stable disease.
  - Reductions in bone marrow and/or peripheral blasts and neutrophil count recovery observed in a subset of patients across dose levels.
- Enrollment into the monotherapy dose escalation portion of the study is complete.
- Based on nonclinical, translational, and monotherapy clinical data, FHD-286 in combination with decitabine or LDAC is being evaluated in the combination dose escalation portion of the study.

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