A First-in-Human Study of the Oral CLK Inhibitor BH-30236 in Adults with Relapsed/Refractory Acute Myeloid Leukemia or Higher-Risk Myelodysplastic Syndrome: Monotherapy and Venetoclax Combination

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Background: Alternative Splicing

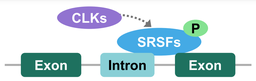
Importance of Alternative Splicing

- Alternative splicing (AS) is a regulated cellular process during gene expression where specific exons of a pre-mRNA are included or excluded, allowing a single gene to produce multiple distinct mRNA transcripts.
- These varied mRNAs are then translated into diverse protein isoforms with unique structures and functions.

Addressing Aberrant Alternative Splicing Extends the Targetable Proteome

- Dysregulated AS is a hallmark of cancer and regulates proliferation, apoptosis, immune surveillance and therapeutic resistance. Acute myeloid leukemia (AML) and higher-risk myelodysplastic syndrome (HR-MDS) are especially dependent upon aberrant AS.
- Chromatin-Spliceosome (CS) mutations occur in 40-85% of HR-MDS and 10-25% of AML cases, while aberrant AS is observed in myeloid malignancies even in the absence of CS mutations.

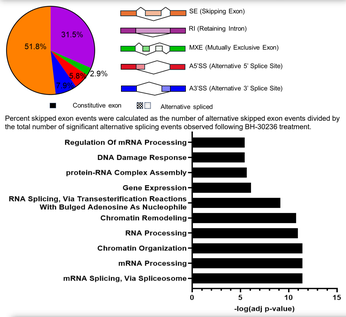
Importance of CLK and SRSF



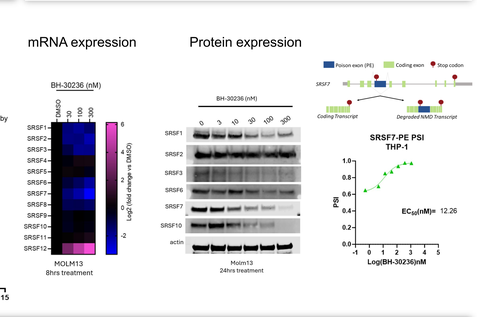
- CDC-like kinases (CLKs) can modulate aberrant splicing via phosphorylation of serine/arginine-rich splicing factor (SRSF) proteins, which control splice-site recognition and spliceosome assembly.
- BH-30236 is a first-in-class, orally bioavailable, ATP-competitive, macrocyclic CLK inhibitor.

BH-30236: A Macrocyclic CLK Inhibitor

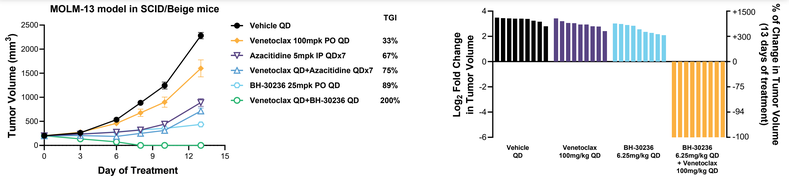
Common Alternative Splicing Events and Gene Ontology Analysis following Treatment with BH-30236 across 6 Primary AML Samples[1]



BH-30236 Downregulated SRSF Expression via Nonsense Mediated Decay in an AML Cell Line Model



CLK inhibition with BH-30236 plus venetoclax could overcome venetoclax resistance, even when dosed at low dose levels (6.25 mg/kg QD of BH-30236, equivalent to 30 mg QD in humans) in MOLM-13 CDX tumor model of AML harboring FLT3-ITD and KMT2A-MLLT3 fusion[1]



Study Design and Objectives

Therapy Arm	Participant Population	Dose Escalation & Backfill Schema
BH-30236 Monotherapy (ongoing)	R/R AML, HR-MDS, CMML* and MPNs* (MF, PV, ET)	DL1*, DL2, DL3, DL4, DL5, etc. + BACKFILL; *Initial BH-30236 dosing at 5 mg QD continuous dosing
BH-30236 + Venetoclax Combination (ongoing)	R/R AML, HR-MDS and CMML*	DL3*, DL4, DL5, etc. + BACKFILL; *Initial BH-30236 dosing at 20 mg QD continuous dosing
BH-30236 + Azacitidine + Venetoclax Combination (pending activation)	ND Unfit AML*	DL4*, DL5, DL6, etc. + BACKFILL; *Initial BH-30236 dosing at least one dose level below SRC cleared combination of BH-30236 + venetoclax

*pending ongoing protocol amendment

Upcoming Phase 1b expansion cohorts pending RDE selection

Primary Objectives

- To evaluate the safety/ tolerability of BH-30236 as a monotherapy or in combination in adult participants with R/R AML or HR-MDS and determine the MTD.
- To evaluate the preliminary anti-cancer activity in terms of ORR, CR/CRh rate of BH-30236 as a monotherapy or in combination at selected RDEs to determine the RP2D.

Secondary Objectives

- To characterize PK properties of BH-30236 as a monotherapy or in combination.
- To characterize the preliminary anti-cancer activity in terms of CRc, TTR, DOR of BH-30236 as a monotherapy or in combination, and the frequency of transfusions.

Exploratory Objectives

- To characterize the MRD response.
- To evaluate effect of BH-30236 on EFS/ OS.
- To characterize PD effects of BH-30236.

MTD: maximum tolerated dose, ORR: objective response rate, CR: complete remission, CRh: complete remission with partial hematologic recovery, RDE: recommended dose for expansion, RP2D: recommended phase 2 dose, PK: pharmacokinetic, CRc: composite complete remission rate, TTR: time to remission, DOR: duration of response, MRD: measurable residual disease, EFS: event-free survival, OS: overall survival, PD: pharmacodynamic

Participant Baseline Characteristics

Characteristic	Category	All Pts (N=48)
Therapy arm, n (%)	Monotherapy	30 (63%)
	Combination therapy	18 (37%)
Diagnosis, n (%)	De novo / primary AML	27 (56%)
	Secondary AML	10 (21%)
	HR-MDS	11 (23%)
Age, years	Median (range)	71 (23-85)
	≥75	17 (35%)
Sex, n (%)	Male	37 (77%)
	Female	11 (23%)
ECOG performance status, n (%)	0	6 (12%)
	1	32 (67%)
	2	10 (21%)
Disease status at baseline, n (%)	Refractory	24 (50%)
	Relapsed/refractory	13 (27%)
	Untreated relapsed	7 (15%)
	Treated relapsed	4 (8%)

Characteristic	Category	All Pts (N=48)
Baseline bone marrow disease burden	Bone marrow blasts, median % (range)	25 (5-92)
	Bone marrow blasts ≤ 30%	24 (50%)
	Bone marrow blasts > 30% and ≤ 50%	8 (17%)
	Bone marrow blasts > 50%	15 (31%)
	Bone marrow blasts missing	1 (2%)
AML risk classification, n (%)	Favorable	0/37 (0%)
	Intermediate	6/37 (16%)
	Adverse	29/37 (78%)
HR-MDS IPSS-R, n (%)	Intermediate	2/11 (18%)
	High	5/11 (46%)
	Very high	4/11 (36%)
Molecular alterations, n (%)	Chromatin-Spliceosome mutation(s)#	26 (54%)
	TP53 mutation	16 (33%)
	FLT3-ITD mutation	1 (2%)
Prior anti-cancer treatment history	Number of prior lines, median	2
	≥4 prior lines	13 (27%)
Prior anti-cancer therapies, n (%)	Prior venetoclax	42 (88%)
	Prior HMA (azacitidine or decitabine)	47 (98%)
	Prior HSCT	11 (23%)

All data as of 10 April 2026 data cut

ECOG: Eastern Cooperative Oncology Group, IPSS-R: Revised International Prognostic Scoring System, HMA: Hypomethylating agent, HSCT: Hematopoietic Stem Cell Transplant

#Chromatin-Spliceosome genes[2]: ASXL1, BCOR, EZH2, KMT2A/MLL, RUNX1, SF3B1, SRSF2, STAG2, U2AF1, ZRSR2.

Safety Profile

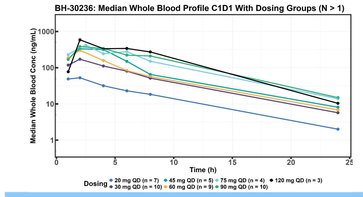
Selected BH-30236-Related Adverse Events

Safety Analysis Set (N=48)	Monotherapy (N=30)		Venetoclax Combination (N=18)	
	All Grades	Grade ≥3	All Grades	Grade ≥3
Any BH-30236 Related AEs	18 (60.0)	9 (30.0)	10 (55.6)	9 (50.0)
Dose Limiting Toxicities (DLTs)	1 Grade 3 diarrhea		0	
Gastrointestinal				
Diarrhea	10 (33.3)	5 (16.7)	5 (27.8)	2 (11.1)
Nausea	9 (30.0)	0	6 (33.3)	0
Vomiting	4 (13.3)	0	4 (22.2)	0
Hematologic				
Neutrophil count decreased	2 (6.7)	1 (3.3)	5 (27.8)	5 (27.8)
Platelet count decreased	2 (6.7)	2 (6.7)	5 (27.8)	4 (22.2)
Anemia	2 (6.7)	2 (6.7)	4 (22.2)	4 (22.2)

All data as of 10 April 2026 data cut

- BH-30236 well tolerated as a continuous QD dose. Manageable GI toxicities were the most frequent TRAEs.
- Combination safety profile displays more frequent cytopenias consistent with a venetoclax-based regimen.
- Three participants had events consistent with a differentiation syndrome (DS). All cases of DS resolved with corticosteroid treatment with or without dose interruption.
- Grade 4 TRAEs were primarily hematologic cytopenias: G4 platelet count decreased (n=4), G4 neutrophil count decreased (n=4).
- Dose reductions due to TRAEs occurred in 2/48 (4.2%) participants.
- Discontinuations due to TRAEs occurred in 1/48 (2.1%) participants.

Preliminary Pharmacokinetic Profile

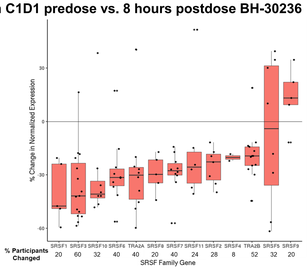


- **Favorable PK Profile**: BH-30236 exhibited appropriate systemic exposure across the evaluated dose range.
- **Exposure**: BH-30236 whole blood exposure (C_{max} and AUC_{0-24}) increased in general with dose in a less than dose proportional manner at higher dose levels, with no meaningful accumulation.
- **No apparent drug-drug interaction (DDI) impact from co-administration with venetoclax**: At dose levels up to 90 mg QD, BH-30236 exposure remained within the monotherapy range when co-administered with venetoclax. Most observed venetoclax concentrations stayed within the range of historical data when co-administered with BH-30236.

Pharmacodynamic Effect

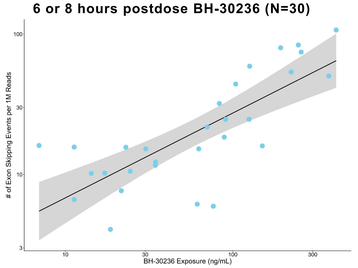
Distribution of gene expression changes across CLK-regulated SRSF family genes on C1D1 predose vs. 8 hours postdose BH-30236

- Plot shows participants dosed at 30 mg BH-30236 and above.
- Number of participants with change in SRSF family gene expression is percentage of N=25.
- Kallisto and DESeq2 were used to quantify differential expression.



Exon skipping events on C1D1 at 6 or 8 hours postdose BH-30236 (N=30)

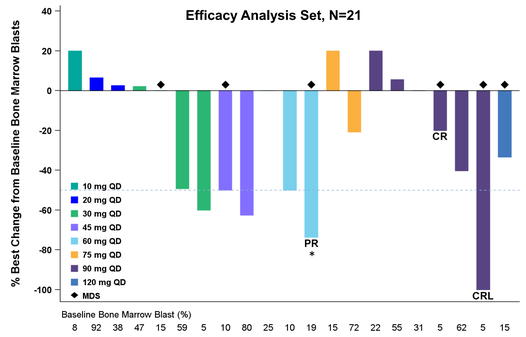
- Exon skipping events detected by centralized plasma RNA sequencing.
- Trend of increased exon skipping by exposure.
- rMATS-turbo was used to quantify alternative splicing events.



Conclusions

- In this FIH study, BH-30236 was well tolerated as a continuous daily dose as a monotherapy and in combination with venetoclax. Most common TRAEs were GI events, with one DLT of G3 diarrhea at the 120 mg QD monotherapy.
- BH-30236 demonstrated on-target exposure-dependent modulation of exon skipping and downregulation of SRSF family genes at doses ≥30 mg QD.
- Preliminary anti-leukemic activity was observed in relapsed/ refractory AML and HR-MDS, both as a monotherapy and venetoclax combination, including in participants previously refractory to venetoclax-based therapy, with MRD-negative CR/CR_L and post-response transition to allo-HSCT.
- Further clinical investigation is ongoing in R/R AML and HR-MDS with planned evaluation in other hematologic malignancies including CMML and MPNs as well as frontline AML in combination with venetoclax and azacitidine.

Preliminary anti-leukemic activity: Monotherapy



- 6/21 (28.6%) participants with post-baseline marrow assessment had ≥50% blast count reduction on therapy.
- Efficacy Analysis Set includes participants with at least one post-baseline marrow assessment resulted.

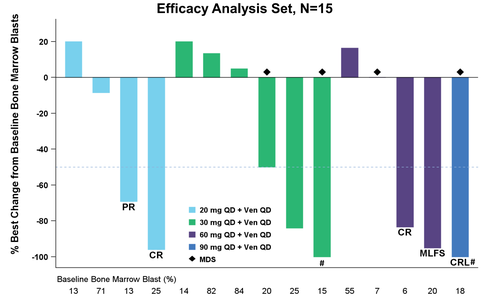
*On therapy PR per protocol version 4.0

Select Clinical Case Descriptions

Dose	Demographics / Disease	Baseline Mutations	Prior Therapy	Key Blood and Marrow Parameters (pre → post)	Objective Response
60 mg QD	81 y/o M Relapsed HR-MDS	ASXL1 DDX41 ETV6, SETBP1 SRSF2 PAX5	1. Azacitidine + SL-172154/ Azacitidine → CR	BM blasts: 19% → 5% ANC: 0.30 → 1.35 PLTs: 25 → 28	NR as overall response; Continuing on treatment in Cycle 13+ (Best response on therapy: **PR***)
90 mg QD	66 y/o M Relapsed HR-MDS	ASXL1 NF1 SETBP1 SRSF2	1. Azacitidine + venetoclax → CR 2. Allogeneic hematopoietic stem cell transplant → CR	BM blasts: 5% → 0% ANC: 0.16 → 1.31 PLTs: 20 → 24	**CR_L** (MRD –) D/C for allogeneic HSCT
90 mg QD	67 y/o F Refractory HR-MDS	TP53	1. Azacitidine + venetoclax → PR	BM blasts: 5% → 4% ANC: 0.85 → 4.42 PLTs: 194 → 113	**CR** after 1 cycle of treatment

All data as of 10 April 2026 data cut, with efficacy follow-up through 20 May 2026 data cut.

Preliminary anti-leukemic activity: Venetoclax combination



- ≥ 50% blast count reduction from baseline observed in 8/15 (53.3%) participants with post-baseline marrow assessments.
- 13/15 participants with prior venetoclax exposure.

Venetoclax-naïve participants

Select Clinical Case Descriptions

Dose	Demographics / Disease	Baseline Mutations	Prior Therapy	Key Blood and Marrow Parameters (pre → post)	Objective Response
20 mg QD	60 y/o M AML 2° to HR-MDS	DDX41 SETD2	1. Azacitidine for MDS 2. 7+3 chemo → NR 3. High dose cytarabine → NR 4. FLAG-idarubicin + venetoclax → NR	BM blasts: 25% → 1% ANC: 0.86 → 5.86 PLTs: 59 → 158	**CR** (MRD−) D/C for allogeneic HSCT
60 mg QD	78 y/o M R/R AML	DNMT3A RAD21 RUNX1 SF3B1 TET2	1. Decitabine + venetoclax → CR 2. Cladribine + low dose cytarabine + venetoclax → PR	BM blasts: 6% → 1% ANC: 1.26 → 2.35 PLTs: 227 → 158	**CR** Treatment ongoing; Awaiting allogeneic HSCT; Loss of RUNX1 & SF3B1 mutations in bone marrow
90 mg QD	79 y/o M Venetoclax-naïve relapsed HR-MDS	ETV6, EZH2	1. Inqovi → NR	BM blasts: 18% → 2% ANC: 1.00 → 1.50 PLTs: 18 → 53	**CR_L** (MRD –) Treatment ongoing

All data as of 10 April 2026 data cut, with efficacy follow-up through 20 May 2026 data cut.

References:
1. Deng W et al. CLK inhibitor BH-30236 synergizes with venetoclax in anti-leukemia activity via splicing modulation in preclinical AML and CLL models. *Cancer Res.* 2026;86(7 Suppl):Abstract 5872. AACR Annual Meeting 2026
2. Papaemmanuil E et al. Genomic Classification and Prognosis in Acute Myeloid Leukemia. *N Engl J Med*. 2016;374(23):2209-2221. doi:10.1056/NEJMoa1516192