Enitociclib (VIP152/formerly BAY1251152) is a Selective and Clinically Active CDK9 Inhibitor: Preliminary Safety and Early Signs of Efficacy in Patients with Non-Hodgkin Lymphoma (NHL) and Chronic Lymphocytic Leukemia (CLL)

Poster #4256

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INTRODUCTION

- Enitociclib is a potent and selective CDK9 inhibitor being developed for the treatment of a wide range of B-cell malignancies.
- Safety/efficacy data of enitociclib administered as monotherapy (IV infusion) in 11 patients (pts) with NHL has been reported previously; including 2/7 pts with double-hit diffuse large B-cell lymphoma (DH-DLBCL) in complete metabolic remissions (CR) for ~5.5+ and ~4.0+ years, of which 3.7 and 2.3 years were on treatment, respectively[1] and 5 pts including 4 NHL and 1 CLL.[2]
- We present updated data on 20 pts, 16 NHL from study VNC-152-101 and 4 CLL pts from study VNC-152-102.
- We also evaluated whether enitociclib inhibits antibody production in a rat model. The COVID-19 pandemic has highlighted the liabilities of anti-CD20 antibodies and BTK inhibitors regarding vaccine efficacy; therefore, a drug that does not inhibit antibody production could be valuable addition to the armamentarium of treatments for B-cell malignancies.

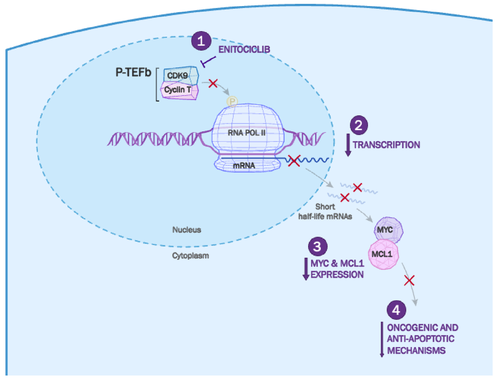

Figure 1. Mechanism of action of enitociclib. (1) Enitociclib inhibits CDK9 preventing activation of RNA polymerase II **(2)** Inactivation of RNA polymerase II causes rapid depletion of short-lived mRNAs **(3)** Expression of known oncogenes, MYC and MCL1, is reduced **(4)** Downregulation of MYC and MCL1 delivers "oncogenic shock" and cell death.

METHODS

- Enitociclib is currently being evaluated in two phase 1 trials in pts with solid tumors and aggressive NHL (VNC-152-101/NCT02635672) and in pts with CLL and Richter syndrome (VNC-152-102/NCT04978779).
- Pts in VNC-152-101 are receiving 30 mg once weekly, while pts in VNC-152-102 received 10 mg for the first week and 15 mg once weekly thereafter, or 15 mg for the first week and 30 mg thereafter.
- Herein, for VNC-152-101 we show safety and preliminary efficacy data for 5 newly enrolled pts (one each): DH-DLBCL, Richter syndrome (RS), transformed follicular lymphoma (tFL), Burkitt lymphoma, and mantle cell lymphoma (MCL), in addition to the previously reported 11 pts[1], making a total of 16 NHL pts.
- For VNC-152-102, we present safety data for 4 CLL pts and efficacy assessments for 3 of the 4 CLL pts.
- Pharmacokinetic (PK) and pharmacodynamic (PD) parameters for NHL/CLL pts are presented. The PD effect of enitociclib in whole blood was evaluated by qPCR or RNAseq.
- A rat study evaluating the T-cell dependent antibody response (TDAR) to KLH of enitociclib was performed to determine the impact on vaccine efficacy.[3]

RESULTS

Baseline characteristics of NHL and CLL patients

- Table 1 provides an overview of the 5 newly enrolled NHL pts and 4 pts with CLL, together with the previously reported 11 NHL pts.
- NHL pts are heavily pretreated (>3 prior therapies).
- Median number of enitociclib doses administered was 4 (range 1-177).
- The 4 CLL pts had received an approved BTKi (with 1 also receiving 2 investigational non-covalent BTKi), 3 pts had received venetoclax, and 2 pts had received CAR-T as part of prior therapy.

Parameter (n=20)	
Median Age in Years	69.5 (Range: 21-84)
Sex, n (%)	
Men	17 (85)
Women	3 (15)
Baseline ECOG, n (%)	
0	6 (30)
1	9 (45)
2	4 (20)
Missing	1 (5)
Baseline LDH (IU/L)	Range: 115-1746
Prior Therapies, n (%)	
1	2 (10)
2	4 (20)
≥3	13 (65)
Missing	1 (5)
Refractory to Last Therapy, n (%)	5 (25)
Bulky Disease, n (%)	
>5cm	14 (70)
>7.5cm	7 (35)
Additional CLL Baseline Characteristics (n=4)	
Cytogenetics (FISH Panel), n (%)	
Del17p	4 (100)
Del11q	3 (75)
Del13q	2 (50)
TP53 Status (Sequencing), n (%)	
Mutated	3 (75)
Unknown	1 (25)
IgVH Mutational Status, n (%)	
Unmutated	3 (75)
Unknown	1 (25)
Prior Therapies	Range: 6-11
ALC (10^9/L)	Range: 1.0-17.2
ANC (10^9/L)	Range: 0.4-2.6
Platelets (10^9/L)	Range: 82-173
Hemoglobin (g/dL)	Range: 9.0-14.2

Table 1. Baseline Characteristics: NHL/CLL pts from studies VNC-152-101 and VNC-152-102 (n=20)

Favorable safety profile

- Pooled safety analysis (n=20; Table 2) demonstrates mainly Grade (Gr) 1 and 2 gastrointestinal adverse events (AEs).
- Hematologic AEs of anemia, neutropenia/neutrophil count decrease (managed with G-CSF support), and platelet count decrease.

Preferred Term	Any Gr n(%)	Gr 1 n(%)	Gr 2 n(%)	Gr 3 n(%)	Gr 4 n(%)
Pt with at least one TEAE	19 (95)	1 (5)	5 (25)	7 (35)	6 (30)
Neutropenia / Neutrophil count decreased	8 (40)	1 (5)	3 (15)	1 (5)	3 (15)
Diarrhea	8 (40)	6 (30)	2 (10)	0	0
Nausea	6 (30)	2 (10)	4 (20)	0	0
Fatigue	6 (30)	3 (15)	2 (10)	1 (5)	0
Vomiting	5 (25)	2 (10)	3 (15)	0	0
Anemia	5 (25)	0	2 (10)	3 (15)	0
Constipation	5 (25)	4 (20)	0	1 (5)	0
Dyspnea	5 (25)	2 (10)	3 (15)	0	0
Pyrexia	4 (20)	4 (20)	0	0	0
Thrombocytopenia	4 (20)	1 (5)	1 (5)	1 (5)	1 (5)
Abdominal pain	3 (15)	1 (5)	2 (10)	0	0
Alkaline phosphatase increased	3 (15)	1 (5)	1 (5)	1 (5)	0
Creatinine increased	3 (15)	3 (15)	0	0	0
Aspartate aminotransferase increased	3 (15)	3 (15)	0	0	0
Alanine aminotransferase increased	3 (15)	3 (15)	0	0	0

Table 2. Treatment Emergent Adverse Events (TEAEs) ≥15%: Pooled safety data for NHL/CLL patients (n=20)

- 10 TEAE SAEs occurred, with only 1 related to enitociclib. A pt with CLL receiving had an SAE/G3 hyperphosphatemia on enitociclib 15 mg. The pt was hospitalized for TLS monitoring but no treatment or intervention was required. The pt received subsequent dosing with 15 mg enitociclib with no recurrence of the event.
- One pt with DH-DLBCL had a reduction in the assigned dose of enitociclib due to an AE of G3 neutropenia (30 mg reduced to 22.5 mg). Two pts had enitociclib interrupted due to an AE (G3 neutropenia x 1, G4 neutropenia x 1).
- There were no discontinuations due to an adverse event. There were 3 deaths due to disease progression.

Neutropenia is an on-target toxicity and is monitorable and manageable with supportive care

- Neutropenia was observed in 8 pts. Supportive care of granulocyte colony stimulating factor (G-CSF) was administered to 3 pts.

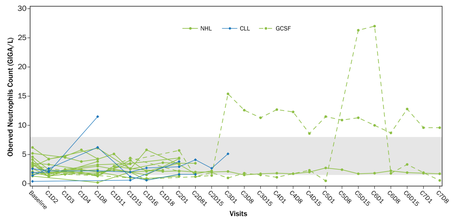

Figure 2. Observed neutrophil count. Normal range shaded; NHL patients treated with G-CSF denoted with dashed line.

Enitociclib monotherapy treatment duration across B-cell malignancies

- Preliminary efficacy signals from the 5 newly enrolled pts include 1 stable disease (SD), 3 radiologic disease progression, and 1 clinical progression.
- The tFL pt with SD had a 16% reduction in tumor burden at the end of cycle 2 response assessment and continues in SD at cycle 7 with a 22% reduction; an observation consistent with the 2 previously reported DH-DLBCL pts who achieved SD at cycle 2 and deeper responses (CR) at cycle 8.
- For CLL pts, disease progression occurred in both pts who received 10/15 mg. One pt who received 15/30 mg had disease progression, while the other is still ongoing (cycle 2).

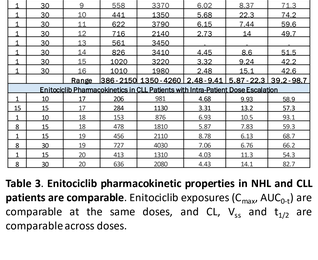

Figure 3. Treatment duration: Pooled data for NHL/CLL patients (n=20).
DH-DLBCL: Double-hit diffuse large B-cell lymphoma, tFL: transformed follicular lymphoma, CLL: chronic lymphocytic leukemia, MCL: mantle cell lymphoma, TH-DLBCL: Triple-hit diffuse large B-cell lymphoma, DE-DLBCL: Double-expressor diffuse large B-cell lymphoma, RS: Richter Syndrome

Enitociclib does not inhibit T-cell dependent antibody response

- In rats dosed with 0.33 mg/kg.week and 1.25 mg/kg/week, anti-KLH IgG serum concentrations were not different at any timepoints. In contrast the positive control, dexamethasone, showed clear inhibition of anti-KLH IgG.
- In this study, enitociclib at 0.33 or 1.25 mg/kg resulted in $AUC_{0\text{-}24}$ of 390 ng*hr/mL and 1820 ng*hr/mL, respectively. The exposure observed for the 1.25-mg/kg group is comparable to the exposure observed in pts receiving enitociclib 30 mg. Based on this preclinical study, enitociclib is not expected to hamper vaccine response.

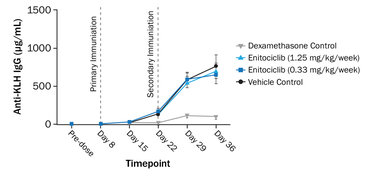

Figure 4. Anti-KLH IgM serum concentrations in rats.

Pharmacokinetic properties are comparable in NHL and CLL pts

Day	Dose (mg)	Subject ID	C_{max} (µg/L)	$AUC_{0\text{-}t}$ (µg*hr/L)	$T_{1/2}$ (hr)	CL (L/h)	V_{ss} (L)
1	30	1	2150	4260	3.88	6.96	39.2
1	30	2	665	1670	3.63	14.3	66.3
1	30	3	506	1930	6.78	8.68	82.4
1	30	4	517	3990	9.15	6.32	80.3
1	30	5	392	3230	8.93	7.87	98.7
1	30	6	386	2030	5.22	14.2	97.9
1	30	7	474	2260	9.41	5.67	76.6
1	30	8	448	3150	5.41	9.19	71.7
1	30	9	558	3370	6.02	8.37	71.3
1	30	10	441	1350	5.68	22.3	74.2
1	30	11	622	3790	6.15	7.44	59.6
1	30	12	716	2140	2.73	14	49.7
1	30	13	561	3450			
1	30	14	826	3410	4.45	8.6	51.5
1	30	15	1020	3220	3.32	9.24	42.2
1	30	16	1010	1980	2.48	15.1	42.6
		Range	386-2150	1350-4260	2.48-9.41	5.67-22.3	39.2-98.7
Enitociclib Pharmacokinetics in CLL Patients with Intra-Patient Dose Escalation							
1	10	17	206	981	4.66	9.93	58.9
15	15	17	284	1130	3.31	13.2	57.3
1	10	18	153	876	6.93	10.5	93.1
8	15	18	478	1810	5.87	7.93	59.3
1	15	19	456	2110	8.78	6.13	68.7
8	30	19	727	4030	7.06	6.76	66.2
1	15	20	413	1310	4.03	11.3	54.3
8	30	20	636	2080	4.43	14.1	82.7

Table 3. Enitociclib pharmacokinetic properties in NHL and CLL patients are comparable. Enitociclib exposures (C_{max}, $AUC_{0\text{-}t}$) are comparable at the same doses, and CL, V_{ss} and $T_{1/2}$ are comparable across doses.

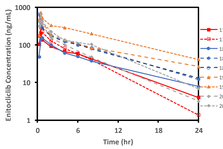

Figure 5. Enitociclib plasma concentration-time profile in CLL (n=4) patients given weekly IV infusions of 10, 15, or 30 mg. Subjects associated with 2 dose levels in the legend were given intra-patient dose escalations.

Intrapatient dose escalation pharmacodynamic effect observed in first two CLL patients dosed with enitociclib at 10/15 mg dose level

- 15 mg dose administered on C1D15 provides a slight improvement of MYC, MCL1, and PCNA mRNA downregulation compared with 10 mg on C1D1. Data are pending for pts with CLL treated with enitociclib at 15/30 mg dose level.
- Preliminary data suggest that the PD effect at these doses is not robust enough to deliver adequate control of oncogenic signals MYC, MCL1, and PCNA as compared with other NHL patients (MCL and DH-DLBCL) dosed at 30 mg. As such, pts treated with 10/15 mg did not respond to enitociclib.

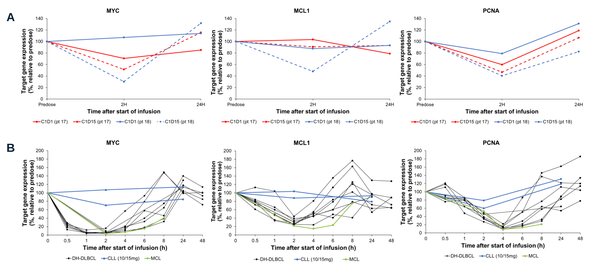

Figure 6. Change of MYC, MCL1, and PCNA mRNA from pre-dose as detected by qPCR from blood samples in patients treated with enitociclib. (A) Pharmacodynamic effect of intrapatient dose escalation of 10/15 mg enitociclib IV in the 2 first CLL patients dosed with enitociclib on C1D1 and C1D15. **(B)** Pharmacodynamic effect of first dose of enitociclib (C1D1) in DH-DLBCL (n=9), MCL (n=1) patients at 30 mg, or CLL (n=2) patients treated with 10 mg on C1D1 and 15 mg every subsequent dose.

Robust MYC down regulation observed across B-cell malignancies

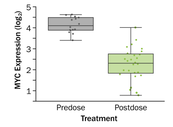

Figure 7. Change of MYC mRNA from predose as detected by RNAseq from blood in patients treated with enitociclib (n=7). Cohort includes 3 DH-DLBCL, 1 TH-DLBCL, 1 CLL, 1 tFL and 1 Burkitt lymphoma patient. Each dot is a timepoint predose or postdose with a pooled fold change of -3.882 with 8.32 [13] adjusted P value.

CONCLUSIONS

- Preliminary PD data suggests 10/15 mg dose is not robust enough to deliver adequate down regulation of oncogenic signals, which is supported by lack of response in pts receiving 10/15 mg (CLL, n=2).
- Significant MYC downregulation is observed in DH-DLBCL pts as well as in pts with other B-cell malignances (tFL, MCL, TH-DLBCL and Burkitt Lymphoma) with the 30 mg dose level.
- Enitociclib is unlikely to abrogate vaccine efficacy, an important feature given the current COVID-19 pandemic.
- Enitociclib PK are consistent with previously reported data[1] in pts with NHL and PK in pts with NHL and CLL are comparable.
- Enitociclib demonstrates evidence of monotherapy clinical activity in DH-DLBCL and perhaps, with longer follow up, in other B-cell malignancies (pt with tFL on study with SD; 22% reduction in tumor burden after 7 cycles). Consequently, enitociclib has garnered Orphan Drug Designation for the treatment of DH-DLBCL from the US Food and Drug Administration and European Medicines Agency.
- Enitociclib monotherapy has a favorable safety profile across a range of B-cell malignancies. The favorable safety profile of enitociclib makes it a good combination partner, as such, enitociclib is being evaluated in combination with BTK inhibitors (NCT04978779) and with venetoclax and prednisone (NCT05371054).

REFERENCES

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ACKNOWLEDGMENTS

Vincerx Pharma, Inc. thanks the patients and families for their participation in the clinical trials.

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Presented at the American Society of Hematology, December 12, 2022, New Orleans, LA