VIP152 is a novel CDK9 inhibitor with improved selectivity, target modulation, and cardiac safety in patients with lymphoma

P1269

Melanie M. Frigault[1], Steven Sher[2], Janani Ravikrishnan[2], Raquel Izumi[1], Joseph Ware[1], Harvey Wong[1], Amy J. Johnson[1], Hermes Garban[1], Beatrix Stelte-Ludwig[3], John C. Byrd[4], Deepa Sampath[5], Kerry Rogers[2], Jennifer A. Woyach[2], Rosa Lapalombella[2], Ahmed Hamdy[1]

[1]Vincerx Pharma Inc., Palo Alto, CA, USA; [2]The Ohio State University, Columbus, OH, USA; [3]Vincerx Pharma GmbH, Monheim, Germany; [4]University of Cincinnati, Cincinnati, OH, USA; [5]MD Anderson, Houston, TX, USA

INTRODUCTION

- Cyclin dependent kinase 9 (CDK9) controls transcription of mRNA by phosphorylation of RNA polymerase II that results in transcription elongation. The transcripts regulated by CDK9 are frequently dysregulated in solid tumors and hematologic malignancies. Thus, inhibition of CDK9 may be effective in controlling cancer, but to date, no CDK9-targeting therapies have been approved due to challenges with therapeutic window.
- High-grade B-cell lymphoma (HGBL), previously known as double-hit lymphoma (DHL), is an aggressive type of B-cell non-Hodgkin lymphoma. HGBL is refractory to standard-of-care chemotherapy and characterized by rearrangements in *MYC* and *BCL2* or *BCL6*, which drive oncogenic transcription and anti-apoptotic signaling, respectively.
- Chronic lymphocytic leukemia (CLL) is effectively treated with therapies targeting Bruton tyrosine kinase (BTK) or B-cell lymphoma 2 (Bcl-2) protein. However, 15.5% of treatment naïve patients have been reported to develop refractory disease, justifying the need for novel therapies.[1–3]
- VIP152 is a highly potent and selective CDK9 inhibitor that has shown preliminary clinical efficacy in double hit diffuse large B-cell lymphoma (DLBCL).[4,5]
- VIP152 is currently being investigated in two phase 1 trials in patients with solid tumors or aggressive non-Hodgkin's lymphoma (NHL) (NCT02635672) and with CLL or Richter Syndrome (NCT04978779). Here, we demonstrate the pharmacodynamic (PD) effects and safety profile of VIP152 in hematologic patients with relapsed/refractory B-cell lymphoma or with CLL who have relapsed or are refractory to ibrutinib and venetoclax (R/R CLL).

METHODS

- The kinase selectivity of VIP152, fadraciclib, alvocidib (flavopiridol), KB-0742, and AZD4573 was evaluated at 1 µM in a KINOMEscan™ assay (Eurofins) and in a CDK9/Cyclin T assay (Nuvisan) in the presence of 10 µM or 2 mM ATP. Potential hits derived from the analysis were further investigated by Kd determination to confirm the interaction with the respective CDK9 inhibitor.
- The effect of VIP152, atuveciclib, and KB-0742 on gene expression was studied in two lymphoma cell lines, SU-DHL-4 and SU-DHL-10, and in whole blood samples obtained from seven VIP152-treated HGBL patients. The differentially expressed (DE) genes were analyzed by RNA-seq (Discovery Life Science).
- The cytotoxicity of VIP152 was evaluated in (1) HG-3 CLL cells where both alleles of the *TP53* gene were edited using CRISPR/Cas9, resulting in p53-stabilizing mutations *R175H* or *R248Q*, and (2) in primary cancer cells obtained from eight R/R CLL patients who had relapsed or were refractory to the BTK inhibitor ibrutinib and Bcl-2 antagonist venetoclax. VIP152- or vehicle-treated cells were stained with Annexin V-FITC and propidium iodide analysed by flow cytometry (Beckman Coulter Cytoflex) followed by data analysis using Kaluza Analysis Software.
- The cardiac safety of VIP152 was evaluated in 57 patients with solid or hematologic cancer. The QTcF duration was determined using concentration-QTc analysis.
- The safety, tolerability, pharmacokinetics, and preliminary efficacy of VIP152 were evaluated in 55 solid and hematologic cancer patients as part of two ongoing phase 1 trials (NCT02635672 in patients with solid tumors or aggressive NHL; NCT04978779 in patients with CLL or Richter Syndrome). The patients were treated once weekly with 5, 10, 15, 22.5, or 30 mg VIP152 as a 30-minute intravenous (i.v.) infusion.
  - 12 patients with lymphoma have been treated with VIP152 so far:
    - 7 patients in an all-comers dose escalation/expansion in Part 1 of NCT02635672 study whose data have been previously reported.[4]
    - 4 patients in Part 2 of NCT02635672 study where R/R aggressive NHL patients are enrolled and where a MYC aberration is required.
    - 1 R/R CLL patient in NCT04978779 study.
- The genetic status of *MYC, BCL2,* and *BCL6* was determined in diagnostic tumor samples of 11 patients with R/R NHL by fluorescence *in situ* hybridization (FISH) by the local laboratories.
- Absolute neutrophil counts were recorded over the course of VIP152 treatment visits and are plotted against each patient's baseline.
- Plasma samples for pharmacokinetic (PK) assessments were collected at predose, 0.25, 0.5, 0.67, 1, 2, 4, 6, 8, 24, 48, 72, and 168 hours after the start of infusion on Cycle 1, Day 1 (C1D1) with VIP152 quantification in plasma using a validated liquid chromatography coupled to mass spectrometry assay. PK parameters were assessed using non-compartmental analysis.
- A pharmacodynamic (PD) analysis of target gene mRNAs was performed in total intracellular RNA extracted from whole blood (PAXgene Blood RNA tubes, BD Biosciences) collected from 11 patients at C1D1 or/and C1D15 (pre-dosing and 0.5, 1, 2, 4, 6, 8, 24 hours after start of infusion).
- Liquid biopsies were taken from patients using Streck™ tubes (Streck) to analyze circulating tumor DNA (ctDNA) on the GuardantOMNI™ (500 gene, 2.145Mb) liquid biopsy panel. Small-nucleotide variants (SNVs), insertions/deletions (Indels), copy number variations (CNVs), fusions, microsatellite instability high (MSI-high) status, and tumor mutation burden (TMB) was reported. Somatic classification and status of SNVs and Indels was performed by a beta-binomial model that incorporates genomic context and variant allele fraction (VAF). Clonal changes in ctDNA during VIP152 treatment were visualized with the statistical software R (version 4.2.0) and a R-package for generating fishplots.[6]

RESULTS

VIP152 demonstrates highest kinase selectivity, independent of ATP concentration, compared with other CDK9 inhibitors

- In a KINOMEscan™ assay, VIP152 and other CDK9 inhibitors (fadraciclib, alvocidib, KB-0742, and AZD4573) were investigated. In the scan, a kinase was regarded as "hit" when less than 35% of the kinase remained captured to the solid phase. Although with VIP152 a higher number of hits were identified compared to KB-0742, in depth evaluation of all potential hits of the CDKi inhibitors was performed by Kd determination to confirm the interaction of the CDK9 inhibitor with the respective kinases (CDK and non-CDKs) (**Fig. 1**).
- Results elicit selectivity of VIP152 for CDK9, while the other studied CDK9 inhibitors showed evidence of being more unselective-CDK inhibitors (**Table 1**).
- VIP152 showed an IC_{50} value of 4.5 nM at low ATP concentration. Both VIP152 and AZD4573 demonstrated highly potent inhibition of kinase activity independent of ATP concentration (**Table 2**).
- In plasma of all patients in the phase 1 clinical trials, the VIP152 IC_{50} of 4.5 nM was maintained for 15 hours at the current clinical dose of 30 mg, administered once weekly, indicating target coverage. The average unbound VIP152 plasma concentration over a 24-hour period was 18 nM, and the exposure was dose-linear and proportional with low intra/inter-subject variability (data not shown).

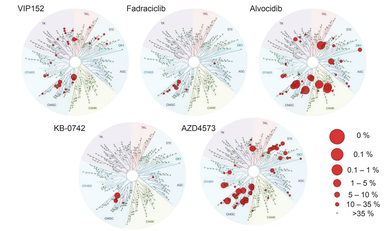

Figure 1. VIP152 demonstrates highest kinase selectivity, independent of ATP concentration, compared with other CDK9 inhibitors. Kinome tree view depicting the kinase selectivity of CDK9 inhibitors VIP152, fadraciclib, alvocidib, KB-0742, and AZD4573.

Table 1. Kd values of VIP152, fadraciclib, alvocidib, KB-0742, and AZD4573 for CDK9, as determined by KINOMEscan™. Fold differences for the other kinases were calculated relative to the Kd values determined for CDK9.

Target	VIP152	Fadraciclib	Alvocidib	KB-0742	AZD4573
	Kd (nM)				
CDK9	0.57	63	2.9	19	0.73
CDK1	> 1,000-fold	> 10-fold	> 50-fold	> 10-fold	< 10-fold
CDK2	> 1,000-fold	< 10-fold	> 1,000-fold	> 10-fold	< 10-fold
CDK3	> 1,000-fold	< 10-fold	> 250-fold	> 10-fold	< 10-fold
CDK4-cyclinD1	> 250-fold	< 10-fold	< 10-fold	> 10-fold	< 10-fold
CDK4-cyclinD3	> 100-fold	< 10-fold	< 10-fold	> 10-fold	> 10-fold
CDK5	> 1,000-fold	< 10-fold	> 10-fold	> 10-fold	> 50-fold
CDK6	> 1,000-fold	> 10-fold	> 1,000-fold	> 10-fold	< 10-fold
CDK7	> 50-fold	< 10-fold	> 10-fold	< 10-fold	< 10-fold
GSK3A	> 10-fold	> 10-fold	> 100-fold	> 10-fold	< 10-fold
IRAK1	> 100-fold	> 10-fold	> 250-fold	> 10-fold	> 10-fold

Table 2. IC_{50} values for VIP152, fadraciclib, alvocidib, KB-0742, and AZD4573 at low (10 µM) and high (2 mM) ATP concentrations.

Compound	IC_{50} at 10 µM ATP (nM)	IC_{50} at 2 mM ATP (nM)
VIP152	4.52	11.8
Fadraciclib	28.2	1,670
Alvocidib	5.96	32.8
KB-0742	29.4	1,130
AZD4573	3.20	4.22

VIP152, not atuveciclib or KB-0742, delivers the most robust downregulation of *MYC* gene expression

- *In vitro* treatment with 1 µM VIP152, atuveciclib, or KB-0742 led to downregulation of 85%, 76%, or 68% genes compared with DMSO treatment in DLBCL cell lines SU-DHL-4 and SU-DHL-10, as shown by a differential expression (DE) analysis (data not shown). This may suggest that a more selective CDK9 inhibitor can downregulate transcription while leading to the least amount of upregulation of off-target genes.
- VIP152, not atuveciclib or KB-0742, delivered the most robust downregulation of MYC expression (**Fig. 2A**).
- The global gene expression changes were reproducible (r=0.9627) after the first (C1D1) and third (C1D15) weekly dose of VIP152 in the whole blood of seven HGBL patients from Part 1 of NCT02635672 study (**Fig. 2B**).

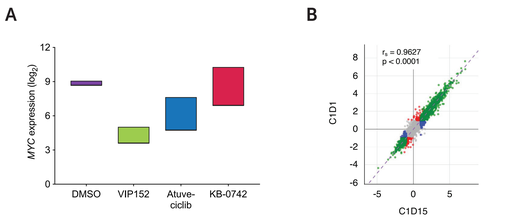

Figure 2. VIP152, not atuveciclib or KB-0742, delivers the most robust downregulation of *MYC* gene expression. (A) Expression of *MYC* mRNA in SU-DHL-4 and SU-DHL-10 DLBCL cells (n=2 per group) upon treatment with 1 µM VIP152, atuveciclib, or KB-0742. DMSO was used as a control. The count data for the samples were normalized using trimmed mean of M-values normalization and transformed with voom, resulting in log2-counts per million with associated precision weights (Fios Genomics). **(B)** Comparison of differential gene expression in whole blood samples from seven VIP152-treated HGBL patients at C1D1 and C1D15. Each point represents the log2 fold change value between C1D1 (Y axis) or C1D15 (X axis) and baseline samples for a gene, and the colors indicate whether the gene reached statistical significance in contrast 2 (C1D1), contrast 4 (C1D15), or both (Fios Genomics). Statistical comparisons were performed on normalized data using linear modeling (Bioconductor package limma) and p values were adjusted for multiple testing by controlling the false discovery rate.

VIP152 is cytotoxic in cells derived from CLL patients who are R/R to ibrutinib and venetoclax independent of their *TP53* mutation status

- VIP152 treatment at 0.5 and 1.0 µM demonstrated cytotoxicity in both wild type HG-3 CLL cells and in HG-3 CLL cells modified to harbor critical p53-stabilizing *R175H* or *R248Q* mutations, mimicking the difficult-to-treat subtypes of CLL (**Fig. 3A**).
- VIP152 treatment led to a concentration-dependent reduction in cell viability both in samples from treatment-naïve patients without *TP53* mutation (**Fig. 3B**) and in samples from CLL patients who had relapsed or were refractory (R/R) to ibrutinib and venetoclax (**Fig. 3C**).

Figure 3. VIP152 is cytotoxic in cells derived from CLL patients who are R/R to ibrutinib and venetoclax independent of their TP53 mutation status . (A) Clonal populations of HG-3 CLL cells with or without *R175H* and *R248Q* mutations were treated with 0.1, 0.5 or 1.0 µM VIP152 for 24 h and cell viability was measured. **(B–C)** A 4-h VIP152 (0.1 or 1 µM) treatment of blood cell samples from **(B)** treatment-naïve CLL patients (n=10; no *TP53* mutations) and **(C)** ibrutinib and venetoclax-relapsed/refractory primary CLL patients (n=8, 6/8 had a *TP53* mutation). Samples were plated with or without human stromal HS5 cells. Statistical analysis was performed using mixed-effects model while taking into account repeated measures for each subject; multiple comparisons were corrected for using Holm's method: **, p<0.01; ***, p<0.001; ****, p<0.0001, compared with vehicle.

VIP152, a selective CDK9 inhibitor, has a favorable cardiac safety profile – a pooled analysis

- In an analysis of triplicate electrocardiogram (ECG) data from 57 patients with solid or hematologic cancer, VIP152 did not prolong (<10 ms) the QTc interval (QTcF) after a single or multiple 5–30 mg doses once weekly (**Fig. 4**), indicating a favorable cardiac safety profile.

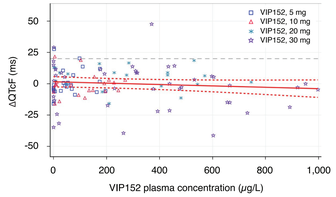

Figure 4. VIP152, a selective CDK9 inhibitor, has a favorable cardiac safety profile – a pooled analysis (data cut-off: Dec 3, 2020). Scatter plot of observed time-matched VIP152 plasma concentrations and ΔQTcF of 57 patients with solid or hematologic cancers. Triplicate 12-lead ECGs were collected according to the following schedule: screening C1D1: predose, 0.5 h (end of infusion), 2 h, and 24 h post infusion start; C1D15: predose, 0.5 h (end of infusion), 2 h, and 24 h post infusion start. The solid red line and dashed red lines denote the model-predicted mean ΔΔQTcF with 90% CIs, which is calculated from the equation ΔΔQTcF (ms) = 1.73 (ms) − 0.00089 (ms per ug/L) × VIP152 plasma concentration (µg/L). The plotted points denote the pairs of observed drug plasma concentrations and estimated placebo-adjusted ΔQTcF (ΔΔQTcF) by subjects for each active dose group and placebo group. The individually estimated placebo-adjusted ΔQTcF$_{i,k}$ (ΔΔQTcF$_{i,k}$) equals the individual ΔQTcF$_i$'s for subject administered with active drug at time point k minus the estimation of the time effect at time point k.

VIP152 shows a favorable safety profile in patients with lymphoma

- In the ongoing phase 1 trials, 12 patients with lymphoma have been treated with VIP152 (data cut-off: May 17, 2022). The treatment-emergent adverse events observed in these 12 patients are presented in **Table 3**.
- Of the 12 treated patients, five were evaluable for best overall response (**Fig. 5**). Of these, two patients with HGBL achieved complete remission and three patients with HGBL showed progressive disease during the treatment period. Reasons for treatment discontinuation for all 12 patients are indicated in the figure.
- Neutropenia is an on-target (CDK9) toxicity and is monitorable and manageable with supportive care. Once weekly dosing of VIP152 allows for recovery of neutrophils before the next dose (**Fig. 6**).

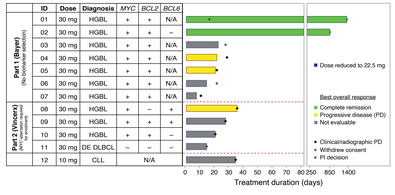

Figure 5. Duration and response to VIP152 treatment in 11 HGBL/DLBCL and one CLL patients (data cut-off: May 17, 2022). The patients (n=11, Part 1 and Part 2 of NCT02635672) were treated once weekly with 30 mg VIP152 as a 30-minute intravenous (i.v.) infusion, except one CLL patient (NCT04978779), who first received 10 mg VIP152, but after the first dose, received 15 mg VIP152. Dosing was lowered from 30 mg to 22.5 mg during the treatment for one patient (ID: 01). In NCT02635672 study (Part 1, no biomarker selection; and Part 2, *MYC*-aberration required), Lugano classification was used for NHL. In NCT04978779 study, the International Workshop on Chronic Lymphocytic Leukemia (iwCLL) guidelines were used for CLL. The status of *MYC, BCL2,* and *BCL6* determined by fluorescence *in situ* hybridization (FISH) is shown on the left. DE, double expressor, N/A, not available.

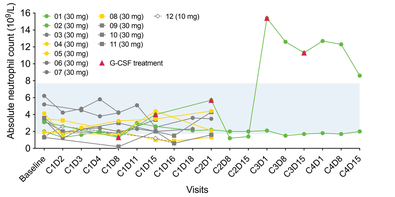

Figure 6. Absolute neutrophil count in patients treated with VIP152. The absolute neutrophil count (ANC, 10^9/L) of HGBL patients (n=11) and one CLL patient (dashed line) was measured at each treatment visit. Light blue area indicates the normal range of ANC. Red triangles indicate additional granulocyte colony-stimulating factor (G-CSF) treatment given at the specific timepoint. The patients were categorized based on their best overall response: complete remission (green lines), progressive disease (yellow lines), or if not evaluable (grey lines).

Table 3. Treatment-emergent adverse events in patients (n=55) with solid tumors, NHL, CLL, or Richter's syndrome treated with 5, 10, 15, 22.5, or 30 mg VIP152 (data cut-off: May 17, 2022, reporting cut off ≥5%).

Preferred term	NHL/CLL (n=12)					Total (n=55)				
	Any grade n (%)	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Any grade n (%)	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)
Subject with at least one TEAE	12 (100.0)	0	3 (25.0)	6 (50.0)	3 (25.0)	55 (100)	4 (7.3)	16 (29.1)	23 (41.8)	10 (18.2)
Nausea	4 (33.3)	2 (16.7)	2 (16.7)	0	0	37 (67.3)	23 (41.8)	14 (25.5)	0	0
Vomiting	4 (33.3)	2 (16.7)	2 (16.7)	0	0	29 (52.7)	20 (36.4)	9 (16.4)	0	0
Fatigue	5 (41.7)	2 (16.7)	2 (16.7)	1 (8.3)	0	20 (36.4)	8 (14.5)	11 (20.0)	1 (1.8)	0
Anaemia	3 (25.0)	0	2 (16.7)	1 (8.3)	0	18 (32.7)	6 (10.9)	8 (14.5)	4 (7.3)	0
Diarrhoea	4 (33.3)	3 (25.0)	1 (8.3)	0	0	15 (27.3)	12 (21.8)	3 (5.5)	0	0
Neutropenia	2 (16.7)	0	1 (8.3)	1 (8.3)	0	12 (21.8)	0	4 (7.3)	5 (9.1)	3 (5.5)
Abdominal pain	3 (25.0)	1 (8.3)	2 (16.7)	0	0	9 (16.4)	3 (5.5)	3 (5.5)	3 (5.5)	0
Constipation	3 (25.0)	3 (25.0)	0	0	0	9 (16.4)	7 (12.7)	2 (3.6)	0	0
Neutrophil count decreased	2 (16.7)	0	0	0	2 (16.7)	8 (14.5)	1 (1.8)	0	3 (5.5)	4 (7.3)
Pyrexia	3 (25.0)	3 (25.0)	0	0	0	8 (14.5)	7 (12.7)	0	1 (1.8)	0
Platelet count decreased	3 (25.0)	1 (8.3)	1 (8.3)	1 (8.3)	0	7 (12.7)	3 (5.5)	3 (5.5)	1 (1.8)	0
Anxiety	0	0	0	0	0	6 (10.9)	4 (7.3)	2 (3.6)	0	0
Chills	1 (8.3)	0	1 (8.3)	0	0	6 (10.9)	4 (7.3)	2 (3.6)	0	0
Dyspnoea	3 (25.0)	1 (8.3)	2 (16.7)	0	0	6 (10.9)	1 (1.8)	4 (7.3)	1 (1.8)	0
Aspartate aminotransferase increased	2 (16.7)	2 (16.7)	0	0	0	5 (9.1)	5 (9.1)	0	0	0
Blood alkaline phosphatase increased	2 (16.7)	0	1 (8.3)	1 (8.3)	0	5 (9.1)	0	2 (3.6)	3 (5.5)	0
Blood creatinine increased	2 (16.7)	2 (16.7)	0	0	0	5 (9.1)	5 (9.1)	0	0	0
Cough	1 (8.3)	1 (8.3)	0	0	0	5 (9.1)	4 (7.3)	1 (1.8)	0	0
Decreased appetite	1 (8.3)	0	0	1 (8.3)	0	5 (9.1)	1 (1.8)	3 (5.5)	1 (1.8)	0
Dizziness	0	0	0	0	0	5 (9.1)	5 (9.1)	0	0	0
Dehydration	2 (16.7)	0	1 (8.3)	1 (8.3)	0	4 (7.3)	1 (1.8)	2 (3.6)	1 (1.8)	0
Hypokalaemia	1 (8.3)	0	1 (8.3)	0	0	4 (7.3)	3 (5.5)	1 (1.8)	0	0
Hypomagnesaemia	1 (8.3)	1 (8.3)	0	0	0	4 (7.3)	3 (5.5)	1 (1.8)	0	0
Hyponatraemia	1 (8.3)	0	0	1 (8.3)	0	4 (7.3)	1 (1.8)	0	3 (5.5)	0
Lymphocyte count decreased	2 (16.7)	0	0	1 (8.3)	1 (8.3)	4 (7.3)	0	0	2 (3.6)	2 (3.6)

CLL, chronic lymphocytic leukemia; NHL, non-Hodgkin's lymphoma; TEAE, treatment-emergent adverse event

PK and PD from patients with DLBCL or CLL treated with VIP152

- A PK analysis of 11 patients with DLBCL showed that VIP152 was rapidly distributed and cleared from the circulation after the completion of the administration by a 30-minute infusion (**Table 4**).
- The half-life of VIP152 ranged between 3–6 h (**Table 4**).
- C_{max} and AUC increased in a dose-proportional manner over a 6-fold dose range (**Table 4**).
- Metabolism via CYP3A is predicted to be the predominant path of VIP152 clearance.
- VIP152 showed robust down-modulation of *MYC, MCL1,* and *PCNA* mRNAs in patients with DLBCL and CLL (**Fig. 7A**).
- Circulating tumor DNA (ctDNA) monitoring for three HGBL patients treated with VIP152 at 30 mg once weekly demonstrated reductions in multiple single-nucleotide variants (SNVs) (**Fig. 7B**) as well as *CDK6* and *MYC* copy numbers (**Fig. 7C**) in one of the three HGBL patients after one full cycle (three weeks) of VIP152 treatment.

Table 4. Pharmacokinetics of VIP152 in patients with HGBL, DLBCL, or CLL.

Patient info		Single dose				Multiple dose			
ID	Dose	C_{max} (µg/L)	t_{max} (h)	AUC_{0-t} (µg*h/L)	$t_{1/2}$ (h)	C_{max} (µg/L)	t_{max} (h)	AUC_{0-t} (µg*h/L)	$t_{1/2}$ (h)
01	30 mg	716	0.500	2140	2.73	592 [b]	0.483 [b]	1670 [b]	2.53 [b]
02	30 mg	1020	0.500	3220	3.32	847	0.617	2490	4.54
03	30 mg	1010	0.517	1980	2.48	844	0.567	1660	2.58
04	30 mg	561	0.583	3450	–	524	0.617	3020	4.27
05	30 mg	622	0.250	3790	6.15	776	0.283	3890	7.03
06	30 mg	826	0.533	3410	4.45	894	0.583	3190	4.08
07	30 mg	441	0.583	1350	5.68	–	–	–	–
08 [a]	30 mg	448	0.670	3110	5.41	410	0.500	2760	5.48
09	30 mg	386	0.500	2030	5.22	599	0.500	2080	4.36
10	30 mg	474	0.500	2260	9.41	783	0.500	3720	7.21
11	30 mg	558	0.500	3370	6.02	581	0.500	3090	7.24
12	10 mg	–	–	–	–	–	–	–	–
Mean		642	0.512	2740	5.09	696	0.519	2880	5.20
SD		225	0.102	803	2.03	170	0.102	724	1.65

[a] 0.5 h (single dose concentration of 12200 ng/mL excluded from analysis. [b] Dose was lowered from 30 mg to 22.5 mg (values not included in mean calculation). AUC_{0-t}: area under the drug concentration-time curve from time 0 to t_{last}; C_{max}: maximum plasma concentration; $t_{1/2}$: half-life; t_{max}: time to reach C_{max}

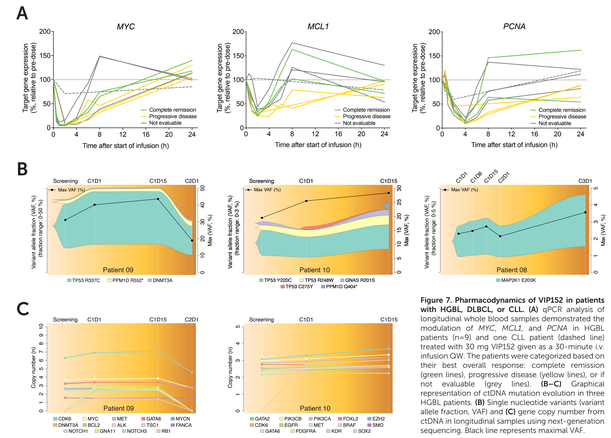

Figure 7. Pharmacodynamics of VIP152 in patients with HGBL, DLBCL, or CLL. (A) qPCR analysis of longitudinal whole blood samples demonstrated the modulation of *MYC, MCL1,* and *PCNA* in HGBL patients (n=9) and one CLL patient (dashed line) treated with 30 mg VIP152 given as a 30-minute i.v. infusion QW. The patients were categorized based on their best overall response: complete remission (green lines), progressive disease (yellow lines), or if not evaluable (grey lines). **(B–C)** Graphical representation of ctDNA mutation evolution in three HGBL patients. **(B)** Single nucleotide variants (variant allele fraction, VAF) and **(C)** gene copy number from ctDNA in longitudinal samples using next-generation sequencing. Black line represents maximal VAF.

CONCLUSIONS

- VIP152 is a potent and selective CDK9 inhibitor currently in development.
- Kd values show VIP152 is the most selective CDK9 inhibitor versus all other CDKs.
- The PK results demonstrate that unbound plasma concentrations of VIP152 in the clinic exceed the IC_{50} values observed in the *in vitro* experiments.
- VIP152 leads to the most robust *MYC* mRNA downregulation as compared to other CDK9 inhibitors.
- Blood samples from patients with CLL are sensitive to VIP152 treatment whether they are treatment-naïve, or R/R and whether *TP53* mutant or wild type.
- The cardiac safety profile associated with a selective CDK9 inhibitor demonstrates that VIP152 does not prolong QTc interval after single or multiple doses.
- VIP152 shows reproducible downmodulation of *MYC, MCL1* and *PCNA* mRNA in the whole blood of patients with HGBL, DLBCL, or CLL.
- In one out of three HGBL patients, ctDNA reduction in *TP53* mutation, and *CDK6* and *MYC* copy number is observed after 3 weeks of VIP152 treatment.
- Clinical evaluation of VIP152 is currently ongoing in two phase 1 trials in patients with solid tumors or aggressive NHL (NCT02635672), and with CLL or Richter Syndrome (NCT04978779).

REFERENCES

1. Seymour *et al. N Engl J Med.* 2018;378(12):1107-1120.
2. Woyach *et al. NEJM org N Engl J Med.* 2014;24:2286-2294.
3. Timofeeva & Gandhi *Blood Cancer J.* 2021;11(4).
4. Diamond *et al. Clin Cancer Res.* 2022;1-9.
5. Lücking *et al. J Med Chem.* 2021;64(15):11651-11674.
6. Miller *et al. BMC Genomics.* 2016;17(1):880.

ACKNOWLEDGMENTS

Differential expression analysis on cell lines and patient RNA-seq was performed by Fios Genomics Ltd. UK. Aurexel Life Sciences Ltd. (www.aurexel.com) is thanked for editorial assistance in the preparation of this poster.

Corresponding author: Melanie Frigault (melanie.frigault@vincerx.com)

Presented at the EHA2022 Hybrid Congress, June 9–17, 2022, Vienna, Austria