



SNDX-5613

**Briefing Document for the 18 June 2020
Oncologic Drugs Advisory Committee
Pediatric Subcommittee**

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List of Abbreviations

Abbreviation /Acronym	Definition
AUC	Area under the plasma-concentration curve
AUC ₀₋₂₄	Area under the plasma-concentration curve from 0 to 24 hours
AE	Adverse event
ALL	Acute lymphoblastic leukemia
AML	Acute myeloid leukemia
BID	Twice-daily
BM	Bone marrow
BSA	Body surface area
C1D1	Cycle 1 Day 1
C _{max}	Maximum plasma concentration
C _{min}	Minimum plasma concentration
CR	Complete remission
CRh	Complete remission with partial hematologic response
DL	Dose level
DLT	Dose limiting toxicity
EFS	Event free survival
FDA	Food and Drug Administration
FIH	First-in-human
FISH	Fluorescence in situ hybridization
IC ₉₀	concentrations that reduce the effect by 90%
ICH	International Council for Harmonisation
K _d	Dissociation constant
K _i	Inhibitory constant
MLL	Mixed lineage leukemia
MLL1	Mixed lineage leukemia 1 gene
MLLr	Mixed lineage leukemia-rearranged
MPAL	Mixed phenotype acute leukemia
MTD	Maximum tolerated dose
NPM1	Nucleophosmin 1
NPM1c	Nucleophosmin 1 mutation
NSG	NOD scid gamma
OCED	Organization for Economic Co-operation and Development
OS	Overall survival
PB	Peripheral blood
PD	Progressive disease
PK	Pharmacokinetic

PO	Administered orally
q12h	Every 12 hours
RP2D	Recommended Phase 2 dose
SC	Subcutaneous
SRC	Safety review committee

1.0 EXECUTIVE SUMMARY

Rearrangement of the mixed lineage leukemia (MLL) gene occurs in 5–10% of acute leukemias and is especially prevalent in infant acute leukemias (up to 70% of cases) (Krivtsov 2007). The MLL-rearranged (MLLr) leukemia subtype is characterized by its aggressive nature, resistance to therapy, and high frequency of early relapse, even after initial complete remission (Armstrong 2002; Krivtsov 2007; Pieters 2007; Muntean 2012; Sanjuan-Pla 2015). MLLr in pediatric ALL is a powerful predictor for adverse outcome (Inaba 2013; Zhang 2019). New therapeutic approaches are urgently needed to improve outcomes for children with poor prognosis MLLr acute leukemia.

SNDX-5613 is a novel, orally available inhibitor of the menin-MLL1 interaction in development for the treatment of adult and pediatric patients with relapsed or refractory MLLr acute leukemias. Acute leukemias in both adult and pediatric patients may arise because of rearrangements involving the MLL gene, located on chromosome 11q23. Depending on the progenitor cell of origin, MLLr can appear phenotypically as acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), or in a minority of cases mixed phenotype acute leukemia (MPAL). Based on nonclinical data and early clinical data in adult patients, it is considered that SNDX-5613, has the potential to deliver effective clinical activity for pediatrics with rare and aggressive leukemias.

SNDX-5613 binds with high affinity to the MLL1 binding pocket on menin ($K_i=0.15\pm 0.03$ nM) and displays activity across a range of cells harboring MLLr fusions. SNDX-5613 disrupts the interaction between menin and the MLL1 fusion proteins which is required for leukemogenic activity, thus impairing expression of critical oncogenes, causing growth arrest and the inhibition of cellular proliferation. SNDX-5613 and close analogues have demonstrated robust single agent activity in multiple leukemic xenograft models and provided profound survival benefit after oral dosing in nonclinical models. Overall, these data indicate that pharmacologic inhibition of the menin-MLL interaction represents a potential targeted strategy for the treatment MLLr acute leukemias.

Recent work has shown that nucleophosmin 1 (NPM1c) cells are dependent on the interaction of menin with wtMLL to maintain this leukemogenesis and these cells are sensitive to blockade of the menin-MLL binding (Uckelmann 2020). Both MLLr and NPM1c can be targeted in the same way as both the MLL fusion protein and wt MLL share a common N terminal domain. While NPM1c AML is a focus in the adult clinical development program, the focus of this briefing book is on pediatric MLLr acute leukemias.

SNDX-5613 is currently being evaluated in a first-in-human study, SNDX-5613-0700. This is a Phase 1/2, open label, dose-escalation and -expansion study of patients aged ≥ 18 years with relapsed/refractory acute leukemia. SNDX-5613 is being administered orally (PO) initially on an every 12-hour (q12h) schedule, in 28-day cycles. Patients are being enrolled into the Phase 1 portion agnostic of genetic mutation status. The first patient was enrolled in November 2019 and as of 30 April 2020, 6 patients have been enrolled onto the study, 4 with MLLr and 2 without. Of the 4 patients with rearrangements, 2 patients have had a response (1 complete remission [CR] and 1 partial remission [PR]).

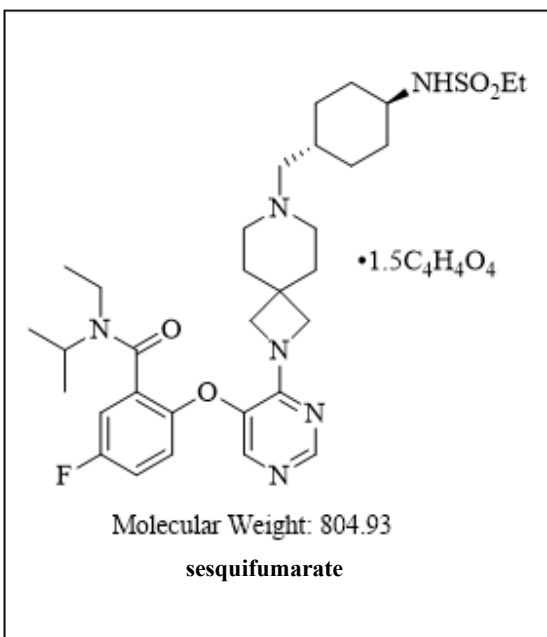
In addition to the ongoing adult study, 6 children with acute leukemia have been treated under single-patient protocols (compassionate-use requests). Despite great efforts to optimize these individual patient studies, their restrictive nature is not the most effective setting in which to provide patients with access to an investigational agent. Across the dose levels evaluated to date in the adult study and pediatric single-patient protocols, SNDX-5613 appears to be tolerable with most events being low grade and manageable with dose modification where necessary.

Syndax is committed to efficiently developing SNDX-5613 for pediatric patients with relapsed/refractory MLLr acute leukemias. Given the high unmet medical need and rarity of the disease, maximizing the learning from each child is crucial. Syndax believes that a formal clinical trial is the most effective setting in which to evaluate SNDX-5613 for the treatment of pediatric patients with acute leukemias and provide patients with access to this investigational agent.

2.0 DESCRIPTION OF THE MOLECULE AND MECHANISM OF ACTION

SNDX-5613 is a potent, orally available, small molecule inhibitor of the binding of wild-type MLL1 and MLL1 fusion proteins to menin. The interaction of MLL1 fusion proteins with menin is the key driver in MLLr acute leukemias. SNDX-5613 bears the IUPAC chemical name of trans N-ethyl-2-((4-(7-((4-(ethylsulfonamido) cyclohexyl)methyl)-2,7-diazaspiro[3.5]nonan-2-yl)pyrimidin-5-yl)oxy)-5-fluoro-N-isopropylbenzamide sesquifumarate salt. The chemical structure of SNDX-5613 is shown in [Figure 1](#).

Figure 1 Chemical structure of SNDX-5613



3.0 REGULATORY HISTORY

Syndax is currently conducting clinical studies under one active Investigational New Drug application. SNDX-5613 has received orphan drug designation in the US for the treatment of patients with AML, including adult and pediatric patients.

4.0 FORMULATION

4.1 Drug Product

SNDX-5613 is manufactured in two oral formulations, capsules, and liquid.

4.2 Capsules

SNDX-5613 capsules are provided in three immediate release strengths: 25, 113 and 156 mg expressed as free base equivalents.

4.3 Liquid

SNDX-5613 liquid drug product consists of a 50 mg/mL SNDX-5613 solution (reported as free base equivalents).

5.0 RATIONALE FOR THE DEVELOPMENT OF SNDX-5613 FOR THE TREATMENT OF PEDIATRIC PATIENTS WITH MLLR ACUTE LEUKEMIAS

5.1 Pediatric MLLr Acute Leukemias

Acute leukemias generally result from acquired mutations in hematopoietic progenitor cells. Chromosomal abnormalities are often a discrete mutational feature in these leukemic disorders. Many of these chromosomal abnormalities are due to specific translocations that lead to the formation of fusion genes which become drivers for tumorigenesis.

Acute leukemias in both adult and pediatric patients may arise because of rearrangements involving the MLL gene, located on chromosome 11q23. Depending on the progenitor cell of origin, MLLr can appear phenotypically as ALL, AML, or in a minority of cases MPAL. Additionally, MLL translocations are observed in ~33% of therapy-related acute leukemias, which typically occur after treatment with topoisomerase II inhibitors ([Winters 2017](#)).

The MLL gene encodes a large histone methyltransferase that directly binds DNA and positively regulates gene transcription, including HOX genes. MLL is involved in chromosomal translocations, partial tandem duplication, and amplifications, all of which result in hematopoietic malignancies due to sustained HOX expression and stalled differentiation ([Djabali 1992](#); [Krivtsov 2007](#)).

Rearrangement of the MLL gene occurs in 5–10% of acute leukemias and is especially prevalent in infant acute leukemias (up to 70% of cases) ([Krivtsov 2007](#)). MLLr ALL incidence has a peak in the first 2 years, then declines during the pediatric and young adult phase and then steadily increases again with age. A similar pattern was observed with MLLr AML patients, with the

exception of the postnatal peak seen for infant ALL (Meyer 2018). The MLLr leukemia subtype is characterized by its aggressive nature, resistance to therapy, and high frequency of early relapse, even after initial complete remission (Armstrong 2002; Krivtsov 2007; Pieters 2007; Muntean 2012; Sanjuan-Pla 2015). MLLr in pediatric ALL is a powerful predictor for adverse outcome (Inaba 2013; Zhang 2019). In the Interfant-06 study, the 6-year event free survival (EFS) for infants with MLLr ALL is 36.4% (Pieters 2019). In a large cohort of pediatric AML patients with a variety of different MLL rearrangements, 5 year EFS and overall survival (OS) were poorer (38% EFS and 58% OS) (Guest 2016) when compared to pediatric AML in general (55% EFS and 70% OS) (Zwaan 2015). Due to the high-risk classification of MLLr leukemia, clinical chemotherapeutic treatment protocols are aggressive and associated with significant short-term toxicity as well as serious long-term health effects for patients who survive. New therapeutic approaches are urgently needed to improve outcomes for children with MLLr acute leukemias, a disease with poor prognosis.

5.2 SNDX-5613 Mechanism of Action

5.2.1 MLLr Acute Leukemias

SNDX-5613 is a novel, orally available inhibitor of the menin-MLL1 interaction in development for the treatment of adult and pediatric patients with relapsed or refractory MLLr acute leukemias. The interaction of MLL1 fusion proteins with menin is a key driver of MLLr acute leukemias. Both MLL1 and MLLr fusions bind to a well-characterized high-affinity site on the chromatin-associated protein menin (Murai 2011). The binding of MLL1 fusions to menin is mediated by amino acid residues 9-13 at the N-terminus of MLL1. Binding to menin localizes these fusions to chromatin, where they enable a leukemic transcription program that includes upregulation of *HOXA* locus and *MEIS1* genes (Yokoyama 2005; Caslini 2007). The interaction between the fusion protein and menin is required to maintain this transcription program (Yokoyama 2005; Caslini 2007).

SNDX-5613 binds with high affinity to the MLL1 binding pocket on menin ($K_i=0.15\pm 0.03$ nM) and displays activity across a range of cells harboring MLLr fusions (Section 6.1). SNDX-5613 disrupts the interaction between menin and the MLL1 fusion proteins which is required for leukemogenic activity, thus impairing expression of critical oncogenes, causing growth arrest and the inhibition of cellular proliferation. In the literature, small molecule inhibitors of the menin-MLL interaction have demonstrated anti-proliferative activity against MLLr cell lines and have shown single agent survival benefit in mouse models of MLLr leukemia (Cierpicki 2014; Borkin 2015). Similarly, SNDX-5613 and close analogues have also demonstrated robust single agent activity in multiple leukemic xenograft models and provided profound survival benefit after oral dosing in nonclinical models (Section 6.3). Overall, these data indicate that pharmacologic inhibition of the menin-MLL interaction represents a potential targeted strategy for the treatment MLLr acute leukemias.

6.0 NONCLINICAL STUDIES WITH SNDX-5613

6.1 Potency of SNDX-5613 In Vitro

A competitive binding assay using a homogeneous time resolved fluorescence format was used to assess the binding of SNDX-5613 to menin and displacement of an MLL1 peptide that contains the conserved N-terminal menin binding motif. The assay conditions used an excess of MLL1 peptide ligand (60x the dissociation constant [Kd]), and inhibition constant (Ki) values were derived from the resultant IC₅₀ curves. The data show that SNDX-5613 is a potent inhibitor of menin-MLL binding with a derived Ki of 0.15± 0.03 nM (n=24).

6.2 Selectivity of SNDX-5613 In Vitro

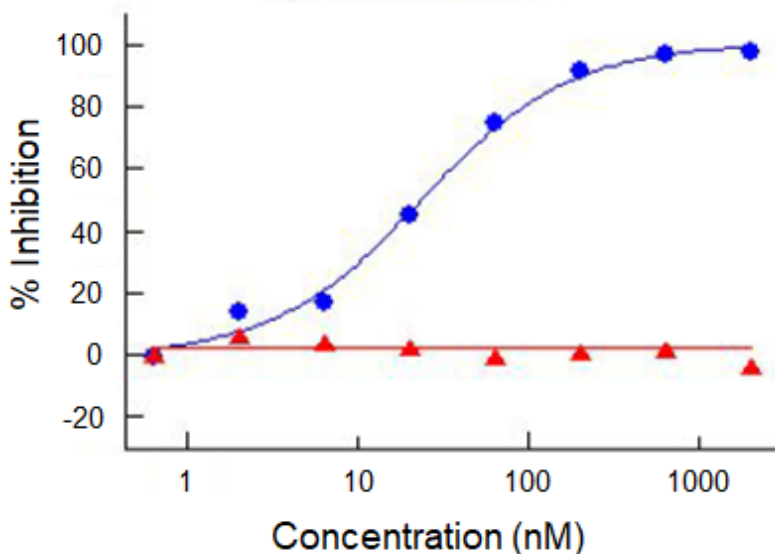
SNDX-5613 has been tested for cross reactivity against >125 molecular targets to assess its off-target binding potential. In a screen of 30 different receptors/ion channels/transporters in standard binding assays (HitProfilingScreen, Eurofins/Panlabs), SNDX-5613 at 10 µM showed no significant cross reactivity with any of the targets in the screening panel. Similarly, in an assay conducted against a panel of 97 kinases, SNDX-5613 at 10 µM displayed no inhibitory activity against any of the target kinases. Overall, the current screening profile indicates that SNDX-5613 is a selective, high affinity binder to the MLL1 binding pocket on menin and shows low potential for off-target activity.

6.3 Efficacy of SNDX-5613 In Vitro and In Vivo

6.3.1 SNDX-5613 Inhibits MLLr Leukemic Cell Line Growth

The anti-proliferative activity of SNDX-5613 against MLLr cell lines was assessed using a standard cell proliferation assay. SNDX-5613 showed anti-proliferative activity against multiple cell lines harboring MLLr translocations (MV4;11, RS4;11, MOLM-13, KOPN-8) with IC₅₀ values ranging from 10-20 nM. SNDX-5613 did not inhibit growth of HL-60, a promyelocytic leukemia cell line lacking an MLL rearrangement (Figure 2), indicating selective activity towards leukemic cells lines that harbor MLLr fusion proteins.

Figure 2 Concentration-Dependent Inhibition of Proliferation of MV4;11 Cells (blue) and HL-60 Cells (red) by SNDX-5613

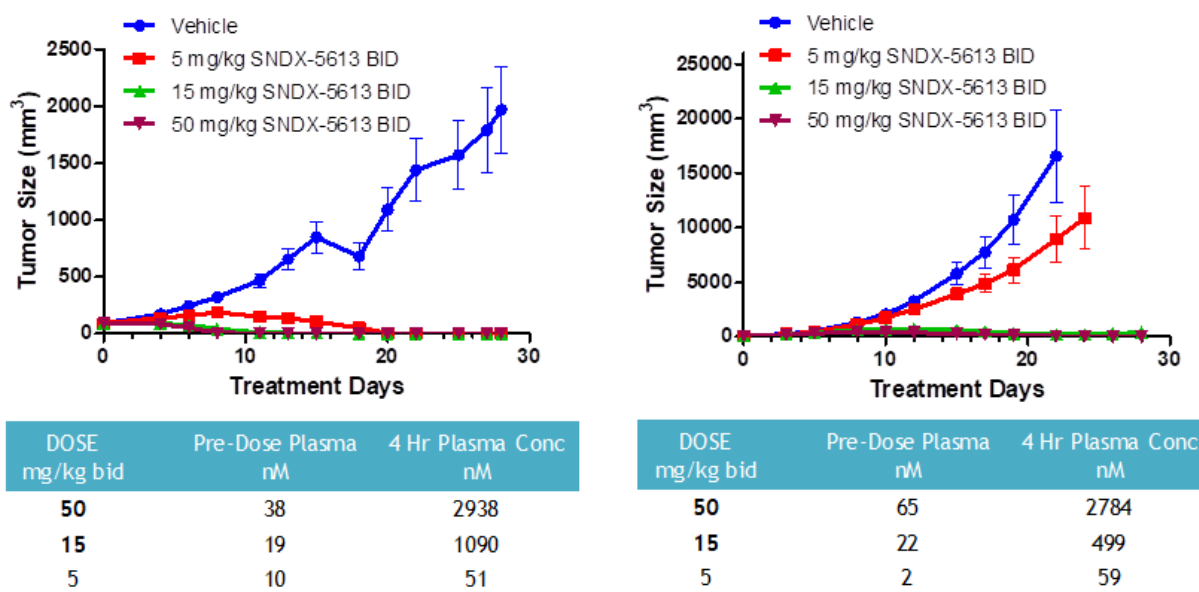


6.3.2 Menin-MLLr Blockage Inhibits MLLr and NPM1c Leukemic Growth in Rodent In Vivo Models

SNDX-5613 administered orally was tested in vivo for its capacity to inhibit the growth of subcutaneous (SC) MLLr tumors in nude rats. These SC xenografts grow as solid tumors and lack the systemic tumor burden seen in disseminated leukemia models (Section 6.3.3). They do, however, serve as a convenient, early measure of anti-leukemic activity. Initial studies evaluated the dose-dependent growth inhibition of MV4;11 and MOLM-13 xenografts. MOLM-13 is a very aggressive MLLr cell line that could serve as an analog of a difficult to treat leukemia in the clinical setting. In these studies, tumors were grown to ~75 mm³ and then animals were randomized to receive vehicle or SNDX-5613 (5, 15 or 50 mg/kg twice daily [BID]). In the MV4;11 tumor model (Figure 3), all doses of SNDX-5613 caused complete tumor regression. In the MOLM-13 model, the tumors grew much more aggressively, reflected by the 10-fold difference in tumor volume on the Y-axis. A dose-dependent treatment effect on tumor growth was observed, with tumor regression observed at the two highest doses (15 and 50 mg/kg BID).

The steady-state plasma exposures for all dose cohorts were determined on Day 21 prior to dosing and at 4 hours post-dose and are shown in Figure 3. The anti-tumor activity can be correlated with drug exposure at 4-hour post-dose in these xenograft models. The MV4;11 tumors were more sensitive to SNDX-5613 treatment and regressed at all doses, including the 5 mg/kg BID cohort where the 4 hr post-dose drug levels ($C_{4h}=51$ nM) were essentially equivalent to the plasma IC_{50} of SNDX-5613 ($C_{4h}=53$ nM). In contrast, the aggressive MOLM-13 tumors required higher multiples of the SNDX-5613 plasma IC_{50} to drive tumor regression, which was observed only at the two highest doses of 15 mg/kg BID ($C_{4h}=499$ nM) and 50 mg/kg BID ($C_{4h}=2800$ nM).

Figure 3 Dose-Dependent, Oral Efficacy of SNDX-5613 on the Growth of Subcutaneous MV4;11 and MOLM-13 Tumors with Day 21 Plasma Drug Concentrations Pre-Dose or 4 hr Post-Dose Administration

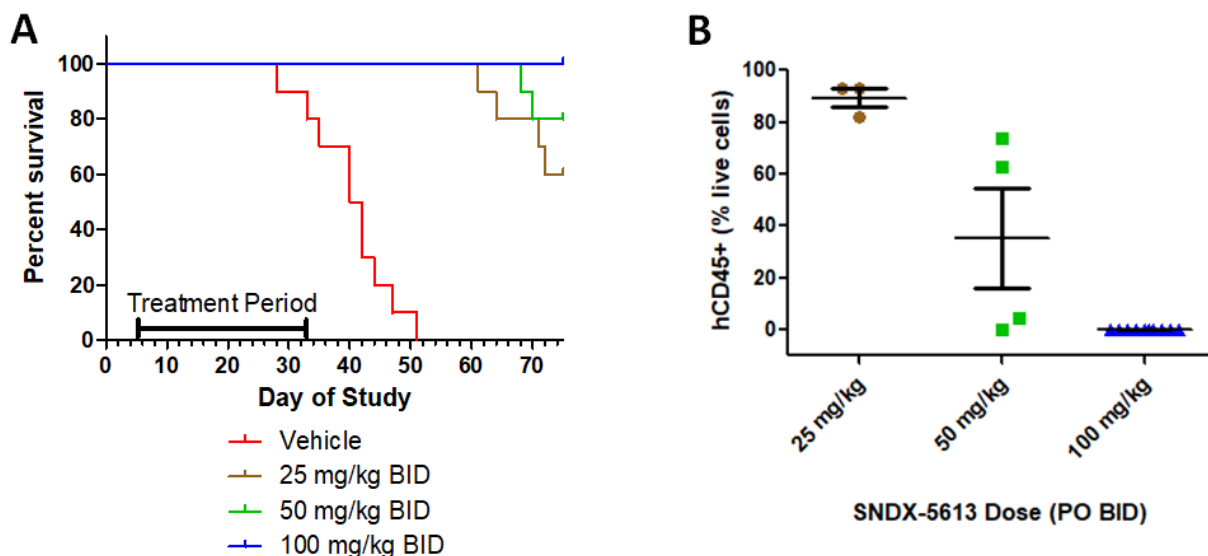


6.3.3 Dose Dependent, Single Agent Efficacy and Survival Benefit in Disseminated Tumor Model with Human MLLr Cell Line MV4:11

The anti-leukemic effect and survival benefit of SNDX-5613 administered orally were evaluated in a disseminated leukemic tumor model using MV4;11 [t(4;11)] cells. NOD scid gamma (NSG) mice were engrafted intravenously with cells. At Day 5 animals were randomized to receive vehicle or SNDX-5613 (25, 50, 100 mg/kg BID) (n=10 per group) by oral gavage for 28 days. After treatment initiation on Day 5, survival was monitored in all groups to Day 76. Surviving animals were sacrificed on Day 76, and bone marrow (BM) was analyzed for the presence of MV4;11 cells. The results show that SNDX-5613 provided a highly significant survival benefit at all doses versus the vehicle treated group ($P<0.001$) (Figure 4). In addition, a dose-dependent suppression of leukemic burden in BM was seen at Day 76, with high dose SNDX-5613 showing $<0.1\%$ MV4;11 cells in BM while the BM in the low dose animals had significant burden of

MV4;11 cells (~90%) (Figure 4). These data indicate that SNDX-5613 had a dose-dependent and durable anti-leukemic effect in NSG mice and provided a significant, single agent survival benefit.

Figure 4 Dose-Dependent Treatment Effects of Orally Administered SNDX-5613 on Disseminated MV4;11 luc⁺ Tumors in NSG Mice. (A) Kaplan-Meier Curve of Survival Benefit. (B) Flow Cytometry of MV4;11 Cells in the Bone Marrow of Treatment Cohorts at Sacrifice on Day 76



6.3.4 Dose Dependent, Single Agent Efficacy and Survival Benefit in Disseminated Tumor Model with Human MLLr Cell Line MOLM-13

A MOLM-13 disseminated xenograft model was used to assess what exposure of SNDX-5613 is needed to produce both survival benefit and confer good leukemic control. MOLM-13 is a very aggressive MLLr cell line that could serve as an analog of a difficult to treat leukemia in the clinical setting. In these studies, mice were treated with custom chow containing multiple dose strengths of SNDX-5613 (0.2%, 0.1%, 0.05%, 0.025%). Delivering drug in chow eliminates BID gavage dosing and delivers plasma exposures with low peak-to-trough drug levels over 24 hr. In parallel to the xenograft studies, a pharmacokinetic (PK) assessment was conducted to measure the steady-state plasma drug levels of SNDX-5613 delivered by all four dose strengths. The graph in Figure 5A shows the plasma levels for all dose strengths over 24 hr and how these exposures compare to projected plasma IC₉₀ or IC₉₅ for SNDX-5613. The average plasma concentration and the estimated 24 hr area under the plasma concentration curve (AUC) for each dose strength are also shown in the table in Figure 5A. These data indicate that plasma levels for the low dose (0.025%) are below the projected IC₉₀ for the entire 24 hr interval. The two high doses (0.1% and 0.2%) are above projected IC₉₅, while the intermediate dose (0.05%) hovers in the IC₉₀ to IC₉₅ range for most of the 24-hr interval.

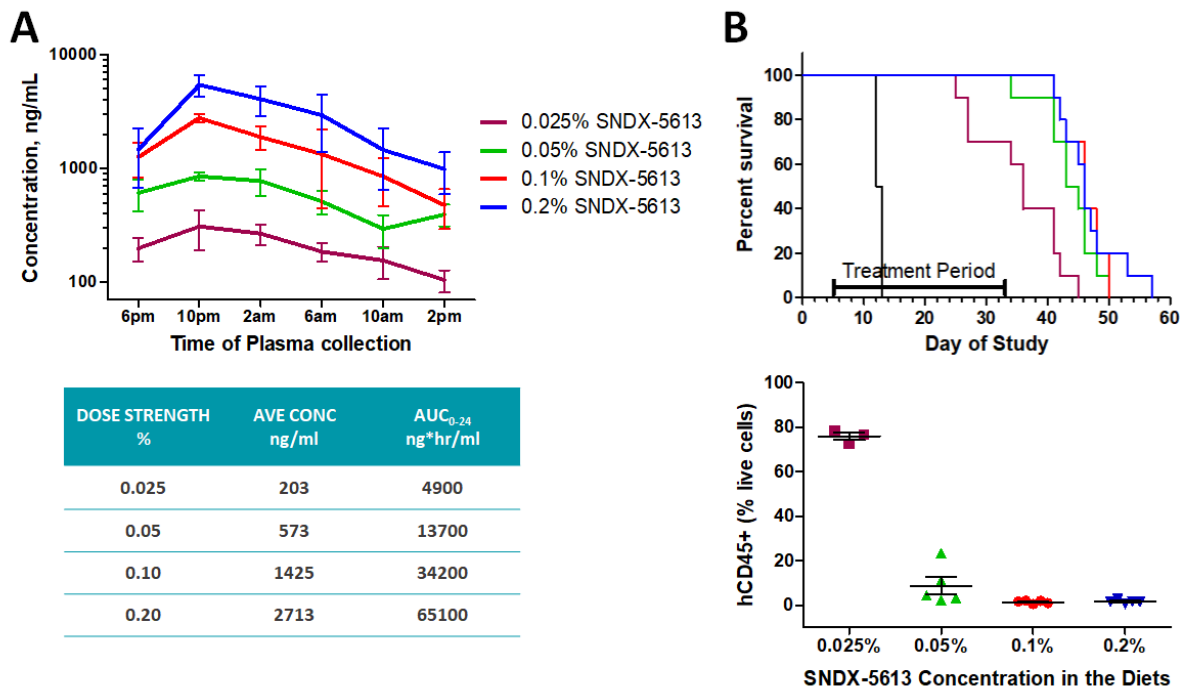
For the MOLM-13 dose/response study, NSG mice were engrafted with cells and randomized at Day 5 to receive either control chow or SNDX-5613 containing chow for 28 days. Survival was

monitored across all dose groups. In addition, leukemic burden in peripheral blood (PB) was assessed from all treatment groups (n=5) at end of treatment (Day 33). The K-M curves in [Figure 5B](#) show that all vehicle treated controls died by Day 13, while all doses of SNDX-5613 produced a highly significant survival benefit vs vehicle treated controls ($p < 0.0001$). However, there was no difference in survival benefit among the high dose groups, so any differential effect due to exposures could not be distinguished. Assessment of leukemic burden in peripheral blood (hCD45+) at Day 33 showed more discrete differences among the 4 dose groups as shown in [Figure 5B](#). At the end of treatment, the low dose group, which had significant survival benefit, showed little leukemic control with ~75% hCD45+ chimerism. The 0.05% dose group had ~9% hCD45+ PB count and appeared to be on the cusp of maintaining leukemic control. The two high doses (0.1%, 0.2%) showed no difference in hCD45+ burden (~1.5%) nor survival, suggesting this may be a maximal response.

Thus, safely achieving adequate target coverage in the Phase 1 trial is important for establishing efficacious exposures of SNDX-5613. Given the MOLM-13 results and the robust treatment effect observed at 0.1% for both survival and leukemic control, a PK target profile was developed. At the 0.1% dose, plasma drug levels ranged from ~500-2500 ng/ml over 24 hr with average plasma levels of ~1400 ng/ml and estimated AUC of ~34,000 ng*h/ml. Based on these exposures, a nominal profile for adequate target coverage for SNDX-5613 is presented below.

1. Maintain plasma levels greater than the projected IC_{95} (600 ng/mL) for most of the dosing interval.
2. Maintain minimum plasma concentration (C_{min}) levels above the projected IC_{90} (300 ng/mL)
3. Target a minimum 24 h AUC of ~30,000 ng*h/ml

Figure 5 Dose-Dependent Treatment Effects of SNDX-5613 Administered in Chow on Disseminated MOLM-13 Tumors in NSG Mice. Steady-State Plasma PK Analysis, Kaplan-Meier Curve of Dose Dependent Survival Benefit and Assessment of Leukemic Burden



6.4 Summary of Nonclinical Toxicology Findings

The toxicology program for SNDX-5613 has been conducted in Sprague Dawley rats and beagle dogs. Based on the *in vitro* metabolism and PK data observed in the rat and dog, they were selected as the rodent and non-rodent species for the pivotal repeat-dose toxicity studies of SNDX-5613.

The pivotal 28-day oral toxicity studies with 4-week recovery were performed in accordance with Organization for Economic Co-operation and Development (OECD) Principles of Good Laboratory Practice (ENV/MC/CHEM(98)17) as accepted by Regulatory Authorities throughout the European Community, United States of America (Food and Drug Administration [FDA]) and Japan (Ministry of Health, Labor and Welfare [MHLW]) and in accordance with International Council for Harmonisation (ICH) guidelines, including ICH M3(R2) and ICH S9.

Off-target screening assays showed no cross reactivity of SNDX-5613 against >125 molecular targets. Therefore, treatment-related adverse events are expected to be due to mechanism-based target effects. Potential main targeted organs of toxicity identified in the 28-day rat and dog toxicology studies were the heart (electrocardiogram changes in dogs), eyes (cataracts in rats only), liver, bone marrow, lymphoid tissues, male reproductive system, and female reproductive system. The observed dose limiting toxicity for SNDX-5613 was weight loss/appetite

suppression in the dog, which was used to establish the highest non-severely toxic dose for calculating the Phase 1 human starting dose.

7.0 CLINICAL

7.1 Safety and Preliminary Anti-Leukemic Data for SNDX-5613

7.1.1 SNDX-5613-0700: A Phase 1/2, Open-label, Dose-Escalation and Dose-Expansion Cohort Study of SNDX-5613 in Patients with Relapsed/Refractory Leukemias, Including Those Harboring an MLL/KMT2A Gene Rearrangement or Nucleophosmin 1 Mutation

Study SNDX-5613-0700 is a Phase 1/2, open-label, dose-escalation and -expansion study of SNDX-5613. Patients aged ≥ 18 years with relapsed/refractory acute leukemia for whom there is no available therapy are being enrolled. In Phase 1, patients with relapsed/refractory acute leukemia may be enrolled agnostic of genetic mutation status.

SNDX-5613 is being investigated initially on a q12h dose schedule; alternative dose schedules may be explored as guided by emerging data. SNDX-5613 is being administered PO in 28-day cycles, with the first study drug dose administered on Cycle 1, Day 1 (C1D1). Patients will continue SNDX-5613 until progressive disease (PD) or unacceptable toxicity.

Upon enrollment, patients will be assigned to one of two dose-escalation arms as described below:

- Arm A: Patients must not be receiving a strong cytochrome P450 3A4 (CYP3A4) inhibitor. Patients who were receiving a strong CYP3A4 inhibitor must have discontinued the medication at least 7 days prior to enrollment.
- Arm B: Patients must be receiving a strong CYP3A4 inhibitor for at least 7 days prior to enrollment and while on SNDX-5613 treatment.

Throughout the study, the Safety Review Committee (SRC) will monitor safety and efficacy parameters as specified in the SRC charter.

Phase 1: Dose-escalation

The primary objective of Phase 1 is identification of the maximum tolerated dose(s) (MTD), or, if different, recommended Phase 2 dose(s) (RP2D) of SNDX-5613 in patients with acute leukemia. These doses may differ between Arm A and Arm B.

Phase 1 initially employed an accelerated titration design, with a single patient enrolled in each cohort (ie, single-patient cohorts). The dose escalation is following a modified Fibonacci sequence ([Le Tourneau 2009](#)) as shown in [Table 1](#).

The exact dose strengths have been rounded down to accommodate capsule size constraint (113 mg/capsule). The starting dose was 113 mg q12h, with escalation to 226 mg q12h, 339 mg q12h, 452 mg q12h and 565 mg q12h doses planned. Doses will be escalated in single-patient

cohorts until either 1 patient experiences \geq Grade 2 toxicity (not otherwise defined as a dose-limiting toxicity [DLT]) in the first 2 cycles or 1 patient experiences a DLT in the first cycle, as determined according to the US National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0. At that point, the current cohort and all subsequent cohorts will follow a classical “3 + 3” dose escalation design. Doses will be further escalated, based on SRC decision, until the MTD is determined.

Table 1 Dose Levels of SNDX-5613 in Study SNDX-5613-0700

Dose Level	Proposed Dose Increment (%)	Dose
-2	-50% of Dose Level -1	50 mg QD
-1	-50% of Dose Level 1	113 mg QD
1	Starting Dose	113 mg q12h
2	100%	226 mg q12h
3	50%	339 mg q12h
4	33%	452 mg q12h
5	25%	565 mg q12h

For a dose level to be determined as the MTD or RP2D, a total of 6 patients must have been treated at that dose level. The RP2D may be equal to or less than the MTD. The RP2D will be determined by the SRC, based on review of PK, safety and tolerability data among patients who are both PK and DLT evaluable. The RP2D will be determined independently for Arm A and Arm B. The RP2D is defined as the maximum dose meeting the following criteria:

1. $\leq 1/6$ of DLT-evaluable patients experience a DLT.
2. At least two-thirds of patients received at least 80% of their prescribed doses in C1 and C2, unless due to PD.
3. At least 3 patients are evaluable for PK.
4. At least two-thirds of patients have area under the plasma concentration curve from time 0 to 24 hours (AUC_{0-24}) values $\geq 15,000$ ng*h/mL.
 - a. If the MTD does not achieve this exposure level, but efficacy is seen in any dose level, then the highest dose level that meets the above safety and tolerability criteria will be selected as the RP2D.

If the highest dose does not meet all RP2D criteria, then the next lower dose level will be expanded to a total of 6 patients. Expansion of lower dose levels will continue in a sequential fashion until identification of a dose meeting these RP2D criteria. If more than one tested dose level meets all the RP2D criteria, the highest dose level meeting the criteria will be selected as the RP2D. If a 100% CR rate is observed at the end of Cycle 1 in a dose level that is safe and tolerable during the 3+3 dose escalation period, then that dose will be defined as the RP2D.

Phase 2: RP2D Cohort Expansion

After identification of the RP2D in Phase 1, the safety and efficacy of SNDX-5613 will be explored in 3 indication-specific Expansion cohorts, as follows:

- Cohort 2A: Patients with MLLr ALL/MPAL
- Cohort 2B: Patients with MLLr AML
- Cohort 2C: Patients with NPM1c AML

Each Expansion Cohort will employ a Simon 2-stage design ([Simon 1989](#)) with up to 34 patients planned in each cohort. Thus, up to 102 patients are planned to be enrolled in Phase 2. Enrollment in each Expansion Cohort will be conducted independently. Initially, up to 21 patients will be enrolled in Stage 1 of each cohort. If at least 4 of 21 patients in the cohort experience a CR or complete remission with partial hematologic recovery (CRh), based on disease-specific response criteria, then 13 additional patients will be enrolled in Stage 2. The number of patients evaluated in each stage and the minimum number of responders needed to continue to the next stage were determined based on the minimax version of Simon's 2-stage design.

Patient Summary

The first patient was enrolled into SNDX-5613-0700 in November 2019. As of a data cutoff of 30 April 2020, 6 patients had been had been enrolled into the study, either into Arm A or Arm B and dosed with SNDX-5613 at either Dose Level (DL) 1 or DL2 ([Table 2](#)).

Patients had previously received between 2 and 8 prior therapies and were included in the study regardless of their MLLr mutation status. As of the data cutoff, 4 patients were still receiving treatment; 2 patients (both without MLL mutation) had discontinued due to progressive disease and one of the patients subsequently died.

Table 2 Patient Summary by Dose Level, Arm, and Mutation Status (N = 6)

Mutation	Arm A		Arm B	
	DL1	DL2	DL1	DL2
No MLLr	1	0	0	1
MLLr	0	1	1	2

Data cutoff date: 30 April 2020

Abbreviations: DL = dose level

7.1.1.1 Preliminary Safety Data from Study SNDX-5613-0700

As of 30 April 2020, six patients had been treated with SNDX-5613. All patients had reported at least one adverse event regardless of causality and 5 patients had reported at least 1 treatment related adverse event. None of the treatment related events were \geq Grade 3 or serious adverse events. No DLT events had been reported. No deaths or discontinuations due to a treatment related AE were reported.

Consistent with the nonclinical toxicology findings, Grade 1-2 QTc prolongation events were observed but were asymptomatic and self-resolved or resolved following a dose reduction.

All treatment related adverse events reported as of the data cutoff are provided in [Table 3](#).

Table 3 All Grade Treatment Related Adverse Events by Treatment Arm (N = 6)

Term*	Arm A (N = 2)	Arm B (N = 4)
Diarrhea	0	1
Edema at ankles bilaterally	0	1
Hyperphosphatemia	0	1
Hyperuricemia	1	0
Nausea	0	2
Pain behind right eye	0	1
QTcF interval prolonged	1	3

Data cutoff date: 30 April 2020

*A patient is only counted once if they experience multiple occurrences of the same event

7.1.1.2 Preliminary Anti-Leukemic Data from Study SNDX-5613-0700

Two of the 4 patients with an MLL mutation at enrollment had an improvement in their disease status at their first response assessment on Cycle 1 Day 28:

- A patient enrolled into Arm B, DL2 had an CR with incomplete blood count recovery at the first response assessment, which, despite a dose reduction for QTc prolongation, improved to a CR (FISH and flow negative).
- A patient enrolled into Arm B, DL1 had a PRi (blast count 40% to 20%) at the first response assessment, the blast count continued to improve.

7.1.2 Summary from Pediatric Compassionate Use Patients

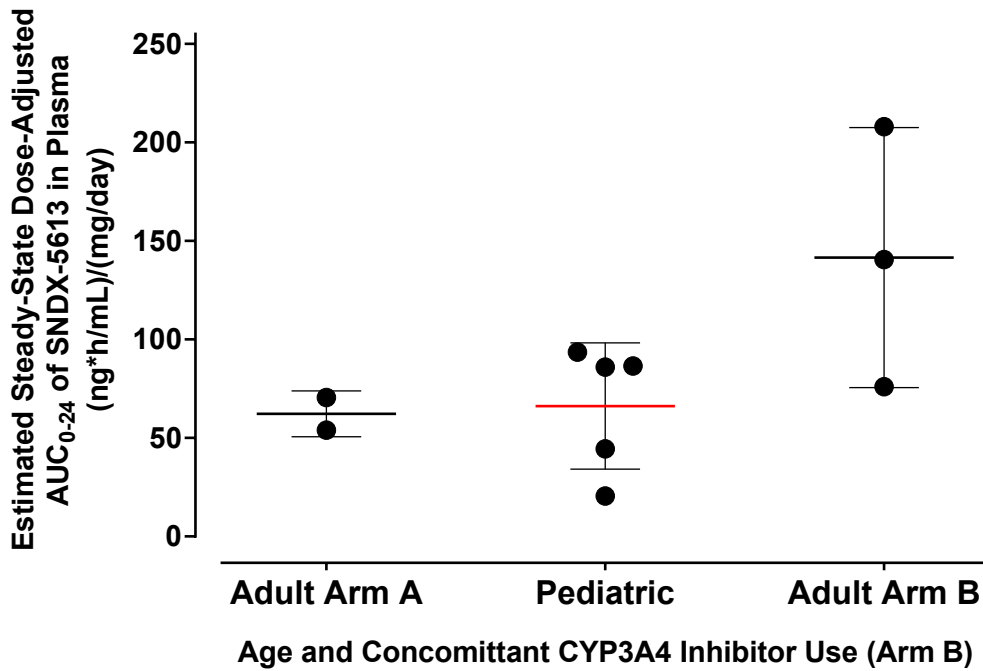
As of 30 April 2020, 6 pediatric patients between the ages of 1.5 to 10 years have been treated under single-patient protocols across a range of doses. Limited safety and PK data are available given the compassionate-use nature of the data collection. All the pediatric patients had MLL-rearrangements and none of the patients were receiving moderate or strong CYP3A4 inhibitors. As of the cutoff date, none of the pediatric patients had a response to therapy. All patients have tolerated therapy. Two patients had treatment-related Grade 3 adverse events (nausea and vomiting) that responded to standard antiemetics. No patient had experienced any grade of QTc prolongation.

7.2 Preliminary Pharmacokinetic Data from SNDX-5613-0700 and Compassionate Use Pediatric Studies

Limited pharmacokinetic data are available from 10 patients treated with SNDX-5613 as of 30 April 2020: 5 are adults who were enrolled in Phase 1 study SDNX-5613-0700 and 5 are children (ages 17 months to 10 years) who were treated under single-patient protocols. For calculation of AUC_{0-24} for q12h dosing at steady-state, the 12-hour trough concentration was imputed from the predose concentration, and AUC_{0-12} calculated and multiplied by two to estimate AUC_{0-24} .

As the patients in pediatric single-patient protocols were among the first patients to be treated with SNDX-5613 the initial patients' treatment plan used a "ramp-up" dosing regimen starting with approximately 50% of the starting dose that would be given to an adult, and doses were increased to 100% dose after 5 days. The PK profiles of SNDX-5613 in the pediatric patients were generally similar to those in adults, although the small number of subjects treated, and limited PK sampling precludes any definitive pharmacokinetic conclusions. Based on a review of preliminary and interim estimated AUC_{0-24} , adjusted for dose, adult and pediatric patients appear to have a similar exposure to SNDX-5613 in systemic circulation (Figure 6).

Figure 6 Dose-Adjusted AUC₀₋₂₄ for Patients Treated with SNDX-5613 in the Presence or Absence of a Concomitant CYP3A4 Inhibitor (N=10)



Data cutoff date: 30 April 2020

Note: Each symbol represents one patient. Doses for pediatric patients (in mg/m²) were adjusted to adult equivalents by multiplying by a typical adult BSA (1.7 m²).

SNDX-5613 is a substrate of CYP3A4 and as such, inhibitors and inducers of CYP3A4 could affect the PK of a CYP3A4 substrate like SNDX-5613. Accordingly, such inhibitors and inducers are typically excluded in clinical trials of SNDX-5613 with one exception. Many patients with AML require treatment with certain azole anti-fungal drugs that are strong CYP3A4 inhibitors, most commonly posaconazole. These subjects that must take a strong CYP3A4 inhibitor are enrolled into Arm B of SNDX-5613 so that their PK and safety may be evaluated separately from other patients. Eventually, patients taking azole anti-fungal medicines that are strong CYP3A4 inhibitors may need a different dose of SDNX-5613 from those who are not. The effect of CYP3A4 inhibitor treatment will continue to be evaluated as more patients are enrolled into Arm A and Arm B.

8.0 POTENTIAL CHALLENGES FOR THE CLINICAL DEVELOPMENT OF SNDX-5613 IN PEDIATRIC PATIENTS

In the US, an average of 3,715 children <20 years of age were diagnosed with leukemia annually between 2011 and 2015, including 2,769 diagnosed with ALL (Howlader 2020). Rearrangement of the MLL gene occurs in 5–10% of acute leukemias and is especially prevalent in infant acute leukemias (up to 70% of cases). NCCN treatment guidelines suggest clinical trials may offer the best treatment option for patients with leukemia and recommends children with ALL enroll into a clinical trial (NCCN 2020).

When evaluating the optimal path for the development of SNDX-5613 in pediatrics, Syndax has considered the following:

- the utility of single-patient protocols in the absence of a formal pediatric clinical trial;
- with the aggressiveness of this rapidly progressing disease, evaluation of SNDX-5613 as a monotherapy and in combination with chemotherapy in a Phase 1 trial;
- the ethical balance between rapidly developing a treatment for children with a life-threatening disease and the desire to avoid potential toxicity of an experimental medication.

Syndax believes that the safety profile observed in adults and pediatric patients in combination with the biological rationale for the target, the pre-clinical data validating the target, and early clinical evidence of activity of SNDX-5613 in patients with MLLr leukemia supports its position that the benefit: risk ratio warrants accelerated clinical investigation of SNDX-5613 in pediatric patients at this time.

8.1 SNDX-5613 Compassionate Use Requests in the Absence of a Phase 1 Clinical Trial

The first SNDX-5613 compassionate-use request for a pediatric patient was received and granted prior to enrollment of an adult patient into the first-in-human study (SNDX-5613-0700). Currently, Syndax receives new compassionate-use requests at the rate of approximately 1 per month. This demand underscores the lack of viable treatment options available for children with MLLr leukemia. Given that these requests are only received from centers of excellence where physicians have visibility to novel therapies, this likely reflects just a proportion of the actual clinical need. As of 30 April 2020, a total of 6 patients had received the drug under a single-patient protocol. Despite the rarity of MLLr leukemia in children, the number of requests for SNDX-5613 are increasing. Due to the lack of a dedicated clinical pediatric study, each child is currently treated under a single-patient protocol. These are set up to provide the best treatment for each child while trying to facilitate acquisition of safety and preliminary anti-leukemic data for SNDX-5613. However, more complete and accurate data that can be meaningfully pooled are essential for optimal drug development. The necessity to generate and collect meaningful clinical data is intensified given the rarity of the disease and the desperate call to expeditiously develop therapies in this area of high unmet medical need. Despite the efforts to collect meaningful data from single-patient protocols, the current paradigm is neither serving the best interests of patients in general, nor enabling effective development of new therapies for pediatric patients with a rare disease.

8.2 Evaluation of SNDX-5613 as a Single Agent or in Combination

When determining whether to treat children with SNDX-5613 as a single agent or in combination, both the SNDX-5613 mechanism of action along with the aggressive nature of the disease should be considered, as follows:

- The mechanism of action of SNDX-5613 suggests that continuous dosing to maintain exposure levels above the plasma IC₉₀ (Section 5.2) is critical to sufficiently inhibit menin-MLL binding. Therefore, sub-optimal dose levels and dosing interruptions reduce suppression of the underlying interaction between MLLr and menin. Emerging safety and PK from previous single patient protocols have been used to escalate the starting dose for subsequent requests. However, PK data from the first 5 pediatric patients dosed with SNDX-5613 indicate that target baseline exposure levels have not yet been met in these patients.
- To maintain control of aggressive acute leukemias in pediatric patients and to manage the associated symptoms, new therapies are often added to standard of care backbone chemotherapy. Thus, patients are provided the best opportunity for a meaningful clinical benefit. This is particularly pertinent when a new investigational agent is being administered prior to fully understanding the biologically active dose and time to response. Additionally, clinical practice will only remove an established chemotherapy backbone when there is compelling single-agent data to support doing so.

Evaluating an investigational agent in combination with chemotherapy brings additional risk. This is the case especially when there is limited clinical experience with the investigational agent. To minimize risk, the single-patient protocols have required that SNDX-5613 be administered as a single agent. In these patients, the aggressive nature of the disease, the lack of a chemotherapy backbone, and the subtherapeutic SNDX-5613 exposure levels achieved to date, have led to the need for cytoreduction therapies to manage disease symptoms. This has resulted in protocol-mandated SNDX-5613 dose interruptions which have further diminished the plasma exposure and utility of SNDX-5613. These experiences indicate that the potential benefit of combining SNDX-5613 with chemotherapy to treat children with aggressive leukemia outweighs the potential risk associated with combination therapy.

8.3 Proposed Phase 1 Clinical Trial

Given the potential utility of SNDX-5613 in the pediatric setting and patient-driven demand to gain access to this investigational drug, it would seem prudent to open a dedicated pediatric clinical trial as soon as possible. Syndax proposes to initiate a clinical trial in pediatric and adolescent patients up to 21 years of age with relapsed or refractory acute leukemia harboring a MLLr or NPM1c mutation. The study will evaluate the safety, tolerability, PK, and exploratory efficacy of SNDX-5613 as monotherapy or in combination with standard of care chemotherapy. Eligible patients will be assigned sequentially to escalating dose levels and initiate treatment with oral SNDX-5613 q12h over 84 days. This study will utilize an iterative continual reassessment method for dose escalation decisions as this approach would theoretically lead to fewer patients being exposed to subtherapeutic doses and more data being collected around the recommended Phase 2 dose. The starting dose for this trial is intended to deliver comparable exposure to that seen in adults for doses cleared by the SRC in SNDX-5613-0700, and with

consideration of the pediatric patients treated with SNDX-5613 under the single-patient protocols.

Dose limiting toxicity assessment window will be 28 days from initiation of treatment with SNDX-5613 monotherapy (through Day 29). If during the first 28 days patients are assessed as having clinical and/or bone marrow PD, they will be eligible to begin a combination regimen of SNDX-5613 with specified standard chemotherapy. For combination regimens, a new DLT assessment window will begin upon initiation of chemotherapy and lasts 28 days. If during the first chemotherapy cycle with SNDX-5613 patients exhibit a CR, they will return to receive monotherapy to complete a total of 84 days with SNDX-5613 treatment. Otherwise, patients will receive a second chemotherapy cycle with SNDX-5613 and then return to monotherapy to complete a total of 84 days with SNDX-5613 treatment. Patients will continue SNDX-5613 until PD or unacceptable toxicity.

In this study, a hybrid approach to define DLTs for combination therapy will be used. Both functional DLT criteria as well as an itemized exclusion of well-characterized backbone chemotherapy toxicities will be delineated. As described in the literature, the functional DLT approach reports both Grade 3 and 4 toxicities but in general Grade 3 toxicities are considered as dose limiting only if they substantially delay the delivery of backbone chemotherapy (Horton 2010). Given the limited availability of safety information of SNDX-5613 in the pediatric population, the protocol will take a more conservative modification to the functional DLT approach as follows:

- Both Grade 3 and 4 toxicities that are considered related to SNDX-5613 will be reported as DLTs.
- Specific Grade 3 and 4 events that are well-described and highly associated with the chemotherapy backbone are excluded as DLTs.
- Consistent with the experience in SNDX-5613-0700 (the adult Phase 1/2 trial), Grade 3 hematologic toxicities are not considered DLTs.

The functional DLT approach was favored by an international panel of pediatric leukemia experts for toxicity assessment of molecularly targeted drugs incorporated into multi-agent chemotherapy regimens for pediatric leukemia (Horton 2010). The approach was previously used in clinical studies of pediatric ALL for testing of novel molecularly targeted agents in the context of multi-agent ALL chemotherapy regimens used for reinduction in relapsed ALL (Raetz 2008) or as post-induction consolidation therapy in newly diagnosed infant ALL (Brown 2008). The functional DLT definition approach also accounts for the potential of a novel agent to exacerbate backbone-related toxicities. This is an important advantage since it is not possible to know a priori which toxicities might be exacerbated by a novel agent (Horton 2010).

Syndax believes that this study design will provide an appropriate setting to effectively establish a recommended dose and manage toxicity while providing the children with the best opportunity for clinical benefit. Effective data pooling and interpretation would be facilitated by consistent patient management, diligent data collection, and cross-functional data scrutiny.

8.4 Ethical Justification of Proposed Approach

Relapsed/refractory MLLr acute leukemias are a rare pediatric disease. Efficient drug development is imperative to meet the high unmet medical need and bring forward a potential therapeutic agent. Given the rarity of the disease, maximizing the learning from each child is crucial. A formal clinical trial is the most effective setting in which to provide patients with access to potentially therapeutic investigational agents and to evaluate SNDX-5613 for the treatment of children with leukemia. Indeed, clinical trials are the NCCN recommended therapeutic option for these children. Because of the aggressive nature of the disease, a clinical trial should allow for experience with targeted drugs as monotherapy while preserving the option to combine chemotherapy regimens that have been the backbone of treatment for acute pediatric leukemias. Syndax considers that the proposed clinical study would best address an effective, iterative, and clinically meaningful development of SNDX-5613 to treat these rare diseases of highly unmet medical need.

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