



Safety and Efficacy Experience of Voreloxin (formerly SNS-595) in Relapsed/Refractory Acute Leukemia Patients ≥60 years old Compared to < 60 years old: Results of a Phase 1b Study

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Abstract-Updated

Background: Voreloxin (formerly SNS-595) is a novel naphthylidine analog, a subclass of quinolones not previously used for the treatment of cancer. Voreloxin has a specific, saturable interaction with DNA and is a topoisomerase II poison, causing replication-dependent site-selective double strand DNA damage, irreversible G2 arrest and rapid apoptosis. Voreloxin is not a substrate for P-glycoprotein and is not p53-family member-dependent, thereby evading common drug-resistance mechanisms, and has low potential for CYP450-mediated drug-drug interactions. Voreloxin is in Phase 1b and 2 clinical trials in acute myeloid leukemia and ovarian cancer, with clinical responses in these indications as well as in NSCLC and SCLC. A Phase 1b dose escalation study of voreloxin as a single agent in patients with relapsed/refractory acute leukemias was recently completed (Proc ASH 2007). Voreloxin was given either weekly for 3 doses or twice weekly for 4 doses. The maximum tolerated dose (MTD) for voreloxin was 72 mg/m² weekly and 40 mg/m² twice weekly. Age greater than 60 y is an adverse prognostic factor for AML patients. A subanalysis of the safety and efficacy results of the study by younger than age 60 y vs. age 60 y and older is presented. **Methods:** Comparative analysis of the data included incidence of adverse events, dose limiting toxicity (DLT), and clinical response (IWG criteria). Voreloxin was administered to patients with advanced acute leukemias within 10 min by IV push weekly on D1, D8 and D15 or twice weekly on D1, D4, D8, and D11. **Results:** Sixty-eight patients across both schedules were evaluable for safety. Twenty-six patients were < 60 y (median=43 y; range: 21-59 y) and 42 patients were ≥ 60 y (median=69 y; range: 60-85 y). Patient demographics were comparable between the two treatment schedules. Ninety-one percent had relapsed/refractory disease and 83% had AML. For the 26 patients who were < 60 y, the most common grade 3 or higher AEs were: febrile neutropenia (36%), thrombocytopenia (23%), neutropenia (19%), and stomatitis (oral mucositis) 15%. Similarly, among the 42 patients who were ≥ 60 y, the most common grade 3 or higher AEs were: febrile neutropenia (36%), neutropenia (26%), thrombocytopenia (24%), and stomatitis (oral mucositis, 12%). The DLT for both schedules was oral mucositis with similar incidence among those < 60 y and ≥ 60 y. Five CR/CRp were observed across both schedules: 2 in patients < 60 y and 3 ≥ 60 y. In addition, a CRi ≥ 60 y was observed. No age-related change was observed in voreloxin CI, Vss, MRT or T1/2 in this study. **Conclusions:** Voreloxin appears to be generally well tolerated in patients with advanced leukemias in patients < 60 y and ≥ 60 y. Complete remissions were observed in both age groups. Pharmacokinetics were not influenced by age. Given this safety profile, a single agent study of voreloxin as front line treatment for AML patients ≥ 60 y is underway as is a combination study with cytarabine for relapsed/refractory AML in patients ≥ 18 y. Preliminary results of the combination study are reported here as well.

Aims

- Compare the safety and pharmacokinetics for patients treated with voreloxin in a Phase 1b single agent study in relapsed/refractory acute leukemias risk stratified by age 60 and older or younger than 60 in order to assess single agent safety of voreloxin in patients older than age 60
- Present preliminary results of a Phase 1b study of voreloxin in combination with cytarabine in relapsed/refractory AML

Study Design

- Phase 1b single agent dose escalation with 2 dose schedules: Weekly IV administration of voreloxin Injection (Days 1, 8, and 15) for 3 doses/cycle and twice weekly IV administration of voreloxin Injection (Days 1, 4, 8, and 11) for 4 doses/cycle
- Relapsed/refractory hematologic malignancy patients (n=68 evaluable for safety)
- Primary endpoints were safety, pharmacokinetics and MTD determination
- Clinical response assessment per IWG Criteria
- Analysis of safety and efficacy completed for patients younger than age 60 and age 60 and older.

Demographics

	< 60 y N = 26	≥ 60 y N = 42
Median Age (Range)	43.5 (21-59)	69 (60-85)
% Female	36%	37%
ECOG PS 0-1	90%	93%
Relapse/Refract/Both	11%/43%/46%	26%/37%/33%
AML	74%	88%

Safety: G3 or Higher AE By < 60 y and ≥ 60 y

System Organ Class Preferred Term	< 60 y N(%)	≥ 60 y N(%)	Total N(%)
Population	26	42	68
Patients who reported any NCI CTCAE v3 G3 or G4	19(73)	32(76)	51(75)
Blood and lymphatic system disorders			
• Febrile neutropenia	10(39)	15(36)	25(37)
• Neutropenia	5(19)	11(26)	16(24)
• Thrombocytopenia	6(23)	10(24)	16(24)
• Pancytopenia	1(4)	5(12)	6(9)
Gastrointestinal disorders			
• Stomatitis (oral mucositis)	4(15)	5(12)	9(13)
General disorders			
• Pyrexia	1(4)	3(7)	4(6)
Infections and infestations			
• Pneumonia	3(12)	4(10)	7(10)
• Bacteraemia	2(8)	2(5)	4(6)
• Sepsis	1(4)	5(12)	6(9)
• Fungal pneumonia	1(4)	3(7)	4(6)

Clinical Responses By < 60 y and ≥ 60 y

Age	Dose and Schedule (mg/m ²)	Relapsed/Refractory (No. Prior Tx)	Cytogenetics	Cycles Received	Response Duration (months)
40	72qw	Refractory relapse (2)	Unfavorable	1	4 followed by BMT
41	72qw	Refractory relapse (3)	Unfavorable	2	5+
66	50qw	Relapsed (1)	Intermediate	4	4
74	60qw	Refractory relapse (2)	Intermediate	1	<1
71	90/72qw	Refractory (1)	Unfavorable	1*	7*
74	40biw	Refractory relapse (1)	Intermediate	3	7/5**

*Patient treated at 90 mg/m² then dose reduced to 72 mg/m². First voreloxin remission was 7 months; patient relapsed and is now receiving second voreloxin induction.
 **First voreloxin remission was 7 months, patient relapsed and was reinduced with voreloxin, achieved complete remission with duration of ~5 months, relapsed and is now receiving 3rd voreloxin induction.

Voreloxin and Cytarabine Combination Study Design

- Multi-center phase 1b dose escalation study of voreloxin given within 10 minute IV infusion on days 1 and 4 in combination with 400 mg/m²/day CIV x 5 days cytarabine
- Patients with relapsed and/or refractory AML
- Primary objectives are safety and pharmacokinetics of voreloxin
- Secondary objectives are preliminary assessment of anti-leukemic responses and pharmacodynamic markers
- Patients can be 18 y and older and have failed up to 3 prior regimens
- Median age for all patients enrolled thus far is 60.4 y (range 44-75 y)

Combination Study Preliminary Results

Cohort	Voreloxin mg/m ²	Tx / Enrolled	DLTs	Responses
1	10	4/4	0	0
2	20	3/4	0	1 CR (sent for BMT)
3	34	4/4	0	2 CR (1 sent for BMT)
4	50	6/6	TBD	2 BM cleared, in recovery 1 BM cleared, relapsed 1 too early for evaluation 1 PD; 1 off-study unrelated AE

Conclusions and Future Directions

- Voreloxin behaves similarly in patients < 60 y and ≥ 60 y:
 - Overall incidence and type of adverse events was similar
 - Complete Remissions (CR/CRp) were observed in both populations with 4 of 6 CR/CRp ≥ 60 y
 - Pharmacokinetics were not affected by age; no age-related change was observed in voreloxin CI, Vss, MRT or T1/2
- Preliminary results of voreloxin in combination with cytarabine show:
 - Complete remissions have been observed in relapsed/refractory patients (Historical single agent cytarabine response in this population 14-29% [SWOG Arch. Int. Med. 1974])
 - No dose limiting toxicities to date, dose escalation continues (at 70 mg/m²)
 - Voreloxin pharmacokinetics are unaffected by cytarabine thus far
- REVEAL-1 phase 2 study of single agent voreloxin in newly diagnosed AML patients ≥ 60 y and unlikely to benefit from standard induction therapy is enrolling patients