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PF886 - DIVESIRAN, A NOVEL GALNAC CONJUGATED SIRNA, REDUCES PHLEBOTOMIES, IMPROVES IRON STORES AND SYMPTOMS IN POLYCYTHEMIA VERA PATIENTS IN SANRECO PHASE 1 STUDY.

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INTRODUCTION

Polycythemia Vera (PV) is a myeloproliferative neoplasm characterized by excessive erythrocytosis and increased risk of thromboembolic events which are linked to elevated hematocrit levels (>45%) (Marchioli et al 2013). Patients experience fatigue, brain-fog and other debilitating symptoms. Hematocrit levels are routinely controlled with phlebotomies, often in combination with cytoreductive therapies. Hepcidin is the central regulator of iron homeostasis and PV patients have reduced levels (Ginzburg et al 2018). We employed a novel approach to alter iron distribution in PV patients using a small interfering RNA (siRNA). siRNAs are precision medicines that engage their mRNA targets and silence gene expression. Divesiran (formally, SLN124) is a GalNAc conjugated siRNA that increases hepcidin synthesis by silencing TMPRSS6 (a negative regulator of hepcidin production), restricting iron availability for erythropoiesis. We present data from the completed phase 1 part of the ongoing Ph1/2 SANRECO trial (NCT05499013) of divesiran in PV pts.

AIM

The aim is to evaluate the safety and tolerability of divesiran and its effects

METHOD

- Phase 1 is an open label dose finding study enrolling phlebotomy dependent PV pts.
- Eligibility criteria included:
  - i) PV diagnosis as per 2016 WHO criteria with ≥3 phlebotomies in the 6 months or ≥5 phlebotomies in 12m prior to screening;
  - ii) treatment with phlebotomy alone or on stable doses of cytoreductive therapy.
- Three dosing cohorts Cohort1, Cohort2 and Cohort3 (3, 6 or 9 mg/kg of divesiran respectively) enrolling up to 8 pts each, given up to 4 doses by subcutaneous injection every 6 weeks. After the last dose (w18), pts were followed up for 16w (w34).
- Symptom scores using MPN-SAF-TSS (MPN-10), iron and erythroid biomarkers were assessed throughout the study.

RESULTS

The phase 1 portion of SANRECO was completed 22 Feb 2025. Baseline Characteristics are summarised in **Table 1**. 21 patients were enrolled with a mean age 56.3 years (range 32 to 71), of which 16/21 were male, 11/21 were white, 10/21were Asian, 12/21 were high-risk PV (age ≥60) and 14/21 were on cytoreductive therapy. The baseline HCT was 47.0% (1.2), mean (SEM), (range 39% to 59%). Divesiran was well tolerated without dose limiting toxicities, most common treatment emergent adverse events (TEAE) were injection site reactions (ISRs) (44/138) in 67% pts (**Table 2**). No treatment-related serious adverse events or TEAEs leading to discontinuation were observed.

In the 6 months prior to dosing, 21 patients had a total of 80 phlebotomies (**Figure 1**). There were a total of 5 phlebotomies in the dosing interval (14% pts), and 4 in follow up of 16 weeks (19% pts). Hematocrit (% points) decreased at w24 (d169) by -3.6 (1.7) in Cohort1, -4.8 (1.2) in Cohort2 and -4.6 (3.5) in Cohort3, mean (SEM) (**Figure 2**). Serum iron (6.0umol (0.9)) (**Figure 3**) and TSAT (8.6% (1.7)) (**Figure 4**) were low at baseline and were further reduced at w34 (d239) (serum iron w34, 3.9umol (0.2); TSAT 5.6%(0.4)) mean (SEM) signalling iron restriction while ferritin (ug/L) levels were increased from baseline 28.1 (15.2) to 48.0 (16.2) at w34 (d239) showing improved iron stores (**Figure 5**). The majority of patients reported significantly improved MPN-10 total symptom scores between baseline and w34 (d239) (**Figure 6**) p= 0.0350. In 14 pts with follow-up data after the last dose received in Ph1 (w18 – d127)), the median time to first phlebotomy was 287 days (**Figure 7**).

Table 1 – Baseline characteristics of patients in SANRECO phase 1.

Cohort	participants	Age range (years)	Sex	Race	High Vs Low risk	Participants on Cytoreductives	*Baseline Phlebotomies	HCT Baseline Range [%]
1 3 mg/kg	6	49-64	4M 2F	3 Caucasian 3 Asian	3 LR 3 HR	4 HU 2 none	2 to 6	39-56
2 6 mg/kg	8	32-69	5M 3F	1 Caucasian 7 Asian	4 LR 4 HR	5 HU 3 none	2 to 8	39-56
3 9 mg/kg	7	40-71	7M	7 Caucasian	2 LR 5 HR	5 HU 1 Ruxo 2 none	2 to 9	40-59
Total	**21**	**32-71**	**16M (76%) 5F (24%)**	**11 Caucasian (52%) 10 Asian (48%)**	**9 LR (43%) 12 HR (57%)**	**13 HU (62%) 1 Ruxo (10%) 7 none (33%)**	**2 to 9**	**39-59**

Table 2 - TEAEs arising in ≥ 2 Patients.

AE preferred term	Cohort 1 (n=6)	Cohort 2 (n=8)	Cohort 3 (n=7)	Total (n=21)
Injection site reaction	5 (83.3%)	5 (62.5)	4 (57.1%)	**14 (66.7%)**
Anemia	2 (33.3%)	1 (12.5%)	3 (42.9%)	**6 (28.6%)**
Fatigue	2 (33.3%)	1 (12.5%)	3 (42.9%)	**6 (28.6%)**
Headache	2 (33.3%)	1 (12.5%)	2 (28.6%)	**5 (23.8%)**
Thrombocytosis	1 (16.7%)	1 (12.5%)	0 (0%)	**2 (9.5%)**
Toothache	2 (33.3%)	0 (0%)	0 (0%)	**2 (9.5%)**
Influenza like illness	1 (16.7%)	0 (0%)	1 (14.3%)	**2 (9.5%)**
Lethargy	2 (33.3%)	0 (0%)	0 (0%)	**2 (9.5%)**
Pruritus	1 (16.7%)	1 (12.5%)	0 (0%)	**2 (9.5%)**

Figure 1. Number of phlebotomies in PV patients participating in SANRECO Phase 1. Predose is in orange and in blue are patients during dosing and follow-up periods.

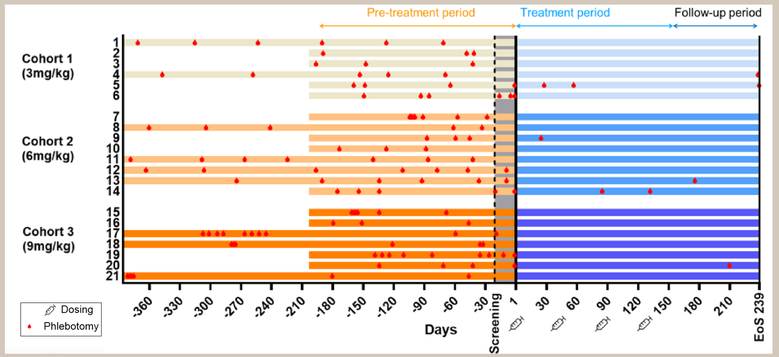


Figure 5. Ferritin (ug/L) levels in PV patients participating in SANRECO Phase 1.

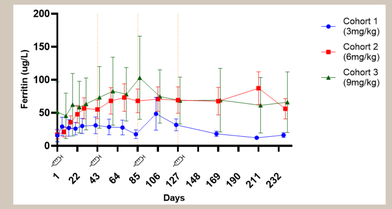


Figure 6. Rank Global MPN-SAF-TSS scores in SANRECO Phase 1.

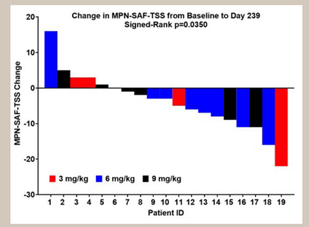


Figure 2. Change from baseline hematocrit (%) in PV patients participating in SANRECO Phase 1.

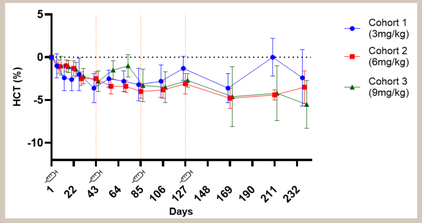


Figure 3. Time course of serum iron (umol/L) in PV patients participating in SANRECO Phase 1.

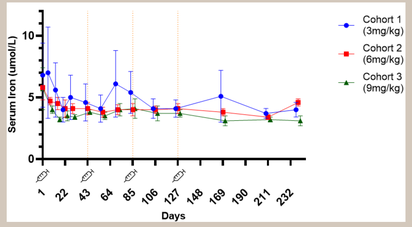


Figure 4. Time course of Transferrin receptor saturation (TSAT %) of PV patients participating in Sanreco Phase 1.

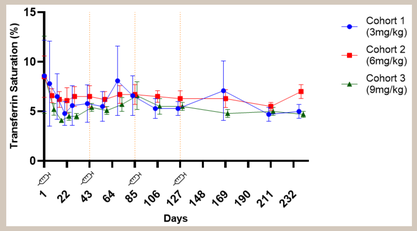
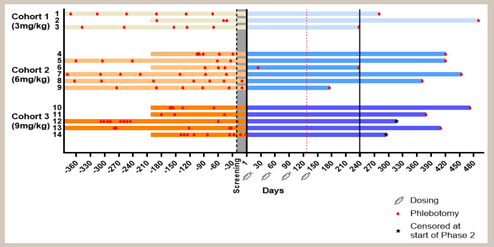


Figure 7. Time to first phlebotomy for 14 patients followed up after completion of phase 1.



CONCLUSIONS

Divesiran is a first in class siRNA targeting the hepcidin pathway.

Divesiran is being developed for treatment of PV.

Divesiran is well-tolerated (doses up to 9 mg/kg) and decreases the need for phlebotomies, improves iron distribution and PV symptoms with a (Q6W) dosing regimen.

Divesiran has a prolonged duration of effect that persists after the final dose suggesting it may be an effective and convenient treatment option for PV.

ACKNOWLEDGEMENT

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