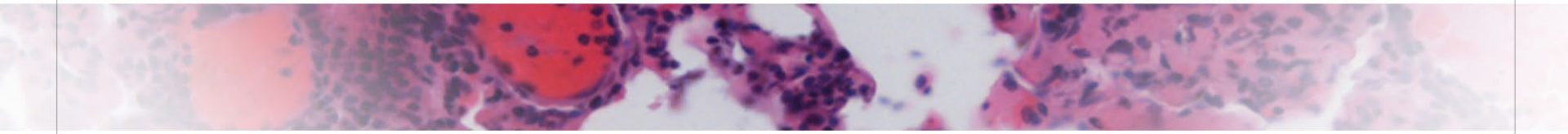
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Initial Results from a Phase 1/2 Study Evaluating Divesiran, a Novel GalNAc Conjugated siRNA, in Patients with Polycythemia Vera (SANRECO)

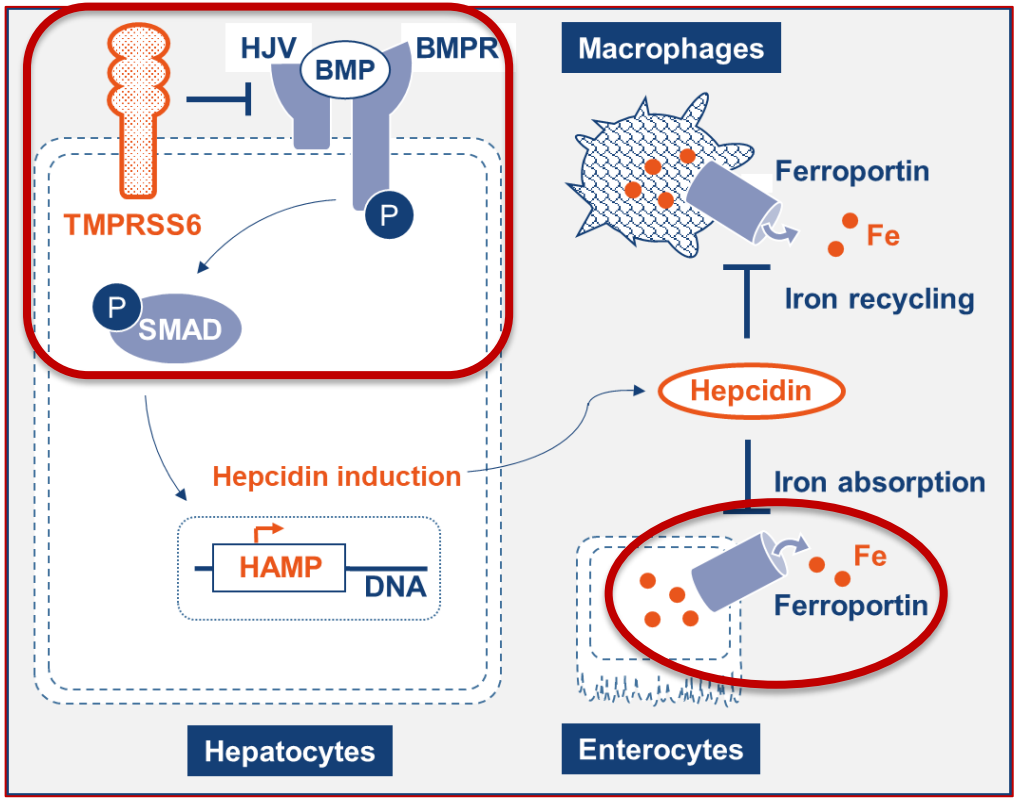
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Background

- Polycythemia vera (PV) is a rare blood cancer with excessive production of red blood cells (RBCs).
- Elevated hematocrit (HCT), an index of RBC mass is a hallmark of the disease and patients are frequently iron deficient.
- Patients are often symptomatic with fatigue, difficulties concentrating, headaches and pruritus.
- Treatment goal is to control HCT <45% with therapeutics phlebotomies and cytoreductive therapies.
- Patients are predicted to have low hepcidin levels (Ginzburg et al 2018).
- PV patients have deranged iron distribution driven by the excess demand of the bone marrow to produce excess red blood cells.
- Increase in hepcidin via administration of hepcidin mimetic has been shown to result in HCT control without the need for phlebotomies (Kremyanskaya et al 2024)

Inhibition of TMPRSS6 Elevates Hepcidin and Redistributes Iron

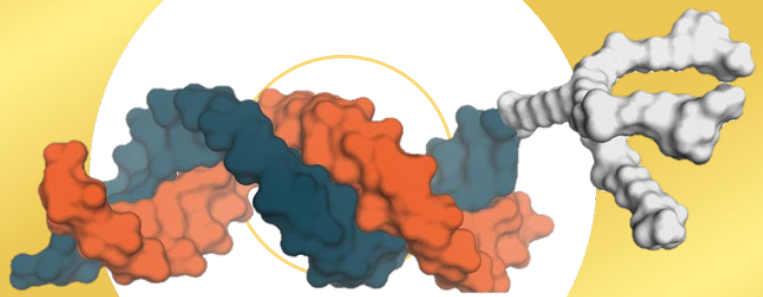


- **Hepcidin** reduces uptake of dietary iron and release of iron from storage cells.
- **HJV/BMP/SMAD** signaling pathway induces hepcidin expression. **TMPRSS6** is a **negative** regulator of this pathway. It is a serine protease which cleaves HJV
- **Hepcidin** levels are low to normal in patients with Polycythemia Vera
- **Therapeutic hypothesis:** inhibition of TMPRSS6 will raise hepcidin and reduce iron delivery to the bone marrow resulting in reduced erythropoiesis.

Divesiran is a GalNAc siRNA conjugate targeting TMPRSS6

19mer, blunt ended siRNA conjugate, synthetised by solid phase

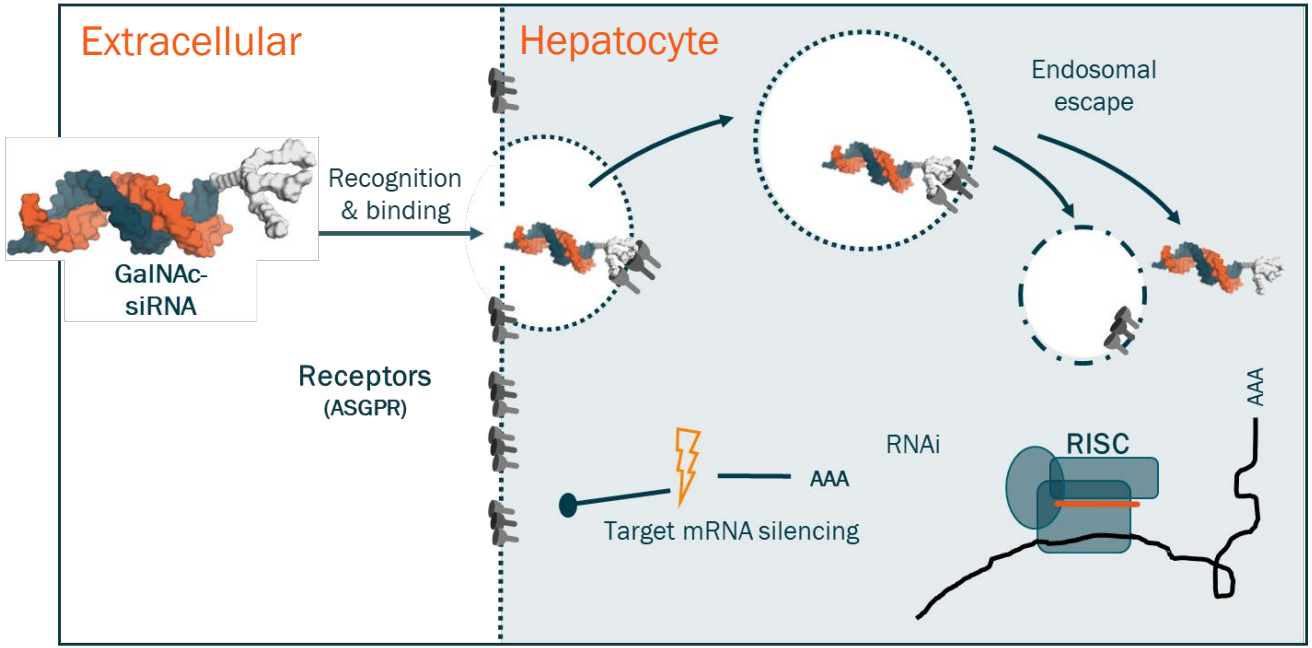
Target sequence is unique to *TMPRSS6* and was selected to maximise *TMPRSS6* knock down.



Stabilised for long duration of action through a specific pattern of modifications

Tri-antennary GalNAc for specific targeting of hepatocytes *via* asialoglycoprotein receptor interaction

Divesiran – Mode of Action

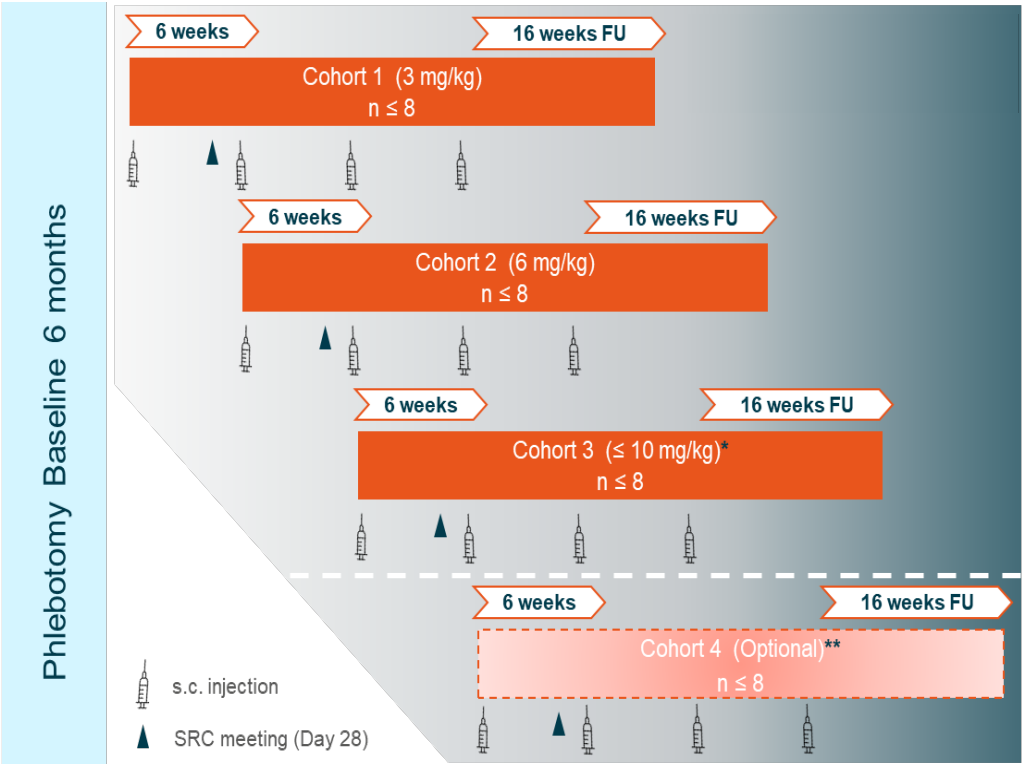


target organ: liver



Liver specific and long-lasting target gene inhibition of TMRSS6 by subcutaneous administration

Phase 1 Study Design



Study stopped enrolment in June 2024 (n=21)

- Divesiran was administered SC Q6W X four doses, followed by 16 week observation
- Cohort 1 – 3 mg/kg, 6 participants
- Cohort 2 – 6 mg/kg, 8 participants
- Cohort 3 – 9 mg/kg, 7 participants

Eligibility Criteria

- PV diagnosis according to WHO 2016
- At least 3 phlebotomies in previous 6 months or 5 in previous 12 month to screening.
- Cytoreductives allowed if patient on stable dose for 12 weeks prior to screening and no planned dose changes.
- Platelets ≤ 1,000,000/uL, WBC ≤ 25,000/uL

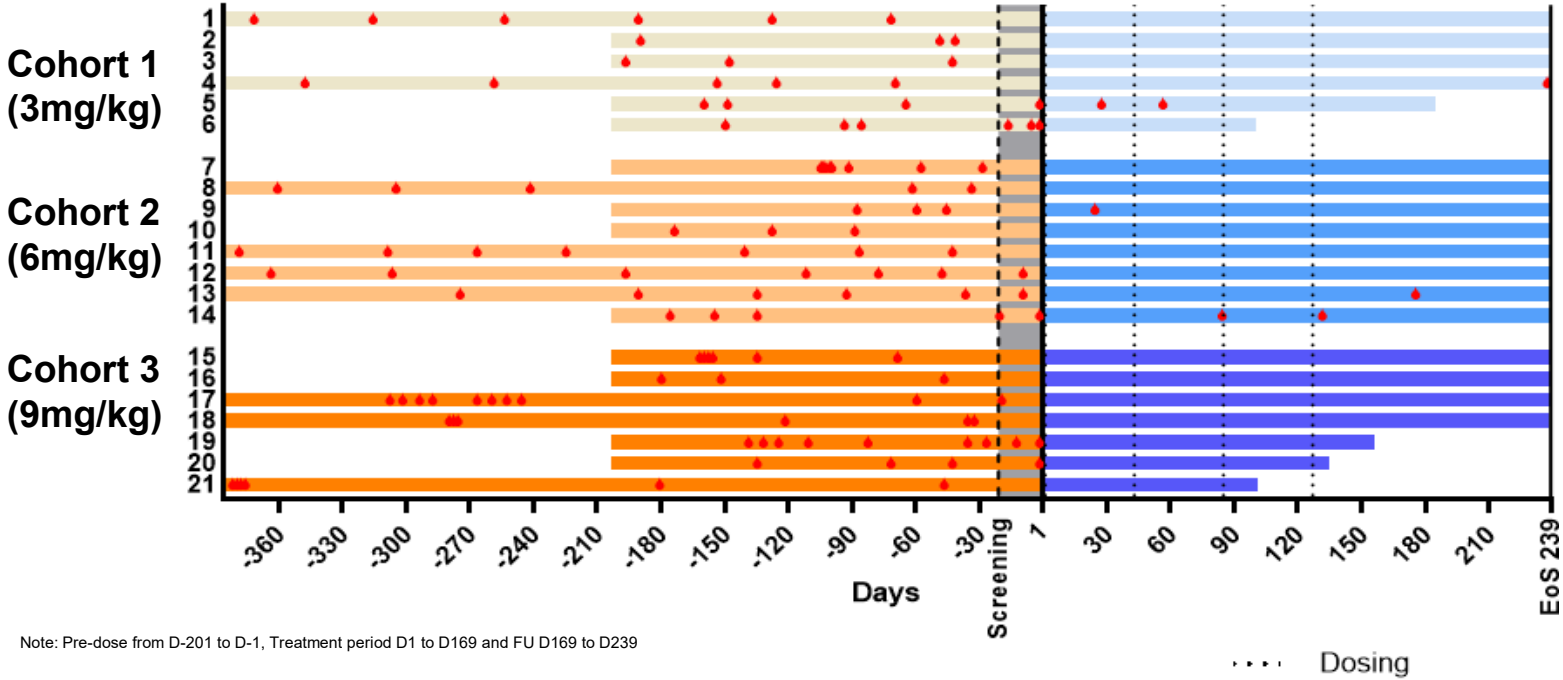
Baseline Characteristics

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**

Note:
Risk stratification based on age.
20/21 participants on Aspirin
*Baseline phlebotomies comprise phlebotomies accrued 6-months prior to screening and those occurring in the screening period.

No previous thrombotic events

Divesiran Reduces Phlebotomy Frequency in PV Patients

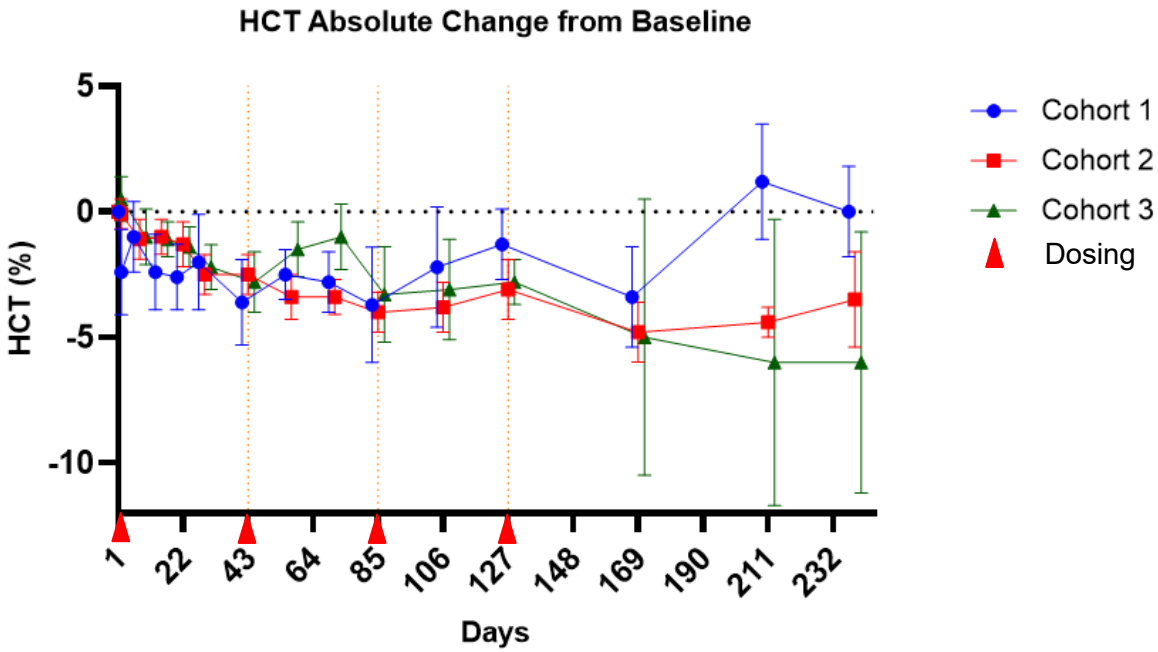


Note: Pre-dose from D-201 to D-1, Treatment period D1 to D169 and FU D169 to D239

79 phlebotomies prior to dosing, 5 in treatment period and 2 in Follow-up.

No well-controlled patients (HCT<45% at baseline) required a phlebotomy

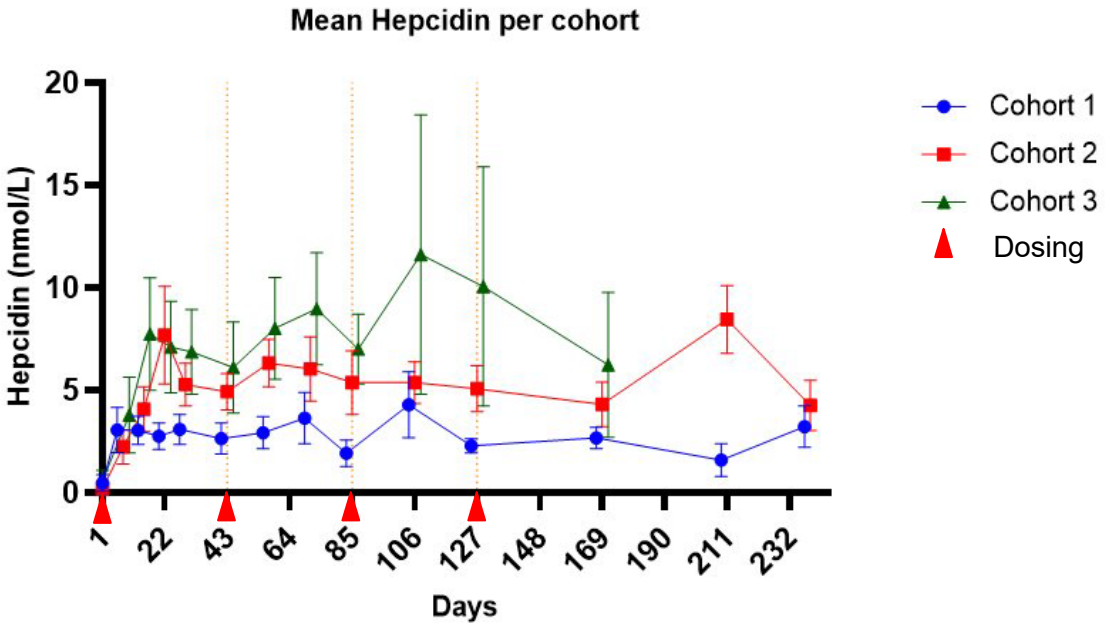
Divesiran Reduces Hematocrit in PV Patients



Divesiran decreases hematocrit in all cohorts

Note: Orange dotted line represent dosing dates. Error bars represent ± SEM

Divesiran Treatment Results in Sustained Increases in Hepcidin

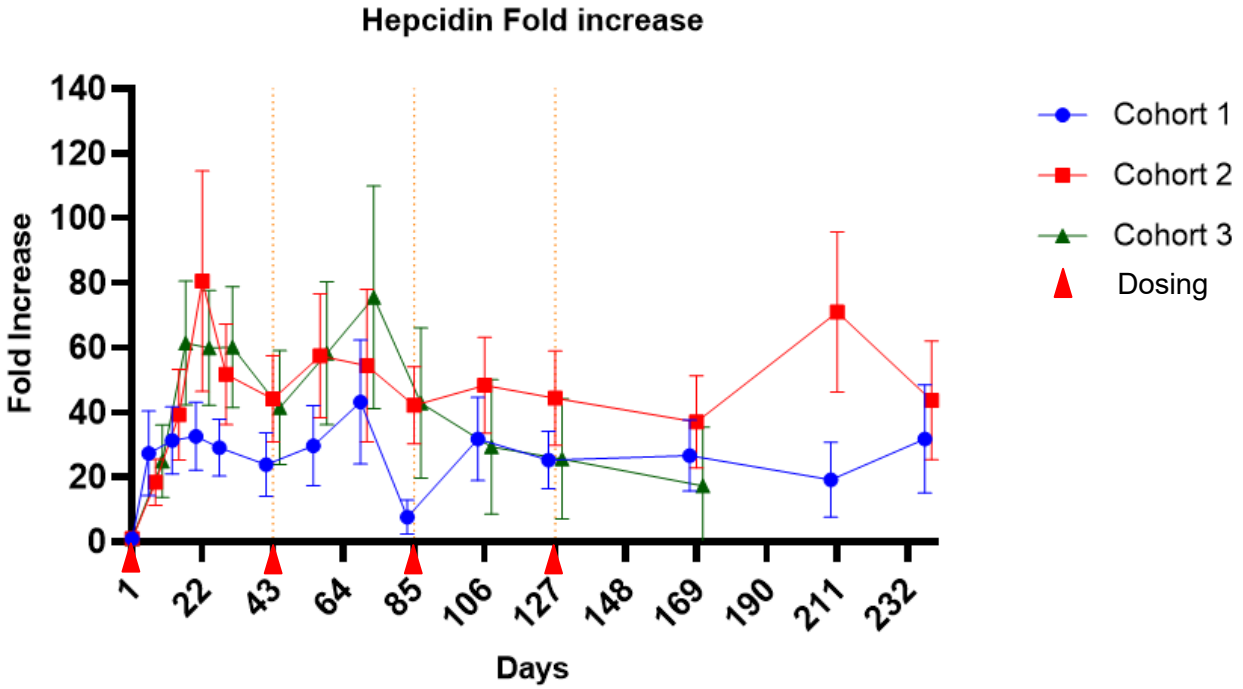


- Divesiran treatment increases hepcidin.
- Hepcidin is induced in all participants.

Divesiran treatment induces hepcidin

Note: Orange dotted line represent dosing dates. Error bars represent ± SEM

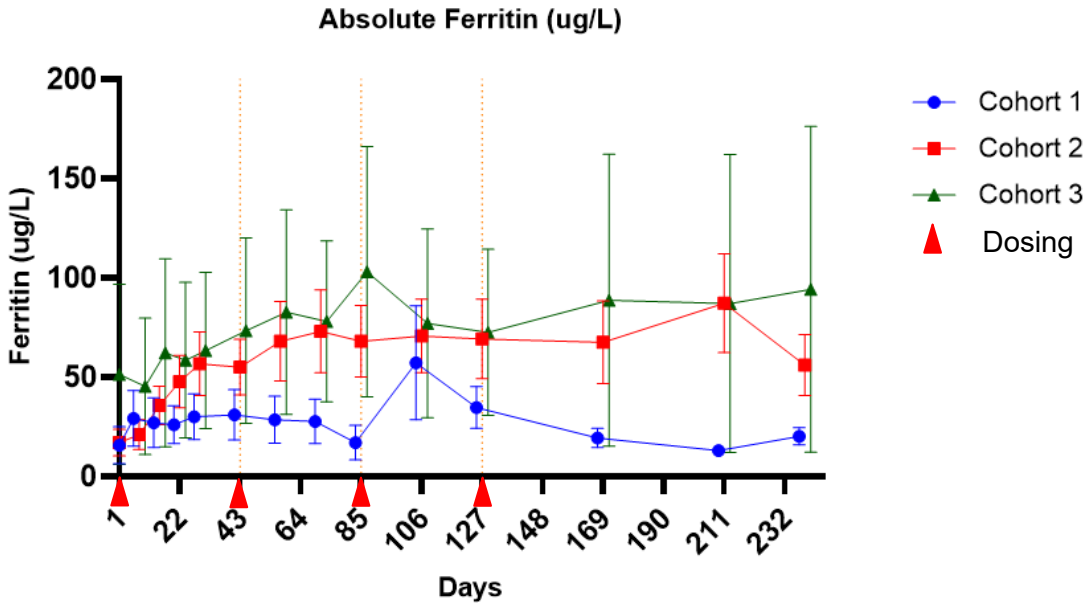
Hepcidin Fold-Increase is Similar at 6 and 9 mg/kg



Cohorts receiving 6mg/kg (cohort 2 - red) and 9mg/Kg (cohort 3- green) increase hepcidin to similar levels.

Note: Orange dotted line represent dosing dates. Error bars represent ± SEM

Divesiran Treatment Results in Elevated Ferritin



Most patients were iron deficient (≤25 ug/L ferritin, n= 18) at baseline.

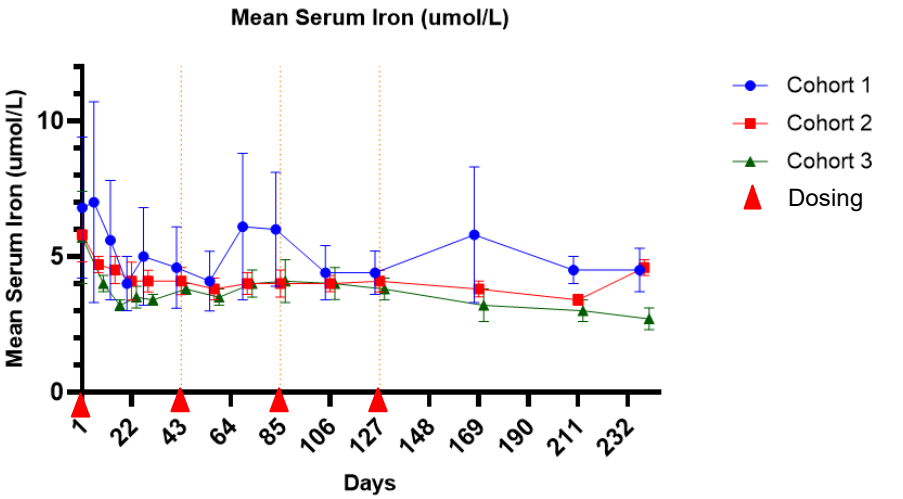
3/21 patients had ferritin >25 ug/L (range 62 to 324 ug/L at baseline).

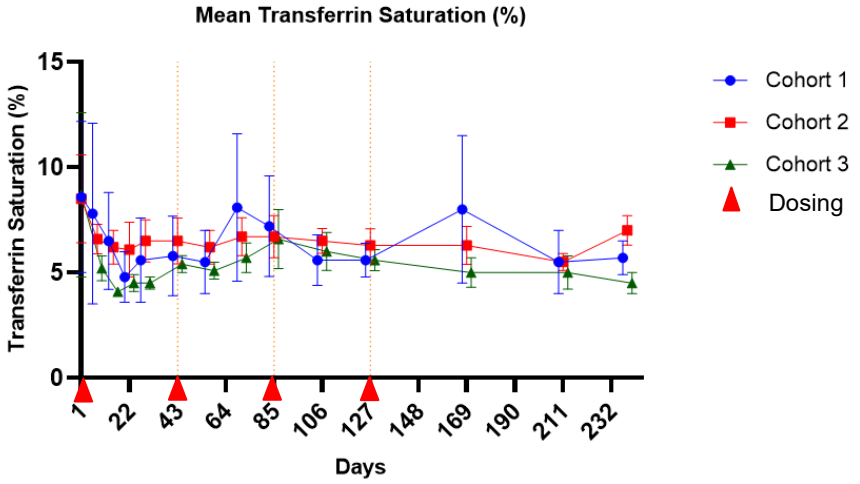
High baseline in cohort 3 due to patient with very high ferritin levels (>320ug/L).

Divesiran treatment increases ferritin

Note: Orange dotted line represent dosing dates. Error bars represent ± SEM

Divesiran Drives Iron Restriction

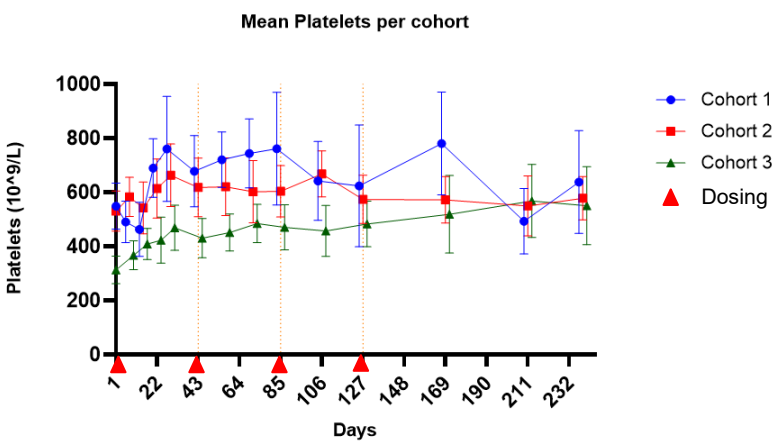


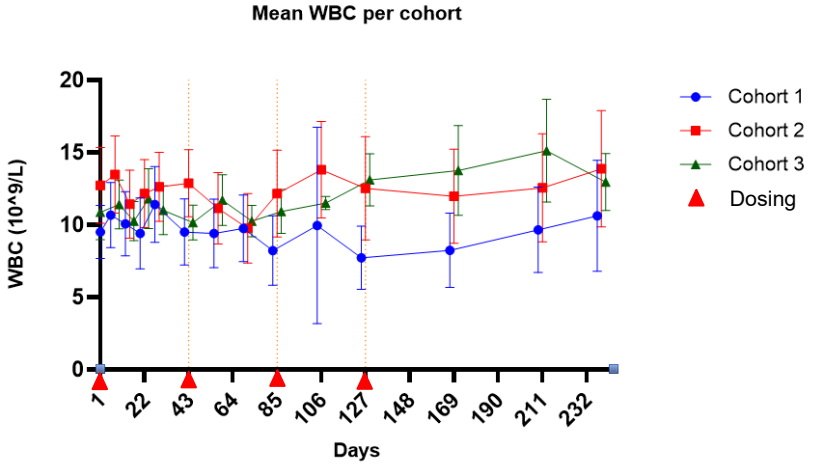


Low Serum iron and TSAT consistent with iron deficiency of PV and divesiran iron restriction effect

Note: Orange dotted line represent dosing dates. Error bars represent ± SEM

Platelets Increase with Divesiran Treatment while WBC Remain Stable





Platelets increase by day 29 in all treatment groups with no dose dependency observed. White blood cells remain stable

Note: Orange dotted line represent dosing dates. Error bars represent ± SEM

Divesiran is Safe and Well Tolerated

- Divesiran is well tolerated without dose-limiting toxicities.
- Treatment emergent adverse events (TEAEs) were recorded in 19/21 participants.
- Majority of TEAEs (84%) were grade 1.
- No TEAEs grade > 2.
- 52 mild self-limiting injection site reactions were observed in 13/21 participants.
- No treatment-related serious adverse events or TEAEs leading to discontinuation.

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)	3 (42.9%)	**13 (61.9%)**
Anaemia	3 (50.0%)	1 (12.5%)	3 (42.9%)	**7 (33.3%)**
Fatigue	2 (33.3%)	1 (12.5%)	2 (28.6%)	**5 (23.8%)**
Headache	2 (33.3%)	1 (12.5%)	1 (14.3%)	**4 (19.0%)**
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%)**

Conclusion: Divesiran in PV

- First in class siRNA in PV
- Safe and well tolerated at doses up to 9mg/kg
- Decreases phlebotomy requirements
- Well-controlled patients (HCT<45%) at baseline remained controlled while eliminating the need for phlebotomy
- Lowers HCT in all patients regardless of baseline levels.
- Increases hepcidin, redistributes iron as indicated by elevation of ferritin resulting in elevation of iron body content improving iron deficiency
- White blood cells are not altered over the time of the study
- Platelets increase reaching a plateau with no dose dependent effect
- These early results support further development of divesiran as a PV treatment

Divesiran increases hepcidin resulting in lower hematocrit and number of phlebotomies while increasing body iron content

Acknowledgements

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  - Medical Centre Leo Clinic EOOD, Plovdiv, Bulgaria
  - Hospital Tengku Ampuan Afzan, Kuantan, Pahang, Malaysia
  - Pindara Private Hospital, Queensland, Australia
  - Linear Clinical Research, Nedlands, Western Australia Australia
  - Clinical Haematology Department, Royal Melbourne Hospital and Peter MacCallum Cancer Centre, Melbourne, Victoria Australia
  - Ashford Cancer Centre Research, Kurralta Park, South Australia Australia
  - Epworth Richmond, Richmond, Victoria Australia
  - Hospital Sultanah Nur Zahirah, Kuala Terengganu, Malaysia
- And the dedication of our patients.