FONDAZIONE ITALIANA SINDROMI MIELODISPLASTICHE

CONVEGNO FISiM

Firenze, CSF Montedomini
"Il Fuligno"
24-25 ottobre 2025

FARMACI CHELANTI DEL FERRO

Federica Pilo

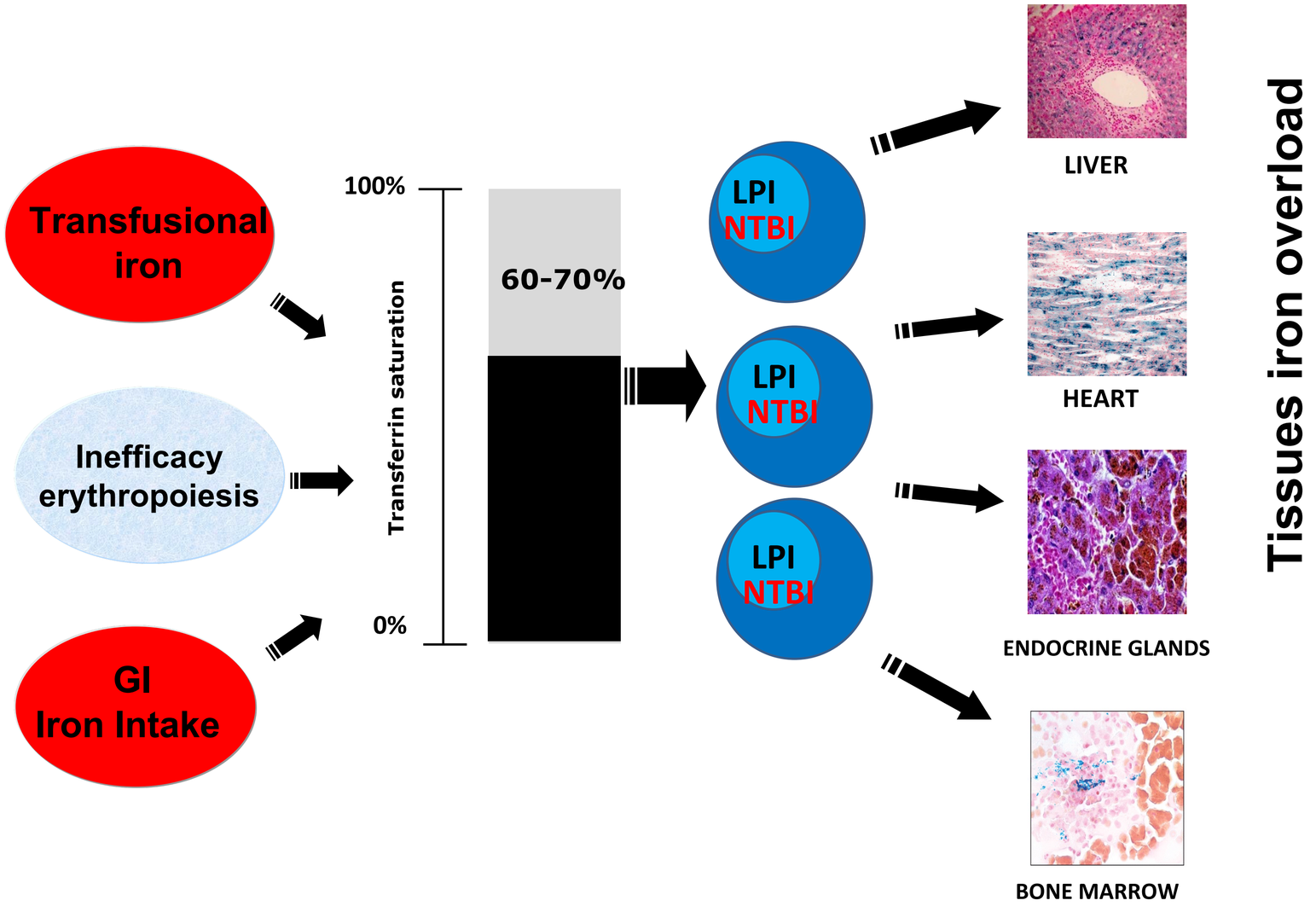
Disclosures of Federica Pilo

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
JAZZ Farma					X	X	
BMS						X	
OTZUKA						X	
ABBVIE					X	X	

Deferasirox

- has been shown to extend the median event-free survival by approximately 1 year compared to placebo [Angelucci *et al*., 2020].
- This effect is mainly driven by a reduction in **cardiac events**, supporting the effect of iron chelation in preventing cardiac damage caused by ironoverload in this patient population [Sarocchi *et al*., 2024].
- In addition, ***s*-ferritin levels** decreased over time with DFX while they increased with placebo [Angelucci *et al*., 2020].

IRON OVERLOAD DAMAGES



Pilo F & Angelucci E. Ann N Y Acad Sci. 2016 Mar;1368(1):115-21

Deferoxamina

- parenteral
- over 8 h/5-7 week
- time consuming
- painful

- monitoring for ocular toxicity, ototoxicity, and growth retardation

Deferasirox

360mg 180mg 90mg

- gastrointestinal disturbances hepatotoxicity
- contraindicated in patients with creatinine clearance <40 mL/min or serum creatinine >2 times the upper limit of normal.

Deferiprone

- requires frequent dosing three times daily

- gastrointestinal disturbances and arthropathy

- neutropenia, and agranulocytosis

Pilo F, unpublished figure

The SP-420 Discovery Process

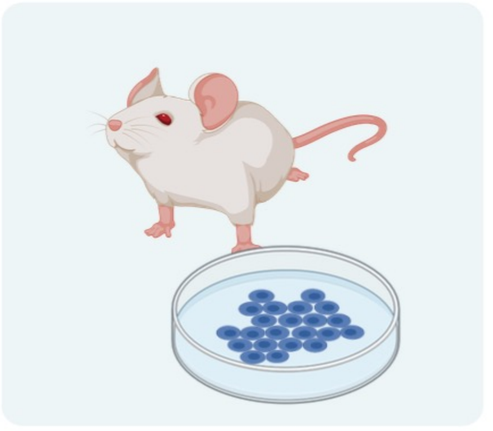
1 **Research & Development** 3-6 years

2 **Preclinical Studies** 1 year

3 **Clinical Trials** 4-7 years

4 **Review & Approval** 1-2 years

- analog of deferitrin
- tridentate iron chelator of the desferrithiocin
- stoichiometry of 2:1 SP-420:Fe(III).



- clinical efficacy but renal toxicity
- addition of polyethers to the phenol ring improve PK tissue distribution and iron chelating efficiency, and to reduce kidney toxicity
- displayed less kidney toxicity than deferasirox

first-in-human study conducted in healthy volunteers, single doses of SP-420 up to 13.2 mg/kg were well tolerated with dose-related PK and a plasma half-life (9–17 hour) which supported either once daily (QD) or twice daily (BID) dosing

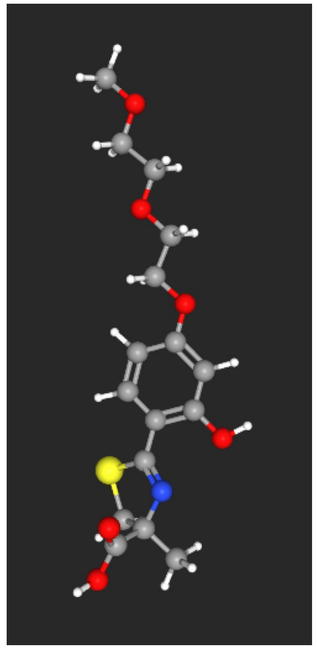
phase I, open-label, multi-center, dose-escalation study evaluated the pharmacokinetics (PK) of SP-420

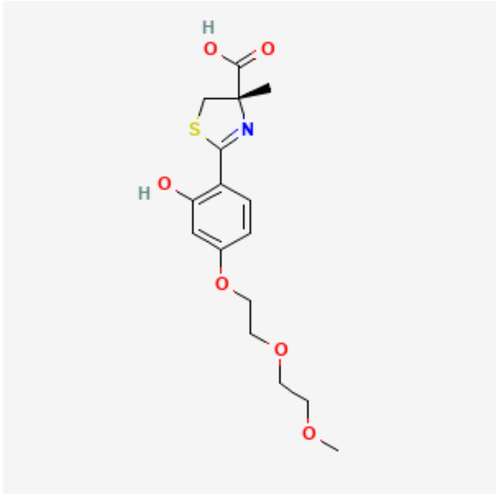
The study was prematurely terminated by the sponsor due to renal adverse events (AE) including proteinuria, increase in serum creatinine, and one case of Fanconi syndrome.

Am J Hematol. 2017;92:1356–1361

Pilo F, unpublished figure

CTID	Title	Title	Title	Phase	Status
NCT04741542	Safety of SP-420 in the Treatment of Transfusional Iron Overload	Iron Overload	SP-420	Phase 1	Terminated
NCT05693909	A Trial Testing SP-420 in Subjects With Transfusion-dependent β-thalassemia	Beta Thalassemia Major Anemia	SP-420	Phase 2	Unknown status
NCT03801889	SP-420 in Subjects With Transfusion-dependent Beta-Thalassemia or Other Rare Anemias	Iron Overload|Beta-Thalassemia	SP-420	Phase 2	Withdrawn
NCT02274233	Safety and Pharmacokinetic Study of Escalating Doses of SP-420, an Iron Chelator, in Patients With β-Thalassemia	Iron Overload|Beta-Thalassemia	SP-420	Phase 1	Terminated





SP-420

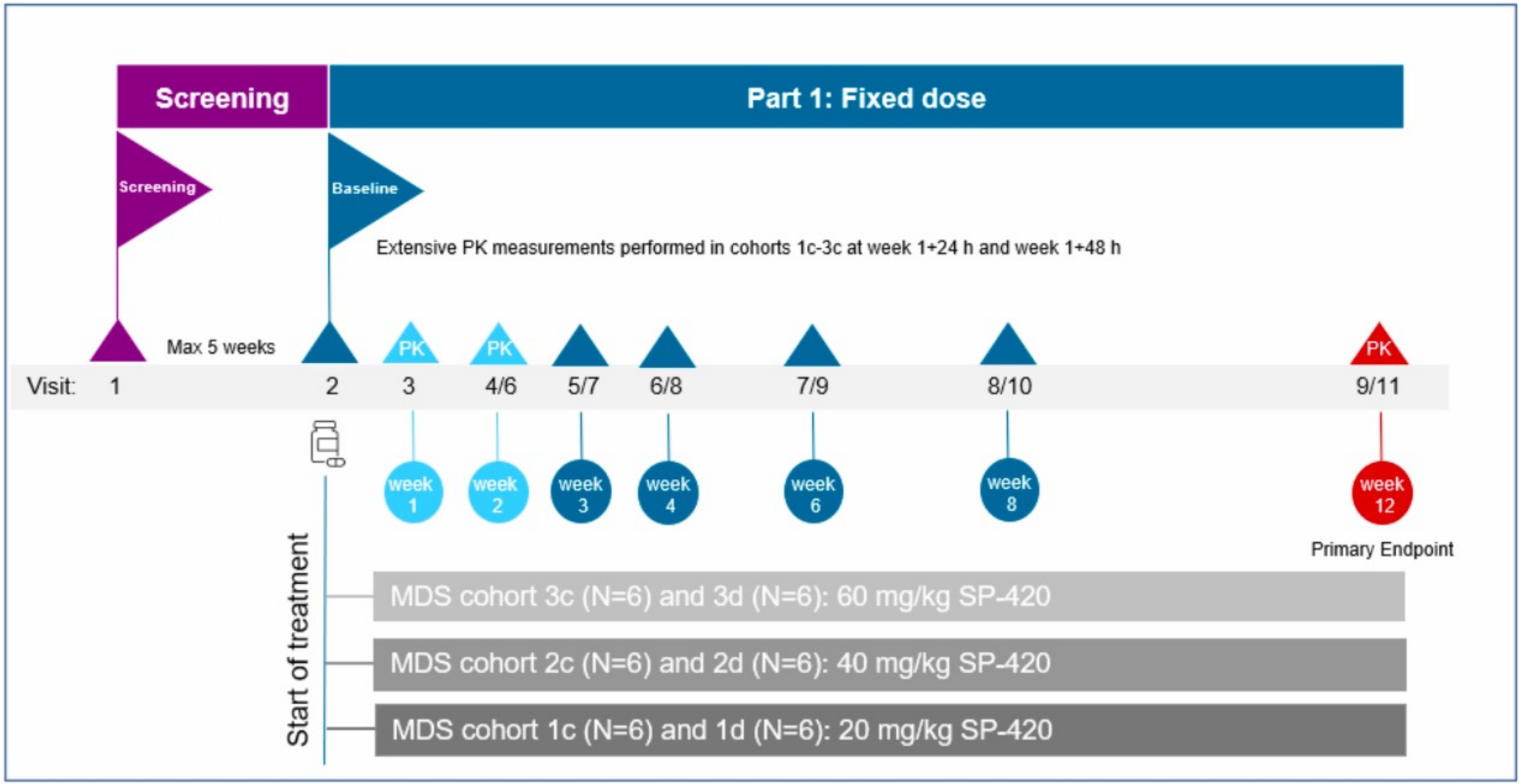
desferrithiocyn

Pilo F, unpublished figure

CLINICAL TRIAL PROTOCOL

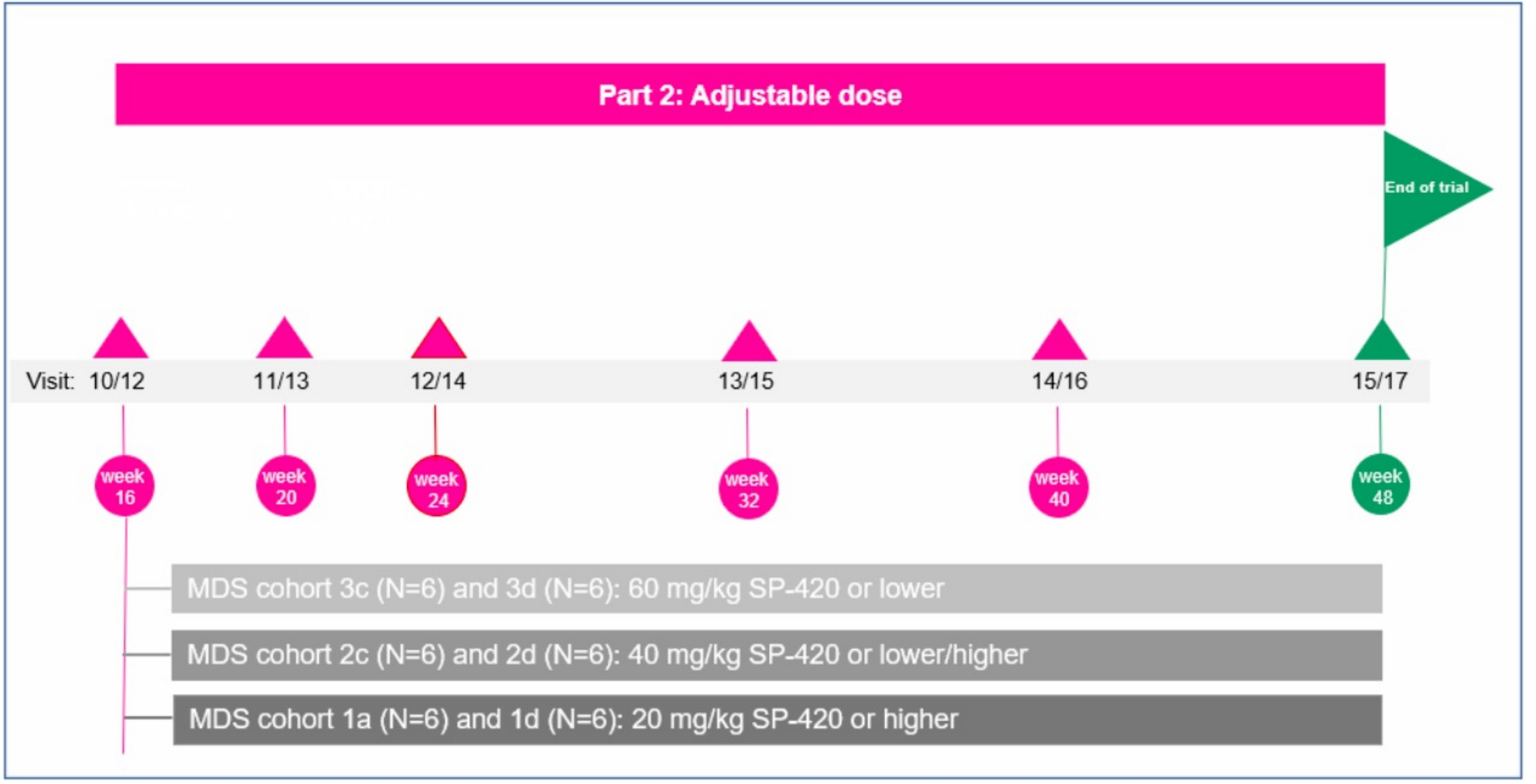
An open-label, dose-escalation, dose-finding, and proof-of-concept trial of SP-420 in subjects with transfusion-dependent α- or β-thalassemia or low-risk myelodysplastic syndromes

Trial ID:	P-SP420-THAL-01
Regulatory Agency Identifier:	UTN: U1111-1277-5903 IND: 119889 Clinicaltrials.gov: NCT05693909 EUCT: 2023-507396-21-00
Compound:	SP-420
Sponsor:	Pharmacosmos A/S, Rørvangsvej 30, DK-4300 Holbæk, Denmark
Protocol Version:	Version 10.0 (amendment 7), 01 July 2025



Note: Subjects in cohort 1c-3c have 2 additional visits at week 1+24 h and week 1+48 h, thus the visit numbers are different for cohorts c and d from week 2 and onwards.

Clinicaltrial.gov NCT05693909



Note: Subjects in cohort 1c-3c have 2 additional visits at week 1+24 h and week 1+48 h, which is why the visit numbers are different for cohorts c and d.

Clinicaltrial.gov NCT05693909

MDS cohorts	
Objectives	**Endpoints**
Primary safety objective	**Primary safety endpoint**
To assess the safety and tolerability of ascending doses of SP-420 after 12 weeks treatment	• Type and incidence of AEs after 12 weeks of treatment
Secondary safety objective	**Secondary safety endpoints**
To assess the safety and tolerability of ascending doses of SP-420	• Type and incidence of AEs • Left ventricular ejection fraction (LVEF) at weeks 24 and 48
	Additional safety assessments
	In addition, physical examination, height, vital signs, ECG, and safety laboratory tests (including urinalysis) will be measured as part of standard safety assessments. In addition, extensive ECG measurement will be performed in the 4 subjects in cohorts 1c-3c (reported separately)
Secondary efficacy objective	**Secondary efficacy endpoints**
To assess the efficacy of SP-420 on *s*-ferritin	• Change in *s*-ferritin from baseline to weeks 1, 2, 3, 4, 6, 8, 12, 16, 20, 24, 32, 40, and 48
PK objective	**PK endpoints (reported separately)**

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Exploratory objectives	Exploratory endpoints
To assess:	
• Efficacy of SP-420 on LPI	• Change in LPI during week 1 (cohorts 1c-3c only) • Change in LPI during week 2 (cohorts 1d-3d only) • Change in LPI from screening to baseline • Change in LPI from baseline to weeks 12, 24, and 48
• Efficacy of SP-420 chelation on *s*-ferritin	• Number of subjects shifting *s*-ferritin category at week 48 (*s*-ferritin categories in ng/mL: ≤1000; >1000 to ≤2500; >2500)
• Efficacy of SP-420 on TIBC, TSAT, *s*-iron, and reticulocytes	• Change in TIBC, TSAT, *s*-iron, and reticulocytes from baseline to weeks 1, 2, 3, 4, 6, 8, 12, 16, 20, 24, 32, 40, and 48 • Change in TIBC, TSAT, and *s*-iron during week 2 (cohorts 1d-3d only)
• Efficacy of SP-420 on soluble transferrin receptor (sTfR), erythroferrone (ERFE), hepcidin, and malondialdehyde (MDA)	• Change in sTfR, ERFE, hepcidin, and MDA from baseline to weeks 4, 8, 12, 16, 20, 24, 32, 40, and 48 • Change in MDA from baseline to week 1 • Change in MDA from baseline to week 2 (cohorts 1d-3d, only)
• Efficacy of SP-420 on QoL	• Change in QoL from screening to baseline measured by SF-36 questionnaire • Change in QoL from baseline to weeks 24 and 48 measured by SF-36 questionnaire
• Treatment satisfaction with SP-420	• Treatment satisfaction with SP-420 at weeks 24 and 48 measured by FACIT-TS-G questionnaire

- Ferritin
- TSAT
- Reticul
- sTfR
- ERFE
- MDA
- LPI

Clinicaltrial.gov NCT05693909

Inclusion criteria

- **aged** ≥18 years at screening
- Very low, low, or intermediate risk MDS according to **IPSS-R**
- **RBC transfusions** of ≥2 units of RBCs within 16 weeks prior to screening
- Willing to discontinue any current **iron chelation** therapy 7 days (± 3 days) prior to the first dose of SP-420 and for the duration of the trial
- If no cardiac **T2*-MRI** is available within the past 6 months prior to screening:

***S*-ferritin >800 ng/mL** 2-4 weeks before the screening visit (in medical records) which is confirmed with a second measurement at screening†,and a history of transfusion of 10 to 100 units of RBCs

or

If a cardiac T2*-MRI is available within the past 6 months prior to screening: a cardiac T2*-MRI score of ≥25 msec

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Treatment with prohibited medication or procedures:

a) Disease modifying treatments for MDS (e.g. **hypomethylating agents**), or granulocyte colony-stimulating factor [**G-CSF**], or **thrombopoietin mimetics**, or **immunotherapy;**

b) chemotherapy, or radiation therapy for any malignancy within 30 days prior to baseline

c) Iron, aluminium-containing antacid therapies, **systemic corticosteroids chronic** use of high dose NSAIDs (as needed and low dose acetylsalicylic acid are allowed), **imetelstat**, **drugs with known renal toxicity**, drugs with known **QTc** prolongation, potent UGT enzyme inducers (e.g., rifampicin, phenytoin, phenobarbital, ritonavir), drugs with a narrow therapeutic index (such as methotrexate or coumarin anticoagulants [e.g.,warfarin]), within 7 days prior to baseline

d) Initiation of treatment with any **bisphosphonate** within 12 weeks prior to baseline.

e) Initiation of treatment with an erythropoiesis stimulating agents (ESAs) or luspatercept within 3 months prior to screening (both are allowed if initiated and the dose is stable ≥3 months prior to screening)

Exclusion Criteria MDS

- Therapy-related MDS or MDS with a known bone marrow fibrosis

- Any other clinically significant malignancy not remitted or in remission <5 years, prior to screening.
  Exceptions are the following diagnoses, which are allowed:
  localized basal cell skin cancer, squamous cell skin cancer, localized prostate cancer, cervical carcinoma *in situ*, ductal carcinoma *in situ*, or completely resected colonic polyps with carcinoma *in situ*

- Prior HSCT or organ transplantation at any time, or planned HSCT or organ transplantation during the trial

- Platelet count <50×109/L at screening, absolute neutrophil count <0.8×109/L at screening

- **Hypertransfused defined as more than 6 units/month on average for the last 6 months prior to screening**

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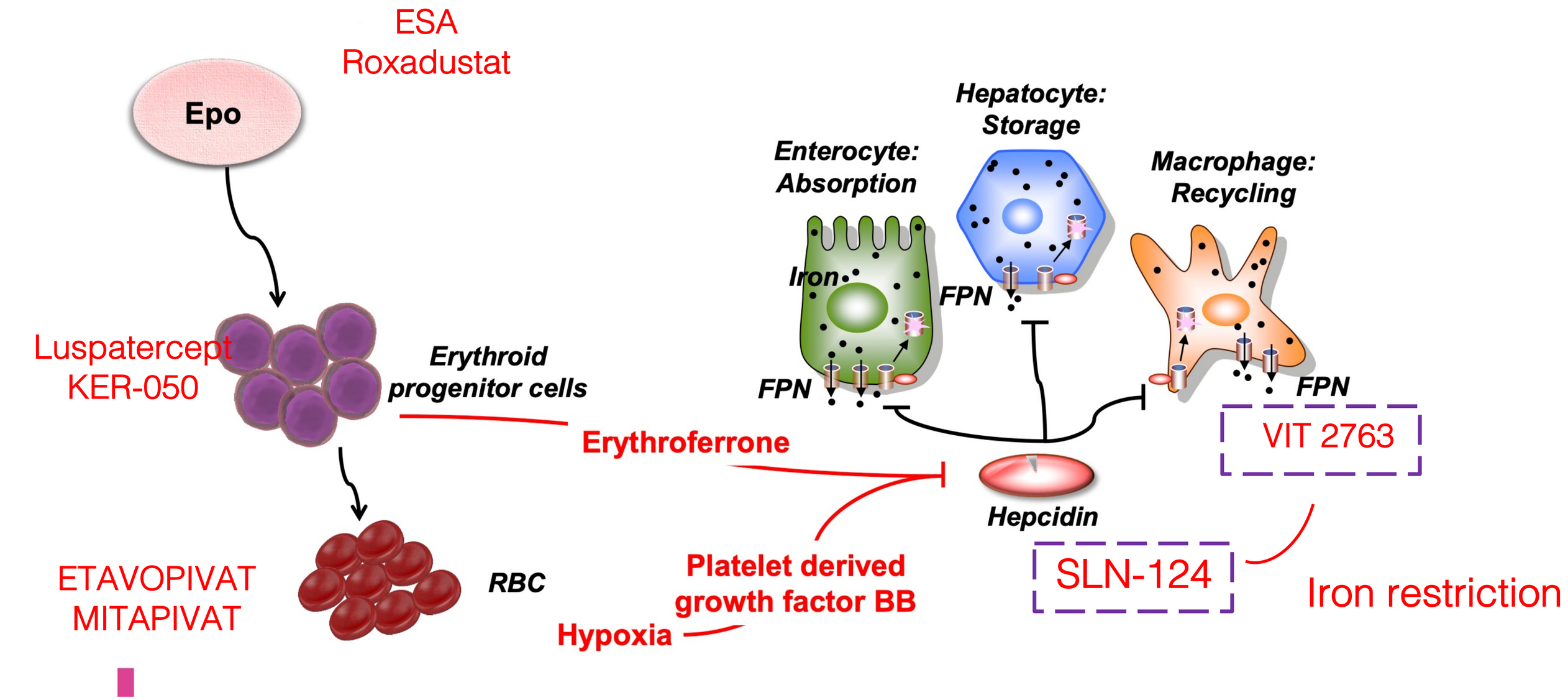
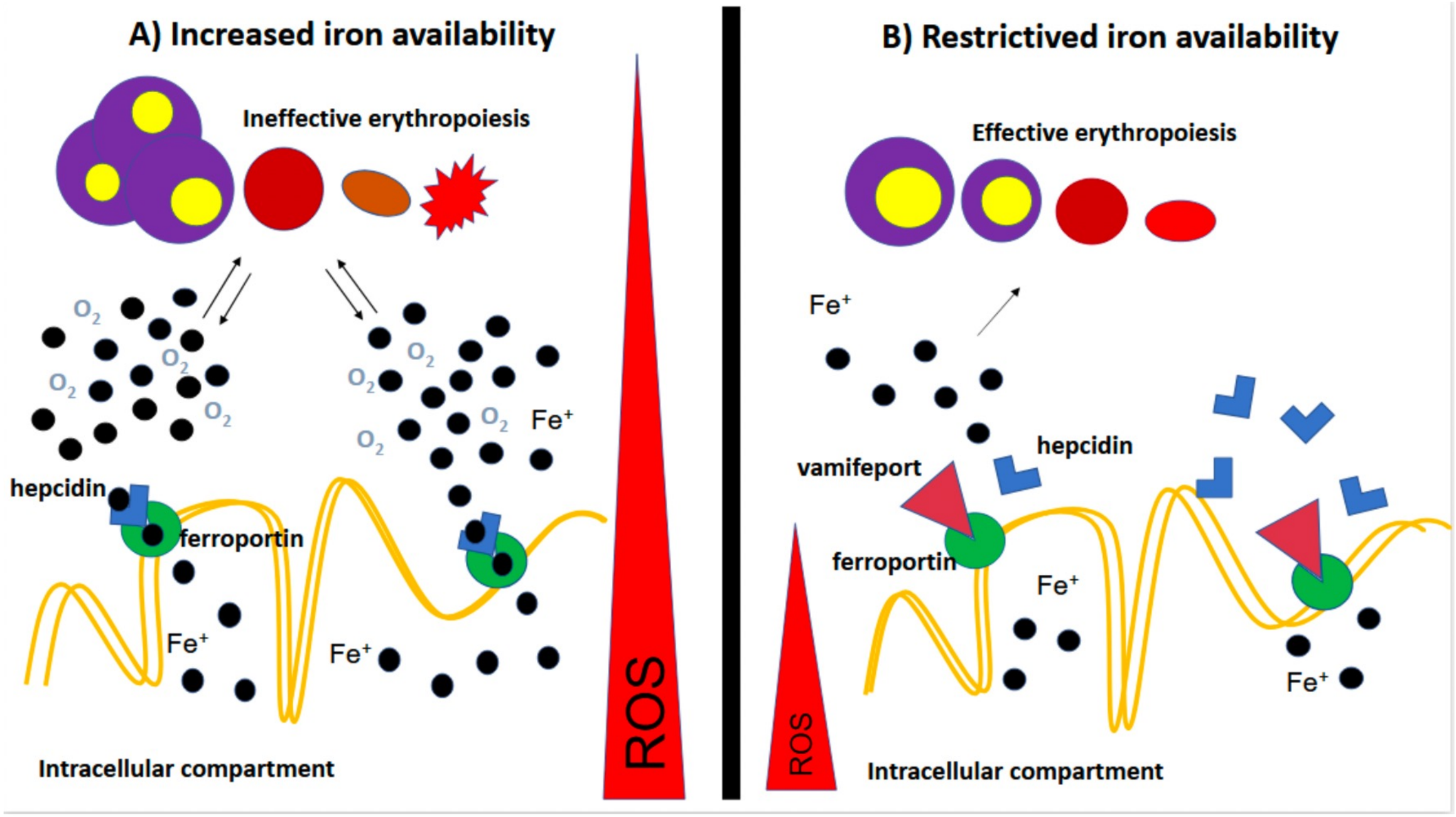
Are drugs acting on iron restriction totally diferent from iron chelators?

FUTURE DRUGS WICH HAVE AS TARGET ERYTROPOIESIS



Modified by Prof Stefano Rivella



Pilo, F.; Angelucci, E. Vamifeport: Monography of the First Oral Ferroportin Inhibitor. *J. Clin. Med.***2024**,*13*,5524.

Role of Iron in the Pathophysiology of Myelodysplastic Syndrome (MDS) in a Preclinical Model

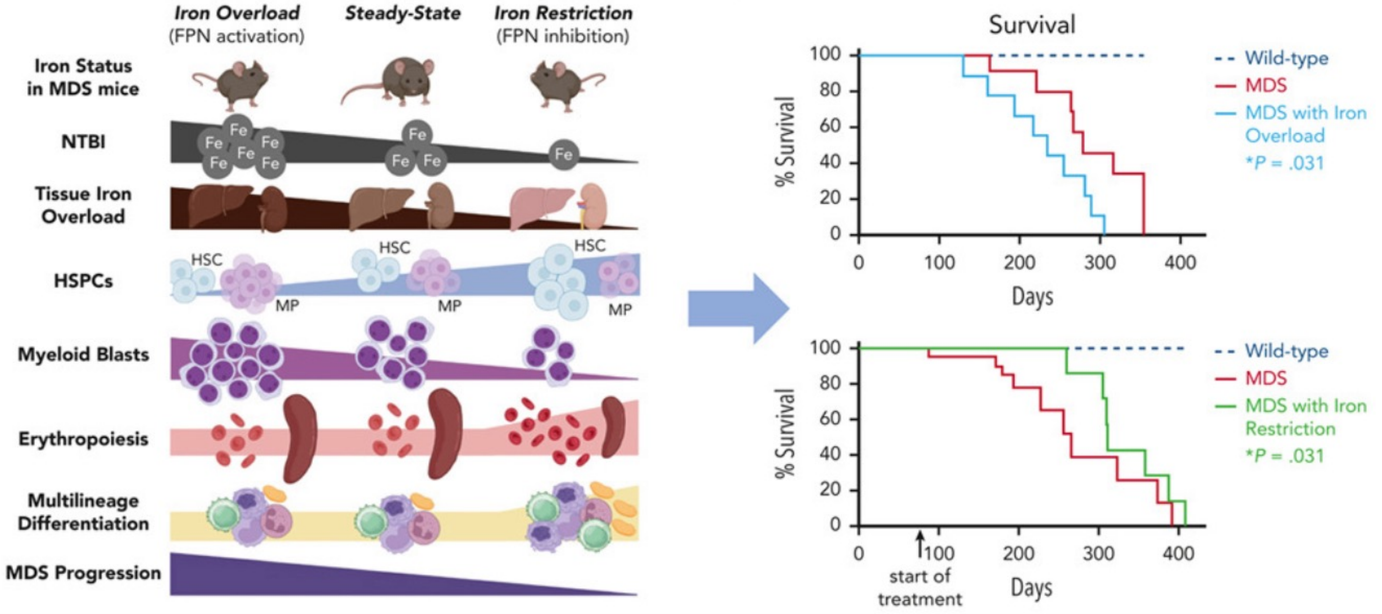
Context of Research

Although iron overload is a common feature of MDS, it remains unclear whether iron excess contributes to disease pathophysiology

Aim of This Study

In a mouse model, we examined the influence of iron overload and restriction on MDS. The latter was achieved through genetic or pharmacologic manipulation of the iron exporter ferroportin (FPN)

Main Findings



Conclusions: In MDS mice, iron restriction improves erythropoiesis, preserves the stem cell pool, limits myeloid expansion, and delays leukemic transformation, providing survival benefit. Combining iron restriction and erythroid maturation drugs results in superior improvement of erythropoiesis and disease-modifying potential in MDS mice.

*Antypiuk et al. DOI: 10.1182/**blood**.2024026135*

blood Visual Abstract

Thanks for your very kind attention

MDS & leukemia team
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