MF Anemia Day

May 9, 2025

disc medicine

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Bitopertin, DISC-0974, and DISC-3405 are investigational agents and are not approved for use as therapies in any jurisdiction worldwide

Agenda

01

Introduction to Disc Medicine

John Quisel, J.D., PhD, Chief Executive Officer

02

KOL Discussion

- **Anemia of Myelofibrosis Disease Overview & Unmet Need**
  Dr. Aaron Gerds, M.D., M.S. – The Cleveland Clinic Taussig Cancer Institute
- **Current & Emerging Treatment Landscape**
  Dr. Prithviraj Bose, M.D. – The University of Texas MD Anderson Cancer Center

03

DISC-0974 in Anemia of Myelofibrosis

Will Savage, M.D., PhD, Chief Medical Officer

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Anemia of Myelofibrosis Market Opportunity

Pamela Stephenson, Chief Commercial Officer

05

Closing Remarks

John Quisel, J.D., PhD, Chief Executive Officer

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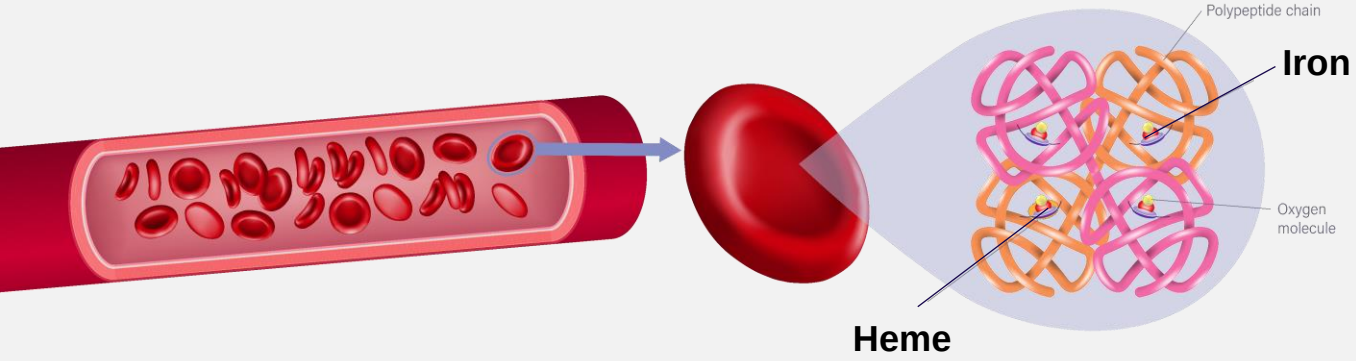
Q&A Session

Targeting Fundamental Pathways of Red Blood Cell Biology using Validated Mechanisms



Iron and heme metabolism are critical pathways in hematology with genetically-validated targets

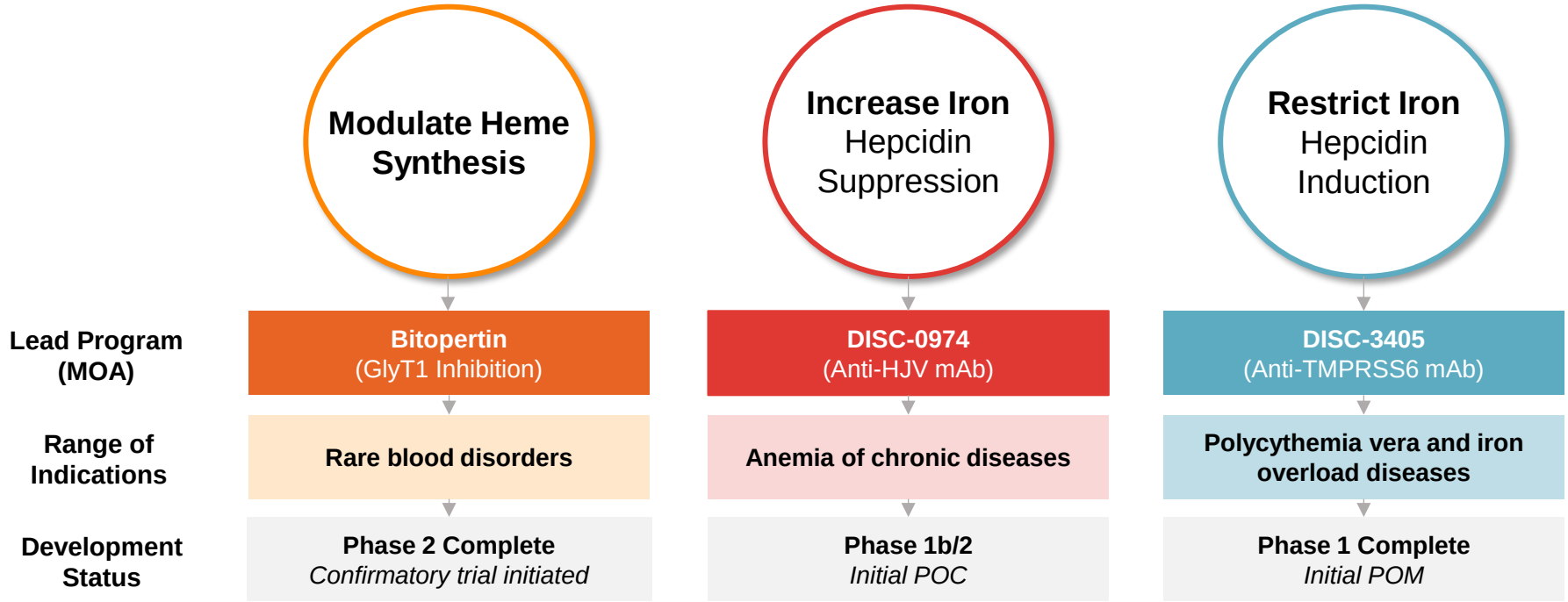
Key points of intervention across a wide range of diseases

Spectrum of Hematologic Diseases Addressable by Disc Portfolio

Severe Rare (000s)			*Moderate Prevalence (100K+)*						*Widely Prevalent (MMs)*
Diamond-Blackfan Anemia	**Erythropoietic Porphyrias**	Beta-Thalassemia	**Anemia of Myelofibrosis**	**Myelodysplastic Syndromes**	Sickle Cell Disease	Polycythemia Vera	Hereditary Hemochromatosis	IBD Anemia	**CKD Anemia**

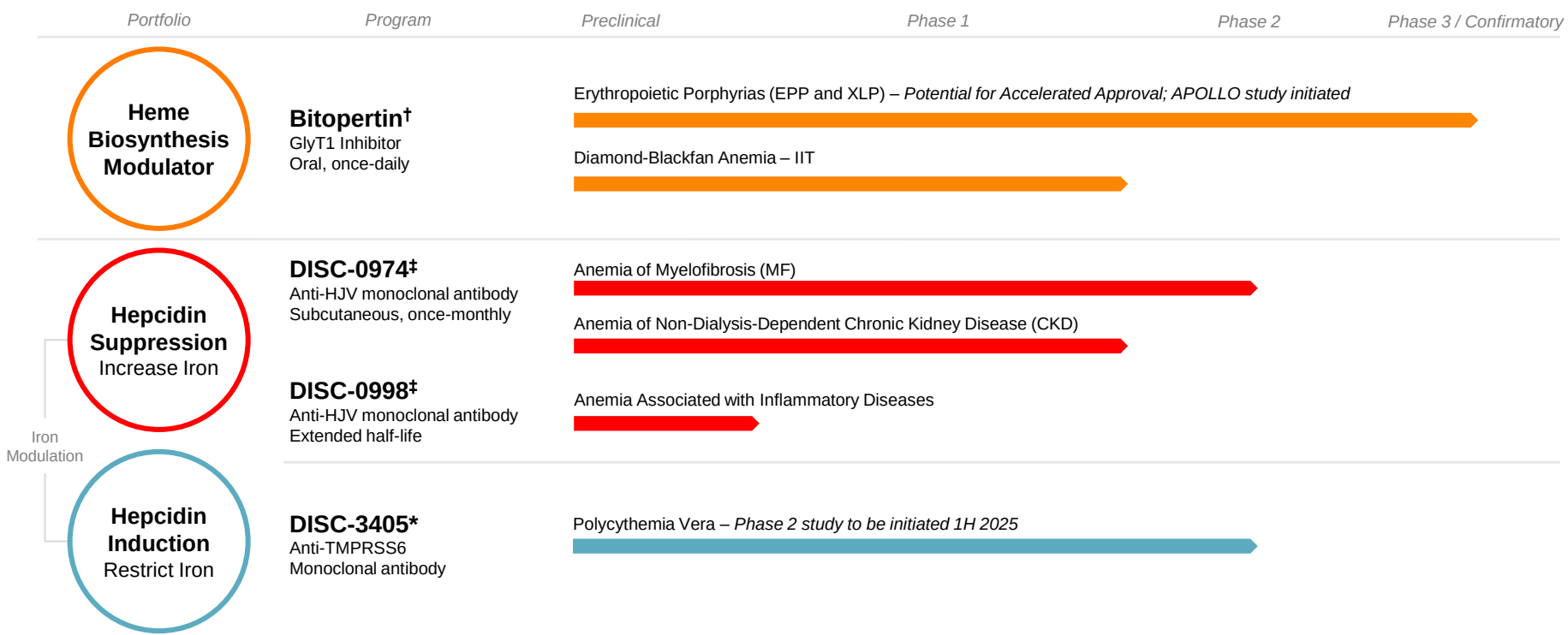
Bold = ongoing Disc trial

By Targeting Heme and Iron, Disc's Portfolio Can Address a Wide Range of Hematologic Disorders



Disc's Hematology-Focused Pipeline

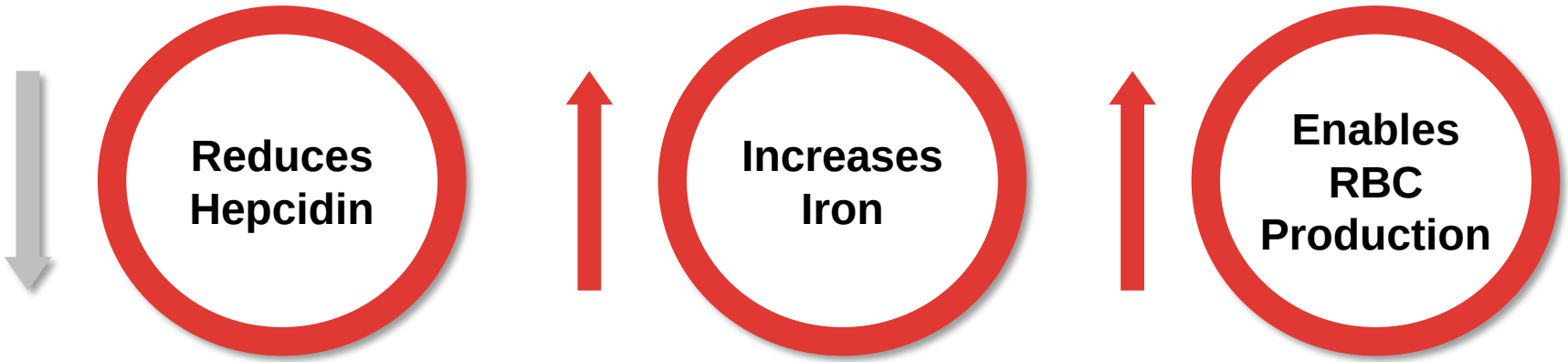
Multiple programs in development with pipeline-in-a-product potential



† Bitopertin in-licensed from Roche; ‡ DISC-0974 and DISC-0998 in-licensed from AbbVie; *DISC-3405 in-licensed from Mabwell (formerly MWTX-003)

DISC-0974: Novel Anti-HJV mAb to Suppress Hepcidin

Designed to enhance iron availability to address a wide range of hematologic disorders



Inhibits endogenous production of hepcidin

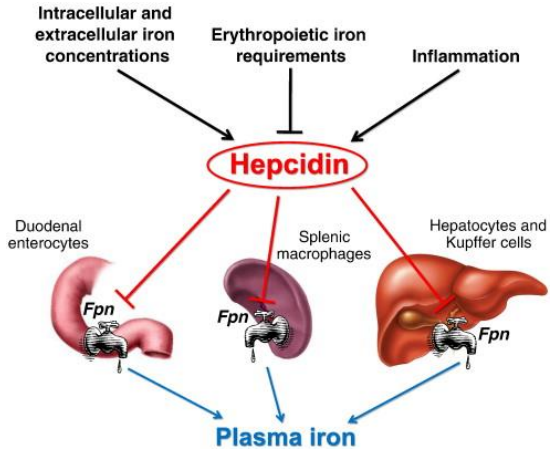
Releases iron stores
Enables GI absorption

Potential to treat wide range of anemias

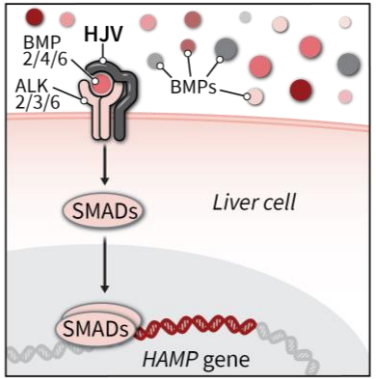
Targeting Hemojuvelin (HJV) to Suppress Hepcidin

Critical and specific target for hepcidin expression

Hepcidin: “Master Regulator” of Iron



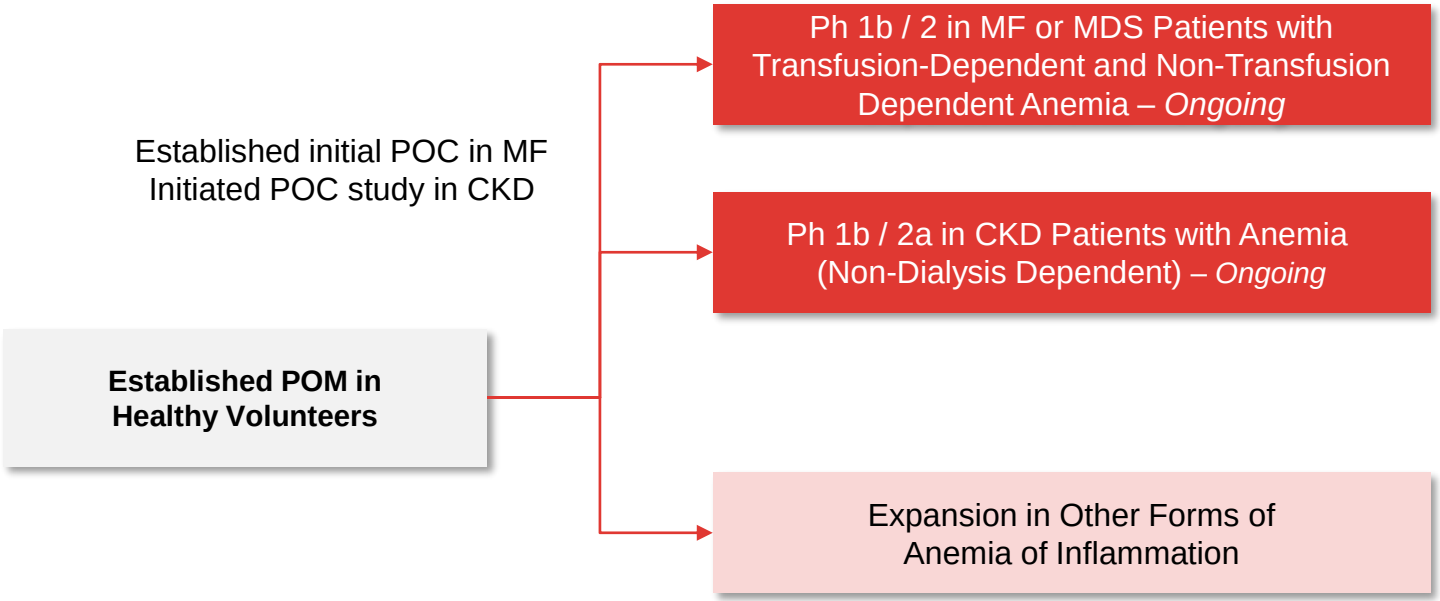
Inhibiting Hemojuvelin (HJV) Prevents Hepcidin Expression and Increases Iron



- **Genetic validation** in patients with Juvenile Hemochromatosis (lower hepcidin and elevated iron levels)
  - Loss-of-function mutations in HJV are phenotypically indistinguishable from mutations in *HAMP* (hepcidin) gene
- **Functionally specific** to hepcidin / iron
- **Tissue specific** expression primarily in the liver

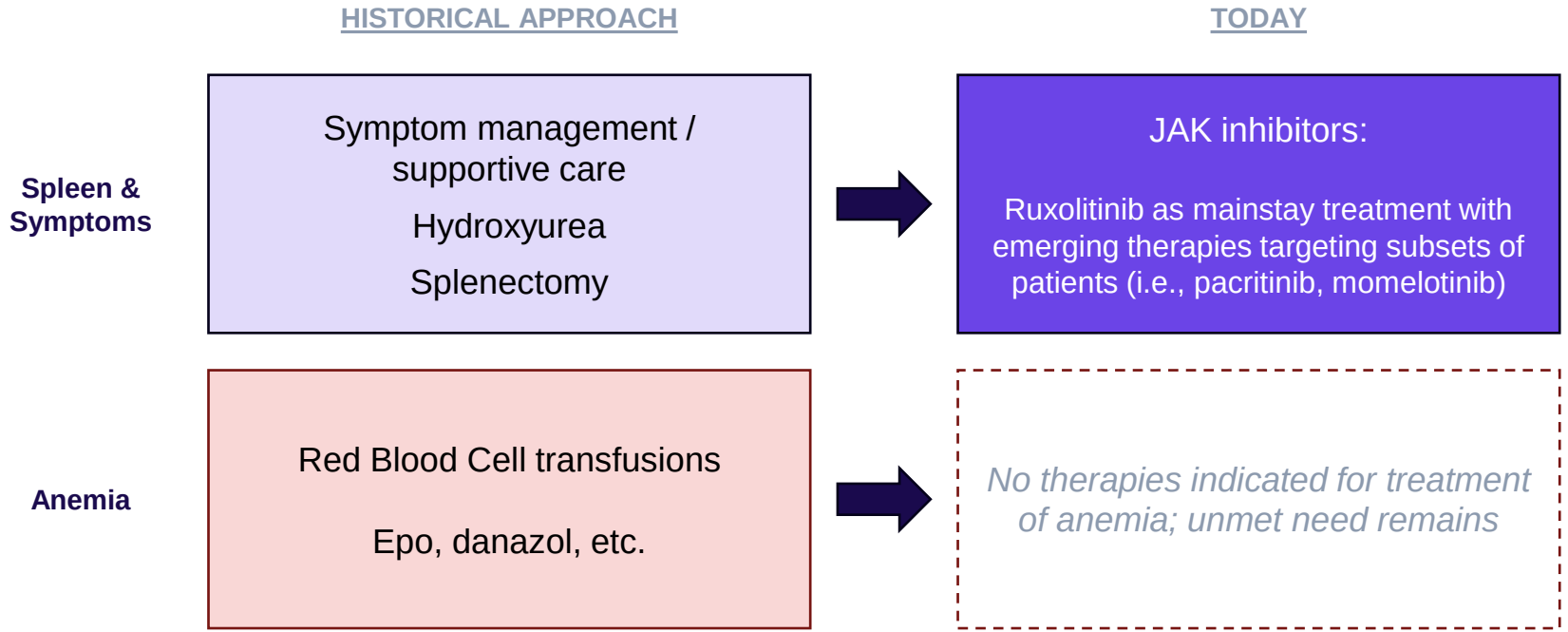
Sources: Finberg et al, (2010) Blood; Zhang et al, (2010) J Biol Chem

DISC-0974 Development Strategy



Assessing safety, PK, hepcidin, iron, hemoglobin and transfusion burden (MF and MDS) and others

JAK inhibitors changed the MF treatment paradigm, but anemia remains a large unmet need



Today's Objectives

- Provide KOL overview of pathogenesis and disease burden of MF anemia
- Highlight KOL perspective on current MF treatment landscape and emerging anemia therapies in development
- Review clinical data and development status for DISC-0974 in MF anemia
- Discuss DISC-0974 market opportunity in MF anemia

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05 **Closing Remarks**
John Quisel, J.D., PhD, Chief Executive Officer

06 **Q&A Session**

Anemia of Myelofibrosis:
Disease Overview & Unmet Need

Dr. Aaron Gerds, M.D., M.S.
The Cleveland Clinic
Cleveland, OH

Hematologist-Oncologist and Associate Professor of Medicine, Cleveland Clinic Lerner College of Medicine of Case Western Reserve University School of Medicine

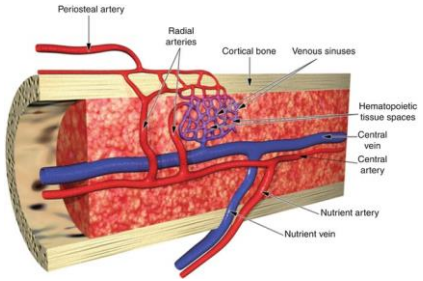
Deputy Director for Clinical Research, Cleveland Clinic Taussig Cancer Institute and Medical Director, Case Comprehensive Cancer Center Clinical Research Office

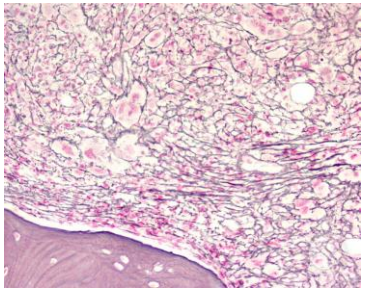
Principal investigator in various clinical trials for treatment of myeloproliferative neoplasms (MPNs)

Disclosures:

- *Consultancy:* AbbVie, Bristol Myers Squibb, Disc Medicine, GlaxoSmithKline, Kartos Therapeutics, MorphoSys, Sierra Oncology, Telios Pharma
- *Advisory Boards:* AbbVie, Bristol Myers Squibb, GlaxoSmithKline, Kartos Therapeutics, MorphoSys, Sierra Oncology, Telios Pharma

Myelofibrosis is a disease of abnormal proliferation of hematopoietic cells in the bone marrow





*Driver mutation causes **uncontrolled proliferation** of hematopoietic cells in the bone marrow:*

- **Inflammatory environment:** Excessive hematocytes release cytokines, leading to inflammation and development of fibrosis
- **Ineffective erythropoiesis:** Fibrosis in marrow prevents production of mature blood cells, leading to cytopenias
- **Extramedullary hematopoiesis:** Formation of blood cells in the liver and spleen causes tissue enlargement and dysfunction

Constitutional symptoms, spleen enlargement, and **anemia**

Myelofibrosis is a rare, chronic blood cancer with significant morbidity and mortality

25,000
US Prevalence

65
Median age at diagnosis

~50%
5-year survival rate

~12%
Progression to AML

THREE THERAPEUTIC FOCUS AREAS:

1 Constitutional Symptoms

Including:

- Fatigue
- Night sweats
- Poor concentration
- Bone Pain
- Itching
- Fever
- Weight Loss

2 Splenomegaly

- Caused by extra-medullary hematopoiesis
- Associated with complications like portal hypertension and cytopenia

3 Anemia

- Multi-factor pathogenesis
- Often results in reduced physical functioning and dependence on RBC transfusions

Anemia is a key prognostic factor used to classify MF patients into risk groups

Dynamic International Prognostic Scoring System (DIPSS) Criteria:

- Age older than 65 years – *1 Point*
- **Hemoglobin lower than 10 g/dL – *2 Points***
- Leukocytes higher than 25 x 10^9 / L – *1 Point*
- Circulating blasts ≥ 1% – *1 Point*
- Constitutional symptoms – *1 Point*

Score	Risk Group	Median Survival
0	Low	Not reached
1-2	Intermediate-1	~14 years
3-4	Intermediate-2	~4 years
5-6	High	~1.5 years

Mutation-Enhanced International Prognostic Scoring System (MIPSS70) Criteria:

Clinical risk factors:

Hemoglobin, leukocytes, platelets, circulating blasts, bone marrow fibrosis grade, constitutional symptoms

Age removed

+

Genetic risk factors:

Presence of high-molecular risk mutation(s)

Increasing severity of anemia predicts worse prognosis

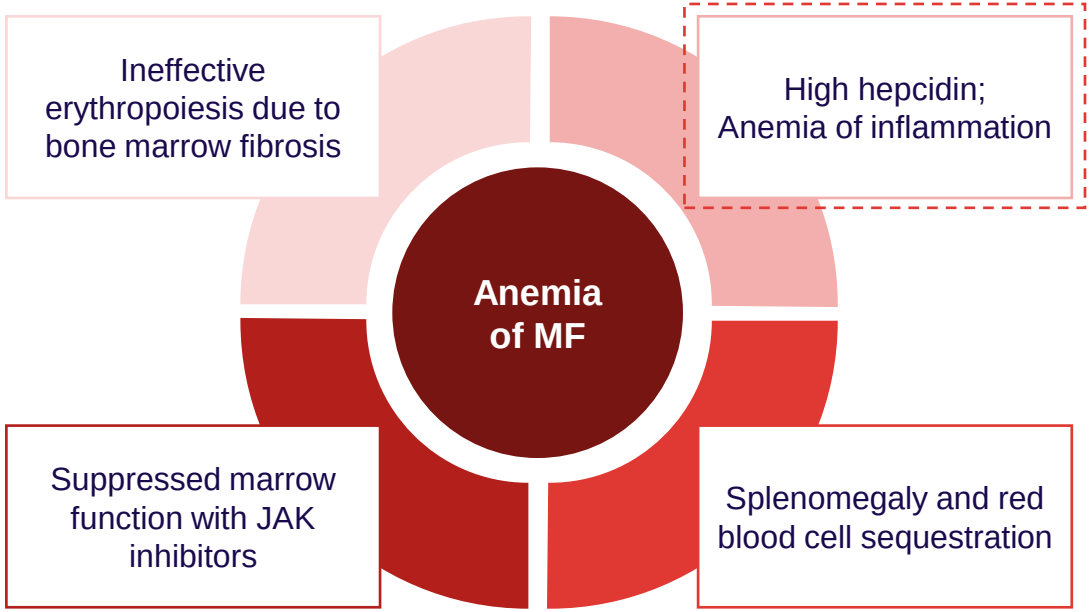
Source: Passamonti et al., Blood 2010; Guglielmelli et al., J. Clin. Oncol. 2017

Anemia is a prevalent and severe manifestation of myelofibrosis, with multi-factorial pathogenesis

25,000
US MF Prevalence

~87%
of MF patients have anemia

~22,000
US MF Anemia Prevalence



Source: Barraco et al., Blood Cancer J. 2016

Hepcidin levels are elevated in myelofibrosis and associated with severity of anemia and transfusion burden

Hepcidin levels are

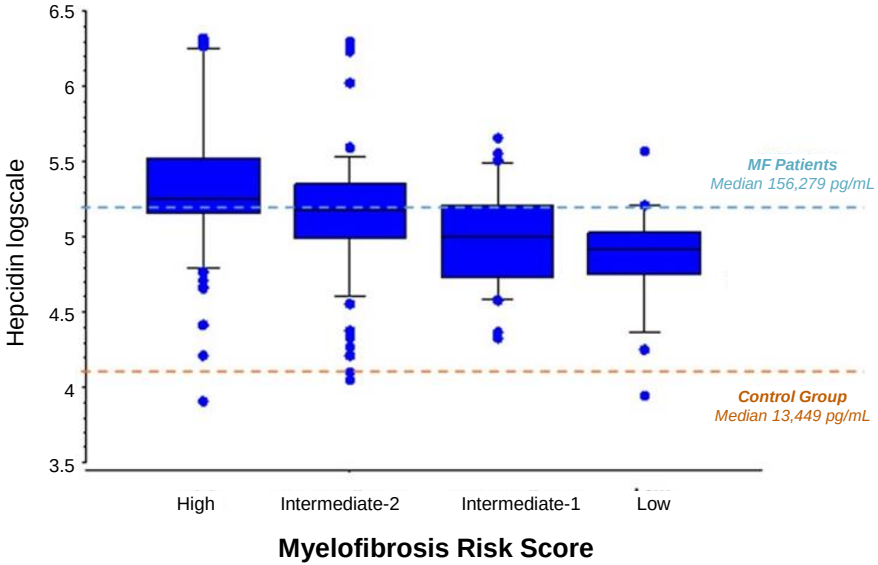
12x higher

in MF patients vs. control
(p<0.0001)

Increased hepcidin levels in MF patients associated with:

- Higher ferritin and **lower hemoglobin** levels
- **Transfusion** requirement
- Higher DIPSS+ **risk** category

Distribution of circulating hepcidin levels in MF patients stratified by DIPSS+ risk category



Source: Pardanani et al., Am. J. Hematol. 2013

Majority of myelofibrosis patients develop anemia, and anemia worsens over the course of disease

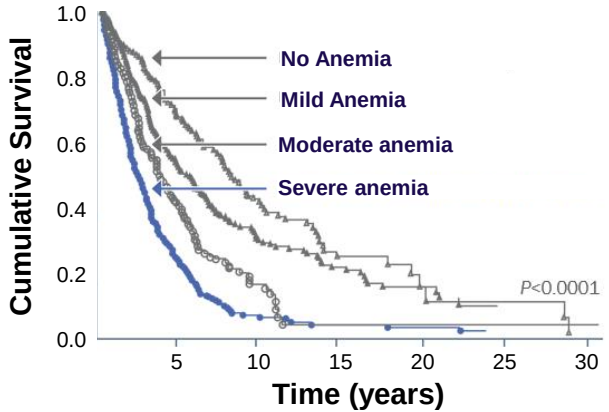
% Patients	*At diagnosis*	*Within 1 year of diagnosis*	*Full course of disease*
Hgb < 10 g/dL	**~40%**	**~60%**	***Nearly all***
Transfusion requiring	**~25%**	**~45%**	***Nearly all***

- **Disease-related:** worsening bone marrow fibrosis, inflammatory cytokine signaling leading to impaired erythroid differentiation, and extramedullary sequestration drive anemia
- **Treatment-related:** JAK inhibitors, the mainstay treatment for myelofibrosis, are myelosuppressive and can contribute to anemia

Source: Tefferi et al., Mayo Clin. Proc. 2012

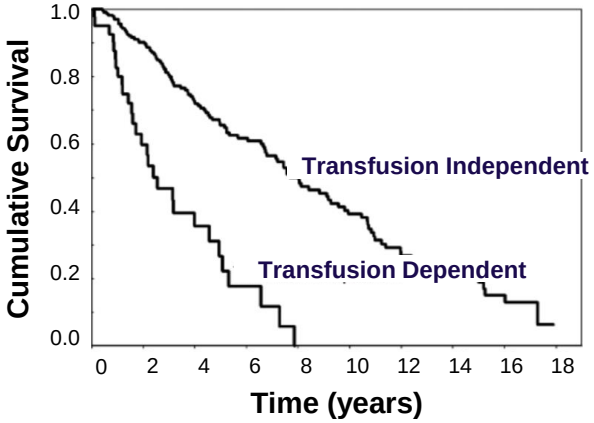
Severity of anemia and transfusion dependency are associated with worse disease prognosis and survival

SEVERITY OF ANEMIA
Associated with reduced survival



Median Survival – All Risk Groups	
No anemia	95 months
Mild anemia	59 months
Moderate anemia	41 months
Severe anemia	25 months

TRANSFUSION DEPENDENCY
Associated with reduced survival

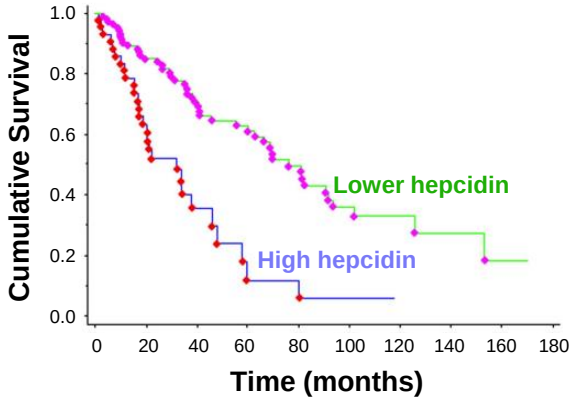


Median Survival – All Risk Groups	
Transfusion Dependent	31 months
Transfusion Independent	96 months

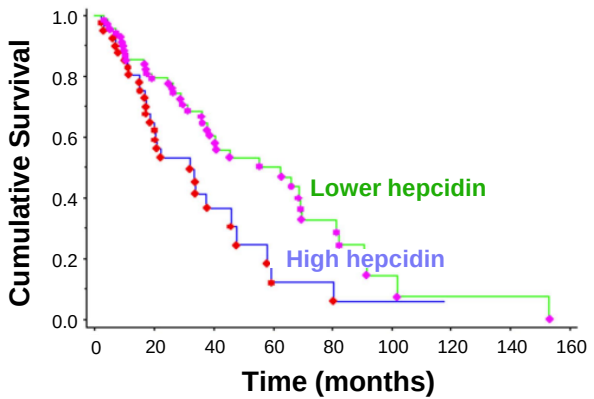
Source: Nicolosi et al., Leukemia 2018; Elena et al., Haematologica 2010

Hepcidin and ferritin levels are associated with worse prognosis and survival independent of other risk factors

INCREASED HEPCIDIN LEVELS
Associated with reduced survival



Median Survival – All Risk Groups	
High hepcidin and ferritin	30 months
Lower hepcidin and ferritin	76 months



Median Survival – Int-2 and High-Risk	
High hepcidin and ferritin	32 months
Lower hepcidin and ferritin	57 months

Source: Pardanani et al., Am. J. Hematol. 2013

Anemia symptoms worsen quality of life, regardless of transfusion status

Physical Consequences

- Increased fatigue
- Worse physical functioning
- Limited ability to perform roles

Psychosocial Impact

- Worse mental health
- Lower social functioning
- Reduced satisfaction with emotional role

Healthcare Utilization

- >3x more hospital visits*
- >3x more ER visits*
- >9x higher healthcare costs

Source: Gerds et al., ASH 2024; Mesa et al., ASCO 2023; Palmer et al., SOHO 2024
*for Transfusion Dependent (TD) vs. Transfusion Independent (TI) patients

Summary: Disease burden and unmet needs in anemia of myelofibrosis

- Anemia is a prevalent, severe, and progressive manifestation of MF
- Inflammation leading to elevated hepcidin and iron dysregulation is a key driver
- JAK inhibitors help manage symptoms and spleen size but can worsen anemia
- Anemia and transfusions are associated with poor prognosis and survival in MF
- Anemia symptoms significantly impact healthcare utilization and quality of life

Anemia of Myelofibrosis:
Current & Emerging Treatment Landscape

Dr. Prithviraj Bose, M.D.
The University of Texas MD Anderson Cancer Center
Houston, TX

Professor, Department of Leukemia, Division of Cancer Medicine, The University of Texas MD Anderson Cancer Center – focus on myeloproliferative neoplasms (MPNs)

Involved in clinical trial design for patients with MPNs and leading multiple clinical trials in myelofibrosis and other MPNs

Disclosures:

- *Research support:* Incyte, Bristol Myers Squibb (BMS), CTI BioPharma, Morphosys, Kartos, Telios, Sumitomo, Karyopharm, Disc Medicine, Ionis, Blueprint Medicines, Cogent, Geron, Janssen, Ajax
- *Honoraria & Consulting Fees:* Incyte, BMS, GlaxoSmithKline, CTI BioPharma, AbbVie, Morphosys, Sumitomo, Karyopharm, Disc Medicine, Ionis, Pharma Essentia, Jubilant, Morphic, Novartis, Blueprint Medicines, Geron, Cogent, Keros, Ono, Raythera

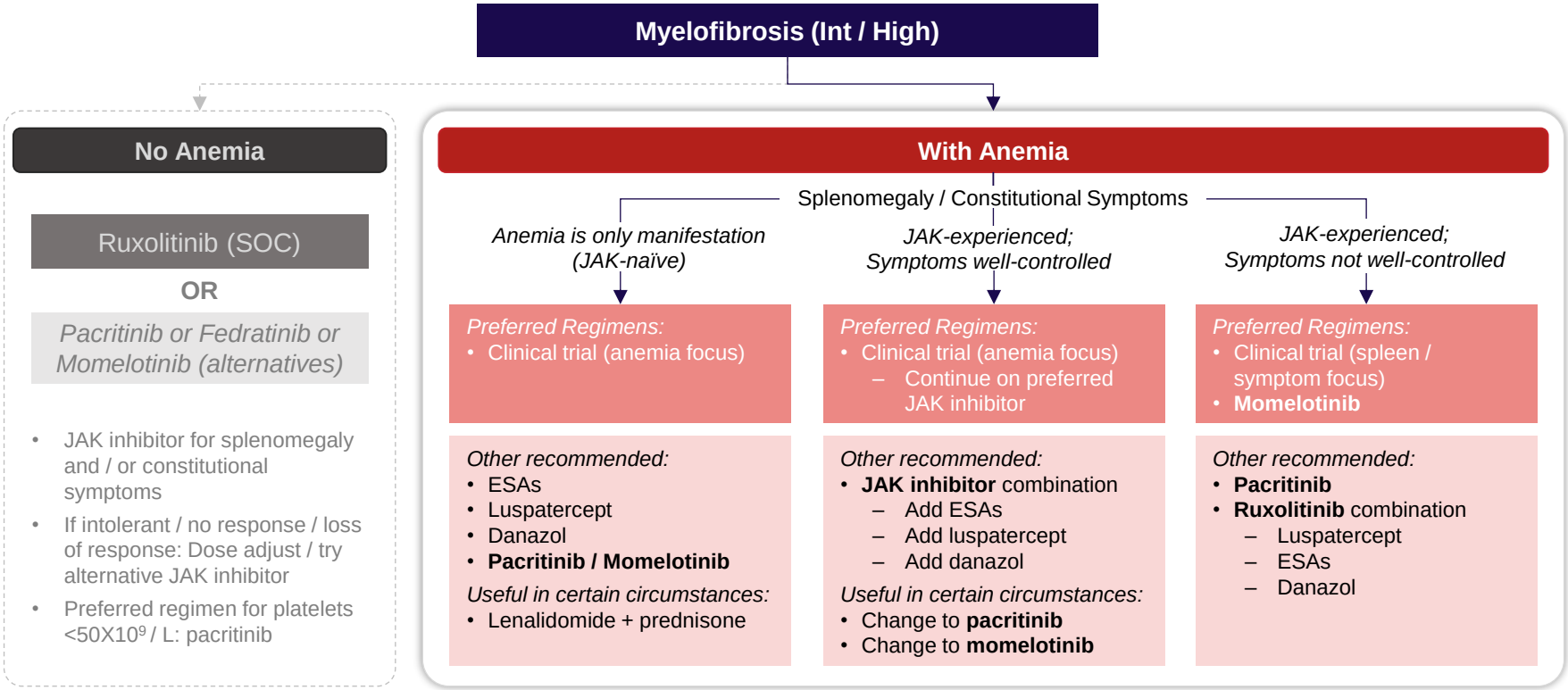
Goals of myelofibrosis treatment include improving symptoms, reducing spleen size, and managing anemia

THREE THERAPEUTIC FOCUS AREAS:

	1 Constitutional Symptoms	2 Splenomegaly	3 Anemia
Clinical Goal	**TSS50:** % patients achieving 50% decrease in Total Symptom Score (MPN-SAF-TSS) at 24 weeks	**SVR35:** % of patients achieving 35% spleen volume reduction (SVR) at 24 weeks	**No FDA-approved treatments**; Anemia response defined as achievement of hemoglobin increase or transfusion independence (TD patients)
Current Treatment Landscape	**JAK inhibitors** Ruxolitinib, fedratinib, pacritinib, momelotinib*		Off label: EPO, danazol, IMiDs, glucocorticoids, iron chelation
Select Clinical Development Pipeline	**BET** Pelabresib INCB057643 **Type II JAK** AJ1-11095 **Telomerase** Imetelstat **CALR mut** INCA033989 **JAK2^{V617F} mut** INCB160058 **MDM2** Navtemadlin **XPO1** Selinexor		**Hepcidin suppression** DISC-0974 (Ph 2) **Erythroid Maturation Agents** Luspatercept (Ph3) – TD patients only Elritercept (Ph 2)

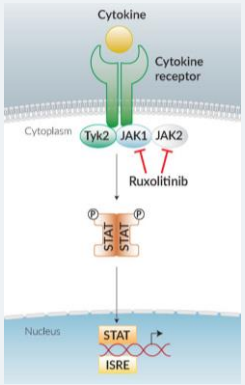
*Indicated for treatment of MF in patients with anemia

MF Anemia Treatment Algorithm



Based on National Comprehensive Cancer Network (NCCN) treatment guidelines version 1.2025

Ruxolitinib is the standard of care for treating spleen and symptoms, but can worsen anemia



JAK inhibitor MOA

- Interrupting overactive JAK pathway reduces inflammation, controls symptoms, and potentially slows progression
- Myelosuppressive activity contributes to anemia

46%
TSS50

42%
SVR35

~55%
MF Patients Treated with Rux

Anemia can limit optimal ruxolitinib treatment

96%
of ruxolitinib-treated patients experience anemia

>50%
on suboptimal dose of ruxolitinib

~50%
discontinue ruxolitinib within 3 years

Anemia is the leading cause of ruxolitinib discontinuation

Sources: Verstovsek et al., NEJM 2012; Verstovsek et al., Haematologica 2015; Harrison et al., Leukemia 2016; Koschmieder et al., Annals of Hemotology 2023; Rossetti et al., Blood 2023; Kuykendall et al., Annals of Hemotology 2018

Alternative JAK inhibitors have emerged to address patient subpopulations, but gaps remain

- Ruxolitinib has the highest efficacy for spleen volume and symptom reduction but worsens anemia
- Alternative JAK inhibitors have been developed to address MF in patient populations with cytopenias
- Tradeoff between spleen / symptom control and anemia toxicity, with no regimen adequately addressing anemia

Agent*	*Indication*	*TSS50*	*SVR35*	*Anemia Response*
Ruxolitinib	Int- or High-Risk MF	**46%**	**42%**	*Transfusion independence:*[a] **-21% vs BL**
Fedratinib	Int-2 or High-Risk MF	**36%**	**36%**	**--**
Pacritinib	Int- or High-Risk MF Platelets <5x10^9 / L	**7-32%**	**9-22%**	*Transfusion independence:*[b] **24%**
Momelotinib	Int- or High-Risk MF with anemia	**25-28%** *Inferior to rux in H2H*	**23-27%** *Noninferior to rux in H2H*	*Transfusion independence:*[a] **-2% to +17% vs BL**

*Direct comparison of results between studies is difficult due to differences in patient populations and efficacy assessments; Response definitions: [a]TI rate defined as no transfusion or Hgb <8 g/dL in the prior 12 weeks (including baseline TD and NTD patients); anemia response shown as change in TI rate from baseline to week 24; [b]TI rate defined as no transfusions and no hemoglobin <8 g/dL over any 12-week interval among patients who were non-TI at baseline and non-TI was defined as any RBC transfusion over the 12 weeks before first dose or baseline hemoglobin of <8 g/dL; BL = baseline

Source: Verstovsek et al., NEJM 2012; Pardanani et al., JAMA Oncol. 2015; Mascarenhas et al., JAMA Oncology 2018; Gerds et al., Blood Advances 2020; Oh et al., Blood Advances 2023; Verstovsek at al., HemaSphere 2022; Mesa et al., JCO 2017; Harrison et al., Lancet 2018

Anemia in myelofibrosis is difficult to treat with available therapies

- Treatment goals for anemia include reducing/eliminating transfusions, increasing hemoglobin, and improving symptoms
- There is no FDA approved therapy indicated for treatment of anemia in myelofibrosis and off-label treatment strategies are limited by eligibility, response rates, and tolerability
- The strong link between anemia and poor QoL / disease prognosis and the limited number of treatment options means there is still a significant unmet need in this patient population

Agent*	*Response Rate†*	*Additional Details*
ESAs	**~20-30%**[a,b]	• Efficacy limited to patients with low epo; limited durability of response • Risk of vascular complications and potential to exacerbate splenomegaly
Androgens (Danazol)	**~5-30%**[c,d] **	• Limited response rate (~5%) in RCT setting • Hepatotoxicity and liver tumors, prostate cancer
Glucocorticoids (Prednisone)	**~40%**[c]	• Not commonly used due to minimal efficacy data and unfavorable safety • Side effects include hyperglycemia, infections, psychiatric disturbances
EMAs (Luspatercept)	**~20-40%**[e] **	• Approved in anemia of MDS with some off-label use in MF • Clinical development ongoing in TD MF patients on JAK inhibitors

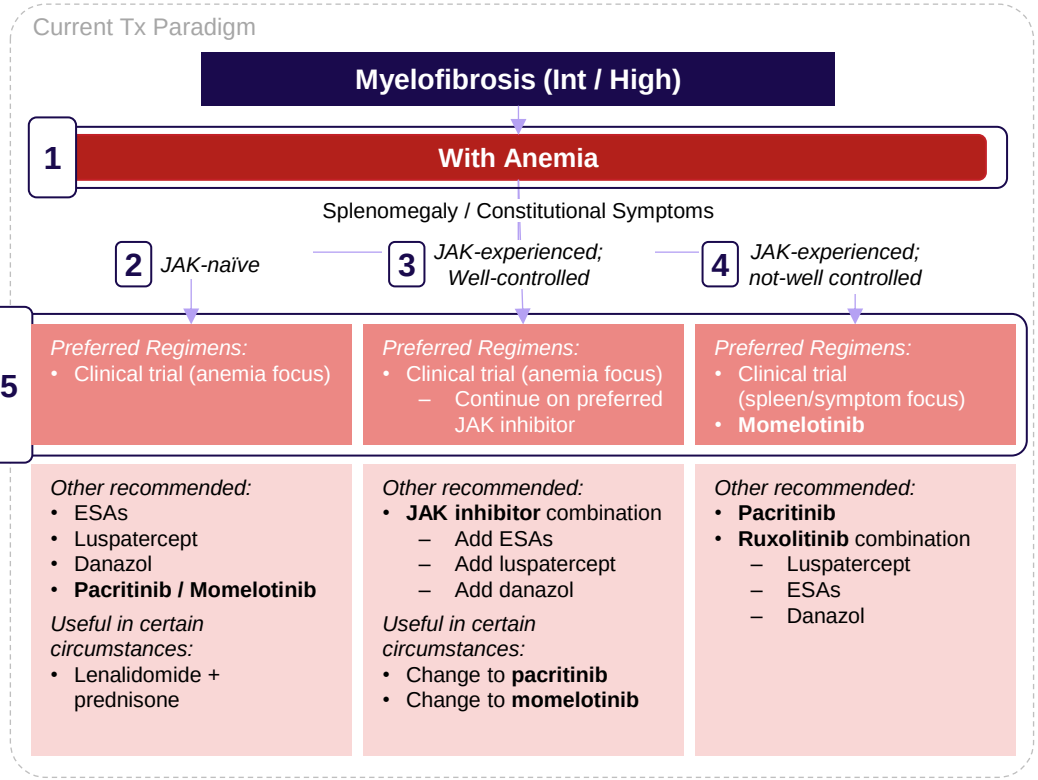
*Direct comparison of results between studies is difficult due to differences in patient populations and efficacy assessments; **Includes data from Randomized Controlled Trial (RCT) setting; †Response definitions very across studies: [a]≥ 2.0 g/dl increase in Hb level or becoming TI over a minimum of a 1-month period; [b]Hgb normalization (≥ 12 g/dl); [c]Revised IWG-MRT criteria: Transfusion cessation in TD patients or Hb increase > 2 g/dl in TI patients, both lasting for a minimum of 12 weeks; [d]TI rate defined as no transfusion or Hgb <8 g/dL in the prior 12 weeks (including baseline TD and NTD patients); anemia response shown as change in TI rate from baseline to week 24; [e]TI over 12 weeks within first 24 weeks for patients with baseline transfusion burden of 2-12 RBC units / week.

Source: Huang and Tefferi, Eur. J. Haematol. 2009; Cervantes et al., Br. J. Haematol. 2006; Cervantes et al, Ann. Hematol. 2015; Verstovsek at al., HemaSphere 2022; Hernandez-Boluda et al., Leuk. Lymphoma 2016; Gerds et al., Blood Advances 2024

Significant need and broad potential utility for anemia-targeted therapy

Key Needs for Anemia Therapy

1. Works across anemia severity levels
2. Works as a monotherapy
3. Works with any JAK inhibitor
4. Supports optimization of JAK inhibitor regimen
5. Superior response rates vs. current off-label anemia therapies



Potential key role for emerging therapies for treatment of anemia of MF

		HEPCIDIN SUPPRESSION				ERYTHROID MATURATION							
Asset		**DISC-0974**				**Luspatercept**				**Elritercept**			
MOA		**Hemojuvelin** Reduces hepcidin to mobilize iron and increase RBC production				**TGF-β** Blocks TGF-β signaling in erythroid progenitor cells thereby promoting erythropoiesis							
ROA		SC				SC				SC			
Development Status		Ph 2				Ph 3				Ph 2			
Target Patient Population		✓TD	✓NTD	✓+JAK	✓-JAK	✓TD	✗NTD	✓+JAK	✗-JAK	✓TD	✓NTD	✓+JAK	✓-JAK
Key Data*	**Transfusions**	TD patients achieving TI[a]: **40-80%** (n=10)				TD patients achieving TI[b]: **10%** monotherapy (n=21) **26%** Rux combination (n=38)				TD patients achieving TI[c]: **24%** (n=41)			
	Hemoglobin	NTD patients mean Hgb increase ≥1.5 g/dL over 12 wks: **50%** (n=22)				NTD patients mean Hgb increase ≥1.5 g/dL over 12 wks: **23%** monotherapy (n=22) **43%** Rux combination (n=14)				NTD6[d] patients mean Hgb increase ≥1.5 g/dL over 12 wks: **21%** (n=29)			

*Direct comparison of results between studies is difficult due to differences in patient populations and efficacy assessments; Response / cohort definitions: [a]TI over 12 weeks for patients with high baseline transfusion burden (3-13 units / 12 weeks) and 16 weeks for patients with low baseline transfusion burden (1-2 units / 12 weeks); [b]TI over 12 weeks within first 24 weeks for patients with baseline transfusion burden of 2-12 RBC units / week; [c]TI over 12 weeks within first 24 weeks for patients with baseline transfusion burden ≥3 units / 12 weeks; [d]NTD6=Patients receiving <6 RBC units / 12 weeks at baseline

Source: Disc Medicine, ASH 2024; Gerds et al., Blood Advances 2024; Harrison, ASH 2024

Summary: Current and emerging treatment landscape for anemia of myelofibrosis

Current FDA-approved MF therapies focus on managing symptoms and spleen

- **Ruxolitinib** is standard of care but can worsen anemia
- **Momelotinib** can improve anemia but has limitations
- Off-label anemia management tools are limited by efficacy, applicability, and tolerability

Significant unmet need for anemia-targeted therapies that improve on current options

- Goals are to reduce/eliminate transfusions, increase hemoglobin, and improve symptoms
- Ideal anemia therapy could be used alone or in combination with any JAK inhibitor

Investigational therapies for anemia of MF include hemojuvelin inhibitors (DISC-0974) and erythroid maturation agents (luspatercept, elritercept)

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- **Current & Emerging Treatment Landscape**
  Dr. Prithviraj Bose, M.D. – The University of Texas MD Anderson Cancer Center

03 **DISC-0974 in Anemia of Myelofibrosis**
Will Savage, M.D., PhD, Chief Medical Officer

04 **Anemia of Myelofibrosis Market Opportunity**
Pamela Stephenson, Chief Commercial Officer

05 **Closing Remarks**
John Quisel, J.D., PhD, Chief Executive Officer

06 **Q&A Session**

DISC-0974 in MF Anemia: Clinical Program Status

TODAY'S FOCUS

Ph 1 Healthy Volunteers → **Phase 1b** → **Phase 2** *Ongoing*

N = 32 **healthy volunteers**

Single ascending dose

- Established **proof of mechanism** based on hepcidin and iron parameters
- Translated to key clinical parameters (Hgb increase)

N = 35 **MF anemia patients**

Open-label, randomized 24-week study

- **Initial proof of concept** in range of MF anemia patients (not transfused to high transfusion burden)
- Data presented at ASH 2024

N = ~90 **MF anemia patients**

Open-label, 24-week study at 50mg SC dose

- Designed to **confirm proof of concept** and inform pivotal study design
- Initial **data expected H2 2025**

Phase 1 SAD Trial in Healthy Volunteers

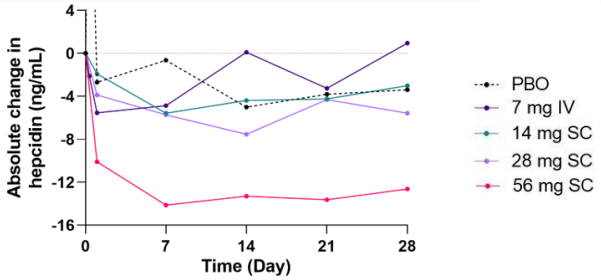
Established proof-of-mechanism based on hepcidin and iron parameters

Trial Design

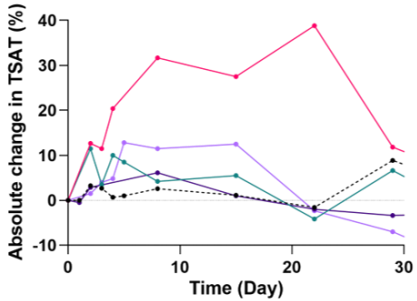
- Single-ascending dose in 32 healthy volunteers
- Key outcome measures:
  - Safety and PK
  - Hepcidin, serum iron, TSAT %
- Dose escalation until TSAT > 40% for at least 2 weeks
- Dose levels: 7 mg dose (IV); 14, 28 and 56 mg doses (SC)

Safety profile was consistent with selective target biology and preclinical studies; no serious or AEs > Grade 1

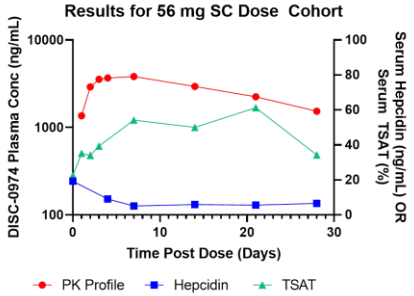
↓ DISC-0974 Reduced Hepcidin Production

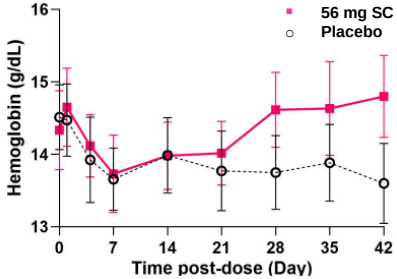


↑ DISC-0974 Increased TSAT



56 mg pharmacodynamic activity improved key clinical parameters (> 1g/dL Hgb)





TSAT = transferrin saturation; IV = intravenous; SC = subcutaneous

DISC-0974 Anemia of MF Phase 1b

Study overview – enrollment data as of October 17, 2024

Screening (28 Days) | **Treatment Period** (6 months) | **Optional Continuation** (Up to 2 years)

	14 mg	28 mg	50 mg	75 mg	100 mg	Overall
Treated, N	1	7	12	9	6	35
Completed study, N (%)	1 (100)	6 (86)	12 (100)	8 (89)	5 (83)	32 (91)
Subjects with early withdrawal (N)*	0	1	0	0	1	2
Participating in continuation, N (%)	0	2 (29)	10 (83)	8 (89)	4 (67)	24 (69)
Concomitant JAK inhibitor, N (%)	0	4 (57)	6 (50)	2 (22)	1 (17)	13 (37)
Baseline hepcidin, median (min, max), ng/mL	48	93 (21, 171)	90 (9, 156)	47 (23, 188)	64 (12, 375)	69 (9, 375)
Baseline hemoglobin, median (min, max), g/dL	8.2	8.4 (6.7, 9.3)	8.4 (5.5, 10)	8.8 (6.7, 9.9)	8.3 (5.5, 9)	8.4 (5.5, 10)

Study Endpoints

Primary: Safety and tolerability; **Secondary:** Hematologic response, pharmacodynamic markers of mechanism engagement

*Reason for early withdrawal: Physician decision due to inadequate response (n=2)

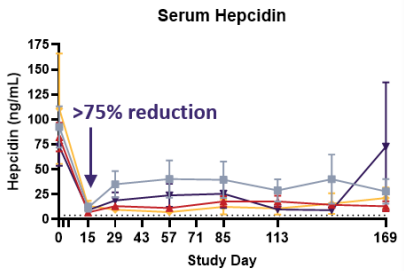
Source: ASH DISC-0974 MF Presentation

DISC-0974 Anemia of MF Phase 1b Results

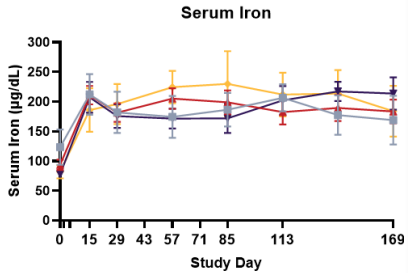
Pharmacodynamics

- DISC-0974 demonstrated consistent decreases in hepcidin and increases in serum iron across patients
- Iron mobilization translated to increased reticulocyte hemoglobin and hemoglobin from baseline

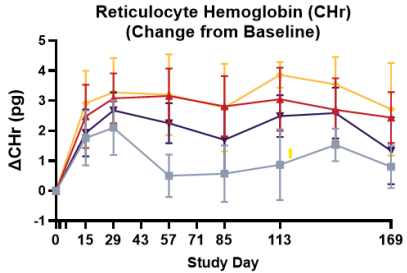
↓ Serum Hepcidin



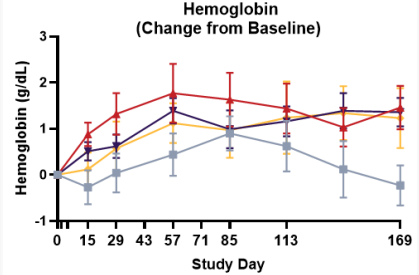
↑ Serum Iron



↑ Reticulocyte Hemoglobin



↑ Hemoglobin



28 mg 50 mg 75 mg 100 mg

Source: ASH DISC-0974 MF Presentation

DISC-0974 Anemia of MF Phase 1b

Overview of patient segmentation and response definitions

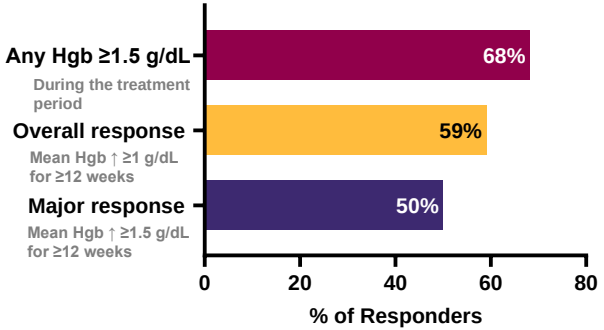
	nTD	TD Low	TD High
Patient Segment	**Hgb <10 and 0 units transfused / 12 weeks at baseline**	**1-2 units transfused / 12 weeks at baseline**	**3-12 units transfused / 12 weeks at baseline**
	N=22*	**N=5***	**N=5***
Overall Response	Mean Hgb increase ≥1.0 g/dL for ≥12 weeks	≥50% reduction in transfusion requirement	≥50% reduction in transfusion requirement
Major Response	Mean Hgb increase ≥1.5 g/dL for ≥12 weeks	Transfusion Independence ≥16 weeks	Transfusion Independence ≥12 weeks

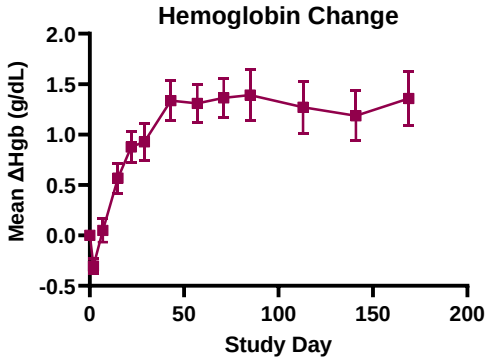
*Includes evaluable patients; 14mg patient was excluded from efficacy analysis and 2 additional patients were not evaluable

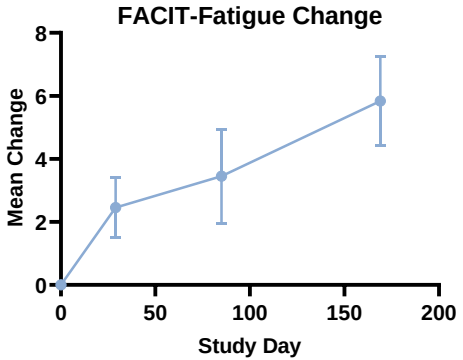
DISC-0974 Anemia of MF Phase 1b Results

Hematologic response: nTD participants* (n=22)

68% of nTD[1] participants achieved a Hgb Increase of ≥1.5 g/dL during study period; 50% achieved a sustained Hgb response for ≥12 weeks







67% of participants (n=9) receiving concomitant JAKi therapy achieved durable response

Response	Mean ± SD (days)
Time to first Hgb increase for major response	36 ± 18
Duration of response during treatment period	150 ± 27

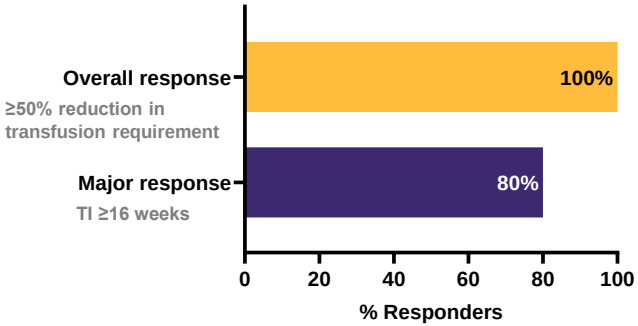
17 of 22 nTD participants have received continuation treatment with median response not reached. Follow-up ongoing (maximum 14.7 months).

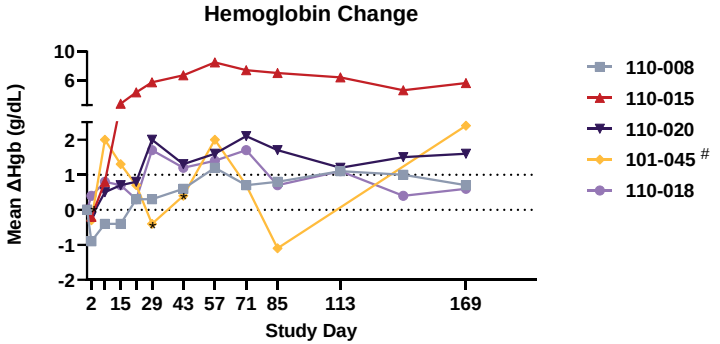
[1]nTD participants: Baseline Hgb <10 with 0 units PRBC in the 84 days prior to screening. * Participants dosed at 28-100 mg dose levels.; Source: ASH DISC-0974 MF Presentation

DISC-0974 Anemia of MF Phase 1b Results

Hematologic response: TD Low participants (n=5)

100% of TD Low[1] participants achieved a ≥50% reduction in transfusion requirement; 80% of participants achieved TI-16 weeks^





No TD Low participants were receiving concomitant JAKi therapy

*Indicates transfusion; #Indicates patient receiving transfusion during treatment period.

Response	Mean ± SD (days)
TD Low duration of major response during treatment period	171 ± 4

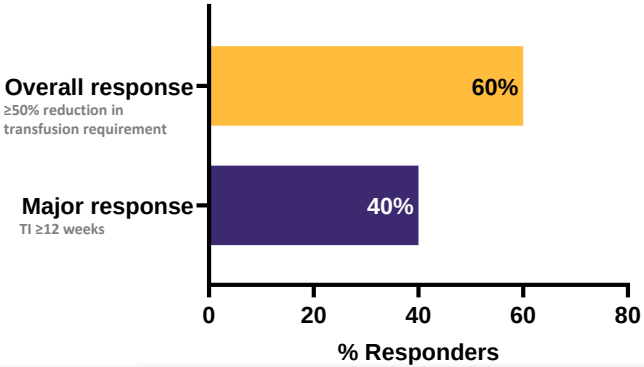
5 of 5 TD Low participants have received continuation treatment with median response not reached. Follow-up ongoing (maximum 16.6 months).

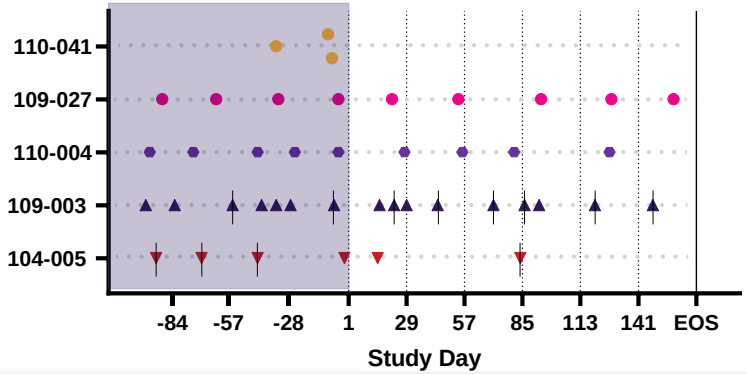
[1]TD Low: Participants receiving 1-2 units PRBC in the 84 days prior to screening. ^ with a minimum Hgb of 7 g/dL.; Source: ASH DISC-0974 MF Presentation

DISC-0974 Anemia of MF Phase 1b Results

Hematologic response: TD High participants (n=5)

60% of TD High[1] participants achieved a ≥50% reduction in transfusion requirement; 40% of participants achieved TI-12 weeks^





50% of participants (n=4) receiving concomitant JAKi therapy achieved ≥50% transfusion reduction; 25% achieved TI-12

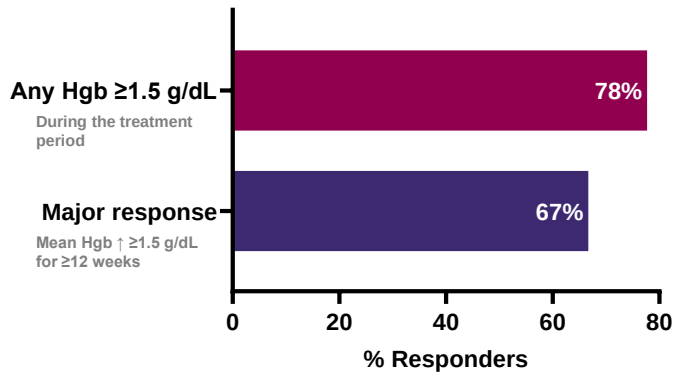
Response	Mean ± SD (days)
TD High duration of major response during treatment period	127 ± 60

[1]TD High: Participants receiving 3-12 units PRBC in the 84 days prior to screening. ^ with a minimum Hgb of 7 g/dL; 2 TD-high participants were considered not evaluable due to incomplete data entry at time of data cut.; Source: ASH DISC-0974 MF Presentation

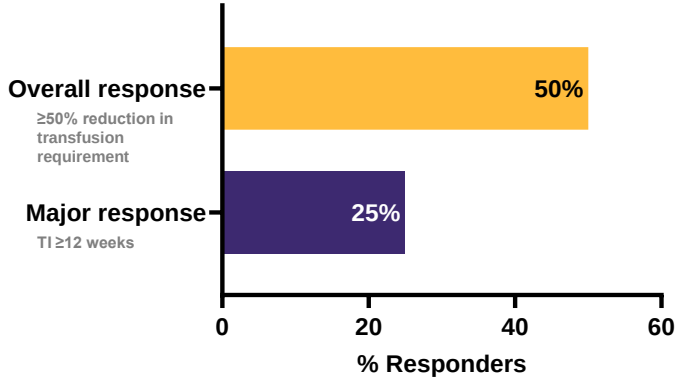
DISC-0974 Anemia of MF Phase 1b Results

Hematologic response with concomitant JAKi therapy (n=13)

nTD Response (n=9)



TD High Response (n=4)



Overall, 54% of participants receiving concomitant JAKi therapy achieved a major hematologic response

Source: ASH DISC-0974 MF Presentation

DISC-0974 Anemia of MF Phase 1b Results

Safety

Preferred Term	28 mg (n=7)	50 mg (n=12)	75 mg (n=9)	100 mg (n=6)	Overall (n=35)
Any TEAE	6 (85.7)	12 (100)	8 (88.9)	6 (100)	32 (94.1)
Related AE	4 (57.1)	6 (50)	5 (55.6)	1 (16.7)	16 (47.1)
SAE	1 (14.3)	2 (16.7)	0	1 (16.7)	4 (11.8)
Common TEAEs in ≥5 participants					
Diarrhea	3 (42.9)	5 (41.7)	5 (55.6)	1 (16.7)	14 (41.2)
Nausea	2 (28.6)	2 (16.7)	2 (22.2)	2 (33.3)	8 (23.5)
Vomiting	1 (14.3)	2 (16.7)	0	3 (50.0)	6 (17.6)
Constipation	0	4 (33.3)	1 (11.1)	0	5 (14.7)
Fatigue	3 (42.9)	3 (25.0)	1 (11.1)	3 (50.0)	10 (29.4)
Lymphocyte count decreased	1 (14.3)	2 (16.7)	2 (22.2)	1 (16.7)	6 (17.6)
Dizziness	0	2 (16.7)	2 (22.2)	3 (50.0)	7 (20.6)
Headache	1 (14.3)	1 (8.3)	1 (11.1)	2 (33.3)	5 (14.7)
Dyspnea	0	1 (8.3)	2 (22.2)	2 (33.3)	5 (14.7)
Hyperhidrosis	1 (14.3)	1 (8.3)	1 (11.1)	2 (33.3)	5 (14.7)
Anemia	5 (71.4)	4 (33.3)	0	0	9 (26.5)
Hypertension	0	3 (25.0)	3 (33.3)	0	6 (17.6)

No TEAEs were reported at the 14 mg dose level. Related AEs occurring in ≥2 participants: diarrhea (n=6); SAEs: arthralgia, cellulitis related to cat scratch, cellulitis related to cat bite, and kidney infection; ≥Grade 3 AEs: anemia, lymphocyte count decreased, platelets decreased, cellulitis, kidney infection (same as SAE), muscular weakness, and headache.; Source: ASH DISC-0974 MF Presentation

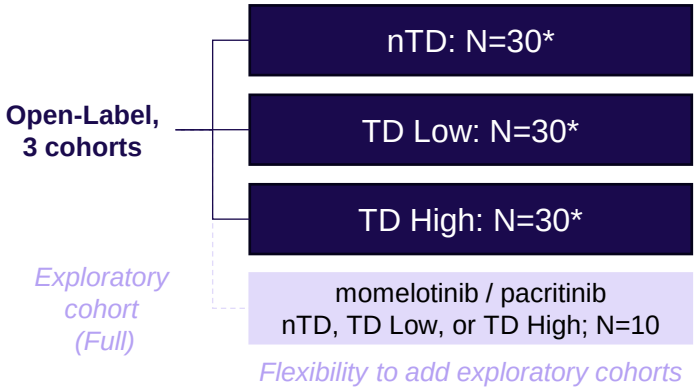
RALLY-MF: Phase 2 Study Overview

Study Population

- N= ~90 (30 per cohort)
  - 12 patients carried over from Phase 1b*
- Adult patients with MF and anemia
  - Hgb <10 g/dL on ≥3 assessments over 12 weeks, or
  - 1 or more PRBC units transfused in 12 weeks
- Severity: DIPSS INT-1/High
- +/- JAK inhibitor permitted

Design

Screening (28 Days) → **Treatment Period** (6 Cycles q28 Days) → **Follow-Up** (28 Days) → **Continuation Treatment** (q28 Days – optional)



Key endpoints:

- Anemia response defined by cohort (TI, transfusion burden reduction, Hgb change)
- Iron, hepcidin, hematologic parameters
- FACIT fatigue score

Phase 2 Dosing: 50 mg, SC, q28 days

*Patients carried over from Phase 1b: nTD n=8, TD (Low + High) n=4

Next Steps

RALLY-MF
Phase 2 Trial Ongoing

- Initial **data expected H2 2025**
- Expect to provide safety and efficacy data for patients with sufficient completion at time of cutoff
- Topline data expected in 2026

End of Phase 2 Alignment

- Regulatory alignment on pivotal trial design
- Expect to discuss registrational endpoints for full range of MF anemia patients

Pivotal Data Generation

- Expecting a **single Phase 3 trial** addressing full range of MF anemia patients
- Design to be driven by Phase 2 data and regulatory guidance

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MF Anemia Opportunity

Anemia remains a high unmet need within an established field

~22K US addressable MF patients with anemia

Severe Condition

Progressive in nature, with significant impact on prognosis and QoL

Clear Unmet Need

HCPs and patients recognize importance of treating anemia and lack of effective options

Well Characterized Market

MF expert network and treatment pathway are well-established

Differentiated Product

Aiming to address anemia in any patient on any MF treatment regimen

Overview of MF Market

MF market has been developed by JAK inhibitors; DISC-0974 aims to address patients on JAKs, discontinued, or JAK-naïve

~$2.0B
Total Est. 2024 JAK Inhibitor US Sales (MF)

MF patients treated with JAK inhibitor

MF patients JAK-naïve or discontinued

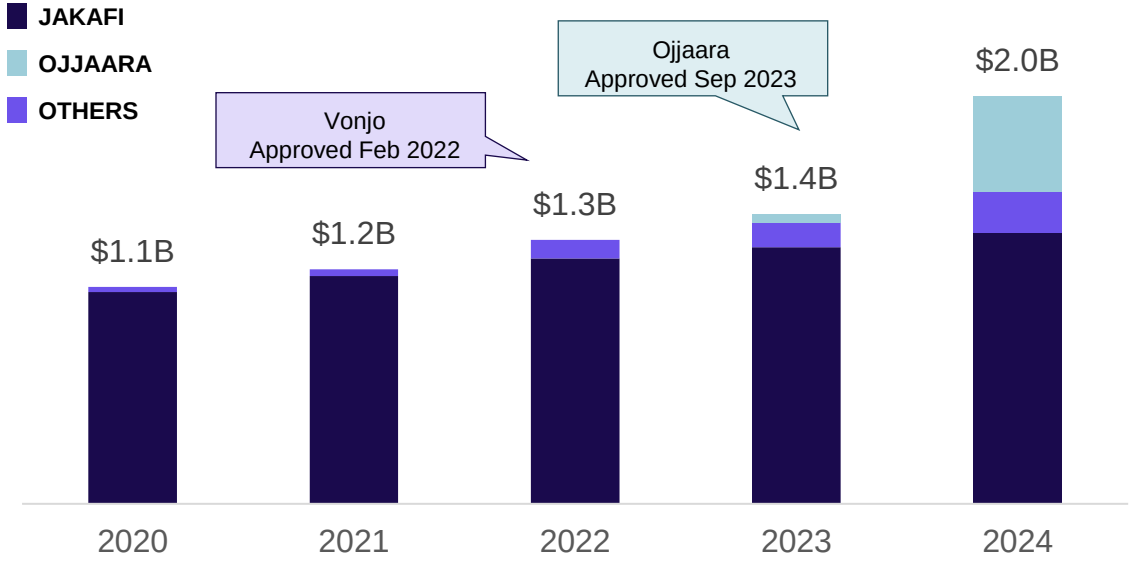
25K US MF patients

87% Anemic

DISC-0974 target profile is designed to address the full MF anemia market:

~22K Addressable Patients

Estimated JAK Inhibitor US Sales – MF (USD $M)



Source: Company earnings reports, Evaluate Pharma

DISC-0974: Emerging product profile aiming to address key needs for MF anemia therapy

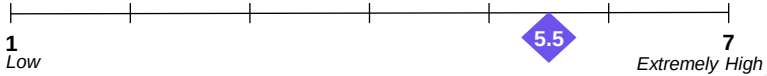
Key Needs for Anemia Therapy	DISC-0974 Emerging Product Profile
1 Works across anemia severity levels	✓ Achieved POC in NTD, TD Low, and TD High patients • Expanding N for each cohort in ongoing / future studies
2 Works as a monotherapy 3 Works with any JAK inhibitor 4 Supports optimization of JAK inhibitor regimen	✓ Showed similar efficacy in monotherapy vs. JAK inhibitor combination • RALLY-MF Phase 2 trial includes patients both on and off JAK inhibitors – Main cohorts allow ruxolitinib/fedratinib – Exploratory cohort for momelotinib/pacritinib • Potential to explore impact of DISC-0974 on optimization of JAK inhibitor regimen in future studies
5 Superior response rates vs. current off-label anemia therapies	✓ Major response rate of **40-80%** in Phase 1b

HCPs highlight high unmet need in MF, specifically related to anemia, and strong enthusiasm for DISC-0974

Based on interviews with select MF **KOLs** and **community treaters**

UNMET NEED

Average rating for unmet need in MF anemia:



Top 3 cited unmet needs in MF:

- Disease modifying therapies
- Anemia-specific treatment
- Treatment that reduces transfusion dependence

Top 3 most burdensome aspects of MF:

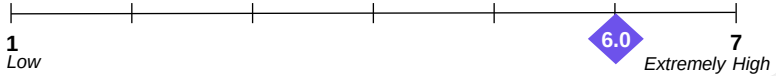
- Anemia
- Fatigue
- Splenomegaly

> *I think we have some treatments available, but essentially the efficacy is less desirable, especially in terms of achieving transfusion independence. This is a very high unmet need there."*
>
> *- KOL*

> *I cannot think of a single patient who did not develop anemia at some point after being diagnosed with myelofibrosis over the years. Sometimes it is the reason why we cannot continue treatment."*
>
> *- HCP*

DISC-0974 PROFILE – *Based on Phase 1b data*

Average rating for likelihood to prescribe DISC-0974:



Key favorable aspects of product profile mentioned:

- ✓ Mechanism of action is novel and addresses pathophysiology of MF anemia
- ✓ Viewed response rates (based on Phase 1b data) as clinically significant and better than current standard of care
- ✓ Considered ability to use with or without JAK inhibitors very meaningful

> *I would use this as first line in patients who have anemia, transfusion dependent or not. [Most MF patients] have some type of anemia so if I can prevent it further, I will. Why would I wait for their Hb levels to be a 9? I'll just immediately put them on this drug"*
>
> *-KOL*

> *I think it's great that it can be used as an adjunct to other therapies. Efficacy is great and when you couple that with a clean safety profile, then that makes it a home run."*
>
> *-HCP*

Source: Primary market research conducted by Trinity Life Sciences

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06 **Q&A Session**

Developing DISC-0974 in Anemias of Chronic Disease

Indication	US Prev.	Est. % Anemic	Key Results	Next Steps
Anemia of Myelofibrosis (MF)	**25K**	**87%**	• Consistent, substantial decrease in hepcidin translating to iron mobilization and hemoglobin increase • Major anemia response: 40-80%	Initial Phase 2 data in anemia of MF in H2
Anemia of Chronic Kidney Disease (CKD)	**37 MM**	**17-50%**	• Hepcidin suppression translating to iron mobilization and increased hematologic activity with a single dose • Dose optimization ongoing	Phase 1b 90mg and multiple-dose in H2

Key readouts for first two indications by end of 2025

Projected Upcoming Milestones and Events

Multiple additional data catalysts anticipated in the next 18 months

Program	Indication	H1 2025	H2 2025	2026
Bitopertin Heme Synthesis Modulator	**Erythropoietic Porphyrias (EPP and XLP)**	✓ Feedback from Type C Meeting with FDA ✓ APOLLO Study initiated	• NDA Submission	
	Diamond-Blackfan Anemia (DBA)	• IIT ongoing →		
DISC-0974 Hepcidin Suppression	**Anemia of Myelofibrosis (MF)**		• Initial RALLY-MF Phase 2 Data	• Topline RALLY-MF Phase 2 Data
	Anemia of Chronic Kidney Disease (CKD)		• Phase 1b Multiple-Dose Data	• Phase 2a Initiation • Initial Phase 2a Data
DISC-3405 Hepcidin Induction	**Polycythemia Vera**	• Phase 2 Study Initiation		• Phase 2 Data

Supported by a strong cash position with runway into 2028

Q&A

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