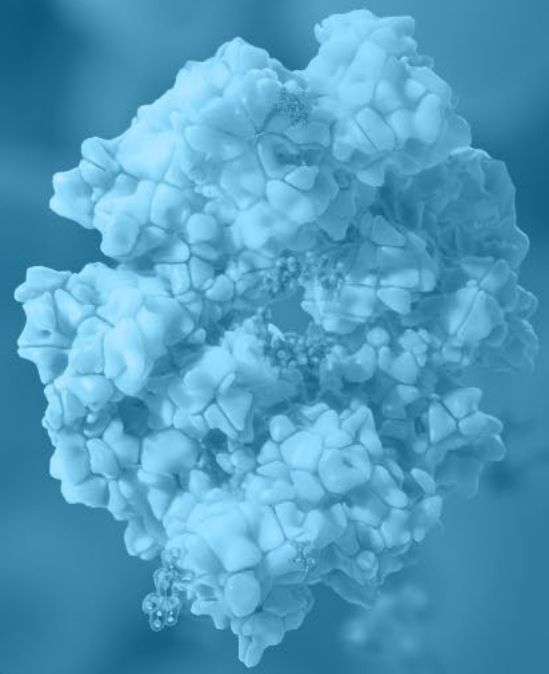
Topline results Phase 3 RISE UP in sickle cell disease

November 19, 2025



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Conference call agenda

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3	**Sickle Cell Disease Overview**	Biree Andemariam, MD (External KOL)
4	**Phase 3 RISE UP results**	Sarah Gheuens, MD, PhD, MMSc Chief Medical Officer and Head of R&D
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6	**CEO Closing Remarks and Q&A**	Brian Goff, Chief Executive Officer

Biree Andemariam, M.D.

- Professor of Medicine and the American Red Cross Endowed Chair in Transfusion Medicine at the University of Connecticut School of Medicine
- Founding Director of the New England Sickle Cell Institute (NESCI)
- Director of the Connecticut Bleeding Disorders Center
- Previously served as Chief Medical Officer and on the Board of Directors of the Sickle Cell Disease Association of America (SCDAA)

CEO Opening Remarks

Brian Goff, Chief Executive Officer

Fueled by Connections to Transform Rare Diseases™

We build deep connections with rare disease communities, collaborating to develop and deliver innovative medicines that transform lives

"The deficit is palpable in sickle cell disease. It's glaringly apparent when I'm discussing treatment options with my provider, the limitations are clear. It's discouraging when most days sickle cell monopolizes my life.

Innovation isn't just necessary, it's urgent. Our community needs bold, life-changing solutions that reflect not just the complexities of this disease, but also the realities of our lives."

- Cassandra, living with Sickle Cell Disease

Sickle Cell Disease Overview

KOL : Biree Andemariam, M.D.

Sickle cell disease is a heterogenous and clinically complex disorder

Sickle cell disease is a multi-system disorder affecting virtually every organ

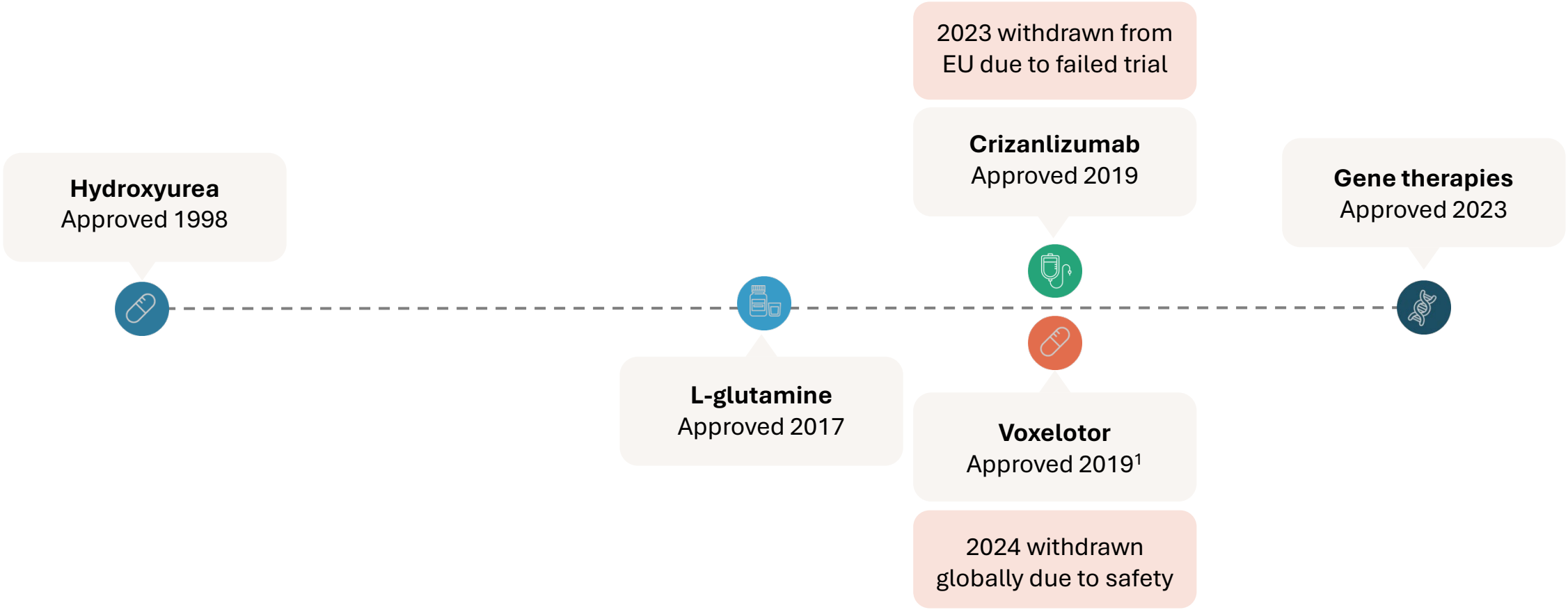
Core pathophysiology of chronic **hemolytic anemia and vaso-occlusion** leads to morbidity and mortality

Hemolysis drives **endothelial dysfunction**, nitric oxide depletion and inflammatory activation – further amplifying the risk of vaso-occlusive events

Patients face a lifetime of managing chronic organ damage and unpredictable acute crises

Kato et. al Nat Rev Dis Primers. 2018 Mar 15:4:18010. doi: 10.1038/nrdp.2018.10.Kavanagh et el. JAMA. 2022 Jul 5;328(1):57-68. doi: 10.1001/jama.2022.10233. Gbotosho et al. Front Immunol. 2021 Jan 27:11:561917. doi: 10.3389/fimmu.2020.561917. eCollection 2020.

Limited treatment options leads to complexity of care



Dates presented in timeline reflect FDA regulatory approval. 1. Approved under FDA's accelerated approval program.

What are the challenges in the treatment of hemolytic anemia and vaso-occlusive crises in Sickle Cell Disease?

Hemolytic Anemia

- Persistent hemolytic burden leads to anemia, vaso-occlusive risk, endothelial dysfunction and drives end-organ damage
- Limited options to meaningfully improve Hb levels or reduce hemolysis
- Transfusions and hydroxyurea are inadequate for large proportion of patients

Vaso-occlusive crises

- VOCs remain the leading cause of acute morbidity
- Palliative approach to management of acute VOCs
- Existing therapies have significant limitations

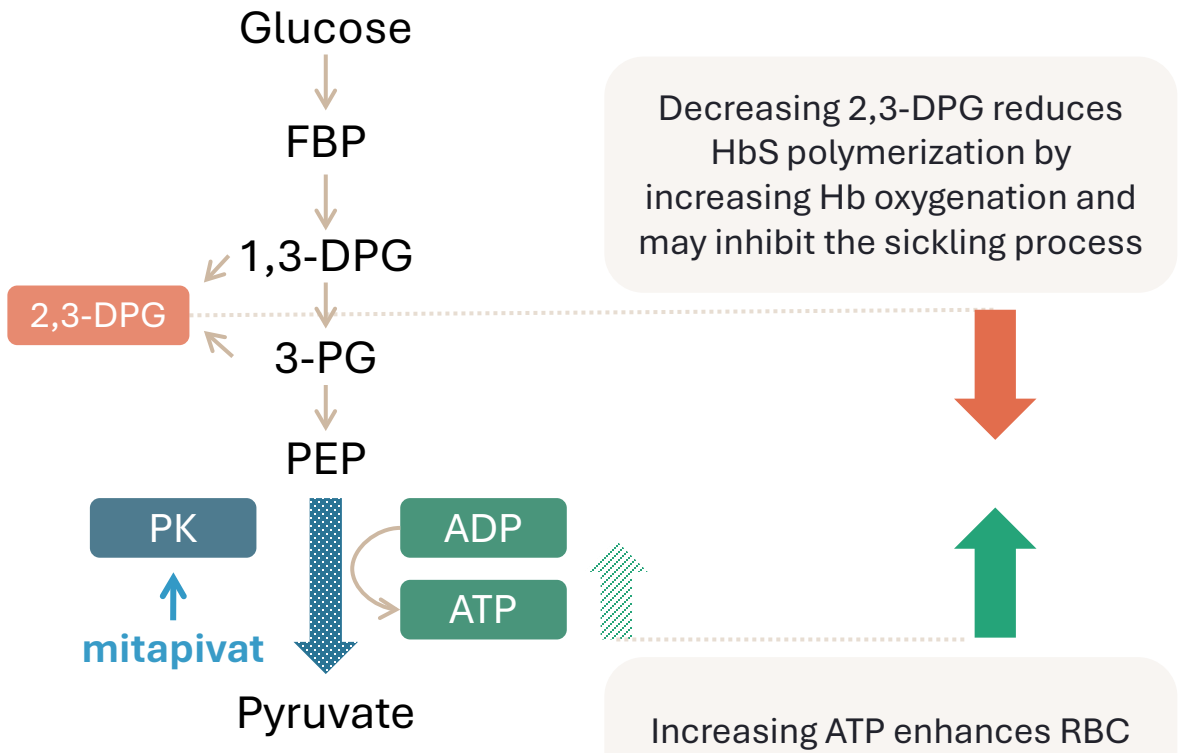
There is a strong need for a physiologically anchored, well-tolerated, predictable therapy

Xu et al. Blood. 2022 May 19;139(20):3030-3039. doi: 10.1182/blood.2021013873. Osunkwo et al Am J Hematol. 2021 Apr 1;96(4):404-417. doi: 10.1002/ajh.26063. Epub 2021 Feb 25. Shah et al J Health Econ Outcomes Res. 2019 May 3;6(3):106-117. doi: 10.36469/9667. eCollection 2019.
VOC = vaso-occlusive crisis.

Topline results RISE UP Phase 3

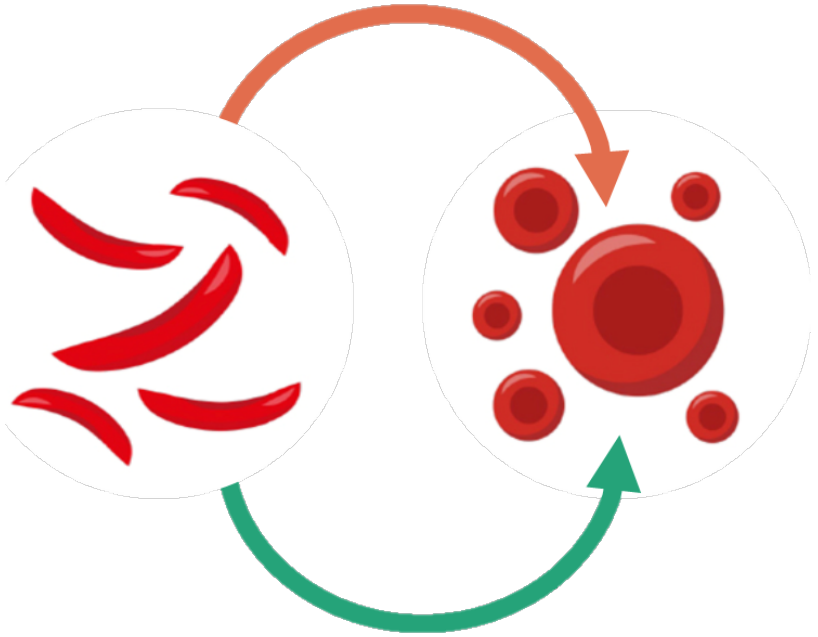
Sarah Gheuens, Chief Medical Officer and Head of R&D

Mitapivat MoA – increases ATP, decreases 2,3-DPG



Decreasing 2,3-DPG reduces HbS polymerization by increasing Hb oxygenation and may inhibit the sickling process

Increasing ATP enhances RBC energy metabolism and may improve membrane integrity



MoA = mechanism of action; ATP = adenosine triphosphate; ADP = adenosine diphosphate; DPG = diphosphoglycerate; PG = phosphoglycerate; RBC = red blood cell; FBP = fructose 1,6-bisphosphate; PEP = phosphoenolpyruvate; PK = pyruvate kinase; Hb = hemoglobin.

Phase 3 RISE UP trial design

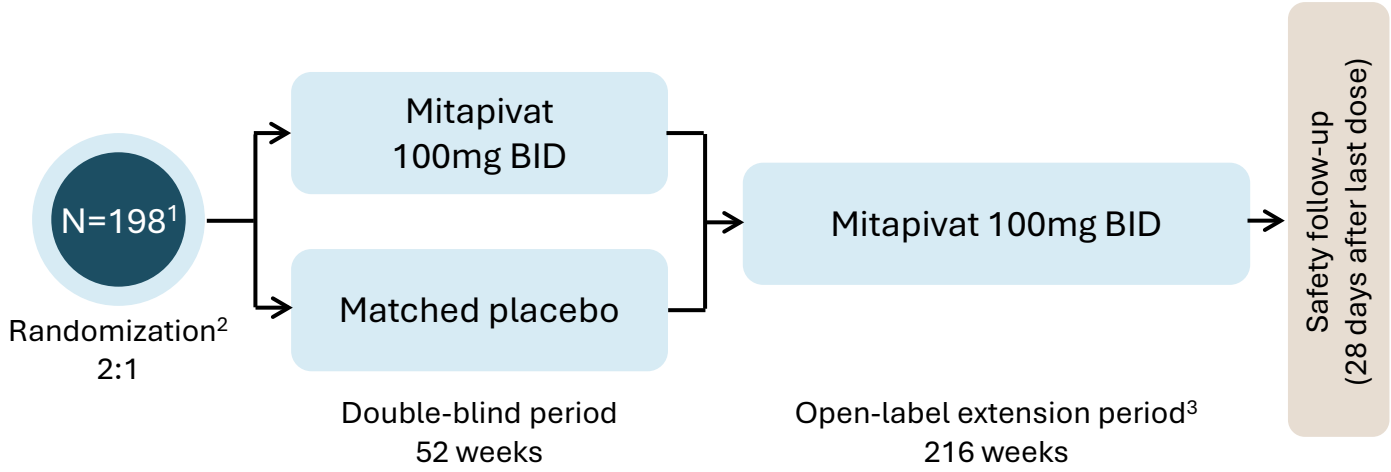
RISE UP

Stratification factors

1. No. of SCPCs in prior 12 months (<5, ≥5)
2. Hydroxyurea use (yes, no)

SCPC inclusion criteria

For inclusion in the study, participants needed to have experienced at least 2 and no more than 10 SCPCs in the 12 months prior to enrollment



Primary endpoints

- Hb response
- Annualized rate of SCPCs

Key secondary endpoints

- Average change in Hb concentration[4]
- Average change in indirect bilirubin[4]
- Average change in PROMIS-Fatigue 13a scores[4]
- Annualized frequency of hospitalizations for SCPC
- Average change in percent reticulocyte[4]

Hb response defined as ≥1.0 g/dL increase in average Hb from Week 24 through Week 52 compared to baseline.
SCPCs defined as: an acute episode of pain that requires medical intervention, acute chest syndrome, priapism, hepatic or splenic sequestration.

1. Actual patients enrolled = 207. 2. Randomization stratified by the number of SCPCs in the prior year (<5, ≥5) and concomitant hydroxyurea use. 3. Patients who complete the double-blind period were eligible to receive mitapivat for an additional 216 weeks in an open-label extension period. 4. Change measured from baseline to average of Week 24 through Week 52.
SCPC = sickle cell pain crisis; Hb = Hemoglobin; PROMIS = patient reported outcome measurement information system.

Baseline characteristics balanced in both trial arms

	Placebo N = 69	Mitapivat 100mg BID N = 138	Total N = 207
Age (yr)			
n	69	138	207
Mean (SD)	31.6 (12.94)	28.9 (11.32)	29.8 (11.92)
Min, Max	17, 67	16, 68	16, 68
Age category 2 (yr), n (%)			
<35	46 (66.7)	105 (76.1)	151 (72.9)
≥35	23 (33.3)	33 (23.9)	56 (27.1)
Sex, n (%)			
Male	26 (37.7)	62 (44.9)	88 (42.5)
Female	43 (62.3)	76 (55.1)	119 (57.5)
Ethnicity, n (%)			
Hispanic or Latino	10 (14.5)	21 (15.2)	31 (15.0)
Not Hispanic or Latino	55 (79.7)	109 (79.0)	164 (79.2)
Not reported	4 (5.8)	8 (5.8)	12 (5.8)
Race, n (%)			
Black or African American	53 (76.8)	103 (74.6)	154 (75.4)
White	8 (11.6)	20 (14.5)	28 (13.5)
Asian	1 (1.4)	1 (0.7)	2 (1.0)
Uknown	2 (2.9)	3 (2.2)	5 (2.4)
Not reported	5 (7.2)	11 (8.0)	16 (7.7)

The denominator used to calculate percentages is N, the number of subjects in the full analysis set within each treatment group.

Disease characteristics balanced in both trial arms

	Placebo N = 69	Mitapivat 100mg BID N = 138	Total N = 207
Number of SCPCs in the Prior Year (randomization stratification factor), n (%)			
<5	57 (82.6)	113 (81.9)	170 (82.1)
≥5	12 (17.4)	25 (18.1)	37 (17.9)
Hydroxyurea use (randomization stratification factor)			
No	18 (26.1)	35 (25.4)	53 (25.6)
Yes	51 (73.9)	103 (74.6)	154 (74.4)
SCD genotyping, n (%)			
HbSS	57 (82.6)	119 (86.2)	176 (85.0)
HbSC	2 (2.9)	4 (2.9)	6 (2.9)
HbS/b0-thalassemia	5 (7.2)	4 (2.9)	9 (4.3)
HbS/b0+thalassemia	3 (4.3)	4 (2.9)	7 (3.4)
Other sickle cell syndrome variants	1 (1.4)	3 (2.2)	4 (1.9)
Missing	1 (1.4)	4 (2.9)	5 (2.4)
Transfusion burden (number of RBC units) in the 52 weeks before IC, n (%)[1]			
0	43 (62.3)	89 (64.5)	132 (63.8)
1-2	12 (17.4)	30 (21.7)	42 (20.3)
3-5	8 (11.6)	13 (9.4)	21 (10.1)
>5	6 (8.7)	6 (4.3)	12 (5.8)
Prior disease modifying SCD-related therapies, n (%)[2]			
No	16 (23.2)	34 (24.6)	50 (24.2)
Yes	53 (76.8)	104 (75.4)	157 (75.8)

The denominator used to calculate percentages is N, the number of subjects randomized within each treatment group.
1. Includes transfusions within 12 months before IC and during screening. 2. Prior disease modifying SCD-related therapies could include hydroxyurea, crizanlizumab, L-glutamine, and voxelotor.
IC = informed consent/assent; RBC = red blood cell; SCD = sickle cell disease; SCPC= sickle cell pain crisis.

Baseline lab characteristics consistent with hemolytic anemia profile

	Placebo N=69	Mitapivat 100 mg BID N=138	Total N=207
Baseline Hemoglobin (g/L)			
n	68	137	205
Mean (SD)	85.39 (12.045)	86.23 (11.046)	85.95 (11.364)
Min, Max	58.0, 104.5	63.5, 109.5	58.0, 109.5
Baseline hemoglobin category, n (%)			
<80 g/L	20 (29.0)	41 (29.7)	61 (29.5)
≥80 g/L	48 (69.6)	96 (69.6)	144 (69.6)
Missing	1 (1.4)	1 (0.7)	2 (1.0)
Baseline indirect bilirubin (umol/L)			
n	68	137	205
Mean (SD)	30.09 (25.831)	32.94 (28.946)	31.99 (27.920)
Min, Max	6.3, 148.7	3.9, 140.1	3.9, 148.7
Baseline lactate dehydrogenase (U/L)			
n	67	136	203
Mean (SD)	449.72 (199.884)	434.40 (178.238)	439.46 (185.305)
Min, Max	189.5, 1162.0	176.5, 1237.0	176.5, 1237.0
Baseline reticulocytes/erythrocytes (fraction of 1)			
n	63	124	187
Mean (SD)	0.0940 (0.06102)	0.0998 (0.05138)	0.0978 (0.05472)
Min, Max	0.020, 0.379	0.020, 0.287	0.020, 0.379

Baseline is defined as the average of all assessments during the screening period up to the randomization date.
Assessments within 8 weeks after an RBC transfusion are excluded from the baseline derivation.

Phase 3 RISE UP statistical testing strategy

Primary endpoints

Hb response[1]
$\alpha_1 = 0.02$

Annualized rate of SCPCs
$\alpha_2 = 0.03$

Key secondary endpoints hierarchy

1. Average change in Hb concentration[2]
2. Average change in indirect bilirubin[2]
3. Average change in PROMIS-Fatigue 13a scores[2]
4. Annualized frequency of hospitalizations for SCPC
5. Average change in percent reticulocyte[2]

Key secondary endpoints tested at the sum of the alpha for the primary endpoint(s) met

1.Defined as ≥1.0 g/dL increase in average Hb from Week 24 through Week 52 compared to baseline. 2. Change measured from baseline to average of Week 24 through Week 52.
Hb = hemoglobin; SCPC = sickle cell pain crises; PROMIS = Patient Reported Outcomes Measurement Information System.

Patient disposition – low discontinuation rate

Double-blind treatment period	Placebo N = 69	Mitapivat 100mg BID N = 138	Total N = 207
Discontinued, n (%)	13 (18.8)	18 (13.0)	31 (15.0)

85%

of patients completed the 52-week double-blind treatment period

174/176

of patients who completed the double-blind treatment period opted onto the OLE portion

The denominator used to calculate percentages is N, the number of subjects in the full analysis set within each treatment group.
OLE = open-label extension.

Primary endpoint – Hemoglobin response[1] (≥1g/dL)

Primary endpoints

Hb Response[1]

Annualized rate of SCPCs

Key secondary endpoints

Average change in Hb concentration[2]

Average change in indirect bilirubin[2]

Average change in PROMIS-Fatigue 13a scores[2]

No conclusions regarding statistical significance can be drawn on following endpoints

Annualized rate of hospitalizations for SCPC

Average change in percent reticulocyte[2]

	Placebo N = 69	Mitapivat 100mg BID N = 138
Hb responders, n (%)	2 (2.9)	56 (40.6)
Adjusted difference in response rate (mitapivat vs placebo), %		37.7
95% CI		(28.6, 46.8)
2-side p-value		<0.0001

Primary endpoint was met – 40.6% response rate was observed in mitapivat arm

1. Defined as ≥1.0 g/dL increase in average Hb from Week 24 through Week 52 compared to baseline. 2. Change from Week 24 through Week 52 compared to baseline.
SCPC = sickle cell pain crises; Hb = hemoglobin, PROMIS = Patient Reported Outcomes Measurement Information System.

Primary endpoint – Annualized rate of Sickle Cell Pain Crisis

Primary endpoints

Hb Response[1]

Annualized rate of SCPCs

Key secondary endpoints

Average change in Hb concentration[2]

Average change in indirect bilirubin[2]

Average change in PROMIS-Fatigue 13a scores[2]

No conclusions regarding statistical significance can be drawn on following endpoints

Annualized rate of hospitalizations for SCPC

Average change in percent reticulocyte[2]

	Placebo N = 69	Mitapivat 100mg BID N = 138
Annualized Rate of SCPC	3.05	2.62
95% CI	(2.57, 3.64)	(2.29, 3.01)
Rate reduction (mitapivat vs placebo) (%)		14
95% CI		(-4.1, 29.2)
Rate ratio (mitapivat/placebo)		0.86
95% CI		(0.71, 1.04)
2-sided p-value		0.1213

Trend favoring mitapivat with 14% reduction in annualized rate of SCPCs vs placebo

1. Defined as ≥1.0 g/dL increase in average Hb from Week 24 through Week 52 compared to baseline. 2. Change from baseline to average of Week 24 through Week 52.
SCPC = sickle cell pain crises; Hb = hemoglobin; PROMIS = Patient Reported Outcomes Measurement Information System

Key secondary endpoint – Average change from baseline in Hemoglobin concentration (g/L)

Primary endpoints

- Hb Response[1]
- Annualized rate of SCPCs

Key secondary endpoints

- **Average change in Hb concentration[2]**
- Average change in indirect bilirubin[2]
- Average change in PROMIS-Fatigue 13a scores[2]

No conclusions regarding statistical significance can be drawn on following endpoints

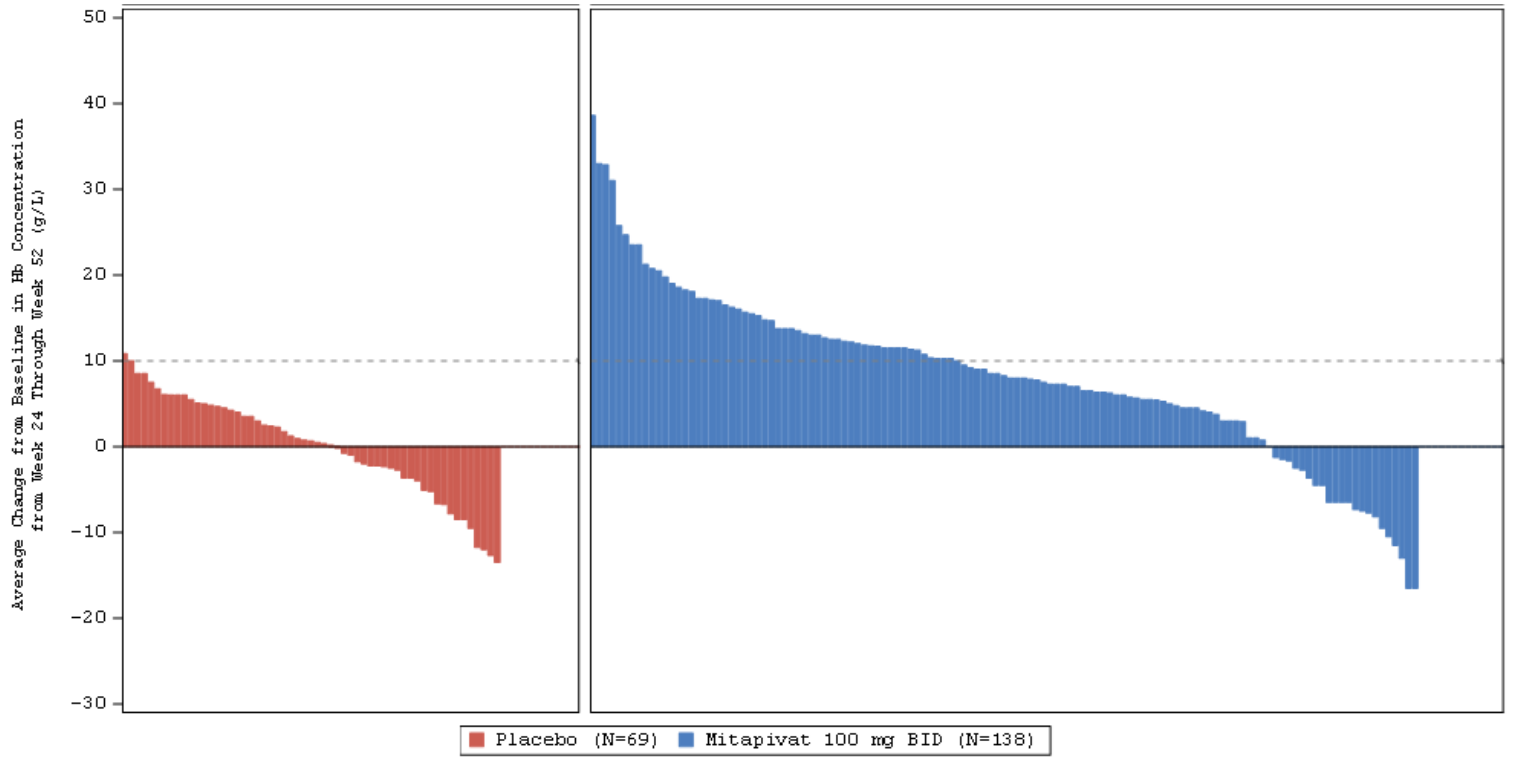
- Annualized rate of hospitalizations for SCPC
- Average change in percent reticulocyte[2]

	Placebo N = 69	Mitapivat 100mg BID N = 138
Baseline		
n	68	137
Mean (SD)	85.39 (12.045)	86.23 (11.046)
Average of week 24 through week 52 change from baseline		
LS mean (SE)	0.26 (1.177)	7.69 (0.862)
95% CI	(-2.06, 2.58)	(5.99, 9.39)
Difference in LS Mean (SE) (mitapivat - placebo)		7.43 (1.309)
95% CI		(4.85, 10.01)
2-sided p-value		<0.0001

Statistically significant 0.7 g/dL difference between mitapivat and placebo for the average change from baseline in Hb concentration

1. Defined as ≥1.0 g/dL increase in average Hb from Week 24 through Week 52 compared to baseline. 2. Change from baseline to average of Week 24 through Week 52.
SCPC = sickle cell pain crises; Hb = hemoglobin; PROMIS = Patient Reported Outcomes Measurement Information System.

Waterfall plot of average change from baseline in Hemoglobin concentration from Week 24 Through Week 52



Robust and sustained Hb response in the mitapivat arm

Key secondary endpoint – Average change from baseline in indirect bilirubin (µmol/L)

Primary endpoints

- Hb Response[1]
- Annualized rate of SCPCs

Key secondary endpoints

- Average change in Hb concentration[2]
- **Average change in indirect bilirubin[2]**
- Average change in PROMIS-Fatigue 13a scores[2]

No conclusions regarding statistical significance can be drawn on following endpoints

- Annualized rate of hospitalizations for SCPC
- Average change in percent reticulocyte[2]

	Placebo N = 69	Mitapivat 100mg BID N = 138
Baseline		
n	68	137
Mean (SD)	30.09 (25.831)	32.94 (28.946)
Average of week 24 through week 52 change from baseline		
LS Mean (SE)	0.88 (1.864)	-16.03 (1.381)
95% CI	(-2.79, 4.55)	(-18.75, -13.31)
Difference in LS Mean (SE) (mitapivat - placebo)		-16.91 (2.077)
95% CI		(-21.01, -12.81)
2-sided p-value		<0.0001

Average change from baseline in indirect bilirubin was significantly reduced in mitapivat arm vs placebo

1. Defined as ≥1.0 g/dL increase in average Hb from Week 24 through Week 52 compared to baseline. 2. Change from baseline to average of Week 24 through Week 52.
SCPC = sickle cell pain crises; Hb = hemoglobin; PROMIS = Patient Reported Outcomes Measurement Information System.

Key secondary endpoint – Average change from baseline in PROMIS-Fatigue 13a scores

Primary endpoints

- Hb Response[1]
- Annualized rate of SCPCs

Key secondary endpoints

- Average change in Hb concentration[2]
- Average change in indirect bilirubin[2]
- **Average change in PROMIS-Fatigue 13a[2]**

No conclusions regarding statistical significance can be drawn on following endpoints

- Annualized rate of hospitalizations for SCPC
- Average change in percent reticulocyte[2]

	Placebo N = 69	Mitapivat 100mg BID N = 138
Baseline		
n	53	102
Mean (SD)	52.72 (10.244)	53.49 (9.833)
Average of week 24 through week 52 change from baseline		
LS Mean (SE)	-2.25 (1.190)	-2.72 (0.906)
95% CI	(-4.60, 0.10)	(-4.51, -0.93)
Difference in LS Mean (SE) (mitapivat - placebo)		-0.47 (1.268)
95% CI		(-2.98, 2.04)
2-sided p-value		0.7112

No statistically significant difference in change from baseline for PROMIS-Fatigue 13a T-scores between mitapivat and placebo

1. Defined as ≥1.0 g/dL increase in average Hb from Week 24 through Week 52 compared to baseline. 2. Change from baseline to average of Week 24 through Week 52.
SCPC = sickle cell pain crises; Hb = hemoglobin; PROMIS = Patient Reported Outcomes Measurement Information System.

Key secondary endpoint – Annualized rate of hospitalizations for SCPC

Primary endpoints

- Hb Response[1]
- Annualized rate of SCPCs

Key secondary endpoints

- Average change in Hb concentration[2]
- Average change in indirect bilirubin[2]
- Average change in PROMIS-Fatigue 13a scores[2]

No conclusions regarding statistical significance can be drawn on following endpoints

- **Annualized rate of hospitalizations for SCPC**
- Average change in percent reticulocyte[2]

	Placebo N = 69	Mitapivat 100mg BID N = 138
Annualized frequency (rate) of hospitalizations for SCPC	1.81	1.56
95% CI	(1.44, 2.27)	(1.31, 1.87)
Rate reduction (mitapivat vs placebo) (%)		14
95% CI		(-10.8, 32.7)
Rate ratio (mitapivat vs placebo) (%)		0.86
95% CI		(0.67, 1.11)
2-sided nominal p-value		0.2498

Trend in favor of mitapivat with 14% reduction in annualized rate of hospitalizations vs placebo

1. Defined as ≥1.0 g/dL increase in average Hb from Week 24 through Week 52 compared to baseline. 2. Change from baseline to average of Week 24 through Week 52.
SCPC = sickle cell pain crises; Hb = hemoglobin; PROMIS = Patient Reported Outcomes Measurement Information System.

Key secondary endpoint – Average change from baseline in percent reticulocyte (fraction of 1)

Primary endpoints

- Hb Response[1]
- Annualized rate of SCPCs

Key secondary endpoints

- Average change in Hb concentration[2]
- Average change in indirect bilirubin[2]
- Average change in PROMIS-Fatigue 13a scores[2]

No conclusions regarding statistical significance can be drawn on following endpoints

- Annualized rate of hospitalizations for SCPC
- **Average change in percent reticulocyte[2]**

	Placebo N = 69	Mitapivat 100mg BID N = 138
Baseline		
n	63	124
Mean (SD)	0.0940 (0.06102)	0.0998 (0.05138)
Average of week 24 through week 52 change from baseline		
LS Mean (SE)	-0.0013 (0.00499)	-0.0236 (0.00367)
95% CI	(-0.0112, 0.0085)	(-0.0309, -0.0164)
Difference in LS Mean (SE) (mitapivat - placebo)		-0.0223 (0.00536)
95% CI		(-0.0334, -0.0112)
2-sided nominal p-value		0.0001

Percent reticulocytes substantially decreased from baseline in the mitapivat arm vs placebo

1. Defined as ≥1.0 g/dL increase in average Hb from Week 24 through Week 52 compared to baseline. 2. Change from baseline to average of Week 24 through Week 52.
SCPC = sickle cell pain crises; Hb = hemoglobin; PROMIS = Patient Reported Outcomes Measurement Information System.

Hemoglobin responders – Substantial clinical benefit observed in SCPC-related endpoints and PROMIS –Fatigue[1]

1.6 g/dL mean increase from baseline in Hb concentration[2] observed in Hb-responders[3] in mitapivat arm

	Annualized rate of SCPC	Annualized rate of hospitalizations for SCPC	Average change from baseline in PROMIS-Fatigue 13a scores[2]
Hb-responder	**2.20 (1.78, 2.71)**	**1.16 (0.87, 1.55)**	**-5.19* (-7.92, -2.46)**
Hb Non-responder	2.98 (2.52, 3.53)	1.76 (1.41, 2.20)	-2.55 (-4.94, -0.17)
	Rate ratio 0.74 (0.58, 0.94)	Rate ratio 0.66 (0.48, 0.91)	
	26% reduction	**34% reduction**	*** ≥4.1 decrease clinically meaningful**

1. Post-hoc analyses. 2. Change from baseline to average of Week 24 through Week 52. 3. 40.6% of patients in mitapivat arm achieved Hb response, defined as ≥1.0 g/dL increase in average Hb from Week 24 through Week 52 compared to baseline.
SCPC = sickle cell pain crises; Hb = hemoglobin; PROMIS = Patient Reported Outcomes Measurement Information System.

Overall summary of safety

Number (%) of Subjects with	Placebo N=69	Mitapivat 100mg BID N=138
Any TEAEs	68 (98.6)	134 (97.1)
Grade ≥ 3 TEAEs	28 (40.6)	46 (33.3)
Treatment-related TEAEs	20 (29.0)	42 (30.4)
Grade ≥ 3 treatment-related TEAEs	2 (2.9)	7 (5.1)
Serious TEAEs	20 (29.0)	28 (20.3)
Serious treatment-related TEAEs	0	1 (0.7)
TEAEs leading to discontinuation of study drug	2 (2.9)	6 (4.3)
TEAEs leading to dose reduction	0	7 (5.1)
TEAEs leading to interruption of study drug	1 (1.4)	5 (3.6)
TEAEs leading to death	1 (1.4)	2 (1.4)
Treatment-related TEAEs leading to death	0	0

Not all deaths are captured as adverse events per protocol. There was one additional death in the placebo group and one in the mitapivat arm, bringing the total fatal cases to 3 (2.2%) in mitapivat and 2 (2.9%) in placebo. There were also 2 deaths in the screening period.

Favorable safety profile observed in RISE UP Phase 3 was consistent with that observed in prior mitapivat sickle cell disease trials

The denominator used to calculate percentages is N, the number of subjects in the safety analysis set within each treatment group.
TEAE = treatment-emergent adverse event.

Summary of key observations related to liver events

- Patients with SCD often have abnormal and fluctuating liver enzymes as part of their underlying disease
- The protocol excluded patients with aspartate aminotransferase >2.5x the upper limit of normal (ULN) (unless due to hemolysis and/or hepatic iron deposition) and alanine aminotransferase >2.5x the ULN (unless due to hepatic iron deposition)
- Liver abnormalities were observed across both treatment arms
- Any event that met pre-specified criteria[1] was reviewed for severity and causality for the likelihood of drug-induced liver injury, as was done for the thalassemia program
- No imbalance between subjects taking mitapivat (7, 5.1%) and placebo (3, 4.3%) with values meeting the lab constellation of concurrent laboratory values with the highest sensitivity for drug-induced liver injury[2]

No similar cases of drug-induced HCI as were observed in thalassemia – no change to safety profile

1. (ALT or AST) >5xULN, ALT or AST >3x ULN + Total Bilirubin >2x ULN (or >2x Baseline if total bilirubin is >ULN at baseline) + direct bilirubin >50%. 2. Any liver test abnormality that led to study drug modification, interruption, or discontinuation.
SCD = sickle cell disease; HCI = hepatocellular injury.

Phase 3 RISE UP trial – summary and next steps

Strong anti-hemolytic profile in total trial population with SCPC trend

- 40.6% of patients achieved significant Hb response (≥1 g/dL)
- Statistically significant improvement in other markers of hemolysis
  - Hb concentration
  - Indirect bilirubin

Clinically meaningful benefits in Hb-responders

- 1.6 g/dL mean increase from baseline in Hb concentration
- Improvement in SCPC-related endpoints:
  - 26% decrease in annualized rate of SCPC
  - 34% reduction in annualized rate of hospitalizations for SCPC
- Reduction in PROMIS-Fatigue T-score

Favorable safety profile

- No similar pattern of HCI as observed in thalassemia
- Low discontinuation rate in the double-blind period
- 174 out of 176 patients opted to rollover into open label extension

Intend to submit a marketing application for mitapivat in the U.S. for sickle cell disease, after having a pre-sNDA meeting with the FDA in Q1 2026

SCPC = sickle cell pain crises; Hb = hemoglobin; HCI = hepatocellular injury; sNDA = supplemental new drug application; PROMIS = patient reported outcomes measurement system.

Clinical perspective

KOL : Biree Andemariam, M.D.

Phase 3 RISE UP data supports mitapivat as meaningful potential treatment option for patients living with SCD

Patients living with sickle cell disease need therapies that –

Reduce anemia and hemolysis	Reduce vaso-occlusion	Lower healthcare utilization	Improve fatigue	Are well tolerated and safe

In Hb-responders, mitapivat showed benefit on measures related to these important factors

SCD = Sickle Cell Disease; Hb = hemoglobin

CEO Closing Remarks

Brian Goff, Chief Executive Officer

Phase 3 RISE UP trial – summary and next steps

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Favorable safety profile

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Clear corporate priorities

Maximize Mitapivat

Potential thalassemia FDA approval (PDUFA December 7th)

Preparation for potential sNDA filing in Sickle Cell Disease

Advance pipeline

Tebapivat Phase 2 LR-MDS and SCD

AG-236 Phase 1 PV

AG-181 Phase 1 PKU

Financial discipline

Remain committed to maximize shareholder value

Proactive steps to reduce operating expenses to extend cash runway; update to be provided early 2026

Remain committed to becoming sustainable rare disease company

PDUFA = Prescription Drug User Fee Act ; sNDA = supplemental new drug application ; SCD = sickle cell disease; LR-MDS = lower-risk myelodysplastic syndromes; PV = polycythemia vera; PKU = phenylketonuria.

Q&A session

Fueled by Connections to Transform Rare Diseases™

We build deep connections with rare disease communities, collaborating to develop and deliver innovative medicines that transform lives

"Unfortunately, many people still don't know what sickle cell disease is or how deeply it affects those living with it. It's striking that for decades there have been so few treatment options for SCD.

Surviving a stroke and multiple-organ failure in 2023 – and losing many friends to this illness – has driven me to advocate for better treatment options."

Kyle, SCD patient and advocate