ODYSSEY: A Phase 2 Open-Label Study of Momelotinib in Combination With Luspatercept in Patients With Transfusion-Dependent Myelofibrosis

ODYSSEY
Clinical Trial for Anemia in Myelofibrosis

Prithviraj Bose,[1] Aaron T. Gerds,[2] Vikas Gupta,[3] Bryan Strouse,[4] Bharat Patel,[4] Catherine E. Ellis,[4] Claire N. Harrison[5]

[1]University of Texas MD Anderson Cancer Center, Houston, TX, USA; [2]Cleveland Clinic Taussig Cancer Institute, Cleveland, OH, USA; [3]Princess Margaret Cancer Centre, Toronto, ON, Canada; [4]GSK plc, Collegeville, PA, USA; [5]Guy's and St Thomas' NHS Foundation Trust, London, UK

Background

- Anemia is a prevalent, progressive, and multifactorial clinical feature of myelofibrosis (MF) associated with negative impacts on health-related quality of life (QOL), survival, and healthcare resource utilization[1-5]
- Red blood cell (RBC) transfusions are frequently used to manage anemia, with nearly 50% of patients with primary MF requiring transfusions within a year after diagnosis[1,2]
  - Although transfusions may improve anemia-related symptoms, transfusion dependence is an independent negative prognostic factor for survival and is associated with poor QOL[5-7]
- Momelotinib is a Janus kinase (JAK) 1/JAK2/activin A receptor type 1 inhibitor approved for the treatment of intermediate- or high-risk MF in adults with anemia[8]
  - Across 3 phase 3 trials, momelotinib provided anemia-related benefits—including transfusion independence, reduced transfusion burden, and increased mean hemoglobin levels over time—as well as spleen and symptom benefits in both JAK inhibitor–naive and –experienced patients with MF[9-11]
- Luspatercept is an erythroid maturation agent approved for the treatment of anemia in β-thalassemia and lower-risk myelodysplastic syndromes[12]
  - Luspatercept was associated with anemia improvements in a phase 2 trial (ACE-536-MF-001) of patients with MF who had anemia across 4 cohorts defined by transfusion status (transfusion dependent [TD] or not) and current JAK inhibitor exposure (receiving a stable dose of ruxolitinib or not)[13]
  - The ongoing phase 3 INDEPENDENCE trial is investigating luspatercept in patients with MF who are receiving a stable dose of a JAK2 inhibitor and require RBC transfusions[14]

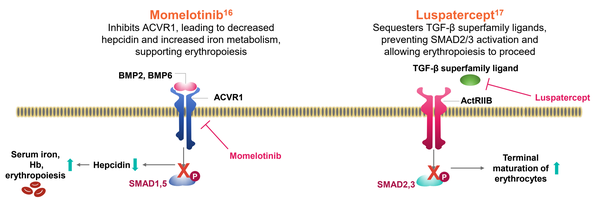
Rationale

- While most patients derive some anemia-related benefit from momelotinib, it is hypothesized that deeper reductions in transfusion burden in more patients may be achieved through combination with an additional anemia-directed therapy

Drug	Momelotinib[15]			Luspatercept[13]	
Trial	SIMPLIFY-1[9]	SIMPLIFY-2[10]	MOMENTUM[11]	ACE-536-MF-001	
Population	JAK inhibitor naive, anemic + nonanemic	JAK inhibitor experienced, anemic + nonanemic	JAK inhibitor experienced, anemic (Hb <10 g/dL)	Cohort 3B: TD, currently receiving a stable RUX dose	Cohort 2: TD, not receiving RUX
n	215	104	130	38	21
TI by week 24 per Gale criteria,[a] n % [95% CI][b]	170 (79.1) [73.0-84.3]	56 (53.8) [43.8-63.7]	63 (48.5) [39.6-57.4]	10 (26.3) [13.4-43.1]	2 (9.5) [1.2-30.4]

Hb, hemoglobin; JAK, Janus kinase; RUX, ruxolitinib; TD, transfusion dependent; TI, transfusion independent.
[a] No RBC transfusions for ≥12 weeks through week 24. [b] 95% CIs for TI by Gale criteria with momelotinib not previously reported.

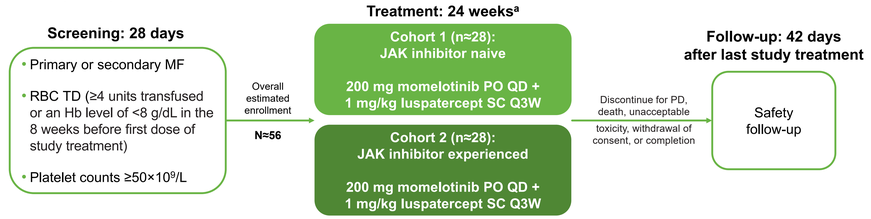
- The complementary mechanisms of action of momelotinib and luspatercept may provide anemia improvement for patients with TD MF by promoting both early- and late-stage erythropoiesis, while also damping inflammation and impacting various disease manifestations of TD MF
  - This combination will be evaluated in the phase 2 ODYSSEY trial



ActRIIB, activin A receptor type 2B; ACVR1, activin A receptor type 1; BMP, bone morphogenetic protein; Hb, hemoglobin; SMAD, mothers against decapentaplegic; TGF-β, transforming growth factor beta.

Study design

- ODYSSEY (NCT06517875) is an open-label, multicenter, global, phase 2 study evaluating the combination of momelotinib and luspatercept in TD patients with MF



The starting dose of luspatercept in combination with RUX was previously identified as **1.33 mg/kg**.[13]

While no additional toxicities are expected with momelotinib, the recommended starting dose is **1 mg/kg**, given the acute and sustained increase in Hb levels associated with momelotinib vs the acute and sustained decrease in Hb levels associated with RUX.[9]

In the absence of safety concerns or rapid increase in Hb levels of ≥2 g/dL compared with the previous cycle predose, **up-titration to 1.33 mg/kg and up to a maximum of 1.75 mg/kg** will be permitted (dose titration to occur not more frequently than Q6W).

Hb, hemoglobin; JAK, Janus kinase; MF, myelofibrosis; PD, progressive disease; PO, orally; Q3W, every 3 weeks; Q6W, every 6 weeks; QD, once daily; RBC, red blood cell; RUX, ruxolitinib; SC, subcutaneous; TD, transfusion dependent.
[a] Patients' final on-treatment study visit may occur in week 25 to ensure a full 24 weeks of treatment.

Endpoints

- All endpoints will be assessed in all patients who receive ≥1 dose of study drug; analyses will be descriptive

Primary endpoint	
TI response by week 24 (rolling 12-week criteria)	• No RBC transfusions (except in the case of clinically overt bleeding) for any ≥12-week interval through week 24
Secondary endpoints	
Safety and tolerability of momelotinib in combination with luspatercept	• Incidence of AEs, serious AEs, and AEs leading to discontinuation • Clinically important changes in laboratory parameters
TI response at week 24 (terminal 12-week criteria)	• No RBC transfusions and all Hb levels of ≥8 g/dL (except in the case of clinically overt bleeding) for ≥12 weeks immediately preceding week 24
Exposure of momelotinib and its active metabolite M21 in combination with luspatercept	• Plasma concentrations of momelotinib and M21
Exploratory endpoints	
Symptoms and QOL	• MFSAF v4.0 TSS response rate at week 24 (≥50% reduction in TSS over the 28 days immediately prior to week 24) • Change from baseline in FACT-An scores • Changes in PGIS and PGIC
Additional measures of anemia-related benefit	• Time to onset of TI (time from first dose until the first date of rolling TI response) • Transfusion burden reduction of ≥50% over any 12-week period through week 24 • Transfusion-free rate through week 24 • Hb improvement of ≥1, 1.5, or 2 g/dL over any 12-week period through week 24
Spleen	• Change in spleen length by palpation below the LCM
Additional pharmacokinetics	• Parameter values of momelotinib and M21, as data permit
Relationship between momelotinib and M21 exposure and clinical endpoints	• Exposure response between momelotinib and/or M21 exposure and clinical endpoints of interest, as data permit • Pharmacokinetic/dynamic modeling of Hb, as data permit
Luspatercept exposure in combination with momelotinib	• Plasma concentration of luspatercept
Biomarkers	• Changes in various biomarkers at baseline and on-treatment via blood-based evaluation (eg, peripheral iron metabolism markers and inflammatory cytokines)

AE, adverse event; FACT-An, Functional Assessment of Cancer Therapy – Anemia; Hb, hemoglobin; LCM, left costal margin; MFSAF, Myelofibrosis Symptom Assessment Form; PGIC, Patient Global Impression of Change; PGIS, Patient Global Impression of Severity; QOL, quality of life; RBC, red blood cell; TI, transfusion independent; TSS, Total Symptom Score.

Eligibility

Inclusion Criteria

- Age **≥18 years**
- Confirmed **primary, post-ET, or post-PV MF**
- **Cohort 1:** JAK inhibitor naive
- **Cohort 2:** Previously treated with **RUX or FED** for ≥90 days or ≥28 days if complicated by transfusion dependence or grade 3/4 thrombocytopenia, anemia, or hematoma
  No taper or washout required
- **High-, intermediate-2–, or intermediate-1–risk** disease per DIPSS/DIPSS-plus
- **TD:** ≥4 RBC units transfused or an Hb level of <8 g/dL in the 8 weeks before first dose of study treatment[a]
- **No allogeneic stem cell transplant** planned
- **Platelet counts of ≥50×10⁹/L** to ≤1000×10⁹/L[b]
- **Adequate organ function:**

Measure	Laboratory value
ANC	≥750/μL (≥0.75×10⁹/L)
Peripheral blast count	<5%
eGFR calculated by CKD-EPI	≥30 mL/min
Direct bilirubin	Bilirubin ≤1.5 × ULN (isolated bilirubin >1.5 × ULN is acceptable if bilirubin is fractionated and direct bilirubin is ≤35%)
AST and ALT *or* **For participants where liver is involved by extramedullary hematopoiesis as judged by investigator or if related to iron chelator therapy that was started within the prior 60 days**	≤3 × ULN ≤5 × ULN

Exclusion Criteria

- History of intestinal disease, IBD, major gastric surgery, or other **GI condition** likely to alter absorption of study drug
- **Invasive malignancy** other than study indication, currently or within the past 5 years
- Clinically significant anemia due to iron, vitamin B_{12}, or folate deficiencies or other **causes of anemia other than MF**
- Uncontrolled intercurrent illnesses, including **active infections, active or chronic bleeding** of grade ≥2**, or liver disease**
- Uncontrolled **hypertension** (repeated elevations of systolic BP ≥140 mm Hg or diastolic BP ≥90 mm Hg)
- Unstable angina pectoris, symptomatic congestive heart failure, uncontrolled cardiac arrythmia, **stroke, DVT, or embolism** within 6 months prior to first dose of study drug
- **QTc interval** of >450 msec or QTc of >480 msec for participants with bundle branch block
- **Peripheral neuropathy** of grade ≥2
- **Active anti-MF therapy** (other than RUX or FED in cohort 2) within 28 days prior to first dose of study drug
- **Prior treatment** with an ACVR1 inhibitor (eg, momelotinib, pacritinib) or inhibitor of TGF-β superfamily signaling (eg, luspatercept, sotatercept, elritercept)
- **Prior splenectomy**
- Known positive status for **HIV or hepatitis A, B, or C**
- Known **contraindication** or **hypersensitivity** to momelotinib and its metabolites, luspatercept, or any of their excipients
- **Psychiatric illness** or social situation that may **limit compliance**
- **Pregnant or breastfeeding**

ACVR1, activin A receptor type 1; ALT, alanine aminotransferase; ANC, absolute neutrophil count; AST, aspartate aminotransferase; BP, blood pressure; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; DIPSS, Dynamic International Prognostic Scoring System; DVT, deep vein thrombosis; eGFR, estimated glomerular filtration rate; ET, essential thrombocythemia; FED, fedratinib; GI, gastrointestinal; Hb, hemoglobin; IBD, inflammatory bowel disease; JAK, Janus kinase; MF, myelofibrosis, PV, polycythemia vera; RBC, red blood cell; RUX, ruxolitinib; TD, transfusion dependent; TGF-β, transforming growth factor beta; ULN, upper limit of normal.
[a] Only transfusions given when Hb levels are ≤9.5 g/dL are counted; transfusions for clinically overt bleeding or accident/injury are not counted. [b] Without need for platelet transfusion within 14 days of study day 1.

Study information

ODYSSEY will begin enrolling in Q1 2025 in:

Canada, France, Germany, Italy, Spain, United States

ClinicalTrials.gov: https://clinicaltrials.gov/study/NCT06517875

Study Contact: GSKClinicalSupportHD@gsk.com

Abbreviations

ActRIIB, activin A receptor type 2B; ACVR1, activin A receptor type 1; AE, adverse event; ALT, alanine aminotransferase; ANC, absolute neutrophil count; AST, aspartate aminotransferase; BMP, bone morphogenetic protein; BP, blood pressure; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; DIPSS, Dynamic International Prognostic Scoring System; DVT, deep vein thrombosis; eGFR, estimated glomerular filtration rate; ET, essential thrombocythemia; FACT-An, Functional Assessment of Cancer Therapy – Anemia; FED, fedratinib; GI, gastrointestinal; Hb, hemoglobin; IBD, inflammatory bowel disease; JAK, Janus kinase; LCM, left costal margin; MF, myelofibrosis; MFSAF, Myelofibrosis Symptom Assessment Form; PD, progressive disease; PGIC, Patient Global Impression of Change; PGIS, Patient Global Impression of Severity; PO, orally; PV, polycythemia vera; Q3W, every 3 weeks; Q6W, every 6 weeks; QD, once daily; QOL, quality of life; RBC, red blood cell; RUX, ruxolitinib; SMAD, mothers against decapentaplegic; SC, subcutaneous; TD, transfusion dependent; TGF-β, transforming growth factor beta; TI, transfusion independent; TSS, Total Symptom Score; ULN, upper limit of normal.

References

1. Naymagon L, et al, *Hemasphere.* 2017;1:e1.
2. Tefferi A, et al. *Mayo Clin Proc.* 2012;87:25-33.
3. Tefferi A, et al. *Clin Ther.* 2014;36:560-566.
4. Nicolosi M, et al. *Leukemia.* 2018;32:1254-1258.
5. Gerds AT, et al. *J Manag Care Spec Pharm.* Published online October 3, 2024.
6. Elena C, et al. *Haematologica.* 2011;96:167-170.
7. Mesa R, et al. ASCO 2023. Poster 7066.
8. Ojjaara (momelotinib). Prescribing information. GSK; 2023.
9. Mesa RA, et al. *J Clin Oncol.* 2017;35:3844-3850.
10. Harrison CN, et al. *Lancet Haematol.* 2018;5:e73-e81.
11. Verstovsek S, et al. *Lancet.* 2023;401:269-280.
12. Reblozyl (luspatercept). Prescribing information. Bristol Myers Squibb; 2024.
13. Gerds AT, et al. *Blood Adv.* 2024;8:4511-4522.
14. ClinicalTrials.gov. Accessed November 15, 2024. https://clinicaltrials.gov/study/NCT04717414.
15. Klencke B, et al. *Future Oncol.* 2024;20:703-715.
16. Asshoff M, et al. *Blood.* 2017;129:1823-1830.
17. Molica M, Rossi M. *Expert Opin Biol Ther.* 2024;24:233-241.

Acknowledgments

ODYSSEY (NCT06517875) is sponsored by GSK (study 220752).

Medical writing support for this Trials in Progress poster was provided by Amy Ghiretti, PhD, of Nucleus Global, an Inizio company, and funded by GSK.

 Presenting author: Prithviraj Bose, PBose@mdanderson.org