(S297) ETAVOPIVAT IMPROVES HEMOGLOBIN LEVELS IN ADULTS AND ADOLESCENTS WITH NON-TRANSFUSION-DEPENDENT ALPHA- OR BETA-THALASSEMIA: RESULTS FROM THE OPEN-LABEL PHASE 2 GLADIOLUS STUDY

Topic: 28. Thalassemias

Sujit Sheth*[1], Kevin H. M. Kuo[2, 3], Theodosia A. Kalfa[4], D. Mark Layton[5], Perla Eleftheriou[6], Anastasios Giakoumis[7], Olga Polyanskaya[8], Navid Nedjatian[9], Ashutosh Lal[10]

[1]Weill Cornell Medicine, New York, New York, United States of America;[2]University of Toronto, Toronto, Ontario, Canada; [3]Scarborough Health Network Research Institute, Toronto, Ontario, Canada;[4]Cincinnati Children's Hospital Medical Center and University of Cincinnati College of Medicine, Cincinnati, OH, United States of America; [5]Hammersmith Hospital, Imperial College Healthcare NHS Trust, London, United Kingdom; [6]University College London Hospital, London, United Kingdom; [7]Novo Nordisk A/S, Bagsvaerd, Denmark; [8]Novo Nordisk Inc., Lexington, MA, United States of America; [9]Novo Nordisk Health Care AG, Zurich, Switzerland; [10]UCSF School of Medicine, San Francisco, CA, United States of America;

Background

People with non-transfusion-dependent thalassemia (NTDT) experience progressive morbidity from chronic anemia driven by ineffective erythropoiesis and hemolysis, leading to iron overload, organ damage, fatigue, and reduced quality of life. Etavopivat is an investigational, once-daily (QD), red blood cell (RBC) pyruvate kinase activator under evaluation as a disease-modifying therapy in people with sickle cell disease and thalassemia.

Aims

Evaluate safety and clinical activity of etavopivat during the phase 2, multicenter, open-label gladiolus study (NCT04987489) in participants (ppts) with thalassemia not receiving chronic RBC transfusions (cohort C).

Methods

Eligible cohort C ppts (aged 12–65 years) with thalassemia gave informed consent, had baseline (BL) hemoglobin (Hb) ≤10 g/dL, and did not have RBC transfusions within 8 weeks of enrollment, ≥4 RBC units or a transfusion-free period ≤35 days in the prior 6 months. Ppts received oral etavopivat 400 mg QD for the main (48-week [wk]) and extension period until rollover to FLORAL (NCT06609226) or discontinuation. The primary endpoint was Hb response rate (increase ≥1.0 g/dL from BL) at wk 12. Secondary endpoints included Hb response rates at wks 24 and 48, changes from BL in Hb and serum ferritin at wks 12, 24, and 48, and liver iron concentration at wk 48. An exploratory endpoint assessed PROMIS Fatigue Scale 7a (≥18 years) and 10a (<18 years). Additional analyses evaluated markers of hemolysis (absolute reticulocyte count, indirect bilirubin, lactate dehydrogenase), ineffective erythropoiesis (erythropoietin, erythroferrone, soluble transferrin receptor), and iron metabolism (hepcidin). Pharmacodynamic markers adenosine triphosphate (ATP) and 2,3-diphosphoglycerate (2,3-DPG) were analyzed. Safety was assessed over the main and extension period + 28 days.

Copyright Information: (Online) ISSN: 2572-9241
©2026 The Author(s). HemaSphere is published by John Wiley & Sons Ltd on behalf of European Hematology Association. This is an open access Abstract Book distributed under the Attribution-NonCommercial-NoDerivs (CC BY-NC-ND), which allows third parties to download the articles and share them with others as long as they credit the author and the Abstract Book, but they cannot change the content in any way or use them commercially.
Abstract Book Citations: Authors, Title, HemaSphere, 2026;10:(S1):pages. The abstract book DOIs can be found on the "Author Information" page.
Disclaimer: Articles published in the journal HemaSphere exclusively reflect the opinions of the authors. The authors are responsible for all content in their abstracts including accuracy of the facts, statements, citing resources, etc.

Results

Twenty ppts (15 female, 16 adults, 11 β-thalassemia [5 Hb E β-thalassemia], 9 Hb H thalassemia, 3 splenectomized) enrolled in cohort C. Mean (SD) age was 31.4 (14.77) years and BL Hb was 7.66 (0.929) g/dL. Four ppts discontinued etavopivat early.
Hb response was achieved in 50% of ppts (n/N=10/20) at wk 12, 39% at wk 24 (7/18), and 38% at wk 48 (6/16). Hb levels increased from wk 2 and were sustained through wk 48 (least squares mean changes [SE] from BL at wks 12, 24, and 48 were 1.12 [0.158] g/dL, 0.88 [0.166] g/dL, 0.91 [0.176] g/dL, respectively; all p<0.0001). Markers of ineffective erythropoiesis, hemolysis, and iron metabolism improved over time (**Table**). Early and sustained changes in ATP and 2,3-DPG supported etavopivat's mechanism of action. At BL, PROMIS Fatigue scores were worse than the general population (mean [SD] adults: 58.41 [9.158]; adolescents: 55.50 [12.633]) and improved in adults over the study; no change was observed in adolescents.
Etavopivat was well tolerated; safety findings were consistent with the underlying disease, with no new safety concerns. Most treatment-emergent adverse events (TEAEs) were mild/moderate; one TEAE (elevated alanine aminotransferase [ALT]) led to treatment discontinuation. Six serious AEs were reported; none considered drug related. Three ppts experienced Grade 2 (n=2) or 3 (n=1) ALT elevations; three experienced Grade 2 aspartate aminotransferase elevations.

Summary/Conclusion

These results from the gladiolus study demonstrated proof of concept for etavopivat, indicating favorable efficacy in people with NTDT, and no new safety findings. These findings support further investigation of etavopivat in thalassemia.

Copyright Information: (Online) ISSN: 2572-9241
©2026 The Author(s). HemaSphere is published by John Wiley & Sons Ltd on behalf of European Hematology Association. This is an open access Abstract Book distributed under the Attribution-NonCommercial-NoDerivs (CC BY-NC-ND), which allows third parties to download the articles and share them with others as long as they credit the author and the Abstract Book, but they cannot change the content in any way or use them commercially.
Abstract Book Citations: Authors, Title, HemaSphere, 2026;10:(S1):pages. The abstract book DOIs can be found on the "Author Information" page.
Disclaimer: Articles published in the journal HemaSphere exclusively reflect the opinions of the authors. The authors are responsible for all content in their abstracts including accuracy of the facts, statements, citing resources, etc.

Table: Summary of endpoints and analyses for cohort C of the gladiolus study.

	Week 12 (n=20)	**Week 24** (n=18)	**Week 48** (n=16)
Primary endpoint			
Ppts achieving Hb ≥1.0 g/dL increase at week 12, % (95% CI)	50 (27.2, 72.8), p<0.0001	-	-
Secondary endpoints			
Ppts achieving Hb ≥1.0 g/dL increase at week 24, % (95% CI)	-	39 (17.3, 64.3), p=0.0012	-
Ppts achieving Hb ≥1.0 g/dL increase at week 48, % (95% CI)	-	-	38 (15.2, 64.6), p=0.0033
CFB in Hb (g/dL)	1.12 (0.158), p<0.0001	0.88 (0.166), p<0.0001	0.91 (0.176), p<0.0001
CFB in serum ferritin (pmol/L)	113.7 (72.25), p=0.12	18.6 (76.40), p=0.81	–56.4 (77.14), p=0.47
Exploratory endpoints			
CFB in PROMIS Fatigue score in adult ppts (n=16)	–5.57 (1.646)	–4.52 (1.718)	–5.45 (1.791)
CFB in PROMIS Fatigue score in adolescent ppts (n=4)	–6.31 (4.326)	–8.75 (5.023)	–3.89 (4.318)
Pharmacodynamic endpoints			
CFB in ATP (µg/mL), mean (SD)	131.0 (56.91)	119.6 (61.55)	86.8 (71.46)
CFB in 2,3-DPG (µg/mL), mean (SD)	–112.9 (99.24)	–187.8 (175.08)	–179.0 (112.32)
Additional analyses			
Markers of hemolysis			
CFB in ARC (10^9/L)	–17.86 (20.985), p=0.40	–36.37 (22.168), p=0.10	–37.16 (24.439), p=0.13
CFB in indirect bilirubin (µmol/L)	–4.93 (2.714), p=0.072	–5.48 (2.825), p=0.055	–3.14 (3.009), p=0.30
CFB in LDH (IU/L)	–63.69 (25.331), p=0.013	–81.16 (27.203), p=0.0034	–75.88 (28.465), p=0.0088
Markers of ineffective erythropoiesis			
CFB in erythropoietin (mIU/mL)	–60.13 (18.180), p=0.0021	–40.69 (19.488), p=0.043	–37.39 (20.366), p=0.074
CFB in erythroferrone (ng/mL)	–8.367 (2.5757), p=0.0023	–8.981 (2.7417), p=0.0022	–12.829 (3.3267), p=0.0004
CFB in sTfR (mg/L)	–1.255 (0.3195), p=0.0016	–1.720 (0.2919), p<0.0001	–2.316 (0.5781), p=0.0039
Markers of iron metabolism			
CFB in hepcidin (ng/mL)	3.41 (3.333), p=0.31	5.16 (3.536), p=0.15	–0.39 (4.293), p=0.93

Table shows LS mean CFB (SE) unless otherwise indicated. BL was defined as the arithmetic mean of the Screening and Day 1 (pre-dose) results for all parameters, except for pharmacodynamic, ineffective erythropoiesis, and iron metabolism markers, where BL was defined as the most recent non-missing measurement prior to the first administration of the study drug. LS mean, SE, 95% CI, and p-value are based on an MMRM with CFB as the response and fixed covariates for BL value and nominal visit and a random effect for ppt. LS means reported for each visit are model-adjusted estimates based on the MMRM fitted to all available post-BL data up to the end of the extension treatment period. The variance–covariance matrix used an autoregressive structure of order 1 for parameter estimation, except for sTfR which used an unstructured structure. The proportion of ppts with an Hb response was compared with a 10% null rate using a one-sided exact binomial test (α = 0.025). P-values were not calculated for pharmacodynamic endpoints. 2,3-DPG, 2,3-diphosphoglycerate; ARC, absolute reticulocyte count; ATP, adenosine triphosphate; BL, baseline; CFB, change from baseline; CI, confidence interval; Hb, hemoglobin; LDH, lactate dehydrogenase; LS, least squares; MMRM, mixed model repeated measures; ppts, participants; SD, standard deviation; SE, standard error; sTfR, soluble transferrin receptor.

Copyright Information: (Online) ISSN: 2572-9241
©2026 The Author(s). HemaSphere is published by John Wiley & Sons Ltd on behalf of European Hematology Association. This is an open access Abstract Book distributed under the Attribution-NonCommercial-NoDerivs (CC BY-NC-ND), which allows third parties to download the articles and share them with others as long as they credit the author and the Abstract Book, but they cannot change the content in any way or use them commercially.
Abstract Book Citations: Authors, Title, HemaSphere, 2026;10:(S1):pages. The abstract book DOIs can be found on the "Author Information" page.
Disclaimer: Articles published in the journal HemaSphere exclusively reflect the opinions of the authors. The authors are responsible for all content in their abstracts including accuracy of the facts, statements, citing resources, etc.