Long-term improvements in patient-reported outcomes in patients with pyruvate kinase deficiency treated with mitapivat

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  - **KHM Kuo**: Agios, Alexion, Apellis, bluebird bio, Celgene, Forma, Novartis, Pfizer – consultancy; Alexion, Novartis – honoraria; Bioverativ – membership on an entity's Board of Directors or advisory committees; Pfizer – research funding
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  - **P Patel**: employee of Agios Pharmaceuticals, Inc.
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  - **J Li**: employee of Agios Pharmaceuticals, Inc.
  - **E Zagadailov**: employee of Agios Pharmaceuticals, Inc.

Pyruvate kinase (PK) deficiency

- Rare, hereditary hemolytic anemia caused by a single gene defect encoding the red blood cell-specific form of PK[1–4]
- Associated with acute and long-term complications[3]
- Spectrum of signs and symptoms, including jaundice, fatigue, and dyspnea, with a wide-ranging impact on health-related quality of life (HRQoL)[5]
- Iron overload, regular transfusions, and pulmonary hypertension have been consistently associated with worse health-related outcomes in PK deficiency[6,7]
- Generic and cancer-specific patient-reported outcome (PRO) instruments of HRQoL are likely insensitive to many of the unique aspects of congenital hemolytic anemias that reduce quality of life in PK deficiency, including iron overload and chronic jaundice[6]

HRQoL, health-related quality of life; PK, pyruvate kinase; PRO, patient-reported outcome

1. Grace RF et al. *Am J Hematol* 2015;90:825–30; 2. Zanella A et al. *Br J Haematol* 2005;130:11–25; 3. Grace RF et al. *Blood* 2018;131:2183–92; 4. van Beers EJ et al. *Haematologica* 2019;104:e51–3; 5. Grace RF et al. *Eur J Haematol* 2018;101:758–65; 6. Al-Samkari et al. *Blood Adv* 2022;6:1844–53; 7. Al-Samkari H et al. *N Engl J Med* 2022;386:1432–42

Patients report physical limitations, negative impacts on social functioning, reduced self-esteem, and concerns for the future

- Conceptual model of the burden and impact of PK deficiency on HRQoL, based on the signs, symptoms, and impacts reported[a] by 21 adult patients with PK deficiency[b,1]

Symptoms of anemia
- Fatigue
- Tiredness
- Lack of/low energy
- Exhaustion
- Weakness
- Dizziness/light-headedness
- Shortness of breath
- Decreased stamina

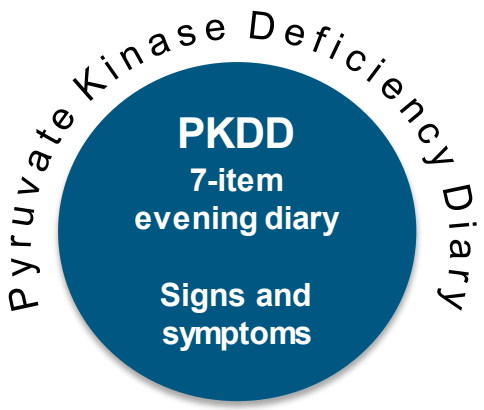
Appearance-related signs due to chronic hemolytic anemia
- Jaundice (yellow eyes and/or skin)
- Pale skin

Other signs and symptoms
- Cognitive impairment
- Bone pain
- Joint pain

Physical limitations	Appearance	Activities of daily living	Social impacts	Emotional impacts
• Need for additional rest • Difficulty with exercise/sports • Difficulty climbing stairs/walking uphill • Susceptibility to illness	• Negative impact on appearance	• Difficulty with household activities • Lack of motivation • Less productive	• Negative impact on social activities • Negative impact on relationships with family/ friends • Receiving unwanted attention	• Concerns about the future

[a]1-hour interviews were conducted to better understand the burden of PK deficiency in terms of signs, symptoms, and impact of the disease on participants' HRQoL; [b]Participants were primarily recruited through the Pyruvate Kinase NHS (NCT02053480) via a recruitment flyer distributed by NHS investigators. Participants were also recruited through a patient advisory board, a PK deficiency patient advocacy/support website, and a Facebook support page; HRQoL, health-related quality of life; PK, pyruvate kinase; 1. Grace RF et al. *Eur J Haematol* 2018;101:758–65

The PKDD and PKDIA were developed as self-administered tools to assess and capture changes in symptom burden and disease impact in patients with PK deficiency



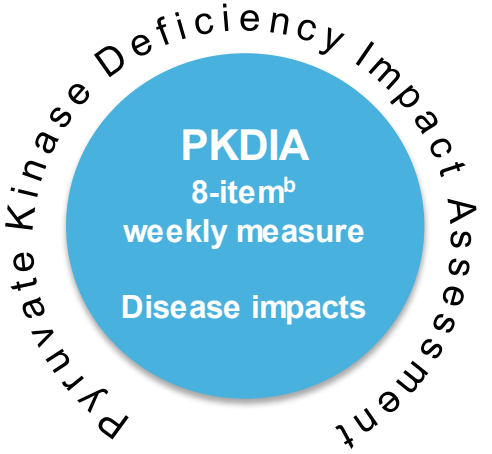
1. Tiredness at its worst
2. Tired after finishing daily activities
3. Jaundice
4. Bone pain
5. Shortness of breath
6. Energy level at beginning of day
7. Energy level at end of day

Daily sum score

Scoring algorithm

T-score
Mean 50, SD 10
Min 25, Max 76

MCIC[a] is a reduction of 4.2



1. Finishing things you wanted to get done
2. Household activities
3. Negative impact on social activities
4. Negative impact on leisure activities
5. Relationships with friends or family negatively affected
6. Difficulty concentrating
7. Difficulty performing moderate physical activity
8. Needing additional rest or sleep

Sum score

Scoring algorithm

T-score
Mean 50, SD 10
Min 30, Max 76

MCIC[a] is a reduction of 5.5

In-trial validation

High internal consistency ☑

Excellent retest reliability ☑

Higher score = higher disease burden

[a]MCIC is estimated using the median change for patients achieving an anchor-based 1-point improvement in PGIS in the ACTIVATE study; [b]Baseline IRT modeling revealed that 4 of the original 12 items were less relevant to the ACTIVATE trial population or did not contribute unique information due to skewness or redundancy and were removed, thus becoming non-scored items; HRQoL, health-related quality of life; IRT, item response theory; MCIC, minimal clinically important change; PGIS, Patient Global Impression of Severity; PK, pyruvate kinase; PKDD, PK Deficiency Diary; PKDIA, PK Deficiency Impact Assessment

Mitapivat

- First-in-class, oral, allosteric activator of PK[1]
- Demonstrated improvements in hemoglobin, hemolysis, and transfusion burden in PK deficiency patients[1]
- Approved by the US Food and Drug Administration for the treatment of hemolytic anemia in adults with PK deficiency[1]
- Improvements in signs, symptoms, and disease impacts via PKDD and PKDIA were observed in two global, phase 3 trials of mitapivat in non regularly (ACTIVATE[a]) or regularly transfused (ACTIVATE-T[b]) adults with PK deficiency[1,2]

[a]ClinicalTrials.gov: NCT03548220; [b]ClinicalTrials.gov: NCT03559699
PK, pyruvate kinase; PKDD, PK Deficiency Diary; PKDIA, PK Deficiency Impact Assessment
1. Al-Samkari H et al. *N Engl J Med* 2022;386:1432–42; 2. Glenthøj A et al. *Lancet Haematol* 2022;S2352–3026(22)00214–9

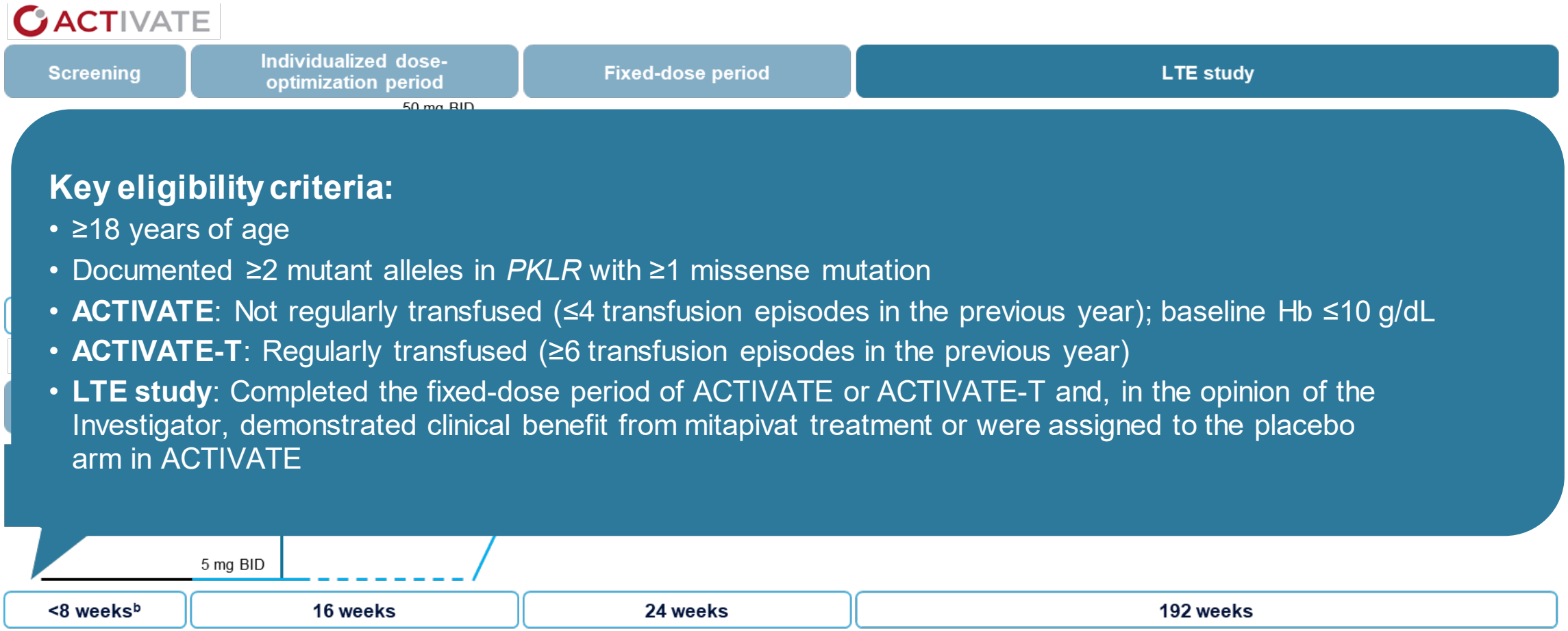
Objectives

- To evaluate the long-term safety, tolerability, and efficacy of treatment with mitapivat in adult participants who were previously enrolled in ACTIVATE or ACTIVATE-T in a multicenter, open-label, long-term extension (LTE) study (ClinicalTrials.gov: NCT03853798)

Here, we report PKDD and PKDIA outcomes up to Week 84 of the LTE study

LTE, long-term extension; PK, pyruvate kinase; PKDD, PK Deficiency Diary; PKDIA, PK Deficiency Impact Assessment

Patients who completed ACTIVATE and ACTIVATE-T could enter the open-label LTE, where all patients received mitapivat



Key eligibility criteria:

- ≥18 years of age
- Documented ≥2 mutant alleles in *PKLR* with ≥1 missense mutation
- **ACTIVATE**: Not regularly transfused (≤4 transfusion episodes in the previous year); baseline Hb ≤10 g/dL
- **ACTIVATE-T**: Regularly transfused (≥6 transfusion episodes in the previous year)
- **LTE study**: Completed the fixed-dose period of ACTIVATE or ACTIVATE-T and, in the opinion of the Investigator, demonstrated clinical benefit from mitapivat treatment or were assigned to the placebo arm in ACTIVATE

[a]Stratified by average of screening Hb values (<8.5 g/dL vs ≥8.5 g/dL) and *PKLR* gene mutation category (missense/missense vs missense/non-missense); [b]Screening may have been extended beyond 8 weeks if there was a delay in obtaining a patient's complete transfusion history or to ensure that the first dose of study drug could be administered 2–7 days after the most recent transfusion
BID, twice daily; Hb, hemoglobin; LTE, long-term extension; M, continued mitapivat; M/M, mitapivat-to-mitapivat; P/M, placebo-to-mitapivat; R, randomized

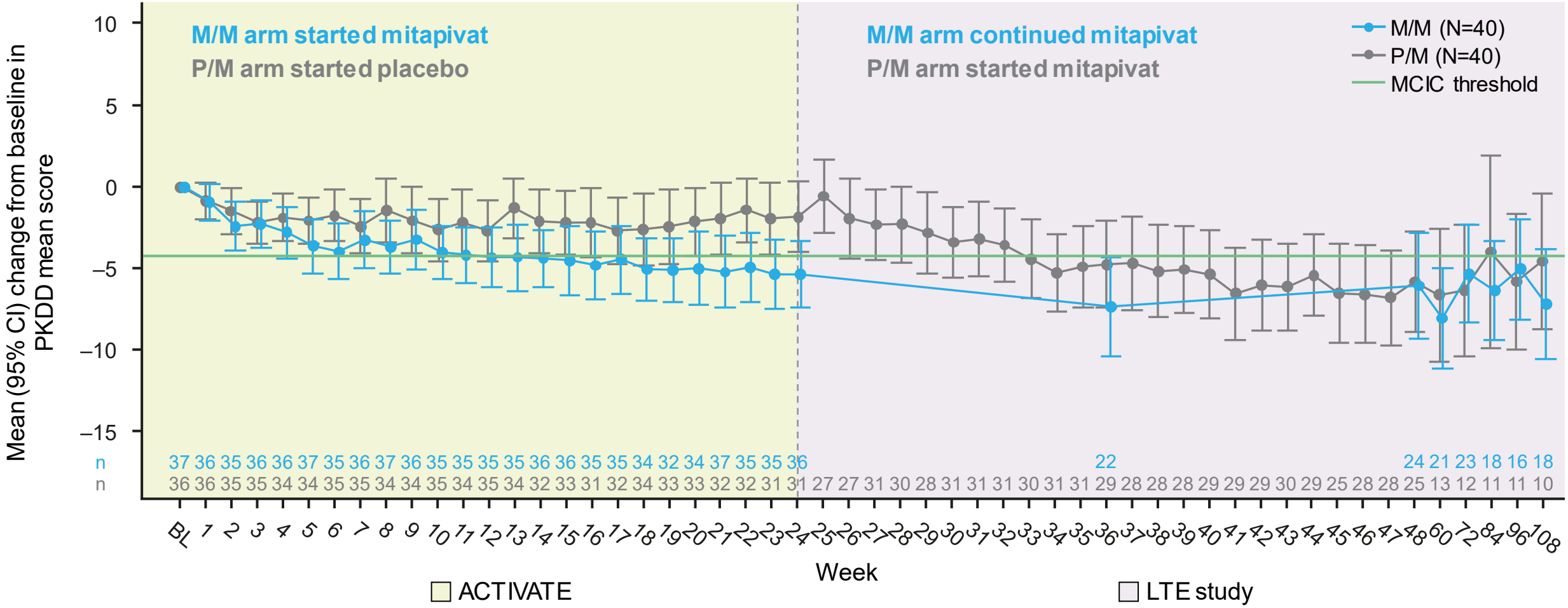
Analyses

- Changes from baseline[a] in PKDD weekly mean and PKDIA scores were assessed at scheduled visits up to Week 84 (data cutoff 27March2022)
  - Summary statistics including mean, SD, min, first quartile (Q1), median, third quartile (Q3), and max were provided
- Results were summarized for each of the 3 treatment arms:
  - Mitapivat in ACTIVATE and continued mitapivat in the LTE (**M/M**)
  - Placebo in ACTIVATE and started mitapivat in the LTE (**P/M**)
  - Mitapivat in ACTIVATE-T and continued mitapivat in the LTE (**M**)
- Proportions of patients who achieved minimal clinically important change (MCIC) at Week 84 of the LTE study were also reported
  - The MCIC is defined as a reduction of 4.2 and 5.5 in PKDD and PKDIA scores, respectively

[a]Defined as the last complete assessment before start of study treatment in ACTIVATE/ACTIVATE-T
LTE, long-term extension; M, mitapivat; MCIC, minimal clinically important change; M/M, mitapivat-to-mitapivat; PK, pyruvate kinase; PKDD, PK Deficiency Diary; PKDIA, PK Deficiency Impact Assessment; P/M, placebo-to-mitapivat; Q, quartile; SD, standard deviation

Patients enrolled in ACTIVATE sustained improvements in PKDD mean scores throughout the extension period

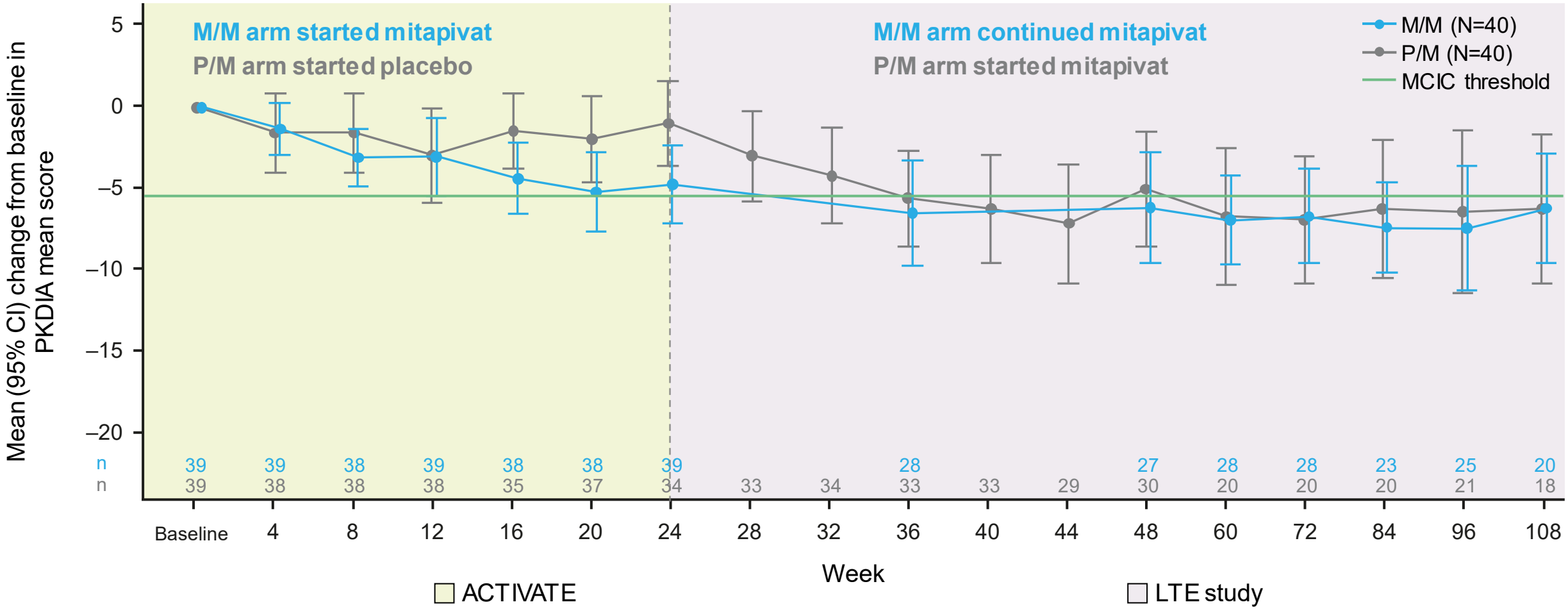
Mean change from baseline in PKDD mean scores in patients randomized to mitapivat or placebo in ACTIVATE who then continued in the LTE study on mitapivat



BL is defined as the last complete assessment (with no missing item in response) before randomization for subjects randomized and not dosed, or before start of study treatment for subjects randomized and dosed.
In the LTE study, PKDIA scores were assessed at 12-week intervals for the M/M arm
BL, baseline; CI, confidence interval; LTE, long-term extension; MCIC, minimal clinically important change; M/M, mitapivat-to-mitapivat; PKDD, Pyruvate Kinase Deficiency Diary; P/M, placebo-to-mitapivat

Patients enrolled in ACTIVATE also sustained improvements in PKDIA mean scores throughout the extension period

Mean change from baseline in PKDIA mean scores in patients randomized to mitapivat or placebo in ACTIVATE who then continued in the LTE study on mitapivat

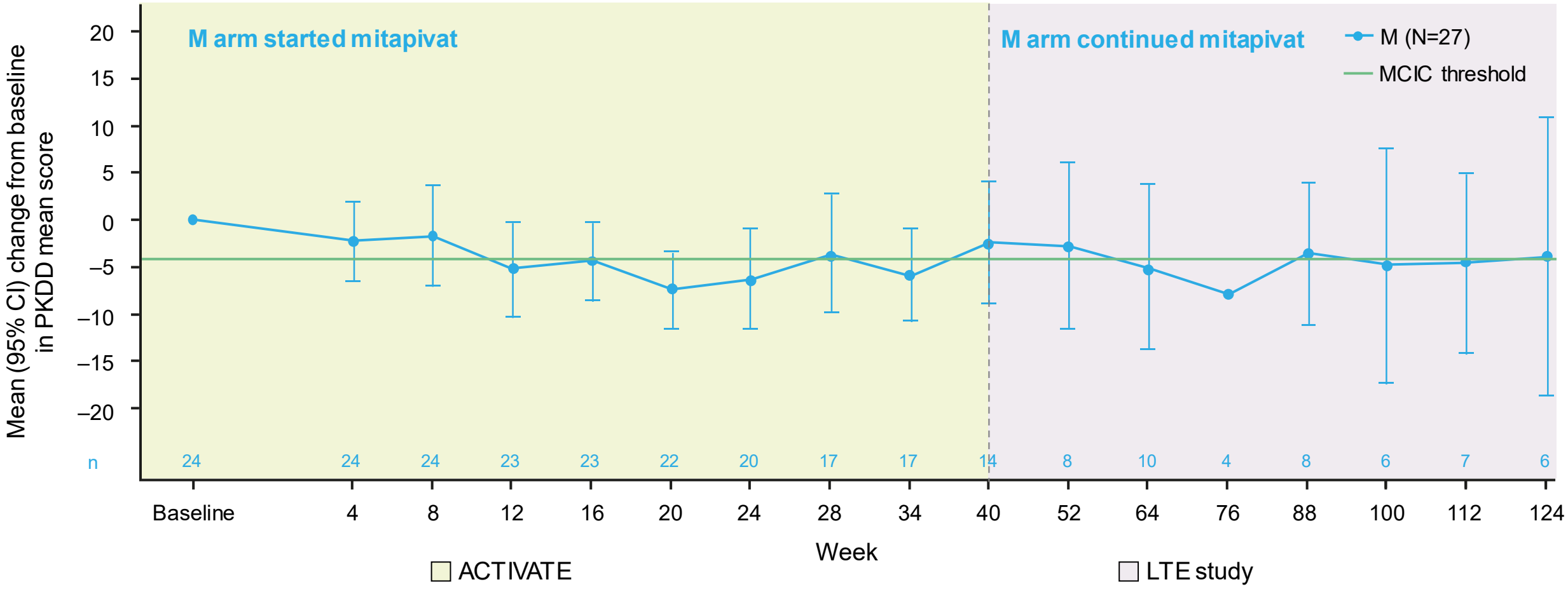


Baseline is defined as the last complete assessment (with no missing item in response) before randomization for subjects randomized and not dosed, or before start of study treatment for subjects randomized and dosed. In the LTE study, PKDIA scores were assessed at 12-week intervals for the M/M arm

CI, confidence interval; LTE, long-term extension; MCIC, minimal clinically important change; M/M, mitapivat-to-mitapivat; PKDIA, Pyruvate Kinase Deficiency Impact Assessment, P/M, placebo-to-mitapivat

Patients enrolled in ACTIVATE-T continued to experience improved PKDD mean scores throughout the extension period

Mean change from baseline in PKDD mean scores in patients enrolled in ACTIVATE-T who then continued in the LTE study

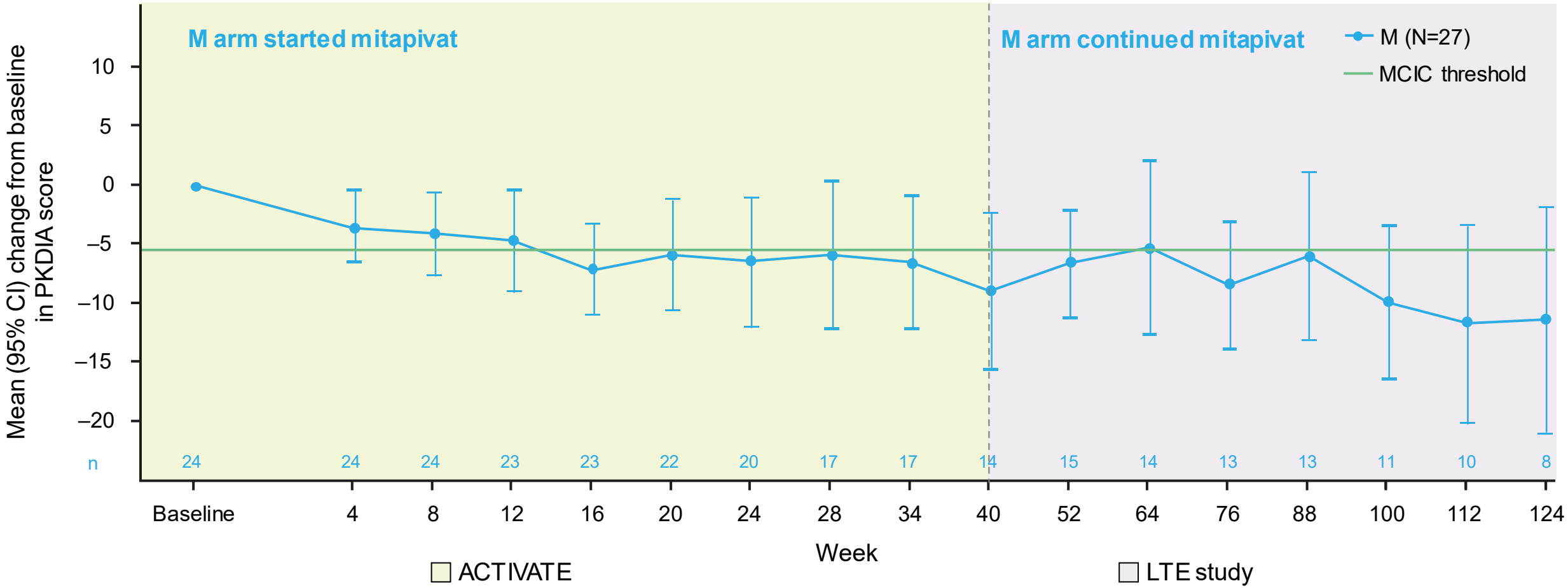


Baseline is defined as the last complete assessment (with no missing item in response) before start of study treatment. Not all patients included in ACTIVATE-T continued into the LTE study period, resulting in a small sample size for this analysis. Further, not all patients who entered the LTE were treated at Week 84 and above; of the patients who did receive treatment up to Week 84, data were unavailable for some individuals

CI, confidence interval; LTE, long-term extension; M, mitapivat; MCIC, minimal clinically important change; PKDD, Pyruvate Kinase Deficiency Diary

Patients enrolled in ACTIVATE-T also continued to experience improvements in PKDIA mean scores throughout the extension period

Mean change from baseline in PKDIA scores in patients enrolled in ACTIVATE-T who then continued in the LTE study



Baseline is defined as the last complete assessment (with no missing item in response) before start of study treatment. Not all patients included in ACTIVATE-T continued into the LTE study period, resulting in a small sample size for this analysis. Further, not all patients who entered the LTE were treated at Week 84 and above; of the patients who did receive treatment up to Week 84, data were unavailable for some individuals

CI, confidence interval; LTE, long-term extension; M, mitapivat; MCIC, minimal clinically important change; PKDIA, Pyruvate Kinase Deficiency Impact Assessment

At Week 84 of the LTE, more than half of patients had clinically meaningful improvements from baseline in both PKDD and PKDIA mean scores

Week 84 of the LTE	M/M arm (N=40)	P/M arm (N=40)	M arm (N=27)
Change from baseline in PKDD scores			
n	18	10	6
Mean (SD)	–7.19 (6.740)	–4.58 (5.758)	–3.94 (14.087)
Median (Q1, Q3)	–6.98 (–13.17, –2.00)	–3.60 (–9.57, 0.29)	–7.93 (–13.60, 10.80)
Min, max	–22.1, 2.9	–14.0, 2.9	–20.0, 15.0
% of patients with reduction in score ≥MCIC threshold (a reduction of 4.2)	**61.1**	**50.0**	**50.0**
Change from baseline in PKDIA scores			
n	20	18	8
Mean (SD)	–6.3 (7.12)	–6.3 (9.09)	–11.5 (11.53)
Median (Q1, Q3)	–6.0 (–10.0, –3.0)	–5.5 (–12.0, –1.0)	–15.0 (–19.0, –8.5)
Min, max	–18, 9	–22, 13	–21, 14
% of patients with reduction in score ≥MCIC threshold (a reduction of 5.5)	**60.0**	**50.0**	**75.0**

Baseline of weekly mean score is defined as the average of daily scores collected within 7 days before randomization for patients randomized and not dosed, or before start of study treatment for patients randomized and dosed. MCIC threshold estimation is calculated using the median change score in ΔPGIS = –1 group; MCIC, minimal clinically important change; M, continued mitapivat; MCIC, minimal clinically important change; LTE, long-term extension; M/M, mitapivat-to-mitapivat; P/M, placebo-to-mitapivat; PGIS, Patient Global Impression of Severity; PK, pyruvate kinase; PKDD, PK Deficiency Diary; PKDIA, PK Deficiency Impact Assessment; Q, quartile

Conclusions

- Across both PK deficiency-specific PRO instruments (PKDD and PKDIA), improvements among mitapivat-treated patients were sustained over time in the LTE through Week 84
- At Week 84 of the LTE study, clinically meaningful improvements in PKDD and PKDIA mean scores were achieved in more than half of patients
- Treatment with mitapivat was associated with long-term, durable, and clinically meaningful improvements in signs, symptoms, and functional impacts based on disease-specific PRO instruments, irrespective of transfusion status

The long-term results of this study suggest that by improving the signs, symptoms, and disease impacts of PK deficiency, treatment with mitapivat may provide meaningful patient-centric benefits

LTE, long-term extension; PK, pyruvate kinase; PKDD, PK Deficiency Diary; PKDIA, PK Deficiency Impact Assessment; PRO, patient-reported outcome

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