Durability of Hemoglobin Response and Reduction in Transfusion Burden is Maintained Over Time in Patients With Pyruvate Kinase Deficiency Treated with Mitapivat in a Long-Term Extension Study

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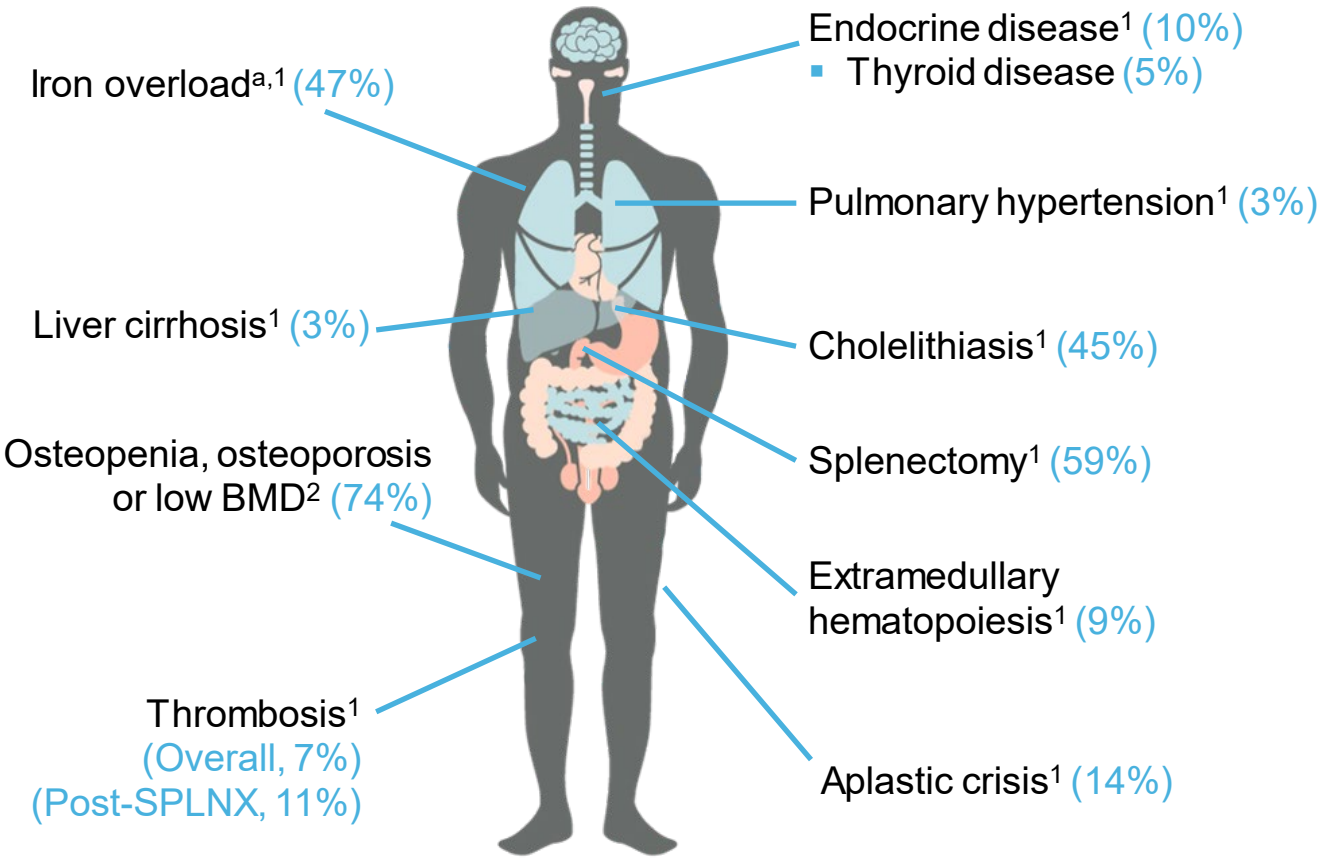
Pyruvate kinase (PK) deficiency is a rare, lifelong, hereditary anemia

Comorbidities and long-term complications are common and affect multiple organ systems[1,2]



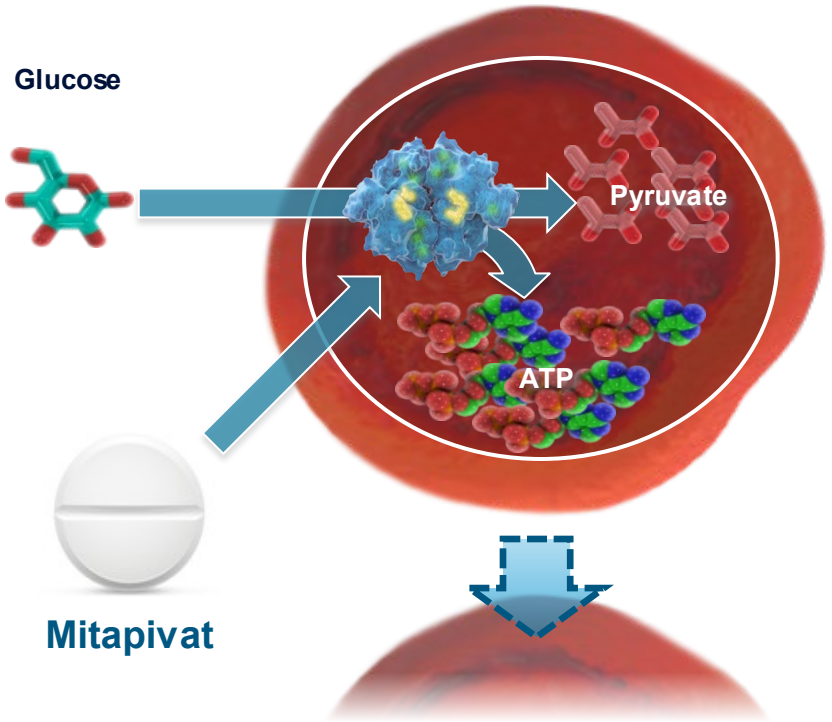
- Caused by mutations in the *PKLR* gene, encoding the red blood cell PK (PKR) enzyme[3,4]
- Defects in PKR lead to chronic hemolytic anemia and serious complications – independent of transfusion needs[1,2,5–7]
- There are no approved disease-modifying pharmacotherapies
- Available supportive therapies are associated with short- and long-term complications[8]

[a]Iron overload is defined as a ferritin level of > 1000 ng/mL or a liver iron concentration > 3 mg Fe/g dry weight liver on T2* MRI in the 12 months prior to enrolment or had received chelation therapy in the 12 months before enrolment.
BMD = bone mineral density; MRI = magnetic resonance imaging; PK = pyruvate kinase; PKR = red blood cell-specific form of PK; post-SPLNX = post-splenectomy.
1. Grace RF et al. *Blood* 2018;131:2183–92. **2.** Al-Samkari H et al. *06/09/21;325452;EP692 EHA Library*. **3.** Grace RF et al. *Am J Hematol* 2015;90:825–30. **4.** Zanella A et al. *Br J Haematol* 2005;130:11–25. **5.** van Beers EJ et al. *Haematologica* 2019;104:e51–3. **6.** Grace RF et al. *Eur J Haematol* 2018;101:758–65. **7.** Boscoe AN et al. *Eur J Haematol* 2021;106:484–92. **8.** Grace RF et al. *Br J Haematol* 2019;184:721–34.

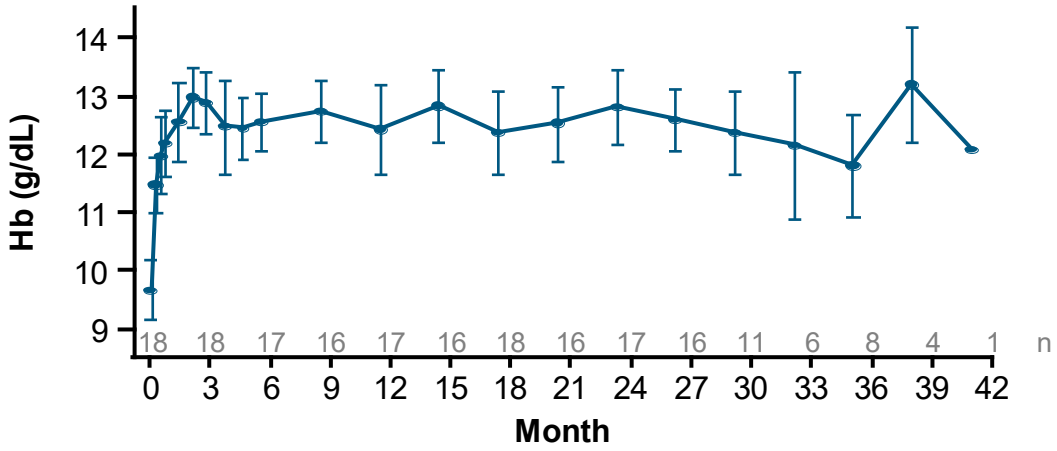
Mitapivat, an investigational, first-in-class, oral allosteric activator

Mitapivat targets the **underlying enzymatic defect** that causes hemolysis in PK deficiency by **restoring PKR activity**[1,2]

RBC post-mitapivat treatment



Hemoglobin[a]



In the phase 2 **DRIVE-PK** study (n = 52) evaluating mitapivat in non-regularly transfused adults with PK deficiency, **mitapivat achieved** a **rapid increase in Hb and markers of hemolysis**, which were **sustained** for up to **42 months**[3]

[a]Hb responses for the patients who continued in the extension period as of 27Mar2019 (N = 18) who received chronic dosing for median of 3 years and ≤ 42 months. Data are presented as mean ± 95% CI.
ATP = adenosine triphosphate; CI = confidence interval; Hb = hemoglobin; PK = pyruvate kinase; PKR = red blood cell-specific form of pyruvate kinase.

1. Yang H et al. *Clin Pharmacol Drug Dev* 2019;8:246–59. **2.** Kung C et al. *Blood* 2017;130:1347–56. **3.** Grace RF et al. 2019 *ASH Annual Meeting*, *Poster 3512*.

Phase 3 studies, ACTIVATE and ACTIVATE-T, met primary endpoints

ACTIVATE

- **Primary efficacy endpoint achieved**: 40% of patients treated with mitapivat achieved a sustained Hb increase of ≥ 1.5 g/dL compared to 0 placebo patients (2-sided $p < 0.0001$)[1]
- Treatment with mitapivat also demonstrated statistically significant improvements over placebo across pre-specified key secondary endpoints, including patient-reported outcomes based on changes from baseline in the *PK deficiency diary* and *PK deficiency impact assessment* scores
- Safety profile was generally consistent with previously reported data

ACTIVATE-T

- **Primary efficacy endpoint achieved**: 37% of patients treated with mitapivat achieved a ≥ 33% reduction in transfusion burden compared to individual historical transfusion burden standardized to 24 weeks (1-sided $p = 0.0002$)[2]
- 22% of patients treated with mitapivat were transfusion-free during the 24-week fixed-dose period
- Safety profile was generally consistent with previously reported data

Hb = hemoglobin; PK = pyruvate kinase.

1. Al-Samkari H. 06/09/21;324678;S270 *EHA Library*. **2.** Glenthøj A. 06/09/21;324679;S271 *EHA Library*.

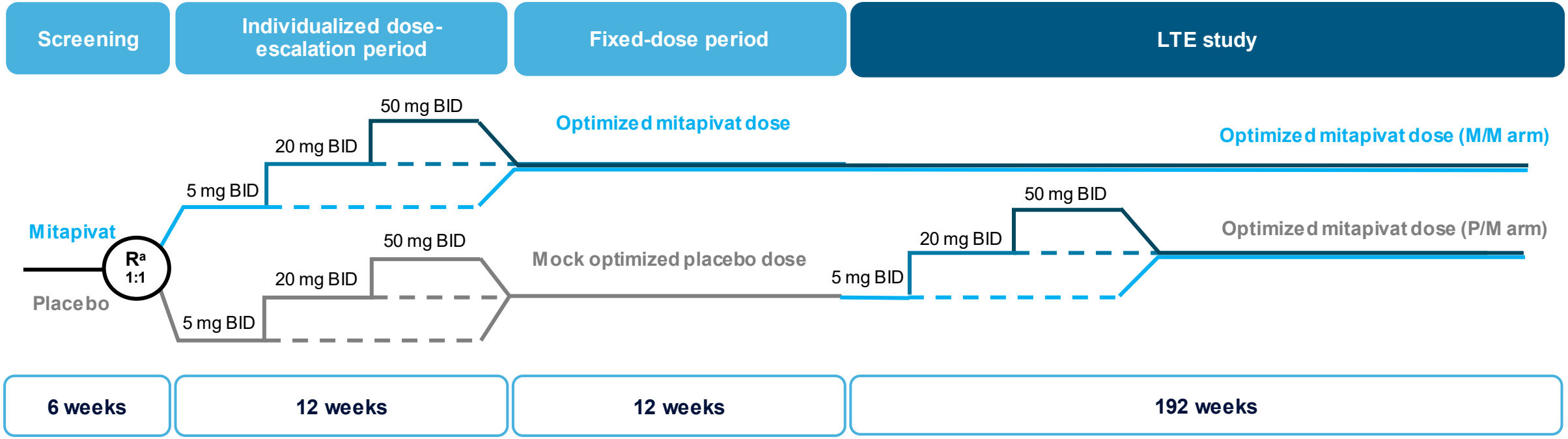
Objective

To assess the duration of effects of mitapivat on Hb response and transfusion burden reduction in patients with PK deficiency in ACTIVATE, ACTIVATE-T, and their long-term extension (LTE) study

Hb = hemoglobin; LTE = long-term extension; PK = pyruvate kinase.

ACTIVATE/LTE study design

ACTIVATE



Key eligibility criteria

- ≥ 18 years of age
- Documented ≥ 2 mutant alleles in *PKLR* (≥ 1 missense mutation)[b]
- Not regularly transfused (≤ 4 transfusion episodes in the previous year)
- Baseline Hb ≤ 10 g/dL
- LTE study: Patient must have completed the fixed-dose period and demonstrated clinical benefit from mitapivat or were assigned to placebo and continued to the LTE

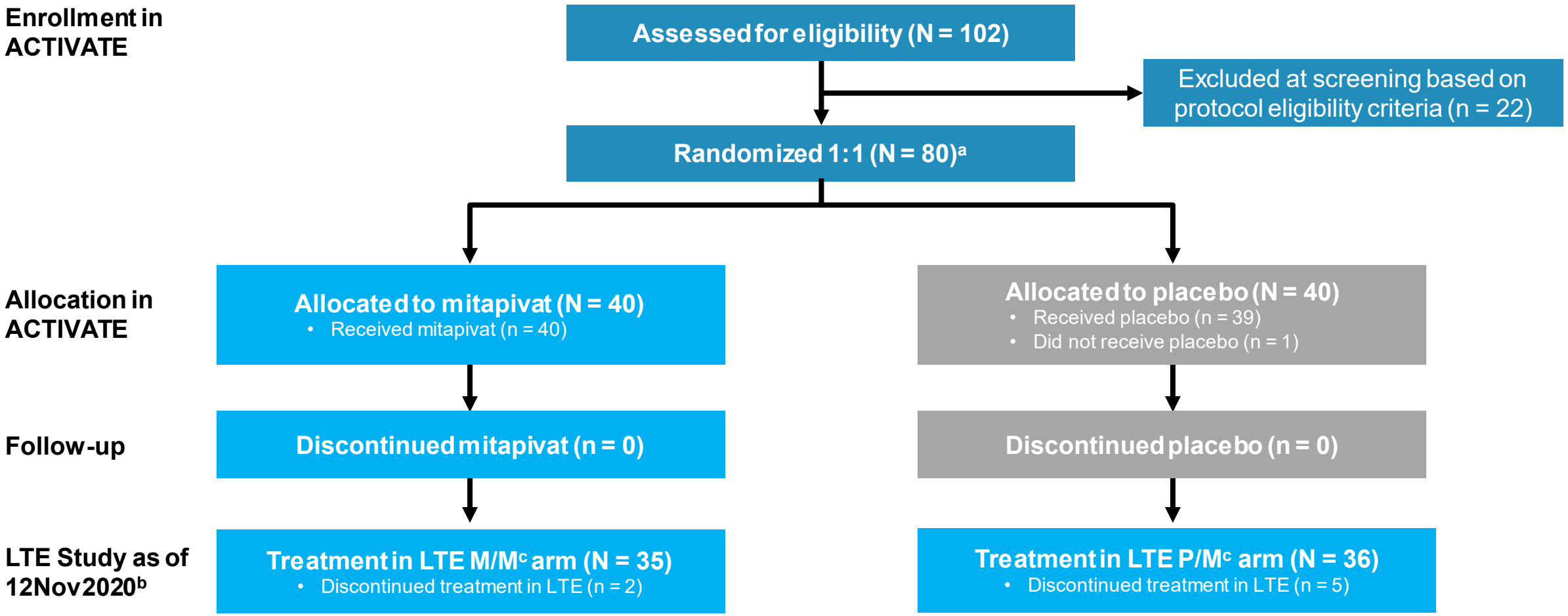
[a]Stratified by average of screening Hb values (< 8.5 g/dL vs ≥ 8.5 g/dL) and *PKLR* gene mutation category (missense/missense vs missense/non-missense. [b]Excluding patients homozygous for R479H mutation or with two non-missense mutations, without another missense mutation. *ClinicalTrials.gov*: ACTIVATE (NCT03548220); LTE study (NCT03853798); BID = twice daily; Hb = hemoglobin; LTE = long-term extension; M/M = mitapivat-to-mitapivat; P/M = placebo-to-mitapivat; R = randomized.

ACTIVATE/LTE study endpoints and analyses

- The **ACTIVATE/LTE** study analysis assessed duration of Hb response in two cohorts:
  - Mitapivat-to-mitapivat (M/M) arm patients who received mitapivat and achieved a Hb response in ACTIVATE (*defined as a ≥ 1.5 g/dL increase in Hb from baseline[a] sustained at ≥ 2 scheduled assessments at Weeks 16, 20, or 24 in ACTIVATE*) and maintained it in the LTE study
  - Placebo-to-mitapivat (P/M) arm patients who received placebo in ACTIVATE and switched to mitapivat in the LTE study and then achieved a Hb response (*defined as a ≥ 1.5 g/dL increase in Hb from baseline[b] sustained at ≥ 2 scheduled assessments at Weeks 16, 20, or 24 in the LTE)* and maintained in the LTE study

[a]Baseline is defined as the average of all screening assessments within 45 (42 + 3) days before randomization for patients randomized and not dosed or before start of study treatment for patients randomized and dosed.
[b]Baseline is the average of all available measurements from the central laboratory within 45 (42 + 3) days before start of study treatment in the LTE study, excluding values within 61 days after a transfusion, or the baseline value from the ACTIVATE study if no assessment is available. Hb = hemoglobin; LTE = long-term extension.

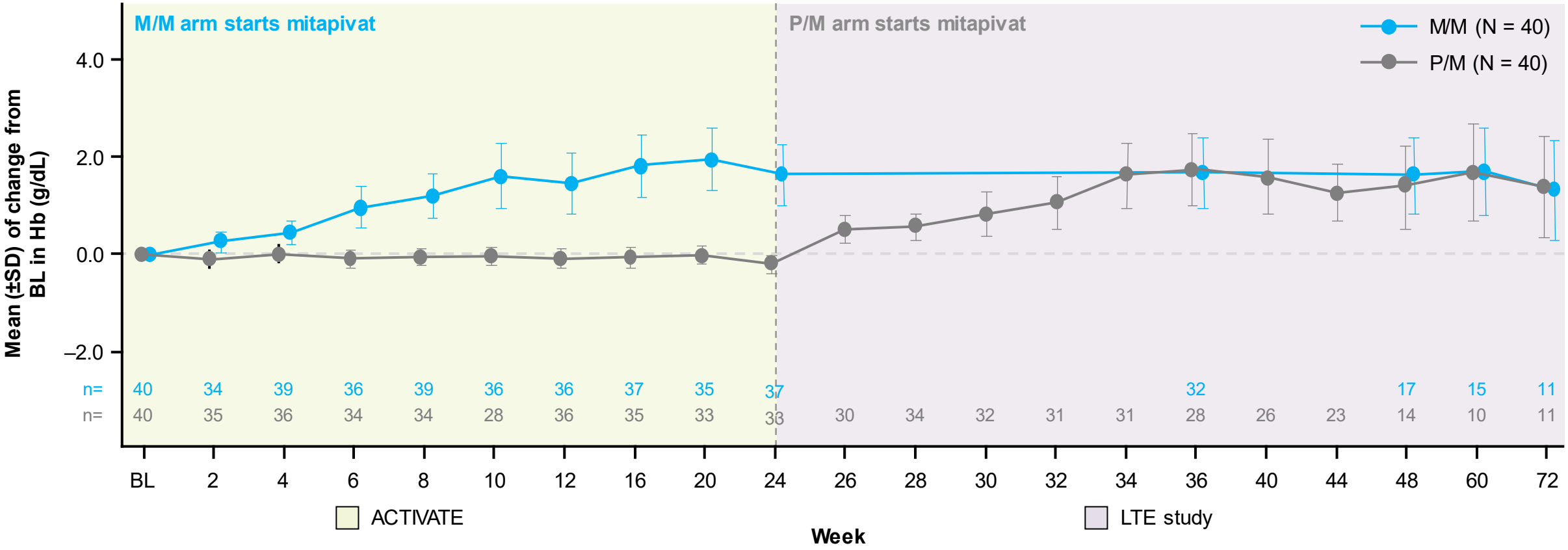
Patient disposition in ACTIVATE and the LTE study



[a]Disposition for end of randomization reflects the disposition after randomization, but before the start of study treatment. [b]As of data cut-off date 12Nov2020 not all the patients from ACTIVATE had been dosed for the LTE study. [c]LTE study is ongoing; 0 patients have completed treatment. LTE = long-term extension; M/M = mitapivat-to-mitapivat; P/M = placebo-to-mitapivat.

Mean improvement in Hb concentrations was maintained with long-term mitapivat treatment in ACTIVATE and the LTE study

Mean change from baseline[a] in Hb over time in patients randomized to mitapivat or placebo in ACTIVATE who then continued in the LTE study on mitapivat[b,c]



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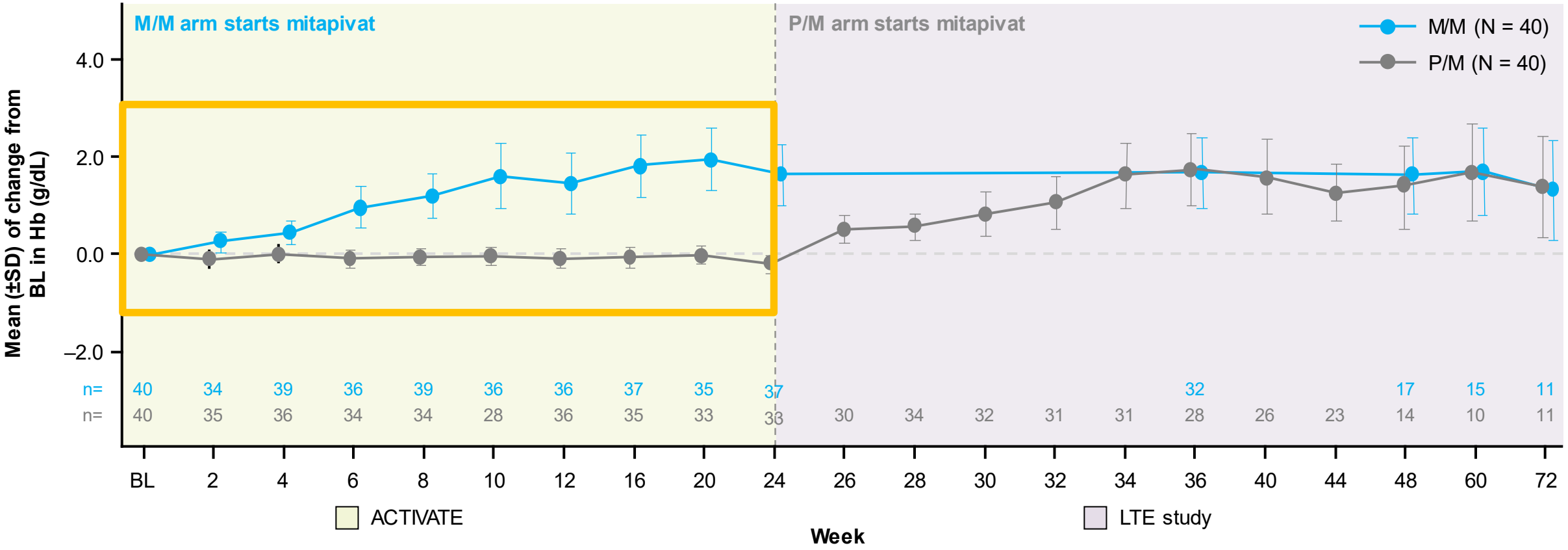

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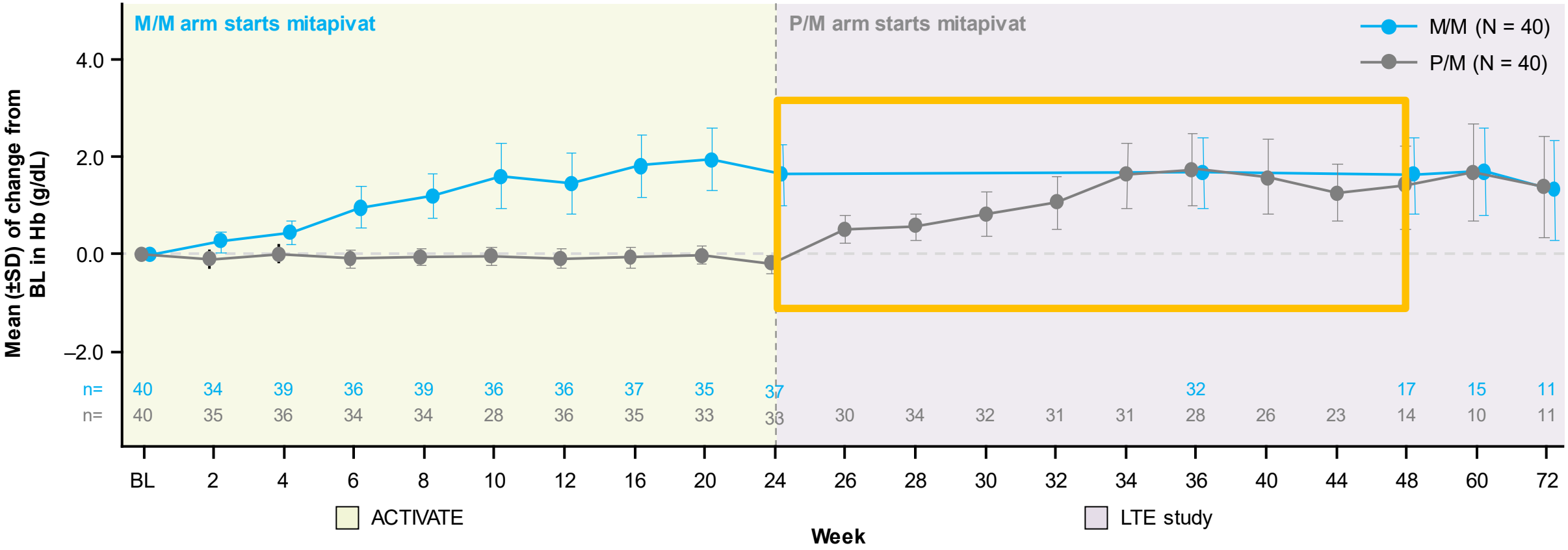

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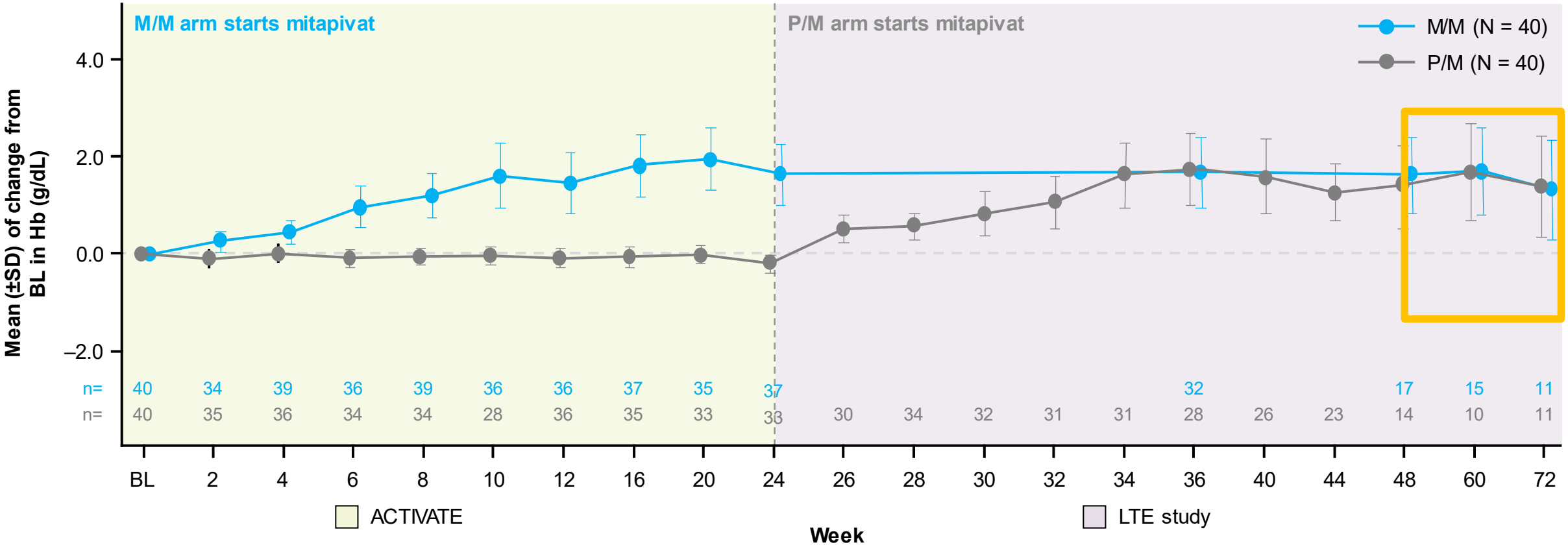
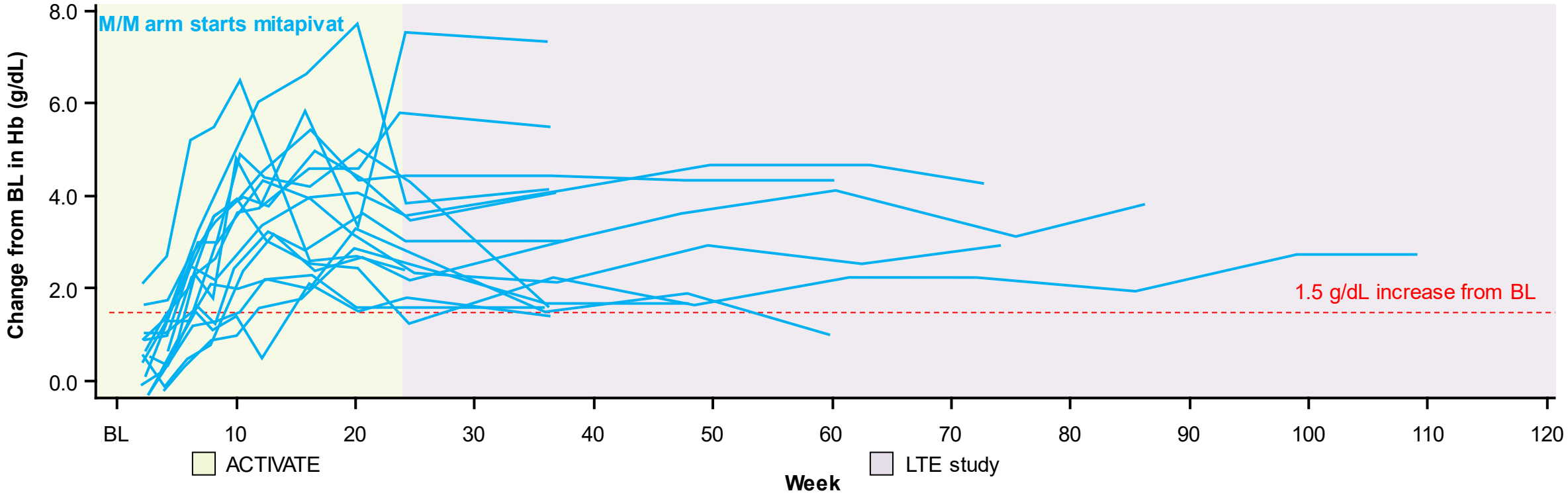


[a]Baseline is defined as the average of all screening assessments within 45 (42 + 3) days before randomization for patients randomized and not dosed or before start of study treatment for patients randomized and dosed. Assessments collected within 61 days after a transfusion are excluded from the baseline derivation. [b]Patients in the M/M arm were assessed every 12 weeks after the completion of the fixed-dose period in ACTIVATE (Week 24) and up to Week 48 of the LTE. [c]Data are shown up to 72 weeks, which is the timepoint where each arm has > 5 patients. BL = baseline; Hb = hemoglobin; LTE = long-term extension; M/M = mitapivat-to-mitapivat; P/M = placebo-to-mitapivat; SD = standard deviation.

Hb response was sustained in mitapivat-to-mitapivat patients in the ACTIVATE and the LTE studies

Change from baseline[a] in Hb over time among patients treated with mitapivat in ACTIVATE who achieved an Hb response in the fixed-dose period and received ongoing treatment in the LTE study

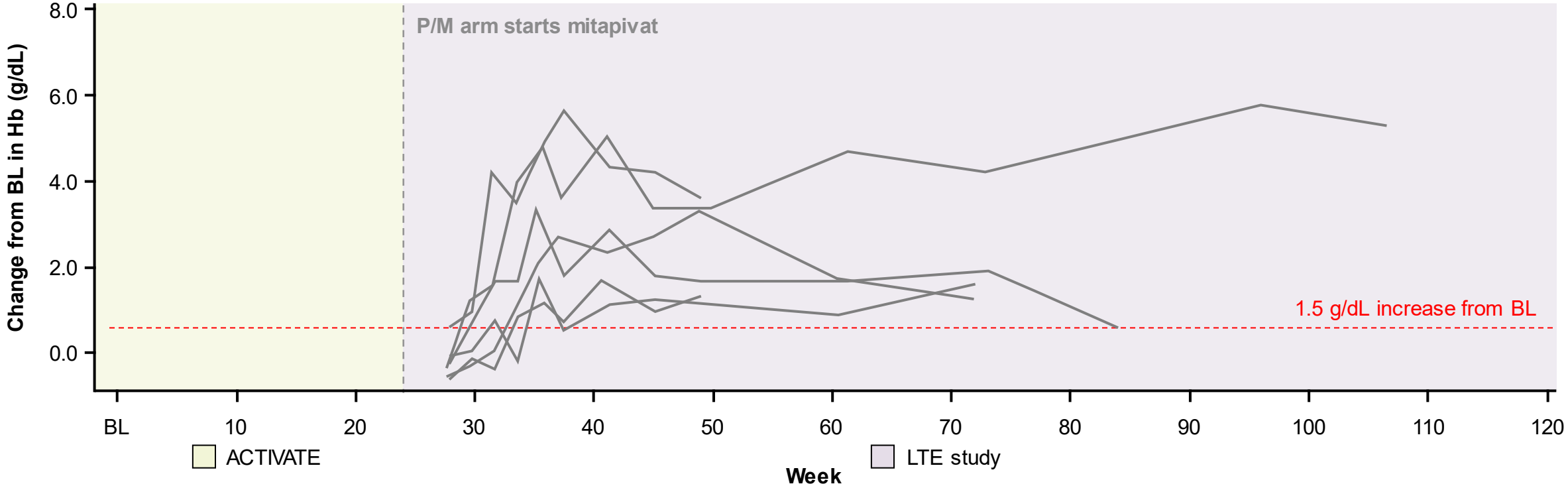


At all Hb assessments, 86.7% (13/15) of M/M patients with a Hb response in ACTIVATE and evaluable timepoints in the LTE maintained increases in Hb concentration from baseline above the response threshold of ≥ 1.5 g/dL up to 19.5 months

[a]Baseline is defined as the average of all screening assessments within 45 (42 + 3) days before randomization for patients randomized and not dosed or before the start of study treatment for patients randomized and dosed. Assessments collected within 61 days after a transfusion are excluded from the baseline derivation. BL = baseline; Hb = hemoglobin; LTE = long-term extension; M/M = mitapivat-to-mitapivat.

Hb response was achieved and sustained in placebo-to-mitapivat patients in the LTE study

Change from baseline[a] in Hb over time among patients randomized to placebo in ACTIVATE and who started mitapivat treatment in the LTE study and achieved a Hb response



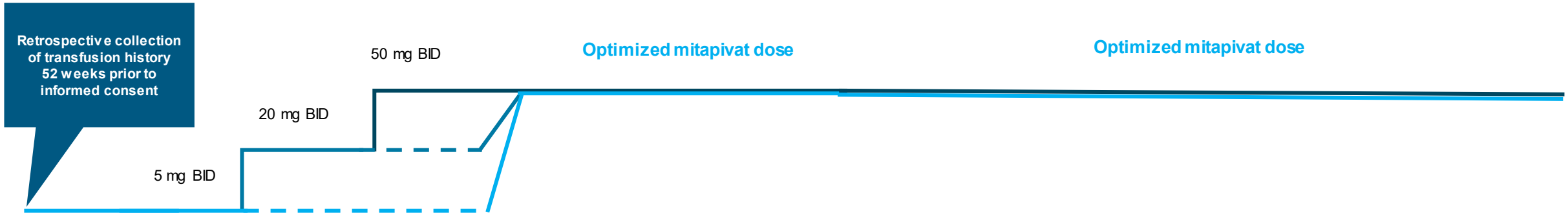
35% (6/17) of P/M patients achieved Hb responses in the LTE, and all maintained Hb responses for the duration of follow-up

[a]Baseline is the average of all available measurements from the central laboratory within 45 (42 + 3) days before start of study treatment in the LTE study, excluding values within 61 days after a transfusion, or the baseline value from the ACTIVATE study if no assessment was available. BL = baseline; Hb = hemoglobin; LTE = long-term extension study; P/M = placebo-to-mitapivat.

ACTIVATE-T/LTE study design

ACTIVATE-T

Screening	Individualized dose-escalation period	Fixed-dose period	LTE study
< 8 weeks[a]	16 weeks	24 weeks	192 weeks



Key eligibility criteria

- ≥ 18 years of age
- Documented ≥ 2 mutant alleles in *PKLR* (≥ 1 missense mutation)[b]
- Regularly transfused (≥ 6 transfusion episodes in the previous year)
- LTE study: Patients must have completed the fixed-dose period of ACTIVATE-T and demonstrated clinical benefit from mitapivat treatment

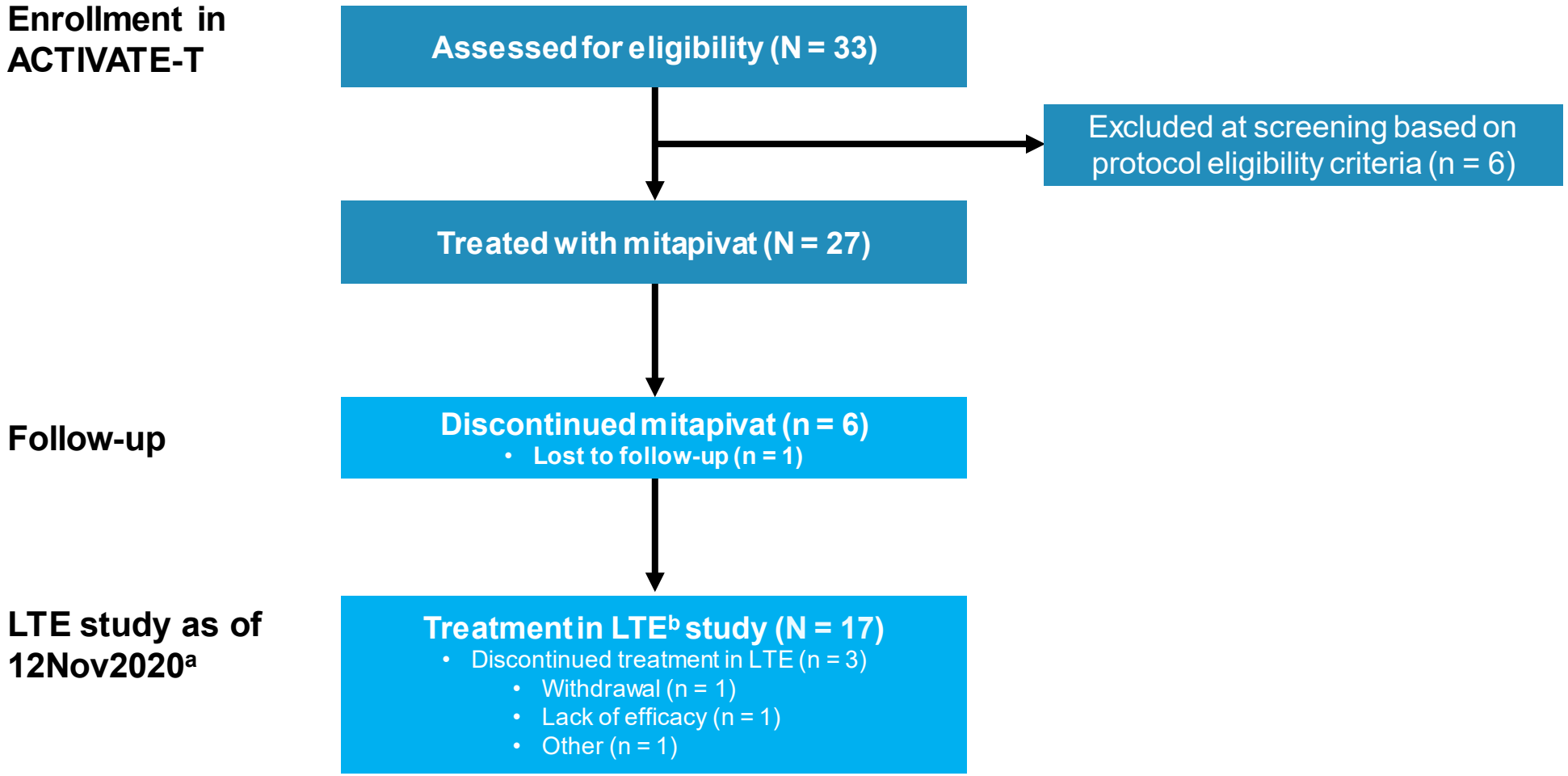
[a]Screening may have been extended beyond 8 weeks if there was a delay in obtaining a patient's complete transfusion history or to ensure that the first dose of study drug could be administered 2–7 days after the most recent transfusion. [b]Excluding patients homozygous for R479H mutation or have who have two non-missense mutations, without another missense mutation. *ClinicalTrials.gov*: ACTIVATE-T (NCT03559699); LTE study (NCT03853798); BID = twice daily; Hb = hemoglobin; LTE = long-term extension.

ACTIVATE-T/LTE study endpoints and analyses

- The **ACTIVATE-T/LTE** study analysis assessed:
  - Transfusion burden reduction response in ACTIVATE-T and the LTE study
    - *Defined as ≥ 33% reduction in number of RBC units transfused during the fixed-dose period in ACTIVATE-T and the LTE study standardized to 24 weeks, compared with the patient's individual historical transfusion burden standardized to 24 weeks*
  - Transfusion-free duration among pts from ACTIVATE-T who achieved transfusion-free status
    - *Defined as no transfusions in the fixed-dose period of ACTIVATE-T*

LTE = long-term extension; Pts = patients; RBC = red blood cell.

Patient disposition in ACTIVATE-T and the LTE study

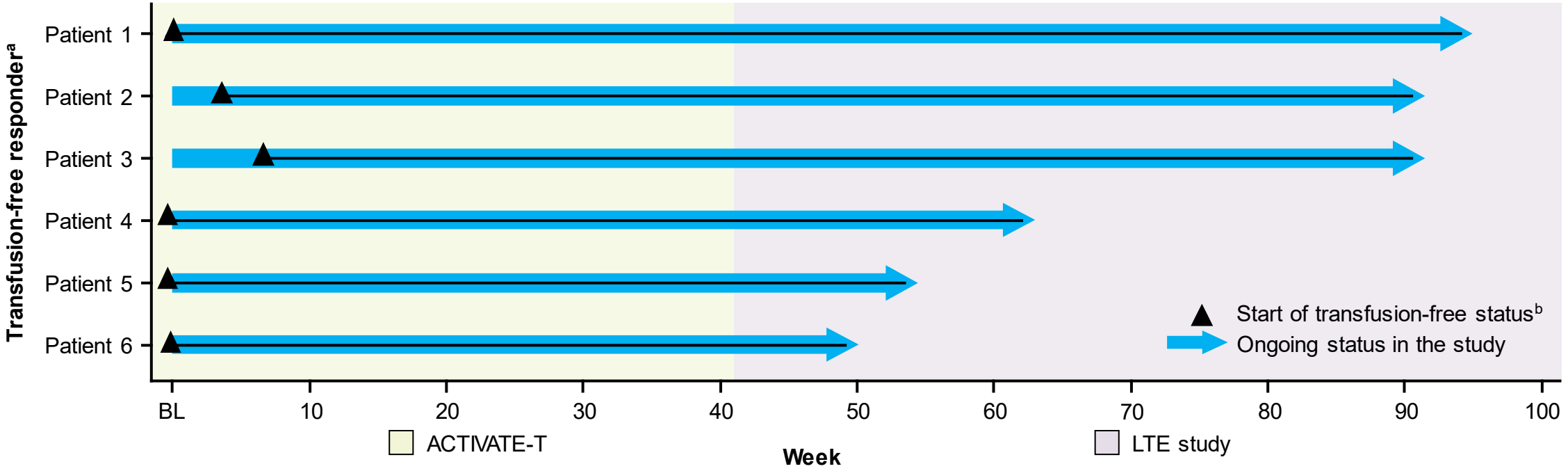


[a]As of data cut-off 12Nov2020, not all the patients from ACTIVATE-T had been dosed for the LTE study. [b]LTE study is ongoing; 0 patients have completed treatment.
LTE = long-term extension.

Transfusion reduction response and duration of transfusion-free status of patients in the ACTIVATE-T and LTE studies

- As of 12Nov2020, 9 patients (33.3%) in the LTE study met the criteria for a transfusion reduction response

Transfusion-free duration among transfusion-free responders from ACTIVATE-T through the LTE study



All 6 patients who achieved transfusion-free status in ACTIVATE-T maintained the status in the LTE study for up to 21.9 months

[a]Patient received no transfusions in the fixed-dose period of ACTIVATE-T. [b]The start of transfusion-free responder status was from 1 day after the last transfusion date.
BL = baseline; LTE = long-term extension.

Conclusion

- PK deficiency is a lifelong serious hemolytic anemia with no approved pharmacotherapies
- Non-regularly transfused patients randomized to mitapivat in ACTIVATE showed maintenance of Hb response through the LTE study for up to 19.5 months
  - Similarly, 35% of ACTIVATE patients who switched from placebo to mitapivat in the LTE study achieved a Hb response, which was maintained for the duration of follow-up
- All regularly transfused patients who achieved transfusion-free status in ACTIVATE-T with mitapivat treatment maintained the status through the LTE study for up to 21.9 months

These data show the consistency and long-term durability of response in patients with PK deficiency, independent of transfusion needs, and continue to support the potential of mitapivat to become the first approved disease-modifying pharmacotherapy for PK deficiency

Hb = hemoglobin; LTE = long-term extension; PK = pyruvate kinase.