Protocol C4951019

A PHASE 3, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY TO EVALUATE THE EFFICACY AND SAFETY OF RIMEGEPANT FOR MIGRAINE PREVENTION IN CHINESE PARTICIPANTS

Statistical Analysis Plan (SAP)

Version: 2

Date: 11 Aug 2025

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1. VERSION HISTORY

Table 1. Summary of Changes

Version/ Date	Associated Protocol Amendment	Rationale	Specific Changes
2 11 Aug 2025	Amendment 1 30 Aug 2023	Revised wording to be more accurate. Aligned with protocol amendment. Modified content structure to be more clear. Removed Covid-19 impact related contents. Moved some content to appendix.	The whole document: updated 'study drug' to 'study intervention'. Section 2.2: removed 'of moderate or severe intensity'; updated 'treated with migraine' to 'on treatment'. Section 2.2.1: updated 'while-on-treatment' to 'hypothetical'. Section 2.2.2 estimand 2.1: updated 'while-on-treatment' to 'composite'; estimand 2.2, 2.3 and 2.5: updated 'while-on-treatment' to 'hypothetical'; estimand 2.4: updated 'while-on-treatment' to 'treatment policy'. Section 2.2.3 endpoints 1, 3 and 6: updated 'while-on-treatment' to 'hypothetical'; endpoints 2, 4 and 8: updated 'while-on-treatment' to 'composite'. Section 2.2.3 endpoints 7-9 and 13: added overall for population-level summary. Section 2.3: removed the prefix '28 days' or 'the first 28 days' from the OP. Changed the Follow-up Week 2 Visit to Follow-up Week 4 Visit. Section 3.1.1, 3.2.1: made clarification in the definition. Section 3.2.2: simplified definition of responder and failure. Section 3.2.3: newly added this section to provide definition of the endpoint for which the analysis method is contained in Section 6.2.5. Section 3.3.3, 3.3.4, 3.3.5: simplified definition to be more clear. Updated the analysis population Section 3.3.6-3.3.7: newly added sections to provide definitions of the endpoints for

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			which the analysis methods are contained in Section 6.3.6, 6.3.8. Section 3.3.8: newly added this section to provide definitions of the endpoints for which the analysis methods are contained in Sections 6.3.2, 6.3.4, and 6.3.8 Section 3.3.9: newly added this section to provide definition of the endpoint for which the analysis method is contained in Section 6.3.9. Section 3.4: removed 'prophylactic medication use at randomization', 'Childbearing potential' and 'Triptan use' from baseline variables. Added 'Race' and 'Ethnicity' to baseline variables. Clarified randomization stratum. Section 3.5.1: added definition of TEAE. Section 3.5.2: changed follow-up Week 2 to follow-up Week 4. Section 3.5.3: changed follow-up Week 2 to follow-up Week 4. Added weight as physical measurements. Section 3.5.5: clarified C-SSRS questions and parameters. Section 4: added follow-up safety, DBT first month migraine, DBT first week EOD treated migraine, OLE efficacy and OLE migraine analysis sets. Updated additional information due to updates of section numbers and analysis sets. Section 5.2: Added that the SE estimation method will be Huber-White robust "sandwich" estimator. Changed 'Cochran-Mantel-Haenszel test' to be 'Mantel-Haenszel risk Estimation'. Clarified analysis method for different endpoints. Clarified randomization stratum and excluded it from MMRM for endpoints related to migraine days.

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			Section 5.2.3.1: changed from 'Randomization Visit Date' to 'study intervention start date'. Section 5.2.3.2: newly added this section to clarify the eDiary day. Section 5.2.3.3 newly added this section to clarify the Efficacy Data Day Section 5.2.4-5.2.5: updated analysis period in Table 2 and analysis window in Table 3. Section 5.2.6.2: added safety subgroups. Section 5.3: J2R method step was updated. Additional methods of NRI is added. Section 6.1-6.3: removed analyses repeated by randomization stratum. Section 6.1.1.1, 6.2.1, 6.2.1.1, 6.2.6-6.2.8, 6.3.1-6.3.4, 6.3.10-6.3.12: revised wording to better describe the analysis. Section 6.2.2-6.2.3: simplified the description by referring to previous Section 6.1.1.1. since analysis method is the same. Section 6.2.5: moved definition of acute migraine medication days into appendix 4. Moved acute migraine medication days per month derivation into section 3.2.3. Section 6.3.3-6.3.5, 6.3.7-6.3.9, 6.3.13: updated the analysis set. Section 6.3.5: specified missing data would be handled by NRI. Section 6.3.6: moved definition of acute migraine-specific medication days into appendix 4. Moved acute migraine-specific medication days per month derivation into section 3.3.6. Section 6.3.7-6.3.9, 6.3.13: updated analysis method from statistical model to descriptive summary to be consistent with method used for open-label phase in similar studies. Section 6.5.3: clarified the analysis set for each baseline summary.

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			Section 6.5.3.3: removed 'primary migraine type' from migraine history as data collected from this variable is not accurate. Section 6.5.3.4: newly added this section for baseline summary of migraine-related events during the OP. Section 6.5.4: removed pIPD as the criteria to determine the eligibility for evaluable participant list as this criterion is critical for per-protocol set which is not defined in the study. Section 6.5.5 and subsections: updated the whole section to better echo the modifications from other sections. Section 6.5.5.2, 6.5.5.3: revised the formulas for a more accurate summary. Section 6.5.6: stated that imputation for missing dates of prior and concomitant medications will follow Pfizer standard rules. Removed summaries for concomitant migraine medications, and added summaries for acute headache medications. Section 6.6.1 and subsections: re-structured and revised the wording for a more accurate summary. Moved significant AEs to Appendix 2. Removed some treatment-related summaries. Added hypertension TEAEs summary for participants with medical history of hypertension. Section 6.6.2, 6.6.4 and subsections: removed shift table analysis. Restructured and revised the wording for better summary. Section 6.6.3: updated vital signs and physical measurement categories. Added vital sign summaries in participants with medical history of hypertension. Section 6.6.5: updated analysis to be correspondent to the definition from Section 3.5.5 and FDA guidance for suicidal ideation and behavior.

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			Section 7: clarified the scope and timing for IA and final analysis. Appendix 1: updated to better fit the change of document. Appendix 2: newly added appendix to contain the significant AEs from AE section. Appendix 4: newly added this appendix to contain definition of migraine days, headache days, acute migraine medication days, and acute migraine-specific medication days.
1 01 Mar 2023	Original 23 Sep 2022	N/A	N/A

2. INTRODUCTION

This statistical analysis plan (SAP) provides the detailed methodology for summary and statistical analyses of the data collected in Study C4951019.

2.1. Modifications to the Analysis Plan Described in the Protocol

Not applicable.

2.2. Study Objectives, Endpoints, and Estimands

Type	Objective	Endpoint	Estimand
	Primary:	**Primary:**	**Primary:**
Efficacy	To compare the efficacy of Rimegepant to placebo as a preventive treatment for migraine, as measured by the mean reduction from the Observation Phase (OP) in the number of migraine days per month over the entire Double-blind Treatment (DBT) Phase.	Mean change from the OP in the number of migraine days per month over the entire DBT Phase (Weeks 1 to 12).	The estimand is the treatment effect of rimegepant relative to placebo in terms of the difference in mean change from the OP in the number of migraine days per month over the entire DBT Phase among all randomized participants with migraine who took study intervention without regard to the use of prophylactic medications. Data collected after study intervention discontinuation will be excluded.
	Secondary:	**Secondary:**	**Secondary:**
Efficacy	To compare the efficacy of rimegepant to placebo on the proportion of participants with ≥ 50% reduction from the OP in the number of moderate to severe migraine days per month over the entire DBT Phase.	Percentage of participants with ≥50% reduction from OP in the number of moderate to severe migraine days per month over the entire DBT Phase.	2.1. The estimand is the treatment effect of rimegepant relative to placebo in terms of the difference in percentage of participants with ≥50% reduction from the OP in the number of moderate to severe migraine days per month over the entire DBT Phase among all randomized participants with migraine who took study intervention without regard to the use of prophylactic medications. Data collected after study intervention discontinuation will be excluded.
	To compare the efficacy of rimegepant to placebo on the mean reduction from the OP in the number of migraine days per month in the first 4 weeks of the DBT Phase.	Mean change from the OP in the number of migraine days per month in the first 4 weeks of the DBT Phase.	2.2. The estimand is the treatment effect of rimegepant relative to placebo in terms of the difference in mean change from the OP in the number of migraine days per month in the first 4 weeks of the DBT Phase among all randomized

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Type	Objective	Endpoint	Estimand
			participants with migraine who took study intervention without regard to the use of prophylactic medications. Data collected after study intervention discontinuation will be excluded.
	To compare the efficacy of rimegepant to placebo on the mean reduction from the OP in the number of migraine days per month in the last 4 weeks of the DBT Phase.	Mean change from the OP in the number of migraine days per month in the last 4 weeks of the DBT Phase.	2.3. The estimand is the treatment effect of rimegepant relative to placebo in terms of the difference in mean change from the OP in the number of migraine days per month in the last 4 weeks of the DBT Phase among all randomized participants with migraine who took study intervention without regard to the use of prophylactic medications. Data collected after study intervention discontinuation will be excluded.
	To compare the change from baseline in the Migraine-Specific Quality-of-Life Questionnaire v 2.1 (MSQoL v2.1) role function - restrictive domain score at Week 12 of the DBT Phase between rimegepant and placebo.	Change from baseline in the MSQoL role function-restrictive domain score at Week 12 of the DBT Phase.	2.4. The estimand is the treatment effect of rimegepant relative to placebo in terms of the difference in change from baseline in the MSQoL role function-restrictive domain score at Week 12 of the DBT Phase among all randomized participants with migraine who took study intervention without regard to the use of prophylactic medications or study intervention discontinuation.
	To compare the efficacy of rimegepant to placebo on the mean number of acute migraine medication days per month over the entire DBT Phase.	Mean number of acute migraine medication days per month over the entire DBT Phase.	2.5. The estimand is the treatment effect of rimegepant relative to placebo in terms of the difference in mean number of acute migraine medication days per month over the entire DBT Phase among all randomized participants with migraine who took study intervention without regard to the use of prophylactic medications. Data collected after study intervention discontinuation will be excluded.
Safety	To evaluate the safety and tolerability of rimegepant during the DBT and Open-label Extension (OLE) Phases.	Number and percentage of participants with adverse events (AEs) by severity, serious adverse events (SAEs), AEs leading to study intervention discontinuation and grade 3 to 4 laboratory test abnormalities on treatment during the DBT Phase and OLE Phase.	Not applicable.
	To evaluate the frequency of alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 3x ULN concurrent with total bilirubin > 2x ULN in participants treated with rimegepant during the DBT and OLE Phases.	Number and percentage of participants with ALT or AST > 3x ULN concurrent with total bilirubin > 2x ULN on treatment during the DBT and OLE Phases.	Not applicable.
	To evaluate the frequencies of hepatic-related AEs and hepatic-related AEs leading to study intervention discontinuation in participants treated with rimegepant during the DBT and OLE Phases.	Number and percentage of participants with hepatic-related AEs and hepatic-related AEs leading to study intervention discontinuation on treatment during the DBT Phase and OLE Phase.	Not applicable.
	Exploratory:	**Exploratory:**	**Exploratory:**
	To compare the efficacy of rimegepant to placebo on the mean reductions from the OP in the number of migraine days per month and number of headache days per month by pain intensity (total; moderate or severe) in each month and over the entire DBT Phase.	Mean change from the OP in the number of migraine days per month and number of headache days per month by pain intensity (total; moderate or severe) in each month and over the entire DBT Phase.	3.1. The estimand is the treatment effect of rimegepant relative to placebo in terms of the difference in mean change from the OP in the number of migraine days per month and number of headache days per month by pain intensity (total; moderate or severe) in each month and over the entire DBT Phase among all randomized participants with migraine who took study intervention without regard to the use of prophylactic medications. Data collected after study intervention discontinuation will be excluded.
	To compare the efficacy of rimegepant to placebo on the	Percentage of participants with ≥50% reduction, ≥ 75%	3.2 The estimand is the treatment effect of rimegepant relative to placebo in terms of the

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Type	Objective	Endpoint	Estimand
	proportions of participants with ≥ 50% reduction, ≥ 75% reduction, and 100% reduction from the OP in the number of migraine days per month and number of headache days per month by pain intensity (total; moderate or severe) in each month and over the entire DBT Phase.	reduction, and 100% reduction from OP in the number of migraine days per month and number of headache days per month by pain intensity (total; moderate or severe) in each month and over the entire DBT Phase.	difference in percentage of participants with ≥50% reduction, ≥ 75% reduction, and 100% reduction from the OP in the number of migraine days per month and number of headache days per month by pain intensity (total; moderate or severe) in each month and over the entire DBT Phase among all randomized participants with migraine who took study intervention without regard to the use of prophylactic medications. Data collected after study intervention discontinuation will be excluded.
	To compare the efficacy of rimegepant to placebo on the mean reduction from the OP in the number of migraine days per week and number of headache days per week by pain intensity (total; moderate or severe) in each week of the first 4 weeks of the DBT Phase.	Mean change from the OP in the number of migraine days per week and number of headache days per week by pain intensity (total; moderate or severe) in each week of the first 4 weeks of the DBT Phase.	3.3. The estimand is the treatment effect of rimegepant relative to placebo in terms of the difference in mean change from the OP in the number of migraine days per week and number of headache days per week by pain intensity (total; moderate or severe) in each week of the first 4 weeks of the DBT Phase among all randomized participants with migraine who took study intervention without regard to the use of prophylactic medications. Data collected after study intervention discontinuation will be excluded.
	To compare the efficacy of rimegepant to placebo on the proportions of participants with ≥ 50% reduction from the OP in the number of migraine days per week and number of headache days per week by pain intensity (total; moderate or severe) in each week of the first 4 weeks of the DBT Phase.	Percentage of participants with ≥50% reduction from OP in the number of migraine days per week and number of headache days per week by pain intensity (total; moderate or severe) in each week of the first 4 weeks of the DBT Phase.	3.4. The estimand is the treatment effect of rimegepant relative to placebo in terms of the difference in percentage of participants with ≥50% reduction from the OP in the number of migraine days per week and number of headache days per week by pain intensity (total; moderate or severe) in each week of the first 4 weeks of the DBT Phase among all randomized participants with migraine who took study intervention without regard to the use of prophylactic medications. Data collected after study intervention discontinuation will be excluded.
	To compare the efficacy of rimegepant to placebo on the proportions of participants with a migraine day and headache day by pain intensity (total; moderate or severe) on each day of the first week of the DBT Phase.	Percentage of participants with a migraine day and headache day by pain intensity (total; moderate or severe) on each day of the first week of the DBT Phase.	3.5. The estimand is the treatment effect of rimegepant relative to placebo in terms of the difference in percentage of participants with a migraine day and headache day by pain intensity (total; moderate or severe) on each day of the first week of the DBT Phase among all randomized participants with migraine who took study intervention without regard to the use of prophylactic medications. Data collected after study intervention discontinuation will be excluded.
	To compare the efficacy of rimegepant to placebo on the mean number of acute migraine-specific medication days per month in each month and over the entire DBT Phase.	Mean number of acute migraine-specific medication days per month in each month and over the entire DBT Phase.	3.6. The estimand is the treatment effect of rimegepant relative to placebo in terms of the difference in mean number of acute migraine-specific medication days per month in each month and over the entire DBT Phase among all randomized participants with migraine who took study intervention without regard to the use of prophylactic medications. Data collected after study intervention discontinuation will be excluded.
	To evaluate the mean reductions from the OP in the number of migraine days per month and number of headache days per month by pain intensity (total; moderate or severe) in each month and over the entire OLE Phase.	Mean change from the OP in the number of migraine days per month and number of headache days per month by pain intensity (total; moderate or severe) in each month and over the entire OLE Phase.	3.7. The estimand is the treatment effect of rimegepant relative to placebo in terms of the difference in mean change from the OP in the number of migraine days per month and number of headache days per month by pain intensity (total; moderate or severe) in each month and over the entire OLE Phase among all randomized participants with migraine who took study intervention without regard to the use of prophylactic medications. Data collected after study intervention discontinuation will be excluded.
	To evaluate the proportions of participants with ≥ 50% reduction, ≥75% reduction, and 100% reduction from the OP in the number of migraine days per month and number	Percentage of participants with ≥50% reduction, ≥ 75% reduction, and 100% reduction from OP in the number of migraine days per month and	3.8. The estimand is the treatment effect of rimegepant relative to placebo in terms of the difference in percentage of participants with ≥50% reduction, ≥ 75% reduction, and 100% reduction from the OP in the number of migraine days per

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Type	Objective	Endpoint	Estimand
	of headache days per month by pain intensity (total; moderate or severe) in each month and over the entire OLE Phase.	number of headache days per month by pain intensity (total; moderate or severe) in each month and over the entire OLE Phase.	month and number of headache days per month by pain intensity (total; moderate or severe) in each month and over the entire OLE Phase among all randomized participants with migraine who took study intervention without regard to the use of prophylactic medications. Data collected after study intervention discontinuation will be excluded.
	To evaluate the mean numbers of acute migraine medication days per month and acute migraine-specific medication days per month in each month and over the entire OLE Phase.	Mean number of acute migraine medication days per month and acute migraine-specific medication days per month in each month and over the entire OLE Phase.	3.9. The estimand is the treatment effect of rimegepant relative to placebo in terms of the difference in mean number of acute migraine medication days per month and acute migraine-specific medication days per month in each month and over the entire OLE Phase among all randomized participants with migraine who took study intervention without regard to the use of prophylactic medications. Data collected after study intervention discontinuation will be excluded.
	To compare the mean changes from baseline in the MSQoL preventive role function and emotional function domain scores at Week 12 of the DBT Phase between rimegepant and placebo.	Mean change from baseline in the MSQoL preventive role function and emotional function domain scores at Week 12 of the DBT Phase.	3.10. The estimand is the treatment effect of rimegepant relative to placebo in terms of the difference in mean change from baseline in the MSQoL preventive role function and emotional function domain scores at Week 12 of the DBT Phase among all randomized participants with migraine who took study intervention without regard to the use of prophylactic medications or study intervention discontinuation.
	To compare the mean changes from baseline in the Migraine Disability Assessment (MIDAS) total score, absenteeism and presenteeism scores at Week 12 of the DBT Phase between rimegepant and placebo.	Mean change from baseline in the MIDAS total score, absenteeism and presenteeism scores at Week 12 of the DBT Phase.	3.11. The estimand is the treatment effect of rimegepant relative to placebo in terms of the difference in mean change from baseline in the MIDAS total score, absenteeism and presenteeism scores at Week 12 of the DBT Phase among all randomized participants with migraine who took study intervention without regard to the use of prophylactic medications or study intervention discontinuation.
	To compare the mean change from baseline in the EuroQol 5-dimensional questionnaire (EQ-5D-5L) index score and Visual Analogue scale (VAS) score at Week 12 of the DBT Phase between rimegepant and placebo.	Mean change from baseline in EQ-5D-5L index score and VAS score at Week 12 of the DBT Phase.	3.12. The estimand is the treatment effect of rimegepant relative to placebo in terms of the difference in mean change from baseline in EQ-5D-5L index score and VAS score at Week 12 of the DBT Phase among all randomized participants with migraine who took study intervention without regard to the use of prophylactic medications or study intervention discontinuation.
	To evaluate the mean changes from baseline in MSQoL domain scores, MIDAS scores, and EQ-5D-5L scores at Week 24 of the OLE Phase.	Mean change from baseline in MSQoL domain scores, MIDAS scores, and EQ-5D-5L scores at Week 24 of the OLE Phase.	3.13. The estimand is the treatment effect of rimegepant relative to placebo in terms of the difference in mean change from baseline in MSQoL domain scores, MIDAS scores, and EQ-5D-5L scores at Week 24 of the OLE Phase among all randomized participants with migraine who took study intervention without regard to the use of prophylactic medications or study intervention discontinuation.

2.2.1. Primary Estimand

The primary estimand of this study is a compound estimand as there is a hypothetical approach for study intervention discontinuation and treatment policy approach for prophylactic migraine medication use. The estimand is defined according to the primary objective and is in alignment with the primary endpoint. It includes the following 4+1 attributes:

- Treatment: Rimegepant and placebo;
- Population: All randomized participants with migraine who took study intervention;

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- Variable: Change from the OP in the number of total migraine days per month over the entire DBT Phase (Weeks 1 to 12);

- Intercurrent events: Study intervention discontinuation will take a hypothetical approach and data collected after this intercurrent event will be excluded. Prophylactic migraine medication use will take a treatment policy approach and will not be considered;

- Population-level summary: Difference in mean changes from the OP between treatment groups.

2.2.2. Secondary Estimands

Secondary estimands to assess secondary objectives will be:

Estimand 2.1: The secondary estimand of this study is a compound estimand as there is a composite approach for study intervention discontinuation and treatment policy approach for prophylactic migraine medication use. The estimand is defined according to the secondary objective and is in alignment with the secondary endpoint. It includes the following 4+1 attributes:

- Treatment: Rimegepant and placebo;

- Population: All randomized participants with migraine who took study intervention;

- Variable: Percentage of participants with ≥50% reduction from the OP in the number of moderate to severe migraine days per month over the entire DBT Phase;

- Intercurrent events: Study intervention discontinuation will take a composite approach and be part of the endpoint definition. Prophylactic migraine medication use will take a treatment policy approach and will not be considered;

- Population-level summary: Difference in percentages of participants with response between treatment groups.

Estimand 2.2: This estimand is a compound estimand as there is a hypothetical approach for study intervention discontinuation and treatment policy approach for prophylactic migraine medication use. The estimand is defined according to the secondary objective and is in alignment with the secondary endpoint. It includes the following 4+1 attributes:

- Treatment: Rimegepant and placebo;

- Population: All randomized participants with migraine who took study intervention;

- Variable: Mean change from the OP in the number of migraine days per month in the first 4 weeks of the DBT Phase;

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- Intercurrent events: Study intervention discontinuation will take a hypothetical approach and data collected after this intercurrent event will be excluded. Prophylactic migraine medication use will take a treatment policy approach and will not be considered;

- Population-level summary: Difference in mean changes from the OP between treatment groups.

Estimand 2.3: This estimand is a compound estimand as there is a hypothetical approach for study intervention discontinuation and treatment policy approach for prophylactic migraine medication use. The estimand is defined according to the secondary objective and is in alignment with the secondary endpoint. It includes the following 4+1 attributes:

- Treatment: Rimegepant and placebo;

- Population: All randomized participants with migraine who took study intervention;

- Variable: Mean change from the OP in the number of migraine days per month in the last 4 weeks of the DBT Phase;

- Intercurrent events: Study intervention discontinuation will take a hypothetical approach and data collected after this intercurrent event will be excluded. Prophylactic migraine medication use will take a treatment policy approach and will not be considered;

- Population-level summary: Difference in mean changes from the OP between treatment groups.

Estimand 2.4: This estimand is a treatment policy approach for prophylactic migraine medication use and study intervention discontinuation. The estimand is defined according to the secondary objective and is in alignment with the secondary endpoint. It includes the following 4+1 attributes:

- Treatment: Rimegepant and placebo;

- Population: All randomized participants with migraine who took study intervention;

- Variable: Mean change from baseline in the MSQoL role function-restrictive domain score at Week 12 of the DBT Phase;

- Intercurrent events: Study intervention discontinuation and prophylactic migraine medication use will take a treatment policy approach and will not be considered;

- Population-level summary: Difference in mean changes from baseline between treatment groups.

Estimand 2.5: This estimand is a compound estimand as there is a hypothetical approach for study intervention discontinuation and a treatment policy approach for prophylactic migraine

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medication use. The estimand is defined according to the secondary objective and is in alignment with the secondary endpoint. It includes the following 4+1 attributes:

- Treatment: Rimegepant and placebo;
- Population: All randomized participants with migraine who took study intervention;
- Variable: Mean number of acute migraine medication days per month over the entire DBT Phase;
- Intercurrent events: Study intervention discontinuation will take a hypothetical approach and data collected after this intercurrent event will be excluded. Prophylactic migraine medication use will take a treatment policy approach and will not be considered;
- Population-level summary: Difference in mean numbers between treatment groups.

2.2.3. Exploratory Estimands

For exploratory endpoints 1-9, the estimand is a compound estimand as there is a hypothetical approach for study intervention discontinuation (endpoints 1, 3 and 6), while-on-treatment approach for study intervention discontinuation (endpoints 7, 8 and 9), composite approach for study intervention discontinuation (endpoints 2 and 4), and a treatment policy approach for prophylactic migraine medication use (all endpoints). The estimand is defined according to the exploratory objectives and is in alignment with the exploratory endpoints. It includes the following 4+1 attributes:

- Treatment: Rimegepant and placebo;
- Population: All randomized participants with migraine who took study intervention;
- Variables:

  1. Mean change from the OP in the number of migraine days per month and number of headache days per month by pain intensity (total; moderate or severe) in each month and over the entire DBT Phase;

  2. Percentage of participants with ≥50% reduction, ≥75% reduction, and 100% reduction from OP in the number of migraine days per month and number of headache days per month by pain intensity (total; moderate or severe) in each month and over the entire DBT Phase;

  3. Mean change from the OP in the number of migraine days per week and number of headache days per week by pain intensity (total; moderate or severe) in each week of the first 4 weeks of the DBT Phase;

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4. Percentage of participants with ≥50% reduction from OP in the number of migraine days per week and number of headache days per week by pain intensity (total; moderate or severe) in each week of the first 4 weeks of the DBT Phase;

5. Percentage of participants with a migraine day and headache by pain intensity (total; moderate or severe) on each day of the first week of the DBT Phase;

6. Mean number of acute migraine-specific medication days per month in each month and over the entire DBT Phase;

7. Mean change from OP in the number of migraine days per month and number of headache days per month by pain intensity (total; moderate or severe) in each month and over the entire OLE Phase;

8. Percentage of participants with ≥50% reduction, ≥75% reduction, and 100% reduction from OP in the number of migraine days per month and number of headache days per month by pain intensity (total; moderate or severe) in each month and over the entire OLE Phase;

9. Mean number of acute migraine medication days per month and acute migraine-specific medication days per month in each month and over the entire OLE Phase;

- Intercurrent events: Study intervention discontinuation will take the following approaches: hypothetical for endpoints 1, 3, and 6; while-on-treatment for endpoints 7 and 9; and composite for endpoints 2, 4 and 8. Prophylactic migraine medication use will take a treatment policy approach and will not be considered;

- Population-level summary:

  - For endpoints 1 and 3, the population-level summary is the difference in mean changes from OP between treatment groups.

  - For endpoints 2, 4, and 5, the population-level summary is the difference in percentages of participants with response between treatment groups.

  - For endpoint 6, the population-level summary is the difference in mean numbers between treatment groups.

  - For endpoint 7, the population-level summary is the mean change from OP by treatment group and overall.

  - For endpoint 8, the population-level summary is the percentage of participants with response by treatment group and overall.

  - For endpoint 9, the population-level summary is the mean number by treatment group and overall.

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For exploratory endpoints 10-13, the estimand is a treatment policy approach for prophylactic migraine medication use and study intervention discontinuation. The estimand is defined according to the exploratory objectives and is in alignment with the exploratory endpoints. It includes the following 4+1 attributes:

- Treatment: Rimegepant and placebo;
- Population: All randomized participants with migraine who took study intervention;
- Variables:

  10. Mean change from baseline in MSQoL preventive role function and emotional function domain scores at Week 12 of the DBT Phase;

  11. Mean change from baseline in the MIDAS total score, absenteeism and presenteeism scores at Week 12 of the DBT Phase;

  12. Mean change from baseline in EQ-5D-5L index score and VAS score at Week 12 of the DBT Phase;

  13. Mean change from baseline in MSQoL domain scores, MIDAS scores, and EQ-5D-5L scores at Week 24 of the OLE Phase.

- Intercurrent events: Study intervention discontinuation and prophylactic migraine medication use will take a treatment policy approach and will not be considered;
- Population-level summary:
  - For endpoints 10-12, the population-level summary is the difference in mean changes from baseline between treatment groups.
  - For endpoint 13, the population-level summary is the mean change from baseline by treatment group and overall.

2.3. Study Design

This is a multicenter, randomized, double-blind, placebo-controlled study to assess the efficacy and safety of rimegepant in migraine prevention in Chinese participants with an OLE Phase. The OP will include the Screening Visit. Upon completion of the Screening Visit, participants will be provided an electronic diary (eDiary) to be used daily to report migraine occurrence, migraine pain features, and associated symptoms during the OP. Participants will record all concomitant medications, including acute migraine medications [both prescribed and over the counter (OTC)] they take in a concomitant medication paper diary. To be eligible for the study, participants must report having had 4 to 18 migraine attacks of moderate to severe intensity per month (4-week period) within the 3 months prior to the Screening Visit, and at least 6 migraine days and no more than 18 headache days during the OP. After completing the OP, participants will return to the study site with both diaries for the Baseline (Randomization) Visit. At the Baseline Visit,

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eligibility for continued study participation will be assessed before randomization occurs and before study intervention is dispensed. Eligible participants will be randomized 1:1 to 2 treatment groups: rimegepant 75 mg orally disintegrating tablet (ODT) dose Every Other Day (EOD) (n = 392) or matching placebo EOD (n = 392). Randomization will be stratified by the number of migraine days during the OP (< 8, ≥ 8). During the 12-week DBT Phase, participants will be instructed that they must take 1 tablet of blinded study intervention (rimegepant 75 mg or placebo) EOD. If participants have a migraine during the DBT Phase, if needed, they may treat the migraine with their permitted acute migraine medication and continue to take study intervention on their scheduled dosing days.

At the completion of the DBT Phase, eligible participants may be entered into the 12-week OLE Phase following laboratory results within acceptable ranges. During the OLE Phase, participants will be instructed that they must take 1 rimegepant 75 mg ODT EOD. If participants have a migraine on a day that they are not scheduled to dose with rimegepant, they may take 1 tablet of rimegepant 75 mg ODT on that calendar day to treat the migraine. Therefore, during the OLE Phase, participants can take a maximum of 1 tablet of rimegepant 75 mg ODT per calendar day up to 12 weeks.

Participants will continue to use the eDiary daily to report migraine occurrence and migraine pain features during the DBT and OLE Phases. Participants are required to report each dose of study intervention taken in a study intervention paper diary throughout the entire study. Participants are also required to record any concomitant medications, including acute migraine medications (both prescribed and OTC) taken in a concomitant medication paper diary throughout the entire study.

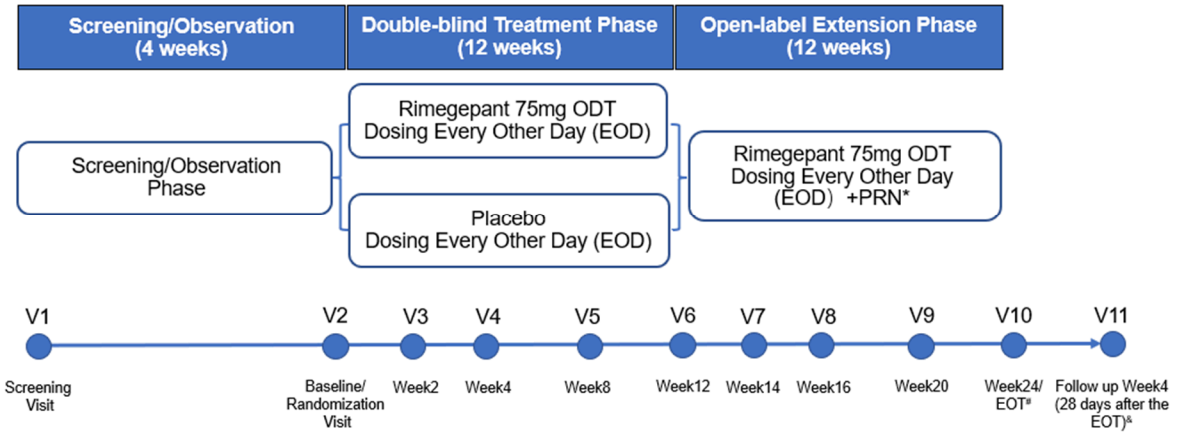
At select study visits, participants will complete or will be administered the MSQoL v2.1, the MIDAS and EQ-5D-5L and the Columbia-Suicide Severity Rating Scale (C-SSRS).

Study visits will occur at the following time points: Screening during the OP; Baseline (Randomization), Week 2, Week 4, Week 8, and Week 12 during the DBT Phase; Week 14, Week 16, Week 20, and Week 24/End of Treatment (EOT) during the OLE Phase. Participants will return to the study site at the end of Week 24 for the EOT visit. Participants who discontinue DBT Phase, or do not enter or complete the OLE Phase, will also return to the site for the EOT visit at the time of study intervention discontinuation. There is a Follow-up Week 4 Visit approximately 28 days after the EOT visit. All randomized participants should complete the Follow-up Week 4 Visit, regardless of completing either treatment phase.

To closely monitor for potential drug induced liver injury, guidance on reporting potential drug-induced liver injury (DILI) events is provided in the protocol. Laboratory results that meet predefined liver function test (LFT) abnormality criteria as potential DILI events should be reported as a SAE. See Protocol Section 9.5 - Potential Drug Induced Liver Injury (DILI).

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Figure 1. Study Schematic



*During the OLE Phase, participants will be instructed that they must take 1 rimegepant 75 mg ODT every other calendar day. If participants have a migraine attack on the day that they are not scheduled to dose with rimegepant, they may take 1 tablet of rimegepant 75 mg ODT on that calendar day to treat a migraine. Therefore, during the OLE Phase, participants can take a maximum of 1 tablet of rimegepant 75 mg ODT per calendar day up to 12 weeks.

#Participants will return to the study site at the end of Week 24 for the EOT visit. Participants who do not complete the DBT Phase, or do not complete the OLE Phase, will complete the EOT visit.

&There is a Follow-up Week 4 Visit approximately 28 days after the EOT visit. The participants who complete the EOT visit, and the participants who complete the DBT Phase (Week 12 Visit) but do not enter the OLE Phase should complete the Follow-up Week 4 Visit.

3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS

3.1. Primary Endpoint

The primary endpoint is the mean change from the OP in the number of migraine days per month over the entire DBT Phase (Weeks 1 to 12).

3.1.1. Endpoint with migraine days per month in DBT phase

The number of migraine days per month in the DBT phase relative to the OP will be calculated for participants in the DBT migraine analysis set, i.e., those with ≥14 days of efficacy data (not necessarily consecutive) in both the OP analysis period and ≥1 month (i.e., 4-week interval) in the on-DBT efficacy analysis period.

Analyses will be based on efficacy data days in the OP and on-DBT efficacy analysis periods. See detailed definitions for analyses periods in Section 5.2.4 , per-month analyses windows in Section 5.2.5, and migraine days in Appendix 4.

The number of migraine days per month will be prorated to 28 days and be derived as follows:

- OP: 28 × (total number of migraine days in the OP analysis period)/(total number of efficacy data days in the OP analysis period).
- Month (i.e., 4-week interval) in the on-DBT efficacy analysis period: 28 × (total number of migraine days in the month)/(total number of efficacy data days in the month).

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Participants must have ≥14 days of efficacy data (not necessarily consecutive) in the specified month of the on-DBT efficacy analysis period to be evaluable.

- Overall DBT in the on-DBT efficacy analysis period: 28 × (total number of migraine days through Month 3)/(total number of efficacy data days through Month 3).

3.2. Secondary Endpoints

- Percentage of participants with ≥50% reduction from OP in the number of moderate to severe migraine days per month over the entire DBT Phase.
- Mean change from the OP in the number of migraine days per month in the first 4 weeks of the DBT Phase.
- Mean change from the OP in the number of migraine days per month in the last 4 weeks of the DBT Phase.
- Mean change from baseline in the MSQoL role function-restrictive domain score at Week 12 of the DBT Phase.
- Mean number of acute migraine medication days per month over the entire DBT Phase.
- Number and percentage of participants with AEs by severity, SAEs, AEs leading to study intervention discontinuation and Grade 3 to 4 laboratory test abnormalities on treatment during the DBT and OLE Phases.
- Number and percentage of participants with ALT or AST > 3x ULN concurrent with total bilirubin > 2x ULN on treatment during the DBT and OLE Phases.
- Number and percentage of participants with hepatic-related AEs and hepatic-related AEs leading to study intervention discontinuation on treatment during the DBT and OLE Phases.

3.2.1. Migraine-Specific Quality-of-Life Questionnaire v 2.1 (MSQoL)

The MSQoL will be assessed at EOT and the following visits: baseline; Week 12 of the DBT phase; and Week 24 of the OLE phase.

Impact of treatment on patient-reported quality of life is assessed using MSQoL Version 2.1 and Scoring Version 1.0 (2017), which is a 14-item questionnaire that has been validated in migraine patients to assess the effects of migraines on their daily activities over the past 4 weeks. The MSQoL consists of 14 items across the following 3 domains: (1) restrictive role function, (2) preventative role function and (3) emotional function. There are 7 items in the restrictive role function domain (raw scores range from 7 to 42), 4 items in the preventative role function domain (raw scores range from 4 to 24), and 3 items in the emotional function domain (raw scores range from 3 to 18). Response options for each of the items are on a 6-point scale where 1

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indicates no impairment of QoL ("none of the time") and 6 indicates maximum impairment ("all of the time").

- The 7 items in the restrictive role function domain are: (1) interference with how well participant dealt with family, friends and others; (2) interference with leisure time activities; (3) difficulty in performing work or daily activities; (4) kept from getting as much done at work or home; (5) limitation of ability to concentrate on work or daily activities; (6) being too tired to do work or daily activities; and (7) impacted the number of days participant felt lethargic.

- The 4 items in the preventative role function domain are: (1) canceled work or daily activities, (2) needed help in handling routine tasks, (3) stopped work or daily activities to deal with migraine symptoms, and (4) inability to go to social activities.

- The 3 items in the emotional function domain are: (1) felt fed up or frustrated, (2) felt like a burden on others, and (3) afraid of letting others down.

Scores will be calculated as the following: First, individual item scores will be recoded as {7 – original item score}. Next, a raw score for a domain will be calculated as the sum of recoded scores across individual items in that domain. If less than or equal to half of the item scores in a domain are missing (i.e., ≤ 3 items for restrictive role function; ≤ 2 for preventative role function; and ≤ 1 for emotional function), then the missing item scores will be imputed with the average of the non-missing item scores in the domain before calculating the raw score for that domain. Otherwise, if more than half of the item scores in a domain are missing, then the raw score for that domain will be considered missing.

The raw score for a domain will then be transformed to a 0 to 100 scale using the following formulas:

  - Restrictive role function = (raw score-7)*100/35

  - Preventative role function = (raw score-4)*100/20

  - Emotional function = (raw score-3)*100/15

Measurements will be slotted into the analysis period as defined in Section 5.2.4.

The baseline questionnaire is defined as the last completed questionnaire administered at the Baseline Visit.

3.2.2. Endpoint with X% reduction in the migraine days per month in DBT phase

The X% reduction in the number of migraine days per month in the DBT phase relative to the OP will be calculated for participants in the DBT migraine analysis set.

The responder and failure per month will be defined as follows:

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- Responder, i.e., participant with ≥ 14 days of efficacy data in both the OP and the specified month of the on-DBT efficacy analysis periods, ≥ X% reduction in the specified month of the on-DBT efficacy analysis period, and ≥ 1 migraine day of appropriate migraine severity in the OP analysis period.

- Failure

  - No migraine days of appropriate migraine severity in OP analysis period.

  - Evaluable but < X% reduction in the month, i.e., participants with ≥ 14 days of efficacy data and < X% reduction in the specified month.

  - ≥ X% reduction but not evaluable in month, i.e., participants with ≥ X% reduction and ≥ 1 to < 14 days of efficacy data in the specified month.

  - No days of efficacy data in month

The responder for the overall DBT will be defined as follows:

- Responder, i.e., participant with ≥ 14 days of efficacy data in both the OP and ≥ 1 month of the on-DBT efficacy analysis periods, ≥ X% reduction in the overall DBT mean and ≥ 1 migraine day of appropriate migraine severity in the OP analysis period.

- Failure

  - No migraine days of appropriate migraine severity in OP analysis period.

  - < X% reduction

In the above description, X = 50, 75, and 100.

3.2.3. Endpoint with acute migraine medication days per month in DBT phase

The number of acute migraine medication days per month in the DBT phase will be calculated for participants in the DBT migraine analysis set.

The number of acute migraine medication days per month in the DBT phase will be prorated to 28 days and derived as follows:

- Month (i.e., 4-week interval) in the on-DBT efficacy analysis period: 28 × (total number of acute migraine medication days in the month)/(total number of efficacy data days in the month). Participants must have ≥14 days of efficacy data (not necessarily consecutive) in the specified month to be evaluable.

- Overall DBT in the on-DBT efficacy analysis period: 28 × (total number of acute migraine medication days through Month 3)/(total number of efficacy data days through Month 3).

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See detailed definitions for analyses periods in Section 5.2.4, and acute migraine medication days in Appendix 4.

3.3. Exploratory Endpoints

The exploratory endpoints include:

- Mean change from the OP in the number of migraine days per month and number of headache days per month by pain intensity (total; moderate or severe) in each month and over the entire DBT Phase.
- Percentage of participants with ≥50% reduction, ≥ 75% reduction, and 100% reduction from OP in the number of migraine days per month and number of headache days per month by pain intensity (total; moderate or severe) in each month and over the entire DBT Phase.
- Mean change from the OP in the number of migraine days per week and number of headache days per week by pain intensity (total; moderate or severe) in each week of the first 4 weeks of the DBT Phase.
- Percentage of participants with ≥50% reduction from OP in the number of migraine days per week and number of headache days per week by pain intensity (total; moderate or severe) in each week of the first 4 weeks of the DBT Phase.
- Percentage of participants with a migraine day and headache day by pain intensity (total; moderate or severe) on each day of the first week of the DBT Phase.
- Mean number of acute migraine-specific medication days per month in each month and over the entire DBT Phase.
- Mean change from the OP in the number of migraine days per month and number of headache days per month by pain intensity (total; moderate or severe) in each month and over the entire OLE Phase.
- Percentage of participants with ≥ 50% reduction, ≥ 75% reduction, and 100% reduction from the OP in the number of migraine days per month and number of headache days per month by pain intensity (total; moderate or severe) in each month and over the entire OLE Phase.
- Mean number of acute migraine medication days per month and acute migraine-specific medication days per month in each month and over the entire OLE Phase.
- Mean change from baseline in the MSQoL preventive role function and emotional function domain scores at Week 12 of the DBT Phase.
- Mean change from baseline in the MIDAS total score, absenteeism and presenteeism scores at Week 12 of the DBT Phase.

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- Mean change from baseline in EQ-5D-5L index score and VAS score at Week 12 of the DBT Phase.

- Mean change from baseline in MSQoL domain scores, MIDAS scores, and EQ-5D-5L scores at Week 24 of the OLE Phase.

3.3.1. Migraine Disability Assessment (MIDAS) Questionnaire

The MIDAS will be assessed at EOT and the following visits: baseline; Week 12 of the DBT phase; and Week 24 of the OLE phase.

The MIDAS is a retrospective, patient-administered, 5-item questionnaire that measures headache-related disability as lost time due to headache from paid work or school, household work, and non-work activities. The 5 questions are as follows:

- Question 1: On how many days in the last 3 months did you miss work or school because of your headaches?

- Question 2: How many days in the past 3 months was your productivity at work or school reduced by half or more because of your headaches?

- Question 3: On how many days in the past 3 months did you not do household work (such as housework, home repairs and maintenance, shopping, caring for children and relatives) because of your headaches?

- Question 4: How many days in the past 3 months was your productivity in household work reduced by half or more because of your headaches?

- Question 5: On how many days in the past 3 months did you miss family, social or leisure activities because of your headaches?

The total score will be calculated as the sum of item scores to all 5 questions. If only 1 item score is missing, then that item score will be imputed with the average of the 4 non-missing item scores before calculating the total score. Otherwise, if ≥ 2 item scores are missing, then the total score will be considered missing.

The absenteeism score will be calculated as the sum of item scores to questions 1, 3, and 5 without imputation. All 3 item scores must be non-missing; otherwise, the absenteeism score will be considered missing.

The presenteeism score will be calculated as the sum of item scores to questions 2 and 4 without imputation. Both item scores must be non-missing; otherwise, the absenteeism score will be considered missing.

Item scores will be calculated using non-missing scores without imputation.

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The baseline questionnaire is defined as the last completed questionnaire administered at the Baseline visit.

3.3.2. EuroQol 5-dimensional questionnaire (EQ-5D-5L) and Visual Analogue scale (VAS)

The EQ-5D-5L will be assessed at EOT and the following visits: baseline; Week 12 of the DBT phase; and Week 24 of the OLE phase.

EQ-5D-5L is a standardized measure of health status. The EQ-5D-5L consists of 2 pages – the EQ-5D-5L descriptive system and the EQ VAS. It is designed for self-completion by respondents.

The descriptive system comprises the 5 dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression). Each dimension has 5 levels: no problems, slight problems, moderate problems, severe problems, and extreme problems. The EQ VAS records the respondent's self-rated health on a 20cm vertical, VAS with endpoints labelled 'the best health you can imagine' and 'the worst health you can imagine'.

The baseline questionnaire is defined as the last completed questionnaire administered at the Baseline visit.

3.3.3. Endpoint with migraine days per week in DBT phase

The number of migraine days per week in the DBT phase relative to the OP will be calculated for participants with ≥24 days of efficacy data (not necessarily consecutive) in both the OP analysis period and first month (Weeks 1 to 4) of the on-DBT efficacy analysis period.

Per-week migraine days in DBT phase will be based on the analysis window defined in Section 5.2.5.

The number of migraine days per week will be prorated to 7 days, and be derived as follows:

- OP: 7 × (total number of migraine days in the OP analysis period)/(total number of efficacy data days in the OP analysis period).
- Week of the on-DBT efficacy analysis period: 7 × (total number of migraine days in the week)/(total number of efficacy data days in the week).

3.3.4. Endpoint with migraine days per month in OLE phase

The number of migraine days per month in the OLE phase relative to the OP will be calculated for participants in the OLE migraine analysis set, i.e., those who are in both the DBT migraine and OLE efficacy analysis sets and had ≥14 days of efficacy data (not necessarily consecutive) in ≥ 1 month (i.e., 4-week interval) in the on-OLE efficacy analysis period.

The number of migraine days per month will be prorated to 28 days using the same formula as those in Section 3.1.1, except that the on-DBT efficacy analysis period will be replaced by the

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on-OLE efficacy analysis period which is defined in Section 5.2.4. Also, participants must have ≥14 days of efficacy data (not necessarily consecutive) in the specified month to be evaluable at that month.

3.3.5. Endpoint with 50% reduction in the migraine days per week in DBT phase

The responder at every week will be defined as follows:

- Responder, i.e., participants with ≥ 24 days of efficacy data (not necessarily consecutive) in both the OP analysis period and first month (Weeks 1 to 4) of the on-DBT efficacy analysis period, ≥ 50% reduction in the specified week of the on-DBT efficacy analysis period, and ≥1 migraine day of appropriate migraine severity in the OP analysis period.

3.3.6. Endpoint with acute migraine-specific medication days per month in DBT phase

The number of acute migraine-specific medication days per month in the DBT phase will be prorated to 28 days and derived as follows:

- Month (i.e., 4-week interval) in the on-DBT efficacy analysis period: 28 × (total number of acute migraine-specific medication days in the month)/(total number of efficacy data days in the month). Participants must have ≥ 14 days of efficacy data (not necessarily consecutive) in the specified month to be evaluable.

- Overall DBT in the on-DBT efficacy analysis period: 28 × (total number of acute migraine-specific medication days through Month 3)/(total number of efficacy data days through Month 3).

See detailed definitions for analyses periods in Section 5.2.4, and acute migraine-specific medication days in Appendix 4.

3.3.7. Endpoint with X% reduction in the migraine days per month in the OLE phase

The X% reduction in the migraine days per month in the OLE phase will be calculated based on the OLE migraine analysis set in the on-OLE efficacy analysis period which is defined in Section 5.2.4.

The responder per month will be defined as follows:

- Responder, i.e., participants with ≥ X% reduction in the specified month, ≥ 14 days of efficacy data in both the OP and the specified month of the on-OLE efficacy analysis period, and ≥ 1 migraine day of appropriate migraine severity in the OP analysis period.

Otherwise, evaluable participants who do not achieve the first criterion are classified as failures in the specified month, and non-evaluable participants are excluded in the specified month.

The responder for the overall OLE will be defined as follows:

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- Responder, i.e., participants with ≥ X% reduction in the overall OLE, ≥ 14 days of efficacy data in both the OP and ≥ 1 month of the on-OLE efficacy analysis period, and ≥ 1 migraine day of appropriate migraine severity in the OP analysis period.

Otherwise, evaluable participants who do not achieve the first criterion are classified as failures, and non-evaluable participants are excluded.

3.3.8. Endpoint with X% reduction in the headache days per month/week in the DBT/OLE phase

The X% reduction in the headache days per month and per week will be using the same definitions as those in Section 3.2.2, Section 3.3.5, and Section 3.3.7 for either the on-DBT efficacy analysis period or the on-OLE efficacy analysis period which are defined in Section 5.2.4.

3.3.9. Endpoint with acute migraine medication days per month in OLE phase

The number of acute migraine medication days per month will be prorated to 28 days using the same formula as those in Section 3.2.3 and Section 3.1.1, except that the on-DBT efficacy analysis period will be replaced by the on-OLE efficacy analysis period which is defined in Section 5.2.4. Also, participants must have ≥14 days of efficacy data (not necessarily consecutive) in the specified month of the on-OLE efficacy analysis period to be evaluable in that month.

3.4. Baseline Variables

The baseline variables in the study contain demographic and other baseline characteristics as follows:

- Age in years at informed consent (years)
- Age category 1: <40, ≥40
- Age category 2: <65, ≥65
- Sex: male, female
- Race
- Height (cm)
- Weight (kg)
- Body mass index (BMI; kg/m^2)
- BMI category: <25, ≥25 to <30, ≥30

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- Number of migraine days during OP (randomization stratum based on actual data): <8, ≥8.

3.5. Safety Endpoints

3.5.1. Adverse Events

SAEs and non-serious AEs should be reported from signing of consent through the Follow-up Week 4 Visit (4 weeks after the last visit).

An AE is considered a Treatment-Emergent Adverse Event (TEAE) if the event started after the study medication start date and time. If an AE starts on the same day as the first dose date, it will be considered treatment emergent.

3.5.2. Laboratory Data

Hematology, serum chemistry and estimated glomerular filtration rate (eGFR) testing will be performed at EOT and the following visits: screening; baseline; Weeks 4, 8, and 12 of the DBT phase; and Weeks 16 and 24 of the OLE phase. Urinalysis will be collected at EOT and the following visits: baseline; Week 12 of the DBT phase; and Week 24 of the OLE phase. Lipids (i.e., cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, and triglycerides) will be collected at EOT and the following visits: screening; baseline; Week 12 of the DBT phase; and Week 24 of the OLE phase. LFTs (ALT, AST, alkaline phosphatase [ALP], total bilirubin level [TBL], and direct bilirubin) will be collected routinely at EOT and the following visits: screening; baseline; Weeks 2, 4, 8, and 12 of the DBT phase; Weeks 14, 16, 20 and 24 of the OLE phase; and follow-up Week 4. The baseline value is defined as the last non-missing value on or before the DBT study intervention start date.

3.5.3. Vital Signs and Physical Measurements

The following vital signs and physical measurements will be measured at EOT and the following visits where appropriate: screening; baseline; Weeks 4, 8, and 12 of the DBT phase; Week 16, 20 and 24 of the OLE phase; and follow-up Week 4:

- Systolic blood pressure (mmHg)
- Diastolic blood pressure (mmHg)
- Pulse rate (beats per minute [bpm])
- Respiratory rate (breaths per minute)
- Body temperature (ºC)
- Weight (kg).

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The baseline value is defined as the last non-missing value on or before the DBT study intervention start date.

3.5.4. Twelve-lead Electrocardiograms (ECG)

A 12-ECG will be measured at EOT and the following visits: screening; Week 12 of the DBT phase; and Week 24 of the OLE phase. ECG parameters will include RR, QRS (msec), PR (msec), QT (msec), QTcF and ventricular heart rate (bpm).

The baseline value is defined as the last non-missing value on or before the DBT study intervention start date.

3.5.5. Columbia-Suicide Severity Rating Scale (C-SSRS)

The C-SSRS is a clinician administrated questionnaire used to help immediate risk of suicide. The C-SSRS will be assessed at EOT and the following visits: screening; baseline; Weeks 2, 4, 8, and 12 of the DBT phase; Weeks 14, 16, 20 and 24 of the OLE phase; and follow-up Week 4.

C-SSRS questions are as follows:

- Suicidal ideation section: 5 questions with yes/no responses: (1) wish to be dead; (2) nonspecific active suicidal thoughts; (3) active suicidal ideation with any methods (not plan) without intent to act; (4) active suicidal ideation with some intent to act, without specific plan; and (5) active suicidal ideation with specific plan and intent:

If the responses to Questions 1 and 2 are both "no", then Questions 3 through 5 and the intensity of ideation section are not completed. If the response to Question 2 is "yes", then Questions 3 through 5 are completed. If the response to Question 1 or 2 is "yes", then the intensity of ideation section is completed.

- Intensity of ideation section:

Most severe ideation is rated as 1 (wish to be dead) to 5 (active suicidal ideation with specific plan and intent). Five questions rated as 0 to 5 regarding: (1) frequency, (2) duration, (3) controllability, (4) deterrents, and (5) reasons for ideation are included in the form.

- Suicidal behavior section: questions with yes/no responses about actual attempt, whether engaged in non-suicidal self-injurious behavior, and behaviors of (1) interrupted attempt, (2) aborted attempt, (3) preparatory acts or behavior, (4) suicidal behavior, (5) completed suicide.

In particular, for actual attempts, actual lethality/medical damage [rated on a scale of 0 (no physical damage) to 5 (death)] and potential lethality [(only when actual lethality = 0), rated on a scale of 0 to 2] are detailed.

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4. ANALYSIS SETS (POPULATIONS FOR ANALYSIS)

Data for all participants will be assessed to determine if participants meet the criteria for inclusion in each analysis population prior to unblinding and releasing the database and classifications will be documented per standard operating procedures.

Population	Description	Applicable Analysis (for additional information refer to Section 6)
Enrolled	Participants who sign an informed consent form and are assigned a participant identification number.	Summary of analysis sets (Section 6.5.2).
Randomized	Participants in the enrolled analysis set who receive a randomized treatment assignment (rimegepant or placebo) from the Interactive Web-based Response System (IWRS).	Baseline and other summaries (Sections 6.5.1 and 6.5.4).
DBT safety	Participants in the enrolled analysis set who take ≥1 dose of double-blind study intervention (rimegepant or placebo).	Secondary endpoints (Sections 6.2.6-6.2.8); Baseline and other summaries (Sections 6.5.3, 6.5.5 and 6.5.6); Safety summaries and analyses (Section 6.6).
OLE rimegepant safety	Participants in the enrolled analysis set who take ≥1 dose of open-label rimegepant.	Secondary endpoints (Sections 6.2.6-6.2.8); Baseline and other summaries (Sections 6.5.3, 6.5.5 and 6.5.6); Safety summaries and analyses (Section 6.6).
DBT or OLE rimegepant safety	Participants in the enrolled analysis set who take ≥1 dose of double-blind or open-label rimegepant.	Secondary endpoints (Sections 6.2.6-6.2.8); Baseline and other summaries (Sections 6.5.3, 6.5.5 and 6.5.6); Safety summaries and analyses (Section 6.6).
Follow-up safety	Participants in the DBT safety analysis set whose last contact date is in the follow-up safety analysis period.	Safety summaries and analyses (Section 6.6).
DBT efficacy	Participants in the randomized analysis set who are randomized only once and take ≥1 dose of double-blind study intervention (rimegepant or placebo).	Secondary endpoints (Section 6.2.4); Exploratory endpoints (Sections 6.3.10-6.3.12).
DBT migraine	Participants in the DBT efficacy analysis set with ≥14 days of efficacy data (not necessarily consecutive) in both the OP and ≥ 1 month (4-week interval) in the DBT Phase.	Primary endpoint (Section 6.1.1); Secondary endpoints (Sections 6.2.1-6.2.3 and 6.2.5); Exploratory endpoints (Sections 6.3.1, 6.3.2 and 6.3.6); Baseline and other summaries (Section 6.5.3).

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Population	Description	Applicable Analysis (for additional information refer to Section 6)
DBT first month migraine	Participants in the DBT efficacy analysis set with ≥24 days of efficacy data (not necessarily consecutive) in both the OP and first month (Weeks 1 to 4) in the DBT Phase.	Exploratory endpoint (Sections 6.3.3 and 6.3.4).
DBT first week EOD treated migraine	Participants in the DBT efficacy analysis set with (1) ≥24 days of efficacy data (not necessarily consecutive) in the OP, (2) 7 consecutive days of efficacy data in the first week of the DBT Phase, and (3) EOD dosing in the first week of the DBT Phase.	Exploratory endpoint (Section 6.3.5).
OLE efficacy	Participants in the DBT efficacy analysis set who take ≥ 1 dose of open-label rimegepant.	Exploratory endpoints (Section 6.3.13)
OLE migraine	Participants in both the DBT migraine and OLE efficacy analysis sets with ≥ 14 days of efficacy data (not necessarily consecutive) in ≥ 1 month (4-week interval) in the OLE Phase.	Exploratory endpoints (Sections 6.3.7-6.3.9)

5. GENERAL METHODOLOGY AND CONVENTIONS

5.1. Hypotheses and Decision Rules

The primary null hypothesis is that rimegepant treatment is not different from placebo in the mean reduction from the OP in the number of migraine days per month across the Weeks 1 to 12 treatment period. The alternative hypothesis is that rimegepant has a different effect than placebo.

Type 1 error will be controlled by the use of hierarchical testing. The significance of the primary endpoint will be evaluated at the 2-sided 0.05 level. If the primary endpoint is not significant, then any further tests on the following secondary endpoints will have p-values presented only for descriptive purposes. If the primary endpoint is significant, then the following secondary efficacy endpoints will be tested hierarchically at the 2-sided 0.05 level in the following order:

- Proportion of participants with ≥50% reduction from the OP in the number of moderate to severe migraine days per month over the entire DBT Phase (Weeks 1 to 12).
- Mean change from the OP in the number of migraine days per month in the first 4 weeks (Weeks 1 to 4) of the DBT Phase.

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- Mean change from the OP in the number of migraine days per month in the last 4 weeks (Weeks 9 to 12) of the DBT Phase.

- Mean change from baseline in the MSQoL role function - restrictive domain score at Week 12 of the DBT Phase.

- Mean number of acute migraine medication days per month over the entire DBT Phase (Weeks 1 to 12).

5.2. General Methods

5.2.1. Analyses for Continuous Endpoints

Continuous variables will be descriptively summarized by as-randomized treatment group (unless otherwise specified) using summary statistics (e.g., n, mean, median, standard deviation (SD) or standard error (SE), minimum, and maximum). Continuous efficacy data during the OLE phase will also be presented with 95% confidence interval (CI) based on normal approximation.

For continuous endpoints with repeated time points a linear mixed effects model with repeated measures (MMRM) that includes a repeated effect of visit, fixed effects of baseline value in OP, randomization stratum based on actual data, treatment group, visit, treatment group by visit interaction, without imputation for missing values (e.g., change from OP in migraine days per month, change from OP in number of headache days per month). For endpoints related to the number of migraine days, the randomization stratum will be excluded from the model, as it is derived from the same data on the number of migraine days in the OP. For endpoints of mean number of acute migraine medication/acute migraine-specific medication days per month, the fixed effects will not include baseline value. A common unstructured variance-covariance matrix will be used, provided the model converges, otherwise an alternative covariance structure, e.g., a heterogeneous Toeplitz error structure will be attempted. If the Toeplitz fails, then an autoregressive order 1 error structure will be attempted.

For endpoints of change from baseline in MSQoL, MIDAS, EQ-5D-5L index score and VAS scores during DBT phase, data will be analyzed using a generalized linear model (GLM) that includes treatment group and randomization stratum based on actual data as fixed effects, and baseline value as a covariate.

In models, the Huber-White robust “sandwich” estimator will be used for the estimation of SEs, which does not require constant response variances between treatment groups and different baseline covariate values.

5.2.2. Analyses for Categorical Endpoints

Categorical variables will be descriptively summarized by as-randomized treatment group (unless otherwise specified) as the number and percentage of participants within each category, including a “not reported” category for missing data if applicable. Percentages in frequency tables will be calculated against the number of participants in each treatment group in the specified analysis set. Categorical efficacy data during the OLE phase will also be presented with

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asymptotic standard error (ASE) and 95% CI based on the normal approximation. Missing data will not be imputed.

The treatment comparison of categorical efficacy data during the DBT phase will be summarized using Mantel-Haenszel risk estimation stratified by randomization stratum based on actual data. The stratified difference estimate (rimegepant – placebo) will be presented with ASE, p-value, and 95% CI based on normal approximation. For individual treatment group, the percentage (i.e. n/N) of participants achieving the endpoint response criteria will be presented with ASE and 95% CI based on normal approximation.

5.2.3. Derived Dates

5.2.3.1. Study Day

Study days are calculated from the study intervention start date (defined as Study Day 1) as follows:

- Measurement date – study intervention start date (i.e. Study Day 1) + 1, if measurement date ≥ study intervention start date
- Measurement date - study intervention start date (i.e. Study Day 1), if measurement date < study intervention start date.

Study Day will be used in defining analysis periods (Section 5.2.4), analysis window (Section 5.2.5), and be presented in individual participant listings.

5.2.3.2. eDiary Day

An eDiary day referred in this SAP is defined as a day with any question been answered by the study participants in the eDiary.

5.2.3.3. Efficacy Data Day

A day of efficacy data is defined as any complete measurement date on which data are collected to assess efficacy parameters (Appendix 4). Efficacy data typically include eDiary efficacy data, but may also include data from other sources (for example, acute migraine-specific medication use collected via CRF) if the eDiary does not collect all efficacy data required to assess the efficacy parameter. The efficacy data days will be cut off until the last study intervention day + 1 day (to account for the treatment effect of the EOD dosing regimen).

5.2.3.4. Last Contact Date

The last contact date is used to determine select parameters (i.e., time on study, imputed nonstudy medication end dates), and is typically defined using non-imputed dates as follows:

1) Earliest complete death date from all sources that collect death dates (e.g., Death CRF), if it exists.

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2) Otherwise, the maximum complete date of the following CRF or external data sources, as applicable: AE start or end; ECG; eDiary assessment; informed consent; IWRS randomization; laboratory test collection; non-study medication start or end; physical exam; procedure; questionnaire; rating scale; study intervention start or end; participant disposition completion/discontinuation; visit; vital signs.

5.2.4. Analyses Periods

The following analysis periods are defined for the analyses of efficacy endpoints based on migraine/headache/medication days, and for safety endpoints:

Table 2. Analysis Periods

Analysis periods	Start date	End date	Usage
OP	Screening Visit date.	Study Day 1 - 1 day.	To be used to calculate the number of migraine/headache/medication days per 4 weeks in this period.
On-DBT efficacy	Study Day 1.	[Later of (1) Week 12 Visit date and (2) DBT study intervention last date + 1 day]/ DBT study intervention last date + 1 day for participants discontinued in DBT phase.	To be used to calculate the number of migraine/headache/medication days per 4 weeks or overall in this period.
On-OLE efficacy	OLE rimegepant start date.	[Later of (1) Week 24 Visit date and (2) OLE study intervention last date + 1 day]/ OLE study intervention last date + 1 day for participants discontinued in OLE phase.	To be used to calculate the number of migraine/headache/medication days per 4 weeks or overall in this period.
On-DBT safety	Study Day 1.	OLE rimegepant start date -1 day/ [Later of (1) EOT Visit date + 7 days and (2) DBT study intervention last date	To be used to assess the safety endpoints of the DBT period for DBT safety analysis set.

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Table 2. Analysis Periods

Analysis periods	Start date	End date	Usage
		+ 7 days] for participants not dosed with OLE rimegepant.	
On-OLE safety	OLE rimegepant start date.	Week 24 Visit date + 7 days / [Later of (1) EOT Visit date + 7 days and (2) OLE rimegepant last date + 7 days] for participants discontinued in OLE phase.	To be used to assess the safety endpoints of the OLE period for OLE rimegepant safety analysis set.
On-DBT or OLE Rimegepant safety	On-DBT safety analysis period start date for the rimegepant group participants; On-OLE safety analysis period start date for placebo group participants.	Later of (1) on-DBT safety end date and (2) on-OLE safety end date.	To be used to assess limited safety endpoints on DBT or OLE rimegepant for the DBT or OLE rimegepant safety analysis set.
Follow-up safety	OLE safety analysis period end date + 1 day / DBT safety analysis period end date + 1 day for participants not dosed with OLE rimegepant.		To be used to assess the safety endpoints of the follow-up period for the follow-up safety analysis set.

5.2.5. Analyses Visit Windows

Below analysis windows will be used for deriving migraine/headache/medication days within the on-DBT efficacy and on-OLE efficacy analysis periods.

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Table 3. Analysis Windows for Migraine/Headache/Medication Days Per Month

DBT and OLE Periods Per 4-week Interval	Analysis Window (**Study Day**)
Month 1: Week 1-Week 4	1-28
Month 2: Week 5 to Week 8	29-56
Month 3: Week 9 to Week 12	57- DBT efficacy end
Month 4: Week 13 to Week 16	OLE efficacy start -112
Month 5: Week 17 to Week 20	113-140
Month 6: Week 21 to Week 24	141- OLE efficacy end

Table 4. Analysis Windows for Migraine/Headache Days Per Week

DBT Period Per-week Interval	Analysis Window (**Study Day**)
Week 1: ≤1 week	1-7
Week 2: >1 to ≤ 2 weeks	8-14
Week 3: >2 to ≤ 3 weeks	15-21
Week 4: >3 to ≤ 4 weeks	22-28

5.2.6. Subgroups

Subgroup tables will present results by subgroup level for participants with non-missing subgroup level data, unless specified otherwise. Subgroup levels may be redefined or combined based on the availability of data.

5.2.6.1. Efficacy subgroups for DBT migraine participants

For DBT migraine participants, the following efficacy subgroups are of interest:

- Age: < 40, ≥ 40, < 65, ≥ 65
- Sex: female, male
- BMI (kg/m^2): < 25, ≥ 25 to < 30, ≥ 30
- Historical number of moderate or severe migraine attacks per month: < 6, ≥ 6, < 8, ≥ 8, < 12, ≥ 12, < 15, ≥ 15
- History of migraine with aura: yes, no

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- Historical chronic migraine: yes, no
- Number of migraine days in OP (randomization stratum based on actual data): $< 8, \geq 8$

5.2.6.2. Safety subgroups

Medical history of hypertension is a safety subgroup of interest for hypertension-related safety endpoints for the DBT and OLE rimegepant safety analysis sets. Medical history of hypertension is defined using the same preferred terms (PTs) as those for hypertension AEs (see Appendix 2).

5.3. Methods to Manage Missing Data

1. For the primary endpoint, the primary analysis will assume missing at random and missing will be taken care of by the MMRM model.

2. In the sensitivity analysis of the primary endpoint, jump to reference (J2R) method will be used to impute missing data (i.e., change from OP in the number of total migraine days per month) in Months 1 to 3 for the DBT migraine analysis set. Placebo is considered the 'reference'.

The analysis is performed using the following steps:

i. Data are imputed using specific multiple imputation SAS macro (the "five macros" [1]):

   a. The imputation model will use the following covariates: age, sex, randomization stratum, and baseline parameters (e.g. number of migraine days per month in the OP).

   b. The macros are run in the following order: %part1A; %part1B using n=500 datasets (Ndraws paramenter), and n=100 for Markov chain Monte Carlo chain thinning (thin parameter); %part2A; and %part2B. Note that the Ndraws and thin parameters may be modified as needed to decrease MCMC error and autocorrelation.

ii. Each imputed data set in step 1 is analyzed using the same MMRM from the main analysis. Note that the fifth macro %part3 will not be used.

iii. Results from each MMRM analysis in step 2 are combined to produce a pooled difference in LSM change, SE, 95% CI, and p-value using SAS proc mianalyze.

3. For the endpoints with percentage reduction of migraine days/headache days change from OP, non-responder imputation (NRI) is used where response will be categorized as failure due to insufficient efficacy data. See Sections 3.2.2, 3.3.5, and 3.3.8.

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6. ANALYSES AND SUMMARIES

6.1. Primary Endpoint

6.1.1. Mean change from the OP in the number of migraine days per month over the entire DBT Phase (Weeks 1 to 12)

6.1.1.1. Main Analysis

- Estimand strategy: The estimand specified in Section 2.2.1.
- Analysis set: DBT migraine (Section 4).
- Analysis methodology: A MMRM will be used (Section 5.2.1).
- Intercurrent events and missing data: Data collected after study intervention discontinuation will be excluded. All data collected after use of prophylactic migraine medications will be included. After taking care of intercurrent events, missing data will be handled by MMRM assuming missing at random.

Values and changes (both absolute and percent) from the OP in the number of migraine days per month will be summarized descriptively as continuous parameters (Section 5.2.1) by treatment group for OP, each month of the DBT phase and overall DBT phase (Section 3.1.1).

For the changes from the OP in the number of migraine days per month, the following model estimates will be reported for each month of the DBT phase and overall DBT phase:

- Least-squares mean (LSM) change from OP, SE, and 95% CI for each treatment group.
- Difference in LSM changes from OP between treatment groups (rimegepant - placebo), SE, 95% CI, and p-value.

Longitudinal plot will display the LSM and 95% CI for change from the OP in the number of migraine days per month (y-axis) versus month of the DBT phase (x-axis) by treatment group.

6.1.1.2. Sensitivity Analyses

The primary endpoint will use the same MMRM as the main analysis, but use J2R to explore the sensitivity of the effect of missing data (Section 5.3).

6.1.1.3. Subgroup Analyses

Subgroup analyses of the primary endpoint based on variables defined in Section 5.2.6.1 will use the same MMRM model specified for the main analysis of the primary endpoint. Values and changes (both absolute and percent) will also be summarized descriptively by subgroup.

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6.2. Secondary Endpoints

6.2.1. Percentage of participants with ≥50% reduction from OP in the number of moderate to severe migraine days per month over the entire DBT Phase

- Estimand strategy: The estimand specified in Section 2.2.2.
- Analysis set: DBT migraine (Section 4).
- Analysis methodology: The stratified Mantel-Haenszel risk estimation method will be used (Section 5.2.2).
- Intercurrent events and missing data: Data collected after study intervention discontinuation will be excluded. All data collected after use of prophylactic migraine medications will be included. After taking care of intercurrent events, missing data for the response of reduction will be handled via NRI method (Section 5.3). Refer to Section 3.2.2 for definition of responder for this endpoint.

The following statistics will be presented for each month of the DBT phase and overall DBT phase by pain intensity (total; moderate or severe):

- Response rate (i.e., "n/N" and percentage), ASE, and 95% normal CI for each treatment group. Percentages will be calculated against the number of participants in the DBT migraine analysis set at all time points.
- Stratified percentage difference between treatment groups (rimegepant - placebo), ASE, 95% CI, and p-value.

6.2.1.1. Subgroup Analysis

This endpoint will also be compared between treatment groups using unstratified Mantel-Haenszel risk estimation for each subgroup level of all efficacy subgroups of interest specified in Section 5.2.6.1.

For each subgroup level, the following statistics will be presented for each month in the DBT phase and overall DBT phase:

- Response rate (i.e., "n/N" and percentage), ASE, and 95% normal CI by treatment group. Percentages will be calculated against the number of participants in the subgroup level in the DBT migraine analysis set at all time points.
- Percentage difference between treatment groups (rimegepant – placebo), ASE, 95% CI, and p-value.

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6.2.2. Mean change from the OP in the number of migraine days per month in the first 4 weeks of the DBT Phase

The same analyses as the primary endpoint will be conducted including the descriptive summaries of value and change from OP, and model estimates based on MMRM method described in Section 6.1.1.1. The first 4 weeks, i.e.. Month 1, of the DBT Phase will be part of the individual months summarized for the mean change from the OP in the number of migraine days per month.

6.2.3. Mean change from the OP in the number of migraine days per month in the last 4 weeks of the DBT Phase

The same analyses as the primary endpoint will be conducted including the descriptive summaries of value and change from OP, and model estimates based on MMRM method described in Section 6.1.1.1. The last 4 weeks, i.e.. Month 3, of the DBT Phase will be part of the individual months summarized for the mean change from the OP in the number of migraine days per month.

6.2.4. Mean change from baseline in the MSQoL role function-restrictive domain score at Week 12 of the DBT Phase

- Estimand strategy: The estimand specified in Section 2.2.2.
- Analysis set: DBT efficacy (Section 4).
- Analysis methodology: A GLM will be used (Section 5.2.1).
- Intercurrent events and missing data: All observed values will be included regardless of study intervention discontinuation or prophylactic migraine medication use. Missing data will not be imputed.

Values and changes (both absolute and percent) from baseline in transformed scores for each domain will be summarized descriptively as continuous parameters (Section 5.2.1) by treatment group and overall at baseline and by treatment group at Week 12.

The following model estimates will be reported:

  - LSM change from baseline at Week 12, SE, and 95% CI for each treatment group.
  - Difference in LSM change from baseline between treatment groups (rimegepant - placebo) at Week 12, SE, 95% CI, and p-value.

6.2.5. Mean number of acute migraine medication days per month over the entire DBT Phase

- Estimand strategy: The estimand specified in Section 2.2.2.

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- Analysis set: DBT migraine (Section 4).

- Analysis methodology: A MMRM model will be used (Section 5.2.1).

- Intercurrent events and missing data: Data collected after study intervention discontinuation will be excluded. All data collected after use of prophylactic migraine medications will be included. After taking care of intercurrent events, missing data will be handled by MMRM assuming missing at random.

The number of acute migraine medication days (Appendix 4) per month (Section 3.2.3) will be summarized descriptively as a continuous parameter (Section 5.2.1) by treatment group in each month of the DBT phase and overall DBT phase.

The following model estimates will be reported for each month of the DBT phase and overall DBT phase:

  - LSM, SE, and 95% CI by month for each treatment group.

  - Difference in LSM between treatment groups (rimegepant - placebo), SE, 95% CI, and p-value.

6.2.6. Percentage of participants with adverse events (AEs) by severity, serious adverse events (SAEs), AEs leading to study intervention discontinuation and grade 3 to 4 laboratory test abnormalities on treatment during the DBT Phase and OLE Phase.

- Analysis sets: DBT safety, OLE rimegepant safety, and DBT or OLE rimegepant safety (Section 4).

- Analysis methodology: The frequencies of endpoints will be assessed descriptively as the number and percentage of participants with events. The investigators' terms will be coded using the latest version of the Medical Dictionary for Regulatory Activities (MedDRA). AEs will be presented by system organ class (SOC) and PT for the as-treated treatment groups. If a participant had an AE with different severities over time during a safety analysis period, then only the worst severity will be reported for that period. Laboratory test results will be graded according to numeric laboratory test criteria in the latest version of Common Terminology Criteria for Adverse Events (CTCAE). If a participant has a laboratory test abnormality with different toxicity grades over time during a safety analysis period, then only the highest toxicity grade will be reported for that period. The frequency of participants with laboratory test abnormalities will be tabulated by toxicity grade using CTCAE.

See also Section 6.6.1 for more details.

6.2.7. Percentage of participants with ALT or AST > 3x ULN concurrent with total bilirubin > 2x ULN treated with rimegepant during the DBT and OLE Phases.

- Analysis sets: DBT safety, OLE rimegepant safety, DBT or OLE rimegepant safety (Section 4).

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- Analysis methodology: The frequencies of endpoints will be assessed descriptively as the number and percentage of participants with findings by the as-treated treatment group.

See also Section 6.6.2.2 for more details.

6.2.8. Percentage of participants with hepatic-related adverse events (AEs) and hepatic-related AEs leading to study intervention discontinuation treated with rimegepant during the DBT Phase and OLE Phase.

- Analysis set: DBT safety, OLE rimegepant safety, DBT or OLE rimegepant safety (Section 4).

- Analysis methodology: The frequencies of endpoints will be assessed descriptively as the number and percentage of participants with events by the as-treated treatment group. The investigators' terms will be coded and grouped by system organ class using the latest version of the Medical Dictionary for Regulatory Activities (MedDRA) available to the analyst. AEs will be presented by SOC and PT. If a participant had an AE with different severities over time during a safety analysis period, then only the worst severity will be reported for that period.

See also Section 6.6.1 for more details.

6.3. Exploratory Endpoints

6.3.1. Mean change from the OP in the number of migraine days per month and number of headache days per month by pain intensity (total; moderate or severe) in each month and over the entire DBT Phase.

- Estimand strategy: The estimand specified in Section 2.2.3.

- Analysis set: DBT migraine (Section 4).

- Analysis methodology: A MMRM will be used (Section 5.2.1).

- Intercurrent events and missing data: Data collected after study intervention discontinuation will be excluded. All data collected after use of prophylactic migraine medications will be included. After taking care of intercurrent events, missing data will be handled by MMRM assuming missing at random.

Values and changes (both absolute and percent) from the OP in the number of migraine and headache days per month will be summarized descriptively as continuous parameters (Section 5.2.1) by pain intensity and treatment group for OP, each month of the DBT phase and overall DBT phase (Section 3.1.1).

The following model estimates will be reported for each month of the DBT phase and overall DBT phase by pain intensity for migraine and headache days, respectively:

- LSM change from OP, SE, and 95% CI for each treatment group.

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- Difference in LSM changes from OP between treatment groups (rimegepant - placebo), SE, 95% CI, and p-value.

Longitudinal plots will display the LSM and 95% CI for change from the OP in the number of migraine and headache days per month (y-axis) versus month of the DBT phase (x-axis) by pain intensity and treatment group.

6.3.2. Percentage of participants with ≥50% reduction, ≥ 75% reduction, and 100% reduction from OP in the number of migraine days per month and number of headache days per month by pain intensity (total; moderate or severe) in each month and over the entire DBT Phase.

- Estimand strategy: The estimand specified in Section 2.2.3.
- Analysis set: DBT migraine (Section 4).
- Analysis methodology: The stratified Mantel-Haenszel risk estimation method will be used (Section 5.2.2).
- Intercurrent events and missing data: Data collected after study intervention discontinuation will be excluded. All data collected after use of prophylactic migraine medications will be included. After taking care of intercurrent events, missing data for the response of reduction will be handled via NRI method. Refer to Section 3.2.2 for definition of responder and failure for this endpoint. The same rule applies to the number of headache days.

The following statistics will be presented for each month of the DBT phase and overall DBT phase by pain intensity for migraine and headache days, respectively:

- Response rate (i.e., "n/N" and percentage), ASE, and 95% normal CI for each treatment group. Percentages are calculated against the number of participants in the DBT migraine analysis set at all time points.
- Stratified percentage difference between treatment groups (rimegepant - placebo), ASE, 95% CI, and p-value.

6.3.3. Mean change from the OP in the number of migraine days per week and number of headache days per week by pain intensity (total; moderate or severe) in each week of the first 4 weeks of the DBT Phase.

- Estimand strategy: The estimand specified in Section 2.2.3.
- Analysis set: DBT first month migraine (Section 4).
- Analysis methodology: A MMRM will be used (Section 5.2.1).
- Intercurrent events and missing data: Data collected after study intervention discontinuation will be excluded. All data collected after use of prophylactic migraine medications will be

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included. After taking care of intercurrent events, missing data will be handled by MMRM assuming missing at random.

Values and changes (both absolute and percent) from the OP in the number of migraine/headache days per week of the DBT phase (Section 3.3.3) will be summarized descriptively as continuous parameters by treatment group and migraine/headache pain intensity (total; moderate or severe). In the percentage change analyses, participants must also have ≥ 1 migraine/headache day (absolute not prorated) of appropriate severity in the OP analysis period to be included.

For each pain intensity, the following model estimates will be reported for endpoint of migraine and headache, respectively:

- LSM change from OP, SE, and 95% CI for each treatment group
- Difference in LSM changes from OP between treatment groups (rimegepant - placebo), SE, 95% CI, and p-value.

Longitudinal plots will display the LSM and 95% CI for change from the OP in the number of migraine and headache days per week (y-axis) versus week of the DBT phase (x-axis) by pain intensity and treatment group.

6.3.4. Percentage of participants with ≥50% reduction from OP in the number of migraine days per week and number of headache days per week by pain intensity (total; moderate or severe) in each week of the first 4 weeks of the DBT Phase.

- Estimand strategy: The estimand specified in Section 2.2.3.
- Analysis set: DBT first month migraine (Section 4).
- Analysis methodology: The stratified Mantel-Haenszel risk estimation method will be used (Section 5.2.2).
- Intercurrent events and missing data: Data collected after study intervention discontinuation will be excluded. All data collected after use of prophylactic migraine medications will be included. After taking care of intercurrent events, missing data for the response of reduction will be handled via NRI method. Refer to Section 3.3.5 for definition of responder for this endpoint. The same rule applies to the number of headache days.

The following statistics will be presented for each week of the first 4 weeks of DBT phase by treatment group and pain intensity for endpoints of migraine and headache, respectively:

- Response rate (i.e., “n/N” and percentage), ASE, and 95% normal CI for each treatment group. Percentages are calculated against the number of participants in the DBT first month migraine analysis set at all time points.
- Stratified percentage difference between treatment groups (rimegepant - placebo), ASE, 95% CI, and p-value

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6.3.5. Percentage of participants with a migraine day and headache day by pain intensity (total; moderate or severe) on each day of the first week of the DBT Phase.

- Estimand strategy: The estimand specified in Section 2.2.3.
- Analysis set: DBT first week EOD treated migraine (Section 4).
- Analysis methodology: The stratified Mantel-Haenszel risk estimation method will be used (Section 5.2.2).
- Intercurrent events and missing data: All data collected after use of prophylactic migraine medications will be included.

The following statistics will be presented for each day (1 to 7) by pain intensity (total; moderate or severe) for migraine and headache days, respectively:

  - Response rate (i.e., "n/N" and percentage), ASE, and 95% normal CI for each treatment group. Percentages are calculated against the number of participants in the DBT first week EOD treated migraine analysis set at all time points.
  - Stratified percentage difference between treatment groups (rimegepant - placebo), ASE, 95% CI, and p-value.

Longitudinal plots will display the percentage of participants with a migraine/headache day versus day of the first week of DBT phase (x-axis) by treatment group and pain intensity. Vertical bars will denote 95% CIs.

6.3.6. Mean number of acute migraine-specific medication days per month in each month and the entire DBT Phase.

- Estimand strategy: The estimand specified in Section 2.2.3.
- Analysis set: DBT migraine (Section 4).
- Analysis methodology: A MMRM will be used (Section 5.2.1).
- Intercurrent events and missing data: Data collected after study intervention discontinuation will be excluded. All data collected after use of prophylactic migraine medications will be included. After taking care of intercurrent events, missing data will be handled by MMRM assuming missing at random.

Values and changes (both absolute and percent) from the OP in the number of acute migraine-specific medication days (Appendix 4) per month (Section 3.3.6) in the on-DBT efficacy analysis period will be summarized descriptively as a continuous parameter by treatment group in each month of the DBT phase and overall DBT mean.

The following model estimates will be reported by each month and overall DBT:

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- LSM, SE, and 95% CI for each treatment group
- Difference in LSMs between treatment groups (rimegepant - placebo), SE, 95% CI, and p-value

6.3.7. Mean change from the OP in the number of migraine days per month and number of headache days per month by pain intensity (total; moderate or severe) in each month and over the entire OLE Phase.

- Estimand strategy: The estimand specified in Section 2.2.3.
- Analysis set: OLE migraine (Section 4).
- Analysis methodology: Descriptive statistics will be provided (Section 5.2.1).
- Intercurrent events and missing data: Data collected after study intervention discontinuation will be excluded. All data collected after use of prophylactic migraine medications will be included.

Values and changes (both absolute and percent) from the OP in the number of migraine days and number of headache days respectively, per month (Section 3.3.4) in the OLE phase will be summarized descriptively (included 2-sided normal 95% CIs for mean change) as continuous parameters by treatment group (including overall) and pain intensity in each month of the OLE phase and overall OLE mean.

Longitudinal plots will display the mean change from OP in the number of migraine/headache days per month (y-axis) versus month of the OLE phase (x-axis) by treatment group and pain intensity. Vertical bars will denote SEs.

Longitudinal plots will display the mean change from OP in the number of migraine days per month (y-axis) versus month of the DBT and OLE phases (x-axis) by pain intensity for the DBT migraine analysis set. For the DBT Phase, results will be displayed by treatment group. For the OLE phase, results will be displayed overall. Vertical bars will denote SEs.

6.3.8. Percentage of participants with ≥50% reduction, ≥75% reduction, and 100% reduction from OP in the number of migraine days per month and number of headache days per month by pain intensity (total; moderate or severe) in each month and over the entire OLE Phase.

- Estimand strategy: The estimand specified in Section 2.2.3.
- Analysis set: OLE migraine (Section 4).
- Analysis methodology: Descriptive statistics will be provided (Section 5.2.2).

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- Intercurrent events and missing data: Data collected after study intervention discontinuation will be excluded. Data collected after use of prophylactic migraine medications will be included. The same rule applies to the number of headache days.

For each endpoint (≥ 50% reduction, ≥ 75% reduction, and ≥ 100% reduction), the following statistics will be presented for each month of the OLE phase and overall OLE phase by pain intensity (total; moderate or severe) for migraine and headache days, respectively (see Sections 3.3.4 and 3.3.7):

  - Response rate (i.e., "n/N" and percentage), and 95% CI for each treatment group and overall. Percentages are calculated against the number of evaluable participants in the OLE migraine analysis set at all time points.

    - For a given month, evaluable participants are those with ≥ 14 days of efficacy data (not necessarily consecutive) in the month and ≥ 1 migraine/headache day (absolute not prorated to 28 days) of appropriate migraine severity in the OP analysis period.

    - For the overall OLE phase, evaluable participants are those with ≥ 1 migraine/headache day (absolute not prorated to 28 days) of appropriate migraine severity in the OP analysis period.

6.3.9. Mean number of acute migraine medication days per month and acute migraine-specific medication days per month in each month and over the entire OLE Phase.

- Estimand strategy: The estimand specified in Section 2.2.3.

- Analysis set: OLE migraine (Section 4).

- Analysis methodology: Descriptive statistics will be provided (Section 5.2.1).

- Intercurrent events and missing data: Data collected after study intervention discontinuation will be excluded. All data collected after use of prophylactic migraine medications will be included.

Summary statistics (included 2-sided normal 95% CIs for mean change) will be provided for the number of acute migraine medication days and number of acute migraine-specific medication days (Appendix 4), respectively, per month (Section 3.3.9) in the OLE phase by treatment group (including overall) in each month of the OLE phase and over the entire OLE phase.

6.3.10. Mean changes from baseline in the MSQoL preventive role function and emotional function domain scores at Week 12 of the DBT Phase

- Estimand strategy: The estimand specified in Section 2.2.3.

- Analysis set: DBT efficacy (Section 4).

- Analysis methodology: A GLM will be used (Section 5.2.1).

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- Intercurrent events and missing data: All observed values will be included regardless of study intervention discontinuation or use of prophylactic medications. Missing data will not be imputed.

Values and changes from baseline in transformed scores for each domain will be summarized descriptively as continuous parameters by treatment group and overall at baseline and by treatment group at Week 12.

The following model estimates will be reported:

  - LSM change from baseline at Week 12, SE, and 95% CI for each treatment group.
  - Difference in LSM changes from baseline between treatment groups (rimegepant - placebo) at Week 12, SE, 95% CI, and p-value.

6.3.11. Mean change from baseline in the MIDAS total score, absenteeism and presenteeism scores at Week 12 of the DBT Phase.

- Estimand strategy: The estimand specified in Section 2.2.3.
- Analysis set: DBT efficacy (Section 4).
- Analysis methodology: A GLM will be used (Section 5.2.1).
- Intercurrent events and missing data: All observed values will be included regardless of study intervention discontinuation or use of prophylactic migraine medications. Missing data will not be imputed.

Values and changes from baseline in total, absenteeism, presenteeism will be summarized descriptively as continuous parameters by treatment group and overall at baseline and by treatment group at Week 12.

The following model estimates will be reported:

  - LSM change from baseline at Week 12, SE, and 95% CI for each treatment group.
  - Difference in LSM changes from baseline between treatment groups (rimegepant - placebo) at Week 12, SE, 95% CI, and p-value.

6.3.12. Mean change from baseline in EQ-5D-5L index score and VAS score at Week 12 of the DBT Phase.

- Estimand strategy: The estimand specified in Section 2.2.3.
- Analysis set: DBT efficacy (Section 4).
- Analysis methodology: A GLM will be used (Section 5.2.1).

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- Intercurrent events and missing data: All observed values will be included regardless of study intervention discontinuation or use of prophylactic migraine medications. Missing data will not be imputed.

Values and changes from baseline in EQ-5D-5L index score and VAS score will be summarized descriptively as continuous parameters by treatment group at baseline and Week 12.

The following model estimates will be reported for EQ-5D-5L index score and VAS score, respectively:

  - LSM change from baseline at Week 12, SE, and 95% CI for each treatment group.
  - Difference in LSM changes from baseline between treatment groups (rimegepant - placebo) at Week 12, SE, 95% CI, and p-value.

The frequency table of dimension function level will display the number and percentage of participants in each current level of function category for each dimension by treatment group and overall at baseline and Week 12 (excluding overall).

6.3.13. Mean change from baseline in MSQoL domain scores, MIDAS scores, and EQ-5D-5L scores at Week 24 of the OLE Phase.

- Estimand strategy: The estimand specified in Section 2.2.3.
- Analysis set: OLE efficacy (Section 4).
- Analysis methodology: Descriptive statistics will be provided (Section 5.2.1).
- Intercurrent events and missing data: All observed values will be included regardless of study intervention discontinuation or use of prophylactic migraine medications. Missing data will not be imputed.

Values and changes from baseline in MSQoL domain scores (restrictive role function, preventive role function, emotional function), MIDAS scores (total, absenteeism, presenteeism), and EQ-5D-5L scores (index and VAS) will be summarized descriptively (included 2-sided normal 95% CIs for mean change) as continuous parameters by treatment group and overall at baseline and Week 24.

6.4. Overall Summary of Primary and Secondary Efficacy Endpoints

An overall summary of treatment comparisons of all primary and secondary efficacy endpoints tested hierarchically will present the following statistics:

Continuous endpoints involving change from OP or baseline:

  - Overall LSM change and 95% CI for each treatment group (i.e., for endpoints by month and overall DBT, report LSM for overall DBT)

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- Difference in overall LSM changes between treatment groups (rimegepant - placebo), 95% CI, and p-value.

This applies to the primary and the following secondary efficacy endpoints: mean change from the OP in the number of migraine days per month in the first 4 weeks (Weeks 1 to 4) of the DBT Phase; mean change from the OP in the number of migraine days per month in the last 4 weeks (Weeks 9 to 12) of the DBT Phase; mean change from baseline in the MSQoL role function - restrictive domain score at Week 12 of the DBT Phase; and mean number of acute migraine medication days per month over the entire DBT Phase (Weeks 1 to 12).

Binary endpoints:

- Response rate (i.e., "n/N" and percentage), and 95% CI for each treatment group
- Stratified percentage difference between treatment groups (rimegepant - placebo), 95% CI, and p-value.

This applies to the secondary efficacy endpoint of proportion of participants with ≥50% reduction from the OP in the number of moderate to severe migraine days per month over the entire DBT Phase (Weeks 1 to 12).

Analyses will be based on principal methods described in Sections 6.1.1.1 and 6.2.1. Endpoints will be displayed in the order presented in Section 5.1. P-values that are determined to be significant based on the testing hierarchy will be flagged.

6.5. Baseline and Other Summaries and Analyses

6.5.1. Participant Disposition

Participant disposition will be summarized for all randomized participants by study phase including the number and percentages of participants who:

- Entered DBT phase

  Completed DBT phase

  Discontinued from DBT phase and discontinuation reasons

- Entered OLE phase

  Completed OLE phase

  Discontinued from OLE phase and discontinuation reasons

- Entered Follow-up phase

  Completed Follow-up phase

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Discontinued from Follow-up phase and discontinuation reasons

A listing of all randomized participants with flags of status in each study phase will be provided.

6.5.2. Summary of Analysis Sets

The number of participants been included in each analysis set as defined in Section 4 will be summarized. A listing flagging participants for each analysis set will be provided for all enrolled participants.

6.5.3. Baseline Summaries

Baseline summaries will include the following: (1) demographics and baseline characteristics, (2) medical history, (3) migraine history, and (4) migraine-related events during the OP. Parameters will be summarized descriptively by treatment group and overall for the following analysis sets:

- DBT migraine analysis set: summaries 1, 3, and 4
- DBT safety analysis set: summaries 1, 2, and 3
- DBT or OLE rimegepant safety analysis set: summary 1
- OLE rimegepant safety analysis set: summary 1.

6.5.3.1. Demographic and Baseline Characteristics

Demographics and baseline characteristics will be summarized for the variables listed in Section 3.4.

6.5.3.2. Medical History

Medical history will be summarized by SOC and PT, and displayed in descending order of overall frequency within SOC and PT.

Medical history of hypertension will be summarized analogously.

6.5.3.3. Migraine History

Migraine history will include the following:

- Age (years) at migraine onset
- Time since last migraine (days) calculated as: (informed consent date – imputed last migraine date) for participants with imputed last migraine date up to 1 year before informed consent date. Last migraine date is imputed for partial and missing dates using the same methodology as AE start dates, but using the informed consent date as the surrogate date

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- Number of moderate to severe migraines per month, also categorized as <6, ≥ 6, <8, ≥8, <12, ≥ 12, <15, and ≥ 15.
- Average duration of untreated migraine attacks (hours)
- Most bothersome symptom (i.e., nausea, photophobia, or phonophobia)
- Migraine symptoms (i.e., headache attacks lasting 4-72 hours, unilateral location, pulsating quality, moderate or severe pain intensity, aggravation by or causing avoidance of routine physical activity, during headache: nausea and/or vomiting, during headache: photophobia and phonophobia)
- History of chronic migraine (yes, no)
- History of migraine without aura (yes, no)
- History of migraine with aura (yes, no)

6.5.3.4. Migraine-Related Events During the OP

Migraine-related event days per month during the OP will be provided only for the DBT migraine analysis set, and will be summarized for the following parameters descriptively as continuous and categorical variables during the OP analysis period:

- Migraine days per month by category: <8, ≥8.
- Migraine days per month by pain intensity (total; moderate to severe).
- Headache days per month by pain intensity (total; moderate to severe).
- Acute migraine medication days per month.
- Acute migraine-specific medication days per month.

Migraine-related event days per week during the OP will be provided only for the DBT first month migraine analysis set, and will summarize the following parameters descriptively as continuous variables during the OP analysis period:

- Migraine days per week by pain intensity (total; moderate to severe).
- Headache days per week by pain intensity (total; moderate to severe).

6.5.4. Protocol Deviations

Protocol deviation identification and documentation will be accomplished for this study according to the Sponsor's standard operating procedures (SOPs) that require periodic review of individual protocol deviations and periodic review of aggregated cumulative protocol deviations.

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Prior to initiation of the study, a list of potentially important protocol deviations (pIPDs) is developed in alignment with the requirements of the protocol. This list is updated, as necessary, to include other deviations identified during the course of the study.

The number and percentage of randomized participants with pIPD will be summarized by deviation type and by treatment group and overall for all randomized participants. Deviation types will be presented in descending order of overall frequency.

Protocol deviations classified as pIPDs will be included in a Protocol Deviation Listing in the clinical study report (CSR).

6.5.5. Exposure

Analyses will be based on as-treated treatment group to support safety, unless specified otherwise.

6.5.5.1. Study Intervention Exposure

DBT Phase Study Treatment Exposure

Rimegepant or placebo exposure during the on-DBT safety analysis period will be summarized descriptively by treatment group for the DBT safety analysis set, and will include the following parameters:

- Time on DBT study intervention (weeks), derived as (DBT study intervention end date - DBT study intervention start date + 1)/7
- Cumulative DBT exposure (tablets), derived by summing the number of tablets from DBT study intervention start date to DBT study intervention end date
- Average DBT exposure (tablets per month), derived as (1) cumulative tablets if time on DBT study intervention < 14 days, or (2) 4 (weeks)× cumulative DBT exposure (tablets) /time on DBT study intervention (weeks) if time on DBT study intervention ≥ 14 days
- Average DBT exposure (tablets per month) categories:
  - >16.8 (> 20% above EOD dosing)
  - >15.4 (> 10% above EOD dosing)
  - ≥12.6 to ≤ 15.4 (± 10% of EOD dosing)
  - ≥ 11.2 to ≤ 16.8 (± 20% of EOD dosing)
  - ≥ 12.6 (≥ 90% compliant with EOD dosing)
  - ≥11.2 (≥ 80% compliant with EOD dosing)
- DBT exposure (tablets per month) for 3 consecutive months categories: ≥12; ≥13; ≥14.

Tablets per month will be assessed by the number of 4-week intervals (Table 3). A participant will be counted as achieved the specified category if the # of tablets per month exceeded selected

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tablet counts for the 4-week intervals of DBT phase consecutively. For example, suppose a participant takes 14 tablets through 4 weeks, 13 tablets after 13 weeks to 16 weeks, and 15 tablets after 8 weeks to 12 weeks. Thus, this participant is considered to have taken ≥ 12 and ≥ 13 (but not ≥ 14) DBT tablets per month for 3 consecutive months.

OLE Phase Rimegepant Exposure

On-OLE analysis period rimegepant exposure will be summarized descriptively by treatment group and overall for the OLE rimegepant safety analysis set, and will include the following parameters:

- Time on OLE rimegepant (weeks), derived as (OLE rimegepant end date - OLE rimegepant start date +1)/7
- Cumulative OLE rimegepant exposure (tablets), derived by summing the number of rimegepant tablets from OLE rimegepant start date to OLE rimegepant end date
- Average OLE rimegepant exposure (tablets per month), derived as (1) cumulative tablets if time on OLE rimegepant < 14 days, or (2) 4 (weeks)× cumulative OLE rimegepant exposure (tablets) /time on OLE rimegepant (weeks) if time on OLE rimegepant ≥ 14 days
- Average OLE exposure (tablets per month) categories:
  - >16.8 (>20% above EOD dosing)
  - >15.4 (>10% above EOD dosing)
  - ≥12.6 to ≤15.4 (± 10% of EOD dosing)
  - ≥ 11.2 to ≤16.8 (± 20% of EOD dosing)
  - ≥ 12.6 (≥90% compliant with EOD dosing)
  - ≥11.2 (≥80% compliant with EOD dosing)
- Average OLE exposure (tablets per month) for 3 consecutive months categories: ≥12; ≥13; ≥14.

Tablets per month will be assessed by the number of 4-week (28-day) intervals (Table 3). A participant will be counted as achieved the specified category if the # of tablets per month exceeded selected tablet counts for the 4-week intervals of OLE phase consecutively. For example, suppose a participant takes 14 tablets from 13 weeks to 16 weeks, 12 tablets after 16 weeks to 20 weeks, and 15 tablets after 20 weeks to 24 weeks. Thus, this participant is considered to have taken ≥12 and ≥13 (but not ≥14) DBT tablets per month for 3 consecutive months.

DBT or OLE Phase Rimegepant Exposure in the Entire Study

On-DBT or OLE analysis period rimegepant exposure in the entire study (i.e., both DBT and OLE phases combined) will be summarized descriptively by treatment group and overall for the DBT or OLE rimegepant safety analysis set, and will include the following parameters:

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- Time on DBT or OLE rimegepant (weeks), derived as (on-DBT or OLE rimegepant end date - DBT or OLE rimegepant start date + 1)/7

- Cumulative DBT or OLE rimegepant exposure (tablets), derived by summing the number of DBT or OLE rimegepant tablets across records in the entire study

- Average DBT or OLE rimegepant exposure (tablets per month), derived as (1) cumulative time on DBT or OLE rimegepant if the time < 14 days, or (2) 4 (weeks)× cumulative DBT or OLE rimegepant exposure (tablets) /time on DBT or OLE rimegepant (weeks) if the time ≥ 14 days

- Total DBT or OLE rimegepant exposure (tablets) summed across all participants, derived by summing cumulative DBT or OLE rimegepant exposure (tablets) across all participants

- Total DBT or OLE rimegepant exposure (patient years), derived by summing (DBT or OLE rimegepant end date – DBT or OLE rimegepant start date + 1)/365.25 across all participants.

- Adjusted average DBT or OLE Rimegepant exposure (tablets per patient-year), derived by [Total DBT or OLE rimegepant exposure (tablets) summed across all participants/(Total DBT or OLE rimegepant exposure (patient years)]

6.5.5.2. Treatment Compliance

Treatment compliance will be calculated for DBT and OLE phases separately as below using the DBT safety analysis set and OLE rimegepant safety analysis set, respectively, and will be summarized descriptively by treatment group as a continuous variable, as well as categorical measure with number and percentage for compliance ≤80%, >80% - ≤90%, >90% - ≤ 100%, 100% - ≤110%, 110% - ≤ 120%, >80% - ≤120%, >120%.

  - Compliance for DBT phase = 100 × (cumulative DBT exposure (tablets))/ Ceiling ([DBT maxdate – DBT study intervention start date + 2]/2), where DBT maxdate is defined as (1) Week 12 Visit date or (2) DBT study intervention end date for early discontinuation.

  - Compliance for OLE phase = 100 × (cumulative OLE rimegepant exposure (tablets))/ Ceiling ([OLE maxdate – OLE rimegepant start date + 2]/2), where OLE maxdate is defined as (1) Week 24 Visit date - 1 day or (2) OLE study intervention end date for early discontinuation.

6.5.5.3. eDiary Usage Compliance

eDiary compliance will be summarized by treatment group using the DBT safety analysis set for OP and DBT phase, and OLE rimegepant safety analysis set for OLE phase, respectively:

- Compliance for OP = 100 × total number of completed eDiary days/number of days during the OP analysis period.

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- Compliance for DBT phase = 100 × total number of completed eDiary days/ (DBT maxdate – DBT study intervention start date + 1), where DBT maxdate is defined as (1) Week 12 Visit date or (2) DBT study intervention end date for early discontinuation.

- Compliance for OLE phase = 100 × total number of completed eDiary days/ (OLE maxdate – OLE rimegepant start date + 1), where OLE maxdate is defined as (1) Week 24 Visit date - 1 day or (2) OLE study intervention end date for early discontinuation.

See Section 5.2.4 for definitions of the above analysis periods used in the formula. For each phase, eDiary compliance will be summarized as a continuous parameter and as the number and percentage of participants with ≥ 80% and ≥ 90% compliance.

6.5.6. Prior and Concomitant Non-Study Medications

- Prior medications are defined as those taken before study intervention start, i.e., imputed start or stop date < study intervention start date. These include the following subtypes:

  - Previous medications, defined as those taken before informed consent, i.e., those with an imputed start or stop date < informed consent date

  - Current medications, defined as those taken on or after informed consent and before study intervention start, i.e., those meeting any of the following criteria (1) informed consent date ≤ imputed start or end date < study intervention start date -1 or (2) informed consent date ≤ imputed start or end date, and study intervention start date is missing or (3) imputed start date ≤ informed consent date < study intervention start date - 1 ≤ imputed end date or (4) imputed start date ≤ informed consent date ≤ imputed end date, and study intervention start date is missing.

- DBT concomitant medications are defined as those taken with DBT study intervention, i.e., meeting any of the following criteria:

  - On-DBT safety analysis period start date ≤ imputed start or imputed end date ≤ on-DBT safety analysis period end date

  - Imputed start date ≤ on-DBT safety analysis period start date ≤ on-DBT safety analysis period end date ≤ imputed end date.

- OLE rimegepant concomitant medications are defined as those taken with OLE rimegepant, i.e., meeting any of the following criteria:

  - On-OLE rimegepant safety analysis period start date ≤ imputed start or imputed end date ≤ on-OLE rimegepant safety analysis period end date

  - Imputed start date ≤ on-OLE rimegepant safety analysis period start date ≤ on-OLE rimegepant safety analysis period end date ≤ imputed end date.

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The imputed start date or end date will follow Pfizer standard rules.

Non-study medications will be summarized by treatment group and overall for the following medication types and analysis sets:

- Prior medications: all. It will be based on DBT safety analysis set (excluding overall).
- DBT concomitant medications: all; acute headache medications. It will be based on DBT safety analysis set (excluding overall).
- OLE rimegepant concomitant medications: all; acute headache medications. It will be based on OLE rimegepant safety analysis set.

Acute headache medications will be displayed within category and standardized medication name. All medications will be displayed in descending order of overall frequency within standardized medication name, unless otherwise specified.

Listings will display abbreviated medication types. Note that a medication may be classified into multiple types.

6.6. Safety Summaries and Analyses

AEs, laboratory tests, vital signs, physical measurements, ECGs, and C-SSRS will be collected for each participant during the study according to the Schedule of Assessments.

In analyses of the worst abnormality or category in a safety analysis period, participants must have a non-missing measurement in the safety analysis period to be included for a given parameter. If the category is based on a shift or change from baseline, then participants must have both a baseline measurement and non-missing measurement in the safety analysis period to be included for a given parameter. In the analyses for DBT safety, OLE safety, DBT or OLE safety, and follow-up safety, the presentations will be provided by original DBT phase as-treated treatment group.

6.6.1. Adverse Events

6.6.1.1. TEAE Overviews

A TEAE overview will be summarized for the following:

- Number of TEAEs
- Number and percentage of participants with:
  - Any TEAEs;
  - Maximum Grade 3 or 4 TEAEs;
  - Maximum Grade 5 TEAEs;
  - Treatment-emergent SAEs;

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- TEAEs leading to study discontinuation;
- TEAEs leading to study intervention discontinuation;
- TEAE leading to dose reduction or temporary discontinuation;
- Hepatic-related TEAEs leading to study intervention discontinuation;
- Significant TEAEs (Appendix 2).

TEAE overviews will be produced by as-treated (of the DBT intervention) treatment group and overall for each of the following safety analysis periods (Section 5.2.4) and analysis sets (Section 4), respectively:

- On-DBT period TEAEs - DBT safety analysis set (excluding overall, all causality and treatment-related)
- On-DBT or OLE rimegepant TEAEs - DBT or OLE rimegepant safety analysis set (all causality and treatment-related)
- On-OLE period TEAEs - OLE rimegepant safety analysis set (all causality and treatment-related)
- Follow-up period TEAEs - follow-up safety analysis set (all causality)

A listing of all AEs will be provided for the enrolled analysis set and will display safety analysis period.

6.6.1.2. On-treatment TEAEs

DBT Phase

TEAEs with onset date within the on-DBT safety analysis period will be summarized by SOC and PT in descending order of rimegepant frequency within SOC and PT, unless otherwise specified, for the DBT safety analysis set by treatment group for the following:

- TEAEs by severity (all causality and treatment-related)
- Treatment-emergent SAEs (all causality)
- TEAEs leading to study intervention discontinuation (all causality)
- Significant TEAEs (all causality and treatment-related). See Appendix 2.
- Hypertension TEAEs in participants with medical history of hypertension (all causality and treatment-related).

DBT or OLE Rimegepant Phase

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TEAEs with onset date within the on-DBT or OLE rimegepant safety analysis period will be summarized by SOC and PT for DBT or OLE rimegepant safety analysis set by treatment group and overall for the following:

- TEAEs by severity (all causality and treatment-related)
- Treatment-emergent SAEs (all causality)
- Exposure-adjusted TEAEs (all causality and treatment-related)

The frequency table of exposure-adjusted TEAEs will display the following:

  - Number and percentage of participants with AEs: total number of multiple occurrences of unique AEs in the safety analysis period summed across all participants.
  - Patient-years: total exposure of duration in the safety analysis period summed across all participants, where a participant's total exposure in the safety analysis period is defined as [min of (last dose date in the analysis period, first AE date of the PT) – first dose date in the analysis period + 1]/365.25.
  - Exposure-adjusted rate per 100 patient-years: 100 × (number of participants with the AE)/patient-years. Note that 1000 patient-years may be used if appropriate.

OLE Phase

TEAEs with onset date within the on-OLE safety analysis period will be summarized by SOC and PT for OLE rimegepant safety analysis set by treatment group for the summaries described above for the DBT phase.

6.6.1.3. Follow-up TEAEs

TEAEs with onset date within follow-up safety analysis period will be summarized by SOC and PT for follow-up safety analysis set by treatment group and overall for the following:

- TEAEs by severity (all causality)
- Treatment-emergent SAEs (all causality).

6.6.2. Laboratory Data

Laboratory test groups of clinical interest will include hematology, serum chemistry, eGFR, and urinalysis.

eGFR will be calculated in units of mL/min/1.73 m^2 using the modification of diet in renal disease (MDRD) formula as follows:

  - eGFR=175 × (serum creatinine in units of mg/dL)$^{-1.154}$ × (age)$^{-0.203}$ × (0.742 if sex is female) × (1.212 if race is Black).

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Summaries will present results by treatment group (and overall if applicable), and laboratory tests alphabetically within laboratory test group, as applicable.

The following by-participant laboratory test listings will be provided for the enrolled analysis set:

- Laboratory test results (SI units). The listing will display all abnormal test results over time for participants with select findings (Grade 3 to 4 laboratory test abnormalities or positive pregnancy tests) at any time point.

- LFT values and ratios to ULN (i.e., ALT, AST, TBL and ALP) in SI units. The listing will display all elevated LFT results over time for participants with select LFT elevations (i.e., ALT > 3x ULN or AST > 3x ULN or ALP > 2x ULN or TBL > 2x ULN) at any time point.

6.6.2.1. Laboratory Tests Abnormalities

Laboratory Test Worst Abnormalities

The number and percentage of participants with the worst (highest) toxicity grade test abnormality will be presented in the following CTCAE toxicity grade categories for each graded laboratory test: Grade 0, Grade 1-2, Grade 3-4, Grade 3, and Grade 4. Grade 3 to 4 abnormalities are considered clinically significant. Bidirectional tests will be assessed separately for each component (e.g., calcium, low; calcium, high). For each laboratory test, percentages are calculated against the number of participants with non-missing laboratory test data in the safety analysis period.

The above analyses will be generated by treatment group and overall for the following safety analysis periods and analysis sets:

- On-DBT for the DBT safety analysis set (excluding overall)

- On-OLE rimegepant for the OLE rimegepant safety analysis set

- On-DBT or OLE rimegepant for the DBT or OLE rimegepant safety analysis set

6.6.2.2. LFT Elevations

Participants must have non-missing LFT data (i.e., ALT, AST, TBL, or ALP) in the safety analysis period to be included. Percentages are calculated against the number of participants in the subset.

LFT Elevations: Cumulative, Mutually Exclusive, and Composite

The number and percentage of participants with LFT elevations will be summarized by treatment group (and overall if applicable) for the following safety analysis periods and analysis sets:

- On-DBT for DBT safety analysis set (excluding overall)

- On-DBT or OLE rimegepant for DBT or OLE rimegepant safety analysis set

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- On-OLE rimegepant for OLE rimegepant safety analysis set
- Follow-up for follow-up safety analysis set.

LFT elevations include the following categories:

- Cumulative elevations:
  - ALT > 1x, > 3x, > 5x, > 10x, and > 20x ULN
  - AST > 1x, > 3x, > 5x, > 10x, and > 20x ULN
  - ALT or AST >1 x, > 3x, > 5x, > 10x, and > 20x ULN
  - TBL > 1x, > 1.5x, and > 2x ULN
  - ALP > 1x, > 1.5x, and > 2x ULN
- Mutually exclusive elevations:
  - ALT > ULN to ≤ 3x ULN, > 3x ULN to ≤ 5x ULN, > 5x ULN to ≤10x ULN, > 10x ULN to ≤ 20x ULN, and > 20x ULN
  - AST > ULN to ≤ 3x ULN, > 3x ULN to ≤ 5x ULN, > 5x ULN to ≤ 10x ULN, > 10x ULN to ≤ 20x ULN, and > 20x ULN
  - ALT or AST > ULN to ≤ 3x ULN, > 3x ULN to ≤ 5x ULN, > 5x ULN to ≤10 x ULN, > 10x ULN to ≤ 20x ULN, and > 20x ULN
  - TBL > 1x to ≤1.5x ULN, > 1.5x to ≤ 2x ULN, and > 2x ULN
  - ALP > 1x to ≤ 1.5x ULN, > 1.5x to ≤ 2x ULN, and > 2x ULN
- Composite elevations:
  - ALT or AST > 3x ULN and TBL > 1.5x ULN
  - ALT or AST > 3x ULN and TBL > 2x ULN
  - ALT or AST > 3x ULN concurrent with TBL > 2x ULN. Concurrent will be defined as elevations on the same collection date.
  - ALT or ALT > 3x ULN concurrent with TBL > 2x ULN and ALP ≤ 2x ULN. Concurrent will be defined as elevations on the same collection date.
  - ALT or AST > 3x ULN concurrent with a select AE

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The following PTs will be used to identify select AEs: nausea, vomiting, decreased appetite, fatigue, and those containing "abdominal pain".

For a given safety analysis period, an LFT elevation will concurrent with an AE of interest if the imputed AE start date is +/- 7 days inclusive of the LFT collection date; both the LFT collection date and the imputed AE start date must also be in the safety analysis period.

Exposure-adjusted Cumulative LFT Elevations

The number and percentage of participants with exposure-adjusted cumulative LFT elevations will be summarized by treatment group and overall on-DBT or OLE rimegepant for the DBT or OLE rimegepant safety analysis set.

Calculations use the same analysis period reference start and end dates as corresponding exposure-adjusted AEs (Section 6.6.1.2).

The frequency table of exposure-adjusted cumulative LFT elevations in a safety analysis period displays cumulative LFT categories defined previously, along with number and percentage of participants with an LFT elevation, patient-years and exposure-adjusted rates.

eDISH Scatter Plots

An evaluation of drug-induced serious hepatotoxicity (eDISH) scatter plot will display the maximum TBL ratio of value to ULN (y-axis) versus the maximum ALT ratio of value to ULN (x-axis), where both maxima will be in the same safety analysis period but not necessarily concurrent. Both axes will be on the $\log_{10}$ scale with minima of 0.1. Ratios < 0.1 x ULN will be set to 0.1. Sample sizes in the legend will represent participants with paired ratios. A horizontal reference line will be placed at 2 x ULN, and a vertical reference line will be placed at 3 x ULN. The lower left quadrant will be labeled "Normal Range", the upper left quadrant will be labeled "Hyperbilirubinemia", the lower right quadrant will be labeled "Temple's Corollary", and the upper right quadrant will be labeled "Possible Hy's Law Range."

eDISH scatter plots will be produced by treatment group for the following safety analysis periods and analysis sets:

- On-DBT for DBT safety analysis set
- On-OLE rimegepant for OLE rimegepant safety analysis set.

6.6.2.3. Laboratory Test Changes from Baseline Over Time

Values and changes from baseline in all hematology and serum chemistry laboratory tests will be summarized as continuous parameters by treatment group and overall at each visit for the following safety analysis periods and analysis sets together in a single table:

- On-DBT for DBT safety analysis set (excluding overall)

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- On-OLE rimegepant for OLE rimegepant safety analysis set
- Follow-up for follow-up safety analysis set.

6.6.3. Vital Signs and Physical Measurements

6.6.3.1. Vital Signs and Physical Measurement Changes from Baseline Over Time

Values and changes from baseline in vital signs and physical measurements will be summarized as continuous parameters by treatment group and overall at each visit for the following safety analysis periods and analysis sets together in a single table:

- On-DBT for DBT safety analysis set (excluding overall)
- On-OLE rimegepant for OLE rimegepant safety analysis set
- Follow-up for follow-up safety analysis set.

Values and changes from baseline in vital signs will be summarized analogously for the subgroup of participants with medical history of hypertension. Parameters will be limited to those based on systolic blood pressure, diastolic blood pressure, and pulse rate.

6.6.3.2. Vital Sign and Physical Measurement Abnormalities

Vital sign and physical measurement abnormalities in safety analysis periods will be summarized by treatment group and overall as the number and percentage of participants in the following categories:

Systolic BP (mmHg)	min. <90	max.>140 , >160
Systolic BP (mmHg) change from baseline	max. decrease ≥30	max. increase ≥30
Diastolic BP (mmHg)	min. <50	max.>90, >100
Diastolic BP (mmHg) change from baseline	max. decrease ≥20	max. increase ≥20
Pulse rate (beats/min)	min. <40, <60	max. >100, >120
Temperature (C)	min. <36	max. > 38
Respiratory rate (breaths/min)	min. <12	max. >20
Weight change from baseline (kg)	max. decrease ≥7%	max. increase ≥7%

Vital sign and physical measurement abnormalities will be summarized for the following safety analysis periods and analysis sets:

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- On-DBT for DBT safety analysis set (excluding overall)
- On-OLE rimegepant for OLE rimegepant safety analysis set
- Follow-up for follow-up safety analysis set.

Vital sign abnormalities will be also summarized for the following safety analysis periods and analysis sets:

- On-DBT for DBT safety analysis set with medical history of hypertension (excluding overall)
- On-OLE rimegepant for OLE rimegepant safety analysis set with medical history of hypertension.

6.6.4. Electrocardiograms

6.6.4.1. ECG Changes from Baseline Over Time

Values and changes from baseline in ECG parameters will be summarized as continuous parameters by treatment group and overall at each visit for the following safety analysis periods and analysis sets together in a single table:

- On-DBT for DBT safety analysis set (excluding overall)
- On-OLE rimegepant for OLE rimegepant safety analysis set

6.6.4.2. ECG Abnormalities

ECG abnormalities in safety analysis periods will be summarized by treatment group and overall as the number and percentage of participants in the following categories:

- QTcF (msec): >450 - ≤480, >480 - ≤500, >500
- QTcF increase from baseline (msec): ≥30 - ≤60, >60

Abnormalities will be summarized for the following safety analysis periods and analysis sets:

- On-DBT for DBT safety analysis set (excluding overall)
- On-OLE rimegepant for OLE rimegepant safety analysis set

6.6.5. Columbia-Suicide Severity Rating Scale

C-SSRS suicidality is tabulated as the number and percentage of participants in the following categories according to guidance of suicidal ideation and behavior from FDA[2]:

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- Suicidal ideation
    - Subcategories: wish to be dead; non-specific active suicidal ideation; active suicidal ideation with any method but no intent or plan; active suicidal ideation with some method and intent but no plan; and active suicidal ideation with method, intent and plan.
- Suicidal behavior
    - Subcategories: preparatory actions toward imminent suicidal behaviors; aborted attempt; interrupted attempt; suicide attempt; and completed suicide.
- Self-injurious behavior, no suicidal intent.

Results for all categories and subcategories will be displayed, even those with 0 counts.

Analyses will be based on the subset of participants with non-missing C-SSRS data at each visit by treatment group and overall for the following safety analysis periods and analysis sets. Percentages will be calculated against the number of participants in the subset.

- On-DBT for DBT safety analysis set (excluding overall)
- On-OLE rimegepant for OLE rimegepant safety analysis set.

7. INTERIM ANALYSES

7.1. Introduction

The primary completion date (PCD) for this study is defined as the last date on which all treated participants have completed the last visit in the DBT phase (Week 12 visit) or have otherwise died, withdrawn consent or been lost to follow-up. A database release will be performed after the PCD date, and a PCD CSR will be developed using all data through the cut-off date to support the new drug application (NDA). Analyses will focus on efficacy and safety endpoints during the DBT phase, plus high-level summaries of safety endpoints during the OLE and follow-up phases.

The last participant last visit (LPLV) date for this study is defined as the last date on which all treated participants have completed the last visit in the follow-up phase, or have otherwise died, withdrawn consent or been lost to follow-up. A database lock will be performed after the LPLV date, and the LPLV final CSR will be developed. Scope of the analyses described in this SAP for the LPLV CSR will be determined based on the outcome of the NDA application using the PCD CSR.

There will be no other interim analysis in the study.

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7.2. Interim Analyses and Summaries

The analyses and summaries planned in this SAP contained all the analyses that will be performed for the PCD and LPLV final clinical study reports.

8. REFERENCES

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APPENDICES

Appendix 1. Summary of Efficacy Analyses

Endpoint	Analysis Type	Population	Data Inclusion and Rules for Handling Intercurrent Events and Missing Data	Analysis Model
Mean change from the OP in the number of migraine days per month over the entire DBT Phase (Weeks 1 to 12)	Main analysis for the primary endpoint	DBT migraine	Data collected after study intervention discontinuation will be excluded. All data collected after use of prophylactic migraine medications will be included.	MMRM
	Sensitivity analysis	DBT migraine	Data collected after study intervention discontinuation will be excluded. All data collected after use of prophylactic migraine medications will be included. Missing data will be imputed.	MMRM, using J2R to impute.
	Subgroup analysis	DBT migraine	Data collected after study intervention discontinuation will be excluded. All data collected after use of prophylactic migraine medications will be included.	MMRM
Percentage of participants with ⩾50% reduction from OP in the number of moderate to severe migraine days per month over the entire DBT Phase	Secondary analysis	DBT migraine	Data collected after study intervention discontinuation will be excluded. All data collected after use of prophylactic migraine medications will be included. Missing data will be imputed as non-response (i.e., failure).	Stratified Mantel-Haenszel risk estimation
	Subgroup analysis	DBT migraine	Data collected after study intervention discontinuation will be excluded. All data collected after use of prophylactic migraine medications will be included. Missing data will be imputed as non-response (i.e., failure).	Unstratified Mantel-Haenszel risk estimation
Mean change from the OP in the number of migraine days per month in the first 4 weeks of the DBT Phase	Secondary analysis	DBT migraine	Data collected after study intervention discontinuation will be excluded. All data collected after use of prophylactic migraine medications will be included.	MMRM
Mean change from the OP in the number of migraine days per month in the last 4 weeks of the DBT Phase	Secondary analysis	DBT migraine	Data collected after study intervention discontinuation will be excluded. All data collected after use of prophylactic migraine medications will be included.	MMRM

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Endpoint	Analysis Type	Population	Data Inclusion and Rules for Handling Intercurrent Events and Missing Data	Analysis Model
Change from baseline in the MSQoL role function-restrictive domain score at Week 12 of the DBT Phase	Secondary analysis	DBT efficacy	All data collected after study intervention discontinuation or use of prophylactic migraine medications will be included.	GLM
Mean number of acute migraine medication days per month over the entire DBT Phase	Secondary analysis	DBT migraine	Data collected after study intervention discontinuation will be excluded. All data collected after use of prophylactic migraine medications will be included.	MMRM
Mean change from the OP in the number of migraine days per month and number of headache days per month by pain intensity (total; moderate or severe) in each month and over the entire DBT Phase.	Exploratory analysis	DBT migraine	Data collected after study intervention discontinuation will be excluded. All data collected after use of prophylactic migraine medications will be included.	MMRM
Percentage of participants with ⩾50% reduction, ⩾ 75% reduction, and 100% reduction from OP in the number of migraine days per month and number of headache days per month by pain intensity (total; moderate or severe) in each month and over the entire DBT Phase.	Exploratory analysis	DBT migraine	Data collected after study intervention discontinuation will be excluded. All data collected after use of prophylactic migraine medications will be included. Missing data will be imputed as non-response (i.e., failure).	Stratified Mantel-Haenszel risk estimation
Mean change from the OP in the number of migraine days per week and number of headache days per week by pain intensity (total; moderate or severe) in each week of the first 4 weeks of the DBT Phase.	Exploratory analysis	DBT migraine	Data collected after study intervention discontinuation will be excluded. All data collected after use of prophylactic migraine medications will be included.	MMRM
Percentage of participants with ⩾50% reduction from OP in the number of migraine days per week and number of headache days per week by pain intensity (total; moderate or severe) in each week of the first 4 weeks of the DBT Phase.	Exploratory analysis	DBT migraine	Data collected after study intervention discontinuation will be excluded. All data collected after use of prophylactic migraine medications will be included. Missing data will be imputed as non-response (i.e., failure).	Stratified Mantel-Haenszel risk estimation
Percentage of participants with a migraine day and headache day by pain intensity (total; moderate or severe) on each day of the first week of the DBT Phase.	Exploratory analysis Descriptive summary	DBT migraine	Data collected after study intervention discontinuation will be excluded. All data collected after use of prophylactic migraine medications will be included.	Stratified Mantel-Haenszel risk estimation

Endpoint	Analysis Type	Population	Data Inclusion and Rules for Handling Intercurrent Events and Missing Data	Analysis Model
Mean number of acute migraine-specific medication days per month in each month and the entire DBT Phase	Exploratory analysis	DBT migraine	Data collected after study intervention discontinuation will be excluded. All data collected after use of prophylactic migraine medications will be included.	MMRM
Mean change from the OP in the number of migraine days per month and number of headache days per month by pain intensity (total; moderate or severe) in each month and over the entire OLE Phase.	Exploratory analysis Descriptive summary	OLE migraine	Data collected after study intervention discontinuation will be excluded. All data collected after use of prophylactic migraine medications will be included.	N/A
Percentage of participants with ⩾50% reduction, ⩾75% reduction, and 100% reduction from OP in the number of migraine days per month and number of headache days per month by pain intensity (total; moderate or severe) in each month and over the entire OLE Phase.	Exploratory analysis Descriptive summary	OLE migraine	Data collected after study discontinuation will be excluded. All data collected after use of prophylactic migraine medications will be included. Missing data will not be imputed.	N/A
Mean number of acute migraine medication days per month and acute migraine-specific medication days per month in each month and over the entire OLE Phase.	Exploratory analysis Descriptive summary	OLE migraine	Data collected after study intervention discontinuation will be excluded. All data collected after use of prophylactic migraine medications will be included.	N/A
Mean changes from baseline in the MSQoL preventive role function and emotional function domain scores at Week 12 of the DBT Phase	Exploratory analysis	DBT efficacy	All observed values will be included regardless of study intervention discontinuation or use of prophylactic migraine medications.	GLM
Mean change from baseline in the MIDAS total score, absenteeism and presenteeism scores at Week 12 of the DBT Phase.	Exploratory analysis	DBT efficacy set	All observed values will be included regardless of study intervention discontinuation or use of prophylactic migraine medications.	GLM
Mean change from baseline in EQ-5D-5L index score and VAS score at Week 12 of the DBT Phase.	Exploratory analysis	DBT efficacy set	All observed values will be included regardless of study intervention discontinuation or use of prophylactic migraine medications.	GLM
Mean change from baseline in MSQoL domain scores, MIDAS scores, and EQ-5D-5L scores at Week 24 of the OLE Phase.	Exploratory analysis Descriptive summary	OLE efficacy	All observed values will be included regardless of study intervention discontinuation or use of prophylactic migraine medications.	N/A

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Appendix 2. Significant AEs

Significant AEs are listed below, and the lists of MedDRA PTs for significant AEs will be in the latest version of the C495 C530 CORE SAP.

1) Medication-overuse headache AE
2) Hepatic-related AE
3) Potential drug abuse AE
4) Cardiovascular AE
5) Suicidality AE
6) Hypertension AE
7) Raynaud's phenomenon AE.

AE overview tables will display a separate row for each significant AE listed above.

For tables by SOC or PT, a separate table will be produced for each significant AE listed above, except (1) and (7) because they are based on a single PT. For potential drug abuse AEs, PTs will be displayed in alphabetical order by PT without SOC.

Appendix 3. Laboratory Test Toxicity Grades

Laboratory test toxicity grades are assigned using CTCAE or DAIDS criteria as specified in Table 5.

Table 5. Laboratory Test Toxicity Grades Using CTCAE/DAIDS Criteria

	Grade				
Test Name	**0**	**1**	**2**	**3**	**4**
Hematology					
Eosinophils *	≤ ULN or ≤ baseline	{> ULN and > baseline} or {> ULN and baseline missing}			
Hemoglobin, high	≤ ULN	> ULN to ≤ ULN + 2.0 g/dL	> ULN + 2.0 g/dL to ≤ ULN + 4.0 g/dL	> ULN + 4.0 g/dL	
Hemoglobin, low	≥ LLN	≥ 10.0 to < LLN g/dL; ≥ 6.2 to < LLN mmol/L; ≥ 100 to < LLN g/L	≥ 8.0 to < 10.0 g/dL; ≥ 4.9 to < 6.2 mmol/L; ≥ 80 to < 100 g/L	< 8.0 g/dL; < 4.9 mmol/L; < 80 g/L	
Lymphocytes, high	≤ 4,000/mm3		> 4,000 to ≤ 20,000/mm3	> 20,000/mm3	
Lymphocytes, low	≥ LLN	≥ 800 to < LLN/mm3;	≥ 500 to < 800/mm3;	≥ 200 to < 500/mm3;	< 200/mm3; < 0.2 x 10e9/L

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	Grade				
Test Name	**0**	**1**	**2**	**3**	**4**
		≥ 0.8 to < LLN x 10e9/L	≥ 0.5 to < 0.8 x 10e9/L	≥ 0.2 to < 0.5 x 10e9/L	
Neutrophils	≥ LLN	≥ 1,500 to < LLN/mm3; ≥ 1.5 to < LLN x 10e9/L	≥ 1,000 to < 1,500/mm3; ≥ 1.0 to < 1.5 x 10e9/L	≥ 500 to < 1,000/mm3; ≥ 0.5 to < 1.0 x 10e9/L	< 500/mm3; < 0.5 x 10e9/L
Platelets	≥ LLN	≥ 75,000 to < LLN/mm3; ≥ 75.0 to < LLN x 10e9/L	≥ 50,000 to < 75,000/mm3; ≥ 50.0 to < 75.0 x 10e9/L	≥ 25,000 to < 50,000/mm3; ≥ 25.0 to < 50.0 x 10e9/L	< 25,000/mm3; < 25.0 x 10e9/L
White blood cell count, high				≥ 100,000/mm3; ≥ 100 x 10e9/L	
White blood cell count, low	≥ LLN	≥ 3000 to < LLN/mm3; ≥ 3.0 to < LLN x 10e9/L	≥ 2000 to < 3000/mm3; ≥ 2.0 to < 3.0 x 10e9/L	≥ 1000 to < 2000/mm3; ≥ 1.0 to < 2.0 x 10e9/L	< 1000/mm3; < 1.0 x 10e9/L
Serum chemistry					
Albumin	≥ LLN	≥ 3 to < LLN g/dL; ≥ 30 to < LLN g/L	≥ 2 to < 3 g/dL; ≥ 20 to < 30 g/L	< 2 g/dL; < 20 g/L	
ALP *	≤ ULN if baseline ≤ ULN or missing; < 2.0 x baseline if baseline > ULN	> ULN to ≤ 2.5 x ULN if baseline ≤ ULN or missing; ≥ 2.0 to ≤ 2.5 x baseline if baseline > ULN	> 2.5 to ≤ 5.0 x ULN if baseline ≤ ULN or missing; > 2.5 to ≤ 5.0 x baseline if baseline > ULN	> 5.0 to ≤ 20.0 x ULN if baseline ≤ ULN or missing; > 5.0 to ≤ 20.0 x baseline if baseline > ULN	> 20.0 x ULN if baseline ≤ ULN or missing; > 20.0 x baseline if baseline > ULN
ALT *	≤ ULN if baseline ≤ ULN or missing; < 1.5 x baseline if baseline > ULN	> ULN to ≤ 3.0 x ULN if baseline ≤ ULN or missing; ≥ 1.5 to ≤ 3.0 x baseline if baseline > ULN	> 3.0 to ≤ 5.0 x ULN if baseline ≤ ULN or missing; > 3.0 to ≤ 5.0 x baseline if baseline > ULN	> 5.0 to ≤ 20.0 x ULN if baseline ≤ ULN or missing; > 5.0 to ≤ 20.0 x baseline if baseline > ULN	> 20.0 x ULN if baseline ≤ ULN or missing; > 20.0 x baseline if baseline > ULN

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	Grade				
Test Name	**0**	**1**	**2**	**3**	**4**
AST *	≤ ULN if baseline ≤ ULN or missing; < 1.5 x baseline if baseline > ULN	> ULN to ≤ 3.0 x ULN if baseline ≤ ULN or missing; ≥ 1.5 to ≤ 3.0 x baseline if baseline > ULN	> 3.0 to ≤ 5.0 x ULN if baseline ≤ ULN or missing; > 3.0 to ≤ 5.0 x baseline if baseline > ULN	> 5.0 to ≤ 20.0 x ULN if baseline ≤ ULN or missing; > 5.0 to ≤ 20.0 x baseline if baseline > ULN	> 20.0 x ULN if baseline ≤ ULN or missing; > 20.0 x baseline if baseline > ULN
Bicarbonate	≥ LLN	< LLN			
Bilirubin (total) *	≤ ULN if baseline ≤ ULN or missing; ≤ 1.0 x baseline if baseline > ULN	> ULN to ≤ 1.5 x ULN if baseline ≤ ULN or missing; > 1.0 to ≤ 1.5 x baseline if baseline > ULN	> 1.5 to ≤ 3.0 x ULN if baseline ≤ ULN or missing; > 1.5 to ≤ 3.0 x baseline if baseline > ULN	> 3.0 to ≤ 10.0 x ULN if baseline ≤ ULN or missing; > 3.0 to ≤ 10.0 x baseline if baseline > ULN	> 10.0 x ULN if baseline ≤ ULN or missing; > 10.0 x baseline if baseline > ULN
Calcium, high	≤ ULN	> ULN to ≤ 11.5 mg/dL; > ULN to ≤ 2.9 mmol/L	> 11.5 to ≤ 12.5 mg/dL; > 2.9 to ≤ 3.1 mmol/L	> 12.5 to ≤ 13.5 mg/dL; > 3.1 to ≤ 3.4 mmol/L;	> 13.5 mg/dL; > 3.4 mmol/L
Calcium, low	≥ LLN	≥ 8.0 to < LLN mg/dL; ≥ 2.0 to < LLN mmol/L	≥ 7.0 to < 8.0 mg/dL; ≥ 1.75 to < 2.0 mmol/L	≥ 6.0 to < 7.0 mg/dL; ≥ 1.5 to < 1.75 mmol/L	< 6.0 mg/dL; < 1.5 mmol/L
Cholesterol (total)	≤ ULN	> ULN to ≤ 300 mg/dL; > ULN to ≤ 7.75 mmol/L	> 300 to ≤ 400 mg/dL; > 7.75 to ≤ 10.34 mmol/L	> 400 to ≤ 500 mg/dL; > 10.34 to ≤ 12.92 mmol/L	> 500 mg/dL; > 12.92 mmol/L
CK #	≤ ULN	> ULN to ≤ 2.5 x ULN	> 2.5 to ≤ 5 x ULN	> 5 to 10 x ULN	> 10 x ULN
Creatinine	≤ ULN	> ULN to ≤ 1.5 x ULN	{> 1.5 to ≤ 3.0 x ULN} or {> 1.5 to ≤ 3.0 x baseline}	{> 3.0 to ≤ 6.0 x ULN} or {> 3.0 x baseline}	> 6.0 x ULN
eGFR MDRD	≥ LLN	≥ 60 to < LLN mLmin/1.73 m2	≥ 30 to < 60 mL/min/1.73 m2	≥ 15 to < 30 mL/min/1.73 m2	< 15 mL/min/1.73 m2

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	Grade				
Test Name	**0**	**1**	**2**	**3**	**4**
Glucose, high, fasting @*	< 110 mg/dL; < 6.11 mmol/L	≥ 110 to ≤ 125 mg/dL; ≥ 6.11 to < 6.95 mmol/L	> 125 to ≤ 250 mg/dL; ≥ 6.95 to < 13.89 mmol/L	> 250 to ≤ 500 mg/dL; ≥ 13.89 to < 27.75 mmol/L	> 500 mg/dL; ≥ 27.75 mmol/L
Glucose, high, nonfasting @*	< 116 mg/dL; < 6.44 mmol/L	≥ 116 to ≤ 160 mg/dL; ≥ 6.44 to < 8.89 mmol/L	> 160 to ≤ 250 mg/dL; ≥ 8.89 to < 13.89 mmol/L	> 250 to ≤ 500 mg/dL; ≥ 13.89 to < 27.75 mmol/L	> 500 mg/dL; ≥ 27.75 mmol/L
Glucose, low @	> 64 mg/dL; ≥ 3.55 mmol/L	≥ 55 to ≤ 64 mg/dL; ≥ 3.05 to < 3.55 mmol/L	≥ 40 to < 55 mg/dL; ≥ 2.22 to < 3.05 mmol/L	≥ 30 to < 40 mg/dL; ≥ 1.67 to < 2.22 mmol/L	< 30 mg/dL; < 1.67 mmol/L
Lactate dehydrogenase	≤ ULN	> ULN			
LDL cholesterol, age ≥ 18 years @	< 130 mg/dL; < 3.37 mmol/L	≥ 130 to < 160 mg/dL; ≥ 3.37 to < 4.12 mmol/L	≥ 160 to < 190 mg/dL; ≥ 4.12 to < 4.90 mmol/L	≥ 190 mg/dL; ≥ 4.90 mmol/L	
LDL cholesterol, age > 2 to < 18 years @*	< 110 mg/dL; < 2.85 mmol/L	≥ 110 to < 130 mg/dL; ≥ 2.85 to < 3.37 mmol/L	≥ 130 to < 190 mg/dL; ≥ 3.37 to < 4.90 mmol/L	≥ 190 mg/dL; ≥ 4.90 mmol/L	
Potassium, high	≤ ULN	> ULN to ≤ 5.5 mmol/L	> 5.5 to ≤ 6.0 mmol/L	> 6.0 to ≤ 7.0 mmol/L	> 7.0 mmol/L
Potassium, low	≥ LLN	≥ 3.0 to < LLN mmol/L		≥ 2.5 to < 3.0 mmol/L	< 2.5 mmol/L
Sodium, high	≤ ULN	> ULN to ≤ 150 mmol/L	> 150 to ≤ 155 mmol/L	> 155 to ≤ 160 mmol/L	> 160 mmol/L
Sodium, low	≥ LLN	≥ 130 to < LLN mmol/L	≥ 125 to < 130 mmol/L	≥ 120 to < 125 mmol/L	< 120 mmol/L
Triglycerides	< 150 mg/dL; < 1.71 mmol/L	≥ 150 to ≤ 300 mg/dL; ≥ 1.71 to ≤ 3.42 mmol/L	> 300 to ≤ 500 mg/dL; > 3.42 to ≤ 5.7 mmol/L	> 500 to ≤ 1000 mg/dL; > 5.7 to ≤ 11.4 mmol/L	> 1000 mg/dL; > 11.4 mmol/L
Uric acid (urate) @	< 7.5 mg/dL; < 0.45 mmol/L	≥ 7.5 to < 10.0 mg/dL; ≥ 0.45 to < 0.59 mmol/L	≥ 10.0 to < 12.0 mg/dL; ≥ 0.59 to < 0.71 mmol/L	≥ 12.0 to < 15.0 mg/dL; ≥ 0.71 to < 0.89 mmol/L	≥ 15.0 mg/dL; ≥ 0.89 mmol/L
Urinalysis					

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	Grade				
Test Name	**0**	**1**	**2**	**3**	**4**
Urine glucose @*	Negative; ≤ 180 mg/dL	Trace or 1+; > 180 to ≤ 250 mg/dL	2+; > 250 to ≤ 500 mg/dL	3+ or higher; > 500 mg/dL	
Urine protein @*	Negative; < 10 mg/dL	Trace or 1+; ≥ 10 to < 100 mg/dL	2+; ≥ 100 to < 300 mg/dL	3+ or higher; ≥ 300 mg/dL	

@ Graded using DAIDS criteria. All other laboratory tests are graded using CTCAE criteria.[3]
* Modified toxicity grade criteria to correct typos, handle missing baseline, or include additional selection criteria. For urine glucose, 180 mg/dL is considered the commonly accepted "normal" threshold.[3]
For urine protein, < 10 mg/dL is considered the commonly accepted "normal" threshold.[4]
CK total measured using any method, i.e., fractionated or not fractionated

Appendix 4. Definition of Migraine Days, Headache Days, Acute Migraine Medication Days, Acute Migraine-Specific Medication Days

Migraine days, headache days, acute migraine medication days, and acute migraine-specific mediation days will be derived based on days of efficacy data (i.e. say reference days). See Section 5.2.3.2 and Section 5.2.3.3.

Migraine Day: A migraine day is defined as a day with either (1) or (2):

1) Qualified migraine headache based on the following criteria per C4951019 Protocol Appendix 2:

- "Yes" response to the question about having a headache yesterday.
- "Yes" response to the question about the headache lasting ≥ 30 minutes.
- Meeting at least one of the following criteria (a or b):
    a. ≥ 2 of the following pain features based on "yes" response to questions:
        i. Unilateral location,
        ii. Pulsating quality (throbbing),
        iii. Moderate or severe pain intensity,
        iv. Avoidance of routine physical activity.
    b. ≥ 1 of the following associated symptoms based on "yes" response to questions:
        i. Nausea
        ii. Vomiting
        iii. Both photophobia and phonophobia

2) Acute migraine-specific medication day:

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- Taking OLE rimegepant (during aura or to treat headache) on a non-scheduled dosing day during the on-OLE efficacy analysis period as defined in Section 5.2.4.
- "Yes' response to question of taking one of the 4 acute migraine-specific medications (triptan, ergotamine, lasmiditan or ubrogepant) during aura or to treat headache on any day (scheduled or non-scheduled dosing day) during OP, on-DBT or on-OLE efficacy analysis periods as defined in Section 5.2.4.

A migraine date is determined using the Event Date from the eDiary. The eDiary device retrospectively collects migraine parameters including a diary entry Start Date/Time, a diary entry Completion Date/Time, and an Event Date. The Event Date is the actual headache date that is automatically calculated by the eDiary device using diary entry Start Date -1 day.

Headache Day:

A day is defined as a headache day if it meets one of the below criteria:

- Counted as a migraine day, or
- "Yes" response to question about the headache lasts ≥ 30 minutes and is not a migraine day, or
- "Yes" response to question about having headache yesterday and 'Yes' response to question of taking any other medications to treat headache or aura.

Acute Migraine-Specific Medication Day:

- An acute migraine-specific medication day is defined as any calendar day (scheduled or non-scheduled) during DBT or OLE during which the participant took one of the 4 migraine-specific medications (i.e., triptan, ergotamine, lasmiditan, or ubrogepant) during aura or to treat headache, or the participant took study intervention during aura or to treat headache on a non-scheduled dosing day during OLE phase. That is, acute migraine-specific medication days are a subset of migraine days.
- Note that ergotamine medication, lasmiditan, and ubrogepant are not listed as permitted medications for acute migraine treatment in this study. However, use of these medications, if taken for migraine treatment, must be documented for the purposes of assessing migraine days and acute migraine-specific medication day, and must be captured as a protocol deviation.

Acute Migraine Medication Day:

Acute migraine medication days are defined as either (1) or (2):

(1) Acute migraine-specific medication day as defined above.

(2) Migraine day (see aforementioned definition) with a "yes" response to the question about taking other medications to treat headache or aura.

Thus, acute migraine medication days are a subset of migraine days. If there are multiple sets of efficacy parameters on the same finding date, then data from all sets are used cumulatively

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to assess acute migraine medication day status on that day, regardless of finding time. For example, if a participant has both “yes” and “no” responses to the question about taking triptan on that day, then the participant is considered to have taken acute migraine medication on that day.

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Appendix 5. List of Abbreviations

Abbreviation	Term
AE	Adverse event
ALT	Alanine aminotransferase
ALP	Alkaline phosphatase
ASE	Asymptotic standard error
AST	Aspartate aminotransferase
BMI	Body mass index
C-CASA	Columbia-Classification Algorithm for Suicide Assessment
C-SSRS	Columbia-Suicide Severity Rating Scale
CI	Confidence interval
CK	Creatine kinase
CRF	Case report form
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
DAIDS	Division of Acquired Immune Deficiency Syndrome
DBT	Double-blind treatment
DILI	Drug-induced liver injury
ECG	Electrocardiogram
eDiary	Electronic diary
eDISH	Evaluation of drug-induced serious hepatotoxicity
eGFR	Estimated glomerular filtration rate
EOD	Every other day
EQ-5D-5L	EuroQol 5-dimensional questionnaire
EOT	End of treatment
GLM	Generalized linear model
HDL	High-density lipoprotein
LDL	Low-density lipoprotein
LFT	Liver function test
IWRS	Interactive Web-based Response System
J2R	Jump to reference
LLN	Lower limit of normal
LPLV	Last participant last visit
LSM	Least-squares mean
MAR	Missing at random
MDRD	Modification of diet in renal disease
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed effects model with repeated measures
MNAR	Missing not at random
MIDAS	Migraine Disability Assessment
MSQoL	Migraine-Specific Quality-of-Life
NRI	Non-responder imputation
N/A	Not applicable
ODT	Orally disintegrating tablet

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Abbreviation	Term
OLE	Open-label extension
OP	Observation phase
OTC	Over the counter
PCD	Primary completion date
pIPD	Potentially important protocol deviation
PT	Preferred term
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
SE	Standard error
SOC	System organ class
SOP	Standard operating procedure
TBL	Total bilirubin level
TEAE	Treatment-emergent adverse event
TLF	Table listing figure
ULN	Upper limit of normal
VAS	Visual analogue scale

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