Supplemental Online Content

Winner PK, McAllister P, Chakhava G, et al. Effects of intravenous eptinezumab vs placebo on headache pain and most bothersome symptom when initiated during a migraine attack: a randomized clinical trial. *JAMA*. Published June 15, 2021. doi:10.1001/jama.2021.7665

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This supplemental material has been provided by the authors to give readers additional information about their work.

eAppendix. Supplemental Methods

Detailed Inclusion Criteria

1. Male or female patients 18–75 years of age, inclusive, at time of informed consent.

2. Willing and able to read, understand, and sign the Informed Consent Form (ICF) for the clinical study approved by the investigator's local Review Board or a central Institutional Review Board (IRB) or Ethics Committee (EC).

3. Has adequate venous access for administration of study drug and collection of blood samples.

4. Greater than 1-year history of migraine, with or without aura, with onset of first migraine before age 50 as defined by International Classification of Headache Disorders, 3rd edition (ICHD-3) criteria.[1]

5. Migraine on 4–15 days/month in the 3 months prior to screening.

6. By history, the patient's typical migraine attacks, if untreated, are associated with headache pain of moderate to severe intensity and a most bothersome symptom of nausea, photophobia, or phonophobia. These migraine attacks must be a minimum duration of 4 hours and maximum duration of 72 hours.

7. History of either previous or active use of triptans for migraine.

8. Headache free for ≥24 hours prior to onset of a qualifying migraine.

9. On day 0, patients must have a moderate to severe headache associated with ≥1 of the following headache characteristics: pulsating quality, unilaterality, and aggravation by or avoidance of routine physical activity. In addition, they must have ≥1 of the following during the headache:

    a. Nausea and/or vomiting
    b. Photophobia and phonophobia

10. On day 0, patient must be able to reliably identify the time of qualifying migraine onset.

11. Able and willing to be dosed with study drug during a qualifying migraine attack within 8 weeks of screening visit.

12. Women of child-bearing potential and males with partners of child-bearing potential must agree to use adequate contraception for the duration of the study. Adequate contraception includes oral, transdermal, or injectable (depot) estrogen and/or progestogen, selective estrogen receptor modulator therapy, intrauterine contraceptive device, double barrier method (e.g., condom with spermicidal gel or diaphragm with spermicidal gel) or vasectomy with use of condom (for male patients). Females are considered of childbearing potential unless they are permanently sterilized (i.e., bilateral tubal ligation,

bilateral salpingectomy, bilateral oophorectomy of hysterectomy) ≥3 months prior to screening or postmenopausal (i.e., no menses for 1 year).

13. Any hormonal therapy (e.g., contraceptives, hormone replacement therapy) use is stable and ongoing for ≥3 months prior to screening and through up to treatment with study drug (day 0).

14. Willing, committed, and able to comply with scheduled clinic visits and complete all study-related procedures.

15. Patient agrees not to post any personal medical data or information related to the study on any website or social media site (e.g., Facebook, Twitter).

16. Patient is willing to complete the eDiary from day 0 through the 48-hour period after dosing and from Day 3 until a new migraine is reported.

17. Patient is willing and able to have study drug administration within 1–6 hours of onset of a qualifying migraine and remain at the site for 4 hours post start of infusion for observation.

Detailed Exclusion Criteria

1. Unable to differentiate migraine from other headache or pain disorders.

2. Use of the following medication, for any indication, within the 24-hour period prior to dosing with study drug:

    a. Triptans, ergotamines, and ergot-derivatives
    b. Analgesics (including but not limited to acetaminophen, tramadol, nonsteroidal anti-inflammatory drugs [NSAIDs], combination analgesics, caffeine-containing analgesics, and opioids/narcotics), and other acute migraine medication(s)
    c. Antiemetic medications (including but not limited to prochlorperazine, promethazine, droperidol, chlorpromazine, metoclopramide)
    d. Antihistamines
    e. Devices, neuromodulation, neurostimulation, or injectable therapy (trigger point injections, extracranial nerve blocks, facet joint injections, spinal manipulation)

3. On day 0, use of magnesium or cannabis-based products intended for acute treatment of the qualifying migraine.

4. History of new daily persistent headache in any of the 3 months prior to screening.

5. History or diagnosis of chronic tension-type headache, hypnic headache, cluster headache, hemicrania continua, new daily persistent headache, or unusual migraine subtypes such as hemiplegic migraine (sporadic and familial), ophthalmoplegic migraine, and migraine with neurological accompaniments that are not typical of migraine aura (e.g., diplopia, altered consciousness, or long duration).

6. History or diagnosis of vestibular migraine.

7. Any changes to preventive migraine treatment(s) within 1 month prior to screening and up to treatment with study drug (day 0).

8. Use of the following medication, for any indication, in each of the 3 months prior to screening:

    a. Opioids/narcotics or butalbital-containing products (including combinations) on >4 days/month; OR
    b. Triptans, ergotamines, or combination analgesics for ≥10 days/month; OR
    c. Acetaminophen, aspirin, or nonsteroidal anti-inflammatory drugs [NSAIDs] for ≥15 days/month (except if patient is taking 81 mg dose of aspirin for cardiac prophylaxis)

9. Any use of approved devices, neuromodulation, neurostimulation, or injectable therapy (trigger point injections, extracranial nerve blocks, facet joint injections) within the 24-hour period prior to treatment with study drug (day 0).

10. Any use of botulinum toxin for migraine or for any other medical/cosmetic reasons requiring injections within 7 days prior to treatment with study drug (day 0).

11. Any use of systemic corticosteroid for migraine or any other reason within 3 months prior to treatment with study drug (day 0).

12. Evidence or medical history of clinically significant psychiatric diseases that are uncontrolled and/or untreated.

13. Clinically significant laboratory findings showing evidence of organ dysfunction, any clinically significant deviation from the normal range (abnormal tests may be repeated for confirmation at the discretion of the investigator), or clinically significant physical exam abnormalities at screening, as evaluated by the investigator.

14. Have present or previous malignancies, except:

    - Squamous or basal skin cell carcinoma with excision without evidence of recurrence

    - Malignancy ≥5 years since diagnosis/treatment without evidence of recurrence

15. Known history or evidence of hereditary fructose intolerance, severe atopy, or life-threatening allergy (e.g., anaphylaxis). If questions arise, the investigator should contact the medical monitor for guidance.

16. Any clinically significant, concurrent medical condition on the day of infusion.

17. Clinically significant abnormal ECG during the screening period.

18. Positive human immunodeficiency virus (HIV), hepatitis B surface antigen (HBsAg), and/or hepatitis C antibody (HCV) at screening.

19. Body mass index (BMI) >35 kg/m^2 at screening.

20. Primary or secondary hypertension that is uncontrolled. Note: Mild primary hypertension that is well-controlled for ≥6 months prior to screening is allowed.

21. The patient is at risk of self-harm or harm to others in the investigator's opinion, based on clinical interview and responses provided on the Columbia-Suicide Severity Rating Scale (C-SSRS). Patients must be excluded if they have a lifetime history of a serious suicide attempt or multiple suicide attempts (i.e., actual, interrupted, or aborted attempts), have had any suicidal behavior in the past 5 years (i.e., preparatory acts or behavior), or have had suicidal ideation of Type 3, 4, or 5 (i.e., suicidal ideation with any method without intent to act or suicidal ideation with intent to act, with or without a plan) in the past 6 months, as measured by the C-SSRS at Screening visit or phone contact during screening period.

22. Any history or evidence of substance abuse or dependence (e.g., alcohol, opiates, amphetamines and barbiturates) within the past 2 years according to the International Classification of Diseases (ICD) 10: F10-19.

23. Pregnant, breastfeeding, or planning to become pregnant during the study.

24. Receipt of any experimental, unregistered therapy (within or outside a clinical study) within 30 days or 5 plasma half-lives (whichever is longer) prior to screening. Note: Patient use of rimegepant and ubrogepant are allowed to screen provided they have discontinued the drug at a total of 5 half-lives.

25. Receipt of any monoclonal antibody treatment, for migraine or any other indication, (within or outside a clinical study) within 6 months prior to screening.

26. Planned or current participation in any other interventional clinical study during the duration of this clinical study, or within 1 month prior to screening.

27. Any condition that, in the opinion of the investigator, would make the patient unsuitable for the clinical study, including but not limited to clinically unstable cardiovascular disease, arteriosclerosis, cardiomyopathy, coronary artery disease, serious heart rhythm abnormalities, neurological disease, cerebrovascular disease, diabetes, Raynaud's disease.

28. Employees of the Sponsor, Clinical Research Organization, or any clinical study site involved in this study and their immediate family members (i.e., parents, spouse, siblings, children).

Data Collection and Outcome Measures

Data collected included baseline demographics, clinical characteristics and medical history, results of physical examinations, and vital signs. An electronic diary (eDiary) was assigned before dosing on the day 0 visit to collect migraine data. The eDiary was completed by the patient pre-dose through 48 hours. Additionally, patients completed eDiary data entry from day 3 until a new migraine attack was reported. The data collected in the eDiary included the timing of the start of infusion, headache severity, presence or absence of migraine-associated symptoms, including nausea, photophobia or phonophobia (one of which was identified on the day of infusion, prior to dosing, as the most bothersome migraine-associated symptom), and use of acute rescue migraine medication.

Co-primary efficacy endpoints were time to headache pain freedom and time to absence of MBS. Headache pain was rated on a 4-point scale with 3 = severe, 2 = moderate, 1 = mild, and 0 = no pain. Pain was required to be 2 or 3 at baseline, and headache pain freedom was defined as no pain (0). Time to headache pain freedom (co-primary endpoint) was the first time point after start of infusion at which the patient reported a score of 0 with no administration of rescue medication (i.e., no rescue medication from the start of infusion to the time of headache pain freedom). Absence of MBS was defined as freedom from the selected symptom (either yes or no). Assessments were made from pre-dose to 48 hours. Time to absence of MBS (co-primary endpoint) was the first post-treatment time point at which absence of MBS was achieved with no administration of rescue medication.

Key secondary efficacy endpoints were headache pain freedom and absence of MBS at 2 hours. Additional secondary efficacy endpoints were headache pain freedom at 4 hours, absence of MBS at 4 hours, and use of rescue medication within 24 hours. Exploratory efficacy endpoints

included time to headache pain relief; headache pain freedom at 2 hours with sustained freedom for 24 and 48 hours; use of rescue medication by 48 hours; and time to next migraine. Time to headache pain relief was the first time point post-infusion start at which headache pain was reduced from a score of 2 or 3 to a score of 0 or 1. Sustained freedom was defined as freedom from headache pain (score of 0) at 2 hours and maintaining this pain-free status through 24 and 48 hours with no administration of rescue medication. Time to next migraine was defined as the first day, beginning from day 3 (72 hours after dosing), at which the patient reported a new migraine; patients were censored at the time of their last diary entry.

Adverse Events of Special Interest

Verbatim descriptions of all adverse events were coded to the Medical Dictionary for Regulatory Activities (MedDRA) version 20.1 and classified by system organ class (SOC) and preferred term (PT). The following adverse events of special interest were identified throughout eptinezumab clinical development program from monitoring and reviewing safety information on an ongoing basis in consideration of guidance documents and areas of interest or concern for the drug class.

- Hypersensitivity and anaphylactic events:
    - SOC: Immune system disorders; PTs: Hypersensitivity, Anaphylactic reaction, and Anaphylactoid reaction.
- Events associated with suicide:
    - SOC: Psychiatric disorders; PTs: Depression suicidal, Intentional self-injury, Suicidal behavior, Suicidal ideation, Suicide attempt, and Self injurious behavior.
- Cardiovascular events:
    - SOC: Cardiac disorders; PTs: Atrial fibrillation, Bradycardia, Chest pressure, Palpitations, Sinus bradycardia, Sinus tachycardia, and Tachycardia; or

- SOC: Investigations; PTs: Blood pressure increase, Blood pressure systolic increase, Elevated blood pressure, Heart rate increased, Heart rate decreased, Heart rate irregular, Electrocardiogram abnormal, Electrocardiogram Q wave abnormal, Electrocardiogram QT interval abnormal, and Electrocardiogram QT prolonged; or

- SOC: Nervous system disorders; PTs: Syncope; or

- SOC: Vascular disorders; PTs: Flushing, Hot flush, Hypertension, Hypotension, Ischemia, and Prehypertension; or

- SOC: General disorders and administration site conditions; PTs: Chest pain and Feeling hot.

- Nervous system events:

  - SOC: Nervous system disorders; PT: Seizure.

- Hepatic events:

  - SOC: Investigations; PTs: Alanine aminotransferase increased, Aspartate aminotransferase increased, Blood bilirubin increased, Hepatic enzyme increased, Liver function test abnormal, Liver function test increased, and Transaminases increased.

- Events associated with study drug infusion (occurring within 1 week of dosing):

  - SOC: Skin and subcutaneous tissue disorders; PTs: Dermatitis bullous, Pruritus, Pruritus allergic, Pruritus generalized, Rash, Rash erythematous, Rash generalized, Rash macular, Rash macularpapular, Rash papular, Rash pruritic, Swelling face, and Urticaria.

  - SOC: General disorders and administration site conditions; PTs: Infusion site discomfort, Infusion site eczema, Infusion site erythema, Infusion site extravasation, Infusion site nerve damage, Infusion site pain, Infusion site paresthesia, Infusion site pruritus, Infusion site rash, Infusion site reaction, Infusion site swelling, and Injection site paresthesia.

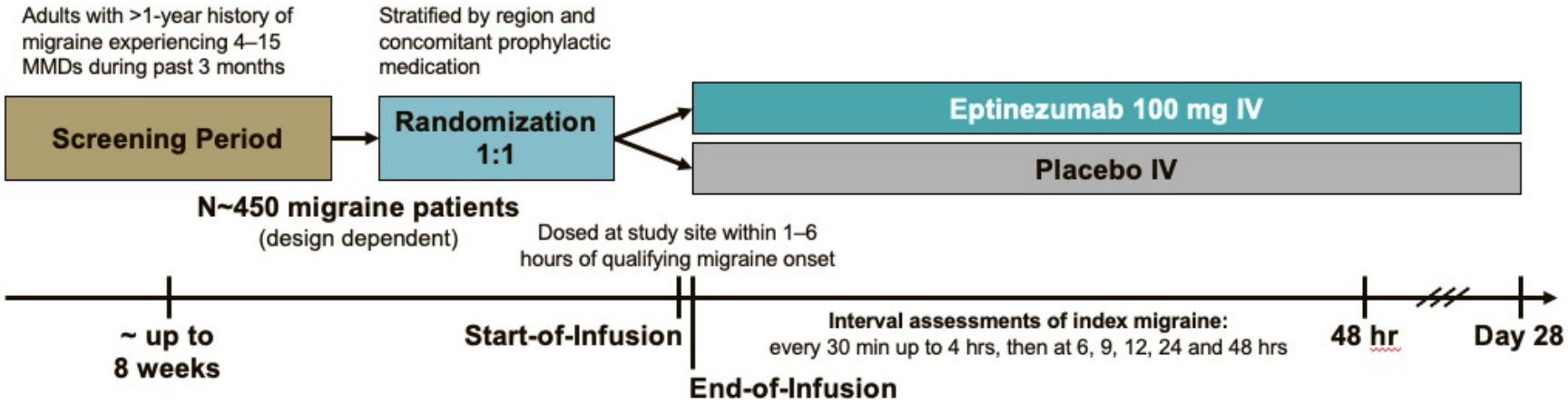
  - SOC: Gastrointestinal disorders; PTs: Lip oedema, Oral pruritus, and Paresthesia oral.

  - SOC: Respiratory, thoracic and mediastinal disorders; PTs: Choking sensation, Cough, Dyspnea, Nasal congestion, Oropharyngeal pain, Rhinitis allergic, Rhinorrhea, Sinus congestion, Sneezing, Throat irritation, and Wheezing.

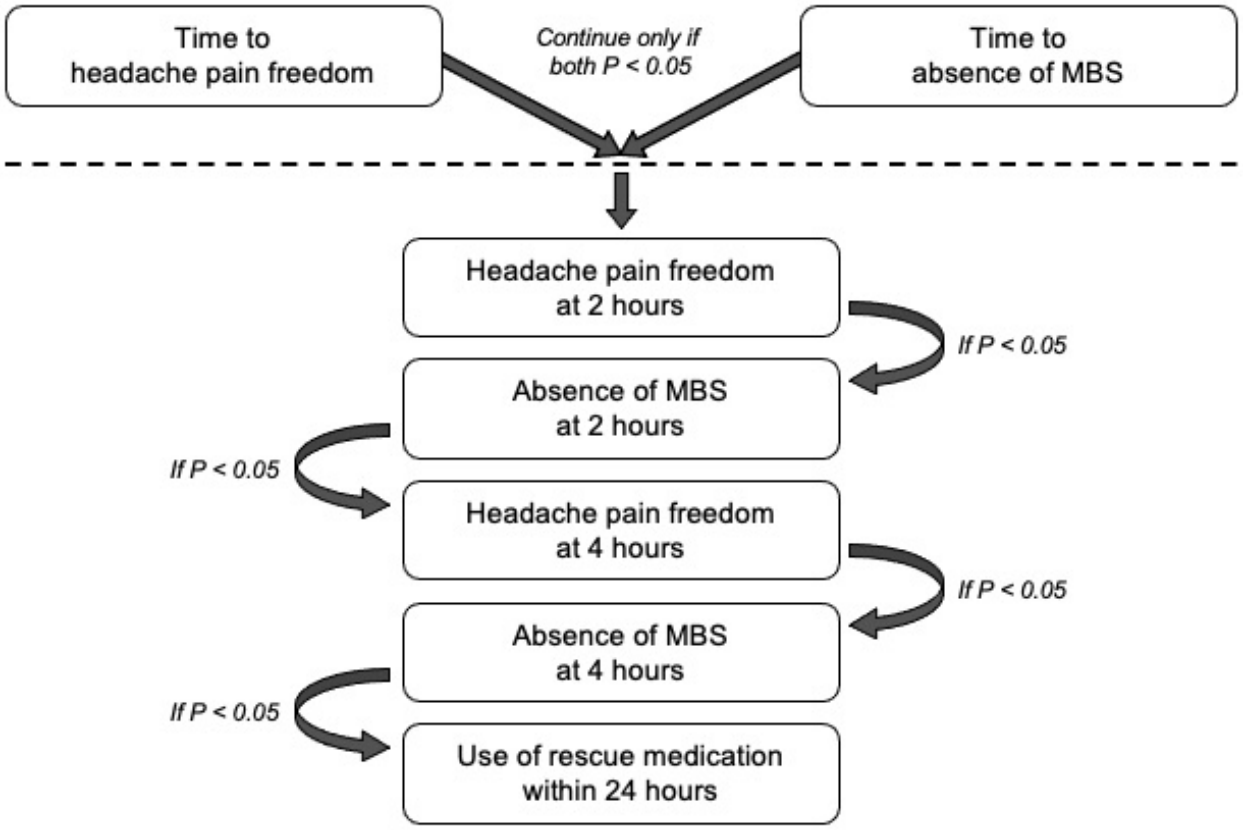
Reference

1. Headache Classification Committee of the International Headache Society (IHS). The International Classification of Headache Disorders, 3rd edition. *Cephalalgia*. 2018;38(1):1-211.

eFigure 1. RELIEF Study Design

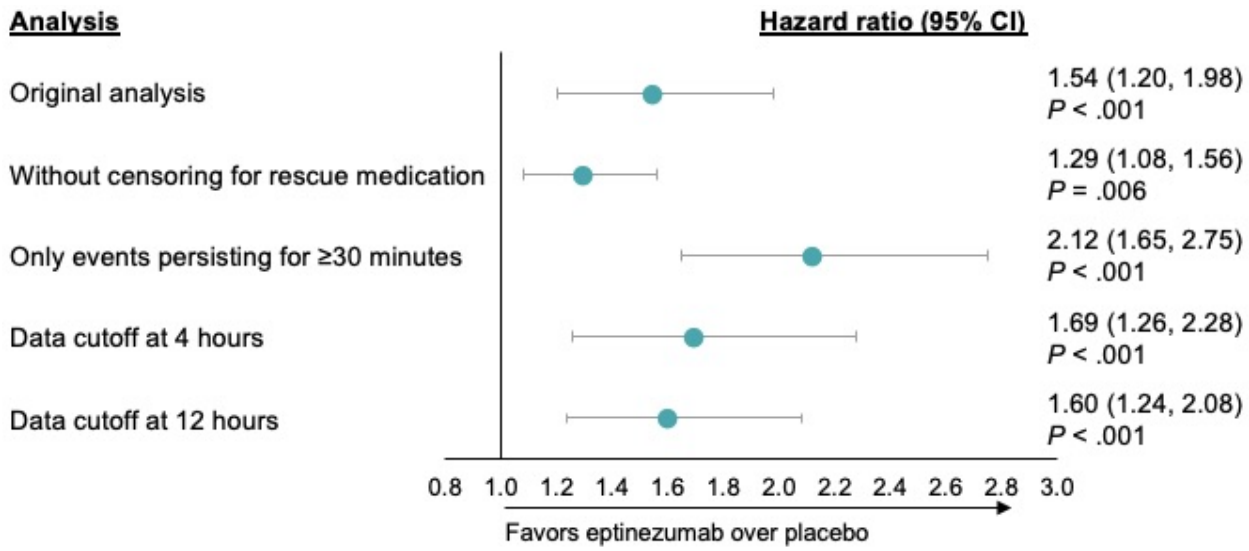


eFigure 2. RELIEF Statistical Testing Hierarchy

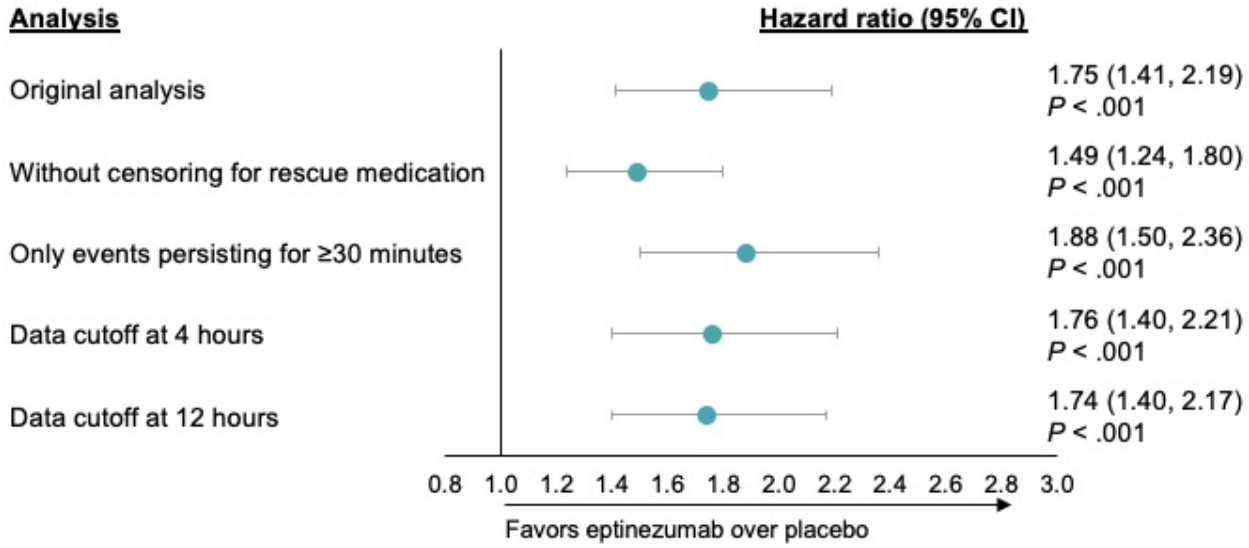


eFigure 3. Results of Sensitivity Analyses for (A) Time to Headache Pain Freedom and (B) Time to Absence of Most Bothersome Symptom (Full Analysis Set)

(A)

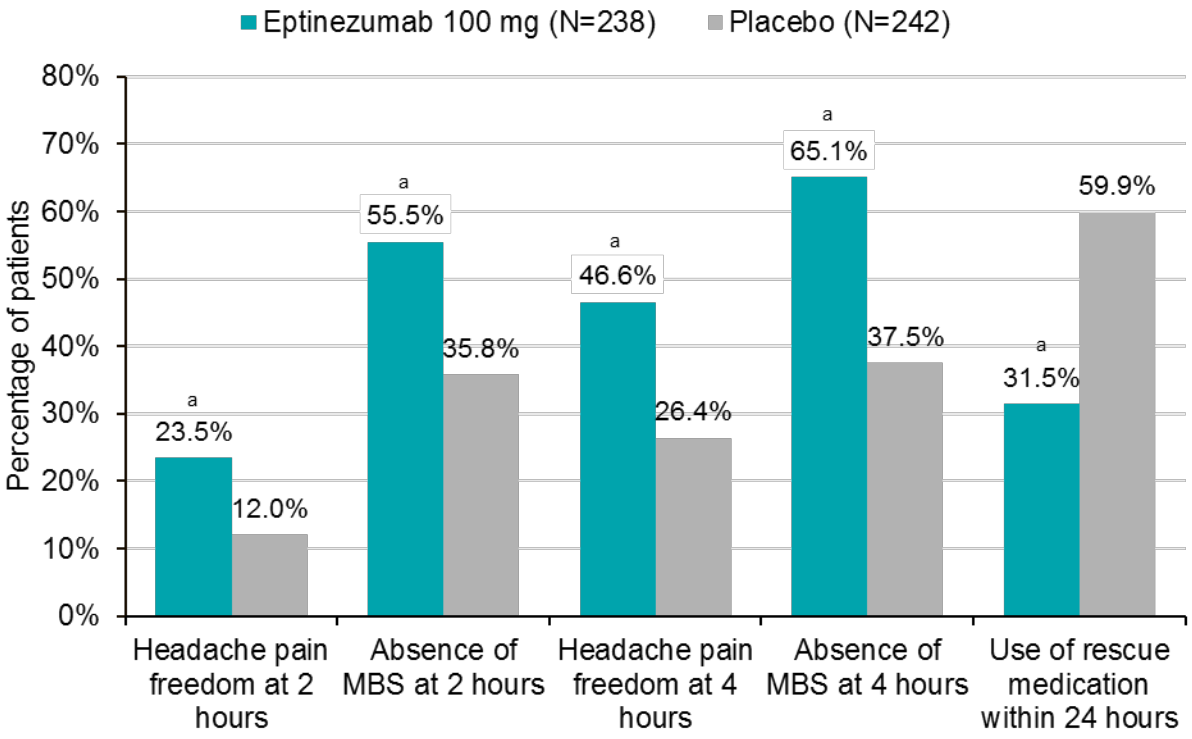


(B)



NOTE: Four sensitivity analyses based on the primary ("original") analysis were conducted for time to headache pain freedom and time to absence of MBS. First, rescue medication censoring was removed; therefore, the time value for each patient was censored only if the patient did not report pain freedom/absence of MBS at all during the 48 hours post-infusion start. Second, the data were calculated based on the requirement for an event to persist for ≥30 minutes; for example, any patient reporting pain freedom at 2 hours but reported pain again at 2.5 hours was still categorized as at risk. In the third and fourth analyses, only data up to and including the 12-hour assessment or the 4-hour assessment, respectively, were used; rules for censoring were identical to those for the primary analysis, except that time values were administratively censored at 12 hours/4 hours, respectively, instead of at 48 hours.

eFigure 4. Secondary Efficacy Endpoints (Full Analysis Set)



Secondary endpoints were those included in the statistical testing hierarchy (headache pain freedom at 2 hours and 4 hours, absence of most bothersome symptom at 2 hours and 4 hours, and use of rescue medication within 24 hours).
[a]$P < .001$ vs placebo.