2 INDICATION

The prophylaxis of chronic migraine in adults ages 18 - 65

3 STUDY PURPOSE

- To evaluate the safety, tolerability, and changes in the number of migraine and headache days with repeated subcutaneous administration of ISIS 546254 or placebo in subjects with chronic migraine.

4 SUMMARY OF STUDY DESIGN

This is a double-blind, placebo-controlled, randomized, multi-center study in subjects with chronic migraine. The study will consist of 7 office visits, 6 Sample collection visits and 3 phone call assessments. Subjects agreeing to participate in the study and meeting the entry criteria assessed at the screening visit, will begin a 28 day baseline period to confirm their diagnosis, and establish a baseline frequency of migraine and headache days. During the baseline period, subjects will continue treating their migraines in their usual manner. They will monitor headache activity, migraine related symptoms, and medication usage with an electronic daily headache diary.

Subjects who, after completing the baseline, continue to meet entrance criteria will be eligible to enter into the 4 month treatment phase. They will be randomized according to the Clinvest generated randomization schedule. A total of 30 randomized subjects will enter the treatment phase receiving ISIS 546254 (SC) or placebo in a 1:1 design. Study drug or placebo will be administered weekly for 16 weeks. A short phone call to assess any treatment related adverse events will take place 1 and 2 days after randomization. Daily electronic diary assessments will collect headache frequency and severity, associated migraine symptoms, acute medication usage, and the emergence of unusual symptoms and adverse events. Subjects will return to the site at weeks 4, 8, and 12 for investigational product (IP) accountability/dispensing, medication and medication updates, biomarker/lab sample collection, and assessment of adverse events. An end of treatment visit will take place 16 weeks after randomization. Subjects will have a follow-up safety visit one month after their last dosage of IP) for assessment of any adverse events (AE) and satisfaction and a final safety phone call 2 months following their last office visit (3 months after last dose of IP) for assessment of any adverse events (AE). Subjects will continue to complete headache diaries through Visit 7. Subjects will also have hematology samples collected every other week starting after Visit 2 through Day 154.

The study consists of 3 phases (Table 1):

Baseline Phase:	Visit 1 (Screening/Baseline Period – Day -28)
Treatment Phase:	Visit 2 (Randomization/Treatment Month 1/Day 0)
	Phone Call Visit 1 (Randomization/Treatment Month 1/Day 1)
	Phone Call Visit 2 (Randomization/Treatment Month 1/Day 2)
	Sample Collection – Day 14
	Visit 3 (Treatment Period Month 2/Day 28)
	Sample Collection – Day 42
	Visit 4 (Treatment Period Month 3/Day 56)
	Sample Collection – Day 70

	Visit 5 (Treatment Period Month 4/Day 84)
	Sample Collection – Day 98
Follow-up Phase:	Visit 6 (End of Treatment/ET/Day 112)
	Sample Collection – Day 126
	Visit 7 (Follow up one month after last IP dosage/Day 140)
	Sample Collection – Day 154
	Phone Call Visit (3 months after last IP dosage/Day 196)

Safety and tolerability will be monitored by the Investigators. Patients who discontinue study treatment prematurely should complete any follow-up visits associated with the most recent dose and should move into and complete the Follow-up Phase.

Subjects will undergo sampling for (pharmacokinetics) PK, coagulation, chemistry, hematology, and optional future biomedical research, as specified in the schedule of procedures.

5 POPULATION SAMPLE

Subjects included in the study are those:

- who have at least a 3 month history of chronic migraine meeting the diagnostic criteria listed in the International Classification of Headache Disorders (ICHD)-3 beta (Appendix B)
- who migraine started prior to the age of 50.
- not currently taking a migraine preventive or has been taking preventive for at least 30 days prior to screening and agrees to not start, stop, or change any medications and/or dosage during the study period.

6 STUDY DRUG

Subjects will receive study drug (ISIS 546254, 200 mg/mL, 1 mL or placebo) which will be provided by Ionis Pharmaceuticals, Inc. All doses will be given by subcutaneous (SC) injection at a volume of 1.00 mL and will be administered at the same volume weekly thereafter through week 16.

Those randomized to ISIS 546254 will receive subcutaneous injections containing 1.00 mL (200mg) weekly for weeks 1-16 of ISIS 546254.

Those randomized to placebo will receive 1.00 mL during weeks 1-16

Unblinded personnel will label and package all study kits provided to subjects following standard operating procedures. The study drug will be drawn by an unblinded staff member. The first dose of study drug will be administered under supervision of the unblinded staff at the study site. Thereafter the study drug may be self-administered per dosing schedule if desired by the subject. All subjects will have the option to return to the site for injections by the unblinded staff member if they prefer.

stable regimen for 30 days prior to and throughout the study period and to be experiencing ≥15 headaches per month despite prophylaxis.

11 INCLUSION/EXCLUSION CRITERIA

Subjects who meet all of the following inclusion criteria and none of the exclusion criteria will be enrolled.

11.1 Inclusion Criteria

Potential subjects must meet the following criteria at the screening visit to enter this study:

1. male or female, in otherwise good health, 18 to 65 years of age.
2. history of chronic migraine meeting the diagnostic criteria listed in the International Classification of Headache Disorders (ICHD-III beta version, 2013), as follows:
    a. History of frequent headaches suggestive of chronic migraine (15 or greater days of qualifying headaches per month) for at least three months prior to screening
    b. Verification of headache frequency through prospectively collected baseline information during the 28-day run-in phase demonstrating headaches on at least 15 days, with at least 8 days per month fulfilling any ONE of the following;
        i. Qualify as being a migraine attack
        ii. Relieved by migraine specific acute medications
3. onset of migraine before age 50.
4. stable pattern of migraine pattern for at least 3 months prior to screening.
5. not currently taking a migraine preventive **OR** has been taking a stable dose of a preventive for at least 30 days prior to screening and agrees to not start, stop, or change medication and/or dosage during the study period.
        i. Subjects on migraine preventative should have stable headache pattern
        ii. Injections of onabotulinumtoxinA are allowable if subject has completed at least 2 injection cycles and agrees to maintain a regular injection cycle for the duration of the study
6. females must be either surgically sterile (e.g., tubal occlusion such as bilateral tubal ligation, hysterectomy, bilateral salpingectomy, bilateral oophorectomy) **OR** post-menopausal (>12 months since last period) **OR** if of child-bearing potential, using an acceptable contraceptive method during, and for 97 days (approximately 5 half-lives of ISIS 546254) after the last dose of study drug.
7. males must be surgically sterile, abstinent, **OR** if engaged in sexual relations of child-bearing potential, the subject must be using an acceptable contraceptive

after their last dosage of IP and receive a phone call at 3 months after last dose to complete for safety assessments. During the treatment and follow-up phases of the study, all patients will have samples taken every two weeks for hematology testing to monitor platelet levels.

12.1 VISIT 1 – SCREENING (Day -28)

The following will be completed at Visit 1:

1. Obtain written Informed Consent. The informed consent will be obtained in accordance with Good Clinical Practices (GCP) and all applicable regulatory requirements from each subject prior to participation in the study.
2. Verify Inclusion/Exclusion Criteria. Subjects will meet all the inclusion and none of the exclusion criteria.
3. Obtain demographics.
4. Obtain medical, medication, and headache history. Data collected will include medical history and diagnoses, age at onset of migraine and other pertinent migraine/headache history, history of acute and prophylactic headache medications within the past 30 days, and history of other recent/concomitant medications.
5. Perform urine pregnancy test, if appropriate. Results of the pregnancy test must be negative to continue in study.
6. Perform physical and neurological examinations.
7. Measure vital signs.
8. Perform electrocardiogram (ECG).
9. Perform urine drug screen.
10. Administer Columbia-Suicide Severity Rating Scale (C-SSRS).
11. Clinical laboratory sample collection for testing hematology, chemistry, PK, biomarkers and urinalysis.
12. Serology for human immunodeficiency virus (HIV), Hepatitis B and C.
13. Instruct subject on diary completion.

12.2 VISIT 2 – RANDOMIZATION (Day 0)

1. Verify Inclusion/Exclusion Criteria. Subjects must continue to meet all inclusion and none of the exclusion criteria.
2. Perform urine pregnancy test, if appropriate. Results of the pregnancy test must be negative to continue in study.
3. Perform brief physical and collect vital signs.
4. Record any changes to concomitant medications.
5. Record any Adverse Events (AE) since signing the Informed Consent.
6. Review Baseline Headache Diary for completeness and continuing eligibility.
7. Perform urine drug screen.
8. Clinical laboratory sample collection for testing hematology, chemistry, PK, biomarkers, plasma for anti-drug antibody screening, and urinalysis.
9. Randomize subject.
10. Review Diary instruction (same instructions as Baseline Headache Diary).
11. Administer Columbia-Suicide Severity Rating Scale (C-SSRS).
12. Administer first dose of study drug (1.00 mL).

accordance with the safety requirements outlined in the adverse event reporting section of this protocol.

23 ADVERSE EVENTS

The investigator will be responsible for the detection, collection, and evaluation of all events meeting the definition of an adverse event (AE). An adverse event is defined as any untoward medical occurrence in a subject or clinical investigation subject administered a medicinal product and which does not necessarily have a causal relationship with the study product. An adverse event can therefore be any unfavorable and unintended sign (including abnormal laboratory finding), symptom, or disease temporally associated with the use of the study product, whether or not related to the study product.

An adverse event observed after the initial dose of the study product will be considered a "treatment-emergent adverse event". Treatment-emergent adverse events will be analyzed and discussed in the clinical study report for this study. Adverse event terms should include a diagnosis, as available, in preference to the listing of individual signs and symptoms. If a diagnosis is not possible, each sign and symptom should be recorded as an individual adverse event.

All adverse events, whether or not related to the study drug, must be completely documented on the appropriate adverse event eCRF (electronic case report form) page. If a subject is withdrawn from the study due to an adverse event, this must also be recorded on the appropriate eCRF pages.

The site staff must record all directly observed AEs and all spontaneously reported AEs. At each visit, the site staff will ask the subject a non-specific question (e.g., "Have you noticed any change in your health since your last visit?") to assess AE occurrence since the last report or visit.

23.1 Non-Serious Adverse Event (NSAE)

Non-serious adverse events (NSAE) will be collected beginning after the first dose of study medication of treatment and will include any change from the subject's condition at Visit 2 though the last follow up phone call 3 months post treatment. These include physical findings, clinical signs and symptoms, or sequelae. Any worsening (i.e. any clinically significant adverse change in the frequency and/or intensity) of a preexisting condition which is temporally associated with the use of the provided product, is also considered to be an adverse event. Events such as elective medical/surgical procedures or anticipated day-to-day fluctuations of pre-existing conditions present at screening that do not worsen are not considered NSAE's.

All NSAE's noted will be captured on the non-serious adverse events eCRF. Information captured will include start date/time, end date/time, severity, relationship of causality to study drug, course of action taken, and outcome.

23.2 Serious Adverse Event (SAE)

An serious adverse event (SAE) is defined as any untoward medical occurring after signing of the informed consent and until cessation of the study which:

1. results in death.
2. is life threatening (Note: The term "life-threatening" in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.).
3. requires subject hospitalization or prolongation of existing hospitalization.
4. results in persistent or significant disability/incapacity; or a congenital anomaly/birth defect.
5. Important medical events that may not result in death, are not life-threatening, or do not require hospitalization may also be considered serious when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse

Medical or scientific judgment should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the definition above. These should also be considered serious.

SAE's will be reported in compliance with all applicable safety reporting requirements as set forth in the Code of Federal Regulations. SAE's assessed as life threatening or death "possibly related to the study medication" will be reported to Clinvest, Sponsor, and Sterling IRB within 24 hours of knowledge of the event by study staff. All other SAE's (such as hospitalization, disability, congenital anomaly, and an important medical event) will be reported to Clinvest, Sponsor, and Sterling IRB within 48 hours of knowledge of the event by study staff. A MedWatch Form FDA 3500A will also be completed and forwarded to Sponsor and Clinvest.

Included in the SAE Report Form will be an assessment of the causal relationship between the Study IP and the SAE. SAE's will be followed by study staff until the event(s) have returned to normal, stabilized, or have been otherwise explained, for at least 2 weeks following the last dose of study drug.

If the investigator learns of any SAEs after a subject has been discharged from the study and he/she considers the event reasonably related to the investigational product, the investigator will notify Clinvest.

24 SAFETY MONITORING RULES

In addition to the standard monitoring of clinical safety parameters, the following guidelines are provided for the monitoring of selected parameters chosen based on preclinical and clinical observations.

Confirmation Guidance: At any time during the Study (Treatment or Post-Treatment Periods), the initial clinical laboratory results meeting the safety monitoring criteria presented below **must be confirmed** by performing measurements (ideally in the same laboratory that performed the initial measurement) on new specimens. All new specimen collections should take place as soon as possible (ideally within 3 days of the initial collection). For stopping rules, if the initial laboratory result is observed during the Treatment Period, the results from the retest **must be available** prior to administering the next dose of Study Drug (ISIS 546254 or placebo).

Re-dosing Guidance: Subjects with initial laboratory test values that reach a stopping rule must not be re-dosed until the re-test results are available. In general, subjects who do not meet the stopping rules based upon retest may continue dosing. However, the Investigator and study drug manufacturer (Ionis Pharmaceuticals Inc.) should confer as to whether additional close monitoring of the subject is appropriate. If any of the stopping criteria described below (Section 25) are met, the subject will be permanently discontinued from further treatment with Study Drug, evaluated fully as outlined below and in consultation Ionis Pharmaceuticals or appropriately qualified designee, and will be followed up in accordance with Section 23 of the protocol.

24.1 Safety Monitoring Rules for Liver Chemistry Tests

The following rules are adapted from the draft guidance for industry, "Drug-Induced Liver Injury: Premarketing Clinical Evaluation," issued by the U.S. Department of Health and Human Services, Food and Drug Administration, July 2009. For a definition of Baseline, please refer to guidance in Section 8.5 above.

In the event of an ALT or AST measurement that is > 3 x ULN (or the greater of 2 x baseline value or 3 x ULN if the baseline value was > ULN) at any time during the Study (Treatment or Post-Treatment Period), the initial measurement(s) should be confirmed as described above. Additional, confirmatory measurements should also be performed if ALT or AST levels increase to 5 x ULN.

Frequency of Repeat Measurements: Subjects with confirmed ALT or AST levels > 3 x ULN (or the greater of 2 x baseline value or 3 x ULN if the baseline value was > ULN) should have their liver chemistry tests (ALT, AST, ALP, INR and total bilirubin) retested at least once-weekly until ALT and AST levels become ≤ 1.2 x ULN *(* or 1.2 x baseline value if the baseline value was > ULN).

4. Macroscopic hematuria (spontaneous or lasting > 24 hours if associated with an intervention)
5. Spontaneous rectal bleeding; epitastaxis, gingival bleeding, hemoptysis, hematemesis
6. Bleeding after venipuncture for > 5 minutes

25 STOPPING RULES

25.1 Liver Chemistry Elevations

In the event of laboratory results meeting the following criteria, **and the event is without an alternative explanation,** dosing of a subject with Study Drug will be stopped permanently; values that are not confirmed due failure to retest or missing lab values will be presumed confirmed:

1. ALT or AST > 8 x ULN, which is confirmed
2. ALT or AST > 5 x ULN, which is confirmed and persists for ≥ 2 weeks
3. ALT or AST > 3 x ULN (or the greater of 2 x baseline value or 3 x ULN if the baseline value was > ULN), which is confirmed **and** total bilirubin > 2 x ULN or INR > 1.5
4. ALT or AST > 3 x ULN (or the greater of 2 x baseline value or 3 x ULN if the baseline value was > ULN), which is confirmed, and the new appearance (i.e. onset coincides with the changes in hepatic enzymes) of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or concomitant eosinophilia (> ULN)

25.2 Renal Function Test Results

In the event of laboratory results for either of the following criteria, dosing of a subject with Study Drug (ISIS 546254 or placebo) will be stopped permanently:

1. Confirmed serum creatinine increase that is both ≥ 0.3 mg/dL (26.5 μmol/L) and ≥ 40% above Baseline creatinine values
2. Proteinuria, dipstick 2 + (confirmed by dipstick retest and then further confirmed by a quantitative total urine protein measurement of > 1.0 g/24 hour)

The follow-up schedule for any events meeting either of these stopping criteria will be determined by the Investigator **in consultation with** Ionis Pharmaceuticals or designee.

25.3 Platelet Count Results

In the event of a confirmed platelet count less than 100,000/mm^3, dosing of a subject with Study Drug (ISIS 546254 or placebo) will be stopped permanently. The follow-up schedule for any

36.4 ECG

Twelve-lead ECG will be performed at the study site, per institutional guidelines, at all study visits. At each of these visits, 1 ECG reading will be collected and will be reviewed by the investigator. The overall interpretation and determination of the clinical relevance of ECG findings will be the responsibility of the investigator and will be recorded in the patient's eCRF.

36.5 Laboratory Assessments

Laboratory assessment samples are to be obtained at designated visits as detailed in the Schedule of Assessments.

36.6 List of Laboratory Analytes

Based on emerging data from this or future studies, additional tests not listed below may be performed on stored samples to better characterize the profile of ISIS 546254 or other similar oligonucleotides

Table 2. Laboratory assessments

Clinical Chemistry Panel	**Screening Tests**	**Hematology**	**Inflammatory**

• Sodium
• Potassium
• Chloride
• Bicarbonate
• Total protein
• Albumin
• Calcium
• Magnesium
• Phosphorus
• Glucose
• BUN
• Creatinine
• Cholesterol
• Uric Acid
• Total bilirubin
• Direct bilirubin (conjugated)
• Indirect bilirubin (unconjugated)
• ALT
• AST
	• Hepatitis B surface antigen
	• Hepatitis C antibody
	• HIV antibody
	• Drug/EtOH
	• C1 Esterase Inhibitor Functional Activity
	• Thyroid Panel
	
	Females only
	• FSH
	• Serum βhCG
	• Urine Pregnancy
	
	Coagulation
	• aPTT (sec)
	• PT (sec)
	• INR
		• Red blood cells
		• Hemoglobin
		• Hematocrit
		• MCV, MCH, MCHC
		• Platelets
		• White blood cells
		• WBC Differential (% and absolute)
		  • Neutrophils
		  • Eosinophils
		  • Basophils
		  • Lymphocytes
		  • Monocytes
		
		Pharmacokinetics
		1. ISIS 546254 levels in plasma
			1.Hs-CRP
			
			Urinalysis
			• Color
			• Appearance
			• Specific gravity
			• pH
			• P/C Ratio
			• Protein
			• Blood
			• Ketones
			• Urobilinogen
			• Glucose
			• Bilirubin
			• Leukocyte esterase
			• Nitrate
			• Microscopic examination[1]

- Alkaline phosphatase
- Creatinine kinase
- GGT

[1] Will be performed on abnormal findings unless otherwise specified

Hematology, clinical chemistry, urinalysis laboratory, urine drug screen, HIV, HbsAg, and HCV serology will be performed at sites local laboratory. Plasma samples for anti-drug-antibody screening will also be collected and stored for potential future analysis. Reference ranges will be supplied by local laboratory and used by the Investigator to assess the laboratory data for clinical significance and pathological changes.

37 FUTURE BIOMEDICAL RESEARCH

Blood samples will be collected from all patients who consent to participate in the optional Future Biomedical Research substudy. If possible, the samples to be used in the substudy will be obtained at the same time that the patient is scheduled to have blood drawn for clinical laboratory assessments as required at the Screening visit for the main study. All samples collected for the substudy will be sent to the designated central laboratory and later shipped to a biorepository for storage. Samples collected for the substudy may be stored at the biorepository for potential analysis under separate protocols for up to 15 years. Substudy samples may be stored for a longer time if a regulatory or governmental authority has active questions that are being answered. In this special circumstance, such substudy samples will be stored until these questions have been adequately addressed.
All patients enrolled in the clinical trial will be considered for enrollment in the Future Biomedical Research substudy; however, participation is optional and will require a separate informed consent form. A patient who initially consents can withdraw that consent at any time and have his or her substudy sample destroyed, including any by-products of the sample.

38 SUMMARY OF METHODS OF DATA COLLECTION

Data required for the evaluation of the primary and some secondary measures will be recorded by subjects using a daily e-diary. The following data will be collected daily with the e-diary:

- Onset and duration of headache
- Severity of headache (mild, moderate, or severe)
- Acute headache medication(s) usage
- Study drug usage
- Associated symptoms
- Unusual symptoms

Questionnaire data required to be directly collected from subject will be obtained at each appropriate visit using an electronic device as defined in the protocol. Questionnaires are to be completed by the subject and the answers to the questions on the questionnaires should come directly form the subject directly, not from family, friend or the study personnel.

2. Compare the efficacy of ISIS 546254 in the preventive treatment of chronic migraine, measured by mean change in the monthly headache days comparing baseline to the final month of the 4-month treatment period for subjects treated with ISIS 546254 vs. placebo.
3. Compare the proportion of patients meeting 50% response criteria, response defined as a ≥ 50% reduction in the number of headaches from baseline to the final month of the 4-month treatment period for subjects treated with ISIS 546254 vs. placebo.
4. Compare the change in frequency in the number of headache days requiring use of medication for the treatment of migraine or headache pain (i.e., acute and rescue or breakthrough medication use) from baseline to the final month of the 4-month treatment period for subjects treated with ISIS 546254 vs. placebo.
5. Compare change from baseline to the final month of the 4-month treatment period in the Migraine Specific Quality of Life (MSQ) Questionnaire for subjects treated with ISIS 546254 vs. placebo.
6. Compare the end of treatment month 4 in the physician global impress of change (PGIC) for subjects treated with ISIS 546254 vs. placebo.
7. Compare the end of treatment month 4 in the subjects' global impression of change (SGIC) for subjects treated with ISIS 546254 vs. placebo.

42 COLLECTION AND DERIVATION OF ENDPOINTS

Data required for the evaluation of endpoints will be recorded for the duration of the study using electronic data capture and include subject reported outcomes. The headache variables will be derived from variables collected daily using an electronic headache diary. On each day, the subject will be asked to record their diary data for the previous 24-hour period.

42.1 Primary Efficacy Variable

1. The variable used to measure mean change in migraine days will be derived from subjects self-reported data entered into the e-diary. It will be based on the number of days with migraine headaches, fulfilling ICHD-3 beta criteria, and/or headaches of any duration with the use of migraine-specific acute headache medication(s).

42.2 Secondary Efficacy Variables

1. The variable used to measure mean change in headache severity will be derived from subjects self-reported data entered into the e-diary. It will be based on the severity recorded for each headache.
2. The variable used to measure mean change in headache days will be derived from subjects self-reported data entered into the e-diary. It will be based on the number of days recorded as headache.
3. The variable used to measure the proportion of subjects experiencing a 50% reduction in the number of headaches will be derived from subjects self-reported data entered into the e-diary. It will be based on the number of days recorded as headache.

4. The variable used to measure change in frequency of headache days requiring medication usage will be derived from subjects self-reported data entered into the e-diary. It will be based on the total number of days that any acute, rescue, or breakthrough medication use is recorded in the e-diary.
5. The variable used to measure change in the MSQ score will be derived from the total score on the MSQ subject questionnaire.
6. The variables used to measure PGIC and SGIC scores will be derived from the total score on the PGIC and SGIC subject questionnaires.

7 BACKGROUND & STUDY RATIONALE

Migraine is a highly prevalent neurovascular disorder that affects a significant proportion of the adult population worldwide: up to 6% of males and 18% of females, with the highest prevalence occurring between 25 and 55 years of age. Migraine represents an enormous socio-economic burden to the individual as well as to the society and affects the quality of life. A migraine attack is characterized by recurrent, severe, debilitating headache associated with nausea, vomiting, photophobia, phonophobia, and/or osmophobia, and fatigue, along with other disturbances in autonomic, mental, sensory and motor functions. Migraine attacks typically last 4 to 72 hours and may be precipitated by endogenous factors (i.e., hormonal changes, psychosocial stress, sleep deficit or surplus, hunger), or by exogenous factors (i.e., certain kinds of food; stimulation of different sensory modalities). Migraine attacks can be preceded by abnormal visual, sensory, motor and/or speech functions (migraine with aura) or start with no warning signs (migraine without aura).

Chronic migraine (CM), defined as migraine occurring on ≥ 15 days per month, is a disabling neurological condition with an estimated global prevalence of up to 4 - 5%, and represents approximately half of all cases of chronic primary headache (Stovner et al. 2006; Stovner et al. 2007; Diener et al. 2012; Paemeleire et al. 2014). Episodic migraine (EM) has a complex relationship with CM as approximately 2.5–3 % of EM patients per year evolve into a CM state (‘‘progression’’) and CM can remit back to EM, with a 2-year remission rate of around 25%(Bigal 2008; Manack 2011). CM patients are most commonly females in their 40s and have longer attacks, experience greater pain severity, are more disabled, and more likely to have a lower quality of life than patients with EM (Paemeleire et al. 2014). Mood and anxiety disorders, respiratory disorders and cardiac risk factors, including hypertension, diabetes mellitus and high cholesterol, were also reported significantly more by CM patients (Buse et al. 2010).

Treatment of Chronic Migraine

The goal of CM treatment is to reduce the frequency and severity of attacks and return the patient to an episodic pattern and includes counseling on risk factors such as caffeine and analgesic use and stress management. Drug therapy for prevention of migraine revolves around a variety of nonspecific drugs that primarily reduce neuronal hyperexcitability, the putative pathophysiological hallmark for migraine.

Various pharmacologic classes of medication are used for migraine prophylaxis. Four of the more effective classes include effective classes include beta blockers, anticonvulsants, calcium antagonists, tricyclic antidepressants. In the US, topiramate and valproate sodium are approved for migraine prophylaxis, and botulinum toxin type A (BoNT-A) is approved for prophylaxis of CM. Regardless of class, effect sizes are modest and data from randomized, placebo-controlled trials (RCT) is scant. Topiramate, one of the best-studied medications, established efficacy at a daily dose of 100 mg during 16 weeks via two multicenter, parallel-group RCT in Europe (59 patients) and the USA (328 patients) (Diener et al. 2007; Silberstein et al. 2007). The topiramate studies demonstrated a mean reduction in monthly migraine days of 3.5 (versus a reduction of 0.2 for placebo) and a number needed-to-treat of 12.5. There is no standard definition for drug refractory CM, but generally at least three or four drugs should have been adequately tested

method as defined in Section 14 during and for at least 97 days after the last dose of study drug.

8. completion of online diary must be ≥ 80 % compliance, unless otherwise approved by Clinvest.
9. must have given written, informed consent and obtain any authorizations required by local law.
10. be able and willing to comply with all study requirements.

11.2 Exclusion Criteria

Potential subjects meeting any of the following criteria will be excluded from entering this study:

1. unable to understand the study requirements, the informed consent, or complete headache records as required per protocol.
2. pregnant, actively trying to become pregnant, or breast-feeding.
3. history of medication overuse (MO) of opioids, or butalbital, as defined by ICHD-3 beta criteria and/or MO during baseline period (Appendix C).
4. history of substance abuse and/or dependence, in the opinion of the Investigator.
5. unstable neurological condition or a significantly abnormal neurological examination with focal signs or signs of increased intracranial pressure.
6. suffers from a serious illness, or an unstable medical condition, one that could require hospitalization, or could increase the risk of adverse events.
7. any psychiatric condition with psychotic features, and/or any other psychiatric disorder not stable or well controlled, that would interfere in the ability to complete study activities.
8. history of thrombocytopenia.
9. history of bleeding, diathesis or coagulopathy
10. use of any anticoagulant
11. received any investigational agents within 30 days prior to Visit 1, or 5 half-lives of study drug, whichever is longer.
12. has significant risk of suicide, defined as a "yes" answer to any of the following questions on the Columbia-Suicide Severity Rating Scale (C-SSRS), either at the screening visit (when assessing the prior 12 months) or at visit 2 (when assessing time since the screening visit):
    a. Questions 4 or 5 on the suicidal ideation section
    b. Any question on any item in the suicidal behavior section
13. plans to participate in another clinical study at any time during this study.
14. malignancy within 5 years, except for basal or squamous cell carcinoma of the skin or carcinoma in situ of the cervix that has been successfully treated.
15. treatment with any non-Ionis oligonucleotide (including siRNA) at any time or prior treatment with an Ionis oligonucleotide within 6 months of screening. Subjects that have previously received only a single dose of an ISIS oligonucleotide as part of a clinical study may be included as long as a duration ≥4 months elapsed since dosing.

13. Dispense and instruct subjects on how to inject study drug. Subjects will also be educated on prohibited medications, dosage limitations of study drug, and storage requirements. Subjects will be instructed to return all used/partially used/unused study drug at next office visit to the unblinded staff and drug reconciliation will be performed.
14. Administer MSQ.
15. Schedule Visit 3.

12.3 PHONE CALL 1 – SAFETY FOLLOW UP (DAY 1)

1. Record any changes to concomitant medications.
2. Record any Adverse Events.
3. Answer any subject questions on IP administration.

12.4 PHONE CALL 2 – SAFETY FOLLOW UP (DAY 2)

1. Record any changes to concomitant medications.
2. Record any AEs.
3. Answer any subject questions on IP administration.

12.5 HEMATOLOGY SAMPLE COLLECTION (DAY 14 +/- 3 DAYS)

1. Patient to submit sample through contract lab

12.6 VISIT 3 – END OF TREATMENT MONTH 1 (DAY 28 +/- 3 DAYS)

1. Perform urine pregnancy test, if appropriate. Results of the pregnancy test must be negative to continue in study.
2. Perform brief physical and collect vital signs.
3. Record any changes to concomitant medications.
4. Record any AEs.
5. Review Diary for completeness maintaining an 80% compliance and continuing eligibility.
6. Clinical laboratory sample collection for testing hematology, chemistry, PK, biomarkers, plasma for anti-drug antibody screening, and urinalysis.
7. Collect unused study drug and used packaging.
8. Unblinded staff to perform drug accountability.
9. Administer Columbia-Suicide Severity Rating Scale (C-SSRS).
10. Dispense and review how to inject study drug, prohibited medications, dosage limitations of study drug, and storage requirements. Subjects will be instructed to return all used/partially used/unused study drug at next office visit to unblinded staff .
11. Schedule Visit 4.

12.7 HEMATOLOGY SAMPLE COLLECTION (DAY 42 +/- 3 DAYS)

1. Patient to submit sample through contract lab

12.8 VISIT 4 – END OF TREATMENT MONTH 2 (DAY 56 +/- 3 DAYS)

1. Perform urine pregnancy test, if appropriate. Results of the pregnancy test must be negative to continue in study.
2. Perform brief physical and collect vital signs.

Further Investigation into Liver Chemistry Elevations: For subjects with confirmed ALT or AST levels > 3 x ULN (or the greater of 2 x baseline value or 3 x ULN if the baseline value was > ULN), the following evaluations should be performed:

1. Obtain a more detailed history of symptoms and prior and concurrent diseases
2. Obtain further history for concomitant drug use (including nonprescription medications, herbal and dietary supplement preparations), alcohol use, recreational drug use, and special diets
3. Obtain a history for exposure to environmental chemical agents and travel
4. Serology for viral hepatitis (HAV IgM, HBsAg, HCV antibody, CMV IgM, and EBV antibody panel)
5. Serology for autoimmune hepatitis (e.g., antinuclear antibody (ANA))

Additional liver evaluations, including gastroenterology/hepatology consultations, hepatic CT or MRI scans, may be performed at the discretion of the Investigator, in consultation with Ionis Pharmaceuticals. Repetition of the above evaluations should be considered if a subject's ALT and/or AST levels reach 5 x ULN.

24.2 Safety Monitoring Rules for Platelet Count Results

All patients will have platelet measures taken every two weeks for the duration of the study.

24.3 Safety Monitoring for Bleeding Events

Minor bleeding events are those that do not fulfill the criteria for major bleeding or clinically relevant, non-major bleeding events (which are defined below), for example excess bruising, petechiae, gingival bleeding on brushing teeth. If a minor bleeding event occurs, the Investigator should notify Ionis Pharmaceuticles and additional testing of coagulation parameters (aPTT, PT, INR) and platelet count should be performed.

24.3.1 Definition of Major Bleeding Events

1. Fatal bleeding, and/or
2. Symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intra-articular or pericardial, or intramuscular with compartment syndrome, and/or
3. Bleeding causing a fall in hemoglobin level of 2.0 mg/dL (1.24 mmol/L) or more within 24 hours, or leading to transfusion of two or more units of whole or red cells

24.3.2 Definition of Clinically Relevant, Non-Major Bleeding Events

1. Multiple-source bleeding
2. Spontaneous hematoma > 25 cm^2
3. Excessive wound hematoma (not injection site related)

events meeting this stopping criterion will be determined by the Investigator in consultation with Ionis Pharmaceuticles or designee.

26 PREGNANCY

All pregnancies of women participating in the study that occur during the study, are to be reported immediately, and the site must complete the pregnancy form.

Any female patient becoming pregnant during the study will immediately discontinue the study drug. All
patients who become pregnant will be monitored for the outcome of the pregnancy (including spontaneous or voluntary termination). If the pregnancy continues to term, the outcome (health of the infant up to 8 weeks of age), including details of birth and presence or absence of any birth defect, congenital abnormalities, or maternal and newborn complications, will be reported to the sponsor. Any complication of pregnancy during the study and any complication of pregnancy that the investigator becomes aware of after termination from the study will be reported as an adverse event or serious adverse event, as appropriate.
If the pregnancy does not continue to term, 1 of the following actions will be taken:

1. For a spontaneous abortion, report as a serious adverse event.
2. For an elective abortion due to developmental anomalies, report as a serious adverse event.
3. For an elective abortion not due to developmental anomalies, report on the pregnancy form; do not report as an adverse event.

For pregnancies of partners of men participating in the study, Clinvest will determine the procedure to appropriately follow up after notification as described above. All partners who become pregnant and provide appropriate consent will be monitored until the completion or termination of the pregnancy.

27 CLINICAL SUPPLIES

Clinical supplies will be packaged for subjects in accordance to an allocation schedule generated by Clinvest.

28 STORAGE REQUIREMENTS

The study drug and clinical supplies must be received by a designated person at the study site, handled and stored safely and properly, and kept in a secured location to which only the designated staff have access. Clinical supplies and medications are to be dispensed only as defined in the protocol. It is the Investigator's responsibility to keep accurate records of the supplies received, the amount dispensed to and returned by subjects, and the remaining amount at the end of the study. Study staff should not open individual study drug containers prior to dispensing to the subject.

Study drug will be inventoried and accounted for throughout the study. Drug Accountability will be maintained for subjects randomized in the study. Unblinded study staff will record the

Questionnaire data required to be collected directly from clinicians will be obtained at the appropriate visit and recorded in the eCRF per protocol.

39 STATISTICAL ANALYSIS

Subjects will be randomized 1:1 into the treatment groups. Randomization will not include any type of stratification.

An alpha of .05 will be used for statistical significance. All statistical tests will be two-tailed. Descriptive statistics will establish baseline characteristics and adverse event frequency. Data for the safety primary endpoint will be statistically analyzed via Chi-squared analyses and a 2-tailed Repeated Measures ANOVA for the efficacy primary endpoint. Data for each of the secondary outcome measures will be statistically analyzed via a 2-tailed Repeated Measures ANOVA, chi-squared, and/or independent or dependent t-tests as appropriate. All ANOVAs will be followed by univariate post-hoc tests as appropriate. Multiple comparison adjustments will be made if needed.

39.1 Modified Intent-to-Treat Population (mITT)

The modified intent-to-treat (mITT) population will include all randomized subjects who received at least one dose of study drug and obtained at least one primary endpoint measurement after treating. The mITT population will be used for efficacy analyses.

39.2 Safety Population

The safety population will include all randomized subjects who received at least one dose of study drug.

A last observation carried forward (LOCF) method will be utilized to impute missing values within a single headache diary. This type of imputation replaces the missing value with the last observation value obtained. If an e-diary day is not recorded, the day will be considered a non-headache day.

40 PRIMARY ENDPOINTS

1. Compare the number of adverse events and laboratory abnormalities through the study for subjects treated with ISIS 546254 vs. placebo.
2. Compare the efficacy of ISIS 546254 in the preventive treatment of chronic migraine, measured by mean change in the monthly migraine days comparing baseline to the final month of the 4-month treatment period for subjects treated with ISIS 546254 vs. placebo.

41 SECONDARY ENDPOINTS

1. Evaluate the efficacy of ISIS 546254 in the preventive treatment of chronic migraine, measured by mean change in the monthly headache severity comparing baseline to the final month of the 4-month treatment period for subjects treated with ISIS 546254 vs. placebo.

43 APPENDIX A

Proposed Revised International Headache Society Criteria for Migraine Without and With Aura

Headache Classification Committee: J Olesen, et al. The International Classification of Headache Disorders, 3rd edition (beta version). *Cephalalgia*. 2013;33:629-808.

1.1 Migraine without aura

Description:

Recurrent headache disorder manifesting in attacks lasting 4-72 hours.

Diagnostic criteria:

A. At least five attacks1 fulfilling criteria B–D
B. Headache attacks lasting 4-72 hours (untreated or unsuccessfully treated)
C. Headache has at least two of the following four characteristics:
    1. unilateral location
    2. pulsating quality
    3. moderate or severe pain intensity
    4. aggravation by or causing avoidance of routine physical activity (e.g. walking or climbing stairs)
D. During headache at least one of the following:
    1. nausea and/or vomiting
    2. photophobia and phonophobia
    E. Not better accounted for by another ICHD-3 diagnosis.

1.2 Migraine with aura

Description:

Recurrent attacks, lasting minutes, of unilateral fully reversible visual, sensory or other central nervous system symptoms that usually develop gradually.

Diagnostic criteria:

A. At least two attacks fulfilling criteria B and C
B. One or more of the following fully reversible aura symptoms:
    1. visual
    2. sensory
    3. speech and/or language
    4. motor
    5. brainstem
    6. retinal
C. At least two of the following four characteristics:
    1. at least one aura symptom spreads gradually over ≥5 minutes, and/or two or more symptoms occur in succession
    2. each individual aura symptom lasts 5-60 minutes
    3. at least one aura symptom is unilateral
    4. the aura is accompanied, or followed within 60 minutes, by headache
D. Not better accounted for by another ICHD-3 diagnosis, and transient ischemic attack has