Revised Clinical Study Protocol

Drug Substance	ZOMIG (zolmitriptan)
Study Code	D1220C00001
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A Multicenter, Double-blind, Randomized, Placebo-controlled, 4-Armed Parallel Group Study to Evaluate the Efficacy of Zolmitriptan 0.5-, 2.5- and 5-mg Nasal Spray in the Treatment of Acute Migraine Headache in Adolescents

Sponsor: AstraZeneca AB, 151 85 Södertälje, Sweden

Quintiles Global Project Manager

_____ _____

Date

The following Amendment(s) and Administrative Changes are included in this revised protocol:

Amendment No.	Date of Amendment	Local Amendment No.	Date of Local Amendment
3			

Administrative Change No.	Date of Administrative Change	Local Administrative Change No.	Date of Local Administrative Change

AstraZeneca

PROTOCOL SYNOPSIS

A Multicenter, Double-blind, Randomized, Placebo-controlled, 4-Armed Parallel Group Study to Evaluate the Efficacy of Zolmitriptan 0.5-, 2.5- and 5-mg Nasal Spray in the Treatment of Acute Migraine Headache in Adolescents

International Co-ordinating Investigator

Study centre(s) and number of subjects planned

This will be a global, multicenter study conducted in the United States (US), Latin America, and Europe. A sufficient number of male and female adolescent patients, age 12 to 17 years with an established diagnosis of migraine, will be screened to ensure that approximately 1000 patients (312 in the zolmitriptan 5 mg and placebo arms) are randomized into the study to obtain 800 evaluable patients (250, 150, 150, and 250 patients in the placebo, zolmitriptan 0.5 mg, zolmitriptan 2.5 mg, and zolmitriptan 5 mg treatment groups, respectively). Based on the results from a blinded interim analysis, the sample size could be increased to obtain a maximum of 1036 evaluable patients. Approximately 150 centers will participate in the study.

Study period	Phase of development
Estimated date of first patient enrolled	III
Estimated date of last patient completed	

Objectives

Primary objective: The primary objective of this study is to compare the efficacy of zolmitriptan nasal spray 0.5, 2.5, and 5 mg with placebo in the acute treatment of migraine headache in adolescents (aged 12 to 17), as measured by the primary outcome variable of pain-free status at 2 hours post treatment.

Secondary objectives:

- To evaluate the efficacy of zolmitriptan nasal spray 0.5, 2.5, and 5 mg as compared with placebo in the acute treatment of migraine headache in adolescents (aged 12 to 17 years), as assessed by:
  - pain-free status
  - headache response
  - sustained headache response
  - presence and resolution of associated symptoms of photophobia, phonophobia, or nausea
  - incidence and time to use of rescue medication
  - ability to perform normal activities
  - headache recurrence
  - bilateral headache (yes/no)
  - intensity increased by movement (yes/no)
- To assess safety and tolerability of zolmitriptan when used for the acute treatment of migraine headache in adolescents.

Study design

This is a global, multicenter, double-blind, randomized, placebo-controlled study with a parallel group design to evaluate the efficacy of zolmitriptan 0.5, 2.5, and 5 mg nasal spray in the acute treatment of migraine headache in adolescent patients. Patients will be randomized to treatments in the ratio of 5:3:3:5 for placebo, zolmitriptan 0.5, 2.5, and 5 mg, respectively.

Target subject population

Adolescents, age 12 to 17 years with an established diagnosis of migraine, as defined by the International Headache Society (IHS) or IHS-Revised (IHS- R) criteria (see Appendix D).

Investigational product, dosage and mode of administration

ZOMIG® (zolmitriptan) Nasal Spray 0.5, 2.5, and 5 mg. The nasal spray will contain 1 dose of ZOMIG®.

Comparator, dosage and mode of administration

Placebo for ZOMIG® (zolmitriptan) Nasal Spray. The placebo nasal spray will contain 1 dose of ZOMIG® placebo.

Duration of treatment

Eligible patients will be randomized to 1 of 4 treatment groups (zolmitriptan 0.5, 2.5, 5 mg nasal spray, or matching placebo nasal spray) to treat 1 attack of moderate or severe migraine headache during a 10-week study period after successful completion of the run-in period. When the headache pain reaches moderate to severe intensity, patients will treat it with a single dose of study drug (zolmitriptan 0.5, 2.5, 5 mg nasal spray, or matching placebo nasal spray). Headache response is defined as a reduction in migraine headache pain intensity from severe or moderate at the time of initial treatment to mild or none at a specific assessment time. If the headache pain continues at moderate or severe intensity for at least 2 hours after study drug treatment, patients will be allowed to treat it with an approved rescue medication specified by the investigator.

Outcome variables:

- Efficacy

  Primary outcome variable: pain-free status at 2 hours post treatment.

  Secondary outcome variables:

  - Pain-free status at 15 minutes and at 1, 2, 3, 4, and 24 hours post treatment
  - Headache response at 15 minutes and at 1, 2, 3, 4, and 24 hours post treatment
  - Sustained headache response at 2 hours subsequent to a 1-hour headache response
  - Presence of associated symptoms of photophobia, phonophobia, or nausea at 15 minutes and at 1, 2, 3, 4, and 24 hours post treatment
  - Resolution of associated symptoms of photophobia, phonophobia, or nausea at 15 minutes and at 1, 2, 3, 4, and 24 hours post treatment
  - Incidence and time to use of rescue medication up to 24 hours post treatment
  - Ability to perform normal activities at 15 minutes and at 1, 2, 3, 4, and 24 hours post treatment
  - Headache recurrence 2 to 24 hours post treatment
  - Bilateral headache (yes/no) at 15 minutes and at 1, 2, 3, 4, and 24 hours post treatment
  - Intensity increased by movement (yes/no) at 15 minutes and at 1, 2, 3, 4, and 24 hours post treatment

- **Safety**

  - Incidence, nature, and intensity of AEs; vital signs; physical examination changes; laboratory assessments (ie, chemistry, hematology, and urinalysis); electrocardiogram (ECG); and incidences of suicidal behavior and suicidal ideation as measured by the Columbia-Suicide Severity Rating Scale (C-SSRS).

Statistical methods

Efficacy analyses will be based on the full analysis set (FAS), which will include all randomized treated patients who provide post-treatment efficacy data, classified according to randomized treatment.

Safety and tolerability assessments will be based on the safety analysis set, which will include all randomized treated patients who provide post-treatment safety data, classified according to the treatment actually received.

The primary null hypothesis to be tested is that the different doses of zolmitriptan 0.5, 2.5, and 5 mg are not different from placebo, using pain-free status at 2 hours post treatment as the primary endpoint.

The primary endpoint will be analyzed using a logistic regression model with 2-hour pain-free status as the response variable, and treatment and center as fixed factors in the model. A step-down approach is used for securing the alpha level when comparing the 3 doses of zolmitriptan against placebo for 2-hour pain-free status. Initially, zolmitriptan 5 mg is compared with placebo in terms of odds ratio. If this is significant at the 2-sided 5% level, then zolmitriptan 2.5 mg is compared with placebo and if this is significant at the 2-sided 5% level then zolmitriptan 0.5 mg is compared with placebo at the 2-sided 5% level. If the first comparison between zolmitriptan 5 mg and placebo is not significant, then the zolmitriptan 2.5 mg is not to be compared with placebo, etc. The primary analysis will be based on the FAS with the LOCF approach.

The secondary endpoints will be analyzed at the 5% significance level without multiplicity correction for descriptive purposes.

A total of 2400 patients will be enrolled to ensure 1000 randomized patients, assuming a 56% drop-out rate prior to randomization. Assuming 20% of the randomized patients drop out before treatment of a migraine headache attack, 800 patients (250, 150, 150, and 250 patients in the placebo, zolmitriptan 0.5 mg, zolmitriptan 2.5 mg, and zolmitriptan 5 mg treatment arms, respectively) will be evaluable for the primary analysis. This will provide 80% power to detect a treatment difference at the 2-sided significance level 0.05 if the true difference between zolmitriptan 5 mg treatment and placebo is 0.11 for the primary endpoint of pain-free status at 2 hours.

The power to detect a treatment difference between zolmitriptan 2.5 mg and 0.5 mg versus placebo will be 67% if the true treatment difference is 0.11. A 2-treatment, continuity-corrected, chi-square test of equal proportions is used as an approximation for the intended analysis approach in the power calculations. A difference of 0.11 in response rates is considered a clinically relevant effect. The 2-hour pain-free rate for the placebo treatment group is assumed to be the same as in a previous study (D1221C00005) conducted on zolmitriptan nasal spray in adolescent patients for both periods combined, 0.18.

Since the assumptions for the sample size calculations are uncertain, an interim analysis is planned after approximately one third of the planned patients have been treated. The sample size will be re-estimated at the interim analysis using a blinded estimation of the observed total that were 2 hours pain-free. Depending on the interim results, the sample size can increase to a maximum of 1036 total evaluable patients, requiring approximately 1295 patients to be randomized and 2943 patients to be enrolled.

The interim analysis will be performed by an independent statistician who is not involved with this trial.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

The following abbreviations and special terms are used in this Clinical Study Protocol.

Abbreviation or special term	Explanation
5HT	5-hydroxytryptamine
AE	Adverse event (see definition in Section 6.4.1)
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BMI	Body mass index
BP	Blood pressure
CRO	Contract research organization
CSA	Clinical Study Agreement
CSP	Clinical Study Protocol
CSR	Clinical Study Report
C-SSRS	Columbia-Suicide Severity Rating Scale
DM	Data Management
DMC	Data monitoring committee
ECG	Electrocardiogram
E-code	Enrollment code
eCRF	electronic Case Report Form
eDC	electronic Data Capture
EE	Ethinyl estradiol
ET	Early termination
FAS	Full analysis set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
IATA	International Airline Transportation Association
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
IHS, IHS-R	International Headache Society, International Headache Society-Revised
IPS	Investigational Products
IRB	Institutional Review Board

Abbreviation or special term	Explanation
IVRS	Interactive voice response system
LOCF	Last Observation Carried Forward
MAO-A	Monoamine oxidase inhibitor-A
MedDRA	Medical Dictionary for Regulatory Activities
National Co-ordinating Investigator	If a study is conducted in 1 country with several centers, the National Co-ordinating Investigator is the investigator co-ordinating the investigators and/or activities.
NSAID	Non-steroidal anti-inflammatory drug
OAE	Other significant adverse event (see definition in Section 11.2.1)
OC	Observed case
PI	Principal Investigator: A person responsible for the conduct of a clinical study at an investigational study site. Every investigational study site has a principal investigator
SAE	Serious adverse event (see definition in Section 6.4.2)
SAP	Statistical analysis plan
SDV	Source data verification
SNRI	Serotonin norepinephrine re-uptake inhibitors
SSR	Sample size re-estimation
SSRIs	Selective serotonin re-uptake inhibitors
US	United States

1. INTRODUCTION

1.1 Background

Migraine is a debilitating and recurring neurological disorder affecting approximately 18% of females and 6.5% of males of all ages in the United States (US) population. The prevalence of this disorder increases through the teen years, peaking at approximately 40 years of age. There is a considerable risk of developing migraine during childhood, and a publication reports a 1-year prevalence of migraine in 7- to 15-year-olds to be 11%, diagnosed according to the International Headache Society (IHS) criteria. Prevention and treatment of migraine are particularly important in teenage girls, since they have a high prevalence (17% in 13- to 15-year-old girls), frequent attacks, and a poor outcome.

Although the pathogenesis of migraine in adolescents (ages 12 to 17) is considered to be similar to that in adults, the clinical characteristics of migraine in adolescents can differ substantially from those in adults. Older adolescents (>15 years of age) have migraines that mimic the adult migraine, ie, unilateral and greater than 4 hours in duration. In younger adolescents (≤15 years of age), the location of headaches is usually bilateral, and the minimum duration is generally less than the typical 4 hours required to consider the diagnosis in adults. These clinical differences have led to significant challenges in convincingly demonstrating efficacy of triptans in adolescents. Most studies have failed using their identified primary endpoint, and demonstrated high placebo response rates. Placebo response rates are typically close to 50% at 2 hours with respect to the headache response endpoint, likely due to the variable/short duration of adolescent migraines.

Despite these challenges, there is still reason to believe that triptans are efficacious in the adolescent population. For example, sumatriptan nasal spray at 10 and 20 mg doses was superior to placebo at 1 hour post dose. Superiority was lost for both doses at 2 hours. However, the 5 mg dose was superior to placebo, 66% versus 53% ($p<0.05$), respectively, at 2 hours (Winner et al 2000). Likewise, rizatriptan 5 mg also failed to differentiate from placebo at 2 hours for both headache response and pain-free rates, but a small subgroup analysis suggested that it was effective when freely accessible, such as on weekends (Winner et al 2002).

Because of the high placebo rates, enrichment has been used as a strategy to enhance the likelihood of demonstrating efficacy. Using both a unique placebo challenge/cross-over design, ZOMIG® (zolmitriptan) Nasal Spray 5 mg demonstrated potential efficacy in adolescents (Trial D1221C00005) in contrast to ZOMIG® tablets at doses of 2.5, 5, and 10 mg (Trial 311CUS/0005), which failed to differentiate from placebo at any dose at any timepoint using a standard parallel group design. However, the US Food and Drug Administration (FDA) did not consider this study an adequate test of zolmitriptan nasal spray in adolescents. Most recently, a randomized, controlled trial was able to demonstrate a significant treatment effect of orally administered almotriptan at the 2-hour timepoint in adolescent patients. This parallel group design enriched the study population by requiring that patients have a longer duration of headaches than typical for this age group, while providing a 30-day lead in period

to ensure that patients meet all entry criteria prior to randomization. This study resulted in the first approval of a triptan in the adolescent population.

The current study design builds on recent advances in understanding both adolescent migraine, as well as trial design in this area. The patient population will be enriched by requiring a history of ≥3-hour headache duration, and a failed-response to a single-blind placebo challenge. All patients will have appropriate history of migraine frequency and the ability to adequately participate in the study evaluated prior to randomization. The study will also have a parallel group design, thereby avoiding issues with possible carryover effects and bias that could be present in a cross-over design. Lastly, the statistical assumptions of the design will be evaluated after randomization of one third of the patients with an interim analysis specifically designed to increase sample size if needed.

More information on the compound can be found in the Investigator's Brochure (IB).

1.2 Research hypothesis

The primary goal of this study is to test the hypothesis that the different doses of zolmitriptan and placebo are not different, as measured by the primary outcome variable of pain-free at 2 hours post treatment in adolescent patients with an established diagnosis of migraine.

1.3 Rationale for conducting this study

This study is being conducted to fulfill the post-marketing study commitment as stated in the approval letter of 30 September 2003 for the acute treatment of migraine headache in adolescents and as required under the US FDA Pediatric Research Equity Act (PREA).

The underlying rationale of the study is to widen treatment options for adolescent migraine patients. In addition to efficacy, this study will also study the safety and tolerability of zolmitriptan in a wide range of doses with a goal of identifying the highest and lowest safe and efficacious dose. Doses of 0.5, 2.5, and 5 mg were chosen because these doses are all efficacious in adults, and represent the full range of approved doses of zolmitriptan nasal spray.

1.4 Benefit/risk and ethical assessment

To date, 1 efficacy study (D1221C00005) and 1 pharmacokinetics study (D122100004) have been conducted with zolmitriptan nasal spray 5 mg in this patient population. Zolmitriptan nasal spray 5 mg was safe and well tolerated by the study patients. Also in adults, the doses of zolmitriptan nasal spray 0.5 mg and 2.5 mg were similarly judged to be safe and well tolerated and are approved doses for the acute treatment of migraine in adults.

The assessment of risks associated with zolmitriptan nasal spray is based on previous clinical experience (including post-marketing safety surveillance) and preclinical safety and toxicology studies. The risks described below were developed both from adult patients and from the limited clinical trial experience with an adolescent population similar to that being studied in this protocol.

Zolmitriptan should only be used where a clear diagnosis of migraine has been established. Care should be taken to exclude other potentially serious neurological conditions. There are no data on the use of zolmitriptan in hemiplegic or basilar migraine. Migraineurs may be at increased risk for certain cerebrovascular events. Cerebral hemorrhage, subarachnoid hemorrhage, stroke and other cerebrovascular events have been reported in patients treated with 5-hydroxytryptamine (5HT) agonists. Zolmitriptan should not be given to patients with symptomatic Wolff-Parkinson-White syndrome or arrhythmias associated with other cardiac accessory conduction pathways. In very rare cases, as with other $5HT_{1B/1D}$ agonists, coronary vasospasm, angina pectoris, and myocardial infarction have been reported. In patients with risk factors for ischemic heart disease, cardiovascular evaluation prior to commencement of treatment with this class of compounds, including zolmitriptan, is recommended. These evaluations, however, may not identify every patient who has cardiac disease, and in very rare cases, serious cardiac events have occurred in patients without underlying cardiovascular disease. As with other $5HT_{1B/1D}$ agonists, atypical sensations over the precordium have been reported after the administration of zolmitriptan. Where such symptoms are thought to indicate ischemic heart disease, no further doses of zolmitriptan should be given and appropriate evaluation carried out. As with other $5HT_{1B/1D}$ agonists, transient increases in systemic blood pressure (BP) have been reported in patients with and without a history of hypertension; very rarely these increases in BP have been associated with significant clinical events. As with other $5HT_{1B/1D}$ agonists, there have been rare reports of anaphylaxis/anaphylactoid reactions in patients receiving zolmitriptan.

Serotonin syndrome has been reported with combined use of triptans, and selective serotonin re-uptake inhibitors (SSRIs) and serotonin norepinephrine re-uptake inhibitors (SNRIs). Serotonin Syndrome is a potentially life-threatening condition, and may include signs and symptoms such as: mental status changes (eg, agitation, hallucinations, coma), autonomic instability (eg, tachycardia, labile BP, hyperthermia), neuromuscular aberrations (eg, hyperreflexia, incoordination), and/or gastrointestinal symptoms (eg, nausea, vomiting, diarrhea). Careful observation of the patient is advised, if concomitant treatment with zolmitriptan and an SSRI or SNRI is given, particularly during treatment initiation and dosage increases.

All efforts will be taken to minimize risk to patients enrolled in this trial. No patient will be enrolled who has had a previous adverse reaction to zolmitriptan or other triptans. Patients with medical conditions that would put them at increased risk for adverse reactions will also be excluded from this study.

In order to ensure that the population enrolled in the study is representative of the patient population at large, individuals who have medically stable chronic conditions will not be excluded. These patients will not be required to stop their treatment for their chronic conditions (eg, high BP) prior to or during the trial. Of particular concern are those patients who are taking SSRI/SNRIs. Concomitant use of a triptan with an SSRI/SNRI has been associated with the Serotonin Syndrome. To minimize this risk, only patients who have been stabilized on an SSRI or SNRI for at least 2 months will be enrolled and no dosage

adjustments of these agents will be allowed. These patients will also be carefully monitored for any signs and symptoms of the Serotonin Syndrome.

Migraine in adolescents is a debilitating neurological condition. At present, only 2 triptan oral formulations (almotriptan and rizatriptan) are approved for acute treatment of migraine in adolescents. This trial will fully explore the efficacy and safety of zolmitriptan nasal spray as an alternative for the acute treatment of migraine. This single-attack trial is specifically designed to minimize risk to patients while potentially identifying a new treatment option for these patients.

2. STUDY OBJECTIVES

2.1 Primary objective

The primary objective of this study is to compare the efficacy of zolmitriptan nasal spray 0.5, 2.5, and 5 mg with placebo in the acute treatment of migraine headache in adolescents (aged 12 to 17 years), as measured by the primary endpoint (outcome variable) of pain-free status at 2 hours post treatment.

2.2 Secondary objectives

The secondary objectives are:

- To evaluate the efficacy of zolmitriptan nasal spray 0.5, 2.5, and 5 mg as compared with placebo in the acute treatment of migraine headache in adolescents (aged 12 to 17 years), as assessed by:
  - pain-free status
  - headache response
  - sustained headache response
  - presence and resolution of associated symptoms of photophobia, phonophobia, or nausea
  - incidence and time to use of rescue medication
  - ability to perform normal activities
  - headache recurrence
  - bilateral headache (yes/no)
  - intensity increased by movement (yes/no).

2.3 Safety objective

The safety objectives are to assess safety and tolerability of zolmitriptan when used for the acute treatment of migraine headache in adolescents.

3. STUDY PLAN AND PROCEDURES

This Clinical Study Protocol (CSP) has been subject to a peer review according to AstraZeneca standard procedures.

3.1 Overall study design and flow chart

This is a global, multicenter, double-blind, randomized, placebo-controlled study with a parallel group design and single-blind run-in period. The study will comprise treatment of a single attack of migraine headache during the run-in period and placebo challenge with 1 dose of single-blind placebo. If the patient meets conditions for randomization, a single attack of migraine headache will be treated with 1 dose of zolmitriptan nasal spray 0.5, 2.5, 5 mg, or matching placebo in a blinded manner. Approximately 1000 patients will be randomized at approximately 150 study sites in the US, Latin America, and Europe.

Adolescent patients, age 12 to 17 years with an established diagnosis of migraine, as defined by the IHS or IHS-Revised (IHS-R) criteria (see Appendix D) will be enrolled in the study. Patients will be screened for eligibility during Visit 1 (screening visit) after the informed consent and assent have been obtained. Medical history, migraine headache history and prior medication history will be obtained, and a complete physical examination (including vital sign measurements), 12-lead electrocardiogram (ECG), laboratory assessments (clinical chemistry, hematology and urinalysis), urine drug screen, urine pregnancy test (for all females), and Columbia-Suicide Severity Rating Scale (C-SSRS) will be performed.

Eligible patients will enter a 30-day run-in period beginning at Visit 1 to establish whether or not the patient has a headache pattern of appropriate severity and duration to qualify for the study. Patients will be dispensed 1 dose of single-blind placebo and will treat 1 episode of migraine headache. Patients will not receive any double-blind, active study drug during the run-in period, but will be permitted – with the exception of the placebo challenge – to treat their migraine(s) headache with their usual migraine treatment medications. For the placebo challenge, the patient should attempt to treat the first migraine headache during the run-in period with single-blind placebo. However, the patient may elect not to treat the first migraine headache experienced during the run-in period. It is most important that the patient treat the first migraine headache which allows for diary and dosing compliance, including accurate and timely completion of all diary assessments, and the ability to follow pre-treatment and post-treatment rules. The patient is not required to treat the first migraine headache experienced during the run-in period if the objectives noted above cannot be met.

At 2 hours after treating with single-blind placebo, if the patient's migraine headache has not responded (ie, not reduced to mild or none), the patient may use rescue medication(s). For

any subsequent migraine episodes, the patient will use their usual acute migraine medication. During this run-in period, patients will be asked to complete a diary of symptoms.

Visit 2 (randomization) occurs at the end of the 30-day run-in period. When the 30-day run-in period is complete, the patient will come in to the study site for Visit 2. At this visit, patients will only be randomly assigned if they did not respond to the placebo challenge, completed their diary correctly, and have the correct untreated headache duration required in the protocol criteria. A responder to placebo challenge is defined as mild or none in headache intensity at 2 hours. A non-responder to placebo challenge is defined as still moderate or severe headache intensity at 2 hours. Patients not treating a migraine headache with blinded placebo during the 30-day run-in period should be considered screen failures.

At Visit 2, eligible patients with an established diagnosis of migraine (moderate or severe) who have met the criteria for randomization (no response to placebo challenge, headache characteristics consistent with the inclusion criteria, and ability to complete the study diary) will be randomized to zolmitriptan nasal spray 0.5, 2.5, 5 mg, or matching placebo spray to treat a migraine headache. Paper patient diaries will be provided to patients to record the severity of the headache (mild, moderate, or severe). Patients will complete the diary for 24 hours for the migraine headache treated with the study drug, as well as record any AEs and medications taken at any time. Further dosing instructions will also be provided during this visit.

Patients are to treat 1 migraine headache with 1 dose of zolmitriptan nasal spray 0.5, 2.5, 5 mg, or matching placebo within 10 weeks of randomization (Visit 2). Headache response is defined as a reduction in migraine headache pain intensity from severe or moderate at the time of initial treatment to mild or none at a specific assessment time.

Before taking the study drug, patients cannot have:

- Treated headache with other medication;
- Received any triptan, ergotamine or ergot-type medications (eg, dihydroergotamine or methysergide) in the last 24 hours; or
- Used opiates in the last 24 hours.

If headache pain persists after taking the study drug, approved rescue medication, as agreed by the treating physician, is permitted after 2 hours post-study treatment. Triptans and ergots are not allowed as rescue medications. Allowable drugs include non-steroidal anti-inflammatory drugs (NSAIDs), antiemetics, analgesics (eg, opioids), and sedatives. Rescue medications will not be provided by AstraZeneca.

After taking the study drug, patients may not:

- Sleep or nap for 2 hours;

- Use rescue medications for 2 hours;
- Use other triptan or any ergotamine or ergot-type medications (eg, dihydroergotamine or methysergide) for 24 hours.

Patients will be allowed to continue throughout the study on medications normally taken for migraine prophylaxis, or to correct a long-standing condition provided the condition is stable in the investigator's opinion and that this ongoing treatment won't be adversely affected by study participation.

If there is no treatment with study drug within 4 weeks of randomization, patients will return to the study site for the interim visit to review the study dosing instructions.

Patients will have approximately 14 weeks to complete the study, which consists of a 30-day run-in period followed by 10 weeks to complete treatment. Patients will return to the study site after treating a single migraine headache within 2 weeks of using the study drug for the final study visit (Visit 3), or within 10 weeks after randomization (Visit 2) if no migraine headache is treated. At that time, end-of-study assessments (physical examination, vital signs, prior and concomitant medications, ECG, laboratory assessments, pregnancy tests for females, adverse event (AE) assessments, and C-SSRS) will be performed. The nasal spray device will be returned. Patient diaries will be returned and reviewed.

An interim analysis will be performed during the study to re-estimate the sample size based on blinded data for the observed total response rates for pain-free at 2 hours.

3.1.1 Visit 1 (Screening/run-in period and placebo challenge)

The following procedures will be performed at Visit 1:

- Signed informed consent (parent or legal guardian);
- Signed assent by patient;
- Review of inclusion and exclusion criteria;
- Demography (date of birth, sex, and race);
- Review of all relevant medical history for 1 year (12 months) and relevant surgical history;
- Review of migraine headache history;
- Review of prior and concomitant medications for 1 year (12 months);
- Vital signs (BP and pulse, and oral body temperature);
- Physical examination;

- Height will be recorded;
- Weight will be measured;
- 12-lead ECG;
- Blood samples will be collected for laboratory assessments (clinical chemistry and hematology);
- Urine sample will be collected for urine drug screen to test for drug abuse and for urinalysis;
- Urine pregnancy test (for all females);
- C-SSRS to assess suicidal risk, ideation, and behavior;
- Placebo nasal spray device will be dispensed and study dosing instructions will be provided for the placebo challenge portion of the study. Dosing instructions will include training the patient on how to use the nasal spray by using the training device provided to the investigator;
- The practice paper patient diary will be dispensed for the placebo challenge portion of the study and instructions will be provided to record symptoms, AEs, and medications;
- After other eligibility criteria are met, the patient will begin the run-in period.

During the run-in period, the patient should attempt to treat the first migraine headache during the run-in period with single-blind placebo. However, the patient may elect not to treat the first migraine headache experienced during the run-in period. It is most important that the patient treat the first migraine headache which allows for diary and dosing compliance, including accurate and timely completion of all diary assessments, and the ability to follow pre-treatment and post-treatment rules. The patient is not required to treat the first migraine headache experienced during the run-in period if the objectives noted above cannot be met.

At 2 hours after treating with single-blind placebo, if the patient's migraine headache has not responded (ie, not reduced to mild or none), the patient may use rescue medication(s). For any subsequent migraine episodes, the patient will use their usual acute migraine medication. Patients will be asked to complete a diary of symptoms, and also record any AEs and medications taken at any point during the run-in period. The run-in period will last approximately 30 days prior to Visit 2.

3.1.2 Visit 2 (randomization)

Visit 2 will occur within 30±3 days after Visit 1. The following procedures will be performed after the patient has accurately completed the practice diary, shows headache duration consistent with the study requirements (eg, numerous short duration <1 hour untreated

migraines would not be acceptable), and does not respond to the placebo challenge (see Section 3.1):

- Patient will be randomized;
- Review of migraine headache history;
- Review of prior and concomitant medications for 1 year (12 months);
- Review of inclusion/exclusion criteria;
- Reporting of any AEs since Visit 1;
- Urine pregnancy test (for all females);
- Placebo challenge nasal spray device will be returned;
- Patient diary for the run-in portion of the study will be returned and reviewed;
- Study drug nasal spray device will be dispensed;
- Dosing instructions on how and when to use the study drug nasal spray device will be provided. Dosing instructions will also include training the patient on how to use the nasal spray by using the training device provided to the investigator;
- Detailed instructions for use of the paper patient diary will be provided;
- Additional paper patient diaries for the study drug treatment period will be provided;
- C-SSRS to assess suicidal risk, ideation, and behavior.

3.1.3 Treatment of 1 migraine attack within 10 weeks

Throughout the treatment period, patients will record details of any AEs and medications taken in the diary provided.

If a migraine headache or attack occurs within 10 weeks of randomization (Visit 2), patients will treat it with 1 dose of study drug. Patients will record the details regarding the migraine headache using the diary provided, including AEs and medications.

3.1.4 Interim visit (4 weeks from randomization visit)

If there is no treatment of a migraine headache or attack with the study drug within 4 weeks of randomization (Visit 2), patients will return to the study site to review dosing instructions. Detailed instructions for use of the paper patient diary will also be reviewed. Adverse events that occurred since the last visit will be reported. The interim visit will be captured in the electronic case report form (eCRF), and the visit date and confirmation that dosing and diary

instructions have been provided will be collected. The nasal spray training device will not be used at the interim visit.

3.1.5 Visit 3 (final visit/end-of-study) or early termination (ET) visit

Visit 3 (final visit/end-of-study) will occur after patients have treated 1 migraine attack. Patients will return to the investigative site for the final study visit within 2 weeks after treating 1 migraine attack, or within 10 weeks after Visit 2 (randomization) if no migraine headaches or attacks are treated.

Patients who discontinue early from the study will undergo Visit 3 procedures at the early termination (ET) visit. The following procedures will occur at Visit 3 and at the time of discontinuation (ET visit) from the study:

- Vitals signs (seated BP and pulse, and oral body temperature);
- 12-lead ECG;
- Physical examination;
- Review of concomitant medications;
- Blood samples will be collected for laboratory assessments (clinical chemistry and hematology);
- Urine sample will be collected for urinalysis and pregnancy test (females only);
- Return of study drug nasal spray device;
- Review and return of paper patient diaries;
- Reporting of any AEs since Visit 2;
- C-SSRS to assess suicidal risk, ideation, and behavior.

Table 1 Study plan

Study procedures	Visit 1 (-Day 30 to Day 0)		Visit 2 (30±3 days after Visit 1) Day 0 Randomization	Migraine attack, treatment, and patient's diary recording	Interim visit if no study treatment 4 weeks from randomization[a]	Visit 3 Final visit after treating 1 attack or within 10 weeks after Visit 2 or ET
	Screening	Run-in period and placebo challenge				
Signed informed consent and assent forms	X					
Inclusion/exclusion criteria	X		X			
Demography	X					
Medical & relevant surgical history	X					
Migraine headache history	X		X			
Medications, prior[b] and concomitant	X	X[c]	X	X[c]		X
Physical examination	X					X
Height	X					
Weight	X					
Urine test for drug abuse	X					
Urine pregnancy test	X		X			X
Dispense placebo nasal spray device	X					
Dispense study drug nasal spray device			X			
Dose instructions	X		X		X	
Dispense patient diary	X		X			

Table 1 Study plan

Study procedures	Visit 1 (-Day 30 to Day 0)		Visit 2 (30±3 days after Visit 1) Day 0 Randomization	Migraine attack, treatment, and patient's diary recording	Interim visit if no study treatment 4 weeks from randomization[a]	Visit 3 Final visit after treating 1 attack or within 10 weeks after Visit 2 or ET
	Screening	Run-in period and placebo challenge				
Patient diary instructions	X		X		X	
Administer placebo nasal spray		X[d]				
Administer study drug nasal spray				X		
Patient enters diary data		X[d]		X		
Review and return of patient diaries, and record data on eCRF			X			X
Return placebo nasal spray device			X			
Return study drug nasal spray device						X
Safety assessments						
Vital signs (seated BP and pulse, oral body temperature)	X					X
12-lead ECG	X					X
Laboratory assessments (clinical chemistry, hematology, urinalysis)	X					X
AE reporting		X[c]	X	X[c]	X	X

Table 1 Study plan

Study procedures	Visit 1 (-Day 30 to Day 0)		Visit 2 (30±3 days after Visit 1) Day 0 Randomization	Migraine attack, treatment, and patient's diary recording	Interim visit if no study treatment 4 weeks from randomization[a]	Visit 3 Final visit after treating 1 attack or within 10 weeks after Visit 2 or ET
	Screening	Run-in period and placebo challenge				
Rating scale						
C-SSRS	X		X			X

BP blood pressure; ET early termination.

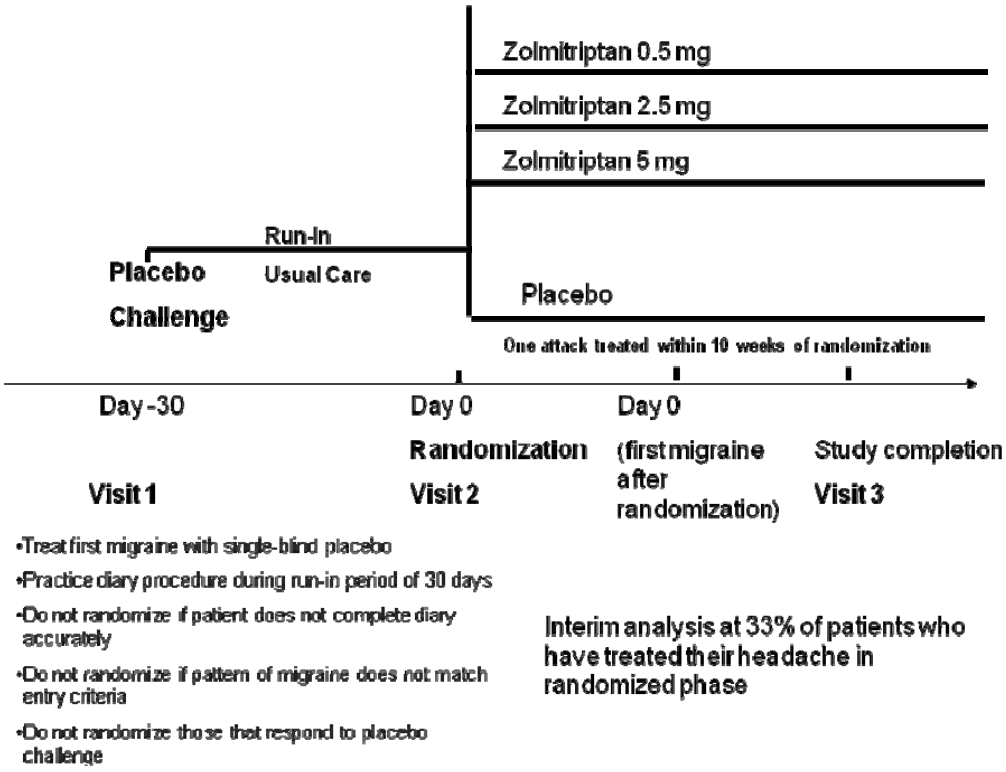
[a] Patients will return for the interim visit to review study instructions. Visit date and confirmation that dosing and diary instructions were provided will be documented on the eCRF. The nasal spray training device will not be used at the interim visit.

[b] For 1 year (12 months)

[c] Concomitant medications and AEs collected in patient diary

[d] Patients will receive instructions for placebo nasal spray and patient diaries in order to complete the run-in and placebo challenge portion of the study.

Figure 1 Study flow chart



3.2 Rationale for study design, doses and control groups

The study design was selected because it is an easy, simple design of high quality and interpretable results. Adolescents must be aged 12 to 17 years at the time of screening and will not be enrolled if they turn 18 years of age at the time of randomization. This is consistent with the FDA guidelines.

Patients must be able to differentiate between migraine and non-migraine headaches to ensure they are able to participate in the protocol. Patients with a history of a minimum of 2 migraine attacks (moderately or severely disabling) per month are included to maximize the chance of a migraine occurring during the study period.

To address the differences in migraine diagnosis between adolescents and adults, this study will use both the International Headache Society (IHS) and International Headache Society-Revised (IHS-R) (Winner et al 1997) criteria in the inclusion criteria. As patients mature, their migraines become more adult-like, thus the use of both criteria will capture the appropriate population across the age range. IHS-R is the most robust diagnostic tool, incorporating the expanded symptoms complex for pediatric and adolescent migraine. If a patient satisfies the IHS criteria, then by definition he/she will satisfy the IHS-R criteria.

Doses of 0.5, 2.5, and 5 mg of zolmitriptan nasal spray have been selected for this trial. Patients are randomized to the different treatment arms with different probabilities. It is believed that the probability to show a treatment effect is greatest for the zolmitriptan 5 mg treatment arm; hence, this treatment arm is powered with 80% to be able to detect a true difference of 0.11 between placebo and zolmitriptan 5 mg. However, in order to be able to perform the study with a reasonable number of centers, the 2 other zolmitriptan arms are powered at a lower power, ie, 67% power to detect a treatment difference of 0.11 versus placebo. It is anticipated that the true treatment difference with an effective dose might be as large as 0.15 with this study design, including the enriched population obtained by the enrollment period and placebo challenge treatment. With a true difference of 0.15, there will be 90% power to detect a difference for the 2 lower doses compared with placebo and 96% power for zolmitriptan 5 mg versus placebo.

The pharmacokinetics in adolescents of nasally administered zolmitriptan has been evaluated (Trial D122100004). A 5 mg dose of zolmitriptan nasal spray in both male and female adolescents has similar area under the plasma concentration curve (AUC), maximum plasma (peak) drug concentration after single-dose administration (C_{max}), and clearance as the adult population; and therefore, similar drug exposure as in the adult population.

Dosing in adolescents is generally based on body mass index (BMI) and weight as this ensures a relatively standardized population.

The rationale for the primary objective is to demonstrate that the effect of zolmitriptan is superior to placebo after single-dose administration in the acute treatment of migraine headache in adolescents between 12 to 17 years of age. The 2-hour pain-free endpoint is the IHS recommended primary outcome in guidelines for migraine studies. This ensures migraine headache relief of appropriate duration. The endpoints for the secondary objectives are commonly used endpoints in migraine studies. Endpoints collected before and after the 2-hour timepoint are included to support the primary endpoint.

Placebo is used as the comparator since the primary objective is to evaluate the efficacy of zolmitriptan.

Baseline assessments of headache intensity and associated symptoms are included as they are needed for derivation of the endpoints.

There is no evidence of a link between triptan use and suicidal behavior. Recent research studies have noted the increased risk of suicidality in frequent adolescent migraineurs. It is important to understand if treatment affects these symptoms when present. The C-SSRS (Posner et al 2007) will be performed to assess this.

No safety monitoring committee will be required since there are no specific safety concerns. Safety will be monitored on an ongoing basis and will include AEs, vital signs, laboratory assessments, ECG, and the C-SSRS to assess suicidal risks prior to and after treatment.

An external Data Monitoring Committee (DMC) consisting of an independent statistician will perform the interim analysis for sample size re-estimation based on blinded data only. The DMC will decide on the total sample size needed for the study.

4. SUBJECT SELECTION CRITERIA

The investigator(s) should keep a record, the patient screening log, of patients who entered pre-study screening.

Each patient should meet all of the inclusion criteria and none of the exclusion criteria for this study. Under no circumstances can there be exceptions to this rule.

4.1 Inclusion criteria

For inclusion in the study, patients must fulfill all of the following criteria:

1. Parent or legal guardian is able to provide written informed consent and patient is able to provide written assent.

2. Adolescents aged 12 to 17 years at the time of screening; patients must not be enrolled if they will turn 18 years of age within 10 weeks after randomization (Visit 2).

3. An established diagnosis of migraine (history indicating the presence of migraine for at least 1 year) with or without aura as defined by the IHS or IHS-R criteria. Patients with medical history of migraine for at least 1 year prior to screening as defined by IHS or IHS-R criteria without a historic documentation of migraine may be considered for entry after the history has been established and discussed with the medical monitor.

4. A minimum of 2 migraines, considered to be moderately/severely disabling, per month (by history);

5. A medical history of usual untreated migraine duration of ≥3 hours for any 3-month period prior to screening (Visit 1);

6. A history of migraine attacks occurring at intervals of >24 hours apart, which is confirmed by medical history;

7. Have the ability to differentiate between migraine and non-migraine headaches;

8. All females in a relationship capable of producing a pregnancy should use a highly effective form of birth control. All females will have a pregnancy test. They must have a negative urine pregnancy test and confirmed (by the investigator) use of a highly effective form of birth control. The highly effective form of birth control includes, but is not limited to, total sexual abstinence, a vasectomized male partner

with confirmation of azoospermia plus condom, female sterilization by tubal occlusion plus condom, intrauterine devices (IUD, ie, copper banded coils plus condom, intrauterine systems (IUS, ie, levonorgestrel [eg, Mirena] plus condom), Depo-Provera plus condom, etonogestrel implants (eg, Implanon, Norplant, Nuva ring) plus condom, Ortho Evra plus condom, normal and low-dose combined oral contraceptives plus condom, norelgestromin/ethinyl estradiol (EE) transdermal system plus condom, intravaginal device (eg, EE and etonogestrel) plus condom, and Cerazette (desogestrel) – currently the only highly effective progesterone-based pill – plus condom. A diaphragm and foam or condom or sponge and condom are not acceptable. Females should be on a stable method of birth control for a minimum of 3 months prior to study entry.

9. Absence of clinically significant abnormalities indicated from the medical history, physical examination, laboratory assessments (clinical chemistry, hematology, urinalysis), and urine drug screen results;

10. Clearly understands and is likely to comply with all study procedures and scheduled visits, as demonstrated during the run-in and placebo challenge period;

11. Ability to read and write and use the patient diary;

12. The investigator believes participation in the study will not be harmful to the patient.

4.2 Exclusion criteria

Patients must not enter the study if any of the following exclusion criteria are fulfilled:

1. Involvement in the planning and/or conduct of the study (applies to both AstraZeneca staff and/or staff at the study site);

2. Had previous randomization of treatment in this study;

3. Is currently participating or has participated in another clinical study within 30 days prior to screening for this study;

4. Any medical condition that may put the patient at increased risk with exposure to zolmitriptan or that may interfere with the safety or efficacy assessments (in the opinion of the investigator);

5. A history of basilar, ophthalmoplegic, or hemiplegic migraine headache or any potentially serious neurological condition that is associated with headache;

6. Had an unacceptable adverse experience following previous use of any $5HT_{1B/1D}$ agonist drug (in the opinion of the investigator);

7. Evidence of ischemic heart disease, arrhythmia (eg, atrial fibrillation or flutter, frequent premature ventricular contractions, atrioventricular block), accessory conduction pathway disorder (eg, Wolff-Parkinson-White syndrome) as determined by central cardiologist using predetermined and agreed upon pediatric standards;

8. History, symptoms, or significant risk factors for ischemic heart (eg, silent ischemia, angina, myocardial infarction) or other cardiovascular disease, including coronary vasospasm, cardiac accessory conduction pathways, arrhythmias, cerebrovascular syndromes (eg, stroke), or peripheral vascular disease;

9. Clinically significant abnormalities indicated from the medical history, physical examination, clinical chemistry, hematology, and urine drug screen (eg, stable diabetes mellitus would not qualify as a clinically significant abnormality for the purposes of this study);

10. Had a diagnosis or suspicion of drug-induced or chronic daily headaches within 1 year;

11. Has 14 or more non-migraine headache days each month for 3 months before the screening visit;

12. Has uncontrolled hypertension defined as systolic or diastolic BP that exceeds the 95th percentile for age and height (Appendix E; NHBPEP 2005);

13. Has used monoamine oxidase-A (MAO-A) inhibitor, methysergide, methylergonovine, or cimetidine in the 2 weeks before randomization or an SSRI 4 weeks before randomization; if the patient has been on stable dose of SSRI for 8 weeks (2 months) prior to randomization, they may be included in the study.

14. Has any recent history of abuse (in the previous year) of alcohol or other drugs including drugs for the acute treatment of headache;

15. Is a female who is pregnant or breast-feeding;

16. Has severe hepatic impairment or any serious condition which, in the opinion of the investigator, would present a risk to the patient participating in the study;

17. Has a clinically relevant abnormality on nasopharyngeal examination as determined by the investigator; nasopharyngeal examination means a standard physical examination to rule out gross abnormalities of the nasopharynx and does not imply specialist examination prior to enrolling a patient.

18. Has a positive urine test for drug abuse not explained by the use of appropriately prescribed rescue medications.

19. Responds to the placebo challenge during the run-in period (ie, migraine headache intensity is mild or none at 2 hours after the placebo challenge).

For procedures for withdrawal of incorrectly enrolled patients, see Section 5.3.

5. STUDY CONDUCT

5.1 Restrictions during the study

The following restrictions apply in this study during the placebo challenge and treatment period:

1. Patients must treat headache within 30 minutes of onset of moderate to severe headache pain reaching moderate or severe intensity.

2. Patients must be completely symptom-free from any previous headache.

3. Patients must initiate treatment of the migraine headache with only the study drug provided. The nasal spray device is for single use and will contain only 1 dose of study drug. If the migraine does not improve from moderate to severe to none or mild pain at 2 hours post dose, the patient has the option to use rescue medication. A 2nd dose of study drug will not be allowed as rescue medication, nor will it be provided. Rescue medications, as determined by the protocol and the investigator, may be taken 2 hours after taking the study drug and may include NSAIDS, anti-emetics, analgesics (eg, opioids), or sedatives. Rescue medication will not be provided by AstraZeneca.

4. Before taking the study drug, patients must not have:

   - Treated this headache with any other medication,
   - Received any ergotamine or ergotamine-like derivative (eg, dihydroergotamine, methysergide) or triptan ($5HT_{1B/1D}$ agonist) in the 24-hour period before treatment with the study drug,
   - Used opiates in the last 24 hours;

5. After taking the study drug, patients must not:

   - Sleep or nap for 2 hours,
   - Use rescue medication within 2 hours of taking the study drug (see above for use of rescue medication),
   - Use an ergotamine or ergotamine-like derivative (eg, dihydroergotamine, methysergide) or non-study triptans ($5HT_{1B/1D}$ agonist) for 24 hours.

Patients will be allowed to continue any medication being taken at the time of entry into the study (other than medication referred to above for the **acute treatment of migraine or**

restricted medications noted in Section 5.6). This includes medication normally taken for migraine prophylaxis or medication normally taken to control a long-standing condition, provided it is for a condition that is stable, and in the investigator's opinion, not adversely affected by participation in the study.

5.2 Subject enrollment and randomization

The Principal Investigator (PI) will:

1. Obtain signed informed consent from the patient's parent or guardian/legal representative and signed assent from the patient before any study-specific procedures are performed;

2. Assign potential patient a unique enrollment number, beginning with "E#";

3. Determine patient eligibility (see Sections 4.1 and 4.2);

4. Assign an eligible patient a unique randomization code (patient number), beginning with "#."

As patients are screened for the study, they must be allocated an enrollment code (E-code). The E-code is a 7-digit number made up of the center number and the patient number within that particular center.

If a patient withdraws from participation in the study, then his/her enrollment/randomization code cannot be reused.

5.2.1 Procedures for randomization

This study will be established with a center-stratified randomization. A blocked randomization schedule will be generated. The first patient randomized to a particular center will cause the next available block of randomization code to be allocated to that center. Where a patient is randomized to a center with a block already allocated, and with available entries in that block, the next entry in that open block will be used for the patient. Randomization will continue in this way, either allocating a new block if there are no available entries for a particular stratum, or using the next available entry in an open block. The patient E-code will be used to identify the patient throughout study participation.

A patient should not proceed to randomization after the run-in period if any of the following conditions are present:

- Patient has not reported migraine headaches of sufficient duration; or
- Has not completed the diary successfully; or
- Has responded to the placebo challenge treatment (see Section 3.1).

Patients not treating a migraine headache with blinded placebo during the 30-day run-in period should be considered a screen failure.

If a patient experiences only 1 migraine during the run-in period as documented on the Screening/Run-in diary, there must be clear evidence from medical records that the patient's general migraine pattern is 2 or more moderate to severely disabling migraines per month.

Eligible patients will be randomized in balanced blocks to receive zolmitriptan 5, 2.5, or 0.5 mg, or matching placebo in a 5:3:3:5 ratio. The actual treatment given to individual patients will be determined by a randomization scheme that has been loaded into the interactive voice response system (IVRS) database. If a patient is discontinued from the study, his/her patient or enrollment number will not be reused, and the patient will not be allowed to re-enter the study. Randomized patients who discontinue early from the study will not be replaced.

If a randomization number is allocated incorrectly (randomized to the wrong treatment, not due to the patient not meeting the inclusion/exclusion criteria), no attempt should be made to remedy the error once study material has been dispensed. The patient will continue with the allocated number and study material. AstraZeneca or its representative should be notified as soon as the error is discovered and the error should be adequately documented. Subsequent patients will continue using the first unallocated randomization number in the original numbering sequence.

Enrollment will be monitored during randomization to ensure balanced distribution between the age groups 12 to 14 years and 15 to 17 years.

5.3 Procedures for handling subjects incorrectly enrolled

Patients who fail to meet the inclusion/exclusion criteria should not, under any circumstances, be enrolled or randomized. There can be no exceptions to this rule.

Where patients that do not meet the selection criteria are randomized in error or incorrectly started on treatment, or where patients subsequently fail to meet the study criteria post initiation, a discussion should occur between the AstraZeneca Study Delivery Team Physician or its representative and the investigator regarding whether to continue or discontinue the patient from treatment.

The AstraZeneca Study Delivery Team Physician or its representative is to ensure all such decisions are appropriately documented. In situations where an agreement cannot be reached, the patient should have their study drug stopped.

5.4 Blinding and procedures for unblinding the study

5.4.1 Methods for ensuring blinding

Zolmitriptan and matching placebo spray will be identical in size and color. Packaging and labeling of the investigational products will be performed in a way to ensure blinding throughout the study.

No member of the study team in AstraZeneca or its representative, at investigational centers, or any contract research organization (CRO) handling data, will have access to the randomization scheme during the conduct of the study with the exception of AstraZeneca's Investigational Products (IPS) and Patient Safety.

The randomization schedule for blinding of randomized treatment will be maintained by AstraZeneca and will not be disclosed until after database lock.

5.4.2 Methods for unblinding the study

If the treatment code is broken, then the investigator(s) must document and report to AstraZeneca or its representative. If a treatment code break is required, this will be done via the IVRS.

The treatment code must not be broken except in medical emergencies when the appropriate management of the patient requires knowledge of the treatment randomization. If the treatment code is broken, then the investigator must document and report the action to AstraZeneca or its representative, without revealing the treatment given to the patient to AstraZeneca staff or its representative.

AstraZeneca retains the right to break the code for serious adverse events (SAEs) that are unexpected and are suspected to be causally related to an investigational product and that potentially require expedited reporting to regulatory authorities. Treatment codes will not be broken for the planned analyses of data until all decisions on the evaluability of the data from each individual patient have been made and documented.

5.5 Treatments

It is the investigator's/institution's responsibility to establish a system for handling study treatments, including investigational medicinal products to ensure that:

- Deliveries of such products from AstraZeneca are correctly received by a responsible person (eg, a pharmacist);
- Such deliveries are recorded; study treatments are handled and stored safely and properly.
- Study treatments are only dispensed to healthy volunteers in accordance with the protocol.

- Any unused products are accounted for and returned to designated facility or AstraZeneca or its representative for destruction.

At the end of the study, it must be possible to reconcile delivery records of usage and returned stocks. Any discrepancies must be accounted for. The Certificates of Delivery and Return must be signed, preferably by the investigator or a pharmacist.

5.5.1 Identity of investigational product(s)

AstraZeneca will provide the study treatment as follows:

Investigational product	Dosage form and strength	Manufacturer	Formulation number
ZOMIG® (zolmitriptan) Nasal Spray 5 mg/mL	0.5 mg nasal spray	AstraZeneca	F12438
ZOMIG® (zolmitriptan) Nasal Spray 25 mg/mL	2.5 mg nasal spray	AstraZeneca	F12440
ZOMIG® (zolmitriptan) Nasal Spray 50 mg/mL	5 mg nasal spray	AstraZeneca	F12441
Placebo for ZOMIG® (zolmitriptan) Nasal Spray	Placebo	AstraZeneca	F12787

5.5.2 Doses and treatment regimens

The study will comprise treatment of a single migraine headache or attack with 1 dose of zolmitriptan nasal spray 0.5, 2.5, or 5 mg, or matching placebo in a blinded manner.

Zolmitriptan nasal spray 0.5, 2.5, and 5 mg, and matching placebo nasal spray will be provided by AstraZeneca. Each nasal spray applicator will contain 1 dose of 100 µL volume, the active treatment containing zolmitriptan at the strength of 5, 25, or 50 mg/mL.

Patients will administer 1 dose in a blinded fashion. The blinded dose will contain a single spray that will be administered into 1 nostril.

When headache pain reaches moderate or severe intensity, patients will treat the migraine headache once with the study treatments (zolmitriptan nasal spray or placebo). Patients will assess headache pain at 15 minutes and at 1, 2, 3, 4, and 24 hours post treatment.

At Visit 1 (screening visit), eligible patients will be provided with verbal and written instructions for the proper use of the study nasal spray (see Appendix F for written instructions).

Patients will return the blinded placebo challenge nasal spray device during Visit 2 (randomization visit). For those patients that continue to be eligible, the study nasal spray will

be assigned and dosing instructions will be reviewed to ensure continued study dosing compliance.

The patient will be trained on the proper use of the study nasal spray using a training nasal spray device beginning at the screening visit. The training nasal spray device will not be dispensed to the patient and will be retained at the investigational site. A training device will be used at the randomization visit in order to reinforce proper dosing technique. Adjustments to the patient's dosing technique should be made as necessary to ensure appropriate dosing.

Supplemental training should be provided at the interim visit, if no attack is treated within 4 weeks of randomization, and as needed to ensure compliance. The patient will return the assigned study drug at Visit 3 (final study visit or ET visit).

5.5.3 Labeling

AstraZeneca will provide the study drug to the study sites. Labeling of the study drug will be performed in accordance with Good Manufacturing Practice. The labels will be produced in the local language and in accordance with local regulations for each participating country.

All clinical trial material will be packaged and labeled by AstraZeneca. The clinical trial material will be clearly marked according to national requirements regarding use for clinical trial investigation only.

Each patient will be supplied with a patient-specific migraine attack pack. The attack pack will have enough study drug to treat 1 migraine attack. Each pack within the patient-specific attack pack will contain 1 nasal spray device. Each nasal spray device will be numbered identically to the outside pack and will be labeled with an identification label stating the study number. Each patient-specific attack pack will be labeled with a single-panel, double-blind label. The carton will be clearly labeled with the study number, patient number, number of nasal sprays, and storage conditions.

5.5.4 Storage

All study drug must be kept in a secure place under appropriate storage conditions. A description of the appropriate storage and shipment conditions are specified on the study drug label and the IB. All study drug will be stored in original containers in a lockable storage facility until dispensed to the study patients.

5.6 Concomitant and post-study treatment(s)

The use of cimetidine and MAO-A inhibitors are not permitted. The dose of any SSRIs or migraine prophylactic agent must be stabilized within 2 months prior to randomization. If the patient has been on stable dose of SSRI for 8 weeks (2 months) prior to randomization, they may be included in the study. No triptan, ergotamine or ergotamine-containing medications may be used 24 hours before, concurrently, or after study drug. Opiates should not be used 24 hours before study drug treatment. NSAIDs, antiemetics, analgesics (eg, opioids), and

sedatives are permitted as rescue medications, as agreed by the treating physician, at ≥2 hours post study drug treatment.

Other medication, which is considered necessary for the patient's safety and well being, may be given at the discretion of the investigator permitting that this ongoing treatment won't be adversely affected by study participation, and recorded in the appropriate sections of the eCRF.

5.7 Treatment compliance

The administration of all medication (including study drug) should be recorded in the appropriate sections of the eCRF. Compliance will be assessed by patient-reported outcomes in the patient diaries.

5.7.1 Accountability

The study drug provided for this study will be used only as directed in the study protocol.

The study personnel will account for all study drugs dispensed to and returned from the patient.

AstraZeneca personnel or its representative will account for all study drugs received at the site, unused study drugs and for appropriate destruction. Certificates of delivery, destruction, and return should be signed.

The investigational materials are to be prescribed only by the investigator or sub-investigators named in the US FDA 1572 form. Under no circumstances will the investigator allow the study drug to be used other than as directed by the protocol without prior AstraZeneca or its representative's approval.

The investigator must maintain accurate records accounting for the receipt of the investigational materials and for the disposition of the material. This record-keeping consists of a dispensing record that includes the identification of the person to whom the drug is dispensed, the quantity and the date of dispensing, and the amount of any unused drug returned to the investigator. This record is in addition to any drug accountability information recorded on the eCRF. Patients must return unused drug supplies to the investigator.

At the termination of the study or at the request of the Sponsor, the investigator must return any unused supplies to AstraZeneca or its representative for study drug destruction.

5.8 Withdrawal from study

Patients may be discontinued from the study in the following situations:

- Patient decision: Voluntary discontinuation by the patient or the parent/legal guardian who is at any time free to discontinue the patient's participation in the study, without prejudice to further treatment;

- Severe non-compliance to the study protocol as judged by the investigator and/or AstraZeneca;
- Incorrectly enrolled patients;
- Patient is lost to follow-up.
- The patient has a clinically significant or serious AE that would not be consistent with continuation in the study, as determined by the investigator, AstraZeneca or its representative, or the patient.
- Safety reasons as judged by the investigator, particularly if the patient becomes pregnant;
- The condition under investigation worsened.
- The patient is unable to comply with the restrictions on the use of concomitant medications as detailed in Section 5.6.
- The patient is unable to tolerate the assigned dose of study drug.

Patients are at any time free to withdraw from the study without prejudice to further treatment (withdrawal of consent). A patient that decides to withdraw from the study will always be asked about the reason(s) and the presence of any AEs. If possible, they will be seen and assessed by an investigator(s).

Patients who withdraw from the study will be required to complete Visit 3 (final visit/end-of-study) assessments at the ET visit. AEs will be followed up (see Sections 6.4.3 and 6.4.4); the nasal spray device and patient diaries used to collect data on migraine attacks and study drug should be returned by the patient. Patients who withdraw from the study will not be replaced.

6. COLLECTION OF STUDY VARIABLES

6.1 Recording of data

The electronic Data Capture (eDC) system will be used for data collection and query handling. The investigator will ensure that data are recorded on the eCRFs as specified in the study protocol and in accordance with the instructions provided.

The investigator ensures the accuracy, completeness, and timeliness of the data recorded and of the provision of answers to data queries according to the Clinical Study Agreement (CSA). The investigator will sign the completed eCRFs. A copy of the completed eCRFs will be archived at the study site.

Patients will use paper diaries to collect data on the migraine attacks treated and the characteristics of the attack and treatment. Paper diaries will be entered into the eDC system by trained personnel at the investigator's site.

6.2 Data collection and enrollment

6.2.1 Screening and demographic measurements

The following data will be collected and recorded in the appropriate sections of the eCRF at the time of the screening visit (Visit 1) (refer to the Study Plan, Table 1):

- Signed informed consent and assent forms will be obtained.
- Inclusion/exclusion criteria;
- Medical and relevant surgical history. The most relevant surgical history is ear, nose, and throat (ENT) surgery (eg, rhinoplasty or other surgical manipulations of nasal mucosa).
- History of migraine headache;
- Prior (1 year [12 months]) and current medications;
- Demography (date of birth, sex and race);
- Vital signs (seated BP and pulse, and oral body temperature);
- Laboratory assessments;
- 12-lead ECG;
- Urine toxicology/drug screen;
- Urinalysis;
- Urine pregnancy test for all females;
- Patient diary and instructions will be given.
- Blinded placebo nasal spray device and dosing instructions will be given.
- Physical examination (see Section 6.4.6 for details);
- Height and weight;
- C-SSRS

6.2.2 Follow-up procedures

Not applicable. Additional procedures completed during the visits after screening (Visit 1) are referenced in the Study Plan (Table 1).

6.3 Efficacy

6.3.1 Efficacy variables

The primary efficacy endpoint is pain-free status at 2 hours post treatment based on headache intensities recorded in the patient diary (see Section 6.5).

The secondary efficacy endpoints (or outcome variables):

- Pain-free status at 15 minutes and at 1, 2, 3, 4, and 24 hours post treatment;
- Headache response at 15 minutes and at 1, 2, 3, 4, and 24 hours post treatment;
- Sustained headache response at 2 hours subsequent to a 1-hour headache response;
- Presence of associated symptoms of photophobia, phonophobia or nausea at 15 minutes and at 1, 2, 3, 4, and 24 hours post treatment;
- Resolution of associated symptoms of photophobia, phonophobia, or nausea at 15 minutes and at 1, 2, 3, 4, and 24 hours post treatment;
- Incidence and time to use of rescue medication up to 24 hours post treatment;
- Ability to perform normal activities at 15 minutes and at 1, 2, 3, 4, and 24 hours post treatment;
- Headache recurrence 2 to 24 hours post treatment;
- Bilateral headache (yes/no) at 15 minutes and at 1, 2, 3, 4, and 24 hours post treatment;
- Intensity increased by movement (yes/no) at 15 minutes and at 1, 2, 3, 4, and 24 hours post treatment.

Pain-free status is a reduction in headache pain intensity from severe or moderate at baseline to none at a specific assessment time. Pain-free status is a binary response variable (yes or no).

Headache response is defined as a reduction in migraine headache pain intensity from severe or moderate at the time of initial treatment to mild or none at a specific assessment time. Headache response is a binary response variable (yes or no).

Sustained headache response is defined as a reduction in migraine headache pain intensity from severe or moderate to mild or none at 1 hour and maintained at 2 hours after study drug treatment.

Time to use of rescue medication starts with the dosing time of the study drug and ends with the first use of rescue medication. If an event has not occurred by the final assessment point, the response is considered censored for the purpose of analysis.

Resolution of associated symptoms of migraine is defined for those patients who have associated symptoms at baseline who are then symptom free at the assessment timepoints. Associated symptoms of migraine are nausea, vomiting, photophobia, and phonophobia.

Headache recurrence is defined for those patients having no headache pain at 2 hours, but worsening of headache between 2 and 24 hours and/or requirement for rescue medication within 24 hours.

6.4 Safety

The PI is responsible for ensuring that all staff involved in the study is familiar with the content of this section.

6.4.1 Definition of adverse events

An AE is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered causally related to the product. An undesirable medical condition can be symptoms (eg, nausea, chest pain), signs (eg, tachycardia, enlarged liver), or the abnormal results of an investigation (eg, laboratory findings, ECG). In clinical studies, an AE can include an undesirable medical condition occurring at any time, including run-in or washout periods, even if no study treatment has been administered.

The term AE is used to include both serious and non-serious AEs.

6.4.2 Definitions of serious adverse event

A serious adverse event (SAE) is an AE occurring during any study phase (ie, run-in, treatment, washout, follow-up), that fulfills 1 or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Is a congenital abnormality or birth defect

- Is an important medical event that may jeopardize the patient or may require medical intervention to prevent one of the outcomes listed above.

For further guidance on the definition of an SAE, see Appendix B to the CSP.

6.4.3 Recording of adverse events

Time period for collection of adverse events

Adverse events and SAEs will be collected from time of informed consent (ie, in source documents).

For the purpose of this study, non-serious AEs will be recorded in the eCRF only if they occur in the 24 hours immediately following a dose of study drug or increase in intensity in the 24 hours immediately following a dose of study drug, as migraine is an episodic condition and patients will be using study drug only for acute treatment of attacks. Twenty-four hours is more than 5 times the half-life of zolmitriptan and is therefore considered to be in excess of the elimination period for the study drug. Non-serious AEs that lead to patient discontinuation from the study will also be recorded in the eCRF.

Serious adverse events will be recorded in the eCRF if they occur at any point during the study.

Follow-up of unresolved adverse events

Any AEs that are unresolved at the patient's last AE assessment in the study are followed up by the investigator for as long as medically indicated, but without further recording in the eCRF. AstraZeneca or its representative retains the right to request additional information for any patient with ongoing AEs/SAEs at the end of the study, if judged necessary.

Variables

The following variables will be collected for each AE:

- AE (verbatim);
- The date when the AE started and stopped (duration of AE);
- Maximum intensity or intensity or changes in intensity;
- Whether the AE is serious or not;
- Investigator causality rating against the study drug (yes or no);
- Action taken with regard to study drug;
- AE caused patient's withdrawal from the study *(*yes or no);
- Outcome.

In addition, the following variables will be collected for SAEs:

- Date AE met criteria for SAE;
- Date investigator became aware of SAE;
- AE is serious due to;
- Date of hospitalization;
- Date of discharge;
- Probable cause of death;
- Date of death;
- Autopsy performed;
- Causality assessment in relation to study procedure(s);
- Causality assessment in relation to study drug;
- Causality assessment in relation to other medication;
- Description of AE.

Intensity is defined as follows:

- Mild (awareness of sign or symptom, but easily tolerated);
- Moderate (discomfort sufficient to cause interference with normal activities);
- Severe (incapacitating, with inability to perform normal activities).

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity, whereas seriousness is defined by the criteria in Section 6.4.2. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not a SAE. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke, but would be a SAE.

If a diagnosis of the patient's condition has been made, then the diagnosis should be recorded as the SAE or the AE. In instances of well-recognized symptoms, they can be recorded as the commonly used diagnosis (eg, fever, runny nose, and cough can be recorded as "flu"). However, if a diagnosis of the patient's condition has not been made, or if the individual symptoms are not well recognized, then the individual symptoms should be recorded separately.

The patient's usual non-headache symptoms of migraine (ie, nausea, vomiting, photophobia, or phonophobia) will not be recorded as AEs. However, migraine symptoms that are atypical or of unusual intensity for the patient must be recorded as AEs.

Where there is a deterioration in the condition for which the study drug is being used, there may be uncertainty as to whether this is normal disease progression (resulting from a lack of efficacy) or an AE. In these circumstances, if it is believed that the study drug did not contribute to the deterioration, then the deterioration should be considered lack of efficacy. However, if it is believed that the study drug may have contributed to the deterioration, then the deterioration should be treated as an AE.

Patients should record all unusual experiences (signs, symptoms, feelings, etc) on the symptom/medication log provided in the patient diary. At the final visit, the investigator should discuss the experience with the patient and, if appropriate, record the experience as an AE on the eCRF provided.

Should an overdose occur, it must be reported in accordance with the procedures described in Section 13.2. All overdoses, with or without associated symptoms, should be reported as AEs.

Suicide and attempted suicide, irrespective of the method, but occurring in connection with the use of the study drug, should be reported as AEs (serious or non-serious). This event should be identified as suicide or attempted suicide, and the method of the suicide or attempt should be provided. If an attempted suicide meets the criteria for an SAE, the event must be reported according to the guidelines in Section 6.4.4. Suicidal thoughts should also be regarded as AEs.

All events of suicidality will be carefully monitored. These include events of suicide attempts, suicidal ideation, completed suicides, and suicidal behavior. The last category includes behavioral AEs or SAEs in which the investigator cannot rule out underlying suicidal thinking, eg, motor vehicle accident or behaving in a dangerous or unsafe way, and other self-injurious behaviors.

Pregnancy in itself is not regarded as an AE unless there is a suspicion that the study drug has interfered with the effectiveness of a contraceptive medication. (To be eligible for this study, females of childbearing potential and at risk of pregnancy must be using a reliable method of contraception; see inclusion criterion #9, Section 4.1). Should a pregnancy occur, it must be reported in accordance with the procedures described in Section 13.3.

In the clinical study report, the terms used by the investigator to record AEs will be mapped to preferred terms using a standard AE dictionary, Medical Dictionary for Regulatory Activities (MedDRA).

Causality collection

The investigator will assess causal relationship between the study drug and each AE (ie, their relationship to study drug), and answer "yes" or "no" to the question, "*Do you consider that there is a reasonable possibility that the event may have been caused by the study drug?*"

For SAEs, causal relationship will also be assessed for other medication and study procedures. Note that for SAEs that could be associated with any study procedure, the causal relationship is implied as "yes."

A guide to the interpretation of the causality question is found in Appendix B to the CSP.

Adverse events based on signs and symptoms

All AEs spontaneously reported by the patient or reported in response to the open question from the study personnel, "*Have you/the child had any health problems since the previous visit/you were last asked?*" or revealed by observation will be collected and recorded in the eCRF. When collecting AEs, the recording of diagnoses is preferred (when possible) to recording a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

Adverse events based on examinations and tests

The results from protocol-mandated laboratory tests and vital signs will be summarized in the clinical study report. Deterioration as compared with baseline in protocol-mandated laboratory values and vital signs should therefore only be reported as AEs if they fulfill any of the AE criteria or are the reason for discontinuation of treatment with the study drug.

If deterioration in a laboratory value/vital sign is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated laboratory result/vital sign will be considered as additional information. Wherever possible the reporting investigator uses the clinical, rather than the laboratory term (eg, anemia versus low hemoglobin value). In the absence of clinical signs or symptoms, clinically relevant deteriorations in non-mandated parameters should be reported as AE(s).

Deterioration of a laboratory value, which is unequivocally due to disease progression, should not be reported as an AE/SAE.

Any new or aggravated clinically relevant abnormal medical finding at a physical examination as compared with the baseline assessment will be reported as an AE.

Disease progression, worsening migraine, and migraine-associated symptoms

Disease progression can be considered as a worsening of a patient's condition attributable to the disease for which the study drug is being studied. It may be an increase in the severity of the disease under study and/or increases in the symptoms of the disease. The development of worsening migraines should be considered as disease progression and not an AE. Events, which are unequivocally due to disease progression, should not be reported as an AE during the study.

Where there is a deterioration in the condition (ie, worsening migraine) for which the study treatment is being used, there may be uncertainty as to whether this is normal disease progression (resulting from a lack of efficacy) or an AE. Generally speaking, recurrence of

migraines that is otherwise typical for a given patient should not be considered an AE (and is instead considered a lack of efficacy). Additionally, migraine-associated symptoms such as nausea, vomiting, photophobia, or phonophobia should generally not be recorded as AEs if they are typical for a given patient.

In certain circumstances, however, events related to worsened migraine should be considered as AEs:

- Headaches that are clearly atypical or of unusual intensity for a given patient;
- Clinical symptoms that otherwise meet criteria for an SAE (Section 6.4.2).

Migraine symptoms resulting in trial discontinuation should not be counted as AEs unless they also meet at least 1 of the 2 criteria listed above.

6.4.4 Reporting of serious adverse events

All SAEs have to be reported, whether or not considered causally related to the study drug, or to the study procedure(s). All SAEs will be recorded in the eCRF.

If any SAE occurs in the course of the study, then investigators or other site personnel will inform appropriate AstraZeneca representatives within 1 day, ie, immediately, but **no later than the end of the next business day**, of when he or she becomes aware of it.

The designated AstraZeneca representative works with the investigator to ensure that all the necessary information is provided to the AstraZeneca Patient Safety data entry site **within 1 calendar day** of initial receipt for fatal and life-threatening events **and within 5 calendar days** of initial receipt for all other SAEs.

For fatal or life-threatening AEs where important or relevant information is missing, active follow-up is undertaken immediately. Investigators or other site personnel will inform AstraZeneca representatives of any follow-up information on a previously reported SAE within 1 calendar day, ie, immediately, but **no later than the end of the next business day**, of when he or she becomes aware of it.

Once the investigators or other site personnel indicate an AE is serious in the eDC system, an automated email alert is sent to the designated AstraZeneca representative.

If the eDC system is not available, then the investigator or other study site personnel reports a SAE to the appropriate AstraZeneca representative by telephone.

The AstraZeneca representative will advise the investigator/study site personnel how to proceed.

6.4.5 Laboratory safety assessment

Laboratory assessments will be conducted by a central laboratory. Blood and urine samples for determination of clinical chemistry, hematology, and urinalysis will be taken at the times indicated in the Study Plan (Table 1).

The following clinical laboratory tests (chemistry, hematology, and urinalysis) will be performed at Visit 1 (screening visit) and at Visit 3 (final/end-of-study visit).

Table 2 Laboratory assessments

Hematology (whole blood)	**Clinical chemistry (serum)**	**Urinalysis**
B-Hemoglobin	S-Creatinine	Specific gravity
B-Leukocyte (WBC) differential count	S-Uric acid	pH
B-Platelet count	S-Total bilirubin (direct and indirect)	Glucose
B-Hematocrit	S-Albumin	Protein
B-RBC	S-Alkaline phosphatase	Ketones
	S-ALT	Blood/hemoglobin
	S-AST	Leukocytes
	S-Potassium, S-Calcium, S-Sodium	Nitrates
	S-Chloride	Bilirubin
	S-Bicarbonate	Urobilinogen
	S-Glucose	Microscopic examination (if the urine dipstick is abnormal for leukocytes or blood.
	BUN	
	Protein	
	LDH	**Urine drug screen**
		Cocaine
	Urine pregnancy test	Cannabinoids
		PCP
		Amphetamines class
		Benzodiazepines class
		Barbiturates class
		Opiates class
		Propoxyphene
		Methaqualone
		Methadone
		Ethanol

Prefix: B for blood and S for serum.

ALT alanine aminotransferase; AST aspartate aminotransferase; BUN blood urea nitrogen; LDH lactate dehydrogenase; PCP phencyclidine; RBC red blood cell; WBC white blood cell.

Urine drug screening tests will be performed on all patients at Visit 1 (screening visit). Urine pregnancy tests will be performed on all females at Visit 1 (screening visit), Visit 2 (randomization), and Visit 3 (final visit/end-of-study).

For blood volume, see Section 7.1.

6.4.6 Physical examination

A medical history will be obtained at Visit 1 (screening). A complete physical examination (including a nose and throat examination) will be performed at Visits 1 and 3, and at time of discontinuation (ET visit) from the study:

- The complete physical examination will include an assessment of the following: general appearance, skin, head and neck (including ears, eyes, nose, and throat), lymph nodes, thyroid, abdomen, musculoskeletal (including spine and extremities), cardiovascular, respiratory, and neurological systems.
  - Nasal examination – using a nasal speculum and otoscope, examine the following inside each nostril: nasal mucosa, nasal septum, turbinates.
  - Throat examination – using a tongue depressor and adequate illumination, examine the following inside the oral cavity and pharynx: hard and soft palate, buccal mucosa and tongue, tonsils (if present), posterior pharynx.
  - Signs of abnormality including inflammation, hypertrophy, ulceration, and necrosis. Any signs of abnormality are to be documented on the eCRF. If the investigator feels any abnormality warrants further evaluation, the patient should be referred to a specialist. The specialist will inform the investigator whether the abnormality is clinically significant and whether the patient should be randomized into the study because of this abnormality.

6.4.7 ECG

6.4.7.1 Resting 12-lead ECG

Digital ECGs for all patients will be conducted at the study center using a machine provided by the central ECG laboratory (eRT) and will be transmitted to eRT (Section 13). Digital ECG will be performed at Visit 1 (screening), Visit 3 (final visit) and at the ET visit.

Digital ECGs will be obtained after the patient has been resting in a semi-reclining position for at least 10 minutes. Each digital ECG will be performed only once at Visits 1 and 3/ET visit.

All digital ECGs will be documented by recording date, time, heart rate, QRS duration, PR interval, RR interval, QT, and QTcF. QTcF intervals will be calculated using the Fridericia formula (Puddu et al 1988).

If indicated, additional ECG assessments can be made at the discretion of the investigator. These assessments should be entered as an unscheduled assessment on the appropriate eCRF.

The investigator will judge the overall interpretation as normal or abnormal. If abnormal, it will be decided as to whether or not the abnormality is clinically significant or not clinically significant and the reason for the abnormality will be recorded on the eCRF. Abnormal values shall not be recorded as AEs unless deemed clinically significant.

Quality assurance of the ECG waveform and patient demographics will be conducted by a central laboratory operator at eRT. Digital ECGs will be processed through a computer interpretation program and then reviewed, first by an ECG analyst and then by a board-certified cardiologist. Central Analysis Results will be printed by the investigator from eRT website MyStudyPortal.com.

6.4.8 Vital signs

6.4.8.1 Pulse and blood pressure

Blood pressure (seated for 10 minutes) and pulse (seated for 10 minutes) will be measured at Visit 1 (screening), Visit 3 (final visit), and at the ET visit. Blood pressure measurement may be repeated one time after an additional 10 minutes of rest. An appropriately sized cuff will be used to obtain systolic and diastolic BP.

6.4.8.2 Body temperature

Body temperature (oral) will be measured at Visit 1 (screening), Visit 3 (final visit) and at the ET visit. Oral body temperature will be measured in °C.

6.4.9 Other safety assessments

6.4.9.1 Columbia-Suicide Severity Rating Scale (C-SSRS)

The C-SSRS is a unique, simple and short method of assessing both behavior and ideation that tracks all suicidal events, and provides a summary of suicidality (Posner et al 2007). It assesses the lethality of attempts and other features of ideation (frequency, duration, controllability, reasons for ideation and deterrents), all of which are significantly predictive of completed suicide.

The C-SSRS will be administered at the screening visit and at each scheduled visit throughout the study by a trained rater. The trained rater will record the clinical observation on the scale that will be used as the source document. If at all possible, the same individual should perform the assessment at each visit to reduce scoring variability. In the event the primary rater is not available, a designated back-up rater who meets the same qualifications may perform the C-SSRS.

The timing of the C-SSRS evaluations is found in the Study Plan, Table 1.

6.5 Patient reported outcomes (PRO)

6.5.1 Patient diary (self-assessment of headache pain, symptoms, and treatment response)

A paper patient diary will be used for date and time stamping of patients' self-assessment of headache pain, symptoms, and treatment response.

Patients will assess migraine pain severity and rate the intensity as severe (3), moderate (2), mild (1), or none (0).

Patients will record the following data relevant to their migraine headaches:

- Headache frequency and type (run-in period only);
- Date and time headache intensity is moderate or severe prior to study treatment (baseline);
- Date and time of treatment with study drug;
- Presence of associated migraine symptoms (photophobia, phonophobia, nausea, vomiting) at baseline;
- Headache intensity prior to treatment with study drug, and at 15 minutes (±10 minutes) and 1 hour (±30 minutes), 2 hours (±20 minutes), 3 hours (±30 minutes), 4 hours (±30 minutes), and 24 hours (±8 hours) after treatment;
- Presence of associated migraine symptoms at 15 minutes (±10 minutes) and 1 hour (±30 minutes), 2 hours (±20 minutes), 3 hours (±30 minutes), 4 hours (±30 minutes), and 24 hours (±8 hours) after treatment;
- Rescue medications taken, time, and date;
- Ability to perform normal activities prior to treatment with study drug, and at 15 minutes (±10 minutes) and 1 hour (±30 minutes), 2 hours (±20 minutes), 3 hours (±30 minutes), 4 hours (±30 minutes), and 24 hours (±8 hours) post treatment;
- Headache recurrence 2 to 24 hours post treatment;
- Bilateral headache (yes/no) prior to treatment with study drug, and at 15 minutes (±10 minutes) and 1 hour (±30 minutes), 2 hours (±20 minutes), 3 hours (±30 minutes), 4 hours (±30 minutes), and 24 hours (±8 hours) post treatment;

- Intensity increased by movement (yes/no) prior to treatment with study drug, and at 15 minutes (±10 minutes) and 1 hour (±30 minutes), 2 hours (±20 minutes), 3 hours (±30 minutes), 4 hours (±30 minutes), and 24 hours (±8 hours) post treatment.

6.5.2 Administration of patient diary

At the time of screening, a paper diary will be assigned to each eligible patient. Diary instructions will be reviewed at Visit 1 (screening visit) to ensure they are aware and capable of diary compliance. The diary will be completed during the run-in period to collect migraine pattern, practice diary procedure, and assess the patient's response to placebo challenge. Practice diaries will be used during the run-in/placebo challenge period. Diary data will be reviewed with the patient at Visit 2 (randomization) and recorded on the eCRF.

At the time of randomization, eligible patients will receive additional paper diaries. The diary will be used to collect the patients' self-assessment of headache pain, symptoms, and treatment response. Diary completion instructions will be reviewed during the Visit 2 (randomization) instruction period and as needed to ensure patient compliance.

At the time migraine reaches moderate to severe intensity and study drug is administered, the patient must record details in the diary about the migraine at specified timepoints as noted in Section 6.5.1.

Diary data will be reviewed with the patient at Visit 3 (final visit) and recorded on the eCRF.

Patients will receive a symptom/medication log (as part of the patient diary) to record any additional medications taken and unusual experiences that may occur during the study. Investigators will review these logs to determine if any experiences may be considered AEs and should be captured on the eCRF. Concomitant medications will be reviewed and recorded on the eCRF.

7. BIOLOGICAL SAMPLING PROCEDURES

7.1 Volume of blood

The total volume of blood that will be drawn from each patient in this study is as follows:

Table 3 Volume of blood to be drawn from each patient

Assessment		Sample volume (mL)	No. of samples	Total volume (mL)
Safety	Clinical chemistry and hematology[a]	**9**	**2**	**18**
Total		**9**	**2**	**18**

[a] Two separate pediatric blood draw tubes will be used for clinical chemistry (serum separating tube or SST) and hematology (ethylenediamine tetraacetic acid or EDTA tube). Each tube has an approximate maximum volume of 4.5 mL.

Urine samples will be taken from each patient for the purpose of drug screening and urinalysis. Urine samples from all females will be used to test for pregnancy.

7.2 Handling, storage and destruction of biological samples

The samples will be used up or disposed of after analyses or retained for further use as described here.

The laboratory will provide detailed instructions of all laboratory procedures, handling, and shipment of laboratory samples before the study start. The samples should be properly taken, handled, labeled, and shipped in accordance with the instructions provided by the laboratory. Samples should be shipped to the laboratory by courier unless otherwise agreed.

The analyte stability limits defined by the laboratory will be applied to all analyses performed on behalf of AstraZeneca. The laboratory will not analyze samples that fall outside these stability limits. Analytical data found to have been derived from a sample that fell outside these stability limits would not be reported. The standards of procedures followed by the laboratory may be amended in accordance with their Standard Operating Procedures. The laboratory will inform AstraZeneca or its representative of the stability limits relevant to this study before the first patient gives informed consent to take part in the study.

7.3 Labeling and shipment of biohazard samples

The PI ensures that samples are labeled and shipped in accordance with the Laboratory Manual and the Biological Substance, Category B Regulations (materials containing or suspected to contain infectious substances that do not meet Category A criteria), see Appendix C "International Airline Transportation Association (IATA) 6.2 Guidance Document."

Any samples identified as Infectious Category A materials are not shipped and no further samples will be taken from the patient unless agreed with AstraZeneca and appropriate labeling, shipment, and containment provisions are approved.

7.4 Chain of custody of biological samples

A full chain of custody is maintained for all samples throughout their life cycle.

The PI at each study center keeps full traceability of collected biological samples from the patients while in storage at the study center until shipment or disposal (where appropriate) and keeps documentation of receipt of arrival.

The sample receiver keeps full traceability of the samples while in storage and during use until used or disposed of or until further shipment and keeps documentation of receipt of arrival.

AstraZeneca or its representative keeps oversight of the entire life cycle through internal procedures, monitoring of study sites, and auditing of external laboratory providers.

Samples retained for further use are registered in the AstraZeneca biobank system during the entire life cycle.

7.5 Withdrawal of informed consent for donated biological samples (Not applicable)

8. ETHICAL AND REGULATORY REQUIREMENTS

8.1 Ethical conduct of the study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with the International Conference on Harmonisation (ICH)/Good Clinical Practice (GCP), applicable regulatory requirements and the AstraZeneca policy on Bioethics and Human Biological Samples.

8.2 Subject data protection

The Informed Consent and Assent Forms will incorporate (or, in some cases, be accompanied by a separate document incorporating) wording that complies with relevant data protection and privacy legislation.

8.3 Ethics and regulatory review

An IRB should approve the final study protocol, including the final version of the Informed Consent Form and any other written information and/or materials to be provided to the patients. The investigator will ensure the distribution of these documents to the applicable IRB, and to the study site staff.

The opinion of the IRB should be given in writing. The investigator should submit the written approval to AstraZeneca before enrollment of any patient into the study.

The IRB should approve all advertising used to recruit patients for the study.

AstraZeneca should approve any modifications to the Informed Consent and Assent Forms that are needed to meet local requirements.

If required by local regulations, the protocol should be re-approved by the IRB annually.

Before enrollment of any patient into the study, the final study protocol, including the final versions of the Informed Consent and Assent Forms, is approved by the national regulatory authority or a notification to the national regulatory authority is done, according to local regulations.

AstraZeneca will handle the distribution of any of these documents to the national regulatory authorities.

AstraZeneca will provide regulatory authorities, IRBs, and PIs with safety updates/reports according to local requirements.

Each PI is responsible for providing the IRB with reports of any serious and unexpected adverse drug reactions from any other study conducted with the investigational product. AstraZeneca will provide this information to the PI so that he/she can meet these reporting requirements.

8.4 Informed consent

The PIs at each center will:

- Ensure each patient is given full and adequate oral and written information about the nature, purpose, and possible risk and benefit of the study.
- Ensure each patient is notified that they are free to discontinue from the study at any time.
- Ensure that each patient is given the opportunity to ask questions and allowed time to consider the information provided.
- Ensure each patient provides signed and dated informed consent and assent before conducting any procedure specifically for the study.
- Ensure the original, signed Informed Consent and Assent Form(s) are stored in the investigator's Study File.
- Ensure a copy of the signed Informed Consent and Assent Form is given to the patient and parent/legal guardian.
- Ensure that any incentives for patients who participate in the study as well as any provisions for patients harmed as a consequence of study participation are described in the Informed Consent Form that is approved by an IRB.

8.5 Changes to the protocol and informed consent form

Study procedures will not be changed without the mutual agreement of the International Co-ordinating Investigator and AstraZeneca.

If there are any substantial changes to the study protocol, then these changes will be documented in a study protocol amendment, and where required, in a new version of the study protocol (Revised CSP).

The amendment should be approved by each IRB and if applicable, also the national regulatory authority, before implementation. Local requirements should be followed for revised protocols.

AstraZeneca will distribute any subsequent amendments and new versions of the protocol to each PI. For distribution to IRB, see Section 8.3.

If a protocol amendment requires a change to a center's Informed Consent Form, AstraZeneca and the center's IRB should approve the revised Informed Consent Form before the revised form is used.

If local regulations require, any administrative change will be communicated to or approved by each IRB.

8.6 Audits and inspections

Authorized representatives of AstraZeneca, a regulatory authority, or an IRB may perform audits or inspections at the center, including source data verification. The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents, to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, GCP, guidelines of the ICH, and any applicable regulatory requirements. The investigator will contact AstraZeneca or its representative immediately if contacted by a regulatory agency about an inspection at the center.

9. STUDY MANAGEMENT BY ASTRAZENECA

9.1 Pre-study activities

Before the first patient is entered into the study, it is necessary for a representative of AstraZeneca to visit the study site to:

- Determine the adequacy of the facilities;
- Determine availability of appropriate patients for the study;
- Discuss with the investigator(s) (and other personnel involved with the study) their responsibilities with regard to protocol adherence, and the responsibilities of AstraZeneca or its representatives. This will be documented in a CSA between AstraZeneca and the investigator.

9.2 Training of study site personnel

Before the first patient is entered into the study, an AstraZeneca representative will review and discuss the requirements of the CSP and related documents with the study site staff and also train them in any study-specific procedures and system(s) utilized.

The PI will ensure that appropriate training relevant to the study is given to all of these staff, and that any new information relevant to the performance of this study is forwarded to the staff involved.

The PI will maintain a record of all individuals involved in the study (medical, nursing, and other staff).

9.3 Monitoring of the study

During the study, an AstraZeneca representative will have regular contacts with the study site, including visits to:

- Provide information and support to the investigator(s);
- Confirm that facilities remain acceptable;
- Confirm that the study site team is adhering to the protocol, that data are being accurately and timely recorded in the eCRFs, biological samples are handled in accordance with the Laboratory Manual, and that study drug accountability checks are being performed.
- Perform source data verification (a comparison of the data in the eCRFs with the patient's medical records at the hospital or practice, and other records relevant to the study) including verification of informed consent of participating patients. This will require direct access to all original records for each patient (eg, clinic charts).
- Ensure withdrawal of informed consent to the use of the patient's biological samples is reported and biological samples are identified and disposed of/destroyed accordingly, and the action is documented, and reported to the patient.

The AstraZeneca representative will be available between visits if the investigator(s) or other staff at the center needs information and advice about the study conduct.

9.3.1 Source data

Refer to the CSA for location of source data.

9.4 Study agreements

The PI at each center should comply with all the terms, conditions, and obligations of the CSA for this study. In the event of any inconsistency between this CSP and the CSA, the terms of CSP shall prevail with respect to the conduct of the study and the treatment of patients and in all other respects, not relating to study conduct or treatment of patients, the terms of the CSA shall prevail.

Agreements between AstraZeneca and the PI should be in place before any study-related procedures can take place or patients are enrolled.

Prior to a patient's enrollment in the study and any study-related procedures are undertaken, the following should be fulfilled:

- Signed CSA between AstraZeneca and the PI/study center;

- Signed CSP and other agreements between AstraZeneca and the PI/study center;
- Written approval of the study by the IRB;
- Signed and dated Financial Disclosure forms.

9.4.1 Archiving of study documents

The investigator will follow the principles outlined in the CSA.

9.5 Study timetable and end of study

The end of the study is defined as "the last visit of the last patient undergoing the study." The end-of-study definition is for the entire study.

The study is expected to start in and to end by .

The study may be terminated at individual centers if the study procedures are not being performed according to GCP, or if recruitment is slow. AstraZeneca may also terminate the entire study prematurely if concerns for safety arise within this study or in any other study with zolmitriptan.

Discontinuation or suspension of the whole study program

If AstraZeneca decides to prematurely terminate or suspend the study, the PI, sub-investigator, the head of the institution, and regulatory authorities should receive written notification of the reasons for the premature termination or suspension.

The PI/sub-investigator will immediately notify the decision to the patients, give appropriate medical treatment; take necessary measures, and record treatment or measures provided on the source documents.

Completion of the study

Upon terminating the study, the PI will report in writing the completion of the study to the IRB and AstraZeneca or its representative.

10. DATA MANAGEMENT

Data Management (DM) will be performed by the CRO.

10.1 Electronic case report form

The eCRF and the protocol are both confidential. The eCRF will be created by the CRO and programmed into the eDC system. All sites will need internet access to access the eCRFs and will only have access to data for patients at their own sites. Data management and other co-ordinator teams will have access to data at all sites.

All eCRFs are to be completed by an authorized member of the investigational staff and reviewed and signed by the investigator. All entries, corrections, and alterations are to be made by the responsible investigator or an authorized member of the investigational staff. All eCRFs are to be completed in a manner that ensures accurate interpretation of data.

It is each investigator's responsibility to ensure that all discontinued orders or changes in the study or other medications entered on the patient's eCRF correspond to the entries on the patient's medical records.

The eCRFs for any patient leaving the study should be completed at the time medication is terminated for whatever reason.

The eCRFs must accurately reflect data contained in the patient's records (eg, source documents).

10.2 Dataflow

After data are entered into the eCRF by study sites, autoqueries that are generated by the eDC system should be addressed by sites. Data queries will be raised for inconsistent, impossible, or missing data. All entries to the study database will be available in an audit trail.

Data entered in the eDC system will be immediately saved to a central database and changes tracked to provide an audit trail. When the PI has signed the eCRF electronically as per eCRF instructions, then the patient's data will be locked.

The data collected through third party sources will be obtained and reconciled against study data.

The data will be validated as defined in the DM Plan. Quality control procedures will be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly.

At the monitoring visit, the Study Monitor must perform the Source Data Verification (SDV) of the required fields on completed forms and if there are no open queries, freeze the form. Data management will run manual consistency checks outside of the eDC system and will raise manual queries for sites to address; if the form is frozen, DM will unfreeze to allow sites to amend data. The same process is to be followed by any other groups creating manual queries in the eDC system (eg, for SAE reconciliation). Once all data are entered, SDV is completed on required fields, manual queries and electronic data reconciliation are completed, and all queries closed, then the casebook can be signed. Once the casebook is signed, DM will then lock the casebook so that no amendments can be made.

10.3 Database lock

10.3.1 Final analysis

When all data have been coded, validated, signed and locked, a clean file will be declared. Any treatment revealing data may thereafter be added and the final database will be locked.

Once all patient casebooks are locked, the final data transfer can be sent to statistics. A database lock checklist will also be completed by DM and the programmer to confirm all applicable quality control checks were performed.

10.3.2 Interim analysis

A partial clean file will be declared for data included in the interim analysis.

10.4 Coding

All AEs and medical/surgical histories recorded in the eCRF will be coded using MedDRA. All medications will be classified according to the AstraZeneca Drug Dictionary (AZDD). All coding will be performed by the CRO. The coding will occur outside of the eDC system and will be merged with the clinical datasets sent to statistics.

10.5 Investigator site file

At the beginning of the study, an investigator's Study File will be established at the study center. The investigator/institution is responsible for maintaining the study documents as specified in the guideline for ICH GCP (Committee for Proprietary Medicinal Products [CPMP]/ICH/135/95) and as required by the applicable regulatory requirement(s). The investigator/institution must take measures to prevent accidental or premature destruction of these documents.

10.6 SAE reconciliation

The CRO will perform SAE reconciliation between the CRO Clinical Study database and the AstraZeneca Clinical Patient Safety database.

10.7 ECG data

ECG data will be processed by a central laboratory and the results will be sent electronically to AstraZeneca or its representative.

11. EVALUATION AND CALCULATION OF VARIABLES

11.1 Calculation or derivation of efficacy variable(s)

A patient diary will be used for collecting the patients' self-assessment of headache pain, symptoms, and treatment response. Patients will assess migraine pain severity and rate the intensity as severe (3), moderate (2), mild (1), or none (0). Baseline is defined as the last non-missing pre-treatment value.

11.1.1 Pain-free status

Pain-free status is a reduction in headache pain intensity from severe or moderate at baseline to none at a specific assessment time. Pain-free status is a binary response variable (yes or no).

11.1.2 Headache response

Headache response is defined as a reduction in migraine headache pain intensity from severe or moderate at the time of initial treatment to mild or none at a specific assessment time. Headache response is a binary response variable (yes or no).

11.1.3 Resolution of associated symptoms of migraine

Resolution of associated symptoms of migraine is defined for those patients who have associated symptoms at baseline who are then symptom free at the assessment timepoints. Associated symptoms of migraine are photophobia, phonophobia, nausea, or vomiting.

11.1.4 Time to use of rescue medication

Time to use of rescue medication starts with the dosing time of study drug and ends with the first use of rescue medication. If an event has not occurred by the final assessment point, the response is considered censored for the purpose of analysis.

11.1.5 Ability to perform normal activities

Ability to perform normal activities will be assessed before treatment, at 15 minutes and at 1, 2, 3, 4, and 24 hours post treatment in the patient's diary as follows by the question: "*Are you able to perform normal activities at this time?*" (yes/no).

11.1.6 Increase of intensity with movements

Increase of migraine headache intensity by movement (yes/no) will be recorded before treatment, at 15 minutes and at 1, 2, 3, 4, and 24 hours post treatment in the patient's diary.

11.2 Calculation or derivation of safety variable(s)

11.2.1 Other significant adverse events (OAE)

During the evaluation of the AE data, an AstraZeneca medically qualified expert or its representative will review the list of AEs that were not reported as SAEs and discontinuations due to AEs. Based on the expert's judgment, significant AEs of particular clinical importance may, after consultation with the Global Drug Safety Physician, be considered OAEs and reported as such in the Clinical Study Report (CSR).

A similar review of laboratory, vital signs, and ECG data will be performed for identification of OAEs. Examples of these are marked hematological and other laboratory abnormalities, and certain events that lead to intervention (other than those already classified as serious), dose reduction, or significant additional treatment.

12. STATISTICAL METHODS AND SAMPLE SIZE DETERMINATION

Statistical analyses will be conducted using SAS (Version 8.2 or above). A comprehensive statistical analysis plan (SAP) will be prepared before the interim analysis is conducted. The final version of the SAP will be attached as an appendix to the clean file document.

12.1 Description of analysis sets

12.1.1 Safety analysis set

The safety analysis set includes all randomized treated patients who provide post-treatment safety data, classified according to the treatment actually received. Throughout the safety results sections, erroneously treated patients (eg, those randomized to treatment A, but actually given treatment B) will be accounted for in the actual treatment group. The analysis of all safety and tolerability variables will be performed using the safety analysis set.

12.1.2 Full analysis set

The full analysis set (FAS) includes all randomized treated patients who provide post-treatment efficacy data, classified according to randomized treatment. The analysis of all efficacy variables will be performed using the FAS.

12.2 Methods of statistical analyses

All statistical comparisons will be based on a 2-sided significance level of α=0.05 unless otherwise specified.

Descriptive statistics will be used to present efficacy and safety variables. For continuous variables, n, mean, standard deviation, median, minimum, and maximum will be presented. For categorical variables, n, frequency, and percentage will be presented.

Two types of datasets, both derived from the FAS, will be used for efficacy analyses: the observed case (OC) dataset and the last observation carried forward (LOCF) dataset. In general, the OC data for a visit will consist of the actual observations recorded for the visit. If missing, the OC data will remain missing – no data imputation will be performed. The LOCF data will be the corresponding OC data or, if that is missing, the last non-missing data carried forward from the most recent preceding assessment time. However, baseline values will not be carried forward for LOCF imputation. Baseline is defined as the last non-missing pre-treatment value. No other data imputation will be performed.

12.2.1 Interim analyses

An interim analysis will be performed based on the results of approximately 267 evaluable patients. Furthermore, available data from the diary will be included in the interim analysis for a sample size re-estimation calculation.

The sample size re-estimation (SSR) will be based on blinded data, ie, the pooled response rate of the primary variable, pain-free status at 2 hours. The clinically relevant treatment effect of 0.11 difference in response rates, 80% power and a 2-sided significance of 0.05 will be used. An approximative method based on the 2-treatment, continuity-corrected, chi-square test of equal proportions (Friede and Kieser 2006) will be used as a approximation for the intended analysis approach in the power calculations. Friede and Kieser 2006 discuss the 2-sample parallel group design; however, in this case since pairwise comparisons will be the primary analysis, this method can be used for this 4-sample parallel group design. For further detail please refer to the Friede and Kieser article.

$$\text{N/arm}_{SSR} = (2 + \theta + \frac{1}{\theta}) \cdot \frac{(z_{1-\alpha/2} + z_{1-\beta})^2}{2 \cdot (\Delta^*)^2} \pi \cdot (1-\pi)$$

$\theta = 1$ *with a balanced design*

Δ^* *clinically relevant difference*

$z_{1-\alpha/2}$ 1.96 *with a* α *– level* = 0.05 2 *– sided*

$z_{1-\beta}$ 0.842 *with power*(β) = 0.8

π *the estimated total response rate*

The estimated sample size (N/arm) will be used for the zolmitriptan 5 mg and placebo treatment arms. The 2 lower dose treatment arms, zolmitriptan 2.5 mg and zolmitriptan 0.5 mg, will be assigned to patients at a ratio of 5:3:3:5 (placebo:zolmitriptan 0.5 mg:zolmitriptan 2.5 mg:zolmitriptan 5 mg) at randomization. The estimated sample size obtained from the analysis are rounded up to the nearest larger integer and should not be rounded any further. The total sample size after the SSR will be N_{Total} = 2* N/arm_{SSR} + 2*3/5* N/arm_{SSR}. The maximum sample size required after the SSR will be 2*324 + 2*3/5* 324 = 1036 evaluable patients. The sample size will not decrease from the original sample size.

More details will be specified prior to the interim analysis in a DMC charter. No adjustment for the significance level will be done since the analysis is preformed on blinded data and there is no analysis assessing the efficacy.

12.2.2 Primary efficacy variable

The primary null hypothesis to be tested is that the different doses of zolmitriptan 0.5 mg, 2.5 mg and 5 mg are not different from placebo, using pain-free status at 2 hours post treatment as the primary variable.

The primary variable will be analyzed using a logistic regression model with 2-hour pain-free status as the response variable including treatment and center as fixed factors in the model. A step-down approach is used for maintaining the alpha level when comparing the 3 doses of zolmitriptan against placebo for 2-hour pain-free status. Initially, zolmitriptan 5 mg is compared with placebo in terms of odds ratio. If zolmitriptan 5 mg is significantly better than

placebo at the 2-sided 5% level, then zolmitriptan 2.5 mg is compared with placebo, and if it is significantly better than placebo at the 2-sided 5% level, then zolmitriptan 0.5 mg is compared with placebo. If the first comparison between zolmitriptan 5 mg and placebo is not significant, then the zolmitriptan 2.5 mg is not to be compared with placebo, etc. The primary analysis will be based on the FAS with the LOCF approach.

12.2.3 Secondary efficacy variables

The following secondary efficacy variables will be analyzed for OC and/or LOCF in the FAS:

- Pain-free status at 15 minutes and at 1, 2, 3, 4, and 24 hours post treatment;
- Headache response at 15 minutes and at 1, 2, 3, 4, and 24 hours post treatment;
- Sustained headache response at 2 hours subsequent to a 1-hour headache response;
- Presence of associated symptoms of photophobia, phonophobia, or nausea at 15 minutes and at 1, 2, 3, 4, and 24 hours post treatment;
- Resolution of associated symptoms of photophobia, phonophobia, or nausea at 15 minutes and at 1, 2, 3, 4, and 24 hours post treatment;
- Incidence and time to use of rescue medication up to 24 hours post treatment;
- Ability to perform normal activities at 15 minutes and at 1, 2, 3, 4, and 24 hours post treatment.
- Headache recurrence 2 to 24 hours post treatment;
- Bilateral headache (yes/no) at 15 minutes and at 1, 2, 3, 4, and 24 hours post treatment;
- Intensity increased by movement (yes/no) at 15 minutes and at 1, 2, 3, 4, and 24 hours post treatment.

For the binary secondary efficacy variables, the same logistic regression model as for the analysis of primary efficacy variable will be used. Time to use of rescue medication will be displayed graphically using Kaplan-Meier curves by treatment group. Comparison of treatment doses versus placebo will be based on the Cox proportional hazard model. The secondary endpoints will be analyzed at the 2-sided 5% significance level without any multiplicity correction.

12.2.4 Secondary safety variables

The following secondary safety variables will be analyzed in the safety analysis set:

- Incidence, nature and intensity of AEs;

- Vital signs;
- Laboratory assessments;
- ECG;
- Suicidal risks (C-SSRS).

Change from baseline will be calculated for laboratory, ECG, and vital signs variables. Flags for high/low for laboratory measurements, ECG, and vital signs will also be created based on project reference ranges.

12.3 Determination of sample size

A total of 2400 patients will be enrolled to ensure 1000 randomized patients. This assumes a 56% drop-out rate prior to randomization. Assuming 20% of the randomized patients drop out before treatment of a headache attack, 800 patients (250, 150, 150, and 250 patients in the placebo, zolmitriptan 0.5 mg, zolmitriptan 2.5 mg, and zolmitriptan 5 mg treatment arms, respectively) will be evaluable for the primary analysis. This will give 80% power to detect a treatment difference at the 2-sided significance level of 0.05 if the true difference between a zolmitriptan 5 mg treatment and placebo in terms of difference in pain-free rates is 0.11 for the primary endpoint, 2-hour pain-free status. The power to detect a treatment difference between zolmitriptan 2.5 mg and 0.5 mg versus placebo will be 67% if the true treatment difference is 0.11. A 2-treatment, continuity-corrected, chi-square test of equal proportions is used as an approximation for the intended analysis approach in the power calculations. A difference of 0.11 in response rates is considered a clinically relevant effect. The pain-free rate for the placebo treatment group is assumed to be the same as in a previously conducted study (D1221C00005) on zolmitriptan nasal spray in adolescent patients for both periods combined, 0.18.

Since the assumptions for the sample size calculations are uncertain, an interim analysis is planned for after approximately one third of the planned patients have been treated. The sample size will be re-estimated at the interim analysis using a blinded estimation of the observed total 2-hour pain-free status. The sample size can increase depending on the interim results; the maximum number will be 1036 evaluable patients in total, ie, approximately 1295 patients need to be randomized and 2943 patients need to be enrolled.

The interim analysis will be performed by an independent statistician who is not involved with this trial.

12.4 Data monitoring committee

A DMC will perform the interim analysis. The DMC will consist of a statistical expert independent of the study and project team. The DMC will decide on the total sample size needed for the study. The DMC will only communicate the decision on the total sample size to the project team. The DMC will have written operating procedures. The operating procedures will be described in a separate document (DMC charter).

13. IMPORTANT MEDICAL PROCEDURES TO BE FOLLOWED BY THE INVESTIGATOR

13.1 Medical emergencies and AstraZeneca contacts

The PI is responsible for ensuring that procedures and expertise are available to handle medical emergencies during the study. **A medical emergency usually constitutes an SAE and is to be reported as such, see Section 6.4.4.**

In the case of a medical emergency, the investigator should contact the following personnel below:

Name	Role in the study	Address & telephone number
	Study Medical Monitor - Responsible for protocol implementation in US	
	Study Medical Monitor - Responsible for protocol implementation in Latin America	
	Study Medical Monitor - Responsible for protocol implementation in Europe	
	SAE reporting (USA)	

Name	Role in the study	Address & telephone number
Other contact information		
Name	**Role in the study**	**Address & telephone number**
	Central laboratory	
	Central ECG laboratory	
	IVRS	
	Study drug return and destruction	

13.2 Overdose

Patients receiving single oral doses of 50 mg commonly experienced sedation.

The elimination half-life of zolmitriptan administration is approximately 3 hours; and therefore, monitoring of patients after overdose with zolmitriptan should continue for at least 15 hours or while symptoms or signs persist.

There is no specific antidote to zolmitriptan. In cases of severe intoxication, intensive care procedures are recommended, including establishing and maintaining a patent airway, ensuring adequate oxygenation and ventilation, and monitoring and support of the cardiovascular system.

It is unknown what effect hemodialysis or peritoneal dialysis has on the serum concentrations of zolmitriptan.

An overdose is a dose in excess of the dose specified for the dose group. For recording purposes:

- Use of study drug in doses in excess of that specified in the protocol should not be recorded in the eDC system as an AE of "Overdose" unless there are associated

symptoms or signs. The associated symptoms or signs will be the AE terms documented in the source documentation and eDC system.

- An overdose with associated SAE(s) must be recorded as the SAE diagnosis/symptoms on the relevant AE forms in the source documentation and eDC system only.

- An overdose with associated non-serious AEs must be recorded as the AE diagnosis/symptoms on the relevant AE forms in the source documentation and in eDC, and on the separate AstraZeneca "Clinical Study Overdose Report Form." Only overdoses of study drug will be reported.

- An overdose without associated symptoms is only reported on the separate AstraZeneca "Clinical Study Overdose Report Form."

If an overdose on an AstraZeneca study drug occurs in the course of the study, then investigators or other site personnel must inform appropriate AstraZeneca representatives **within 1 day**, ie, immediately, but no later than **the end of the next business day** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site.

For overdoses associated with SAE, standard reporting timelines apply, see Section 6.4.4. For other overdoses, reporting should be done within 30 days.

13.3 Pregnancy

All outcomes of pregnancy should be reported to AstraZeneca or its representative on the pregnancy form.

13.3.1 Maternal exposure

Requirements for contraception in females of childbearing potential are specified in inclusion criterion #9 (see Section 4.1).

If a patient becomes pregnant during the course of the study, the study drug should be discontinued immediately.

Pregnancy itself is not regarded as an AE unless there is a suspicion that the study drug under study may have interfered with the effectiveness of a contraceptive medication. Congenital abnormalities/birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth, or congenital abnormality) should be followed up and documented even if the patient was discontinued from the study.

If any pregnancy occurs in the course of the study, then investigators or other site personnel must inform appropriate AstraZeneca representatives **within 1 day**, ie, immediately, but no later than the **end of the next business day** of when he or she becomes aware of it.

The designated AstraZeneca representative will work with the investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site within 1 or 5 days for SAEs, see Section 6.4.4 and within 30 days for all other pregnancies.

The same timelines apply when outcome information is available.

AstraZeneca's Pregnancy Outcome Report, part 1, is used to report the pregnancy and the Pregnancy Outcome Report, part 2, is used to report the outcome of the pregnancy.

13.3.2 Paternal exposure

There is no restriction on fathering children or donating sperm during the study.

Pregnancy of the patient's partners is not considered to be an AE. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth, or congenital abnormality) should, if possible, be followed up and documented.

14. LIST OF REFERENCES

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Clinical Study Protocol Appendix B

Drug Substance	ZOMIG (zolmitripitan)
Study Code	D1220C00001
Edition Number	1.0
Date	

Appendix B
Additional Safety Information

FURTHER GUIDANCE ON THE DEFINITION OF A SERIOUS ADVERSE EVENT (SAE)

Life threatening

'Life-threatening' means that the subject was at immediate risk of death from the AE as it occurred or it is suspected that use or continued use of the product would result in the subject's death. 'Life-threatening' does not mean that had an AE occurred in a more severe form it might have caused death (eg, hepatitis that resolved without hepatic failure).

Hospitalisation

Outpatient treatment in an emergency room is not in itself a serious AE, although the reasons for it may be (eg, bronchospasm, laryngeal oedema). Hospital admissions and/or surgical operations planned before or during a study are not considered AEs if the illness or disease existed before the subject was enrolled in the study, provided that it did not deteriorate in an unexpected way during the study.

Important medical event or medical intervention

Medical and scientific judgement should be exercised in deciding whether a case is serious in situations where important medical events may not be immediately life threatening or result in death, hospitalisation, disability or incapacity but may jeopardize the subject or may require medical intervention to prevent one or more outcomes listed in the definition of serious. These should usually be considered as serious.

Simply stopping the suspect drug does not mean that it is an important medical event; medical judgement must be used.

Examples of such events are:

- Angioedema not severe enough to require intubation but requiring iv hydrocortisone treatment
- Hepatotoxicity caused by paracetamol (acetaminophen) overdose requiring treatment with N-acetylcysteine
- Intensive treatment in an emergency room or at home for allergic bronchospasm
- Blood dyscrasias (eg, neutropenia or anaemia requiring blood transfusion, etc) or convulsions that do not result in hospitalisation
- Development of drug dependency or drug abuse.

A GUIDE TO INTERPRETING THE CAUSALITY QUESTION

The following factors should be considered when deciding if there is a "reasonable possibility" that an AE may have been caused by the drug.

- Time Course. Exposure to suspect drug. Has the subject actually received the suspect drug? Did the AE occur in a reasonable temporal relationship to the administration of the suspect drug?

- Consistency with known drug profile. Was the AE consistent with the previous knowledge of the suspect drug (pharmacology and toxicology) or drugs of the same pharmacological class? OR could the AE be anticipated from its pharmacological properties?

- Dechallenge experience. Did the AE resolve or improve on stopping or reducing the dose of the suspect drug?

- No alternative cause. The AE cannot be reasonably explained by another aetiology such as the underlying disease, other drugs, other host or environmental factors.

- Rechallenge experience. Did the AE reoccur if the suspected drug was reintroduced after having been stopped? AstraZeneca would not normally recommend or support a rechallenge.

- Laboratory tests. A specific laboratory investigation (if performed) has confirmed the relationship?

A "reasonable possibility" could be considered to exist for an AE where one or more of these factors exist.

In contrast, there would not be a "reasonable possibility" of causality if none of the above criteria apply or where there is evidence of exposure and a reasonable time course but any dechallenge (if performed) is negative or ambiguous or there is another more likely cause of the AE.

In difficult cases, other factors could be considered such as:

- Is this a recognised feature of overdose of the drug?

- Is there a known mechanism?

Ambiguous cases should be considered as being a "reasonable possibility" of a causal relationship unless further evidence becomes available to refute this. Causal relationship in cases where the disease under study has deteriorated due to lack of effect should be classified as no reasonable possibility.

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Clinical Study Protocol Appendix C

Drug Substance	ZOMIG (zolmitripitan)
Study Code	D1220C00001
Edition Number	1.0
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Appendix C
International Airline Transportation Association (IATA) 6.2 Guidance Document

LABELLING AND SHIPMENT OF BIOHAZARD SAMPLES

International Airline Transportation Association (IATA) classifies biohazardous agents into 3 categories **(http://www.iata.org/whatwedo/cargo/dangerous_goods/infectious_substances.htm).** For transport purposes the classification of infectious substances according to risk groups was removed from the Dangerous Goods Regulations (DGR) in the 46th edition (2005). Infectious substances are now classified either as Category A, Category B or Exempt. There is no direct relationship between Risk Groups and categories A and B.

Category A Infectious Substances are infectious substances in a form that, when exposure to it occurs, is capable of causing permanent disability, life-threatening or fatal disease in otherwise healthy humans or animals. Category A pathogens are eg, Ebola, Lassa fever virus:

- are to be packed and shipped in accordance with IATA Instruction 602.

Category B Infectious Substances are infectious Substances that do not meet the criteria for inclusion in Category A. Category B pathogens are eg, Hepatitis A, B, C, D, and E viruses, Human immunodeficiency virus (HIV) types 1 and 2. They are assigned the following UN number and proper shipping name:

- UN 3373 – Biological Substance, Category B
- are to be packed in accordance with UN3373 and IATA 650

Exempt - all other materials with minimal risk of containing pathogens

- Clinical trial samples will fall into Category B or exempt under IATA regulations
- Clinical trial samples will routinely be packed and transported at ambient temperature in IATA 650 compliant packaging **(http://www.iata.org/whatwedo/cargo/dangerous_goods/infectious_substances.htm)**
- **Biological samples transported in dry ice require additional dangerous goods specification for the dry-ice content**
- IATA compliant courier and packaging materials should be used for packing and transportation and packing should be done by an IATA certified person, as applicable

- Samples routinely transported by road or rail are subject to local regulations which require that they are also packed and transported in a safe and appropriate way to contain any risk of infection or contamination by using approved couriers and packaging / containment materials at all times. The IATA 650 biological sample containment standards are encouraged wherever possible when road or rail transport is used.

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Clinical Study Protocol Appendix D

Drug Substance	ZOMIG (zolmitriptan)
Study Code	D1220C00001
Edition Number	1.0
Date	

Appendix D
International Headache Society (IHS and IHS-R) Diagnostic Criteria for Migraine Headaches

1. SUMMARY OF INTERNATIONAL HEADACHE SOCIETY (IHS) CRITERIA FOR MIGRAINE HEADACHES

Migraine without aura:

1. At least 5 headaches fulfilling (2) – (4)

2. Headache attacks lasting 4 – 72 hours (untreated or unsuccessfully treated)

3. Headache has at least 2 of the following characteristics:

   - unilateral location
   - pulsating quality
   - moderate or severe intensity (inhibits or prohibits daily activities)
   - aggravation by walking stairs or similar routine physical activity

4. During headache, at least 1 of the following:

   - nausea and/or vomiting
   - photophobia and phonophobia

Migraine with aura:

5. At least 2 headaches fulfilling (2)

   At least 3 of the following 4 characteristics:

   - 1 or more fully reversible aura symptoms indicating focal cerebral cortical and/or brain stem dysfunction
   - at least 1 aura symptom develops gradually over more than 4 minutes or, 2 or more symptoms occur in succession
   - no aura symptom lasts more than 60 minutes. If more than 1 aura symptom is present, accepted duration is proportionally increased
   - headache follows aura with a free interval of less than 60 minutes (it may also begin before or simultaneously with aura)

2. SUMMARY OF INTERNATIONAL HEADACHE SOCIETY CRITERIA REVISED (IHS-R) FOR PEDIATRIC MIGRAINE HEADACHES

Pediatric migraine without aura:

A. At least 5 attacks fulfilling (B) – (D)

B. Headache attack lasting 1 – 48 hours

C. Headache has at least 2 of the following:

- bilateral (Frontal/temporal) or unilateral location
- pulsating quality
- moderate or severe intensity (inhibits or prohibits daily activities)
- aggravation by routine physical activity

D. During headache, at least 1 of the following:

- nausea and/or vomiting
- photophobia and phonophobia

Pediatric migraine with aura:

A. At least 2 headaches fulfilling (B)

B. At least 3 of the following 4 characteristics:

- 1 or more fully reversible aura symptoms indicating focal cerebral cortical and/or brain stem dysfunction
- at least 1 aura symptom develops gradually over more than 4 minutes or, 2 or more symptoms occur in succession
- no aura symptom lasts more than 60 minutes.
- headache follows less than 60 minutes

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Clinical Study Protocol Appendix E	
Drug Substance	ZOMIG (zolmitriptan)
Study Code	D1220C00001
Edition Number	1.0
Date	

Appendix E
Pediatric blood pressure normative

1. PEDIATRIC BLOOD PRESSURE NORMATIVE (BOYS)[a]

Age (Year)	BP Percentile ↓	Systolic BP (mmHg) ← Percentile of Height →							Diastolic BP (mmHg) ← Percentile of Height →						
		5th	10th	25th	50th	75th	90th	95th	5th	10th	25th	50th	75th	90th	95th
1	50th	80	81	83	85	87	88	89	34	35	36	37	38	39	39
	90th	94	95	97	99	100	102	103	49	50	51	52	53	53	54
	95th	98	99	101	103	104	106	106	54	54	55	56	57	58	58
	99th	105	106	108	110	112	113	114	61	62	63	64	65	66	66
2	50th	84	85	87	88	90	92	92	39	40	41	42	43	44	44
	90th	97	99	100	102	104	105	106	54	55	56	57	58	58	59
	95th	101	102	104	106	108	109	110	59	59	60	61	62	63	63
	99th	109	110	111	113	115	117	117	66	67	68	69	70	71	71
3	50th	86	87	89	91	93	94	95	44	44	45	46	47	48	48
	90th	100	101	103	105	107	108	109	59	59	60	61	62	63	63
	95th	104	105	107	109	110	112	113	63	63	64	65	66	67	67
	99th	111	112	114	116	118	119	120	71	71	72	73	74	75	75
4	50th	88	89	91	93	95	96	97	47	48	49	50	51	51	52
	90th	102	103	105	107	109	110	111	62	63	64	65	66	66	67
	95th	106	107	109	111	112	114	115	66	67	68	69	70	71	71
	99th	113	114	116	118	120	121	122	74	75	76	77	78	78	79
5	50th	90	91	93	95	96	98	98	50	51	52	53	54	55	55
	90th	104	105	106	108	110	111	112	65	66	67	68	69	69	70
	95th	108	109	110	112	114	115	116	69	70	71	72	73	74	74
	99th	115	116	118	120	121	123	123	77	78	79	80	81	81	82
6	50th	91	92	94	96	98	99	100	53	53	54	55	56	57	57
	90th	105	106	108	110	111	113	113	68	68	69	70	71	72	72
	95th	109	110	112	114	115	117	117	72	72	73	74	75	76	76
	99th	116	117	119	121	123	124	125	80	80	81	82	83	84	84
7	50th	92	94	95	97	99	100	101	55	55	56	57	58	59	59
	90th	106	107	109	111	113	114	115	70	70	71	72	73	74	74
	95th	110	111	113	115	117	118	119	74	74	75	76	77	78	78
	99th	117	118	120	122	124	125	126	82	82	83	84	85	86	86
8	50th	94	95	97	99	100	102	102	56	57	58	59	60	60	61
	90th	107	109	110	112	114	115	116	71	72	72	73	74	75	76
	95th	111	112	114	116	118	119	120	75	76	77	78	79	79	80
	99th	119	120	122	123	125	127	127	83	84	85	86	87	87	88
9	50th	95	96	98	100	102	103	104	57	58	59	60	61	61	62
	90th	109	110	112	114	115	117	118	72	73	74	75	76	76	77
	95th	113	114	116	118	119	121	121	76	77	78	79	80	81	81
	99th	120	121	123	125	127	128	129	84	85	86	87	88	88	89
10	50th	97	98	100	102	103	105	106	58	59	60	61	61	62	63
	90th	111	112	114	115	117	119	119	73	73	74	75	76	77	78
	95th	115	116	117	119	121	122	123	77	78	79	80	81	81	82
	99th	122	123	125	127	128	130	130	85	86	86	88	88	89	90

Age (Year)	BP Percentile ↓	Systolic BP (mmHg) ← Percentile of Height →							Diastolic BP (mmHg) ← Percentile of Height →						
		5th	10th	25th	50th	75th	90th	95th	5th	10th	25th	50th	75th	90th	95th
11	50th	99	100	102	104	105	107	107	59	59	60	61	62	63	63
	90th	113	114	115	117	119	120	121	74	74	75	76	77	78	78
	95th	117	118	119	121	123	124	125	78	78	79	80	81	82	82
	99th	124	125	127	129	130	132	132	86	86	87	88	89	90	90
12	50th	101	102	104	106	108	109	110	59	60	61	62	63	63	64
	90th	115	116	118	120	121	123	123	74	75	75	76	77	78	79
	95th	119	120	122	123	125	127	127	78	79	80	81	82	82	83
	99th	126	127	129	131	133	134	135	86	87	88	89	90	90	91
13	50th	104	105	106	108	110	111	112	60	60	61	62	63	64	64
	90th	117	118	120	122	124	125	126	75	75	76	77	78	79	79
	95th	121	122	124	126	128	129	130	79	79	80	81	82	83	83
	99th	128	130	131	133	135	136	137	87	87	88	89	90	91	91
14	50th	106	107	109	111	113	114	115	60	61	62	63	64	65	65
	90th	120	121	123	125	126	128	128	75	76	77	78	79	79	80
	95th	124	125	127	128	130	132	132	80	80	81	82	83	84	84
	99th	131	132	134	136	138	139	140	87	88	89	90	91	92	92
15	50th	109	110	112	113	115	117	117	61	62	63	64	65	66	66
	90th	122	124	125	127	129	130	131	76	77	78	79	80	80	81
	95th	126	127	129	131	133	134	135	81	81	82	83	84	85	85
	99th	134	135	136	138	140	142	142	88	89	90	91	92	93	93
16	50th	111	112	114	116	118	119	120	63	63	64	65	66	67	67
	90th	125	126	128	130	131	133	134	78	78	79	80	81	82	82
	95th	129	130	132	134	135	137	137	82	83	83	84	85	86	87
	99th	136	137	139	141	143	144	145	90	90	91	92	93	94	94
17	50th	114	115	116	118	120	121	122	65	66	66	67	68	69	70
	90th	127	128	130	132	134	135	136	80	80	81	82	83	84	84
	95th	131	132	134	136	138	139	140	84	85	86	87	87	88	89
	99th	139	140	141	143	145	146	147	92	93	93	94	95	96	97

BP = Blood pressure.

[a] National High Blood Pressure Education Program (NHBPEP) Working Group on Hypertension Control in Children and Adolescents. The fourth report on the diagnosis, evaluation, and treatment of high blood pressure in children and adolescents. US Department of Health and Human Services, National Institutes of Health, National Heart, Lung, and Blood Institute, National High Blood Pressure Education Program. NIH Publication No. 05-5267. Bethesda, MD; Revised May 2005.

2. PEDIATRIC BLOOD PRESSURE NORMATIVE (GIRLS)[a]

Age (Year)	BP Percentile ↓	Systolic BP (mmHg) ← Percentile of Height →							Diastolic BP (mmHg) ← Percentile of Height →						
		5th	10th	25th	50th	75th	90th	95th	5th	10th	25th	50th	75th	90th	95th
1	50th	83	84	85	86	88	89	90	38	39	39	40	41	41	42
	90th	97	97	98	100	101	102	103	52	53	53	54	55	55	56
	95th	100	101	102	104	105	106	107	56	57	57	58	59	59	60
	99th	108	108	109	111	112	113	114	64	64	65	65	66	67	67
2	50th	85	85	87	88	89	91	91	43	44	44	45	46	46	47
	90th	98	99	100	101	103	104	105	57	58	58	59	60	61	61
	95th	102	103	104	105	107	108	109	61	62	62	63	64	65	65
	99th	109	110	111	112	114	115	116	69	69	70	70	71	72	72
3	50th	86	87	88	89	91	92	93	47	48	48	49	50	50	51
	90th	100	100	102	103	104	106	106	61	62	62	63	64	64	65
	95th	104	104	105	107	108	109	110	65	66	66	67	68	68	69
	99th	111	111	113	114	115	116	117	73	73	74	74	75	76	76
4	50th	88	88	90	91	92	94	94	50	50	51	52	52	53	54
	90th	101	102	103	104	106	107	108	64	64	65	66	67	67	68
	95th	105	106	107	108	110	111	112	68	68	69	70	71	71	72
	99th	112	113	114	115	117	118	119	76	76	76	77	78	79	79
5	50th	89	90	91	93	94	95	96	52	53	53	54	55	55	56
	90th	103	103	105	106	107	109	109	66	67	67	68	69	69	70
	95th	107	107	108	110	111	112	113	70	71	71	72	73	73	74
	99th	114	114	116	117	118	120	120	78	78	79	79	80	81	81
6	50th	91	92	93	94	96	97	98	54	54	55	56	56	57	58
	90th	104	105	106	108	109	110	111	68	68	69	70	70	71	72
	95th	108	109	110	111	113	114	115	72	72	73	74	74	75	76
	99th	115	116	117	119	120	121	122	80	80	80	81	82	83	83
7	50th	93	93	95	96	97	99	99	55	56	56	57	58	58	59
	90th	106	107	108	109	111	112	113	69	70	70	71	72	72	73
	95th	110	111	112	113	115	116	116	73	74	74	75	76	76	77
	99th	117	118	119	120	122	123	124	81	81	82	82	83	84	84
8	50th	95	95	96	98	99	100	101	57	57	57	58	59	60	60
	90th	108	109	110	111	113	114	114	71	71	71	72	73	74	74
	95th	112	112	114	115	116	118	118	75	75	75	76	77	78	78
	99th	119	120	121	122	123	125	125	82	82	83	83	84	85	86
9	50th	96	97	98	100	101	102	103	58	58	58	59	60	61	61
	90th	110	110	112	113	114	116	116	72	72	72	73	74	75	75
	95th	114	114	115	117	118	119	120	76	76	76	77	78	79	79
	99th	121	121	123	124	125	127	127	83	83	84	84	85	86	87
10	50th	98	99	100	102	103	104	105	59	59	59	60	61	62	62
	90th	112	112	114	115	116	118	118	73	73	73	74	75	76	76
	95th	116	116	117	119	120	121	122	77	77	77	78	79	80	80
	99th	123	123	125	126	127	129	129	84	84	85	86	86	87	88

Age (Year)	BP Percentile ↓	Systolic BP (mmHg) ← Percentile of Height →							Diastolic BP (mmHg) ← Percentile of Height →						
		5th	10th	25th	50th	75th	90th	95th	5th	10th	25th	50th	75th	90th	95th
11	50th	100	101	102	103	105	106	107	60	60	60	61	62	63	63
	90th	114	114	116	117	118	119	120	74	74	74	75	76	77	77
	95th	118	118	119	121	122	123	124	78	78	78	79	80	81	81
	99th	125	125	126	128	129	130	131	85	85	86	87	87	88	89
12	50th	102	103	104	105	107	108	109	61	61	61	62	63	64	64
	90th	116	116	117	119	120	121	122	75	75	75	76	77	78	78
	95th	119	120	121	123	124	125	126	79	79	79	80	81	82	82
	99th	127	127	128	130	131	132	133	86	86	87	88	88	89	90
13	50th	104	105	106	107	109	110	110	62	62	62	63	64	65	65
	90th	117	118	119	121	122	123	124	76	76	76	77	78	79	79
	95th	121	122	123	124	126	127	128	80	80	80	81	82	83	83
	99th	128	129	130	132	133	134	135	87	87	88	89	89	90	91
14	50th	106	106	107	109	110	111	112	63	63	63	64	65	66	66
	90th	119	120	121	122	124	125	125	77	77	77	78	79	80	80
	95th	123	123	125	126	127	129	129	81	81	81	82	83	84	84
	99th	130	131	132	133	135	136	136	88	88	89	90	90	91	92
15	50th	107	108	109	110	111	113	113	64	64	64	65	66	67	67
	90th	120	121	122	123	125	126	127	78	78	78	79	80	81	81
	95th	124	125	126	127	129	130	131	82	82	82	83	84	85	85
	99th	131	132	133	134	136	137	138	89	89	90	91	91	92	93
16	50th	108	108	110	111	112	114	114	64	64	65	66	66	67	68
	90th	121	122	123	124	126	127	128	78	78	79	80	81	81	82
	95th	125	126	127	128	130	131	132	82	82	83	84	85	85	86
	99th	132	133	134	135	137	138	139	90	90	90	91	92	93	93
17	50th	108	109	110	111	113	114	115	64	65	65	66	67	67	68
	90th	122	122	123	125	126	127	128	78	79	79	80	81	81	82
	95th	125	126	127	129	130	131	132	82	83	83	84	85	85	86
	99th	133	133	134	136	137	138	139	90	90	91	91	92	93	93

BP = Blood pressure.

[a] National High Blood Pressure Education Program (NHBPEP) Working Group on Hypertension Control in Children and Adolescents. The fourth report on the diagnosis, evaluation, and treatment of high blood pressure in children and adolescents. US Department of Health and Human Services, National Institutes of Health, National Heart, Lung, and Blood Institute, National High Blood Pressure Education Program. NIH Publication No. 05-5267. Bethesda, MD; Revised May 2005.

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Clinical Study Protocol Appendix F

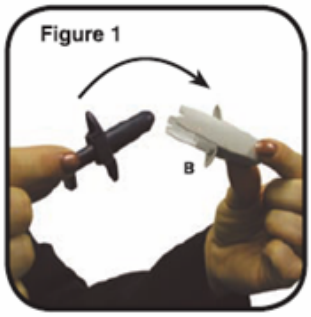
Drug Substance	ZOMIG (zolmitriptan)
Study Code	D1220C00001
Edition Number	1.0
Date	

Appendix F
STEPS FOR USING STUDY NASAL SPRAY

Product Instructions

Steps for using ZOMIG Nasal Spray (please read all steps before using for the first time):

1. Blow your nose gently before use. Remove the protective cap (B) (Figure 1). Hold the nasal sprayer device gently with your fingers and thumb as shown in the picture to the right (Figure 2). There is only one dose in the nasal sprayer. Do not try to prime the nasal sprayer or you will lose the dose. Do not press the plunger until you have put the tip into your nostril or you will lose the dose.



2. Block one nostril by pressing firmly on the side of your nose (Figure 3). Either nostril can be used. Put the tip (A) of the sprayer device into the other nostril as far as feels comfortable and tilt your head slightly as shown in the picture to the right (Figure 4).

Do not press the plunger yet.

Do not spray the contents of the device in your eyes.

3. Breathe in gently through your nose and at the same time press the plunger (D) firmly with your thumb. The plunger may feel stiff and you may hear a click. Keep your head slightly tilted back and remove the tip from your nose. Breathe gently through your mouth for 5-10 seconds. You may feel liquid in your nose or the back of your throat. This is normal and will soon pass.

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