PROTOCOL TITLE:

A Phase 3, Multicenter, Randomized, Double-blind, Placebo-controlled Study to Assess the Safety and Efficacy of ONZETRA® Xsail® (Sumatriptan Nasal Powder) for the Acute Treatment of Episodic Migraine With or Without Aura in Adolescents.

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Sponsor:	Currax Pharmaceuticals, LLC 10 North Park Place, Suite 201 Morristown, NJ 07690
Medical Monitor:	Dr. Robert Pennington
Phone:	1-908-239-0292
Mobile:	1-732-589-2478
Email:	robert.pennington@ecrscorp.com

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

Abbreviation	Definition
5-HT	5-hydroxytryptamine
AAN	American Academy of Neurology
AE	Adverse event
ADE	Adverse device effect
BMI	Body mass index
CFR	Code of Federal Regulations
CMH	Cochran-Mantel-Haenszel
CRF	Case report form
CRO	Contract research organization
C-SSRS	Columbia Suicide Severity Rating Scale
DMP	Data management plan
eCRF	Electronic case report form
EDC	Electronic data capture
ET	Early termination
FDA	US Food and Drug Administration
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
HPMC	Hydroxypropyl methylcellulose
ICF	Informed consent form
ICH	International Conference on Harmonisation
ICHD	International Classification of Headache Disorders
IFU	Instructions for use
IP	Investigational product
IRB	Institutional Review Board
IWRS	Interactive web response system
LOCF	Last observation carried forward
MAO-A	Monoamine oxidase-A
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified intent-to-treat
MM	Medical Monitor
NF	National Formulary
NSAID	Non-steroidal anti-inflammatory drug
OTC	Over–the-counter
SAE	Serious adverse event
SDV	Source data verification
UADE	Unanticipated adverse device effect
USP	United States Pharmacopoeia
WHO	World Health Organization

PROTOCOL AGREEMENT

Protocol Title:

A Phase 3, Multicenter, Randomized, Double-blind, Placebo-controlled Study to Assess the Safety and Efficacy of ONZETRA® Xsail® (Sumatriptan Nasal Powder) for the Acute Treatment of Episodic Migraine With or Without Aura in Adolescents

Protocol Number: 17-AVP-825-301

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The signatures of the principal investigator and representative of the sponsor below constitute their approval of this protocol and further provide the necessary assurances that:

1. This study will be conducted according to Good Clinical Practice (GCP) and to all stipulations, as specified in both clinical and administrative sections of the protocol including the Declaration of Helsinki.
2. The conduct and results of this study will be kept confidential, and the electronic case report forms (eCRFs) and other pertinent data will become the property of Currax Pharmaceuticals.
3. The protocol contains all necessary information required to conduct the study, as outlined in the protocol, and that the study will not be initiated without the approval of an appropriate Institutional Review Board (IRB).
4. All participants in this study will provide written informed consent in accordance with the requirements specified in the Code of Federal Regulations (21 CFR Parts 50, 56, 312) and/or the Declaration of Helsinki. All participants will also be informed that their medical records will be kept confidential except for review by Currax or its representatives, the U.S. Food and Drug Administration (FDA), or other regulatory agencies if applicable.

Principal Investigator Signature	Date
Principal Investigator Name: _____	
Currax Representative Signature	02 February 2021 Date
Currax Representative Name: Errol M. Gould, PhD	

STUDY SYNOPSIS

Title: A Phase 3, Multicenter, Randomized, Double-blind, Placebo-controlled Study to Assess the Safety and Efficacy of ONZETRA® Xsail® (Sumatriptan Nasal Powder) for the Acute Treatment of Episodic Migraine With or Without Aura in Adolescents.

Study Objectives

The objective of the study is to evaluate the safety and efficacy of ONZETRA Xsail (AVP-825) compared to placebo in the acute treatment of migraine in adolescent subjects, 12 through 17 years of age.

Study Population

Number of Subjects: Approximately 236 adolescent subjects will be randomized (~420 subjects to be enrolled for placebo run-in), at approximately 30 centers in the United States.

Condition/Disease: Acute migraine with or without aura.

Key Inclusion Criteria:

- Male and female subjects 12 to 17 years (inclusive) of age at the time of informed consent;
- Have a diagnosis of episodic migraine with or without aura according to International Classification of Headache Disorders-3rd edition, beta version (ICHD-IIIB, 1.2.1 or 1.1) criteria, for at least 1 year prior to the screening/enrollment visit;
- Experienced migraine attacks or moderate-to-severe intensity and typically lasting ≥ 3 hours untreated, occurring at a frequency of ≥ 2 to ≤ 14 attacks per month for the past 6 months prior to the screening/enrollment visit;
- Subject's parent or legal guardian must be willing to sign a copy of informed consent form (ICF) as well as documentation for Written Authorization for Use and Release of Health and Research Study Information, after the nature and risks of study participation have been fully explained. Subjects must be willing to provide informed assent.

Key Exclusion Criteria:

- Subjects with ≥ 15 headache days per month in total (migraine, probable migraine, or tension-type);

- Subjects with the following headache types: retinal [ICHD-IIIB 1.2.4], with brainstem aura [ICHD-IIIB 1.2.2], hemiplegic [ICHD-IIIB 1.2.3], status migrainosus [ICHD-IIIB 1.4.1], other forms of complicated migraine, or secondary headaches
- Subjects who have not responded to an adequate dose and appropriate duration of treatment with 2 or more triptans;
- Subjects with known nasal obstruction, current uncontrolled nasopharyngeal illness, or known velum insufficiency (i.e., a cleft palate and/or structural abnormalities in the soft palate and nasopharynx) which may interfere with the proper use of study medication;
- Subjects whose conditions in the investigator's opinion may put the subject at significant safety risk or confound the study results. This include subjects who in the investigator's opinion should not be enrolled in the study due to the risks described in the Warnings and Precautions or Contraindications sections of the ONZETRA Xsail Prescribing Information.

A complete list of inclusion/exclusion criteria is presented in Section 4 of the study protocol.

Study Design

Design: This is a Phase 3, multicenter, randomized, double-blind, placebo-controlled study evaluating AVP-825 in adolescent subjects for the treatment of acute migraine with or without aura. This study includes 2 treatment phases; a single-blind placebo run-in phase and a double-blind placebo-controlled treatment phase. A schematic of the study design is presented in Figure 1.

Duration: Subjects will be enrolled in the study for up to approximately 28 weeks, with up to 12-weeks in a single-blind placebo run-in period and up to 12-weeks in a double-blind treatment period, and an exit/early termination visit 10 days after treatment in the double-blind treatment phase.

Study Treatment: The investigational product is ONZETRA Xsail 22 mg (AVP-825, sumatriptan nasal powder 11 mg per nosepiece).

Control: The control treatment will be the same device as AVP-825 with matching placebo nosepieces containing capsules filled with lactose instead of sumatriptan.

Randomization/Stratification: All eligible patients will treat one migraine attack of moderate to severe pain intensity during the single-blind phase (Migraine Attack 1). Placebo non-responders (defined as subjects who are not headache pain free 2 hours post treatment of Migraine Attack 1)

who meet all inclusion/exclusion criteria will be randomized in a 1:1 ratio (active: placebo) to treat one migraine attack of moderate to severe pain intensity in the double-blind treatment phase (Migraine Attack 2). Randomization will be stratified by age (12 to 14 years inclusive versus 15 to 17 years inclusive). Enrollment will be monitored to ensure that number of patients in either age group does not exceed 70% or drop below 30%.

Dose Regimen: Study medication will be administered as soon as possible after the development of a migraine attack associated with moderate-to-severe headache pain during each phase, per the instructions for use (IFU) provided to the subject.

Assessments and Visits

There are up to 3 scheduled clinic visits including: screening/enrollment (Visit 1), randomization (Visit 2), and exit/early termination (Visit 3). Monthly follow-up phone calls will be made after Visits 1 and 2, up to 12 weeks after the visit depending on when Migraine Attacks 1 and 2 are treated. Study procedures will be performed at each visit as outlined in the Schedule of Evaluations and Visits (Table 1) and for each migraine attack (at 15, 30, 60, 120 minutes, and 24 hour post dose) as outlined in Table 2. The randomization visit should occur approximately 10 days after treatment of Migraine Attack 1.

Outcome Measures

Efficacy Endpoints and Patient Satisfaction Measures

Primary efficacy endpoint:

The primary endpoint of the study is headache pain-free at 120 minutes following treatment of Migraine Attack 2.

Secondary efficacy endpoints (Migraine Attack 2):

- Headache relief (defined as a reduction in pain intensity from moderate or severe [grade 2 or 3] at baseline to none or mild [grade 0 or 1]) at 120 minutes
- Headache pain-free by time (other than at 120 minutes)
- Headache relief by time (other than at 120 minutes)
- Change from baseline in headache severity by time
- Sustained headache relief, defined as headache relief [headache severity mild (grade 1) or none (grade 0)] at 2 hours with no worsening of headache, use of a second dose of study medication, or rescue medication taken through 24 hours after dose

- Sustained pain freedom, defined as pain freedom [headache severity none (grade 0)] at 2 hours with no recurrence of headache, use of a second dose of study medication or rescue medication taken through 24 hours after dose
- Rescue medication use and time to rescue medication
- Number of subjects with nausea, phonophobia, photophobia, or vomiting by time
- Number of subjects who return to 'normal' functioning by time
- Time to recurrence of headache defined as an increase from a headache severity score of 0 (none) or 1 (mild) at 2 hours to 2 (moderate) or 3 (severe) within 24 hours

Exploratory efficacy endpoints (Migraine Attack 2):

- Sustained headache relief (1 to 2 hours), defined as headache relief [headache severity mild (grade 1) or none (grade 0)] at 60 minutes with no worsening of headache, use of a second dose of study medication, or rescue medication taken through 120 minutes after dose
- Sustained pain freedom (1 to 2 hours), defined as pain freedom [headache severity none (grade 0)] at 60 minutes with no recurrence of headache, use of a second dose of study medication or rescue medication taken through 120 minutes after dose
- Bilateral headache at predefined timepoints
- Headache intensity increased by movement at predefined timepoints

Safety

- Adverse events
- Physical and neurological examination
- Vital signs
- Columbia Suicide Severity Rating Scale (C-SSRS)

General Statistical Methods and Types of Analyses

Analysis Populations

Two analysis populations will be used; modified intent-to-treat (mITT) and safety. The mITT population includes all subjects randomized and treated for Migraine Attack 2 who have at least one post-baseline efficacy assessment and will be used for all analyses of efficacy. Subjects in the mITT population will be included in the treatment group to which they were randomized

regardless of treatment received. The safety population includes all subjects who received study treatment and will be used for all analyses of safety. Subjects will be included in the treatment group based on the actual treatment received.

Efficacy Analyses

The primary efficacy endpoint of the study is headache pain-free (no headache) at the 120-minutes following treatment of Migraine Attack 2. Treatment comparison will be performed by using the Cochran-Mantel-Haenszel (CMH) test stratified by age group (12-14 years or 15-17 years) and baseline migraine pain severity (moderate or severe). Secondary efficacy endpoints will be analyzed similarly, or by appropriate statistical tests. Missing data will be imputed by treatment failure, i.e., headache pain-free equals no.

Safety Analyses

Safety measures will be summarized by treatment.

Sample Size Calculation

Power calculations are based on the results of the completed pivotal trial for adults (OPN-SUM-MIG-3301, Avanir data on file). The observed percentage (n) of subjects who are headache pain-free at 120 minutes was 34.3% (37) vs. 17.3% (18) for AVP-825 vs. placebo, respectively. For this study in adolescents with single-blind placebo run-in, if it is assumed that the percentage of subjects who are headache pain free at 120 minutes is 30% vs. 15%, a sample size of 236 (118/arm) randomized and treated at Migraine Attack 2 would provide approximately 80% power with 2-sided $\alpha = 0.05$. In consideration of the attrition rate during the run-in phase, it is estimated that approximately 420 subjects would be needed to enter the single-blind placebo run-in phase in order to have 236 subjects randomized and treated for Migraine Attack 2.

Figure 1 Study Schematic

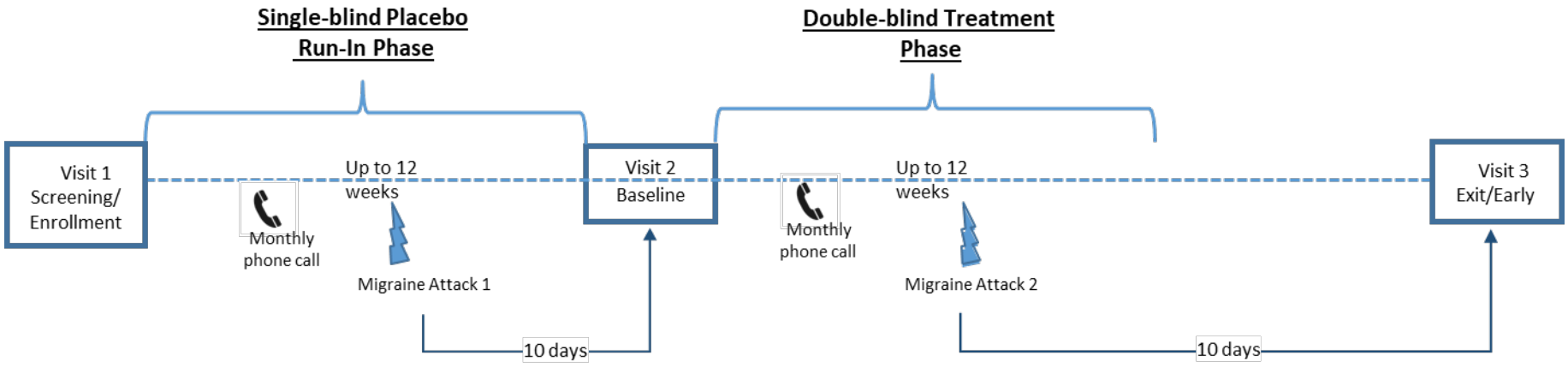

Table 1 Schedule of Evaluations and Visits

	Screening/ Enrollment	**Single-Blind Placebo Run-in (up to 12 weeks) Migraine Attack 1**	**Randomization (Baseline)**	**Double-Blind Treatment (up to 12 weeks) Migraine Attack 2**	**Exit/ET**
Visit	Visit 1	Monthly phone call	Visit 2	Monthly phone call	Visit 3
Window	Day -3 to 1	Every 30 ± 3 days after Visit 1	10 ± 4 days after Attack 1	Every 30 ± 3 days after Visit 2	10 ± 4 days after Attack 2
Sign informed consent/minor assent	X				
Medical and migraine history	X		X[1]		
Review of eligibility	X		X[2]		
Physical (including nasal examination) and neurological examination	X		X[3]		X
Randomization			X		
Vital signs, height and weight	X				
Urine drug screen	X		X		X
Urine pregnancy test[4]	X		X		X
C-SSRS	X		X		X
Adverse events	X	X	X	X	X
Prior and concomitant medications	X	X	X	X	X
Training on use of study medication	X		X		
Provide/collect diary	X		X[5]		X
Access IWRS	X		X		X
Dispense and/or collect study medication	X		X		X

C-SSRS = Columbia-Suicide Severity Rating Scale; ET = early termination; IWRS = interactive web response system;
Note: Subjects who do not have a migraine attack within 12 weeks of the screening/enrollment visit (single-blind phase) or randomization visit (double-blind treatment phase) may be granted another 12 weeks in each period based on sponsor approval.

1 Update any new information on medical and migraine history obtained since screening/enrollment.

2 A protocol eligibility form must be completed for subjects to be randomized.

3. Nasal examination only should be performed before randomization

4 For females of childbearing potential only.

5 Diary will be reviewed and returned to the subjects who are eligible to continue in the study.

Table 2 Time and Event Schedule for Migraine Attacks 1 and 2

	Pre-Dose	Dosing	15 min	30 min	60 min	120 min	3 Hours	4 Hours	24 Hours
Record efficacy assessments in diary:									
Pain free (Yes/No)			X	X	X	X	X	X	X
Headache severity score	X		X[1]	X[1]	X[1]	X[1]	X[1]	X[1]	X[1]
Migraine symptoms (separate questions): Nausea, vomiting, photophobia, phonophobia	X		X	X	X	X			X
Dose of study drug medication		X							
Bilateral headache (Yes/No)	X		X[1]		X[1]	X[1]	X[1]	X[1]	X[1]
Intensity increased by movement (Yes/No)	X		X[1]		X[1]	X[1]	X[1]	X[1]	X[1]
Ability to function question	X		X	X	X	X			X
Time of recurrence of headache						X[2]	X[2]		
Rescue medication						X[2]	X[2]		

Min = minutes;
1 Assessed only if response to pain free question is "No"
2 Assessment should be made after 120 minutes.

1 BACKGROUND AND CLINICAL RATIONALE

Migraine is a common disabling primary headache disorder in adults. Epidemiological studies have documented its high prevalence and high socioeconomic and personal impacts. An overall US prevalence of migraine has been reported to be 17.5% among females and 8.6% among males.[1] Migraine attacks are recurrent and associated with moderate to severe headache that are usually associated with gastrointestinal, neurologic, and autonomic symptoms. Migraine attacks generally occur several times per month, typically last 4 to 72 hours, and are characterized by moderate to severe headaches, often unilateral, and with a pulsating quality. Migraines are often associated with nausea and/or vomiting, phonophobia, and/or photophobia. Approximately 30% of headaches also have associated aura, which is characterized by the transient focal neurological symptoms that usually precede or sometimes accompany the headache.[2,3]

Migraine is the most common acute and recurrent headache syndrome in children. Prevalence data estimate that 3% to 23% of children and adolescents have migraines.[4–8] Migraine in children and adolescents appears to be a similar nosological entity as migraine in adults with minor differences due to either different lifestyle (school/vacation) or due to incomplete neurological development.[9–13] Although the clinical characteristics of migraine are similar to adults, some key differences have been noted in children and adolescents which can impact diagnosis and treatment, including shorter duration of the attacks, more frequent bilateral headaches, fewer aura symptoms, and prominent gastrointestinal symptoms.[14] Along with the pain and associated symptoms, migraine in adolescents can result in decreased functional ability and a significant burden on quality of life. The impact of headaches on quality of life in this population is similar to that found for other chronic illness conditions such as childhood cancer, heart disease, and rheumatic disease.[15] Migraine disability can lead to reduced school performance and missed school days, in addition to limiting participation in organized activities and socializing with friends.[16] If uncontrolled, these effects of migraine may adversely affect the educational/social growth and development of adolescents with migraine.

The management of migraine in children, as in adults, consists of general measures, abortive treatment, and prophylactic treatment. An individual patient may need all three approaches.[6,7,17,18] Both prescription and over-the-counter (OTC) medications have been utilized in the treatment of migraines in pediatric patients and similar efficacy of such medicines in adult and pediatric migraineurs has been reported.[19,20] However, the number of drugs studied and approved for the abortive treatment of migraine attacks in children and adolescents is limited compared with adults. This is due both to the practical challenges of conducting studies in children and the difficulty of demonstrating efficacy of treatments in young migraineurs due to

high placebo response.[21,22] Non-prescription medications like acetaminophen and ibuprofen have been shown to be safe and effective for acute migraine treatment in children.[23,24] Triptans are the only class of medication developed specifically for the treatment of acute migraine, and there are three triptans and one triptan/nonsteroidal anti-inflammatory drug (NSAID) combination product which have been approved by the Food and Drug Administration (FDA) for acute migraine therapy in the pediatric population.[25] In 2009, Almotriptan tablets became the first triptan approved for treatment in 12–17 year-olds,[26] but the indication was only for pain and not migraine associated symptoms. Since then, rizatriptan tablets (6–17 year-olds),[27] sumatriptan/naproxen sodium tablets (12–17 year-olds)[28] and zolmitriptan nasal spray (12–17 year-olds)[29] have been approved for the acute treatment of migraine in children and/or adolescents.

There are 2 non-blinded, single-dose, single-center studies that examine the pharmacokinetics of intranasal sumatriptan in children aged 6 to 11 years (Study SUM40254)[30] and in adolescents aged 12 to 17 years (Study SUMB1006).[31] Both studies were conducted in patients diagnosed with migraine and demonstrated that pharmacokinetic parameters outside of a migraine attack in adolescents are similar to those previously reported in adults, suggesting that adolescents should be dosed similarly to adults. Given the dose adjustment scheme used in these studies based on age and bodyweight, there were no clinically significant differences in sumatriptan exposure between adults, adolescents, and children. Various doses and formulations of sumatriptan have been widely studied in adolescents, including subcutaneous,[32,33] oral,[34] and nasal spray formulations.[35–38] Of the studies designed as placebo-controlled trials evaluating pain relief following treatment of a moderate-to-severe migraine attack, all failed to demonstrate efficacy for the primary endpoints, primarily due to high placebo response. For this reason, sumatriptan has not yet been approved by the FDA for use in adolescents with migraine. However, efficacy was demonstrated through secondary endpoints and pooled analysis suggesting a high probability of achieving pain freedom at 2 hours following treatment with 20 mg sumatriptan nasal spray. Based on these results, the 2004 American Academy of Neurology (AAN) Practice parameter on the pharmacologic treatment of migraine headache in children and adolescents concluded that sumatriptan nasal spray is effective and should be considered for the acute treatment of migraine in adolescents.[7]

ONZETRA® Xsail® (AVP-825) is a novel intranasal delivery system containing low-dose sumatriptan powder, approved for the acute treatment of migraine with and without aura in adults (ONZETRA Xsail Prescribing Information, 2016). AVP-825 uses a Breath Powered® intranasal delivery system that widens nasal passages and naturally seals the soft palate, while using the patients' exhaled air to propel sumatriptan-powder into the nostril and deliver drug

beyond the narrow nasal valve to the upper posterior nasal regions, an area of richly vascular mucosa conducive to rapid drug absorption into the systemic circulation.[39] The recommended dose of AVP-825 is 22 mg sumatriptan nasal powder, administered as two nosepieces, one in each nostril, using the Breath Powered delivery system. Each nosepiece contains 11 mg sumatriptan nasal powder, and a full dose from two nosepieces delivers ~15-16 mg sumatriptan.

Treatment with AVP-825 delivers sumatriptan powder efficiently across a significantly wider area of absorbent mucosa in the posterior nasal cavity, resulting in proven faster absorption of sumatriptan relative to traditional liquid nasal spray and oral tablets,[40] with the potential for less drug swallowing and reduced first-pass hepatic metabolism due to closure of the soft palate. Treatment with AVP-825 is also associated with significantly lower overall systemic sumatriptan exposure versus oral tablet (100 mg) or subcutaneous injection (6 mg), which may lead to improved tolerability.[40] Phase 2 and 3 placebo-controlled AVP-825 trials in the acute treatment of migraine in adults showed early onset of efficacy (significantly higher rates of pain relief as early as 30 minutes post-dose vs. placebo, and significantly higher rates of pain relief and pain freedom from 15 minutes compared to 100 mg oral sumatriptan in the Phase 3 trials) accompanied by sustained headache relief through 48 hours and a low level of triptan-related adverse effects.[41–43]

The purpose of this study is to evaluate efficacy and safety of AVP-825 for the acute treatment of migraine with and without aura in adolescent subjects (age 12-17 years). Pharmacokinetic samples will also be collected to confirm there is no significant differences between this patient population and the adult patient population. In the pharmacokinetic study of intranasal sumatriptan in adolescents aged 12 to 17 years (Study SUMB1006),[31] pharmacokinetic parameters for sumatriptan in adolescents were similar to those previously reported in adults with no clinically significant differences in sumatriptan exposure between adults and adolescents. A 22 mg dose of AVP-825 administered as two nosepieces offers efficient non-oral drug delivery, faster absorption of sumatriptan with low overall drug exposure and early onset of efficacy in adults. Therefore, AVP-825 may be an effective treatment for adolescents with migraine, where acute attacks may be shorter in duration and gastrointestinal symptoms may occur more frequently.

2 STUDY OBJECTIVES

The objective of the study is to evaluate the safety and efficacy of ONZETRA Xsail (AVP-825) compared to placebo in the acute treatment of migraine in adolescent subjects, 12 through 17 years of age.

3 STUDY DESIGN

This is a Phase 3, multicenter, randomized, double-blind, placebo-controlled study evaluating AVP-825 for the acute treatment of migraine with or without aura in adolescent subjects (12 to 17 years old). This study includes 2 treatment phases; a single-blind placebo run-in phase and a double-blind placebo-controlled treatment phase. A schematic of the study design is presented in Figure 1.

Approximately 420 subjects will be enrolled in the single-blind placebo run in phase to obtain approximately 236 subjects randomized in the double-blind treatment phase. Subjects will be enrolled in the study for up to approximately 28 weeks; with up to 12-weeks in a single-blind placebo run-in period, and up to 12-weeks in a double-blind treatment period. An exit/early termination visit will occur 10 days after treatment of Migraine Attack 2. The investigational product in this study is ONZETRA Xsail 22 mg (AVP-825, sumatriptan nasal powder 11 mg per nosepiece) and the control treatment is the same device as AVP-825 with matching placebo nosepieces filled with lactose (i.e. contain no active drug).

All eligible subjects will treat one migraine attack of moderate to severe intensity during the single-blind phase (Migraine Attack 1). Placebo non-responders (defined as subjects who are not headache pain free 2 hours after treatment of Migraine Attack 1) who meet all inclusion/exclusion criteria will be randomized in a 1:1 ratio (active: placebo) to treat one migraine attack of moderate to severe intensity in the double-blind treatment phase (Migraine Attack 2). Randomization will be stratified by age (12 to 14 years versus 15 to 17 years). Enrollment will be monitored to ensure that number of subjects in either age group does not exceed 70% or drop below 30%. Study medication will be administered as soon as possible after the development of a migraine attack associated with moderate-to-severe headache pain during each phase, per the instructions for use (IFU) provided to the subject, and relevant data will be collected in a subject diary.

There are up to 3 scheduled clinic visits including: screening/enrollment (Visit 1), randomization (Visit 2), and exit/early termination (Visit 3). Monthly follow-up phone calls will be made after Visits 1 and 2 for up to 12 weeks after the visit, depending on when Migraine Attacks 1 and 2 are treated.

The primary endpoint of the study is headache pain free at 120 minutes following treatment of Migraine Attack 2. Secondary efficacy endpoints include: headache relief at 120 minutes, headache pain-free by time (other than 120 minutes), headache relief by time (other than 120 minutes), change from baseline in headache severity by time, sustained pain relief (2 to 24 hours), sustained pain freedom (2 to 24 hours), rescue medication use and time to rescue

medication use, number of subjects with nausea, phonophobia, photophobia, or vomiting by time, number of subjects who return to 'normal' functioning at each timepoint, and time to recurrence of headache in 24 hours. Exploratory efficacy endpoints include sustained pain relief (1 to 2 hours), sustained pain freedom (1 to 2 hours), bilateral headache at predefined timepoints, and headache intensity increased by movement at predefined timepoints. The safety measures in this study are standard measures used for controlled trials and include adverse events reported, physical and neurological examination, vital signs, and the Columbia Suicide Severity Rating Scale (C-SSRS).

4 STUDY POPULATION

4.1 Inclusion Criteria

1. Male and females 12 to 17 years (inclusive) of age at the time of informed consent.
2. Have a diagnosis of episodic migraine with or without aura according to International Classification of Headache Disorders-3rd edition, beta version (ICHD-IIIB, 1.2.1 or 1.1) criteria for at least 1 year prior to the screening/enrollment visit.
3. Experienced migraine attacks of moderate-to-severe intensity and typically lasting ≥ 3 hours untreated, occurring at a frequency of ≥ 2 to ≤ 14 attacks per month for the past 6 months prior to the screening/enrollment visit.
4. Subject's parent or legal guardian must be willing to sign a copy of informed consent form (ICF) as well as documentation for Written Authorization for Use and Release of Health and Research Study Information, after the nature and risks of study participation have been fully explained.
5. Subjects also must be willing to provide minor assent according to the state law and Institutional Review Board (IRB) requirements, after the nature and risks of study participation have been fully explained.
6. Subjects must have a verified airflow through both nostrils and an ability to close the soft palate.
7. Subjects must demonstrate the ability to use the Breath Powered delivery device correctly.
8. Able and willing to read and comprehend written instructions and complete the diary. Subjects with ≥ 75% diary data entry for Migraine Attack 1 are eligible to be randomized.
9. Female patients who are of childbearing potential (post-menarche) must:
    a. agree to practice a medically acceptable method of birth control during the entire study duration (oral contraceptive tablets, hormonal implant device, hormone patch, intrauterine device, diaphragm and contraceptive cream or foam, condom with spermicide, or abstinence) or be surgically sterile, and
    b. have a negative urine pregnancy test at screening/enrollment and baseline visits.

4.2 Exclusion Criteria

1. Subjects who weigh less than 30 kg.

2. Subjects with a body mass index (BMI) of more than 40.
3. Subjects with ≥15 headache days per month in total (migraine, probable migraine, or tension-type).
4. Subjects with the following headache types: retinal [ICHD-IIIB 1.2.4], with brainstem aura [ICHD-IIIB 1.2.2], hemiplegic [ICHD-IIIB 1.2.3)], status migrainosus [ICHD-IIIB 1.4.1], other forms of complicated migraine, or secondary headaches.
5. Subjects who have not responded to an adequate dose and appropriate duration of treatment with 2 or more triptans.
6. Current use of medication for migraine prophylaxis that has not been stable or requires dose adjustment within 7 days prior to the screening/enrollment visit or if a dose adjustment is expected during the study.
7. Received chronic opioid therapy for more than 3 consecutive days within the 30 days prior to the screening/enrollment visit.
8. Current treatment with monoamine oxidase A (MAO-A) inhibitors or use within 4 weeks before the screening/enrollment visit.
9. Subjects with known nasal obstruction, current uncontrolled nasopharyngeal illness, or known velum insufficiency (i.e., a cleft palate and/or structural abnormalities in the soft palate and nasopharynx) which may interfere with the proper use of study medication.
10. History of clinically significant abnormality in electrocardiogram.
11. History or current symptoms or signs of ischemic cardiac, cerebrovascular or peripheral vascular syndrome.
12. Uncontrolled hypertension defined as systolic or diastolic blood pressure that exceeds the 90th percentile for age and height (Appendix 1).[44]
13. Any disease or condition which in the opinion of the investigator would contraindicate study participation such as a history of coronary artery disease, coronary vasospasm or a cardiac accessory conduction pathway disorder; a history of stroke, transient ischemic attack, or hemiplegic or basilar migraine; peripheral vascular disease; ischemic bowel disease; uncontrolled hypertension; severe hepatic impairment; epilepsy; drug or alcohol abuse; any systemic disease, neurological or psychiatric condition.
14. Subjects who fail urine drug screen test at the screening/enrollment visit.
15. Current suicide risk, as evidenced by any of the following:
    a. It is the judgment of the investigator that the subject may be at risk for suicide.

b. The subject is rated a "yes" to question 4 or question 5 on the C-SSRS at screening/enrollment or randomization visit, and the most recent episode occurred within the past 6 months prior to the screening/enrollment visit.

c. The subject has attempted suicide within the past 12 months prior to the screening/enrollment visit.

16. Hypersensitivity or intolerance to sumatriptan, any of its components, or sulphonamides.
17. Subjects whose conditions in the investigator's opinion may put the subject at significant safety risk or confound the study results. This include subjects who in the investigator's opinion should not be enrolled in the study due to the risks described in Warnings and Precautions or Contraindications sections of the ONZETRA Xsail Prescribing Information.
18. Have taken any investigational medication within 4 weeks before the screening/enrollment visit, or are scheduled to receive an investigational drug, other than sumatriptan for this study, while participating in the study.
19. Females who are pregnant or breast-feeding.

4.3 Subject Withdrawal from the Study

Subjects and their parent/legal guardian will be advised verbally and in the written ICF that they have the right to withdraw from the study at any time without prejudice or loss of benefits to which they are otherwise entitled. The investigator or sponsor may discontinue a subject from the study in the event of an intercurrent illness, adverse event, other reasons concerning the health or well-being of the subject, or in the case of lack of cooperation, non-compliance, protocol violation, or other administrative reasons. Subjects who are placebo responders (defined as subjects who are headache pain free 2 hours post treatment of Migraine Attack 1) will be withdrawn from the study and procedures specified at the exit/early termination visit (Visit 3) will be performed. Subjects who do not have a migraine attack within 12 weeks of the screening/enrollment visit (single-blind phase) or randomization (double-blind treatment phase) may be granted another 12 weeks in each period based on sponsor approval. If a subject does not return for a scheduled visit, every effort should be made to contact the subject. Regardless of the circumstance, every effort should be made to document subject outcome, if possible. The investigator should inquire about the reason for withdrawal, request the subject/parent/legal guardian to return all unused investigational product (IP), and follow-up with the subject and

their parent/legal guardian regarding any unresolved adverse events.

If the subject and their parent/legal guardian withdraws from the study, and consent is withdrawn for disclosure of future information, no further evaluations should be performed, and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent. Subjects who withdraw from the study will not be replaced.

5 STUDY TREATMENTS

5.1 Treatments Administered

All medication used in this study will be prepared, packaged, and labeled in accordance with Good Manufacturing Practice (GMP) guidelines, International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) guidelines, and applicable laws and regulations.

5.1.1 Description and Composition of Study Medications

Clinical study medication will be provided in individual cartons containing one dose. Each carton/dose will consist of one ONZETRA Xsail reusable device body, and one foil laminated pouch containing 2 single-use nosepieces, equivalent to one dose of study medication. Each nosepiece will contain sumatriptan succinate or placebo (lactose monohydrate) dry powder in a clear, size 3, hydroxypropyl methylcellulose (HPMC) inhalation capsule printed with black ink on the cap.

Two different strengths of study medication will be provided as follows:

- AVP-825 22 mg of sumatriptan; 2 nosepieces in a pouch with each nosepiece/capsule containing 11 mg sumatriptan (equivalent to 15.4 mg of sumatriptan succinate).
- AVP-825 Placebo; 2 nosepieces in a pouch with each nosepiece/capsule containing lactose monohydrate.

The composition of each nosepiece of the IP is shown in Table 3.

Table 3 Composition of One Capsule/Nosepiece

Ingredient	AVP-825 11 mg (mg)	Placebo (mg)
Sumatriptan succinate, USP dry powder	15.4	0
Lactose monohydrate, NF dry powder	0	30.0[1]
HPMC inhalation capsule	45	45

HPMC = Hydroxypropyl methylcellulose; NF = National Formulary; USP = United States Pharmacopoeia

1 Volume of 30 mg of lactose monohydrate is equivalent to the volume of 15.4 mg of sumatriptan succinate; volume of powder in a clear capsule shell is critical for blinding purpose

Demonstration kits will be provided for training purposes. The demonstration kit will be clearly marked with the ONZETRA Xsail name and ‘demonstration kit contains no medication’. The kit

will consist of the reusable device body (the same device body as in the study medication kit but with a different label) and one foil laminated pouch containing 2 single-use nosepieces with the empty capsules marked with 'demo' on one side of the capsule.

5.1.2 Packaging

The IP will be supplied as a blinded, pre-labeled, individually packaged drug device combination product kit. Each kit will contain a reusable device body, one pouch containing 2 nosepieces of active study medication or 2 nosepieces of placebo, and instructions for use.

5.1.3 Labeling

All labels for the individual cartons will contain the protocol number, kit number, description of the content of the package, dosing instructions, an investigational drug warning, storage conditions, and the sponsor company name and address. It will also contain space to document subject number, site number, subject initial, and dosing period number or date dispensed.

The carton label will consist of 2 panels, with 1 detachable panel that will be removed and kept with the site's study records (e.g., affixed to the study medication dispensing log page or subject source records) at the time of dispensing. Space is provided on both panels of the card label to record subject number, dispensing date and assigned treatment period. All IP labels comply with all applicable federal and local regulations.

5.1.4 Storage of Clinical Supplies

Clinical supplies must be stored in compliance with label requirements in a secure place and kept at room temperature; 20° - 25°C (68° -77°F) with excursions permitted to 15°C to 30°C (59°F-86°F). The approved expiration date for ONZETRA Xsail is 36 months.

5.1.5 Study Medication Administration

All subjects will receive AVP-825 or matching placebo according to the kit number assigned by an Interactive Web Response System (IWRS) randomization scheme. Designated staff at each site will dispense study medication and train subjects on the use of a drug device combination product using a demonstration kit clearly labelled as 'demo kit'. The subject will self-administer the study medication following instruction for use provided in the study medication kit.

5.2 Accountability of Study Supplies

Receipt of Supplies

The IP will be shipped by the sponsor directly to the study sites.

The investigator is responsible for maintaining an inventory of each shipment of IP received and comparing it with the accompanying Drug Accountability Report/Material Shipping Form. The investigator will verify the accuracy of the information on the form, sign and date it, and return the form to the sponsor or its representative. All IP supplied is for use only in this study and should not be used for any other purpose. All study drug material kit numbers will also be recorded and tracked at the site using the Drug Accountability Log.

Record of Dispensing

Accurate records of all kits dispensed for individual subjects will be made in the appropriate section of the subject's drug accountability records. This document will contain the following information: (i) the subject number to whom the drug was dispensed; (ii) the date(s) and quantity of the drug dispensed to the subject; and (iii) the kit number assigned to the subject via IRT system.

Additionally, the detachable panel of the 2-panel label from each kit will be removed and kept with the site's study records (e.g., affixed to a study medication subject drug dispensing logpage) at the time of dispensing. Space is provided on both panels of the kit label to record subject number, site number, subject initial, and dosing period number or date dispensed.

Unused Supplies

At the end of the study, all unused investigational supplies must be inventoried on the Drug Accountability Log and returned to the sponsor or its representative, along with a completed and signed Drug Accountability Report/Material Shipping Form. If any study medication is lost or damaged, it should be indicated on the form.

5.3 Subject Compliance

At screening/enrollment (Visit1) and randomization (Visit 2), subjects will be trained on the use of the study medication and completion of the diary. Subjects will be instructed to treat their migraine headache as soon as it reaches an intensity of moderate to severe, and record information in the diary for each attack during the treatment phases. Subjects will be instructed to bring their diary and used study medication to the site at Visits 2 and 3 for review and compliance check.

5.4 Concomitant and Prohibited Medication

All medications and other treatments taken by the subjects during the study, including those treatments initiated 30 days prior to the start of the study, must be recorded on the electronic

Case Report Form (eCRF).

During the study, subjects will be permitted to continue to take migraine prophylactic medications they were taking at screening/enrollment provided they had been on a constant regimen for at least 7 days prior to screening/enrollment. The regimen is to remain constant throughout the study, except for necessary changes for medical or safety reasons. If a prophylactic regimen changes after screening/enrollment, then the subject is to postpone treatment of a migraine with investigational product until the new prophylactic regimen has been in place for at least 7 days.

The following medications, OTC or prescription, are prohibited during the specified timeframe:

- Any acute medications for migraine, including short acting NSAID-containing compound, other simple analgesics, as well as anti-emetic medications are prohibited for the following duration: 6 hours before dosing to 2 hours after treatment with investigational product.
- Analgesics containing morphine, codeine, a barbiturate or an opioid derivative 24 hours before and 24 hours after taking investigational product.
- Ergotamine containing drugs, ergotamine derivatives or any 5-hydroxytryptamine 1 (5-HT1) agonist (including but not limited to sumatriptan, naratriptan, zolmitriptan, almotriptan, frovatriptan, eletriptan or rizatriptan) are also excluded within 24 hours before, and 24 hours after treatment with investigational product.
- Monoamine oxidase-A (MAO-A) inhibitors are excluded for at least 4 weeks before screening/enrollment or at any time during the course of this study.
- In addition, use of any investigational drug within 4 weeks prior to randomization or during the study is prohibited.

5.5 Rescue Medication

Subjects are allowed to take recue medication 2 hours after taking the study treatment and after completing the 2-hour post-dose diary questions. The use of rescue medication will be recorded on the diary. Rescue medication may include the following:

- OTC pain reliever – OTC monotherapy pain reliever such as acetaminophen or nonsteroidal anti-inflammatory drugs (NSAIDs), not exceeding the maximum recommended dose
- Prescription NSAIDs – prescription NSAID monotherapy should be prescribed by the

investigator specifically for the subject for the acute treatment of migraine, and should be used according to the package insert

- OTC anti-emetics – OTC anti-emetics commonly used to treat nausea symptoms during migraine attacks, not exceeding the maximum recommended dose
- Prescription anti-emetics – prescription anti-emetics should be prescribed by the investigator specifically for the subject for the symptoms of migraine, and should be used according to the package insert

For any questions regarding rescue medication, the Medical Monitor (MM) should be consulted. Rescue medications will not be supplied by the sponsor.

6 STUDY ASSESSMENTS AND PROCEDURES

6.1 Efficacy Measures

6.1.1 Primary Measure

Subjects will record in the diary if they are headache pain free for each migraine attack (1 and 2), at the following timepoints post dose: 15, 30, 60, 120 mins, 3, 4, and 24 hours.

The primary endpoint is headache pain-free at 120 minutes following treatment of Migraine Attack 2.

6.1.2 Secondary Measures

Subjects will record the following in the diary for each migraine attack (1 and 2) at the timepoints specified in Table 2:

- Headache severity score (scale of 0 to 3, where 0 = none, 1 = mild, 2 = moderate, 3 = severe)
- Nausea, vomiting photophobia, phonophobia (yes/no for each symptom)
- Ability to function (response to 'how do you rate your ability to do school-work or perform your usual activities?' on a 5-point scale [normal, mildly impaired, moderately impaired, severely impaired, I require bedrest])
- Time of recurrence of headache, defined as an increase from a headache severity score of 0 (none) or 1 (mild) pain to 2 (moderate) or 3 (severe)
- Use and time of rescue medication
- Bilateral headache (yes/no)
- Intensity increased by movement (yes/no)

6.2 Safety

6.2.1 Adverse Events

6.2.1.1 Definitions

An adverse event (AE) is any untoward medical occurrence or unintended change (including physical, psychological, or behavioral) from the time ICF is signed, including inter-current

illness, which occurs during the course of a clinical trial after treatment has started, whether considered related to treatment or not. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. Changes associated with normal growth and development that do not vary in frequency or magnitude from that ordinarily anticipated clinically are not AEs (e.g., onset of menstruation occurring at a physiologically appropriate time).

Clinical AEs should be described by diagnosis and not by symptoms when possible (e.g., cold, seasonal allergies, instead of "runny nose").

Migraine headache and associated symptoms (i.e., photophobia, phonophobia, nausea, vomiting) will not be captured as AEs unless the investigator feels they differ in frequency, intensity or duration from the subject's baseline condition.

An overdose is a deliberate or inadvertent administration of a treatment at a dose higher than specified in the protocol and higher than known therapeutic doses. It must be reported irrespective of outcome even if toxic effects were not observed.

AEs will be graded on a 3-point scale and reported in detail as indicated on the eCRF:

Mild: easily tolerated, causing minimal discomfort and not interfering with normal everyday activities

Moderate: sufficiently discomforting to interfere with normal everyday activities

Severe: incapacitating and/or preventing normal everyday activities

The relationship of each AE to study medication should be determined by the investigator using the following explanations:

Not related: the event is clearly related to other factors such as the subject's clinical state, therapeutic interventions, or concomitant medications administered to the subject

Unlikely related: the event is most likely produced by other factors such as the subject's clinical state, therapeutic interventions, or concomitant medications administered to the subject; and does not follow a known response pattern to the study medication

Possibly related: the event follows a reasonable temporal sequence from the time of drug administration; and/or follows a known response pattern to the study medication; but could have been produced by other factors such as the subject's clinical state, therapeutic interventions, or concomitant medications

administered to the subject

Related: the event follows a reasonable temporal sequence from the time of drug administration; and follows a known response pattern to the study medication; and cannot be reasonably explained by other factors such as the subject's clinical state, therapeutic interventions, or concomitant medications administered to the subject

6.2.1.2 Serious Adverse Events

A Serious Adverse Event (SAE) is any AE occurring at any dose that results in any of the following outcomes:

1. Death
2. Life-threatening experience (one that places the subject, in the view of the initial reporter, at immediate risk of death from the AE as it occurred, i.e., it does not include an AE that, had it occurred in a more severe form, might have caused death)
3. Persistent or significant disability/incapacity (disability is a substantial disruption of a person's ability to conduct normal life functions)
4. In-patient hospitalization or prolongation of hospitalization
5. Congenital anomaly/birth defect

Important medical events that may not result in death, or be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the subject or require medical or surgical intervention to prevent one of the outcomes listed in the definition.

The terms "cancer" and "overdose" are not considered to be SAEs, but if a subject experiences cancer or overdose, they are still reportable as AEs.

Pregnancy is not considered to be an AE or an SAE, unless a complication occurs that meets the requirements for an AE or SAE but must be reported on a pregnancy report form. Women who are pregnant or likely to become pregnant are excluded from this study. In the event a subject becomes pregnant during the study, study medication must be discontinued, a pregnancy report form must be completed to capture potential drug exposure during pregnancy, and the pregnancy must be reported within 24 hours of notice. Any pregnant subject must be followed until the outcome of her pregnancy is known (i.e., normal delivery, abnormal delivery, spontaneous/voluntary/therapeutic abortion). The pregnancy (i.e., the mother and the fetus) must be followed up through delivery with regard to outcome.

A pregnancy report form must also be completed in the event that a female partner of a male subject becomes pregnant within 30 days after his last dose of study medication.

The term 'severe' is a measure of intensity; thus, a severe AE is not necessarily serious. For example, nausea of several hours' duration may be rated as severe but may not be clinically serious.

6.2.1.3 Reporting

Subjects will be queried regarding AEs at all in-clinic visits and at follow-up phone calls during the single-blind placebo run-in phase and the double-blind phase. The investigator will assess and record all reported AEs. Any AE newly reported after receiving the last dose of study medication will be followed up until 30 days.

A death occurring during the study, or which comes to the attention of the investigator within 30 days after stopping the treatment whether considered treatment-related or not, must be reported to the sponsor.

For all SAEs, including an abnormal laboratory test value, the investigator must inform the Medical Monitor (MM) by telephone no later than 24 hours after becoming aware of the event. Subsequently, the SAE must be assessed for the following details: seriousness of event, start date, stop date, intensity, frequency, relationship to study drug, action taken regarding study drug, treatment required, outcome to date, and other data as indicated on the SAE form. All details regarding the SAE must be recorded on the SAE form that is provided. The SAE reporting contact information is as follows:

Medical Monitor 1-908-239-0292 (direct) or 1-732-589-2478 (mobile) and email everestsafety-Vielight-P17.03@ecrscorp.com. Such preliminary reports will be followed by detailed descriptions later, which may include copies of hospital case reports, autopsy reports, and other related documents when requested.

The IRB will be notified of such an event in writing as soon as is practical in compliance with federal and local regulations.

6.2.1.4 Suspected Technical Device Issues

If a device is suspected of having technical issues (e.g., damaged device, missing parts, inoperable device), the nature of the technical issue should be reviewed by the investigator to determine if the issue resulted in an AE or SAE and that this event is documented and reported appropriately.

If the investigator suspects that a technical device issue does exist, then the issue must be

reported by the investigational staff within 1 working day of their knowledge of the event using the Technical Device Issue Notification Form.

Unanticipated Adverse Device Effects

The definition of unanticipated adverse device effects (UADEs), which are device effects that are reportable on an expedited basis in the United States is as follows:

An UADE is defined as a serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the right, safety, or welfare of subjects.

For investigational devices, sponsors are required to collect, track, and review all potential UADEs.

1) Site collects all AEs on CRF form
2) AEs that are deemed to be related to the investigational device are called adverse device effects (ADEs). ADEs require further review, typically done by the MM.
3) The site would complete an ADE form (similar to an SAE form), submit to the contract research organization (CRO)/sponsor. Medical Monitor would review and determine if the ADE complies with the definition of a UADE.
4) If the effect is indeed a UADE, the UADE is then reported to the FDA within 10 days of notification to sponsor. Reporting time is 5 days if remedial action is needed, such as changes to instructions for use of device, subject population or stopping clinical trial altogether.
5) Anything reported to FDA must also be reported to IRBs.

6.2.2 Physical and Neurological Examination

Physical and neurological examination will be performed at Visits 1 and 3, and will include assessments of head, eyes, ears, nose, throat, lymph nodes, skin, extremities, respiratory, gastrointestinal, musculoskeletal, cardiovascular, and nervous systems. A nasal examination using a speculum will be conducted at Visits 1, 2, and 3 to ensure that the subject does not have nasal obstruction due to nasal septum deviation, polyposis, severe mucosal swelling, or any other reason. The physical/neurological and nasal examinations should be performed by the same person each time, whenever possible.

Physical examination abnormalities determined by the investigator to be clinically significant at screening/enrollment should be recorded as medical history. Any clinically significant changes in physical examination findings from the screening examination should be recorded as AEs.

6.2.3 Vital Signs

Vital signs, systolic and diastolic blood pressure (mm Hg), heart rate (beats/minute), respiratory rate (breaths/minute) and body temperature (ºF) should be recorded at Visit 1.

Weight and height should be measured at Visit 1.

6.2.4 Urine Drug Screen Tests

Urine samples will be analyzed at the study site at all clinic visits (Visit 1 to 3) for the following: marijuana, opiates, amphetamines, cocaine, phencyclidine, barbiturates, benzodiazepines and methadone.

6.2.5 Pregnancy Tests

Urine pregnancy tests are to be performed for females of childbearing potential at all clinic visits (Visit 1 to 3).

All female subjects of childbearing potential should be instructed to use appropriate birth control methods for up to 4 weeks following the last dose of study medication.

6.2.6 Columbia Suicide Severity Rating Scale (C-SSRS)

The C-SSRS (Appendix 3) is a low-burden measure of the spectrum of suicidal ideation and behavior that was developed by Columbia University researchers for the National Institute of Mental Health Treatment of Adolescent Suicide Attempters Study to assess severity and track suicidal events through any treatment.[46] It is a clinical interview providing a summary of both ideation and behavior that can be administered during any evaluation or risk assessment to identify the level and type of suicidality present. The C-SSRS can also be used during treatment to monitor for clinical worsening.

The C-SSRS evaluation will be performed at all clinic visits (Visit 1 [‘baseline/screening’ version], Visit 2 and Visit 3 [‘since last visit’ version]).

6.3 Schedule of Evaluations and Procedures

A schedule of evaluations and procedures by study visit is provided in Table 1. The schedule for

evaluations and their frequency during a migraine attack is provided in Table 2.

6.3.1 Description of Study Procedures

6.3.1.1 Visit 1 (Screening/Enrollment)

The following procedures should be performed at screening/enrollment (Day -3 to 1)

1. The investigator will provide the subject and their parent/legal guardian with assent /ICF and privacy documents for signature and will explain the rationale for the study, providing ample time for participants, and/or authorized representatives to ask questions
2. Review and record medical and migraine history
3. Review and record prior and concomitant medications
4. Query subject on any adverse events
5. Review eligibility (inclusion/exclusion criteria)
6. Perform physical and neurological examination including nasal examination
7. Measure and record vital signs, height and weight
8. Collect urine specimen for drug screen
9. Urine pregnancy test (for females of childbearing potential only)
10. Administer the C-SSRS
11. Train subject on the use of study medication
12. Access IWRS to obtain assigned kit number for study medication
13. Dispense diary and study medication

Subjects will be instructed to treat one migraine headache of moderate to severe intensity in the subsequent 12 weeks (84 days) with the study medication and to respond to questions on the study diary. Diary should be used before taking the study treatment and at 15, 30, 60, 120 min, 3 hours, 4 hours, and 24 hours after dosing. A monthly phone call to the subject or their parent/legal guardian will be placed by site personnel to inquire about any adverse events and to answer study question.

Following treatment in the single-blind placebo run-in phase, the site will complete a protocol eligibility form and submit to the MM for approval. Subjects deemed eligible by the investigator and the MM will be enrolled into the study.

6.3.1.2 Visit 2 (Randomization)

The following procedures should be performed at Visit 2

1. Review and record medical and migraine history
2. Review and record prior and concomitant medications
3. Review eligibility (inclusion/exclusion criteria)
4. Collect urine specimen for drug screen
5. Urine pregnancy test (for females of childbearing potential only)
6. Administer the C-SSRS
7. Train subject on the use of study medication
8. Query subject on any adverse events
9. Perform nasal examination
10. Review diary and return to subject
11. Randomization
12. Access IWRS to obtain assigned kit number for study medication
13. Dispense study medication

Subjects will be instructed to treat one migraine headache of moderate to severe intensity in the subsequent 12 weeks (84 days) with the study medication and to respond to questions on the study diary. Diary should be used before taking the study treatment and at 15, 30, 60, 120 min, 3 hours, 4 hours, and 24 hours after dosing. A monthly phone call to the subject or their parent/legal guardian will be placed by site personnel to inquire about any adverse events or to answer study question.

6.3.1.3 Visit 3 (Exit/Early Termination)

The following procedures should be performed at Visit 3.

1. Review and record concomitant medications
2. Perform physical and neurological examination including nasal examination
3. Query subject on any adverse events
4. Collect urine specimen for drug screen
5. Urine pregnancy test (for females of childbearing potential only)

6. Administer the C-SSRS
7. Collect diary and study medication
8. Access IWRS to record subject exit

6.3.1.4 Follow-up Phone Visits

The investigator will follow-up with monthly telephone calls after the screening/enrollment visit and after the randomization visit for up to 12 weeks depending on when a migraine attack is treated. During these phone visits, subjects will be queried on adverse events and any concomitant medications taken.

6.3.1.5 Procedures During Treatment

Subjects will be instructed to administer their study medication at the onset of a migraine attack and enter the information in the diary. The schedule of procedures is outlined in Table 2.

7 DATA MANAGEMENT

7.1 Data Collection

The sponsor or designated representative (e.g., CRO) will perform the data management activities in accordance with the data management plan (DMP). The DMP will outline the systems and procedures to be used in the study.

Clinical study data will be reported (captured) by study site personnel on eCRFs. An eCRF must be completed for every subject enrolled in the study. The eCRF data will be entered by trained study-site personnel and then reviewed for completeness and accuracy and electronically signed by the investigator or authorized designee. All study-site personnel must use a password-protected user account to enter, review, or correct study data. Electronic signature procedures shall comply with the CFR Title 21 Part 11. Passwords will be strictly confidential.

All eCRF data will be exported from the electronic data capture (EDC) system and transferred to the sponsor or representative. The sponsor or representative will also receive electronic transfers of non-eCRF data from third-party vendors as appropriate. The electronic data format of all transfers will be agreed upon with the sponsor or representative and documented in the DMP or vendor data transfer requirements document as appropriate.The clinical monitoring staff will perform source data verification (SDV) of the data recorded in the EDC system with source documents at the clinical study sites according to the data management plan and clinical monitoring plan. The data will be subjected to consistency and validation checks within the EDC system with supplemental data reviews performed outside of the EDC system.

Medical history and adverse events will be coded using a current version of Medical Dictionary for Regulatory Activities (MedDRA), and concomitant medications using a current version of the World Health Organization (WHO) Drug Dictionary. The sponsor or representative will perform a medical safety review of the coding.

Completed eCRF images with a date- and time-stamped electronic audit trail indicating the user, the data entered, and any reason for change (if applicable) will be archived at the investigator's site and at the sponsor's site.

8 STATISTICAL METHODS

8.1 Analysis Populations

Two analysis populations will be used; modified intent-to-treat (mITT) and safety. The mITT population includes all subjects randomized and treated for Migraine Attack 2 who have at least one post-baseline efficacy assessment and will be used for all analyses of efficacy. Subjects in the mITT population will be included in the treatment group to which they were randomized regardless of treatment received. The safety population includes all subjects who received study treatment and will be used for all analyses of safety. Subjects will be included in the treatment group based on the actual treatment received.

8.2 Efficacy Analysis

The primary efficacy endpoint of the study is headache pain-free at 120 minutes following treatment of Migraine Attack 2. Treatment comparison will be performed by using the Cochran-Mantel-Haenszel (CMH) test stratified by age group (12-14 years or 15-17 years) and baseline migraine pain severity (moderate or severe). Secondary and exploratory efficacy endpoints will be analyzed similarly, or appropriate statistical tests will be used. Efficacy assessments after taking rescue medication will be set to missing. Missing data will be imputed by treatment failure, i.e., headache pain-free = no.*Secondary efficacy endpoints (Migraine Attack 2):*

- Headache relief (defined as a reduction in pain intensity from moderate or severe [grade 2 or 3] at baseline to none or mild [grade 0 or 1]) at 120 minutes
- Headache pain-free by time (other than at 120 minutes)
- Headache relief by time (other than at 120 minutes)
- Change from baseline in headache severity by time
- Sustained pain relief, defined as headache relief [headache severity mild (grade 1) or none (grade 0)] at 2 hours with no worsening of headache, use of a second dose of study medication, or rescue medication taken through 24 hours after dose
- Sustained pain freedom, defined as pain freedom [headache severity none (grade 0)] at 2 hours with no recurrence of headache, use of a second dose of study medication or rescue medication taken through 24 hours after dose
- Rescue medication use and time to rescue medication
- Number of subjects with nausea, phonophobia, photophobia, or vomiting by time
- Number of subjects who return to ‘normal’ functioning by time

- Time to recurrence of headache defined as an increase from a headache severity score of 0 (none) or 1 (mild) at 2 hours to 2 (moderate) or 3 (severe) within 24 hours

Exploratory efficacy endpoints (Migraine Attack 2):

- Sustained pain relief (1 to 2 hours), defined as headache relief [Headache severity mild (grade 1) or none (grade 0)] at 60 minutes with no worsening of headache, use of a second dose of study medication, or rescue medication taken through 120 minutes after dose
- Sustained pain freedom (1 to 2 hours), defined as pain freedom [Headache severity none (grade 0)] at 60 minutes with no recurrence of headache, use of a second dose of study medication or rescue medication taken through 120 minutes after dose
- Bilateral headache at predefined timepoints
- Headache intensity increased by movement at predefined timepoints

8.3 Safety Analysis

Safety will be assessed by the following measurements: AEs, physical examination, vital signs, and urine pregnancy test. All safety measures will be summarized by treatment.

8.3.1 Interim Analysis

No interim analysis is planned.

8.4 Sample Size Calculations

Power calculations are based on the results of the completed pivotal trial for adults (OPN-SUM-MIG-3301, Avanir data on file). The observed percentage (n) of subjects experiencing migraine headache pain free at 120 minutes was 34.3% (37) vs. 17.3% (18) for AVP-825 vs. placebo, respectively. For this study in adolescents with single-blind placebo run-in, if it is assumed that the percentage of subjects who are migraine headache pain free at 120 minutes is 30% vs. 15%, a sample size of 236 (118/arm) randomized and treated at Migraine Attack 2 would provide approximately 80% power with 2-sided $\alpha = 0.05$. In consideration of the attrition rate during the run-in phase, it is estimated that 420 subjects would be needed to enter the single-blind placebo run-in phase in order to have approximately 236 subjects randomized and treated for Migraine Attack 2.

9 ADMINISTRATIVE PROCEDURES

9.1 Institutional Review Board Approval

Institutional Review Boards must meet the guidelines set out by the FDA and conform to local laws and customs where appropriate. Written IRB approval for the protocol and the signed ICF must be obtained and transmitted to Currax Pharmaceuticals or representative before the study can be initiated. The IRB must be informed of and approve all protocol amendments. The investigator will ensure that this study is conducted in full conformance with the laws and regulations of the US (see Appendix 4, Investigator Responsibilities). The complete text of the World Medical Association Declaration of Helsinki is given in Appendix 5.

9.2 Informed Consent Form

The ICF will follow the principles outlined in the current version of the Declaration of Helsinki. For each patient found to be eligible for the study, informed assent/consent will be obtained from the patient and their parent/legal guardian. The patients and patient's parent/legal guardian will be properly informed of the purpose of the study. A signed ICF will be obtained from all patient's parent/legal guardian and an informed assent from all patients will be obtained prior to patient entry into this study. Patients and patient's parent/legal guardian will be provided with a copy of their signed ICF/assent form.

9.3 Subject's Diary

Subjects will be provided with an electronic device (e-diary) to prompt and record subject responses at various intervals during a treated migraine attack. The subject's e-diary will be reviewed by clinical study personnel at Visits 2 and 3, for confirmation of medication dosage, rescue medication taken, and subject responses. The study personnel are responsible for (i) ensuring that subjects are properly collecting data and recording it into the diaries; and (ii) transcribing the relevant diary recordings into the eCRF.

9.4 Electronic Case Report Forms

For each subject enrolled who has given informed consent, an eCRF must be completed and electronically signed by the investigator to certify that the data within each eCRF are complete and correct. This also applies to those subjects who fail to complete the study. If a subject is withdrawn from the study because of a treatment-limiting AE, thorough efforts should be made to document the outcome.

Any site personnel delegated responsibility for data entry, query resolution, or eCRF approval must complete training prior to accessing the eCRF. The electronic data capture (EDC) vendor will provide user-specific access to the live (production) eCRF once training completion has been confirmed and the account has been approved by the sponsor. Changes to the data once it has been initially saved will be tracked via audit trail and will require a reason for the change. The audit trail will also include who made the change and a date/time stamp.

The eCRFs will be reviewed by the study monitor at the study site. Errors detected by subsequent in-house data review may necessitate clarification or correction of errors. All changes will be documented and approved by the investigator.

All investigators will be provided with copies of the eCRFs for their site on a CD-ROM at the end of the study.

9.5 Quality Assurance

9.5.1 Documentation

For each process, evaluation, or test that generates study data but is not described in the protocol or eCRF, a written description of the data generation procedures shall be retained in the quality assurance section of the study files. In the case of routine clinical diagnostic procedures, only a copy of the relevant certification document is required.

9.5.2 Monitoring

Throughout the course of the study, the study monitor will make frequent contacts with the investigator. This will include telephone calls and on-site visits. The study will be routinely monitored to ensure compliance with the study protocol and the overall quality of data collected. During the on-site visits, the eCRFs will be reviewed for completeness and adherence to the protocol. As part of the data audit, source documents will be made available for review by the study monitor. The study monitor may periodically request review of the investigator study file to assure the completeness of documentation in all aspects of clinical study conduct.

The study monitor will verify that each subject has proper consent documentation from the subject and subject's authorized representative for study procedures and for the release of medical records to the sponsor, FDA, other regulatory authorities, and the IRB. The investigator or appointed delegate will receive the study monitor during these onsite visits and will cooperate in providing the documents for inspection and respond to inquiries. In addition, the investigator will permit inspection of the study files by authorized representatives of the regulatory agencies.

On completion of the study, the study monitor will arrange for a final review of the study files after which the files should be secured for the appropriate time period.

9.6 Record Retention

To enable evaluations and/or audits from regulatory authorities or Currax, the investigator agrees to keep records, including the identity of all participating subjects (sufficient information to link records, e.g., CRFs and hospital records), all original signed ICFs, copies of all eCRFs, SAE forms, source documents, and detailed records of treatment disposition, and adequate documentation of relevant correspondence (e.g., letters, meeting minutes, telephone call reports). The records should be retained by the investigator according to ICH, local regulations, or as specified in the Clinical Trial Agreement, whichever is longer.

If the investigator is unable for any reason to continue to retain study records for the required period (e.g., retirement, relocation), Currax should be prospectively notified. The study records must be transferred to a designee acceptable by Currax, such as another investigator, another institution, or to Currax. The investigator must obtain Currax's written permission before disposing of any records, even if retention requirements have been met.

9.7 Source Data

The documents that will form the source data for the clinical study (e.g., patient charts, laboratory reports) must be defined and documented in the in-house study master file prior to the start of the study. Data on the eCRFs which will be checked against source data during monitoring visits must also be defined and documented in the in-house study master file including the percentage of each of the source data to be verified and the percentage of subjects' eCRFs to be monitored.

9.8 Data Handling

Data collected on the eCRFs will be entered into EDC system by trained site staff. Any queries arising from data entry will be checked with the investigator and changes approved.

9.9 Guidelines for Good Clinical Practice

Standards for GCP must be adhered to for all study-based procedures.

9.10 Conditions for Amending the Protocol

Protocol modification to the ongoing study which could potentially adversely affect the safety of

subjects or which alter the scope of the investigation, the scientific quality of the study, the experimental design, dosages, duration of therapy, assessment variables, the number of subjects treated, or subject selection criteria must be made only after appropriate consultation between an appropriate representative of Currax and the investigator.

Protocol modifications must be prepared by a representative of Currax or the investigator and reviewed and approved by Currax.

All protocol modifications must be reviewed and approved by the appropriate IRB in accordance with local requirements, before the revised edition can be implemented. Modifications which eliminate an apparent immediate hazard to subjects do not require pre-approval by the IRB.

9.11 Conditions for Terminating the Study

Both Currax and the principal investigator reserve the right to terminate the study at the site at any time. Should this be necessary, the procedures to effect study termination will be arranged after review and consultation by both parties. In terminating the study, Currax and the investigator will assure that adequate consideration is given to the protection of the subject's interests.

9.12 Confidentiality of Study Documents and Patient Records

The investigator must assure that the subject's anonymity will be maintained. On eCRFs or other documents submitted to Currax, subjects should not be identified by their names but by an identification code.

The investigator should keep a separate log of subject's codes, names, and addresses. Documents not for submission to Currax, for example, subjects signed ICFs, should be maintained by the investigator in strict confidence.

9.13 Reports

At the completion of the study, the investigator shall provide the sponsor with an adequate report shortly after completion of the investigator's participation in the study as described in the Code of Federal Regulations (CFR) Title 21, Part 312.64.

9.14 Publications

It is anticipated that a report of this study will be published in the scientific literature by the sponsor. The investigator will not seek to arrange for publication of any of the information or results from the study in any scientific journal, or other publication or by way of lecture without

Currax's prior review and written consent.

9.15 Audits/Inspections

The investigator should understand that source documents for this study should be made available to appropriately qualified personnel or designee(s) from Currax or to health authority inspectors after appropriate notification. The verification of the eCRF data may be by direct inspection of source documents (where permitted by law) or through an interview exchange.

The inspector from the regulatory authority will be especially interested in the following items:

- Visits from the sponsor's representatives
- IRB approval(s)
- Study medication accountability
- Study protocol and amendments
- ICFs of the subject
- Medical records supportive of eCRF data
- Reports to the IRB and the sponsor
- Record retention

The sponsor will be available to help investigators prepare for an inspection.

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11 APPENDICES

Appendix 1: Blood Pressure Levels by Age and Height Percentile

Reference: The fourth report on the diagnosis, evaluation, and treatment of high blood pressure in children and adolescents. *Pediatrics*. 2004;114(2 Suppl 4th Report):555-76.

TABLE 3

Blood Pressure Levels for Boys by Age and Height Percentile*

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

* The 90th percentile is 1.28 SD, 95th percentile is 1.645 SD, and the 99th percentile is 2.326 SD over the mean. For research purposes, the standard deviations in appendix table B–1 allow one to compute BP Z-scores and percentiles for boys with height percentiles given in table 3 (i.e., the 5th, 10th, 25th, 50th, 75th, 90th, and 95th percentiles). These height percentiles must be converted to height Z-scores given by (5% = -1.645; 10% = -1.28; 25% = -0.68; 50% = 0; 75% = 0.68; 90% = 1.28; 95% = 1.645) and then computed according to the methodology in steps 2–4 described in appendix B. For children with height percentiles other than these, follow steps 1–4 as described in appendix B.

TABLE 4

Blood Pressure Levels for Girls by Age and Height Percentile*

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 (Years)	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

* The 90th percentile is 1.28 SD, 95th percentile is 1.645 SD, and the 99th percentile is 2.326 SD over the mean. For research purposes, the standard deviations in appendix table B–1 allow one to compute BP Z-scores and percentiles for girls with height percentiles given in table 4 (i.e., the 5th, 10th, 25th, 50th, 75th, 90th, and 95th percentiles). These height percentiles must be converted to height Z-scores given by (5% = -1.645; 10% = -1.28; 25% = -0.68; 50% = 0; 75% = 0.68; 90% = 1.28; 95% = 1.645) and then computed according to the methodology in steps 2–4 described in appendix B. For children with height percentiles other than these, follow steps 1–4 as described in appendix B.

Appendix 2: Columbia Suicide Severity Rating Scale (C-SSRS)

COLUMBIA-SUICIDE SEVERITY RATING SCALE

Visit 2 and Visit 3 Exit/Early Termination Visit

SITE NUMBER	PATIENT NUMBER	PATIENT INITIALS	VISIT NUMBER	VISIT DATE	EXAMINER INITIALS

Since Last Visit

Version 1/14/09

Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.; Burke, A.; Oquendo, M.; Mann, J.

Disclaimer:

This scale is intended to be used by individuals who have received training in its administration. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidal ideation or behavior depends on the judgment of the individual administering the scale.

Definitions of behavioral suicidal events in this scale are based on those used in ***The Columbia Suicide History Form****, developed by John Mann, MD and Maria Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY, 10032. (Oquendo M. A., Halberstam B. & Mann J. J., Risk factors for suicidal behavior: utility and limitations of research instruments. In M.B. First [Ed.]* Standardized Evaluation in Clinical Practice*, pp. 103 -130, 2003.)*

For reprints of the C-SSRS contact Kelly Posner, Ph.D., New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032; inquiries and training requirements contact posnerk@nyspi.columbia.edu

SUICIDAL IDEATION

Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.

Since Last Visit

1. Wish to be Dead
Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up.
Have you wished you were dead or wished you could go to sleep and not wake up?

If yes, describe:

Yes ☐ **No** ☐

2. Non-Specific Active Suicidal Thoughts
General, non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period.
Have you actually had any thoughts of killing yourself?

If yes, describe:

Yes ☐ **No** ☐

3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act
Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g., thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it…and I would never go through with it."*
Have you been thinking about how you might do this?

If yes, describe:

Yes ☐ **No** ☐

4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan
Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them."*
Have you had these thoughts and had some intention of acting on them?

If yes, describe:

Yes ☐ **No** ☐

5. Active Suicidal Ideation with Specific Plan and Intent
Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out.
Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?

If yes, describe:

Yes ☐ **No** ☐

INTENSITY OF IDEATION

The following features should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe).

Most Severe Ideation: ____ _____
Type # (1-5) ***Description of Ideation***

Most Severe

Frequency
How many times have you had these thoughts?
(1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day

____

Duration
When you have the thoughts, how long do they last?
(1) Fleeting - few seconds or minutes
(2) Less than 1 hour/some of the time
(3) 1-4 hours/a lot of time
(4) 4-8 hours/most of day
(5) More than 8 hours/persistent or continuous

____

Controllability
Could/can you stop thinking about killing yourself or wanting to die if you want to?
(1) Easily able to control thoughts
(2) Can control thoughts with little difficulty
(3) Can control thoughts with some difficulty
(4) Can control thoughts with a lot of difficulty
(5) Unable to control thoughts
(0) Does not attempt to control thoughts

____

Deterrents
Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?
(1) Deterrents definitely stopped you from attempting suicide
(2) Deterrents probably stopped you
(3) Uncertain that deterrents stopped you
(4) Deterrents most likely did not stop you
(5) Deterrents definitely did not stop you
(0) Does not apply

____

Reasons for Ideation
What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?
(1) Completely to get attention, revenge or a reaction from others
(2) Mostly to get attention, revenge or a reaction from others
(3) Equally to get attention, revenge or a reaction from others and to end/stop the pain
(4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling)
(5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling)
(0) Does not apply

____

SUICIDAL BEHAVIOR

(Check all that apply, so long as these are separate events; must ask about all types)

Since Last Visit

Actual Attempt:

A potentially self-injurious act committed with at least some wish to die, *as a result of act.* Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm***, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt.

Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred.

Have you made a suicide attempt?

Have you done anything to harm yourself?

Have you done anything dangerous where you could have died?

What did you do?

Did you_____as a way to end your life?

Did you want to die (even a little) when you_____?

Were you trying to end your life when you_____?

Or did you think it was possible you could have died from_____?

Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)? *(*Self-Injurious Behavior without suicidal intent)

If yes, describe:

Yes ☐ **No** ☐

Total # of Attempts _____

Has subject engaged in Non-Suicidal Self-Injurious Behavior?

Yes ☐ **No** ☐

Interrupted Attempt:

When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred)*.

Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so.

Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?

If yes, describe:

Yes ☐ **No** ☐

Total # of interrupted _____

Aborted Attempt:

When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else.

Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?

If yes, describe:

Yes ☐ **No** ☐

Total # of aborted _____

Preparatory Acts or Behavior:

Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note).

Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?

If yes, describe:

Yes ☐ **No** ☐

Suicidal Behavior:

Suicidal behavior was present during the assessment period?

Yes ☐ **No** ☐

Suicide:

Yes ☐ **No** ☐

Answer for Actual Attempts Only

Most Lethal Attempt Date:

Actual Lethality/Medical Damage:

Enter Code _____

0. No physical damage or very minor physical damage (e.g., surface scratches).
1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains).
2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel).
3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures).
4. Severe physical damage; *medical* hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area).
5. Death

Potential Lethality: Only Answer if Actual Lethality=0

Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over).

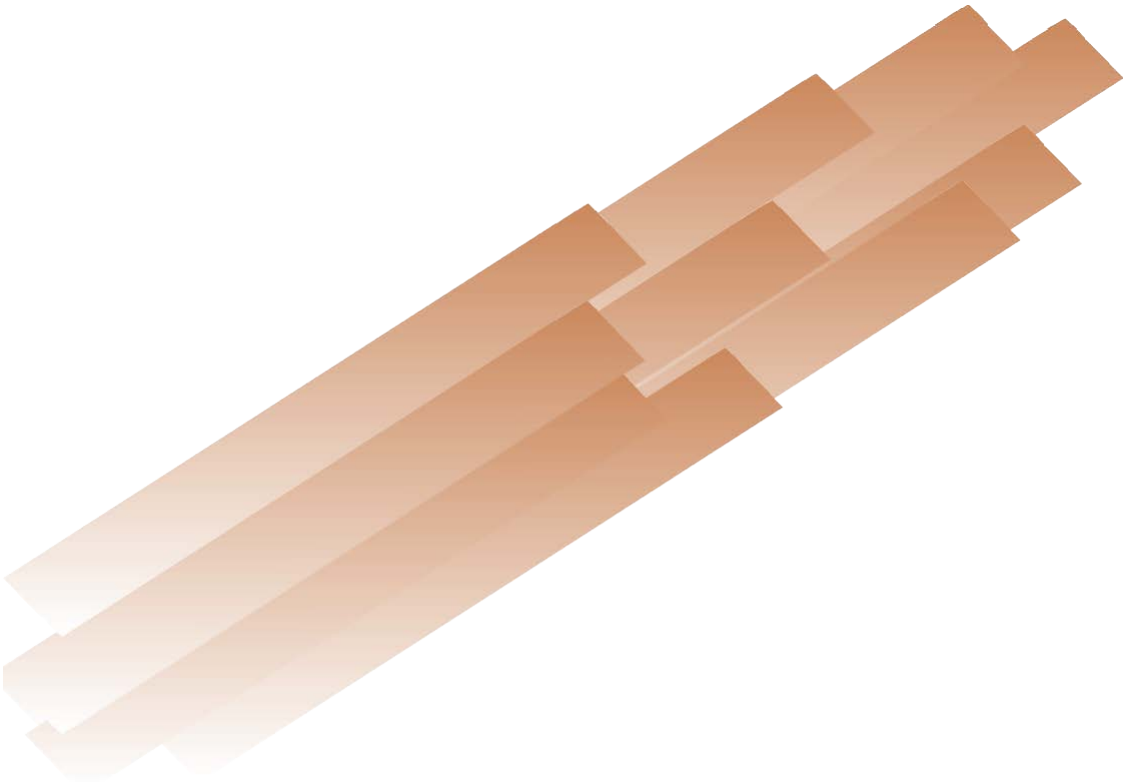
Enter Code _____

0 = Behavior not likely to result in injury
1 = Behavior likely to result in injury but not likely to cause death
2 = Behavior likely to result in death despite available medical care

Appendix 3: Investigator Responsibilities

Guidance for Industry

E6 Good Clinical Practice: Consolidated Guidance



ICH
April 1996

Guidance for Industry

E6 Good Clinical Practice: Consolidated Guidance

Additional copies are available from:
the Drug Information Branch (HFD-210),
Center for Drug Evaluation and Research (CDER),
5600 Fishers Lane, Rockville, MD 20857 (Tel) 301-827-4573
http://www.fda.gov/cder/guidance/index.htm
or
Office of Communication,
Training, and Manufacturers Assistance (HFM-40)
Center for Biologics Evaluation and Research (CBER)
1401 Rockville Pike, Rockville, MD 20852-1448,
http://www.fda.gov/cber/guidelines.htm
(Fax) 888-CBERFAX or 301-827-3844
(Voice Information) 800-835-4709 or 301-827-1800

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
April 1996
ICH

(b) Changes increasing the risk to subjects and/or affecting significantly the conduct of the trial (see section 4.10.2).

(c) All adverse drug reactions (ADRs) that are both serious and unexpected.

(d) New information that may affect adversely the safety of the subjects or the conduct of the trial.

3.3.9 Ensuring that the IRB/IEC promptly notify in writing the investigator/institution concerning:

(a) Its trial-related decisions/opinions.
(b) The reasons for its decisions/opinions.
(c) Procedures for appeal of its decisions/opinions.

3.4 Records

The IRB/IEC should retain all relevant records (e.g., written procedures, membership lists, lists of occupations/affiliations of members, submitted documents, minutes of meetings, and correspondence) for a period of at least 3 years after completion of the trial and make them available upon request from the regulatory authority(ies).

The IRB/IEC may be asked by investigators, sponsors, or regulatory authorities to provide copies of its written procedures and membership lists.

4. INVESTIGATOR

4.1 Investigator's Qualifications and Agreements

4.1.1 The investigator(s) should be qualified by education, training, and experience to assume responsibility for the proper conduct of the trial, should meet all the qualifications specified by the applicable regulatory requirement(s), and should provide evidence of such qualifications through up-to-date curriculum vitae and/or other relevant documentation requested by the sponsor, the IRB/IEC, and/or the regulatory authority(ies).

4.1.2 The investigator should be thoroughly familiar with the appropriate use of the investigational product(s), as described in the protocol, in the current Investigator's Brochure, in the product information, and in other information sources provided by the sponsor.

4.1.3 The investigator should be aware of, and should comply with, GCP and the applicable regulatory requirements.

4.1.4 The investigator/institution should permit monitoring and auditing by the sponsor, and inspection by the appropriate regulatory authority(ies).

4.1.5 The investigator should maintain a list of appropriately qualified persons to whom the investigator has delegated significant trial-related duties.

4.2 Adequate Resources

4.2.1 The investigator should be able to demonstrate (e.g., based on retrospective data) a potential for recruiting the required number of suitable subjects within the agreed recruitment period.

4.2.2 The investigator should have sufficient time to properly conduct and complete the trial within the agreed trial period.

4.2.3 The investigator should have available an adequate number of qualified staff and adequate facilities for the foreseen duration of the trial to conduct the trial properly and safely.

4.2.4 The investigator should ensure that all persons assisting with the trial are adequately informed about the protocol, the investigational product(s), and their trial-related duties and functions.

4.3 Medical Care of Trial Subjects

4.3.1 A qualified physician (or dentist, when appropriate), who is an investigator or a sub-investigator for the trial, should be responsible for all trial-related medical (or dental) decisions.

4.3.2 During and following a subject's participation in a trial, the investigator/institution should ensure that adequate medical care is provided to a subject for any adverse events, including clinically significant laboratory values, related to the trial. The investigator/institution should inform a subject when medical care is needed for intercurrent illness(es) of which the investigator becomes aware.

4.3.3 It is recommended that the investigator inform the subject's primary physician about the subject's participation in the trial if the subject has a primary physician and if the subject agrees to the primary physician being informed.

4.3.4 Although a subject is not obliged to give his/her reason(s) for withdrawing prematurely from a trial, the investigator should make a reasonable effort to ascertain the reason(s), while fully respecting the subject's rights.

4.4 Communication with IRB/IEC

4.4.1 Before initiating a trial, the investigator/institution should have written and dated approval/favorable opinion from the IRB/IEC for the trial protocol, written informed consent form, consent form updates, subject recruitment procedures (e.g., advertisements), and any other written information to be provided to subjects.

4.4.2 As part of the investigator's/institution's written application to the IRB/IEC, the investigator/institution should provide the IRB/IEC with a current copy of the Investigator's Brochure. If the Investigator's Brochure is updated during the trial, the investigator/institution should supply a copy of the updated Investigator's Brochure to the IRB/IEC.

4.4.3 During the trial the investigator/institution should provide to the IRB/IEC all documents subject to its review.

4.5 Compliance with Protocol

4.5.1 The investigator/institution should conduct the trial in compliance with the protocol agreed to by the sponsor and, if required, by the regulatory authority(ies), and which was given approval/favorable opinion by the IRB/IEC. The investigator/institution and the sponsor should sign the protocol, or an alternative contract, to confirm their agreement.

4.5.2 The investigator should not implement any deviation from, or changes of, the protocol without agreement by the sponsor and prior review and documented approval/favorable opinion from the IRB/IEC of an amendment, except where necessary to eliminate an immediate hazard(s) to trial subjects, or when the change(s) involves only logistical or administrative aspects of the trial (e.g., change of monitor(s), change of telephone number(s)).

4.5.3 The investigator, or person designated by the investigator, should document and explain any deviation from the approved protocol.

4.5.4 The investigator may implement a deviation from, or a change in, the protocol to eliminate an immediate hazard(s) to trial subjects without prior IRB/IEC approval/favorable opinion. As soon as possible, the implemented

deviation or change, the reasons for it, and, if appropriate, the proposed protocol amendment(s) should be submitted:

(a) To the IRB/IEC for review and approval/favorable opinion;
(b) To the sponsor for agreement and, if required;
(c) To the regulatory authority(ies).

4.6 Investigational Product(s)

4.6.1 Responsibility for investigational product(s) accountability at the trial site(s) rests with the investigator/institution.

4.6.2 Where allowed/required, the investigator/institution may/should assign some or all of the investigator's/institution's duties for investigational product(s) accountability at the trial site(s) to an appropriate pharmacist or another appropriate individual who is under the supervision of the investigator/institution.

4.6.3 The investigator/institution and/or a pharmacist or other appropriate individual, who is designated by the investigator/institution, should maintain records of the product's delivery to the trial site, the inventory at the site, the use by each subject, and the return to the sponsor or alternative disposition of unused product(s). These records should include dates, quantities, batch/serial numbers, expiration dates (if applicable), and the unique code numbers assigned to the investigational product(s) and trial subjects. Investigators should maintain records that document adequately that the subjects were provided the doses specified by the protocol and reconcile all investigational product(s) received from the sponsor.

4.6.4 The investigational product(s) should be stored as specified by the sponsor (see sections 5.13.2 and 5.14.3) and in accordance with applicable regulatory requirement(s).

4.6.5 The investigator should ensure that the investigational product(s) are used only in accordance with the approved protocol.

4.6.6 The investigator, or a person designated by the investigator/institution, should explain the correct use of the investigational product(s) to each subject and should check, at intervals appropriate for the trial, that each subject is following the instructions properly.

4.7 Randomization Procedures and Unblinding

The investigator should follow the trial's randomization procedures, if any, and should ensure that the code is broken only in accordance with the protocol. If the trial is blinded,

the investigator should promptly document and explain to the sponsor any premature unblinding (e.g., accidental unblinding, unblinding due to a serious adverse event) of the investigational product(s).

4.8 Informed Consent of Trial Subjects

4.8.1 In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirement(s) and should adhere to GCP and to the ethical principles that have their origin in the Declaration of Helsinki. Prior to the beginning of the trial, the investigator should have the IRB/IEC's written approval/favorable opinion of the written informed consent form and any other written information to be provided to subjects.

4.8.2 The written informed consent form and any other written information to be provided to subjects should be revised whenever important new information becomes available that may be relevant to the subject's consent. Any revised written informed consent form, and written information should receive the IRB/IEC's approval/favorable opinion in advance of use. The subject or the subject's legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the subject's willingness to continue participation in the trial. The communication of this information should be documented.

4.8.3 Neither the investigator, nor the trial staff, should coerce or unduly influence a subject to participate or to continue to participate in a trial.

4.8.4 None of the oral and written information concerning the trial, including the written informed consent form, should contain any language that causes the subject or the subject's legally acceptable representative to waive or to appear to waive any legal rights, or that releases or appears to release the investigator, the institution, the sponsor, or their agents from liability for negligence.

4.8.5 The investigator, or a person designated by the investigator, should fully inform the subject or, if the subject is unable to provide informed consent, the subject's legally acceptable representative, of all pertinent aspects of the trial including the written information given approval/favorable opinion by the IRB/IEC.

4.8.6 The language used in the oral and written information about the trial, including the written informed consent form, should be as nontechnical as practical and should be understandable to the subject or the subject's legally acceptable representative and the impartial witness, where applicable.

4.8.7 Before informed consent may be obtained, the investigator, or a person designated by the investigator, should provide the subject or the subject's legally acceptable representative ample time and opportunity to inquire about details of the trial and to decide whether or not to participate in the trial. All questions about the trial should be answered to the satisfaction of the subject or the subject's legally acceptable representative.

4.8.8 Prior to a subject's participation in the trial, the written informed consent form should be signed and personally dated by the subject or by the subject's legally acceptable representative, and by the person who conducted the informed consent discussion.

4.8.9 If a subject is unable to read or if a legally acceptable representative is unable to read, an impartial witness should be present during the entire informed consent discussion. After the written informed consent form and any other written information to be provided to subjects is read and explained to the subject or the subject's legally acceptable representative, and after the subject or the subject's legally acceptable representative has orally consented to the subject's participation in the trial, and, if capable of doing so, has signed and personally dated the informed consent form, the witness should sign and personally date the consent form. By signing the consent form, the witness attests that the information in the consent form and any other written information was accurately explained to, and apparently understood by, the subject or the subject's legally acceptable representative, and that informed consent was freely given by the subject or the subject's legally acceptable representative.

4.8.10 Both the informed consent discussion and the written informed consent form and any other written information to be provided to subjects should include explanations of the following:

(a) That the trial involves research.

(b) The purpose of the trial.

(c) The trial treatment(s) and the probability for random assignment to each treatment.

(d) The trial procedures to be followed, including all invasive procedures.

(e) The subject's responsibilities.

(f) Those aspects of the trial that are experimental.

(g) The reasonably foreseeable risks or inconveniences to the subject and, when applicable, to an embryo, fetus, or nursing infant.

(h) The reasonably expected benefits. When there is no intended clinical benefit to the subject, the subject should be made aware of this.

(i) The alternative procedure(s) or course(s) of treatment that may be available to the subject, and their important potential benefits and risks.

(j) The compensation and/or treatment available to the subject in the event of trial-related injury.

(k) The anticipated prorated payment, if any, to the subject for participating in the trial.

(l) The anticipated expenses, if any, to the subject for participating in the trial.

(m) That the subject's participation in the trial is voluntary and that the subject may refuse to participate or withdraw from the trial, at any time, without penalty or loss of benefits to which the subject is otherwise entitled.

(n) That the monitor(s), the auditor(s), the IRB/IEC, and the regulatory authority(ies) will be granted direct access to the subject's original medical records for verification of clinical trial procedures and/or data, without violating the confidentiality of the subject, to the extent permitted by the applicable laws and regulations and that, by signing a written informed consent form, the subject or the subject's legally acceptable representative is authorizing such access.

(o) That records identifying the subject will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available. If the results of the trial are published, the subject’s identity will remain confidential.

(p) That the subject or the subject's legally acceptable representative will be informed in a timely manner if information becomes available that may be relevant to the subject's willingness to continue participation in the trial.

(q) The person(s) to contact for further information regarding the trial and the rights of trial subjects, and whom to contact in the event of trial-related injury.

(r) The foreseeable circumstances and/or reasons under which the subject's participation in the trial may be terminated.

(s) The expected duration of the subject's participation in the trial.

(t) The approximate number of subjects involved in the trial.

4.8.11 Prior to participation in the trial, the subject or the subject's legally acceptable representative should receive a copy of the signed and dated written informed consent form and any other written information provided to the subjects. During a subject's participation in the trial, the subject or the subject's legally acceptable representative should receive a copy of the signed and dated consent form updates and a copy of any amendments to the written information provided to subjects.

4.8.12 When a clinical trial (therapeutic or nontherapeutic) includes subjects who can only be enrolled in the trial with the consent of the subject's legally acceptable representative (e.g., minors, or patients with severe dementia), the subject should be informed about the trial to the extent compatible with the subject's understanding and, if capable, the subject should assent, sign and personally date the written informed consent.

4.8.13 Except as described in 4.8.14, a nontherapeutic trial (i.e., a trial in which there is no anticipated direct clinical benefit to the subject) should be conducted in subjects who personally give consent and who sign and date the written informed consent form.

4.8.14 Nontherapeutic trials may be conducted in subjects with consent of a legally acceptable representative provided the following conditions are fulfilled:

(a) The objectives of the trial cannot be met by means of a trial in subjects who can give informed consent personally.

(b) The foreseeable risks to the subjects are low.

(c) The negative impact on the subject's well-being is minimized and low.

(d) The trial is not prohibited by law.

(e) The approval/favorable opinion of the IRB/IEC is expressly sought on the inclusion of such subjects, and the written approval/favorable opinion covers this aspect.

Such trials, unless an exception is justified, should be conducted in patients having a disease or condition for which the investigational product is intended. Subjects in these trials should be particularly closely monitored and should be withdrawn if they appear to be unduly distressed.

4.8.15 In emergency situations, when prior consent of the subject is not possible, the consent of the subject's legally acceptable representative, if present, should be requested. When prior consent of the subject is not possible, and the subject's legally acceptable representative is not available, enrollment of the subject should require measures described in the protocol and/or elsewhere, with documented approval/favorable opinion by the IRB/IEC, to protect the rights, safety, and well-being of the subject and to ensure compliance with applicable regulatory requirements. The subject or the subject's legally acceptable representative should be informed about the trial as soon as possible and consent to continue and other consent as appropriate (see section 4.8.10) should be requested.

4.9 Records and Reports

4.9.1 The investigator should ensure the accuracy, completeness, legibility, and timeliness of the data reported to the sponsor in the CRFs and in all required reports.

4.9.2 Data reported on the CRF, which are derived from source documents, should be consistent with the source documents or the discrepancies should be explained.

4.9.3 Any change or correction to a CRF should be dated, initialed, and explained (if necessary) and should not obscure the original entry (i.e., an audit trail should be maintained); this applies to both written and electronic changes or corrections (see section 5.18.4(n)). Sponsors should provide guidance to investigators and/or the investigators' designated representatives on making such corrections. Sponsors should have written procedures to assure that changes or corrections in CRFs made by sponsor's designated representatives are documented, are necessary, and are endorsed by the investigator. The investigator should retain records of the changes and corrections.

4.9.4 The investigator/institution should maintain the trial documents as specified in Essential Documents for the Conduct of a Clinical Trial (see section 8.) and as required by the applicable regulatory requirement(s). The investigator/institution should take measures to prevent accidental or premature destruction of these documents.

4.9.5 Essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained (see section 5.5.12).

4.9.6 The financial aspects of the trial should be documented in an agreement between the sponsor and the investigator/institution.

4.9.7 Upon request of the monitor, auditor, IRB/IEC, or regulatory authority, the investigator/institution should make available for direct access all requested trial-related records.

4.10 Progress Reports

4.10.1 Where required by the applicable regulatory requirements, the investigator should submit written summaries of the trial's status to the institution. The investigator/institution should submit written summaries of the status of the trial to the IRB/IEC annually, or more frequently, if requested by the IRB/IEC.

4.10.2 The investigator should promptly provide written reports to the sponsor, the IRB/IEC (see section 3.3.8), and, where required by the applicable regulatory requirements, the institution on any changes significantly affecting the conduct of the trial, and/or increasing the risk to subjects.

4.11 Safety Reporting

4.11.1 All serious adverse events (SAEs) should be reported immediately to the sponsor except for those SAEs that the protocol or other document (e.g., Investigator's Brochure) identifies as not needing immediate reporting. The immediate reports should be followed promptly by detailed, written reports. The immediate and follow-up reports should identify subjects by unique code numbers assigned to the trial subjects rather than by the subjects' names, personal identification numbers, and/or addresses. The investigator should also comply with the applicable regulatory requirement(s) related to the reporting of unexpected serious adverse drug reactions to the regulatory authority(ies) and the IRB/IEC.

4.11.2 Adverse events and/or laboratory abnormalities identified in the protocol as critical to safety evaluations should be reported to the sponsor according to the reporting requirements and within the time periods specified by the sponsor in the protocol.

4.11.3 For reported deaths, the investigator should supply the sponsor and the IRB/IEC with any additional requested information (e.g., autopsy reports and terminal medical reports).

4.12 Premature Termination or Suspension of a Trial

If the trial is terminated prematurely or suspended for any reason, the investigator/institution should promptly inform the trial subjects, should assure appropriate therapy and follow-up for the subjects, and, where required by the applicable regulatory requirement(s), should inform the regulatory authority(ies). In addition:

4.12.1 If the investigator terminates or suspends a trial without prior agreement of the sponsor, the investigator should inform the institution, where required by the applicable regulatory requirements, and the investigator/institution should promptly inform the sponsor and the IRB/IEC, and should provide the sponsor and the IRB/IEC a detailed written explanation of the termination or suspension.

4.12.2 If the sponsor terminates or suspends a trial (see section 5.21), the investigator should promptly inform the institution, where required by the applicable regulatory requirements, and the investigator/institution should promptly inform the IRB/IEC and provide the IRB/IEC a detailed written explanation of the termination or suspension.

4.12.3 If the IRB/IEC terminates or suspends its approval/favorable opinion of a trial (see sections 3.1.2 and 3.3.9), the investigator should inform the institution, where required by the applicable regulatory requirements, and the investigator/institution should promptly notify the sponsor and provide the sponsor with a detailed written explanation of the termination or suspension.

4.13 Final Report(s) by Investigator/Institution

Upon completion of the trial, the investigator should, where required by the applicable regulatory requirements, inform the institution, and the investigator/institution should provide the sponsor with all required reports, the IRB/IEC with a summary of the trial's outcome, and the regulatory authority(ies) with any report(s) they require of the investigator/institution.

Appendix 4 World Medical Association Declaration of Helsinki

Special Communication

World Medical Association Declaration of Helsinki Ethical Principles for Medical Research Involving Human Subjects

World Medical Association

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and amended by the:
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
52nd WMA General Assembly, Edinburgh, Scotland, October 2000
53rd WMA General Assembly, Washington, DC, USA, October 2002 (Note of Clarification added)
55th WMA General Assembly, Tokyo, Japan, October 2004 (Note of Clarification added)
59th WMA General Assembly, Seoul, Republic of Korea, October 2008
64th WMA General Assembly, Fortaleza, Brazil, October 2013

Preamble

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data.

   The Declaration is intended to be read as a whole and each of its constituent paragraphs should be applied with consideration of all other relevant paragraphs.

2. Consistent with the mandate of the WMA, the Declaration is addressed primarily to physicians. The WMA encourages others who are involved in medical research involving human subjects to adopt these principles.

General Principles

3. The Declaration of Geneva of the WMA binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act in the patient's best interest when providing medical care."

4. It is the duty of the physician to promote and safeguard the health, well-being and rights of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.

5. Medical progress is based on research that ultimately must include studies involving human subjects.

6. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best proven interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

7. Medical research is subject to ethical standards that promote and ensure respect for all human subjects and protect their health and rights.

8. While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects.

9. It is the duty of physicians who are involved in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects. The responsibility for the protection of research subjects must always rest with the physician or other health care professionals and never with the research subjects, even though they have given consent.

10. Physicians must consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

11. Medical research should be conducted in a manner that minimises possible harm to the environment.

12. Medical research involving human subjects must be conducted only by individuals with the appropriate ethics and scientific education, training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional.

13. Groups that are underrepresented in medical research should be provided appropriate access to participation in research.

14. Physicians who combine medical research with medical care should involve their patients in research only to the extent that this is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.

15. Appropriate compensation and treatment for subjects who are harmed as a result of participating in research must be ensured.

Risks, Burdens and Benefits

16. In medical practice and in medical research, most interventions involve risks and burdens.

    Medical research involving human subjects may only be conducted if the importance of the objective outweighs the risks and burdens to the research subjects.

17. All medical research involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and groups involved in the research in comparison with foreseeable benefits to them and to other individuals or groups affected by the condition under investigation.

    Measures to minimise the risks must be implemented. The risks must be continuously monitored, assessed and documented by the researcher.

18. Physicians may not be involved in a research study involving human subjects unless they are confident that the risks have been adequately assessed and can be satisfactorily managed.

    When the risks are found to outweigh the potential benefits or when there is conclusive proof of definitive outcomes, physicians must assess whether to continue, modify or immediately stop the study.

Vulnerable Groups and Individuals

19. Some groups and individuals are particularly vulnerable and may have an increased likelihood of being wronged or of incurring additional harm.

    All vulnerable groups and individuals should receive specifically considered protection.

20. Medical research with a vulnerable group is only justified if the research is responsive to the health needs or priorities of this group and the research cannot be carried out in a non-vulnerable group. In addition, this group should stand to benefit from the knowledge, practices or interventions that result from the research.

Scientific Requirements and Research Protocols

21. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.

22. The design and performance of each research study involving human subjects must be clearly described and justified in a research protocol.

    The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, potential conflicts of interest, incentives for subjects and information regarding provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study.

    In clinical trials, the protocol must also describe appropriate arrangements for post-trial provisions.

Research Ethics Committees

23. The research protocol must be submitted for consideration, comment, guidance and approval to the concerned research ethics committee before the study begins. This committee must be transparent in its functioning, must be independent of the researcher, the sponsor and any other undue influence and must be duly qualified. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration.

    The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No amendment to the protocol may be made without consideration and approval by the committee. After the end of the study, the researchers must submit a final report to the committee containing a summary of the study's findings and conclusions.

Privacy and Confidentiality

24. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information.

Informed Consent

25. Participation by individuals capable of giving informed consent as subjects in medical research must be voluntary. Although it

may be appropriate to consult family members or community leaders, no individual capable of giving informed consent may be enrolled in a research study unless he or she freely agrees.

26. In medical research involving human subjects capable of giving informed consent, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, post-study provisions and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information.

    After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.

    All medical research subjects should be given the option of being informed about the general outcome and results of the study.

27. When seeking informed consent for participation in a research study the physician must be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent must be sought by an appropriately qualified individual who is completely independent of this relationship.

28. For a potential research subject who is incapable of giving informed consent, the physician must seek informed consent from the legally authorised representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the group represented by the potential subject, the research cannot instead be performed with persons capable of providing informed consent, and the research entails only minimal risk and minimal burden.

29. When a potential research subject who is deemed incapable of giving informed consent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorised representative. The potential subject's dissent should be respected.

30. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research group. In such circumstances the physician must seek informed consent from the legally authorised representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research must be obtained as soon as possible from the subject or a legally authorised representative.

31. The physician must fully inform the patient which aspects of their care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never adversely affect the patient-physician relationship.

32. For medical research using identifiable human material or data, such as research on material or data contained in biobanks or similar repositories, physicians must seek informed consent for its collection, storage and/or reuse. There may be exceptional situations where consent would be impossible or impracticable to obtain for such research. In such situations the research may be done only after consideration and approval of a research ethics committee.

Use of Placebo

33. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best proven intervention(s), except in the following circumstances:

    Where no proven intervention exists, the use of placebo, or no intervention, is acceptable; or

    Where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention

    and the patients who receive any intervention less effective than the best proven one, placebo, or no intervention will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention.

    Extreme care must be taken to avoid abuse of this option.

Post-Trial Provisions

34. In advance of a clinical trial, sponsors, researchers and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial. This information must also be disclosed to participants during the informed consent process.

Research Registration and Publication and Dissemination of Results

35. Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject.

36. Researchers, authors, sponsors, editors and publishers all have ethical obligations with regard to the publication and dissemination of the results of research. Researchers have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. All parties should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results must be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest must be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

Unproven Interventions in Clinical Practice

37. In the treatment of an individual patient, where proven interventions do not exist or other known interventions have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorised representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. This intervention should subsequently be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information must be recorded and, where appropriate, made publicly available.

ARTICLE INFORMATION

Corresponding Author: World Medical Association, 13, ch. du Levant, CIB - Bâtiment A, 01210 Ferney-Voltaire, France; wma@wma.net.

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