1 SYNOPSIS

Title of Study:	RESTOR: A Multicenter, Randomized, Double-Blind, Placebo-Controlled Efficacy, Tolerability and Safety Study of DFN-11 Injection (Sumatriptan 3 mg) in Episodic Migraine With or Without Aura
Protocol Number:	DFN-11-CD-004
Investigators/Study Sites:	Approximately 18 sites in United States of America
Phase of Development:	3
Objectives:	**Primary Objective** Double-Blind (Period 1) • To assess the proportion of subjects who are pain-free at 2 hours postdose in the double-blind period **Key Secondary objectives** Double-Blind (Period 1) • To assess the proportion of subjects who are pain-free at 1 hour postdose • To assess the proportion of subjects with their most bothersome symptom (MBS) among nausea, photophobia, and phonophobia, absent at 2 hours postdose **Other Secondary Objectives** Double-Blind and Open-Label Extension (Period 1 and Period 2) • To assess the proportion of subjects who are free from nausea, photophobia, and phonophobia [redacted] • [redacted] [redacted] • To assess the proportion of subjects who have pain relief [redacted] • To assess the proportion of subjects who are pain-fre [redacted] • To assess the proportion of subjects with their MBS absent [redacted] • To assess change in functional disability score [redacted]

[redacted]

- To assess the proportion of subjects who have sustained pain freedom [redacted]
- To assess the proportion of subjects who use a second dose of the study medication or rescue medication after 2 hours (2-24 hours) postdose
- To assess treatment satisfaction at 2 hours postdose (7 point scale)
- To assess treatment satisfaction as measured by Patient Perception of Migraine Questionnaire-Revised (PPMQ-R) at 24 hours postdose
- To evaluate safety and tolerability

Exploratory Objectives

[redacted]

Study Design:	This is a randomized, double-blind study, with an open-label extension, to be conducted at approximately 18 centers in the United States (US). Male and female subjects, 18-65 years old (inclusive), previously diagnosed with episodic migraine (at least 12 months medical history prior to screening) who do not have medication overuse headaches (MOH), who experience 2 to 6 migraine attacks (with or without visual aura) per month, with 14 or fewer migraine headache days per month, and who can demonstrate 48 hours of headache free time between migraine attacks, will be initially randomized in a 1:1 ratio in a double-blind fashion to receive by subcutaneous (SC) injection either DFN-11 or placebo, to be used in 1 migraine attack within 1 hour of experiencing moderate to severe pain level. This double-blind period is up to 4 weeks (+ 3 days) or within 5 days (+ 3 days) postdose, whichever is earlier, depending on when, and if, the subject will get migraine attack during the double-blind period. Subjects may subsequently continue into an open-label period where they will receive active DFN-11 for 8 weeks to treat their migraine within 1 hour of migraine pain onset at any pain level. During the 2 treatment periods, data regarding the study medication effect and the associated impact on function and subjects' satisfaction will also be collected. All subjects will receive the study medication via self-administered SC injections (DFN-11 or placebo) using an autoinjector during the study. After study completion or discontinuation, subjects should be referred to their usual healthcare professional to resume pre-study standard of care, as per the Investigator's discretion. Subjects will return the autoinjector to the study site at the end of the study. During both treatment periods of the study, subjects will have an option to take another dose of study medication, if they experience relief but feel the first dose is insufficient, or rescue medication 2 hours after the first dose of study medication if required and after the efficacy data has been recorded. No more than 2 doses of study medication will be taken in a 24 hour period. Rescue medication will be decided between the Investigator and the subject.
Selection of Subjects:	Main Inclusion Criteria: Subjects may be included in the study if they meet the following criteria:

	1. Able and willing to provide written informed consent 2. Male or female, 18 to 65 years of age, inclusive, at screening Notes: a. If female, a subject must have a negative serum pregnancy test at screening, does not plan to become pregnant during the study, and is not lactating b. If female, a subject also must have a negative urine pregnancy test at all subsequent study visits after the Screening Visit, and agree to practice a reliable form of contraception or abstinence during the study (except if surgically, or otherwise, sterile or >1 year post-menopausal). Acceptable forms of contraception include implants, injectables, combined oral contraceptives, an intrauterine device, a vasectomized partner, an exclusively female partner, and double-barrier methods. c. If male (with female partner), a subject must agree to practice a reliable form of contraception or abstinence during the study. 3. A history of episodic migraine (using International Classification of Headache Disorders criteria, 2nd edition [ICHD II]) who experience 2 to 6 migraine attacks a month for at least the past 12 months with no more than 14 migraine headache days per month, and with 48 hours of headache free time between migraine headaches 4. Have migraine with or without aura; if with aura, the aura cannot last longer than 60 minutes 5. Subjects who, in the opinion of the Investigator, are willing and able to: • Evaluate and record pain, migraine symptoms, and study medication effectiveness information in real time using a subject eDiary for the duration of the study • Record each instance of the use of study medication and rescue medication in real time using a subject eDiary for the duration of the study • Comply with all other study procedures and scheduling requirements

	6. In the opinion of the Investigator, subjects understand and are able to use SC device correctly after instructions from the study site staff Main Exclusion Criteria: Subjects will be excluded from participating in the study if they meet any of the following criteria: 1. Minors, even if they are in specified study age range 2. Medication overuse headache as defined by ICHD II: • Opioids ≥ 10 days a month during the 90 days prior to screening • Combination medications (e.g., Fiorinal®) ≥ 10 days a month during the 90 days prior to screening • Nonsteroidal anti-inflammatory drugs (NSAIDs) or other simple medications > 14 days a month during the 90 days prior to screening • Triptans or ergots ≥ 10 days a month during the 90 days prior to screening 3. Subjects treated with onabotulinumtoxin A (Botox®) or other botulinum toxin treatment; or history of receiving such treatment during the 180 days prior to screening 4. On unstable dosages of migraine prophylactic medications during the 30 days prior to and through screening 5. Taking mini-prophylaxis for menstrual migraine 6. Subjects with hemiplegic or basilar migraine or other forms of neurologically complicated migraine 7. Subjects who have prolonged aura (i.e., more than 1 hour) 8. Cerebrovascular disease including but not limited to a history of stroke or transient ischemic attack (TIA) 9. A history of migralepsy (seizure following a migraine) or a concurrent diagnosis of seizure disorder 10. Subjects who cannot differentiate between a migraine headache and tension-type or cluster headache or other types of headache 11. Subjects with a history of more than occasional (based on Investigator's judgment) tension-type headache (distinct from migraine headache days count).

	12. Subjects with a history of cluster headaches 13. Subjects with the diagnosis of "probable migraine" (ICHD II) 14. Subjects who have intolerance to any formulation of sumatriptan or who have experienced a significant AE related to any other triptan 15. A history of resistance or non-responsiveness to SC sumatriptan (6 mg or lower dose) or non-response to two or more other triptans at an adequate dose and treatment duration in the opinion of the Investigator 16. Ischemic coronary artery disease (CAD): including but not limited to angina pectoris, history of myocardial infarction or documented silent ischemia or coronary artery vasospasm, including Prinzmetal's angina 17. Subjects with Wolff-Parkinson-White syndrome or arrhythmias associated with other cardiac accessory conduction pathway disorders 18. Subjects with a history of congenital heart disease 19. Uncontrolled hypertension or screening systolic blood pressure (SBP) > 140 mmHg or diastolic blood pressure (DBP) > 90 mmHg (the values should be reconfirmed to rule out a transient fluctuation; see Section 7.3 for details. 20. Have peripheral vascular disease including but not limited to ischemic bowel disease (IBD) and Raynaud's disease. 21. Use of monoamine oxidase (MAO) inhibitor at least 30 days prior to screening 22. Have contradictions to SC therapies such as a history of any bleeding disorder or is currently taking an anti-coagulant or any antiplatelet medication; subjects on stable doses of aspirin up to 100 mg/day for cardiac prophylaxis or the occasional use of medications containing a higher dose of aspirin, such as Excedrin, for pain, fever and as rescue medication are allowed 23. Any abnormal physiology and/or pathology which, in the opinion of the Investigator or Sponsor, which would be contraindicated for study participation and would not allow the objectives of the study to be met 24. Subjects who show any clinical laboratory or electrocardiogram (ECG) abnormality that in the opinion of

	the Investigator would endanger the subject or interfere with the study conduct. If the results of the clinical laboratory or ECG are outside of normal reference range the subject may still be enrolled but only if these findings are determined to be not clinically significant by the Investigator. This determination must be recorded in the subject's source document prior to enrolment. 25. Fridericia's corrected QT (QTcF) interval greater than 450 msec 26. Severe renal impairment (creatinine > 2 mg/dl) 27. Serum total bilirubin > 2.0 mg/dL 28. Serum aspartate aminotransferase (AST), alanine aminotransferase (ALT), or alkaline phosphatase > 2.5 times the upper limit of normal 29. Subjects with uncontrolled diabetes mellitus, or a glycosylated hemoglobin (HbA1c) > 7.0%, or with diabetes mellitus requiring insulin 30. A history of alcohol or substance use disorder according to the Diagnostic and Statistical Manual of Mental Disorders, Edition V (DSM-V) (including marijuana) within 1 year prior to screening 31. Current treatment with antipsychotics or use of antipsychotics within 30 days of screening 32. Subjects with a positive urine drug screen for recreational drugs, alcohol, marijuana (whether legal or not) or for prescription drugs not explained by stated concomitant medications • Subjects consuming opioids for the treatment of migraine or using opioids or barbiturates temporarily for a legitimate medical cause may participate as long as they do not meet the MOH criteria • Chronic use of benzodiazepines is allowed if used for legitimate medical use, as long as the regimen has been stable for at least 3 months prior to screening and is expected to remain stable throughout the study • Chronic use of amphetamines to treat attention deficit disorder (ADD) or attention deficit hyperactivity disorder (ADHD) and related disorders is allowed as long as the regimen has been stable for at least

	3 months prior to screening and is expected to remain stable throughout the study Note: For the above-mentioned conditions, the site must have appropriate documentation to justify the mentioned drug use (e.g., documented medical history and a valid prescription-based dispensation) 33. A history of or current neurological or psychiatric impairment, including but not limited to psychosis, current major depression, bipolar disorder or cognitive dysfunction that, in the opinion of the Investigator, would compromise data collection 34. Subjects who have received treatment with an investigational drug or device within 30 days of the screening visit or participated in a central nervous system clinical trial in the 3 months prior to screening 35. Subjects with any other medical condition that, in the judgment of the Investigator and/or Medical Monitor, would confound the objectives of the study (e.g., positive screening test for human immunodeficiency virus [HIV], hepatitis B surface antigen positive or hepatitis C positive, a known history of systemic lupus erythematosis) 36. History of cancer within the past 5 years (except adequately treated basal cell or squamous cell skin carcinoma or in situ cervical cancer) 37. History of any skin condition that may adversely affect the injection or use of subcutaneously administered medication such as scleroderma 38. Subjects who should not be enrolled per the precautions, warnings, and contraindications section of the Imitrex® product label or package insert 39. Subjects who plan to donate blood, sperm, or oocytes during the study and for 30 days after the last dose of study medication 40. Subjects who are employees or immediate relatives of the employees of the Sponsor, any of its affiliates or partners, or of the study center
Planned Sample Size:	A total of approximately 266 subjects will be randomized in a 1:1 ratio into 2 treatment arms. The study may be stopped sooner based on an independent Data Monitoring Committee (DMC) recommendation after reviewing study efficacy data

	(see Statistical Methods and Planned Analysis section for details) at an interim analysis (IA).
Investigational Therapy:	DFN-11 Injection (sumatriptan 3 mg)
Reference Therapy:	Placebo injection
Treatment Duration:	The duration of study participation will be approximately 15 weeks, including screening period of approximately 3 weeks, double-blind treatment period of up to 4 weeks (+ 3 days) or within 5 days (+ 3 days) postdose, whichever is earlier, and an open-label treatment period of 8 weeks (± 3 days).
Criteria for Evaluation:	Efficacy: • Subjects will be provided with an eDiary at Screening Visit (Visit 1) to collect at least 1 migraine episode data in real time and, if randomized, to continue to collect migraine data in real time through End of Treatment (ET) Visit (Visit 5/ET): o Migraine pain start and end (date and time) o Level of headache pain predose and at various timepoints postdose (Levels: 0 = none; 1 = mild; 2 = moderate; 3 = severe) o [redacted] o Migraine symptoms and MBS other than pain: nausea, photophobia, and phonophobia, predose and at various timepoints postdose • PPMQ-R • Functional disability scale (0 = no disability, able to function normally; 1 = performance of daily activities mildly impaired, can still do everything but with difficulty; 2 = performance of daily activities moderately impaired, unable to do some things; 3 = performance of daily activities severely impaired, cannot do all or most things, bed rest may be necessary) • Treatment satisfaction (7 point scale) • Study medication and rescue use Safety: • Adverse events: Adverse events will be collected from signing of the informed consent form (ICF) at Screening Visit (Visit 1) until a subject's completion or discontinuation from the study • Concomitant medication review

	• Physical examinations • Pregnancy tests in females • Measurement of vital signs (sitting systolic and diastolic blood pressure, pulse rate, and body temperature) • Clinical laboratory examination (hematology, chemistry, and urinalysis) • Urine drug screen • 12-lead ECG
Study Endpoints:	**Primary Endpoints:** <u>Double-Blind Period (Period 1)</u> The proportion of subjects who are pain-free (defined as a reduction from predose moderate [Grade 2] or severe [Grade 3] pain to none [Grade 0]) 2 hours after the first dose of study medication compared between DFN-11 and placebo in the double-blind period. **Key Secondary Endpoints:** <u>Double-Blind Period (Period 1)</u> • [redacted] • The proportion of subjects who are pain-free (defined as a reduction from predose moderate [Grade 2] or severe [Grade 3] pain to none [Grade 0]) 1 hour after the first dose of study medication compared between DFN-11 and placebo in double-blind period. • The proportion of subjects who are free from their MBS among nausea, photophobia, and phonophobia 2 hours after the first dose of study medication compared between DFN-11 and placebo in double-blind period. **Other Secondary Endpoints:** <u>Double-Blind and Open-Label Extension (Period 1 and Period 2)</u> *Efficacy Endpoints* The secondary efficacy endpoints are as follows: • [redacted]

	[redacted] • [redacted] [redacted] • The proportion of subjects who have pain relief [redacted] • The proportion of subjects who are pain-free [redacted] • The proportion of subjects with their MBS absent [redacted] • Change in functional disability score [redacted] • [redacted] • The proportion of subjects who use a second dose of the study medication or rescue medication after 2 hours (2-24 hours) postdose study medication compared between DFN-11 and placebo in double-blind period, and DFN-11

in the open-label period

- Treatment satisfaction at 2 hours postdose as determined on a 7 point scale after study medication compared between DFN-11 and placebo in double-blind period, and DFN-11 in the open-label period.
- Treatment satisfaction as measured by PPMQ-R at 24 hours postdose study medication compared between DFN-11 and placebo in double-blind period, and DFN-11 in the open-label period.

Safety Endpoints

The safety endpoints of this study are as follows:

- Proportion of subjects with treatment emergent adverse events (TEAEs) and SAEs after study medication compared between DFN-11 and placebo in double-blind period, and DFN-11in the open-label period.
- Changes in the clinical laboratory tests, vital signs, and ECG after study medication for DFN-11 and placebo in the double-blind period, and DFN-11 in the open-label period.

Exploratory Endpoints:

[redacted]

	• [redacted] *Safety Endpoints* The safety exploratory endpoints of this study are as follows: • Proportion of subjects with AEs of interest: classic triptan-related AEs (may include but are not limited to tingling, dizziness/vertigo, warm/hot sensation, cold sensation, burning sensation, feeling of heaviness, feeling strange, paraesthesia, dysesthesia, prickling sensation pressure sensation, flushing, feeling of tightness, and numbness) occurring upon dosing; and injection site reactions (may include but are not limited to injection site swelling, irritation, erythema, hemorrhage, pain, and bruising) within 24 hours of dosing with study medication compared between DFN-11 and placebo in the double-blind period, and DFN-11 in the open-label period.
Statistical Methods and Planned Analyses:	The statistical analysis method for the primary endpoint is described below. Detailed analyses of secondary and exploratory endpoints will be provided in the Statistical Analysis Plan (SAP), which will be finalized before database lock and unblinding of the data.

Study Populations

The primary analysis population will be the full analysis set (FAS) excluding subjects taking rescue pain medications or second dose of study medication within the first 2 hours postdose. [redacted]

Primary Efficacy Analysis

The primary efficacy analysis will be performed using Fisher's exact test.

Safety

Treatment-emergent AEs (TEAEs) will be coded using the latest version of the Medical Dictionary for Regulatory Activities (MedDRA). Adverse events and serious AEs (SAEs) will be summarized by treatment group for overall number of AEs, severity, and relationship to study medication. The incidence of AEs will be summarized by body system and treatment group. The incidence of AEs will also be summarized by system organ class and preferred term. Electrocardiogram and vital sign measurements will be summarized by group and time point along with the change from baseline. During the double-blind period, Visit 2 will be considered the baseline, i.e. the visit occurring just before treatment. If a subject will miss Visit 2 assessment but will have Visit 1 assessments, then Visit 1 will be used as baseline for the change from baseline calculations. All AEs, clinical laboratory data, vital signs, study medication use and concomitant medication use will be presented in data listings.

Interim analysis

One or more interim analyses (IA) for potential early stopping for an efficacy conclusion are planned [redacted] A conservative alpha spending function will be used to preserve most of the type 1 error for the final analysis in case the trial does not stop for an efficacy conclusion at IA(s).

[redacted]