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APPLICATION NUMBER:

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MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type NDA 505 (b)(2)
Application Number(s) 208223
Priority or Standard Standard

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Division / Office DNP

Reviewer Name(s) Ramesh Raman, MD, FACP
Review Completion Date December 7, 2015

Established Name DFN-11 injection (Sumatriptan succinate)
(Proposed) Trade Name Zembrace SymTouch
Therapeutic Class Triptan: serotonin (5-HT_{1B/1D}) receptor agonist
Applicant Dr. Reddy's Laboratories Inc.

Formulation(s) Sumatriptan 3mg/0.5mL for subcutaneous injection
Dosing Regimen 3mg/0.5mL as a single dose
Indication(s) Acute treatment of migraine with or without aura in adults
Intended Population(s) Adults

Template Version: March 6, 2009

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

Approval.

1.2 Risk Benefit Assessment

Since the approval of sumatriptan injection (Imitrex) in 1992 (under NDA 020080), the risks associated with sumatriptan and the benefits it can provide is well known and established. The safety profile and the risks associated with Zembrace, a different dosage form of sumatriptan, can therefore be considered to be the similar to that of the known risks associated with sumatriptan. Although the purpose of the studies that were conducted was to establish the PK comparability of Zembrace to the reference drug Imitrex and safety assessment was not its primary objective, the safety profile of Zembrace from these PK studies did not raise any specific clinical safety concerns.

Given its unique formulation and administration attributes, Zembrace will provide (b) (4) (b) (4). The reference drug is indicated for the acute treatment of migraine with or without aura in adults and for the acute treatment of cluster headache in adults. Based on the indication, the following is the approved dosage for Imitrex- single dose of 1 to 6 mg for acute treatment of migraine and a single dose of 6 mg for the acute treatment of cluster headache. Zembrace is a pre-filled, ready to use, single dose, disposable auto-injector that is uniquely designed to deliver 3 mg of sumatriptan succinate (3mg/0.5mL) into the subcutaneous tissue.

(b) (4)

(b) (4)

Approval of Zembrace, with an established PK and safety profile that is comparable to the referenced approved drug Imitrex, for the treatment of migraine (b) (4) in adults, is therefore justified.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

None.

1.4 Recommendations for Postmarket Requirements and Commitments

None.

2 Introduction and Regulatory Background

2.1 Product Information

ZembraceSymTouch (syn. DFP-11 or DFP-11 injection or DFP- 11 autoinjector or DFN-11 or DFN-11 injection or DFN-11 autoinjector or Zembrace®), is a drug and device combination injection that contains 3 mg/0.5 mL sumatriptan in a pre-filled syringe fitted into an auto-injector. DFN-11Injection is a single use product intended for subcutaneous administration.

Sumatriptan belongs to a class of drugs that are 5-HT agonists with an empirical (molecular) formula of C₁₄H₂₁N₃O₂S C₄H₆O₄. Sumatriptan binds with high affinity to human 5-HT_{1B/1D} receptors. Sumatriptan putatively exerts its therapeutic effects in the treatment of migraine ^{(b) (4)} by binding to 5-HT_{1B/1D} receptors located on intracranial blood vessels and sensory nerves of the trigeminal cranial nerve system.

An injectable formulation of sumatriptan succinate administered as a subcutaneous (SC) injection was first approved under the Imitrex® Injection NDA, (NDA 020080), on December 28, 1992. Sumatriptan is also available as Imitrex® Tablets, for oral use (NDA 020132), which was approved on June 1, 1995, and as Imitrex® Nasal Spray (NDA 020626), which was approved on August 26, 1997. This 505(b)(2) application will rely on the Agency's previous findings of safety and efficacy of Imitrex® injection (NDA 020080) (sumatriptan succinate SC injection).

2.5 Summary of Presubmission Regulatory Activity Related to Submission

This 505(b)(2) NDA application submitted on March 30, 2015, supported by PK bridging studies (see section 5 below), relies on the reference listed drug (RLD) Imitrex Injection (under NDA 020080) for both non-clinical and clinical data. Reference is made to the pre-IND (September 30, 2013) and pre-NDA (March 25, 2015) meetings that provided the direction for the drug development program via the bridging studies and to the agreements made on the content and format of the NDA submission.

Reviewer comments

The proposed proprietary name "ZembraceSymTouch" was found acceptable by the Agency (ref: DMEPA review, Nov 19, 2015).

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2.6 Other Relevant Background Information

Reviewer comments



3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

Reviewer comments

These are acceptable.

3.2 Compliance with Good Clinical Practices

Reviewer Comments

According to the Sponsor, the clinical studies were conducted according to Good Clinical Practices (GCP).

3.3 Financial Disclosures

Reviewer Comments

The submitted Financial Certification and Disclosure information (section 1.3 Administrative Information) and the completed FDA form 3454 is noted.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

Reviewer's comments

Reference is made to the respective reviews from the other review disciplines. It should be noted that the final review for some the disciplines is still pending at the time of this writing.

4.1 Chemistry Manufacturing and Controls

Dr. Sherita McLamore-Hines, the OPQ reviewer, did not identify issues that impacted clinical assessments and has concluded that the information provided in the current submission is adequate to support approval.

4.2 Clinical Microbiology

Dr. David Bateman, the microbiology reviewer, provided the product quality microbiology review and recommends approval.

4.3 Preclinical Pharmacology/Toxicology

Dr. Charles Thompson, the non-clinical reviewer, did not identify issues that required further non-clinical assessments or issues that impacted clinical assessments.

4.4 Clinical Pharmacology

Dr. Om Anand, the Biopharmaceutics reviewer, concluded that the results demonstrated that DFN-11 was BE to the referenced drug Imitrex and recommends approval. The PK and BE studies that served as the basis to support a 505(b)(2) application is discussed in section 5 of this review.

5 Sources of Clinical Data

The Sponsor conducted clinical PK studies served as the basis for the clinical data. In support of the 505(b)(2) application, Sponsor submitted results from the following three studies:

- Study DFP-11/CD/001: A Randomized Single-Dose, Two-Way Crossover Study to Determine the Relative Bioavailability of DFP-11 Sumatriptan Succinate 3 mg/0.5 mL Injection versus Imitrex® Injection 3 mg/0.25 mL (using Imitrex® 6 mg/0.5 mL) Following Subcutaneous Injection in Healthy Adult Male and Female Subjects.
- Study DFP-11/CD/002: A Randomized Single-Dose, Three-Way Crossover Study to Determine the Relative Bioavailability of DFP-11 Sumatriptan Succinate 3 mg/0.5 mL Injection versus Imitrex® Injection 3 mg/0.25 mL and 6 mg/0.5 mL (both using Imitrex® 6 mg/0.5 mL) Following Subcutaneous Injection in Healthy Adult Male and Female Subjects.
- Study DFP-11/CD/003: A Randomized Single-Dose, Three-Way Crossover Study to Determine the Dose-Normalized Bioequivalence of DFP-11 Sumatriptan Succinate 3 mg/0.5 mL Injection versus Imitrex® STATdose System 4 mg/0.50 mL and Imitrex® STATdose System 6 mg/0.50 mL Following Subcutaneous Injection in Healthy Adult Male and Female Subjects.

5.1 Tables of Studies/Clinical Trials

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status
BA ¹	Study DFP-11/CD/001	5.3.1.1	Relative Bioavailability of DFP-11 Sumatriptan 3 mg/0.5 mL Injection versus Imitrex® Injection 3 mg/0.25 mL	Randomized, two-way crossover study	<p>Treatment A: A single SC injection of 3 mg DFN-11 from Dr. Reddy's Laboratories, Ltd. (0.5 mL of sumatriptan 3 mg/0.5 mL solution administered as sumatriptan succinate) on Day 1 using the Auto-injector (b) (4) device, following an overnight fast. (Lot No. F1404001).</p> <p>Treatment B: A single SC injection of 3 mg Imitrex® from GlaxoSmithKline (0.25 mL of sumatriptan 6 mg/0.5 mL solution administered as sumatriptan succinate) on Day 1, administered manually, following an overnight fast. (Lot No. C675070).</p>	26 Subjects were randomized and 25 completed the study and were included for the PK and safety analysis	Healthy subjects	Single dose	Completed

Copied Sponsor's Table. Edited for format only. 1= Bioavailability.

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Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status
BA ¹	Study DFP-11/CD/002	5.3.1.1	Relative Bioavailability of DFP-11 Sumatriptan 3 mg/0.5 mL Injection versus Imitrex® Injection 3 and 6 mg/0.5 mL (both using Imitrex® 6 mg/0.5 mL)	Randomized, three-way crossover study	<p>Treatment A (Test): A single SC injection of 3 mg DFN-11 from Dr. Reddy's Laboratories Limited (0.5 mL of sumatriptan 3 mg/0.5 mL solution administered as sumatriptan succinate) on Day 1 using the DFP 11 Auto-injector device, following an overnight fast. (Lot No. F1404001).</p> <p>Treatment B (Reference 1): A single SC injection of 3 mg Imitrex® Injection from GlaxoSmithKline (0.25 mL of sumatriptan 6 mg/0.5 mL solution administered as sumatriptan succinate) on Day 1, administered manually using a syringe, following an overnight fast. (Lot No. C683680).</p> <p>Treatment C (Reference 2): A single SC injection of 6 mg Imitrex® Injection from GlaxoSmithKline (0.5 mL of sumatriptan 6 mg/0.5 mL solution administration as sumatriptan succinate) on Day 1, administered manually using a syringe, following an overnight fast (Lot No. C683680).</p>	36 Subjects were randomized and 32 completed the study and were included for the PK and safety analysis	Healthy subjects	Single dose	Completed

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Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status
BE ²	Study DFP-11/CD/003	5.3.1.2	Dose-Normalized Bioequivalence of DFP-11 Sumatriptan 3 mg/0.5 mL Injection versus Imitrex® STATdose System 4 mg/0.50 mL and Imitrex®STAT dose System 6 mg/0.50 mL	Randomized, three-way crossover study	Treatment A (Test): A single SC injection of 3 mg DFN-11 from Dr. Reddy's Laboratories Limited (0.5 mL of sumatriptan 3 mg/0.5 mL solution administered as sumatriptan succinate) on Day 1 using the DFN-11 Auto-injector device, following an overnight fast. (Lot No. F1404001). Treatment B (Reference 1): A single SC injection of 4 mg Imitrex® STATdose system from GlaxoSmithKline (0.50 mL of sumatriptan 4 mg/0.5 mL solution administered as sumatriptan succinate) on Day 1, following an overnight fast. (Lot No. C671631). Treatment C (Reference 2): A single SC injection of 6 mg Imitrex® STATdose system from GlaxoSmithKline (0.5 mL of sumatriptan 6 mg/0.5 mL solution administered as sumatriptan succinate) on Day 1, following an overnight fast. (Lot No. C689979).	36 Subjects were randomized and 36 completed the study and were included for the PK and safety analysis	Healthy subjects	Single dose	Completed

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5.2 Review Strategy

Although there was no formal clinical Phase 3 equivalent or pivotal studies, the clinical safety findings data from the PK studies was the primary focus of this clinical review. In addition, emphasis was placed on the salient findings by the other disciplines if it impacted, if any, the overall recommendation and labeling. These were summarized as appropriate. The studies including the safety findings are discussed under section 5.3. The specific details pertaining to certain PK related aspects such as the PK analytical methodology, modeling, statistical methodology, criteria for relative bioavailability, etc., are not discussed in this review and reference is made to Dr. Om Anand 's clinical pharmacology review for further details on PK and BE. Reference is made to the separate label review that involved multiple disciplines. The approved label for the RLD, Imitrex, served as the template for the Zembrace label.

5.3 Discussion of Individual Studies/Clinical Trials

Study DFP-11/CD/001

Study Phase

Phase 1.

Study Title

A randomized single-dose, two-way crossover study to determine the relative bioavailability of DFP-11 sumatriptan succinate 3 mg/0.5 ml injection versus Imitrex® injection 3 mg/0.25 ml (using Imitrex® 6 mg/0.5 ml) following subcutaneous injection in healthy adult male and female subjects.

Study Center (s)

Celerion, 621 Rose St, Lincoln, Nebraska 68502, USA.

Study Period

Date of first enrollment: 26 July 2014
Date of last completed: 19 August 2014

Study Objectives

- Primary Objective (s)

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To assess the bioequivalence (relative bioavailability [BA]) of a test formulation of DFP-11, a subcutaneous (SC) injection of sumatriptan succinate (3 mg/0.5 mL) from Dr. Reddy's Laboratories Limited, versus Imitrex® SC injection 3 mg/0.25 mL (using Imitrex® 6 mg/0.5 mL injection manufactured by GlaxoSmithKline) following a 3 mg SC injection in healthy adult male and female subjects.

- Secondary Objective (s)

To evaluate and compare the safety and tolerability of DFP-11 and Imitrex® in healthy adult male and female subjects.

Methodology

This was an open-label, randomized, single-dose, 2-way crossover, relative BA study of DFP-11 sumatriptan succinate 3 mg/0.5 mL injection versus Imitrex® injection 3 mg/0.25 mL (using Imitrex® 6 mg/0.5 mL) following SC injection in healthy adults under fasting conditions.

Twenty-six (26) healthy, adult, non-tobacco using male and female subjects between 19 and 45 years of age (inclusive) were enrolled. Screening of subjects occurred within 28 days prior to the first dose. On Day 1 of Period 1, subjects were randomized to one of the 2 treatment sequences (AB or BA). In each period, a single dose of 3 mg sumatriptan was administered SC as a bolus of approximately 5 seconds. Blood for pharmacokinetic (PK) evaluation of sumatriptan was collected at the specified times until 12 hours post-dose and safety was monitored throughout the study. The washout period was at least 5 days between doses of sumatriptan. In each period, subjects were confined from at least 8 hours prior to dosing and remained confined until after the 12-hour blood draw and/or other study procedures as appropriate. The clinic attempted to contact subjects using their standard procedures 5 (\pm 1) days after the last PK sample collection to determine if any adverse events (AE) had occurred since the last dose of study drug. Subjects who terminated the study early were contacted if the Principal Investigator (PI) deemed it necessary.

Number of Subjects (Planned and Analyzed)

A total of 26 subjects were enrolled in the study, and 25 subjects completed the study. One (1) subject was discontinued by the PI on Day -1 of Period 2, due to a positive pregnancy screen. All 26 subjects enrolled in the study were included in the PK and safety populations; however, only the 25 subjects who completed the study were included in the PK summary statistics and statistical comparisons of PK parameters.

Demographics

– Of the 26 subjects in the study, 13 were female and 13 were male.

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- 3 subjects were Black or African American, 21 were White, and 2 subjects were listed under multiple races.
- 6 subjects were Hispanic or Latino and 20 were not.
- The mean age for all subjects was 29.1 years (range 21 – 45 years), the mean weight was 78.28 kg (range 47.7 – 113.2 kg), the mean height was 169.9 cm (range 151 – 193 cm), and the mean BMI was 27.031 kg/m² (range 19.18 – 34.82 kg/m²).

Diagnosis and Main Criteria for Inclusion

All subjects enrolled in this study were judged by the PI to be normal, healthy volunteers who met all inclusion and none of the exclusion criteria.

Study Treatment (s)

Treatment A: A single SC injection of 3 mg DFN-11 injection (0.5 mL of sumatriptan 3 mg/0.5 mL solution administered as sumatriptan succinate) on Day 1 following an overnight fast (Lot No. F1404001). Subjects received a single SC dose over the deltoid muscle in the non-dominant arm.

Treatment B: A single SC injection of 3 mg Imitrex® from GlaxoSmithKline (0.25 mL of sumatriptan 6 mg/0.5 mL solution administered as sumatriptan succinate) on Day 1, administered manually, following an overnight fast. (Lot No. C675070).

Duration of Treatment

The anticipated study duration for each subject was up to 34 days, including a screening period of up to 28 days, a confinement period of approximately 1 day for each study period, and a washout period of 5 days.

Reference Product, Dose, Duration, Mode of Administration, and Batch Number

Imitrex® (sumatriptan succinate) injection 6 mg/0.5 mL (Lot No.: C675070). Subjects received a single SC dose over the deltoid muscle in the non-dominant arm.

Criteria for Evaluation

- Pharmacokinetics: Serial blood samples were obtained for the determination of sumatriptan in plasma, and PK parameters were calculated, including AUC_{0-t}, AUC_{0-inf}, C_{max}, AUC_{%extrap}, AUC₀₋₂, t_{max}, k_{el}, and t_{1/2}, using Phoenix® WinNonlin® Version 6.3.
- Safety: Safety endpoints included all types of AEs, physical examinations, vital signs (heart rate, blood pressure, and temperature), 12-lead electrocardiograms (ECG), injection site reaction assessments, and clinical laboratory tests (hematology, serum chemistry, and urinalysis).

Statistical Methods

- Pharmacokinetic

Reviewer Comments

Reference is made to the Agency PK review for further details.

- Safety

All clinical safety and tolerability data were listed by subject. Safety data including AEs, ECGs, vital signs, injection site assessments, and clinical laboratory evaluations were summarized descriptively by treatment and time point of collection. AEs were coded with Version 17.0 of Medical Dictionary for Regulatory Activities (MedDRA®) and all concomitant medications recorded during the study were coded with the 01 MAR 2014 version of World Health Organization (WHO) drug dictionary.

Results: Study DFP-11/CD/001

Pharmacokinetic Results

Reviewer Comments

Reference is made to the Agency PK review for further details.

According to the Sponsor, the PK results from Study DFP-11/CD/001 *failed to meet the bioequivalence criteria* between DFN-11 Injection and Imitrex® manual injection. Consequently, Sponsor performed a Root Cause Analysis (RCA) (by a cross-functional team involving representatives from Regulatory Affairs, Formulation Development, Device Development, Clinical, Drug Metabolism and Pharmacokinetics, Quality, Commercial and Project Management functions within DRL) and postulated that one or more of the following may have contributed to the failure:

- DFP-11 Auto-Injector (AI) performance
- Variability in the amount of injectable volume between different subjects who received the vial-drawn product
- Variability in the manual injection/administration of Imitrex®
- Conduct and performance of the bioanalytical method
- Subject/Participant anthropometric and/or demographics

Sponsor concluded by stating that the RCA team was not able to identify a definitive root cause that resulted in failure to achieve bioequivalence between DFN-11 Injection and Imitrex® manual injection in Study DFP-11/CD/001. However, based on analysis of

the registration batches of DFN-11 Injection, and a review of the bioanalytical methods, performance of the auto-injector and the bioanalytical methods were considered as unlikely contributory factors whereas consistency/variability of technique of skin pinch, the angle of manual injection, and the variability in the amount of injection volume between subjects who received the vial drawn product were considered as potential contributory factors. According to the Sponsor, the subsequently conducted PK studies (Study DFP-11/CD/002 and Study DFP-11/CD/003) were designed to prospectively address these potential causes for failure.

Safety Results

Summary

- There were no reports of deaths.
- There were no reports of SAEs.
- One (1) subject was discontinued due a positive pregnancy test (see Reviewer comments below).

Description of the subject who discontinued:

- In Study DFP-11/CD/001 one subject was discontinued due to the AE of positive pregnancy test. Subject 14 (a 36-year-old female; Treatment Sequence AB) exhibited a positive serum pregnancy test at check-in for Period 2 with a level of 505 IU/L. All serum pregnancy tests up until that point were reported negative. Subject reported using condoms and spermicide as birth control. The PI considered the pregnancy to be unrelated to the study drug. Sponsor stated that this event is being followed up
- Overall, a total of 21 AEs were experienced by 11 (42%) subjects in this study, with more subjects reporting AEs following DFN-11 (3 mg) injection (35%) compared to Imitrex® 3 mg injection (16%). All of the AEs were mild in severity and resolved without therapy, with the exception of the positive pregnancy test for Subject 14 that was considered severe in intensity. The PI considered 7 AEs to be possibly related to DFN-11 (3 mg) injection (dizziness, headache, neck pain, paresthesia, and urticaria), and the remaining 14 AEs to be unlikely or unrelated to DFN-11 (3 mg) injection or Imitrex® 3 mg injection.
- Injection site pain and headache were the most common AEs.
- Injection Site Reactions:
 - Mild injection site pain was reported a total of 6 times by 5 (19%) subjects, with 4 subjects following DFN-11 (3 mg) injection and 2 subjects following Imitrex® 3 mg injection. Onset ranged from 26 minutes to 11.5 hours post-dose, and duration ranged from approximately 18 hours to 10.9 days.
 - One (1) subject was reported to have 1 cm ecchymosis and swelling at the injection site at the 5.5 and 11.5-hour assessments following Imitrex® 3 mg injection that were not large enough to meet the grading criteria. A total of 5 subjects were reported to experience mild (Grade 1) tenderness site reactions

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- post-dose: 2 subjects each following DFN-11 (3 mg) injection and Imitrex® 3 mg injection at the 5.5-hour assessment; and 4 subjects following DFN-11 (3 mg) injection and 2 subjects following Imitrex® 3 mg injection at the 11.5-hour assessment. There were no subjects who experienced erythema/redness or pain at the injection site.
- Mild headache was reported a total of 4 times by 4 (15%) subjects, with 2 subjects each following DFN-11 (3 mg) injection and Imitrex® 3 mg injection. Onset ranged from 9 minutes post dose to 6.5 days post dose, and duration ranged from 1 hour to 22 hours.
 - Subject 13 (a 28-year-old male; Treatment Sequence BA) experienced the AE of urticaria (verbatim term: atypical urticarial rash on chest) with accompanying AE of pruritus approximately 1 day after dosing with DFN-11 (3 mg) injection. The subject reported 5 flat, red rings approximately 4 mm in diameter with white centers on his upper chest. The urticaria and pruritus events were resolved in 21 hours.
 - All remaining AEs were reported by 2 or fewer ($\leq 8\%$) subjects each.
 - There were no concomitant medications or non-drug therapies administered for AE resolution in this study.
 - Overall, mean serum chemistry, hematology, and urinalysis parameters were all reported to be within reference range at the post-dose assessments. No treatment- or dose-related changes from baseline were reported. For individual subjects there were no reports of clinically important shifts from normal at pre-dose to abnormal post-dose for any laboratory parameter with respect to either treatment administered.
 - Vital Signs: Mean blood pressure, pulse rate, respiration rate, and temperature results fluctuated during the study, but were reported as remaining within normal limits at assessed post-dose time points. No clinically important changes from pre-dose were reported for any vital sign parameter with respect to study treatment. There were no vital sign AEs reported in this study.
 - Electrocardiograms: All mean ECG parameters (heart rate, PR, QRS, QT, and QTcB intervals) were reported to be within normal limits at the Day 1 post-dose and end-of-study assessments. No clinically important changes were reported from pre-dose. There were no ECG AEs reported in this study. There were no subjects reported with QTcB intervals > 450 msec at any post-dose time point.
 - Physical Exams: There were reports of some minor post-dose physical examination abnormalities that were documented as AEs.
 - There were no reports of DFN-11 autoinjector malfunctions or failures.

Study DFP-11/CD/002

Study Phase

Phase 1.

Title of Study

A randomized single-dose, three-way crossover study to determine the relative bioavailability of DFP-11 sumatriptan succinate 3 mg/0.5 mL injection versus Imitrex® injection 3 mg/0.25 mL and 6 mg/0.5 mL (both using Imitrex® 6 mg/0.5 mL) following subcutaneous injection in healthy adult male and female subjects.

Study Center(s)

Celerion, 2420 West Baseline Road, Tempe, Arizona 85283, USA.

Studied Period

Date of first enrollment: 18 November 2014

Date of last completed: 28 November 2014

Study Objectives

- Primary Objective (s)

To assess the relative bioavailability (BA) of a test formulation of DFP-11 (also known as DFN-11), a subcutaneous (SC) injection of sumatriptan (3 mg/0.5 mL) as sumatriptan succinate from Dr. Reddy's Laboratories Limited, versus 2 different doses of Imitrex® SC injection (3 mg/0.25 mL and 6 mg/0.5 mL; both using Imitrex® 6 mg/0.5 mL manufactured by GlaxoSmithKline) following a SC injection in healthy adult male and female subjects.

- Secondary Objective (s)

- To assess the impact of the SC injection volume of Imitrex® on the pharmacokinetics (PK) of sumatriptan.
- To evaluate and compare the safety and tolerability of DFP-11 and Imitrex® in healthy adult male and female subjects.

Methodology

This was an open-label, randomized, single-dose, 3-way crossover, relative BA study under fasting conditions. Thirty-six (36) healthy, adult, non-tobacco using male and female subjects between 18 and 45 years of age (inclusive) were enrolled. Screening of subjects occurred within 28 days prior to the first dose. On Day 1 of Period 1, subjects were randomized to one of 6 treatment sequences (ABC, ACB, BAC, BCA, CAB, or CBA). In each period, a single dose of sumatriptan was administered SC as a bolus of approximately 5 seconds. Blood for PK evaluation of sumatriptan was collected at the specified times until 12 hours post-dose and safety was monitored

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throughout the study. *The washout period was at least 2 days between doses of sumatriptan.* Subjects were confined from at least 8 hours prior to dosing on Day 1 of Period 1 and remained confined until after the 12-hour blood draw in Period 3 and/or other study procedures, as appropriate. At all times, a subject may have been required to remain at the clinical research unit (CRU) for longer, at the discretion of the Principal Investigator (PI). The clinic attempted to contact subjects using their standard procedures 5 (\pm 1) days after the last PK sample collection to determine if any adverse event (AE) had occurred since the last dose of study drug. Subjects who terminated the study early were contacted if the PI deemed it necessary.

Number of Subjects (Planned and Analyzed)

A total of 36 subjects were enrolled in the study, and 32 subjects completed the study. All 36 subjects enrolled in the study were included in the PK and safety populations; however, only the 32 subjects who completed the study were included in the PK summary statistics and the statistical comparisons of PK parameters.

Demographics

Of the 36 subjects participating in the study, 19 were female and 17 were male. 5 subjects were Black or African American and 31 were White. 27 subjects were Hispanic or Latino and 9 were not. The mean age for all subjects was 31.7 years (range 18 – 45 years), the mean weight was 73.43 kg (range 49.3 – 109.6 kg), the mean height was 166.4 cm (range 151 – 184 cm), and the mean BMI was 26.431 kg/m² (range 19.55 – 34.64 kg/m²).

Diagnosis and Main Criteria for Inclusion

All subjects enrolled in this study were judged by the PI to be normal, healthy volunteers who met all inclusion and none of the exclusion criteria.

Study Treatment (s)

- Test Product

The test product was DFP-11 Injection (sumatriptan succinate) (Lot No. F1404001). The treatment was administered as described below.

Treatment A (Test): A single SC injection of 3 mg DFP-11(0.5 mL of sumatriptan 3 mg/0.5 mL solution administered as sumatriptan succinate) on Day 1 using the DFP-11 autoinjector device, following an overnight fast.

Subjects received a single SC dose over the deltoid muscle in the non-dominant arm.

Duration of Treatment: The anticipated study duration for each subject was up to 35 days, including a screening period of up to 28 days and a confinement period of 7 days from Day -1 check-in of Period 1 to the end of Period 3 (washout of 2 days between periods).

- Reference Product

The reference product was Imitrex® Injection 6 mg/0.5 mL sumatriptan (administered as sumatriptan succinate; Lot No. C683680) from GlaxoSmithKline. The treatments were administered as described below:

Treatment B (Reference 1): A single SC injection of 3 mg Imitrex® Injection from GlaxoSmithKline (0.25 mL of sumatriptan 6 mg/0.5 mL solution administered as sumatriptan succinate) on Day 1, administered manually using a syringe, following an overnight fast.

Treatment C (Reference 2): A single SC injection of 6 mg Imitrex® Injection from GlaxoSmithKline (0.5 mL of sumatriptan 6 mg/0.5 mL solution administered as sumatriptan succinate) on Day 1, administered manually using a syringe, following an overnight fast.

Subjects received a single SC dose over the deltoid muscle in the non-dominant arm.

Criteria for Evaluation

- Pharmacokinetics: Serial blood samples were obtained for the determination of sumatriptan in plasma, and PK parameters were calculated, including AUC_{0-t} , $AUC_{0-\infty}$, C_{max} , $AUC_{\%extrap}$, AUC_{0-2} , t_{max} , k_{el} , and $t_{1/2}$, using Phoenix® WinNonlin® Version 6.3.
- Safety: Safety endpoints included all types of AEs, physical examinations, vital signs (heart rate, blood pressure, and temperature), 12-lead electrocardiograms (ECG), injection site reaction assessments, and clinical laboratory tests (hematology, serum chemistry, and urinalysis).

Statistical methods

- Pharmacokinetic

Reviewer Comments

Reference is made to the Agency PK review for further details.

- Safety

All clinical safety and tolerability data were listed by subject. Safety data including AEs, ECGs, vital signs, injection site assessments, and clinical laboratory evaluations were summarized descriptively by treatment and time point of collection. AEs were coded with Version 17.1 of Medical Dictionary for Regulatory Activities (MedDRA®) and all concomitant medications recorded during the study were coded with the 01 SEP 2014 version of the World Health Organization (WHO) drug dictionary.

Results: Study DFP-11/CD/002

Pharmacokinetic Results

Reviewer Comments

Reference is made to the Agency PK review for further details.

Safety Results

Summary

- There were no reports of deaths or serious adverse events (SAEs) in this study.
- One (1) subject was discontinued by the PI due to the AE of panic attack and 3 subjects withdrew consent due to AEs. These are described below.

- Discontinued Subject 21- Narrative (post receiving Imitrex)

Subject was a 32-year-old female (Sequence BCA) who was discontinued from the study by the PI due to the AE of panic attack (verbatim term: ataque de nervios secondary to injection site pain) that occurred within 1 minute after dosing with 6 mg/0.5 mL Imitrex® injection (Reference 2) in Period 2. The subject had received 3 mg/0.25 mL Imitrex® injection (Reference 1) in Period 1. After receiving the 6 mg/0.5 mL Imitrex® injection (Reference 2) in Period 2, the subject yelled out and reported injection site pain. The subject was also experiencing dyspnea, dizziness, and sensation of cold and was placed on a non-rebreather oxygen mask. The dyspnea, dizziness, and sensation of cold events were combined into a single AE of panic attack (“ataque de nervios”) secondary to injection site pain. The subject concurrently experienced the AEs of injection site erythema that began within 1 minute of the injection and fatigue that began 24 minutes after injection. The subject was initially unable to respond, but upon further examination she was able to make eye contact and talk very faintly. The paramedics were called, but upon arrival the subject was more responsive, up and moving, and declined transportation to the hospital or receiving treatment by the paramedics. The subject was able to stand and speak

clearly. Vital signs were taken 2 minutes after the onset of the panic attack AE; with a BP of 146/89 mmHg, pulse rate of 105 bpm, and oxygen level of 99%. Repeat vitals taken 16 minutes later revealed a BP of 135/93 mmHg, pulse rate of 87 bpm, and oxygen saturation of 100%. The panic attack and injection site pain were of severe intensity, and all remaining AEs were mild. The fatigue resolved in 20 minutes, the panic attack resolved in 1.2 hours, the injection site pain resolved in 5.3 hours, and the resolution time for the injection site erythema is unknown. The PI considered the panic attack, injection site pain, and injection site erythema to be possibly related to both the study drug and the injection device, and the fatigue possibly related to the study drug alone.

○ Discontinued Subject 11- Narrative (post receiving Imitrex and DFP-11)

Subject 11, a 29-year-old male (Sequence BAC), withdrew consent due to AEs prior to dosing in Period 3. The subject had received 3 mg/0.25 mL Imitrex® injection (Reference 1) and 3 mg/0.5 mL DFP-11 injection (Test) in Periods 1 and 2, respectively. At the time of discontinuation, the subject was experiencing the AEs of injection site pain that began after the 3 mg/0.25 mL Imitrex® injection (Reference 1) in Period 1, injection site tenderness that began approximately 6 hours after dosing with 3 mg/0.5 mL DFP-11 injection (Test) in Period 2, and headache that began approximately 2 days after dosing with 3 mg/0.5 mL DFP-11 injection (Test) in Period 2. The subject had also experienced the brief AEs of nervousness that occurred prior to dosing in Period 1 and dizziness that occurred 1 minute after dosing with 3 mg/0.5 mL DFP-11 injection (Test) in Period 2. The headache resolved in 5 hours, and the injection site pain and injection site tenderness resolved within 12 days. The PI considered the injection site pain possibly related to both the study drug and the injection device, the dizziness definitely related to study drug, and the injection site tenderness possibly related to the injection device.

○ Discontinued Subject 19- Narrative (post receiving DFP-11)

Subject 19, a 37-year-old female (Sequence ACB), withdrew consent due to the mild AEs of *head discomfort* (verbatim term: sensation of pressure, occipital area) and *ocular discomfort* (verbatim term: discomfort, left eye) prior to dosing in Period 2. The subject had received 3 mg/0.5 mL DFP-11 injection (Test) in Period 1. The subject was also experiencing the mild AE of periorbital edema (verbatim term: swelling, left suborbital area). These events all began approximately *1 day after dosing with 3 mg/0.5 mL DFP-11 injection* (Test) in Period 1. The subject reported a feeling like her eye was being stretched, but denied visual problems, eye pain, or any other symptoms. These events all resolved in 3.8 days and the PI considered them possibly related to study drug.

○ Discontinued Subject 34- Narrative (post receiving Imitrex and DFP-11)

Subject 34, a 41-year-old female (Sequence BAC) withdrew consent due to AEs prior to dosing in Period 3. The subject had received 3 mg/0.25 mL Imitrex® injection (Reference 1) and 3 mg/0.5 mL DFP-11 injection (Test) in Periods 1 and 2, respectively. At the time of study withdrawal, the subject was experiencing the mild AEs of *postural dizziness, palpitations, headache, chest pain, and dizziness* that all began the day before, *approximately 1.5 days after dosing with 3 mg/0.5 mL DFP-11 injection (Test)*. The subject reported vision blurriness on and off the day before, along with seeing clear spots. She stated she had difficulty breathing with inspiration and had pain that radiated from her chest to her left arm; she described it as “pinching on the left arm”. She also reported having a headache and postural dizziness that improved when she was lying down. The subject stated it felt like her heart was pounding out of her chest. The subject was instructed to report AEs in real time. Vital signs and ECG were within normal limits. The blurred vision and chest pain had resolved prior to the subject reporting the events, in 15 minutes and 6 hours after onset, respectively. The headache resolved in 13 hours, and the palpitations and postural dizziness resolved within 1.7 days. The PI considered all of these events to be unlikely related to study drug.

- Overall, a total of 181 AEs were reported in 32 (89%) subjects in this study, with similar subject incidence (66 to 67%) reporting AEs following all 3 treatments. All of the AEs were mild in severity, with the exception of severe panic attack and severe injection site pain (both following 6 mg/0.5 mL Imitrex® injection [Reference 2]) and moderate headache (following 3 mg/0.5 mL DFP-11 injection [Test]). The PI considered the majority of AEs (155) to be related to the study drug and 26 unrelated.
- Injection site pain and injection site erythema were the most common AEs, experienced by 26 (72%) and 11 (31%) subjects, respectively.
 - Overall, 24 subjects were reported to have at least one *injection site reaction* (erythema/redness, pain, tenderness, and/or induration/swelling) in this study. All reactions were reported mild (Grade 1), with the exception of 1 severe (Grade 3) injection site pain following 6 mg/0.5 mL Imitrex® injection (Reference 2).
 - *Injection site erythema/redness* was experienced by fewer subjects following 3 mg/0.5 mL DFP-11 injection (Test) compared to 6 mg/0.5 mL Imitrex® injection (Reference 2), but by a greater number of subjects than following 3 mg/0.25 mL Imitrex® injection (Reference 1).
 - *Injection site pain* was experienced by a greater number of subjects following DFP-11 injection (Test) than following 3 mg/0.25 mL Imitrex® injection (Reference 1) or 6 mg/0.5 mL Imitrex® injection (Reference 2). Injection site pain was reported a total of 66 times by 26 (72%) subjects, with 19 subjects following 3 mg/0.5 mL DFN-11 injection (Test), 14 subjects following 3 mg/0.25 mL Imitrex® injection (Reference 1), and 18 subjects following 6 mg/0.5 mL Imitrex® injection (Reference 2). With the exception of 1 severe injection site event following 6 mg/0.5 mL Imitrex® injection (Reference 2), all events were mild in severity. The majority (53) of events began within 1 minute of dosing.

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Resolution times varied; ranging from 1 minute to 11.5 days, with 43 events resolving within 1 hour. The PI considered all but 2 injection site pain AEs to be related to the study drug and all injection site pain AEs related to administration device.

- Incidence of *injection site tenderness* at time of injection was the same following all treatments.
- *Injection site induration* was reported following 6 mg/0.5 mL Imitrex® injection (Reference 2) only.
- Mild *injection site erythema* was reported a total of 23 times by 11 (31%) subjects, with 7 subjects each following 3 mg/0.5 mL DFN-11 injection (Test) and 3 mg/0.25 mL Imitrex® injection (Reference 1), and 9 subjects following 6 mg/0.5 mL Imitrex® injection (Reference 2). Onset for all events was within 1 minute of dosing. Duration was 1 minute for 1 event, unknown for 1 event, and the remaining 21 events resolved within 2 to 10 hours. The PI considered all injection site erythema AEs to be related to both the study drug and administration device.
- Mild *injection site induration* was reported 4 times by 4 (11%) subjects, all following 6 mg/0.5 mL Imitrex® injection (Reference 2). Onset ranged from 1 minute to 5.7 hours after dosing, and duration ranged from 20 minutes to approximately 6 hours. The PI considered all injection site induration AEs to be related to both the study drug and administration device.
- Mild dizziness was reported 13 times by 9 (25%) subjects, with 5 subjects each following 3 mg/0.5 mL DFN-11 injection (Test) and 3 mg/0.25 mL Imitrex® injection (Reference 1), and 2 subjects following 6 mg/0.5 mL Imitrex® injection (Reference 2). Onset ranged from 1 to 37 minutes after dosing, and duration ranged from 2 minutes to 2.2 days. Concomitant therapy for dizziness included leg elevation for 1 subject. The PI considered all dizziness AEs to be related to the study drug alone.
- Headache was reported a total of 13 times by 9 (25%) subjects, with 5 subjects following 3 mg/0.5 mL DFN-11 injection (Test), 4 subjects following 3 mg/0.25 mL Imitrex® injection (Reference 1), and 2 subjects following 6 mg/0.5 mL Imitrex® injection (Reference 2). Twelve (12) events were mild in severity and 1 event (following 3 mg/0.5 mL DFN-11 injection [Test]) was moderate. Onset ranged from 2 minutes to 1.9 days post-dose, and duration ranged from 15 minutes to 1.1 days. One (1) subject received an ice bag for headache resolution. The PI considered 10 headache AEs to be related to study drug alone and the remaining 3 AEs (following 3 mg/0.5 mL DFN-11 injection [Test]) to be unrelated.
- Mild feeling of hot was reported 6 times by 6 (17%) subjects, with 1 subject following 3 mg/0.5 mL DFN-11 injection (Test), 2 subjects following 3 mg/0.25 mL Imitrex® injection (Reference 1), and 3 subjects following 6 mg/0.5 mL Imitrex® injection (Reference 2). Onset ranged from 1 minute to 7.4 hours after dosing, and duration ranged from 1 minute to 4.5 hours. One (1) subject received an ice bag for AE resolution. The PI considered all feeling hot AEs to be related to the study drug.
- All remaining AEs were reported by 3 or fewer ($\leq 8\%$) subjects each; these events are presented by severity, treatment, and relationship in Table 14.3.1.4 (CSR DFP-

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11/CD/002) All AEs resolved without sequelae, with the exception of mild injection site erythema for Subject 19.

- There were no reports of clinically significant safety concerns regarding the clinical laboratory, vital sign, physical examination, or ECG assessments in this study.
- There were no reports of DFP-11 auto-injector malfunctions or failures.

Study DFP-11/CD/003

Study Phase

Phase 1.

Title of Study

A randomized single-dose, three-way crossover study to determine the dose-normalized bioequivalence of DFP-11 sumatriptan succinate 3 mg/0.5 ml injection versus Imitrex® Statdose System 4 mg/0.50 ml and Imitrex® Statdose System 6 mg/0.50 ml following subcutaneous injection in healthy adult male and female subjects.

Study Center(s)

Celerion, 2420 West Baseline Road, Tempe, Arizona 85283, USA

Studied Period

Date of first enrollment: 18 November 2014

Date of last completed: 28 November 2014

Study Objectives

- Primary Objective (s)

To assess the dose-normalized bioequivalence (BE) of a test formulation of DFP-11 (also known as DFN-11), a subcutaneous (SC) injection of sumatriptan (3 mg/0.5 mL) as sumatriptan succinate from Dr. Reddy's Laboratories Limited, versus Imitrex® STATdose system 4 mg/0.50 mL and Imitrex® STATdose system 6 mg/0.50 mL following SC injection in healthy adult male and female subjects.

- Secondary Objective (s)

To evaluate and compare the safety and tolerability of DFP-11 and Imitrex® in healthy adult male and female subjects.

Methodology

This was an open-label, randomized, single-dose, 3-way crossover, relative bioavailability (BA) study under fasting conditions. Thirty-six (36) healthy, adult, non-tobacco using male and female subjects between 18 and 45 years of age (inclusive) were enrolled. Screening of subjects occurred within 28 days prior to the first dose. On Day 1 of Period 1, subjects were randomized to 1 of 6 treatment sequences (ABC, ACB, BAC, BCA, CAB, or CBA). In each period, a single dose of sumatriptan succinate SC injection (3 mg/0.5 mL DFP-11, 4 mg/0.5 mL Imitrex® STATdose system or 6 mg/0.5 mL Imitrex® STATdose system) was administered. Blood for pharmacokinetic (PK) evaluation of sumatriptan was collected at the specified times until 12 hours post-dose and safety was monitored throughout the study. *The washout period was 2 days between doses of sumatriptan.* Subjects were confined from at least 8 hours prior to dosing on Day 1 of Period 1 and remained confined until after the 12-hour blood draw in Period 3 and/or other study procedures, as appropriate. At all times, a subject may have been required to remain at the clinical research unit (CRU) for longer, at the discretion of the Principal Investigator (PI). The clinic attempted to contact subjects using their standard procedures 5 (\pm 1) days after the last PK sample collection to determine if any adverse event (AE) had occurred since the last dose of study drug. Subjects who terminated the study early were contacted if the PI deemed necessary.

Number of Subjects (Planned and Analyzed)

A total of 36 subjects were enrolled, completed the study, and were included in safety and PK analyses.

Demographics

Of the 36 subjects participating in the study, 20 were female and 16 were male. 31 subjects were White, 2 subjects were Black or African American, 1 subject was American Indian/Alaska Native, 1 subject was Native Hawaiian/Pacific Islander, and 1 subject was White and Black or African American. 25 subjects were Hispanic or Latino and 11 were not. The mean age for all subjects was 32.0 years (range 18 – 45 years), the mean weight was 74.75 kg (range 51.3 – 116.5 kg), the mean height was 166.7 cm (range 153 – 188 cm), and the mean BMI was 26.736 kg/m² (range 19.77 – 33.80 kg/m²).

Diagnosis and Main Criteria for Inclusion

All subjects enrolled in this study were judged by the PI to be normal, healthy volunteers who met all inclusion and none of the exclusion criteria.

Treatment (s)

- Test Product

The test product was DFP-11 Injection (sumatriptan succinate) (Lot No. F1404001). Subjects received a single SC dose over the deltoid muscle in the non-dominant arm.

Duration of Treatment

The anticipated study duration for each subject was up to 35 days, including a screening period of up to 28 days and a confinement period of 7 days from Day -1 check-in of Period 1 to the end of Period 3 (washout of 2 days between periods).

- Reference Product

Treatment B (Reference 1) was Imitrex® (sumatriptan succinate) Injection, 4 mg/0.5 mL STATdose System® Lot No. C671631. A single SC injection of 4 mg Imitrex® STATdose system from GlaxoSmithKline (0.50 mL of sumatriptan 4 mg/0.5 mL solution administered as sumatriptan succinate) on Day 1, following an overnight fast.

Treatment C (Reference 2) was Imitrex® (sumatriptan succinate) Injection, 6 mg/0.5 mL STATdose System® Lot No. C689979. A single SC injection of 6 mg Imitrex® STATdose system from GlaxoSmithKline (0.5 mL of sumatriptan 6 mg/0.5 mL solution administered as sumatriptan succinate) on Day 1, following an overnight fast.

Subjects received a single SC dose over the deltoid muscle in the non-dominant arm.

Criteria for Evaluation

- Pharmacokinetics

Serial blood samples were obtained for the determination of sumatriptan in plasma, and PK parameters were calculated, including AUC_{C0-t} , AUC_{0-inf} , C_{max} , $AUC_{\%extrap}$, AUC_{0-2} , t_{max} , k_{el} , and $t_{1/2}$, using Phoenix® WinNonlin® Version 6.3.

- Safety

Safety endpoints included all types of AEs, physical examinations, vital signs (heart rate, blood pressure, and temperature), 12-lead electrocardiograms (ECG), injection site reaction assessments, and clinical laboratory tests (hematology, serum chemistry, and urinalysis).

Statistical Methods

- Pharmacokinetic

Reviewer Comments

Reference is made to the Agency PK review for further details.

- Safety

All clinical safety and tolerability data were listed by subject. Safety data including AEs, ECGs, vital signs, injection site assessments, and clinical laboratory evaluations were summarized descriptively by treatment and time point of collection. AEs were coded with Version 17.1 of Medical Dictionary for Regulatory Activities (MedDRA®) and all concomitant medications recorded during the study were coded with the 01 SEP 2014 version of the World Health Organization (WHO) drug dictionary.

Results: Study DFP-11/CD/003

Pharmacokinetic Results

Reviewer Comments

Reference is made to the Agency PK review for further details.

Safety Results

Summary

- There were no deaths or other serious adverse events (SAEs) or subject discontinuations due to AEs in this study.
- Overall, a total of 151 AEs were experienced by 31 (86%) subjects in this study. The majority of AEs were related to injection site, with a similar incidence of injection site AEs among treatments.
- Of the AEs, 147 were mild in intensity and 4 were moderate (feeling hot, injection site swelling, nausea and presyncope). The PI considered 124 AEs to be possibly related to study drug and 27 AEs unrelated.
- Injection site pain and injection site erythema were the most common AEs, experienced by 26 (72%) and 17 (47%) subjects, respectively.
 - Overall, 27 subjects had at least 1 injection site reaction (erythema/redness, pain, and/or tenderness). All reactions were mild (Grade 1) in severity.
 - Incidence of *erythema at the injection site* was the same following both 3 mg/0.5 mL DFP-11 injection (Test) and 4 mg/0.5 mL Imitrex® STATdose injection (Reference 1), and slightly higher than that following 6 mg/0.5 mL Imitrex® STATdose injection (Reference 2). Mild injection site erythema was reported a total of 26 times by 17 (47%) subjects, with 10 subjects following 3 mg/0.5 mL DFN-11 injection (Test), 9 subjects following 4 mg/0.5 mL Imitrex® STATdose injection (Reference 1), and 7 subjects following 6 mg/0.5 mL Imitrex® STATdose injection (Reference 2). Onset was within 1 minute of dosing for all events, with the exception of 1 event that occurred 19 minutes after dosing. All events were resolved by the 6-hour postdose injection site assessment. The PI

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- considered all injection site erythema AEs to be related to both the study drug and administration device.
- Fewer subjects experienced *injection site pain* following 3 mg/0.5 mL DFP-11 injection (Test) compared to 4 mg/0.5 mL Imitrex® STATdose injection (Reference 1) and 6 mg/0.5 mL Imitrex® STATdose injection (Reference 2). Mild injection site pain was reported a total of 57 times by 26 (72%) subjects, with 14 subjects following 3 mg/0.5 mL DFN-11 injection (Test), 15 subjects following 4 mg/0.5 mL Imitrex® STATdose injection (Reference 1) and 19 subjects following 6 mg/0.5 mL Imitrex® STATdose injection (Reference 2). Onset ranged from 1 minute to 1.9 days postdose, with 39 events occurring within 1 minute of dosing. Duration varied, ranging from 1 minute to approximately 4 days. One (1) subject received a warm pack for AE resolution. The PI considered all injection site pain AEs to be related to both the study drug and administration device.
 - Incidence of *tenderness at the injection site* was similar following 3 mg/0.5 mL DFP-11 injection (Test) and 4 mg/0.5 mL Imitrex® STATdose injection (Reference 1), and lower than that following 6 mg/0.5 mL Imitrex® STATdose injection (Reference 2).
 - There were no subjects with induration/swelling at the injection site following any treatment at any post-dose time point.
- Mild headache was reported a total of 8 times by 6 (17%) subjects, with 2 subjects each following 3 mg/0.5 mL DFN-11 injection (Test) and 4 mg/0.5 mL Imitrex® STATdose injection (Reference 1), and 4 subjects following 6 mg/0.5 mL Imitrex® STATdose injection (Reference 2). Onset ranged from 5 minutes to 3.5 days post-dose and duration ranged from 2 minutes to 8.5 hours. One (1) subject received an ice bag for AE resolution. The PI considered 5 headache events to be related to the study drug and 3 events unrelated; all headache events were considered unrelated to the administration device.
 - Mild dizziness was reported a total of 6 times by 6 (17%) subjects, with 3 subjects following 3 mg/0.5 mL DFN-11 injection (Test), 1 subject following 4 mg/0.5 mL Imitrex® STATdose injection (Reference 1), and 2 subjects following 6 mg/0.5 mL Imitrex® STATdose injection (Reference 2). Onset ranged from 1 to 32 minutes postdose, and duration ranged from 3 minutes to 1.4 hours. One (1) subject was placed in a supine position for dizziness resolution. The PI considered 5 dizziness events to be related to the study drug and 1 event unrelated; all dizziness events were considered unrelated to the administration device.
 - Mild vessel puncture site bruise was reported a total of 5 times by 5 (14%) subjects, with 2 subjects each following 3 mg/0.5 mL DFN-11 injection (Test) and 4 mg/0.5 mL Imitrex® STATdose injection (Reference 1), and 1 subject following 6 mg/0.5 mL Imitrex® STATdose injection (Reference 2). Onset ranged from 12.2 hours post-dose to 1.9 days post-dose and duration ranged from 4.2 days to 9.5 days. One (1) subject received an ice bag application for AE resolution. The PI considered all vessel site puncture bruise AEs to be unrelated to both the study drug and administration device.
 - Mild throat tightness was reported a total of 4 times by 4 (11%) subjects, with 2 subjects following 3 mg/0.5 mL DFN-11 injection (Test), and 1 subject each following

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ZembraceSymTouch; Sumatriptan succinate injection

4 mg/0.5 mL Imitrex® STATdose injection (Reference 1) and 6 mg/0.5 mL Imitrex® STATdose injection (Reference 2). Onset ranged from 2 minutes to approximately 2 days post-dose and duration ranged from 3 minutes to 4.9 days. One (1) subject received ice chips for AE resolution. The PI considered all throat tightness AEs to be related to the study drug and unrelated to the administration device.

- All remaining AEs were reported by 3 or fewer ($\leq 8\%$) subjects each.
- All AEs in this study resolved without sequelae.
- There were no reports of clinically significant or worrisome safety concerns or adverse events related to clinical laboratory, vital sign, physical examination, or ECG assessments following DFP-11 or Imitrex® administration.
- There were no DFP-11 auto-injector malfunctions or failures.

6 Review of Efficacy

Reviewer comments

There were no efficacy studies or data that was collected. As noted above, this 505(b)(2) application supported by PK bridging studies, relies on the reference listed drug (RLD) Imitrex Injection (under NDA 020080) for both non-clinical and clinical data including efficacy data.

7 Review of Safety

Reviewer comments

As with the efficacy data, this 505(b)(2) application relies to a large extent on the safety data of the reference listed drug (RLD) Imitrex Injection (under NDA 020080). The safety findings from the PK & BE studies which served as the bridge to support the 505(b)(2) application was reviewed. See section 5.3 for further details on the safety findings by study. The overall safety conclusions based on findings from these 3 PK/BE studies are summarized below.

Overall Safety Conclusions

- There were no reports of deaths or SAEs in any study.
- Across studies, injection site pain (including bruising, pain, and swelling) and headache were the most commonly reported AEs. The vast majority of AEs (all but 3) were reported as mild in severity and these resolved. In study DFP-11/CD/002 there were reports of three moderate AEs including a severe panic attack and severe injection site pain (both following 6 mg/0.5 mL Imitrex® injection (Reference 2), and moderate headache (following 3 mg/0.5 mL DFN-11 injection (Test).
- There were no reports of clinically significant or worrisome safety concerns pertaining to the clinical laboratory, vital sign, physical examination, or ECG

assessments following DFN-11 administration across all three studies. None of the noted abnormalities (such as lab abnormalities, EKG abnormalities, etc.) were persistent or required intervention nor did they lead to adverse events. They resolved spontaneously.

- In the subjects who discontinued/withdrew due to AE, neither were the events clearly attributable to or unique to ZembraceSymTouch nor were they unusually different than Imitrex. If any, some of the noted AEs with DFN-11 were congruent with the known safety profile of sumatriptan as noted in the Imitrex label.
- Injection site pain and erythema were noted with the DFN-11 autoinjector, but with lower incidence than that observed with the 4mg and 6mg Imitrex® STAT dose devices and comparable to those observed with manual Imitrex® injections. All these effects were mild in nature and resolved without medical intervention.
- In all three studies- DFP-11/CD/00, DFP-11/CD/002 and DFP-11/CD/003, there were no malfunction or failures of the DFN-11 autoinjector device.

The overall safety profile including adverse events, injection site reactions, device malfunctions or failures of DFN-11 Injection were comparable to that of the referenced drug (Imitrex® Injection).

7.3 Major Safety Results

There were no reported deaths or serious adverse events. There were subject discontinuations in Study DFP-11/CD/001 and Study DFP-11/CD/02. These are discussed in section 5.3.

7.4 Supportive Safety Results

See section 5.3.

8 Postmarket Experience

Not applicable.

9 Appendices

9.1 Literature Review/References

Not applicable.

9.2 Labeling Recommendations

Please refer to separate label review that includes comments from multiple disciplines.

9.3 Advisory Committee Meeting

Not applicable.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

RAMESH RAMAN
01/28/2016

HEATHER D FITTER
01/28/2016