CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

210884Orig1s000

NON-CLINICAL REVIEW(S)

MEMORANDUM

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration

Division of Neurology Products (HFD-120)
Center for Drug Evaluation and Research

Date: January 22, 2019

From: Lois M. Freed, Ph.D.
Supervisory Pharmacologist

Subject: NDA 210-884 (Tosymra, sumatriptan nasal spray, DFN-02)

NDA 210-884, a 505(b)(2) application, was submitted by Dr. Reddy's Laboratory Ltd. on March 27, 2018, to request marketing approval of sumatriptan nasal spray (10 mg) for the acute treatment of migraine with or without aura in adults. NDA 210-884 relies, in part, on findings of safety and effectiveness of a previously approved drug. The listed drug is Imitrex (sumatriptan succinate) Injection, approved (NDA 20-080) for the same indication. Clinical development was conducted under IND 108088.

To support clinical development and an NDA, the sponsor conducted nonclinical studies for DFN-02, which consist of a standard safety pharmacology battery (CNS and respiratory in rat, cardiovascular in dog), PK studies (rat, monkey), and general intranasal (IN) toxicology studies (4, 13, and 26 weeks in rat; 28 day and 4, 13, and 39 weeks in dog), and an IN carcinogenicity study (104 weeks in rat) of a novel excipient, 1-O-n-dodecyl-β-maltopyranoside (DDM, (b) (4) (b) (4)). (The sponsor also provided a Letter of Authorization to DMF (b) (4) for additional nonclinical data to support aspects of the clinical formulation.) Studies to assess the local toxicity of DFN-02 were required because the listed drug is approved for subcutaneous administration and does not contain DDM. Evaluation of the systemic toxicity of DDM was not required because of the documented low systemic levels (~2 ng*hr/mL) of DDM in humans.

The nonclinical data were reviewed by Dr. Nesti (Pharmacology/Toxicology NDA Review and Evaluation, NDA 210884, Edmund Nesti, PhD, January 17, 2019). Dr. Nesti has concluded that the nonclinical data support approval of the NDA.

In the general toxicity studies, DDM was administered alone at several IN doses (0.1, 10, or 30 mg/day in Sprague Dawley rat; 1.2, 10, or 90 mg/day in Beagle dog) or in combination with sumatriptan (30 mg/day sumatriptan + 0.3 mg/day DDM) and compared to control and sumatriptan alone (30 mg/day in rat; 90 mg/day in dog). Dosing was daily for up to 26 and 39 weeks in rat and dog, respectively. Microscopic changes in locally exposed tissues were observed in both species. In the chronic toxicity studies, microscopic findings consisted of squamous cell metaplasia in the transitional or respiratory epithelium of the nasal cavity at all

doses of DDM alone in both species and, in dog, with sumatriptan + DDM. Atrophy of the olfactory epithelium was observed in rat only, at the mid and high doses of DDM alone. Local toxicity, although reduced in incidence and severity, was still evident at the end of the 4-week recovery period in both species. Because squamous cell metaplasia can be a preneoplastic change, the sponsor convened a Pathology Working Group (PWG) to review the nasal cavity findings in the subchronic and chronic studies. The PWG concluded that:

> "In the absence of areas of inflammation, cell crowding, disrupted tissue organization, cellular atypia, disturbances of cell maturation and/or keratinization and evidence of nearly complete recovery following cessation of exposure, the squamous cell metaplasia and hyperplasia that was observed was not considered to be an adverse change which might lead to neoplasia with continued treatment."

In the 104-week carcinogenicity study in Sprague Dawley rat, DDM was administered alone at IN doses of 0, 0.1, 0.3, 1.0, and 3.0 mg QD. No test article-related neoplasms were observed.

Recommendations

The nonclinical studies conducted by the sponsor are adequate to support approval of the NDA.

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/s/

LOIS M FREED
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DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number:	210884
Supporting document/s:	1
Applicant's letter date:	March 27, 2018
CDER stamp date:	March 27, 2018
Product:	Tosymra (DFP-02, DFN-02, sumatriptan nasal spray)
Indication:	Acute treatment of migraine, with or without aura
Applicant:	Dr. Reddy's Laboratories (DRL) Limited
Review Division:	DNP
Reviewer:	Edmund Nesti, PhD
Supervisor:	Lois M. Freed, PhD
Division Director:	Billy Dunn, MD
Project Manager:	Michelle Mathers

Disclaimer

Except as specifically identified, all data and information discussed below and necessary for approval of NDA 210884 are owned by Dr. Reddy's Laboratories or are data for which Dr. Reddy's Laboratories has obtained a written right of reference. Any information or data necessary for approval of NDA 210884 that Dr. Reddy's Laboratories does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as reflected in the drug's approved labeling. Any data or information described or referenced below from reviews or publicly available summaries of a previously approved application is for descriptive purposes only and is not relied upon for approval of NDA 210884.

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1 Executive Summary

1.1 Introduction

Dr. Reddy's Laboratories Limited (DRL) has developed an intranasal (IN) formulation of sumatriptan, a 5-$HT_{1B/1D}$ receptor agonist, for the acute treatment of migraine with or without aura. The formulation is intended to improve the PK of sumatriptan by reducing T_{max}, compared to Imitrex nasal spray, by including 1-O-n dodecyl-β-D-maltopyranoside (DDM), (b) (4). For sumatriptan, DRL is relying on the findings of safety and efficacy of Imitrex subcutaneous injection (NDA-020080) via the 505(b)(2) pathway. For DDM, an unqualified excipient, safety is supported by an LOA to DMF (b) (4) and nonclinical studies conducted by DRL.

1.2 Brief Discussion of Nonclinical Findings

In safety pharmacology studies, IN administration of DFN-2 did not show any adverse findings in the central nervous system, respiratory system, or gastrointestinal tract in rats or [**DMF** (b) (4)**:** cardiovascular findings in conscious telemetered dogs**]**.

In general toxicology studies to qualify DDM, IN administration of DDM was assessed in rat and dog in studies of up to 26 and 39 weeks, respectively. In both species, there was minimal to slight squamous metaplasia of the transitional and/or respiratory epithelium, which was observed at all DDM dose levels. In rats, atrophy of the olfactory epithelium was observed in some HD animals, and in the 13-week study, there was squamous epithelial hyperplasia in the nares. The NOAEL was the HD in all DDM toxicity studies.

Embryofetal development was not assessed because of low systemic levels of DDM in patients (see **2.7 Regulatory Background**).

In TK studies, T_{max} after IN administration of sumatriptan + DDM to rat and monkey occurred within ~5 min and C_{max} was 3- to 25-fold higher compared to administration of sumatriptan alone.

The 104-week carcinogenicity study indicated that DDM is not tumorigenic.

The safety margins for DDM in the rat toxicology and carcinogenicity studies, and the dog toxicology studies were 191x, 57x, and 172x, respectively, based on nasal surface area (mg/cm^2).

1.3 Recommendations

1.3.1 Approvability

The nonclinical NDA package supports approval of DFN-2.

1.3.2 Additional Nonclinical Recommendations

None

1.3.3 Labeling

In section **12.1, Mechanism of Action**, the description of (b) (4) should be removed. In section **13.1, Animal Toxicology and/or Pharmacology**, under Impairment of Fertility, the description of (b) (4) should be remove, because (b) (4) (b) (4) In section **13.2**, text related to the 6- and 9-month toxicology studies should be

revised to included safety margins and a description of the drug-related nasal cavity findings in rat and dog.

2 Drug Information

2.1 Drug

CAS Registry Number: 103628-46-2

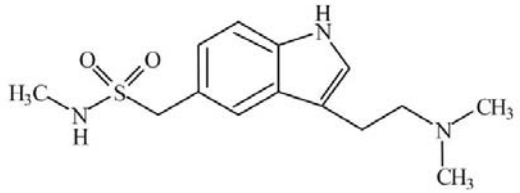
Generic Name: Sumatriptan

Code Names: DFP-02, DFN-02

Chemical Name: 1H-Indole-5-methanesulfonamide, 3-[2-(dimethylamino)ethyl]-N-methylmethanesulfonamide

Molecular Formula/Molecular Weight: $C_{14}H_{21}N_3O_2S$/ 295.40

Structure or Biochemical Description



Sponsor's Figure

Pharmacologic Class: serotonin-1b/1d receptor agonist

2.2 Relevant INDs, NDAs, BLAs and DMFs

- DMF (b) (4) (b) (4)
- IND 108088, for DFN-02.
- NDA 020080, for Imitrex subcutaneous injection (Listed Drug).

2.3 Drug Formulation

Table 3.2.P.1.2-1: Composition of DFN-02 Nasal Spray

Name of Ingredients	Function	Quality standard	Unit	
			mg/0.1 mL	Concentration in % w/v
Sumatriptan	Active ingredient	USP	10	(b) (4)
Citric acid monohydrate	(b) (4)	USP		
Potassium phosphate monobasic		NF		
Sodium phosphate dibasic anhydrous		USP		
1-O-n-Dodecyl-β-D-maltopyranoside		In House		
Sodium chloride*		USP		
Water for injection		USP		(b) (4)

*Quality standard for this excipient was NF at the time of registration batch manufacture

Sponsor's table

2.4 Comments on Novel Excipients

1-O-n-Dodecyl-β-D-Maltopyranoside (DDM) is a novel excipient (b) (4) (b) (4) of sumatriptan through the nasal mucosa.

2.5 Comments on Impurities/Degradants of Concern

None

2.6 Proposed Clinical Population and Dosing Regimen

Tosymra is intended for use in adults for the acute treatment of migraine, with or without aura. The recommended dose is 10 mg given as a single spray. The maximum cumulative dose that may be given in a 24-hour period is 30 mg, with doses separated by at least 1 hour.

2.7 Regulatory Background

In the pre-IND meeting comments on April 28, 2010, DRL was told they would need a Letter of Authorization for DMF (b) (4) (held by (b) (4) for the novel excipient DDM. Per email communication on February 25, 2015, DRL was told a final report for the 2-year intranasal carcinogenicity study of DDM in rat should be submitted by the time of NDA submission. Per the End-of-Phase 2 meeting minutes (November 5, 2013), an embryofetal development study was waived because of the low levels of DDM in patients ((b) (4) ng*h/mL).

3 Studies Submitted

3.1 Studies Reviewed

Safety Pharmacology
- CNS, respiratory, and gastrointestinal studies in rat.

PK/ADME
- PK assessment in monkey following IN and IV administration of DDM.
- PK assessment in rat following IN administration of DDM.
- Validation of analytical methods in rat, dog, and monkey plasma.

General toxicology
- 4-week daily IN administration of DFP-02 in rat + 2-week recovery period.
- 13-week daily IN administration of DFP-02 in rat + 4-week recovery period.
- 26-week daily IN administration of DFP-02 in rat + 4-week recovery period.
- 4-week daily IN administration of DFP-02 in dog.
- 4-week daily IN administration of DFP-02 in dog + 2-week recovery period.
- 13-week daily IN administration of DFP-02 in dog + 4-week recovery period.
- 39-week daily IN administration of DFP-02 in dog + 4-week recovery period.

Genetic toxicology
- *In vitro* Ames and chromosome aberration assays.
- *In vivo* micronucleus assay in rat.

Carcinogenicity
- 104-week carcinogenicity study in rat.

DMF (b) (4)

Safety Pharmacology
- Cardiovascular study in dog.

PK/ADME
- Metabolic profile and tissue distribution assessment of DDM following a single intranasal administration to male albino rats.

General toxicology
- 2 single continuous IV (24 h) DDM dose-rang finding studies in beagle dog.
- 2 continuous IV (24 h) DDM dose-rang finding studies in rat.
- 2-week every other day IN administration of DDM in rat + 2-week recovery period.
- 13-week daily IN administration of DDM in dog + 4-week recovery period.
- 2-week weekly SC administration of DDM in rabbit to assess dermal irritation.

Reproductive and Development toxicology
- Continuous IV (24 h) DDM pilot study in pregnant rat.

3.2 Studies Not Reviewed

None

3.3 Previous Reviews Referenced

- IND 108088, D. Charles Thompson, Ph.D., February 13, 2013
- IND 108088, D. Charles Thompson, Ph.D., April 10, 2015
- IND 108088, D. Charles Thompson, Ph.D., June 05, 2015

4 Pharmacology

4.1 Primary Pharmacology

None

4.2 Secondary Pharmacology

None

4.3 Safety Pharmacology

Study title: DFP-02: Neurobehavioral Safety Evaluation Following a Single Intranasal Administration in Rats

Study no.: DFP-02_SE_01; 8268947
Study report location: EDR
Conducting laboratory and location: (b) (4)
Date of study initiation: August 23, 2012
GLP compliance: Yes
QA statement: Yes
Drug, batch #, and % purity:

Drug	Batch #	% Purity
Vehicle control (b) (4) % DDM	SUN2-282	101.5
DFP-02 5 mg + (b) (4) % DDM	SUN2-290	99.4/102.6
DFP-02 10 mg + (b) (4) % DDM	SUN2-289	100.3/101.0
DFP-02 15 mg + (b) (4) % DDM	SUN2-288	100.9/101.5

Key Study Findings: The NOAEL was the HD.

Methods

Doses:	Vehicle control with (b) (4)% DDM or DFP-02: 5, 10, or 15 mg sumatriptan with (b) (4)% DDM.
Frequency of dosing:	Single dose
Route of administration:	Intranasal
Dose volume:	(b) (4) µL ((b) (4) µL/ nostril)
Formulation/Vehicle:	Citric acid, monobasic potassium phosphate, di basic sodium phosphate, (b) (4) (b) (4) ((b) (4) (b) (4)) and water.
Species/Strain:	Rat, Crl:CD(SD)
Number/Sex/Group:	6/males/group
Age:	At dosing initiation: ~7 weeks old
Weight:	At dosing initiation: 219-276 g
Satellite groups:	None
Unique study design:	None
Deviation from study protocol:	There were minor deviations that did not affect study validity.

Observations and Results

The neurobehavioral effects of single ascending doses of DFP-02 (5, 10, or 15 mg) or vehicle control with DDM were assessed using a functional observational battery consisting of open field, handling, and general observations (according to the method of Irwin, 1968) at 15, 30, 60, 180, and 360 minutes post-dosing. Additionally, body temperature measurements were taken following each Irwin observation. Rats were observed for gross signs of toxicity and mortality for seven days and sacrificed without necropsy.

All animals survived to scheduled sacrifice and no drug-related findings were observed.

(Based on Pharmacology/Toxicology IND Review and Evaluation, IND 108088, D. Charles Thompson, Ph.D., February 13, 2013)

Study title: DFP-02: Measurement of Respiratory Parameters In The Freely Moving Conscious Rat Using Whole Body Plethysmography

Study no.: DFP-02_SE_02; 8268946
Study report location: EDR
Conducting laboratory and location: [redacted]
Date of study initiation: August 30, 2012
GLP compliance: Yes
QA statement: Yes
Drug, batch #, and % purity:

Drug	Batch #	% Purity
Vehicle control [redacted]% DDM	SUN2-282	101.5
DFP-02 5 mg + [redacted]% DDM	SUN2-290	99.4/102.6
DFP-02 10 mg + [redacted]% DDM	SUN2-289	100.3/101.0
DFP-02 15 mg + [redacted]% DDM	SUN2-288	100.9/101.5

Key Study Findings: The NOAEL was the HD.

Methods

Doses: Vehicle control + [redacted]% DDM or DFP-02: 5, 10, or 15 mg sumatriptan + [redacted] %DMM.
Frequency of dosing: Single dose
Route of administration: Intranasal
Dose volume: [redacted] µL ([redacted] µL/ nostril)
Formulation/Vehicle: Citric acid, monobasic potassium phosphate, di basic sodium phosphate, [redacted] and water.
Species/Strain: Rat, Crl:CD(SD)
Number/Sex/Group: 6/males/group
Age: At dosing initiation: ~9 weeks old
Weight: At dosing initiation: 239-366 g
Satellite groups: None
Unique study design: None
Deviation from study protocol: There were minor deviations, with no impact on study validity.

Observations and Results

The respiratory effects of single ascending doses of DFP-02 (5, 10, or 15 mg sumatriptan) or vehicle control with (b) (4)% DDM were evaluated. A plethysmography chamber was used to assess respiratory parameters (tidal volume, minute volume, and respiratory rate) 1 hour prior to dosing and up to 6 hours post-dosing. Plasma drug concentrations were not assessed.

All animals survived to scheduled necropsy. There were statistically significant, but not dose-related, increases in group mean tidal volume values between the MD and HD dosing groups and the DDM vehicle control group. No other notable findings were reported.

(Based on Pharmacology/Toxicology IND Review and Evaluation, IND 108088, D. Charles Thompson, Ph.D., February 13, 2013)

Study title: DFP-02: Effects on Gastrointestinal Transit in the Rat Following Intranasal Administration

Study no.: DFP-02_SE_03; 8268949
Study report location: EDR
Conducting laboratory and location: (b) (4)
Date of study initiation: August 25, 2012
GLP compliance: Yes
QA statement: Yes
Drug, batch #, and % purity:

Drug	Batch #	% Purity
Vehicle control (b) (4)% DDM	SUN2-282	101.5
DFP-02 5 mg + (b) (4)% DDM	SUN2-290	99.4/102.6
DFP-02 10 mg + (b) (4)% DDM	SUN2-289	100.3/101.0
DFP-02 15 mg + (b) (4)% DDM	SUN2-288	100.9/101.5

Key Study Findings: The NOAEL was the HD.

Methods

Doses:	Vehicle control with DDM or DFP-02: 5, 10, or 15 mg sumatriptan.
Frequency of dosing:	Single dose
Route of administration:	Intranasal
Dose volume:	(b) (4) µL ((b) (4) µL/ nostril)
Formulation/Vehicle:	Citric acid, monobasic potassium phosphate, di basic sodium phosphate, (b) (4) and water.
Species/Strain:	Rat, Crl:CD(SD)
Number/Sex/Group:	6/males/group
Age:	At dosing initiation: ~7 weeks old
Weight:	At dosing initiation: 217-268 g
Satellite groups:	None
Unique study design:	None
Deviation from study protocol:	There were minor deviations, with no impact on study validity.

Observations and Results

The gastrointestinal effects of single ascending doses of DFP-02 (5, 10, or 15 mg sumatriptan) or vehicle control ((b) (4) % DDM) were evaluated in fasted animals. Thirty minutes after dosing, each animal was orally administered a 5% (w/v) charcoal suspension (marker) in 0.25% (w/v) methylcellulose using a constant dose volume of 10 mL/kg. Twenty minutes after charcoal administration, the animals were sacrificed, and the full length of the small intestine was dissected. Both the length of the intestinal tract and the distance the charcoal marker had traveled were measured. The stomach and contents were also weighted to assess stomach emptying.

All animals survived to scheduled necropsy. All dose levels of sumatriptan had slightly delayed group mean intestinal transit (~11%) and a reduction in gastric emptying (≤17%).

(Based on Pharmacology/Toxicology IND Review and Evaluation, IND 108088, D. Charles Thompson, Ph.D., February 13, 2013)

Study title: DFP-02: Evaluation of Potential Cardiovascular Effects in the Conscious Dog using Radiotelemetry

Study no.: DFP-02_SE_04; 8268945
Study report location: EDR
Conducting laboratory and location: [redacted]
Date of study initiation: September 21, 2012
GLP compliance: Yes
QA statement: Yes
Drug, batch #, and % purity:

Drug	Batch #	% Purity
Vehicle control [redacted] % DDM	SUN2-279	-
Moxifloxacin	-	-
DFP-02 15 mg + [redacted] % DDM	SUN2-287	100.1
DFP-02 30 mg + [redacted] % DDM	SUN2-286	102.1
DFP-02 45 mg + [redacted] % DDM	SUN2-285	102.5

Key Study Findings: The NOAEL was the HD.

Methods

Doses:	Vehicle control + (b) (4) % DDM or 100 mg/kg Moxifloxacin (positive control) or DFP-02: 15, 30, or 45 mg sumatriptan + (b) (4) % DDM.
Frequency of dosing:	Single dose
Route of administration:	Vehicle control and DFP-02: intranasal moxifloxacin: oral gavage
Dose volume:	Vehicle control and DFP-02: 100 µL (in a single nostril); moxifloxacin: 5 mL/kg
Formulation/Vehicle:	Vehicle control and DFP-02: Citric acid, monobasic potassium phosphate, di basic sodium phosphate, (b) (4) and water. moxifloxacin: 0.5% (w/v) methylcellulose
Species/Strain:	Beagle dogs
Number/Sex/Group:	4/males/group
Age:	At dosing initiation: 25-42 months old
Weight:	At dosing initiation: 14-21 kg
Satellite groups:	None
Unique study design:	Each animal received all doses, with a washout period of 6 days between doses.
Deviation from study protocol:	There were minor deviations, with no impact on study validity.

Observations and Results

The cardiovascular effects of single ascending doses of DFP-02 (5, 10, or 15 mg/rat, sumatriptan) or vehicle control ((b) (4) % DDM) or positive control (100 mg/kg moxifloxacin) were evaluated in non-naïve, telemetered dogs. Dogs were given a 6-day washout period between doses. Telemetry data were recorded from one hour prior to dosing to 24 hours post dosing. The cardiovascular parameters evaluated were: arterial blood pressure, heart rate, and ECG intervals (RR, QRS, PR, QT, and QTc). Blood was collected to determine plasma drug and excipient concentrations. All animals survived to scheduled sacrifice. Sumatriptan was detected in the plasma (at 30 min) in all animals dosed with DFP-02; however, no excipient (DDM) was detected (validated range (b) (4) ng/mL). The sumatriptan levels were highly variable (see sponsor's table).

Subject	Timepoint Concentrations (ng/mL) of Sumatriptan in Dog Plasma following treatment with DFP-02 Pre-dose	30 mins after 0 mg/animal	Pre-dose	30 mins after 15 mg/animal	Pre-dose	30 mins after 30 mg/animal	Pre-dose	30 mins after 45 mg/animal
046	< 1.00	< 1.00	< 1.00	69.7	< 1.00	61.0	< 1.00	83.4
048	< 1.00	< 1.00	33.3	51	< 1.00	138	4.90	260
055	< 1.00	< 1.00	< 1.00	3.66	< 1.00	4.61	10.4	23.0
062	< 1.00	< 1.00	< 1.00	8.00	< 1.00	675	10	630

There were sporadic incidences in which cardiovascular changes between vehicle and DFP-02 dosed animals attained statistical significance; however, there was no dose-related trend. For the positive control (moxifloxacin), increases in QTc were observed, as expected.

(Based on Pharmacology/Toxicology IND Review and Evaluation, IND 108088, D. Charles Thompson, Ph.D., February 13, 2013*)*

5 Pharmacokinetics/ADME/Toxicokinetics

5.1 PK/ADME

In cynomolgus monkeys, the PK following a single IN administration of DDM ((b) (4)%, (b) (4) mg/kg) and sumatriptan (b) (4) mg/kg), and IV administration of DDM (b) (4)%, (b) (4) mg/kg) on Day 1 and 8 was assessed using a crossover design (total of 4/sex/group). There were no sex differences in the PK data. For sumatriptan, T_{max} and half-life were 0.1 and 2.3 hours, respectively. For DDM, T_{max} and half-life were 0.5 (IN only) and 0.6 (IN and IV) hours, respectively, and IN bioavailability was ~3.9%.

(Based on Pharmacology/Toxicology IND Review and Evaluation, IND 108088, D. Charles Thompson, Ph.D., February 13, 2013*)*

In rats (8/sex/group; however, blood samples from 2 animals were pooled to give 4/sex/group), the PK of the IN to-be-marketed formulations used during Phase 3 (A: (b) (4) and prototype, used during Phase I (b) (4) (b) (4) were assessed.

Sumatriptan C_{max} and AUC values for formulation (A) were comparable to (B). The addition of DDM increased sumatriptan C_{max} and AUC values ~7- and 1.4-fold, respectively, and reduced T_{max} between ~4 and 13 minutes. Females had slightly higher sumatriptan C_{max} and AUC values (F/M ranged from (b) (4) to (b) (4)

In males, DDM C_{max} and AUC values were 40% higher in group A compared to group B, where as in females, values were similar. Overall, DDM C_{max} and AUC values in group A and B were 50 and 90% higher in females than males, respectively. The group A formulation was used in the subchronic and chronic toxicity studies.

Mean pharmacokinetic parameter (±)	Sumatriptan					
	Group A		Group B		Group C	
	Male (n=4)	Female (n=4)	Male (n=4)	Female (n=4)	Male (n=4)	Female (n=4)
C_{max} (ng/mL)	1570 ± 829	1740 ± 630	1680 ± 637	2090 ± 866	263 ± 109	267 ± 51.0
t_{max} (hr) #	0.058 0.033-0.083	0.033 0.033-0.150	0.083 0.033-0.083	0.058 0.033-0.083	0.250 0.167-0.250	0.209 0.167-0.267
$t_{½}$ (hr)	NC	NC	NC	4.02 ± 0.839	NC	NC
$AUC_{(0-t)}$ (ng.hr/mL)	764 ± 145	1150 ± 129	806 ± 96.4	1080 ± 143	526 ± 82.6	776 ± 65.6
$AUC_{(0-\infty)}$ (ng.hr/mL)	NC	NC	NC	1180 ± 103	NC	NC
$AUC_{(\%extrap)}$ (%)	NC	NC	NC	12.7 ± 4.81	NC	NC

NC – Not Calculated
- Median and range

Mean pharmacokinetic parameter (±)	DDM			
	Group A		Group B	
	Male (n=4)	Female (n=4)	Male (n=4)	Female (n=4)
C_{max} (ng/mL)	24.7 ± 9.26	39.1 ± 9.73	17.5 ± 6.03	33.0 ± 5.77
t_{max} (hr) #	0.150 0.108-0.167	0.159 0.150-0.167	0.167 0.083-0.167	0.125 0.083-0.250
$t_{½}$ (hr)	0.434 ± 0.0726	0.375 ± 0.0377	0.447 ± 0.0867	0.447 ± 0.0545
$AUC_{(0-t)}$ (ng.hr/mL)	13.4 ± 8.15	17.2 ± 5.38	9.99 ± 4.01	18.4 ± 5.73
$AUC_{(0-\infty)}$ (ng.hr/mL)	17.6 ± 5.30	17.8 ± 5.74	10.8 ± 4.23	19.2 ± 5.94
$AUC_{(\%extrap)}$ (%)	4.72 ± 2.21	2.78 ± 1.03	7.93 ± 5.29	4.22 ± 1.28

- Median and range

Sponsor's tables

A second study was conducted in rat to compare the PK of sumatriptan and DDM following single IN administration of DFN-02 (to-be-marketed) formulations containing DDM from two different vendors (A: (b) (4) and B: (b) (4); C: no DDM). Sumatriptan exposures (C_{max} and AUC) were generally higher in group A, compared to group B, with A/B exposure ratios ranging from 1.03 to 2.88. Sumatriptan AUC values in females were higher in all groups compared to males, with F/M ratios ranging from 1.03 to 1.76. DDM increased sumatrptan C_{max} and AUC 13 and 1.4-fold for group A compared to C, respectively, and 6-fold and no change for group B compared to C, respectively. Females had higher sumatriptan AUC values for all formulations, with F/M ratios up to ~2.

DDM exposure (C_{max} and AUC) values in group A were up to ~2-fold higher, for both sexes, compared to group B. Females in groups A and B had 20 to 50% higher DDM exposure values, respectively, compared to males.

Based on these data, DDM from (b) (4) was used in the subsequent studies.

Mean pharmacokinetic parameter (±)	Sumatriptan					
	Group A		Group B		Group C	
	Male (n=6)	Female (n=6)	Male (n=6)	Female (n=6)	Male (n=6)	Female (n=6)
C_{max} (ng/mL)	5480 ± 2090	3200 ± 1610	1900 ± 1640	1940 ± 768	434 ± 137	319 ± 203
t_{max} (hr) #	0.033 0.033-0.033	0.033 0.033-0.108	0.033 0.033-0.100	0.058 0.033-0.083	0.250 0.167-0.267	0.250 0.167-0.833
$t_{½}$ (hr)	3.54 ± NC	3.47 ± NC	4.91 ± NC	NC	4.35 ± NC	NC
$AUC_{(0-t)}$ (ng.hr/mL)	1310 ± 515	1360 ± 445	750 ± 232	1320 ± 374	959 ± 207	1230 ± 351
$AUC_{(0-\infty)}$ (ng.hr/mL)	1300 ± NC	983 ± NC	1120 ± NC	NC	1090 ± NC	NC
$AUC_{(\%extrap)}$ (%)	4.80 ± NC	8.95 ± NC	8.10 ±NC	NC	12.0 ± NC	NC

NC – Not Calculated, # - Median and range

Mean pharmacokinetic parameter (±)	DDM			
	Group A		Group B	
	Male (n=6)	Female (n=6)	Male (n=6)	Female (n=6)
C_{max} (ng/mL)	40.0 ± 22.6	49.9 ± 16.2	15.1 ± 9.33	23.2 ± 5.17
t_{max} (hr) #	0.083 0.083-0.083	0.096 0.083-0.250	0.167 0.100-0.833	0.500 0.167-0.833
$t_{½}$ (hr)	0.477 ± 0.0986	0.484 ± 0.132	0.458 ± 0.0758	0.351 ± NC
$AUC_{(0-t)}$ (ng.hr/mL)	24.1 ± 12.9	23.8 ± 8.03	11.0 ± 6.76	15.1 ± 3.10
$AUC_{(0-\infty)}$ (ng.hr/mL)	26.1 ± 13.2	27.3 ± 8.41	10.8 ± 5.52	14.5 ± NC
$AUC_{(\%extrap)}$ (%)	9.17 ± 7.54	8.02 ± 3.69	6.41 ± 2.71	3.14 ± NC

- Median and range

Sponsor's tables

Validation of analytical methods assays were conducted to determine DDM and sumatriptan levels in rat and dog plasma using liquid chromatography coupled with tandem mass spectrometric detection (LC-MS/MS). In monkey, a "fit for purpose" LC/MS/MS method was used for quantifying DDM and sumatriptan in PK study 826824, the upper and lower limits of quantification could not be located.

DMF# (b) (4)

The metabolic profile and tissue distribution of DDM following a single intranasal administration to male albino rats were assessed. Overall, DDM was detectable in most rat tissues and was primarily excreted in the urine. C_{max} and AUC_{0-24h} were highest in the liver at 37800 ng equiv/g and 306000 h*ng equiv/g, respectively. $T_{1/2}$ was approximately 8 hours in blood and plasma and 6 hours in the liver.

Matrix	C_{max} (ng equiv/g)	t_{max} (h)	AUC_{0-24} (h*ng equiv/g)	$t_{1/2}$ (h)
Whole blood	224	0.0830	1830	8.47
Plasma	386	1.00	2630	7.00
Kidney	1520	2.00	15700	NCe
Liver	37800	2.00	306000	5.62

NCe Not calculated; a terminal monoexponential decline could not be unambiguously identified.

Sponsor's table

DDM was rapidly metabolized to approximately 20 metabolites; one of the major metabolites was lauric acid.

Autoradiograph tissue distribution studies showed the highest concentrations of DDM in the nasal mucosa between 5 and 30 min post dose. There was also significant distribution to the stomach, intestine, liver and kidney.

6 General Toxicology

6.1 Single-Dose Toxicity

DMF# (b) (4)

Study title: A Range Finding Intravenous (Once Weekly over 24 Hours) Infusion Toxicity Study of Dodecyl Maltoside in the Beagle Dog

Study no.: 504092; 1041076

Study report location: EDR

Conducting laboratory and location: (b) (4)

Date of study initiation: November 04, 2010

GLP compliance: No

QA statement: No

Drug, lot #, and % purity:

Drug	Lot #	% Purity
DDM	P21/148/010	99.0

Key Study Findings: The NOAEL for DDM was the HD.

Methods

Doses:	Dodecyl maltoside: 1, 2.6, or 10 mg/kg
Frequency of dosing:	Single dose
Route of administration:	Intravenous
Dose volume:	3 mL/kg/h
Formulation/Vehicle:	(b) (4) % Sodium Chloride for Injection (USP)
Species/Strain:	Dog, Beagle
Number/Sex/Group:	2/sex/group
Age:	At dosing initiation: ~7 months old
Weight:	Dosing initiation: 7.4 to 8.6 kg
Satellite groups:	None
Unique study design:	None
Deviation from study protocol:	There were minor deviations, with no impact on study validity.

Observations and Results

Mortality

Animals were observed twice a day.

There were no unscheduled animal deaths.

Clinical Signs

Observations were made daily.

There were no DDM-related findings.

Body Weights

Measurements were recorded twice a week.

There were no DDM-related findings.

Food Consumption

Measurements were recorded daily.

There were no DDM-related findings.

Ophthalmoscopy

Not assessed.

ECG

Not assessed

Hematology

Samples were taken once prior to dosing and 24 h after each dose (fasted). A standard battery of parameters was assessed.

There were no DDM-related findings.

Coagulation

Prothrombin time and activated partial thromboplastin time were assessed.

There were no DDM-related findings.

Clinical Chemistry

A standard battery of parameters was assessed.

There were no DDM-related findings.

Urinalysis

Not assessed

Gross Pathology

There were no DDM-related findings.

Organ Weights

Not assessed

Histopathology

Not assessed

Special Evaluation

None

Toxicokinetics

Samples were taken 24 hours after DDM administration.

Plasma levels of DDM increased dose proportionally. Mean plasma concentrations following 1, 2.6, 10, or 10 mg/kg were 64.4, 191.3, 767.8, and 886.5 ng/mL, respectively. Mean plasma levels of metabolite dodecyl-glucopyransoide at the same doses were below 15 mg/kg, 17.4, 53.7, and 57.4, respectively.

n-dodecyl-β-D-maltoside				
Dose mg/kg	**1**	**2.6**	**10**	**10**
Mean ng/mL	64.4	191.3	767.8	886.5

n-dodecyl-β-D-glucopyranoside				
Dose mg/kg	**1**	**2.6**	**10**	**10**
Mean ng/mL	<15.0	17.4	53.7	57.4

Dosing Solution Analysis

The mean concentrations of the dose preparations were within ± (b) (4) % of nominal.

DMF# (b) (4)

Study title: A Continuous Intravenous Infusion (Once Weekly over 24 Hours) Dose-range-finding/MTD Study of Dodecyl Maltoside in the Beagle Dog

Study no.: 504393; 8044P11

Study report location: EDR

Conducting laboratory and location: (b) (4)

Date of study initiation: May 16, 2011

GLP compliance: No

QA statement: No

Drug, lot #, and % purity:

Drug	Lot #	% Purity
DDM	P21/148/010	99.0

Key Study Findings: The NOAEL for DDM was the HD.

Methods

Doses: Dodecyl maltoside: 50, 100, 200, 400, 6-week dose holiday, 10, 30, 200 mg/kg/dose.

Frequency of dosing: Single dose

Route of administration: Intravenous

Dose volume: 3 mL/kg/h

Formulation/Vehicle: (b) (4)% Sodium Chloride for Injection (USP)

Species/Strain: Dog, Beagle

Number/Sex/Group: 2/sex/group

Age: At dosing initiation: ~7 months old

Weight: At dosing initiation: ~10 kg (M) and ~7 kg (F)

Satellite groups: None

Unique study design: Single ascending doses, with 1 week between doses, except between the 400 and 30 mg/kg doses there was a 6-week holiday.

Deviation from study protocol: There were minor deviations, with no impact on study validity.

Observations and Results

Mortality

Animals were observed twice a day.

There were no unscheduled animal deaths.

Clinical Signs

Observations were made daily.

At 400 mg/kg, red urine was observed in the cages of 3 of 4 animals (Day 22) and brown liquid was observed in the cages of 2 females (Day 23).

Body Weights

Measurements were recorded twice a week.

There were no DDM-related findings.

Food Consumption

Measurements were recorded daily.

There were no DDM-related findings.

Ophthalmoscopy

Not assessed.

ECG

Not assessed.

Hematology

Samples were taken once prior to dosing and 24 hours after each dose. A standard battery of parameters was assessed.

Red blood cell parameters were decreased at ≥200 mg/kg/day. Reticulocyte counts were increased at ≥100 mg/kg/day.

Finding		Dose mg/kg/day						Dose mg/kg/day		
		0	50	100	200	400		10	30	200
↓RBC 10^6/µL	M	6.14	5.920	5.900	5.555	5.160	Dosing holiday	6.305	6.145	5.970
	F	6.585	6.720	6.105	6.700	5.420		6.860	6.535	6.305
↑RETIC 10^9/L	M	42.95	25.70	29.15	48.40	78.50		41.60	63.85	75.5
	F	35.40	41.20	61.15	91.75	99.15		23.40	37.65	59.0

Coagulation

Prothrombin time and activated partial thromboplastin time were assessed.

There were no DDM-related findings.

Clinical Chemistry

A standard battery of parameters was assessed.

Total bilirubin was minimally increased at ≥200 mg/kg/day. Haptoglobin was decreased at ≥50 mg/kg/day.

Finding		Dose mg/kg/day						Dose mg/kg/day		
		0	50	100	200	400		10	30	200
↑TBIL mg/dL	M	0.070	0.065	0.080	0.105	0.125	Dosing holiday	0.055	0.050	0.140
	F	0.090	0.070	0.075	0.120	0.175		0.075	0.075	0.160
↓HAPTO mg/mL	M	4.715	1.725	0.445	0.295	0.360		7.695	6.935	0.780
	F	2.345	0.375	0.385	0.315	0.275		3.590	2.635	0.035

Urinalysis

Not assessed

Gross Pathology

There were no DDM-related findings.

Organ Weights

There were no DDM-related findings.

Histopathology

Adequate Battery: Yes

Peer Review: Yes

Signed pathology report: Yes

Histological Findings

There were no DDM-related findings.

Special Evaluation

None

Toxicokinetics

Samples were taken 24 hours after DDM administration.

C_{max} and AUC for both DDM and the metabolite, dodecyl-glucopyranoside, were similar between sexes and increased dose proportionally. T_{max} was between 3 and 7 hours for DDM and 3 and 24 hours for the metabolite. Both DDM and the metabolite were detectable up to ~30 hours post dose.

Table 1 Days 1, 8, 15, 22, 71 and 78 TK results summary

Treatment Duration	Test System	Animals/ Sex/ Dose	Dose (mg/kg/day)		Mean Cmax (ng/mL) M/F	Mean AUC(0-48h) ((ng·h)/mL) M/F
12 weeks (with a 7-week dosing holiday between Week 4 and Week 11)	Beagle Dogs	2			**Dodecyl**	**Maltoside**
			50	Day 1	5430/5680	117000/122000
			100	Day 8	11200/10900	234000/225000
			200	Day15	20800/23900	453000/452000
			400	Day 22	44100/45100	948000/1020000
			10	Day 71	930/1440	21100/27900
			30	Day 78	2890/3520	63800/77100
					Dodecyl	**Glucopyranoside**
			50	Day 1	552/283	11000/6170
			100	Day 8	1190/630	23200/12900
			200	Day15	2200/1230	44700/25100
			400	Day 22	5190/3300	119000/74300
			10	Day 71	96.0/63.7	2130/1320[a]
			30	Day 78	285/187	6350/3910

[a] Single animal value

Sponsor's table

Dosing Solution Analysis

The mean concentrations of the dose preparations were within ± (b) (4) % of nominal.

6.2 Repeat-Dose Toxicity

Study title: DFP-02: 4-Week Intranasal Administration Toxicity Study in the Rat Followed by a 2 Week Treatment-free Period

Study no.: DFP-02_SE_05; 8272935
Study report location: EDR
Conducting laboratory and location: [redacted]
Date of study initiation: October 29, 2012
GLP compliance: Yes
QA statement: Yes
Drug, batch #, and % purity:

Drug	Batch #	% Purity
[redacted] % DDM	SUN-PP-7/043	98.9
[redacted] % DDM	SUN-PP-7/044	103.5
[redacted] % DDM	SUN-PP-7/045	103.2
30 mg Suma	SUN-PP-7/046	101.0
30 mg Suma, [redacted] % DDM	SUN-PP-7/047	99.7,102.5

Key Study Findings: The NOAEL for DDM was the HD.

NOAEL Exposure Values on Day 27 male/female			
Drug	**mg/day**	**C_{max} ng/mL**	**$AUC_{(0-t)}$ ng*h/mL**
DDM	10	996/499	159/219
Suma	30	350/964	1280/2530
DFP-02-DDM	0.3	18.2/37.2	14.6/21.6
Suma	30	3760/13200	2050/3780

Methods

Doses:	Vehicle (no DDM), (b) (4) (DDM), (b) (4) (DDM), 10 (DDM), 30 (Suma), and (b) (4) $_{DDM}$+30$_{Suma}$ (DFP-02) mg/day.
Frequency of dosing:	Daily
Route of administration:	Intranasal
Dose volume:	(b) (4) µL ((b) (4) µL/ nostril)
Formulation/Vehicle:	Citric acid, monobasic potassium phosphate, di basic sodium phosphate, (b) (4) and water.
Species/Strain:	Rat, Crl:CD(SD)
Number/Sex/Group:	Tox: 10/sex/group; recovery: 5/sex/group; TK: 9/sex/dosing group, 3/sex/control group.
Age:	At dosing initiation: 7 to 8 weeks old
Weight:	At dosing initiation: M: 263.2 to 348.5 g; F: 167.1 to 237.5 g
Satellite groups:	Recovery and TK
Unique study design:	None
Deviation from study protocol:	There were minor deviations, with no impact on study validity.

Observations and Results

Mortality

Animals were observed twice a day.

All animals survived until scheduled necropsy.

Clinical Signs

Detailed physical examinations were made daily during the dosing period and weekly during recovery.

Approximately 30% of the DFP-02 dosed animals were observed with thinning fur around the muzzle.

Body Weights

Measurements were recorded weekly.

There were no drug- or excipient-related findings.

Food Consumption

Consumption was measured daily.

There were no drug- or excipient-related findings.

Ophthalmoscopy

All animals were examined in Week 4.
There were no excipient- or drug-related findings.

ECG

An ECG was not conducted.

Hematology

A standard battery of parameters was assessed.

There were no excipient- or drug-related findings.

Coagulation

Prothrombin time and activated partial thromboplastin time were assessed.

There were no excipient- or drug-related findings.

Clinical Chemistry

Blood samples were taken prior to dosing, in Week 4, and at the end of the recovery period. A standard battery of parameters was assessed.

There were no excipient- or drug-related findings.

Urinalysis

Urine samples were collected prior to dosing, in Week 4, and at the end of the recovery period.

There were no excipient- or drug-related findings.

Gross Pathology

There were no excipient- or drug-related findings.

Organ Weights

There were no excipient- or drug-related findings.

Histopathology

Adequate Battery: Yes

Signed pathologists report: Yes

Peer Review: No

Histological Findings
In the DDM and DDM + sumatriptan groups, one or two animals of either sex had minimal squamous cell metaplasia of the respiratory tract.

Special Evaluation

None

Toxicokinetics

There was high inter-animal variation in plasma concentrations due to cross – contamination of DDM and sumatriptan samples. Exposure differences between males and females were not clearly discernable due to high inter-animal variation.

Sumatriptan
T_{max} and half-life (in females only) was 0.25 and 2.6 hours, respectively. Sumatriptan did not accumulate with repeat dosing.

Sumatriptan in DFP-02
T_{max} and half-life (in females only) was 0.033 and 3.3 hours, respectively. Both single and repeat dosing with DFP-02 resulted in a 1.5-fold increase in sumatriptan exposure (C_{max} and $AUC_{(0-t)}$), compared to sumatriptan alone. Sumatriptan in DFP-02 did not accumulate with repeat dosing.

DDM
T_{max} was 0.167 hours and the half-life was between 0.4 and 2.7 hours (HD); by 4 hours DDM was below the limit of quantification (0.5 ng/mL). DDM did not accumulate with repeat dosing.

DDM in DFP-02
T_{max} and half-life (in females only) was 0.033 and 3.3 hours, respectively. Exposure (C_{max} and $AUC_{(0-t)}$) of DDM increased approximately dose proportionally, except at the HD, where exposure increased less then dose proportionally. DDM in DFP-02 did not accumulate with repeat dosing.

1.1 Toxicokinetic parameters of sumatriptan on Day 1

	30 mg/animal/day		DFP-02 (30 mg sumatriptan/animal/day)	
	Males	Females	Males	Females
C_{max} (ng/mL)	2950	1130	8270	12100
t_{max} (h)	0.167	0.250	0.033	0.033
$t_{½}$ (h)	NR	2.63	NR	3.26
$AUC_{(0-t)}$ (ng.h/mL)	1900	3460	3120	4350
$AUC_{(0-\infty)}$ (ng.h/mL)	NR	3680	NR	4700
C_{max}/D	98.3	37.7	276	403
$AUC_{(0-t)}/D$	63.3	115	104	145

1.2 Toxicokinetic parameters of sumatriptan on Day 27

	30 mg/animal/day		DFP-02 (30 mg sumatriptan/animal/day)	
	Males	Females	Males	Females
C_{max} (ng/mL)	350	964	3760	13200
t_{max} (h)	0.167	0.250	0.033	0.033
$t_{½}$ (h)	3.43	5.33	2.53	3.66
$AUC_{(0-t)}$ (ng.h/mL)	1280	2530	2050	3780
$AUC_{(0-\infty)}$ (ng.h/mL)	1410	3110	2150	4280
C_{max}/D	11.7	32.1	125	440
$AUC_{(0-t)}/D$	42.7	84.3	68.3	126
RA_{Cmax}	0.119	0.853	0.455	1.09
RA_{AUC}	0.674	0.731	0.657	0.869

1.3 Toxicokinetic parameters of DDM on Day 1

	0.1 mg/animal/day		0.3 mg/animal/day		10 mg/animal/day		DFP-02 (0.3 mg DDM/animal)	
	Males	Females	Males	Females	Males	Females	Males	Females
C_{max} (ng/mL)	65.1	116	512	46.4	966	499	65.8	55.6
t_{max} (h)	0.150	0.117	0.083	0.167	0.167	0.167	0.167	0.083
$t_{½}$ (h)	0.513	0.415	0.438	NR	1.66	2.65	0.653	0.454
$AUC_{(0-t)}$ (ng.h/mL)	11.6	16.2	48.6	39.5	416	362	34.9	35.4
$AUC_{(0-\infty)}$ (ng.h/mL)	12.3	16.5	50.4	NR	422	377	35.3	37.5
C_{max}/D	651	1160	1707	155	96.6	49.9	219	185
$AUC_{(0-t)}/D$	116	162	162	132	41.6	36.2	116	118

1.4 Toxicokinetic parameters of DDM on Day 27

	0.1 mg/animal/day		0.3 mg/animal/day		10 mg/animal/day		DFP-02 (0.3 mg DDM/animal/day)	
	Males	Females	Males	Females	Males	Females	Males	Females
C_{max} (ng/mL)	4.98	10.1	21.9	7.90	82.4	233	18.2	37.2
t_{max} (h)	0.250	0.500	0.167	0.500	0.083	0.033	0.083	0.083
$t_{½}$ (h)	NR	NR	NR	NR	1.56	2.07	NR	NR
$AUC_{(0-t)}$ (ng.h/mL)	4.65	8.59	21.6	7.77	159	219	14.6	21.6
$AUC_{(0-\infty)}$ (ng.h/mL)	NR	NR	NR	NR	161	224	NR	NR
C_{max}/D	49.8	101	73.0	26.3	8.24	23.3	60.7	124
$AUC_{(0-t)}/D$	46.5	85.9	72.0	25.9	15.9	21.9	48.7	72.0
RA_{Cmax}	0.076	0.087	0.043	0.170	0.085	0.467	0.277	0.669
RA_{AUC}	0.401	0.530	0.444	0.197	0.382	0.605	0.418	0.610

Sponsor's tables

Dosing Solution Analysis

The mean concentrations of the dose preparations were within ± (b) (4) % of nominal.

Study title: DFP-02: 13 Week Intranasal Administration Toxicity Study in the Rat Followed by a 4 Week Treatment-free Period

Study no.: DFP-02_SE_08; 8281781
Study report location: EDR
Conducting laboratory and location: [redacted]
Date of study initiation: April 2, 2013
GLP compliance: Yes
QA statement: Yes
Drug, batch #, and % purity:

Drug	Batch #	% Purity
[redacted] % DDM	SUN-PP-15/158	107.4
[redacted] % DDM	SUN-PP-15/159	104.0
[redacted] % DDM	SUN-PP-15/160	98.6
30 mg Suma	SUN-PP-15/149	102.5
DFP-02: 30 mg Suma, [redacted] % DDM	SUN-PP-15/150	101.5 101.4

Key Study Findings: The NOAEL for DDM was the HD.

NOAEL Exposure Values on Day 89 male/female			
Drug/Excipient	**mg/day**	**C_{max} ng/mL**	**$AUC_{(0-t)}$ ng*h/mL**
DDM	10 (HD)	43.3/101	109/111
Suma	30	269/975	1620/4530
DFP-02- DDM	0.3	5.82/8.80	18.8/21.7
Suma	30	772/1160	2240/4090

Methods

Doses:	Vehicle (no DDM), [(b) (4)] (DDM), [(b) (4)] (DDM), 10 (DDM), 30 (Suma), and [(b) (4)] $_{DDM}$+30$_{Suma}$ (DFP-02) mg/day.
Frequency of dosing:	Daily
Route of administration:	Intranasal
Dose volume:	[(b) (4)] µL ([(b) (4)] µL/ nostril)
Formulation/Vehicle:	Citric acid, monobasic potassium phosphate, di basic sodium phosphate, [(b) (4)] and water.
Species/Strain:	Rat, Crl:CD(SD)
Number/Sex/Group:	Tox: 10/sex/group; recovery: 5/sex/group; TK: 9/sex/dosing group and 3/sex/control group
Age:	At dosing initiation: 6 to 7 weeks old
Weight:	At dosing initiation: M: 167.9 to 290.8 g; F: 144.8 to 225.6 g
Satellite groups:	Recovery and TK
Unique study design:	None
Deviation from study protocol:	There were minor deviations, with no impact on study validity.

Observations and Results

One Main Study control animal and one TK sumatriptan only animal were found dead on Day 93 and 80, respectively. The control animal was found to have enlarged lymph nodes and no cause of death was observed in the sumatriptan only animal. Daily detailed physical examinations revealed a higher incidence of thinning fur in animals given DFP-02. Weekly body weight and food consumption measurements revealed a 16% gain in mean body weight, which corresponded with an 8% increase in food consumption, compared to controls, in males dosed with sumatriptan. In females given 20% DDM or DFP-02, mean food consumption was 10 and 14% higher, respectively, compared to control, with no corresponding effect on weight. An adequate battery of histopathology tissues were assessed. In males given DFP-02, mean adjusted to body spleen weight ratios were 20% higher than control, with no histological correlate. Histological findings consisted of a marginal increase in the incidence/severity of minor squamous cell hyperplasia, in the nose/nares, at 10 mg DDM in males and 0.3 and 10 mg DDM in females.

Group incidence of selected microscopic findings – toxicity animals

		Males						Females					
		1M	2M	3M	4M	5M	6M	1F	2F	3F	4F	5F	6F
Tissue and finding	Level (mg/animal/day)	0	0.1	0.3	10	30*	30*/ 0.3	0	0.1	0.3	10	30*	30*/ 0.3
Nose/nares	No. examined:	10	10	10	10	10	10	10	10	10	10	10	10
squamous cell hyperplasia	Grade -	10	10	9	8	10	10	9	8	6	7	9	9
	1	0	0	1	0	0	0	0	0	3	2	1	0
	2	0	0	0	2	0	0	1	2	1	1	0	1

Key: "-" = finding not present, 1 = minimal, 2 = slight,
* = sumatriptan (mg/50µL)

Sponsor's table

There were no drug- or excipient-related effects observed in ophthalmoscopy, hematology (standard battery), coagulation (prothrombin time and activated partial thromboplastin time), clinical chemistry (standard battery), urinalysis, or gross pathology assessments.

TK assessments showed high inter-animal variation in plasma concentrations. One control sample was positive for DDM (1.87 ng/mL; LLOQ=0.5ng/mL). Three control samples were positive for sumatriptan (1.33, 2.24, and 1.95 ng/mL, respectively; LLOQ = 1.0 ng/mL). The source of the inadvertent DDM and sumatriptan exposure could not be identified. Exposure differences between males and females were sometimes not clearly discernable due to high inter-animal variation. Co-administration of sumatriptan and DDM appeared to markedly increase sumatriptan C_{max} values in both sexes after single and repeated doses.

Sumatriptan AUC values were increased in the presence of DDM but not to the extent of C_{max} values. Exposures (C_{max} and $AUC_{(0-t)}$) to DDM in males increased greater than dose proportionally between 0.1 and 0.3 mg/day and less than dose proportionally at 10 mg/day. In females, exposure increased less than dose proportionally. Co-administration of DDM with sumatriptan in most cases reduced the exposure to DDM relative to that observed with DDM alone.

1.1 Toxicokinetic parameters of sumatriptan on Day 1

	30 mg/animal/day		DFP-02 (30 mg sumatriptan/animal/day)	
	Males	Females	Males	Females
C_{max} (ng/mL)	410	433	10200	10700
t_{max} (h)	0.25	4.0	0.033	0.033
$t_{½}$ (h)	2.38	NR	3.28	5.67
$AUC_{(0-t)}$ (ng.h/mL)	2010	3110	2600	4090
$AUC_{(0-\infty)}$ (ng.h/mL)	2130	NR	2900	5480
C_{max}/D	13.7	14.4	340	357
$AUC_{(0-t)}/D$	67.0	104	86.7	136

1.2 Toxicokinetic parameters of sumatriptan on Day 89

	30 mg/animal/day		DFP-02 (30 mg sumatriptan/animal/day)	
	Males	Females	Males	Females
C_{max} (ng/mL)	269	975	772	1160
t_{max} (h)	2.0	2.0	0.033	0.083
$t_{½}$ (h)	NR	NR	4.23	4.21
$AUC_{(0-t)}$ (ng.h/mL)	1620	4530	2240	4090
$AUC_{(0-\infty)}$ (ng.h/mL)	NR	NR	2690	5020
C_{max}/D	8.97	32.5	25.7	38.7
$AUC_{(0-t)}/D$	54.0	151	74.7	136
RA_{Cmax}	0.656	2.25	0.076	0.108
RA_{AUC}	0.806	1.46	0.862	1.000

1.3 Toxicokinetic parameters of DDM on Day 1

	0.1 mg/animal/day		0.3 mg/animal/day		10 mg/animal/day		DFP-02 (0.3 mg DDM/animal)	
	Males	Females	Males	Females	Males	Females	Males	Females
C_{max} (ng/mL)	15.1	36.4	127	69.0	352	261	46.1	20.9
t_{max} (h)	0.5	0.539	0.2	0.2	0.55	0.167	0.25	0.083
$t_{½}$ (h)	NR	NR	0.650	0.995	NR	1.58	NR	1.90
$AUC_{(0-t)}$ (ng.h/mL)	15.3	30.3	59.3	45.2	277	271	31.1	27.2
$AUC_{(0-\infty)}$ (ng.h/mL)	NR	NR	59.8	48.1	NR	272	NR	35.4
C_{max}/D	151	364	423	230	35.2	26.1	154	69.7
$AUC_{(0-t)}/D$	153	303	198	151	27.7	27.1	104	90.7

1.4 Toxicokinetic parameters of DDM on Day 89

	0.1 mg/animal/day		0.3 mg/animal/day		10 mg/animal/day		DFP-02 (0.3 mg DDM/animal/day)	
	Males	Females	Males	Females	Males	Females	Males	Females
C_{max} (ng/mL)	5.16	10.0	23.6	30.4	43.3	101	5.82	8.80
t_{max} (h)	0.178	0.267	0.3	0.3	0.083	0.244	0.083	0.222
$t_{½}$ (h)	NR	NR	NR	NR	NR	NR	NR	NR
$AUC_{(0-t)}$ (ng.h/mL)	16.5	7.04	13.2	11.0	109	111	15.8	21.7
$AUC_{(0-\infty)}$ (ng.h/mL)	NR	NR	NR	NR	NR	NR	NR	NR
C_{max}/D	51.6	100	78.7	101	4.33	10.1	19.4	29.3
$AUC_{(0-t)}/D$	165	70.4	44.0	36.7	10.9	11.1	52.7	72.3
RA_{Cmax}	0.342	0.275	0.186	0.441	0.123	0.387	0.126	0.421
RA_{AUC}	1.08	0.232	0.223	0.243	0.394	0.410	0.508	0.798

Sponsor's tables

(Based on Pharmacology/Toxicology IND Review and Evaluation, IND 108088, D. Charles Thompson, Ph.D., April 10, 2015)

Study title: DFP-02: 26 Week Intranasal Administration Toxicity Study in the Rat Followed by a 4 Week Treatment-free Period

Study no.: DFP-02_SE_10; 8281782
Study report location: EDR
Conducting laboratory and location: [redacted]
Date of study initiation: April 17, 2013
GLP compliance: Yes
QA statement: Yes
Drug, batch #, and % purity:

Drug	Batch #	% Purity
[redacted] % DDM	SUN-PP-15/158; SUN-PP-20/050	107.4 105.0
[redacted] % DDM	SUN-PP-15/159; SUN-PP-15/154; SUN-PP-20/051	104.0; 103.8; 99.1
[redacted] % DDM	SUN-PP-15/160; SUN-PP-20/052	98.6 104.0
30 mg Suma	SUN-PP-15/149; SUN-PP-20/047	102.5 100.7
DFP-02: 30 mg Suma, [redacted] % DDM	SUN-PP-15/150; SUN-PP-20/048	101.5/101.4; 99.3/99.4

Key Study Findings: The NOAEL for DDM was the HD.

NOAEL Exposure Values on Day 181 male/female			
Drug/Excipient	**mg/day**	**C_{max} ng/mL**	**$AUC_{(0-t)}$ ng*h/mL**
DDM	10 (HD)	572/923	579/507
Suma	30	898/771	2560/4350
DFP-02-DDM	0.3	23.6/17.9	8.49/12.5
Suma	30	4670/7470	2240/4990

Methods

Doses:	Vehicle (no DDM), (b) (4) (DDM), (b) (4) (DDM), 10 (DDM), 30 (Suma), and (b) (4) $_{DDM}$+30$_{Suma}$ (DFP-02) mg/day.
Frequency of dosing:	Daily
Route of administration:	Intranasal
Dose volume:	(b) (4) µL ((b) (4) µL/ nostril)
Formulation/Vehicle:	Citric acid, monobasic potassium phosphate, di basic sodium phosphate, (b) (4) and water.
Species/Strain:	Rat, Crl:CD(SD)
Number/Sex/Group:	Tox: 10/sex/group; recovery: 5/sex/group; TK: 9/sex/dosing group, 3/sex/control group
Age:	At dosing initiation: 6 to 7 weeks old
Weight:	At dosing initiation: M: 196 to 290.8 g; F: 144.8 to 225.6 g
Satellite groups:	Recovery and TK
Unique study design:	None
Deviation from study protocol:	There were minor deviations, with no impact on study validity.

Observations and Results

One DDM LDM was killed in extremis (Day 178) due to physical trauma sustained during blood sampling. One male given sumatriptan 30 mg/day was removed on Day 101 due to severe clinical signs (hunched posture, semi closed eyes, and thin appearance) resulting from focal encephalopathy. One DDM TK LDF was removed (Day 120) due to severe clinical signs (swollen paws), with no clear cause identified. None of the findings in these animals were considered drug-related. Daily detailed physical examinations revealed a higher incidence of thinning fur in animals given DFP-02, which improved but did not completely resolve during the recovery period. There were no drug- or excipient-related effects on body weight, food consumption, ophthalmoscopy, hematology (standard battery), coagulation (prothrombin time and activated partial thromboplastin time), clinical chemistry (standard battery), urinalysis, gross pathology, or organ weight assessments. The histological examinations included an adequate battery of tissues for main study animals of Groups 1, 2, 4, and 6. Animals in Groups 3 and 5 (main study) and Groups 1, 2, 4, and 6 (recovery), only had the nasal passages and gross lesions examined. Dose-related minimal to moderate squamous cell metaplasia of the respiratory epithelium and atrophy of the olfactory epithelium was observed in the nasal cavity of DDM only animals, which partially resolved during the recovery period.

Sumatriptan C_{max} values markedly increased and T_{max} decreased when administered with DDM. In females, sumatriptan AUC values modestly increased with DDM; however, in males AUC values decreased. DDM levels increased less in the presence of sumatriptan compared to DDM alone.

(Based on Pharmacology/Toxicology IND Review and Evaluation, IND 108088, D. Charles Thompson, Ph.D., April 10, 2015)

Study title: DFP-02: 28-Day Intranasal Administration Toxicity Study in Dogs

Study no.: 1115-018
Study report location: EDR
Conducting laboratory and location: (b) (4)
Date of study initiation: July 20, 2010
GLP compliance: Yes
QA statement: Yes
Drug, batch #, and % purity:

Drug/Excipient/Vehicle	Batch #	% Purity
Vehicle without DDM	SUN2-154	-
15 mg Suma + DDM	SUN2-155	101.6
5 mg Suma + DDM	SUN2-156	101.6
15 mg Suma	SUN2-157	101.4

Key Study Findings: The NOAEL for sumatriptan + DDM was the HD.

NOAEL Exposure Values on Day 28 male/female			
Drug/Excipient	**mg/day**	**C_{max} ng/mL**	**$AUC_{(0-t)}$ ng*h/mL**
Suma	15	192/429	663/899
DFP-02 (DDM + Suma)	15	229/263	613/602

Methods

Doses:	Vehicle (no DDM), 5 mg Suma + (b) (4)% DDM, 15 mg Suma + (b) (4)% DDM, 15 mg Suma, no DDM
Frequency of dosing:	Daily
Route of administration:	Intranasal (right nostril)
Dose volume:	100 µL/dose
Formulation/Vehicle:	Citric acid, monobasic potassium phosphate, di basic sodium phosphate, (b) (4) and water.
Species/Strain:	Dog/beagle
Number/Sex/Group:	4/sex/group
Age:	At dosing initiation: 6 to 7 months old
Weight:	At dosing initiation: M: 8.9 to 10.4 g; F: 6.0 to 7.8 g
Satellite groups:	None
Unique study design:	None
Deviation from study protocol:	There were minor deviations, with no impact on study validity.

Observations and Results

All animals survived to scheduled necropsy. There were no drug-related effects observed on clinical signs, body weight, food consumption, ophthalmoscopy, ECG, hematology (standard battery), coagulation (prothrombin time and activated partial thromboplastin time), clinical chemistry (standard battery), urinalysis, gross pathology, or organ weight assessments. The histological examinations included an adequate battery of tissues for in all animals. There was a slight non-dose related increase in the incidence of mixed leukocyte infiltration in the lungs of animals that received drug.

DDM tended to increase sumatriptan exposure (C_{max} and AUC) in males and decrease it in females. Exposure values on Day 28 were lower than Day 1.

(Based on Pharmacology/Toxicology IND Review and Evaluation, IND 108088, D. Charles Thompson, Ph.D., February 13, 2013)

Study title: DFP-02: 4-Week Intranasal Administration Toxicity Study in the Dogs Followed by 2 Week Treatment-free Period

Study no.: DFP-02_SE_06; 8275552
Study report location: EDR
Conducting laboratory and location: [redacted]
Date of study initiation: November 30, 2012
GLP compliance: Yes
QA statement: Yes
Drug, batch #, and % purity:

Drug/Excipient/Vehicle	Batch #	% Purity
Vehicle without DDM	SUN-PP-7/053	-
[redacted] % DDM	SUN-PP-7/054	101.2
[redacted] % DDM	SUN-PP-07/155	103.5
[redacted] % DDM	SUN-PP-07/056	101.7
45 mg Suma	SUN-PP-7/058	102.4
45 mg Suma + [redacted] % DDM	SUN-PP-7/057	101.1

Key Study Findings: The NOAEL for DDM was the HD.

NOAEL Exposure Values on Day 24 male/female			
Drug/Excipient	**mg/day**	**C_{max} ng/mL**	**$AUC_{(0-t)}$ ng*h/mL**
DDM	40 (HD)	58.8/61.9	72.8/64.7
Suma	90	1180/1250	2660/3140
DFP-02-DDM	1.2	1.5/17.9	1.02/0.45
Suma	90	1140/1130	2630/1860

Methods

Doses:	Vehicle (no DDM), [redacted] mg ([redacted]% DDM), 10 mg [redacted]% DDM) , 40 mg [redacted]% DDM), 90 mg Suma (no DDM), 90 mg Suma + [redacted] mg ([redacted]% DDM)
Frequency of dosing:	Daily
Route of administration:	Intranasal (each nostril via the [redacted])
Dose volume:	200 µL/dose (100 µL/nostril)
Formulation/Vehicle:	Citric acid, monobasic potassium phosphate, di basic sodium phosphate, [redacted] and water.
Species/Strain:	Dog/beagle
Number/Sex/Group:	Tox: 3/sex/group; recovery: 2/sex/C, LD (DDM), HD (DDM), and Suma + DDM
Age:	At dosing initiation: 28 to 36 weeks old
Weight:	At dosing initiation: 8.96 to 13.54 kg
Satellite groups:	Recovery period
Unique study design:	None
Deviation from study protocol:	There were minor deviations, with no impact on study validity.

Observations and Results

Mortality

Animals were observed twice a day.

All animals survived until scheduled necropsy.

Clinical Signs

Detailed physical examinations were made daily during the dosing period and weekly during recovery.

Common findings at all doses included sneezing, sniffing, nose rubbing, nose licking, head shaking, and salivation, compared to control without DDM.

Body Weights

Measurements were recorded weekly.

There were no drug- or excipient-related findings.

Food Consumption

Consumption was measured daily.

There were no drug- or excipient-related findings.

Ophthalmoscopy

All animals were examined during pretreatment and in Week 4.

There were no drug- or excipient-related findings.

ECG

Examinations were performed during pre-treatment and Week 4.

There were no drug- or excipient-related findings.

Hematology

Blood samples were taken prior to dosing, in Week 4, and at the end of the recovery period. A standard battery of parameters was assessed.

There were no drug- or excipient-related findings.

Coagulation

Prothrombin time and activated partial thromboplastin time were assessed.

There were no drug- or excipient-related findings.

Clinical Chemistry

Blood samples were taken prior to dosing, in Week 4, and at the end of the recovery period. A standard battery of parameters was assessed.

There were no drug- or excipient-related findings.

Urinalysis

Urine samples were collected prior to dosing, in Week 4, and at the end of the recovery period.

There were no drug- or excipient-related findings.

Gross Pathology

There were no drug- or excipient-related findings.

Organ Weights

The organs weighed are identified in the histopathology table below.

There were no drug- or excipient-related findings.

Histopathology

Adequate Battery: Yes

Signed pathologists report: Yes

Peer Review: No

Histological Findings

In DDM dosed animals, a few animals of both sexes had minimal squamous metaplasia of the respiratory epithelium in the nasal passages, which was not correlated with dose level.

Test Article	Control			Treated		
Group	1	2	3	4	5	6
DDM dose level (mg/animal/day)	0	1.2	10	40	-	1.2
Sumatriptan dose level (mg/animal/day)	0	-	-	-	90	90

Tissue/ Observation	Group/Sex: Number of Animals:	1/M 3	2/M 3	3/M 3	4/M 3	5/M 3	6/M 3	1/F 3	2/F 3	3/F 3	4/F 3	5/F 3	6/F 3
Nasal Cavity	Number Examined:	3	3	3	3	3	3	3	3	3	3	3	3
	Unremarkable:	3	3	2	2	3	2	3	1	3	2	3	3
Respiratory epithelium - squamous metaplasia		0	0	1	1	0	0	0	2	0	1	0	0
Squamous epithelium - erosion		0	0	0	0	0	1	0	0	0	0	0	0
Lumen - inflammatory exudate		0	0	0	0	0	0	0	1	0	0	0	0

Sponsor's table

Special Evaluation

None

Toxicokinetics

Blood samples were taken on Day1 and 24.

Single or repeat administration of DDM had minimal effect on sumatriptan exposure (C_{max} and AUC). Half-life following a single dose of sumatriptan with or without DDM was ~3 to 4 hours.

Generally, DDM exposure (C_{max} and AUC) values increased greater than dose proportionally. Half-life following a single dose of DDM was ~7 hours. When DDM was combined with sumatriptan (DFP-02) exposure of DDM increased. Repeat administration of DDM or DDM + sumatriptan had minimal effect on exposure levels of both substances.

1.1 Mean (± SD) toxicokinetic parameters of sumatriptan on Day 1

	90 mg/animal		DFP-02 (90 mg sumatriptan /animal)	
	Males (n= 3)	Females (n= 3)	Males (n= 5) [1]	Females (n= 5)
C_{max} (ng/mL)	1100 ± 675	1330 ± 764	1420 ± 727	1060 ± 628
t_{max} (h)#	0.62 0.62 -0.63	0.62 0.60 – 1.00	0.35 0.25 – 4.00	0.35 0.33 – 1.00
$t_{½}$ (h)	3.12 ± 0.439	4.02 ± 0.820	3.30 ± 0.869 (n = 4)	3.52 ± 0.516
$AUC_{(0-t)}$ (ng.h/mL)	2910 ± 527	3850 ± 662	2990 ± 502	2510 ± 1280
$AUC_{(0-\infty)}$ (ng.h/mL)	2920 ± 521	3910 ± 692	3130 ± 473 (n = 4)	2520 ± 1280
C_{max}/D	12.2 ± 7.50	14.7 ± 8.49	15.7 ± 8.08	11.7 ± 6.97
$AUC_{(0-t)}$/D	32.3 ± 5.85	42.8 ± 7.36	33.2 ± 5.58	27.8 ± 14.2

Median and range
[1] Unless otherwise stated

1.2 Mean (± SD) toxicokinetic parameters of sumatriptan on Day 24

	90 mg/animal/day		DFP-02 (90 mg sumatriptan /animal/day)	
	Males (n= 3)	Females (n= 3)[1]	Males (n= 5)[1]	Females (n= 5)
C_{max} (ng/mL)	1180 ± 559	1250 ± 477	1140 ± 620	1130 ± 1060
t_{max} (h)#	0.55 0.50 – 1.00	1.00 0.50 -1.00	0.50 0.25 – 4.00	0.50 0.08 – 1.00
$t_{½}$ (h)	3.81 ± 0.392	3.23 (n = 2)	3.53 ± 0.532 (n = 3)	6.45 ± 5.47
$AUC_{(0-t)}$ (ng.h/mL)	2660 ± 604	3140 ± 1166	2630 ± 980	1860 ± 1140
$AUC_{(0-\infty)}$ (ng.h/mL)	2680 ± 603	3780(n = 2)	2690 ± 1390 (n = 3)	1900 ± 1100
C_{max}/D	13.1 ± 6.21	13.8 ± 5.30	12.7 ± 6.89	12.6 ± 11.8
$AUC_{(0-t)}$/D	29.6 ± 6.71	34.9 ± 13.0	29.3 ± 10.9	20.6 ± 12.7
RA_{Cmax}	1.32 ± 0.885	1.03 ± 0.322	0.895 ± 0.345	0.917 ± 0.593
RA_{AUC}	0.922 ± 0.164	0.824 ± 0.300	0.892 ± 0.292	0.712 ± 0.343

Median and range
[1] Unless otherwise stated

1.3 Mean (± SD) toxicokinetic parameters of DDM on Day 1

	1.2 mg/animal		10 mg/animal		40 mg/animal		DFP-02 (1.2 mg DDM/animal)	
	Males (n= 5) [1]	Females (n= 5) [1]	Males (n= 3) [1]	Females (n= 3) [1]	Males (n= 5) [1]	Females (n= 5)	Males (n= 5) [1]	Females (n= 5) [1]
C_{max} (ng/mL)	0.998 (n=2)	2.18 ± 1.78 (n = 4)	11.3 ± 6.85	21.8 ± 13.0	58.5 ± 49.6	188 ± 142	6.10 ± 7.22 (n = 3)	3.37 ± 1.95
t_{max} (h)#	0.65 (n = 2)	0.66 0.33 – 1.15 (n = 4)	0.65 0.37 – 0.65	0.67 0.37 – 0.67	0.65 0.35 – 1.00	0.68 0.35 – 0.70	0.35 0.33 – 0.35 (n = 3)	0.35 0.33 – 0.50
$t_{½}$ (h)	NR	NR	1.14 (n = 2)	0.666 (n = 1)	0.758 (n = 2)	0.750 ± 0.373	0.609 (n = 1)	0.741 (n = 2)
$AUC_{(0-t)}$ (ng.h/mL)	1.09 (n = 1)	1.83 ± 1.63 (n = 4)	15.9 ± 14.1	24.0 ± 17.6	86.9 ± 85.6	190 ± 132	7.78 ± 9.07 (n = 3)	4.48 ± 2.98
$AUC_{(0-\infty)}$ (ng.h/mL)	NR	NR	22.6 (n = 2)	44.6 (n = 1)	38.1 (n = 2)	192 ± 131	20.5 (n = 1)	7.19 (n = 2)
C_{max}/D	0.832 (n=2)	1.82 ± 1.48 (n = 4)	1.13 ± 0.685	2.18 ± 1.30	1.46 ± 1.24	4.69 ± 3.56	5.09 ± 6.02 (n = 3)	2.81 ± 1.63
$AUC_{(0-t)}$/D	0.908 (n = 1)	1.53 ± 1.36 (n = 4)	1.59 ± 1.41	2.40 ± 1.76	2.17 ± 2.14	4.75 ± 3.29	6.49 ± 7.56 (n = 3)	3.74 ± 2.48

Median and range
[1] Unless otherwise stated

1.4 Mean (± SD) toxicokinetic parameters of DDM on Day 24

	1.2 mg/animal/day		10 mg/animal/day		40 mg/animal/day		DFP-02 (1.2 mg DDM/animal/day)	
	Males (n= 5) [1]	Females (n= 5) [1]	Males (n= 3) [1]	Females (n= 3) [1]	Males (n= 5) [1]	Females (n= 5) [1]	Males (n= 5) [1]	Females (n= 5) [1]
C_{max} (ng/mL)	0.902 ± 0.123 (n = 4)	4.94 ± 5.68	4.27 ± 3.55	8.05 ± 5.56	58.8 ± 52.1	61.9 ± 44.3	1.50 ± 1.31 (n = 4)	0.627 ± 0.090
t_{max} (h)#	0.50 0.25- 1.00 (n = 4)	0.50 0.50 – 8.00	0.55 0.28 -0.57	0.57 0.30 – 0.58	0.55 0.32 – 0.57	0.57 0.30 – 0.58	0.50 0.25 – 8.00 (n = 4)	0.30 0.00 – 1.00
$t_{½}$ (h)	NR	NR	5.71 (n = 1)	0.889 (n = 1)	0.731 ± 0.356 (n = 3)	1.89 (n = 2)	NR	NR
$AUC_{(0-t)}$ (ng.h/mL)	0.554 (n = 2)	18.9 (n = 2)	5.34 ± 4.26	10.8 ± 4.48	72.8 ± 60.7	64.7 ± 43.3	1.02 (n = 1)	0.450 (n = 1)
$AUC_{(0-\infty)}$ (ng.h/mL)	NR	NR	12.6 (n = 1)	13.5 (n = 1)	92.6 ± 74.6 (n = 3)	42.4 (n = 2)	NR	NR
C_{max}/D	0.751 ± 0.102 (n = 4)	4.12 ± 4.73	0.427 ± 0.355	0.805 ± 0.556	1.47 ± 1.30	1.55 ± 1.11	1.25 ± 1.09	0.522 ± 0.075
$AUC_{(0-t)}$/D	0.461 (n = 2)	15.8 (n = 2)	0.534 ± 0.426	1.08 ± 0.448	1.82 ± 1.52	1.62 ± 1.08	0.850 (n = 1)	0.375 (n = 1)
RA_{Cmax}	0.626 (n = 1)	4.00 ± 4.42	0.753 ± 1.03	0.560 ± 0.662	1.57 ± 1.47	0.618 ± 0.610	0.598 ± 0.593 (n = 3)	0.256 ± 0.178
RA_{AUC}	0.533 (n = 2)	14.7 (n = 2)	0.735 ± 1.03	0.672 ± 0.648	1.50 ± 1.38	0.578 ± 0.511	0.0567 (n = 1)	0.273 (n = 1)

Median and range
[1] Unless otherwise stated

Sponsor's tables

Dosing Solution Analysis

The mean concentrations of the dose preparations were within ± (b) (4) % of nominal.

Study title: DFP-02: 13 Week Intranasal Administration Toxicity Study in the Dog Followed by a 4-Week Treatment-free Period

Study no.: DFP-02_SE_07; 8281783
Study report location: EDR
Conducting laboratory and location: [redacted]
Date of study initiation: April 17, 2013
GLP compliance: Yes
QA statement: Yes
Drug, batch #, and % purity:

Drug/Excipient/Vehicle	Batch #	% Purity
Vehicle without DDM	SUN-PP-15/153	-
[redacted] % DDM	SUN-PP-15/154	103.8
[redacted] % DDM	SUN-PP-15/155	102.6
[redacted] % DDM	SUN-PP-15/156	97.8
45 mg Sumatriptan without DDM	SUN-PP-15/151	98.8
Sumatriptan 45 mg with [redacted] % DDM	SUN-PP-15/152	98.9

Key Study Findings: The NOAEL for DDM was the HD.

NOAEL Exposure Values on Day 84 male/female			
Drug/Excipient	**mg/day**	**C_{max} ng/mL**	**$AUC_{(0-t)}$ ng*h/mL**
DDM	40 (HD)	137/270	181/321
Suma	90	1280/2450	3470/6080
DFP-02-DDM	1.2	6.07/8.26	4.88/10.7
Suma	90	1690/1410	3010/1770

Methods

Doses:	Vehicle (no DDM), [redacted] mg ([redacted]% DDM), 10 mg ([redacted]% DDM) , 40 mg ([redacted]% DDM), 90 mg Suma (no DDM), 90 mg Suma + [redacted] mg ([redacted]% DDM)
Frequency of dosing:	Daily
Route of administration:	Intranasal (each nostril via the [redacted] [redacted]
Dose volume:	200 µL/dose (100 µL/nostril)
Formulation/Vehicle:	Citric acid, monobasic potassium phosphate, di basic sodium phosphate, [redacted] and water.
Species/Strain:	Dog/beagle
Number/Sex/Group:	Tox: 3/sex/group; recovery: 2/sex/C, LD (DDM), HD (DDM), and Suma + DDM
Age:	At dosing initiation: 28 to 32 weeks old
Weight:	At dosing initiation: 5.2 to 8.9 kg
Satellite groups:	Recovery Period
Unique study design:	None
Deviation from study protocol:	There were minor deviations, with no impact on study validity.

Observations and Results

The toxicity of daily intranasal administration (13 weeks) of 0, 1.2, 10, or 40 mg/day DDM or 90 mg sumatriptan only or 90 mg sumatriptan + [redacted] mg DDM were assessed in dog. All animals survived to scheduled necropsy. Salivation was observed in both control and treated animals; however, the incidence and severity frequently increased with increasing DDM administration. Dilated pupils with reduced pupillary response were seen post-dose in sumatriptan only and sumatriptan + DDM animals. These findings resolved during the recovery period. There were no excipient- or drug-related effects observed on body weight, food consumption, ophthalmoscopy, ECG, hematology (standard battery), coagulation (prothrombin time and activated partial thromboplastin time), clinical chemistry (standard battery), urinalysis, gross pathology, or organ weight assessments. The histological examinations included an adequate battery of tissues for all animals. There were no excipient- or drug-related findings.

Sumatriptan exposure (C_{max} and AUC) was either unaffected or lower with co-administration of DDM (single or repeated dosing). When DDM was administered alone, exposure increased greater than dose proportionally up to 10 mg/kg and increased dose proportionally at 40 mg/kg. When DDM was administered with sumatriptan, exposure values were lower than with DDM alone. Repeat administration did not increase exposure of DDM, Suma, or Suma + DDM.

(Based on Pharmacology/Toxicology IND Review and Evaluation, IND 108088, D. Charles Thompson, Ph.D., April 10, 2015)

Study title: DFP-02: 39 Week Intranasal Administration Toxicity Study in the Dog Followed by a 4-Week Treatment-free Period

Study no.: DFP-02_SE_09; 8281784
Study report location: EDR
Conducting laboratory and location: (b) (4)

Date of study initiation: April 04, 2013
GLP compliance: Yes
QA statement: Yes
Drug, batch #, and % purity:

Drug/Excipient/Vehicle	Batch #	% Purity
Vehicle without DDM	SUN-PP-35/014	-
Vehicle without DDM	SUN-PP-20/014	-
Vehicle without DDM	SUN-PP-15/153	-
(b) (4) DDM	SUN-PP-35/015	103.7
DDM	SUN-PP-20/042	100.7
DDM	SUN-PP-15/154	103.8
(b) (4) % DDM	SUN-PP-20/043	97.6
% DDM	SUN-PP-15/155	102.6
% DDM	SUN-PP-35/016	102.6
(b) (4) % DDM	SUN-PP-35/001	101.5
% DDM	SUN-PP-20/052	104.0

[redacted] % DDM	SUN-PP-20/044	100.3
[redacted] % DDM	SUN-PP-15/156	97.8
45 mg Suma	SUN-PP-35/002	102.2
45 mg Suma	SUN-PP-20/045	97.7
45 mg Suma	SUN-PP-15/151	98.8
Suma 45 mg + [redacted] % DDM	SUN-PP-35/017	102.6
Suma 45 mg + [redacted] % DDM	SUN-PP-20/046	98.4
Suma45 mg + [redacted] % DDM	SUN-PP-15/152	98.9

Key Study Findings: The NOAEL for DDM was the HD.

NOAEL Exposure Values on Day 269 male/female			
Drug/Excipient	**mg/day**	**C_{max} ng/mL**	**$AUC_{(0-t)}$ ng*h/mL**
DDM	40 (HD)	44.2/69.6	53.9/84.4
Suma	90	1750/1750	3660/4850
DFP-02-DDM	1.2	1.2/4.66	2.52/5.89
Suma	90	1040/1630	2970/3330

Methods

Doses:	Vehicle (no DDM), (b) (4) mg ((b) (4)% DDM), 10 mg (b) (4)% DDM), 40 mg ((b) (4)% DDM), 90 mg Suma (no DDM), or 90 mg Suma + (b) (4) mg ((b) (4)% DDM)
Frequency of dosing:	Daily
Route of administration:	Intranasal (each nostril via the (b) (4) (b) (4)
Dose volume:	200 µL/dose (100 µL/nostril)
Formulation/Vehicle:	Citric acid, monobasic potassium phosphate, di basic sodium phosphate, (b) (4) and water.
Species/Strain:	Dog/beagle
Number/Sex/Group:	Tox: 3/sex/group; recovery: 2/sex/C, LD (DDM), HD (DDM), and Suma + DDM
Age:	At dosing initiation: 26 to 31 weeks old
Weight:	At dosing initiation: 5.45 to 9.75 kg
Satellite groups:	Recovery period
Unique study design:	None
Deviation from study protocol:	There were minor deviations, with no impact on study validity.

Observations and Results

All animals survived to scheduled necropsy. Salivation was observed in both control and treated animals. Dilated pupils with reduced pupillary response was seen post-dose in sumatriptan only and sumatriptan + DDM animals. These findings resolved during the recovery period. There were no excipient- or drug-related effects observed on body weight, food consumption, ophthalmoscopy, ECG, hematology (standard battery), coagulation (prothrombin time and activated partial thromboplastin time), clinical chemistry (standard battery), urinalysis, gross pathology, or organ weight assessments. The histological examinations included an adequate battery of tissues for all animals. In animals administered DDM, minimal to slight squamous cell metaplasia in the respiratory epithelium of the nasal cavity and nasopharyngeal ducts was observed, which did not fully resolve during the recovery period.

Sumatriptan exposure (C_{max} and AUC) was generally unaffected by co-administration of DDM (single or repeated dosing). When DDM was administered alone, exposure increased dose proportionally in males and greater than dose proportionally up to 10 mg/kg in females. At 40 mg/kg in females, exposure increased dose proportionally. When DDM was administered with sumatriptan, exposure values were similar to DDM alone. Repeat administration of DDM only or DDM + sumatriptan lowered DDM exposure. Repeat administration of sumatriptan only or sumatriptan +DDM showed no difference in sumatriptan exposure values.

(Based on Pharmacology/Toxicology IND Review and Evaluation, IND 108088, D. Charles Thompson, Ph.D., April 10, 2015)

Study title: Dose Rang-Finding study for: "Dodecyl Maltoside Rat Micronucleus Test"

Study no.: 963116
Study report location: EDR
Conducting laboratory and location: [redacted]
Date of study initiation: January 4, 2011
GLP compliance: Yes
QA statement: Yes
Drug, lot #, and % purity:

Drug	Lot #	% Purity
DDM	P21/148/010	99.0

Key Study Findings: The NOAEL for DDM was at 200 mg/kg.

Methods

Doses: DDM: 20, 50, 200, 1000, or 600 mg/kg
Frequency of dosing: 20 and 1000 mg/kg: single dose
50, 200, and 600 mg/kg: Day 1 and 8.
Route of administration: Intravenous infusion over 24 hours
Dose volume: 3 mL/kg/h
Formulation/Vehicle: [redacted] % Sodium Chloride for Injection (USP)
Species/Strain: Rat, (SD)
Number/Sex/Group: 2/sex/group
Age: At dosing initiation: M: 13 weeks; F: 9 weeks
Weight: At dosing initiation: M: 227 to 334 g; F: 171 to 232 g
Satellite groups: None
Unique study design: None
Deviation from study protocol: There were minor deviations, with no impact on study validity.

Observations and Results

Mortality

Animals were observed twice a day.

All animals survived to scheduled necropsy.

Clinical Signs

Detailed physical examinations were made during infusion and 15 minutes after infusion.

There were no DDM-related findings in the 20 or 50 mg/kg single dose animal. At 200 mg/kg during the first dosing in both sexes, there were observations of erect fur; in

males, partially closed eyes. During or after the first 600 and 1000 mg/kg doses, there were findings of decreased activity, cold to touch, partially closed eyes, slight uncoordination (females only at 600 mg/kg), red urine, and erect fur (1000 mg/kg).

Following the second 200 mg/kg dose in both sexes, there were observations of partially closed eyes and one male had decreased activity. Following the second 600 mg/kg dose, there were signs of slight uncoordination, partly closed eyes, and red urine and material in both males and females. Following the second 1000 mg/kg dose, both sexes had signs of decreased activity, partly closed eyes, erected fur, limited usage of limbs (in males only), slight uncoordination, and red urine and material. All findings resolved within two days of dosing.

Body Weights

Measurements were recorded daily for the 200, 600, and 1000 mg/kg groups.

There were no DDM-related findings.

Food Consumption, Ophthalmoscopy, and ECG

Not assessed.

Hematology

Samples were collected from the 200, 600, and 1000 mg/kg groups. A standard battery of parameters was assessed.

At 600 and 1000 mg/kg, there were dose-dependent decreases of up to 50% in absolute red blood cell counts, compared to the 200 mg/kg group. Additionally, there was decreased hemoglobin and hematocrit; higher MCV, MCH, and RDW; lower MCHC; and up to 2-fold higher percentage and absolute reticulocytes.

Finding		mg/kg		
		200	600	1000
RBC 10^6/µL	M	6.985	3.5	4.405
	F	6.65	3.7	3.95
Hb g/dL	M	12.8	6.85	8.75
	F	12.6	8	8.2
Ht %	M	36.8	23.75	27.85
	F	35.95	26.75	25.8
MCV fL	M	52.85	67.6	63.2
	F	54.05	72.1	65.3
MCH pg	M	18.4	19.45	19.9
	F	18.95	21.5	20.75
RDW %	M	15.75	26.5	24.5
	F	15.3	22.25	24.7
MCHC g/dL	M	34.85	28.85	31.5
	F	35.3	29.8	31.8
RETIC %	M	6.15	30.65	22.65
	F	7.05	25.5	20.2
RETIC x10^9/L	M	429.2	1076.35	951.65
	F	467.65	924.2	798.25

Coagulation

Prothrombin time, activated partial thromboplastin time, and fibrinogen were assessed.

There were no DDM-related findings.

Clinical Chemistry

A standard battery of parameters was assessed.

There were no DDM-related findings.

Urinalysis

Not assessed

Gross Pathology

At the infusion site, at 600 mg/kg, there was thickening in one female; at 1000 mg/kg, there was thickening in one male, swelling in one female; and a mass in one male.

In the spleen at 600 mg/kg, there was enlargement in one male and female; at 1000 mg/kg, there was enlargement in all animals.

Organ Weights

Not assessed

Histopathology

Not assessed:

Special Evaluation

None

Toxicokinetics

Not assessed

Dosing Solution Analysis

The mean concentrations of the dose preparations were within ± (b) (4) % of nominal.

DMF# (b) (4)

Study title: A Two-Week Repeat Dose Intranasal Toxicity Study of n-Dodecyl-β-D-Maltoside (with a Two-Week Recovery) in Rats

Study no.: 0437RA33.001; AF07-021
Study report location: EDR
Conducting laboratory and location: (b) (4)
Date of study initiation: July 23, 2007
GLP compliance: Yes
QA statement: Yes
Drug, batch #, and % purity:

Drug	Batch #		% Purity	
	Day 1	Day 13	Day 1	Day 13
Control	PS07-0963-001	PS07-0964-001	-	-
LD-DDM (b) (4) %, (b) (4) µg	PS07-0963-002	PS07-0964-002	97.1	99.8
MD-DDM (b) (4) %, µg	PS07-0963-003	PS07-0964-003	93.8	96.4
HD-DDM (b) (4) %, µg	PS07-0963-004	PS07-0964-004	96.9	97.3

Key Study Findings: The NOAEL for DDM was the MD.

Methods

Doses: Control, 80, 200, or 400 µg
Frequency of dosing: Every other day
Route of administration: Intranasal
Dose volume: (b) (4) uL ((b) (4) uL/ nostril)
Formulation/Vehicle: (b) (4)
Species/Strain:
Number/Sex/Group: Main Study: 10/sex/group; recovery: 5/sex/group
Age: At dosing initiation: 7 to 8 weeks old
Weight: At dosing initiation: 164-272 g
Satellite groups: Recovery
Unique study design: None
Deviation from study protocol: There were minor deviations, with no impact on study validity.

Observations and Results

Mortality

Animals were observed twice a day.

There were no DDM-related deaths. One HD animal was euthanized after being accidently dropped.

Clinical Signs

Detailed physical examinations were made once on non-dosing days and twice on dosing days.

Sporadic noisy breathing was observed in MD and HD animals.

Body Weights

Measurements were recorded on Day 1(prior to dosing), 8, 14, 21 (recovery), and 27 (recovery).

There were no DDM-related findings.

Food Consumption

Consumption was measured weekly.

There were no DDM-related findings.

Ophthalmoscopy

All animals were examined prior to dosing and in the last week of dosing.

There were no DDM-related findings.

ECG

Not assessed

Hematology

A standard battery of parameters was assessed.

There were no DDM-related findings.

Coagulation

Prothrombin time and activated partial thromboplastin time were assessed.

There were DDM-related findings.

Clinical Chemistry

Blood samples were taken prior to dosing, on Day 15, and at the end of the recovery period (Day 29). A standard battery of parameters was assessed.

There were no DDM-related findings.

Urinalysis

Not assessed

Gross Pathology

There were no DDM-related findings.

Organ Weights

There were no DDM-related findings.

Histopathology

Adequate Battery: Yes

Signed pathologists report: Yes

Peer Review: No

Histological Findings

At the MD and HD in both sexes, there was minimal to moderate nasal cavity inflammation, which was characterized by infiltrates of neutrophils in the epithelium. One HDM had nasal epithelial hyperplasia and necrosis which were an extension of inflammation. One HDM and 2 HDF had areas of epithelial degeneration. There were no DDM-related findings in the recovery animals.

Special Evaluation

No

Toxicokinetics

Not assessed

Dosing Solution Analysis

The mean concentrations of the dose preparations were within ± (b) (4)% of nominal.

DMF# (b) (4)

Study title: An 8-day Intravenous Infusion (Once Weekly over 24 Hours) Dose Range-Finding Study of Dodecyl Maltoside in the Wistar Rat

Study no.:	504091; 815P10
Study report location:	EDR
Conducting laboratory and location:	(b) (4)
Date of study initiation:	November 02, 2010
GLP compliance:	No
QA statement:	Yes

Drug, lot #, and % purity:

Drug	Lot #	% Purity
Control	W0C23A0	-
DDM	P21/148/010	99.0

Key Study Findings: The NOAEL for DDM was the HD.

Methods

Doses:	Control or DDM: 1, 3, or 10 mg/kg/dose
Frequency of dosing:	Weekly (Day 1 and 8)
Route of administration:	Intravenous
Dose volume:	3 mL/kg/h
Formulation/Vehicle:	(b) (4) % Sodium Chloride for Injection (USP)
Species/Strain:	Rat, Crl: WI((b) (4)
Number/Sex/Group:	4/sex/group
Age:	At dosing initiation: 8 to 9 weeks old
Weight:	At dosing initiation: M: 278 to 329 g F: 199 to 258 g
Satellite groups:	None
Unique study design:	None
Deviation from study protocol:	There were minor deviations, with no impact on study validity.

Observations and Results

Mortality

Animals were observed twice a day.

There were no unscheduled animal deaths.

Clinical Signs

Observations were made daily.

There were no DDM-related findings.

Body Weights

Measurements were recorded on Days -5, -1, 3, 7, 9, and prior to necropsy.

There were no DDM-related findings.

Food Consumption

Measurements were recorded on Days -5, -1, 3, 7, and 9.

There were no DDM-related findings.

Ophthalmoscopy

Not assessed.

ECG

Not assessed.

Hematology

Samples were taken at necropsy (Day 10). A standard battery of parameters were assessed.

There were no DDM-related findings.

Coagulation

Prothrombin time and activated partial thromboplastin time were assessed.

There were no DDM-related findings.

Clinical Chemistry

There were no DDM-related findings.

Urinalysis

Not assessed.

Gross Pathology

There were no DDM-related findings.

Organ Weights

Not assessed.

Histopathology

Not assessed.

Special Evaluation

None

Toxicokinetics

Samples were taken on day 8.

Mean plasma levels of DDM in animals administered 1, 3, or 10 mg/kg were 63.9, 213.5, and 813.4 mg/mL, respectively. Plasma levels of the metabolite, dodecyl-glucopyranoside were below the LLOQ (15 ng/mL), except in one HD female (20 ng/mL).

Dosing Solution Analysis

The mean concentrations of the dose preparations were within ± (b) (4)% of nominal.

DMF# (b) (4)

Study title: 13-WEEK INTRANASAL TOXICOLOGY STUDY IN BEAGLE DOGS FOLLOWED BY A 4-WEEK TREATMENT-FREE PERIOD (Draft)

Study no.: 35837; ZT-015-TOX
Study report location: EDR
Conducting laboratory and location: (b) (4)
Date of study initiation: Could not locate
GLP compliance: No
QA statement: No
Drug, lot #, and % purity:

Drug	Lot #	% Purity
Vehicle	-	-
DDM	P21/96/026	99.4
Reference Benzalkonium chloride	1376818	-

Key Study Findings: The NOAEL for DDM was the HD.

Methods

Doses: Vehicle; DDM: (b) (4) (b) (4) or (b) (4) µg/nostril/day; or Benzalkonium chloride: (b) (4) µg/nostril/day
Frequency of dosing: Daily (alternating nostrils)
Route of administration: Intranasal
Dose volume: (b) (4) uL/nostril
Formulation/Vehicle: (b) (4)
Species/Strain: Dog, Beagle
Number/Sex/Group: DDM: 6/males/group; Vehicle: 4 males
Age: At dosing initiation: 7 to 10 months old
Weight: At dosing initiation: 9.1 to 10.5 kg
Satellite groups: None
Unique study design: Daily dosing in alternating nostril. 2 animals from the vehicle, MD, and HD were withheld from sacrifice until the end of the recovery period.
Deviation from study protocol: There were minor deviations, with no impact on study validity.

Observations and Results

Mortality

Animals were observed twice a day.

There were no unscheduled animal deaths.

Clinical Signs

Observations were made daily, which included an otoscope examination of the nasal tracts.

There were no DDM-related findings

Body Weights

Measurements were recorded weekly.

There were no DDM-related findings.

Food Consumption

Measurements were recorded daily.

There were no DDM-related findings.

Ophthalmoscopy

Not assessed.

ECG

Not assessed.

Hematology, Coagulation, Clinical Chemistry, and Urinalysis

Not assessed.

Gross Pathology

There were no DDM-related findings.

Organ Weights

There were no DDM-related findings.

Histopathology

The following tissues were assessed:

TISSUE PROCEDURE TABLE

Organs	Preservation of tissues	Microscopic examination
Macroscopic lesions	X	X
Nose (4 sections)	X	X
Esophagus	X	X
Lungs with bronchi	X	X
Trachea	X	X

Sponsor's table

Adequate Battery: No

Peer Review: Yes (no signature)

Signed pathology report: No

Histological Findings
There were no DDM-related findings.

Special Evaluation

None

Toxicokinetics

Not assessed.

Dosing Solution Analysis

Could not be found in the study report

DMF# (b) (4)

Study title: Dermal Irritation Study Following Two Weekly Subcutaneous Injections of Dodecyl Maltoside in the Rabbit

Study no.:	503595; 8020P10
Study report location:	EDR
Conducting laboratory and location:	(b) (4)
Date of study initiation:	February 9, 2010
GLP compliance:	Yes, except for the pathology peer review.
QA statement:	Yes, except for the pathology peer review.

Drug, lot #, and % purity:

Drug	Lot #	% Purity
Vehicle	W9H27C1	-
DDM	P21/148/010	99.0

Key Study Findings: A NOAEL for DDM was not identified.

Methods

Dose:	~5 mg/kg (30 mg/mL) or vehicle control
Frequency of dosing:	Day 1 and 8
Route of administration:	Subcutaneous
Dose volume:	(b) (4) mL
Formulation/Vehicle:	(b) (4) % Sodium Chloride for Injection, USP
Species/Strain:	New Zealand White Rabbit
Number/Sex/Group:	3/males
Age:	At dosing initiation: ~4 months old
Weight:	At dosing initiation: 2.4 to 2.8 kg
Satellite groups:	None
Unique study design:	A single dosing group administered to the left or right lumbar region, with the vehicle control administered contralaterally.
Deviation from study protocol:	There were minor deviations, with no impact on study validity.

Observations and Results

Mortality

Animals were observed twice a day.

There were no unscheduled animal deaths.

Clinical Signs

Observations were made twice daily and detailed observations made weekly.

There were no DDM-related findings

Body Weights

Measurements were recorded weekly.

There were no DDM-related findings.

Food Consumption

Not assessed.

Ophthalmoscopy

Not assessed.

ECG

Not assessed.

Hematology

Blood was collected prior to necropsy. The following parameters were examined: blood cell morphology, erythrocyte indices (MCV, MCH, and MCHC), hematocrit, hemoglobin, platelet count, red blood cell count, reticulocytes (absolute and percent), and white blood cell count (total, absolute, and percent differential).

There were no DDM-related findings.

Coagulation, Clinical Chemistry, and Urinalysis

Not assessed.

Gross Pathology

There were no DDM-related findings.

Organ Weights

Not assessed.

Histopathology

The following tissue was preserved: injection sites with skin and underlying tissues (site of injection was accordingly identified to correlate to dosing occasion).

Adequate Battery: No

Peer Review: Yes (non-GLP and non-QA)

Signed pathology report: Yes

Histological Findings:
There was minimal to marked subacute inflammation in the dermis and/or subcutis of all 6 DDM injection sites, which was often accompanied by myofiber degeneration.

Special Evaluation

None

Toxicokinetics

Not assessed.

Dosing Solution Analysis

The mean concentrations of the dose preparations were within ± (b) (4)% of nominal.

DMF# (b) (4)

Study title: 1-O-N-DODECYL-ß-D-MALTOPYRANOSIDE: Contact Hypersensitivity in Albino Guinea Pigs, Maximization-Test

Study no.: C78787; 1001D10

Study report location: EDR

Conducting laboratory and location: (b) (4)

Date of study initiation: June 8, 2010

GLP compliance: Yes

QA statement: Yes

Drug, lot #, and % purity:

Drug	Lot #	% Purity
Vehicle	-	-
DDM	P21/148/010	99.6
Freund's Adjuvant	029K8708	-

Key Study Findings: A NOAEL for DDM was not identified.

Methods

Dose: DDM (b) (4)% or vehicle control (purified water)

Frequency of dosing: 3 applications (intradermal induction, epidermal induction, and epidermal challenge)

Route of administration: Epidermal

Dose volume: (b) (4) mL

Formulation/Vehicle: Purified water

Species/Strain: Albino Dunkin Hartley Guinea Pig

Number/Sex/Group: DDM: 10/males/group; control: 5/males/group

Age: Beginning of Acclimatization: ~5 weeks old

Weight: Beginning of Acclimatization: 285 - 351 kg

Satellite groups: None

Unique study design: None

Deviation from study protocol: Could not locate in the study report.

Observations and Results

Mortality

Animals were observed daily.

There were no unscheduled animal deaths.

Clinical Signs

Observations were made daily. Skin reaction assessments were performed after intradermal induction (test day 1), epidermal induction (test day 8), and after skin reaction challenge (day 22).

After epidermal induction, there were discrete/patchy to moderate/confluent erythema in all animals at the 24- and 48-hour time points. After challenge, there was no local skin reaction, indicating DDM does not sensitize the skin.

Body Weights

Measurements were recorded on the first day of treatment and at the termination of the study.

There were no DDM-related findings.

Food Consumption

Not assessed.

Ophthalmoscopy

Not assessed.

ECG

Not assessed.

Hematology, Coagulation, Clinical Chemistry, and Urinalysis

Not assessed.

Necropsy, Organ Weights, and Histopathology.

Not assessed

Special Evaluation

N/A

Toxicokinetics

Not assessed.

Dosing Solution Analysis

Could not located in study report.

7 Genetic Toxicology

7.1 *In Vitro* Reverse Mutation Assay in Bacterial Cells (Ames)

DMF# (b) (4)

Study title: Dodecyl Maltoside/A3: Bacterial Mutation Test

Study no.: 963114

Study report location: EDR

Conducting laboratory and location: (b) (4)

Date of study initiation: July 5, 2010

GLP compliance: Yes

QA statement: Yes

Drug, lot #, and % purity:

Drug	Lot #	% Purity
Vehicle	W0D01C2	-
DDM	P21/148/010	99.6

Methods

Strains: *S. typhimurium* TA1535 *his*G46 *rfa ΔuvrB*; *S. typhimurium* TA1537 *his*C3076 *rfa ΔuvrB*; *S. typhimurium* TA98 *his*D3052 *rfa ΔuvrB* pKM101; *S. typhimurium* TA100 *his*G46 *rfa ΔuvrB* pKM101; and *E. coli* WP2 *trp uvrA*

Concentrations in definitive study: Up to 5000 µg/plate ±S9

Basis of concentration selection: The standard limit of testing recommended by OECD

Negative control: Saline

Positive control: -S9: NaAz, 9AC, 2NF, and NQD.
+S: 2AA and BaP

Formulation/Vehicle: (b) (4)% Sodium chloride for injection USP

Incubation & sampling time: 48 to 72 h

Study Validity

Criteria:

- Mean revertant colony counts of the vehicle controls for each strain should lie close to or within the current historical control range of the laboratory.
- All positive control articles (with S9 mix where required) should produce increases in revertant colony numbers to at least twice the concurrent vehicle control levels with the appropriate bacterial strain (1.5× for strain TA100).

Results

- All dose formulations were within ± (b) (4)% of nominal, except for the (b) (4) and (b) (4) µg/mL doses, which were - (b) (4) and - (b) (4) of nominal, respectively.
- There were no increases in revertant colony counts following exposure to DDM; therefore, there is no evidence of genotoxic activity.

7.2 *In Vitro* Assays in Mammalian Cells

DMF# (b) (4)

Study title: Dodecyl maltoside/A3: Chromosome Aberration Test

Study no.: 963115

Study report location: EDR

Conducting laboratory and location: (b) (4)

Date of study initiation: July 8, 2010

GLP compliance: Yes

QA statement: Yes

Drug, lot #, and % purity:

Drug	Lot #	% Purity
Vehicle	W0D01C2	-
DDM	P21/148/010	99.6

Methods

Cell line: Human peripheral blood lymphocytes

Concentrations in definitive study: Up to 5000 µg/mL

Basis of concentration selection: The standard limit of testing recommended by OECD

Negative control: Saline

Positive control: -S9: MMC; +S9: CP

Formulation/Vehicle: Aqueous (b) (4)% sodium chloride for injection USP

Incubation & sampling time: Cultures were treated for 4 hours in the absence and presence of rat S9 mix and for 21 hours in the absence of S9

Study Validity

Criteria:

- The vehicle/negative control results should lie within or close to the historical control range.
- The positive control should produce a significant increase in the incidence of aberrant cells compared with the concurrent control.

Results

- All dose formulations were within ± (b) (4)% of nominal.
- DDM did not increase the proportion of aberrant metaphases; therefore, there is no evidence of genotoxicity.

7.3 *In Vivo* Clastogenicity Assay in Rodent (Micronucleus Assay)

DMF# (b) (4)

Study title: Dodecyl Maltoside Rat Micronucleus Test

Study no: 963116

Study report location: EDR

Conducting laboratory and location: (b) (4) (b) (4)

Date of study initiation: January 4, 2011

GLP compliance: Yes

QA statement: Yes

Drug, lot #, and % purity:

Drug	Lot #	% Purity
Vehicle (saline)	W0A04C1/W0K08A1/W0K09A0	-
DDM	P21/148/010	99
Positive control (Cyclophosphamide monohydrate)	079K1569	100

Methods

Doses in definitive study: 0 (vehicle), (b) (4) (DDM), or 20 (cyclophosphamide) mg/kg

Frequency of dosing: Single dose

Route of administration: Vehicle and DDM: IV over 24 h; cyclophosphamide: oral

Dose volume: Vehicle control and DDM: 3 mL/kg/h Cyclophosphamide: 10 mL/kg

Formulation/Vehicle: (b) (4)% Sodium Chloride for Injection (USP)

Species/Strain: Rat/Sprague-Dawely

Number/Sex/Group: 5/sex/group

Satellite groups: None

Basis of dose selection: A dose rang finding study

Negative control: Saline

Positive control: Cyclophosphamide monohydrate

Study Validity

Criteria:

- The incidence of micronucleated immature erythrocytes for the vehicle control group should fall close to or within the laboratory historical vehicle/negative control range.
- The positive control group should show a statistically significant increase in the incidence of micronucleated immature erythrocytes ($p \geq 0.01$).

Results

- All dose formulations were within ± (b) (4)% of nominal.
- DDM did not show any evidence of genotoxic activity in this in vivo test for induction of chromosome damage.

8 Carcinogenicity

Study title: 1-O-n-Dodecyl-b-D Maltopyranoside (Dodecylmaltoside/DDM): 104 Week Intranasal Administration Carcinogenicity Study in the Rat

Study no.: DFN-02-SE-11
Study report location: EDR
Conducting laboratory and location: (b) (4)
Date of study initiation: July 10, 2015
GLP compliance: Yes
QA statement: Yes
Drug, Batch #, and % purity: See sponsor's table below.
CAC concurrence: Yes

Delivery batch (date of receipt)	Sponsor Batch Number [a]	Test Article (% DDM)	Retest / Expiration Date [a]	Assay (%) [a]
1 (15 July 2015) [b]	DERCT-223/06-15	(b) (4)		
	DERCT-224/06-15			
	DERCT-225/06-15			
	DERCT-226/06-15			
2 (12 October 2015)	DERCT-240/09-15			
	DERCT-241/09-15			
	DERCT-242/09-15			
	DERCT-243/09-15			
3 (15 January 2016)	DERCT-251/12-15			
	DERCT-252/12-15			
	DERCT-253/12-15			
	DERCT-254/12-15			
4 (21 April 2016) [b]	DERCT-258/03-16			
	DERCT-259/03-16			
	DERCT-260/03-16			
	DERCT-261/03-16			
5 (18 July 2016)	DERCT-263/06-16			
	DERCT-264/06-16			
	DERCT-265/06-16			
	DERCT-266/06-16			

Delivery batch (date of receipt)	Sponsor Batch Number [a]	Test Article (% DDM)	Retest / Expiration Date [a]	Assay (%) [a]
6 (20 October 2016)	DERCT-276/09-16	[redacted]		
	DERCT-277/09-16			
	DERCT-278/09-16			
	DERCT-279/09-16			
7 (17 January 2017)	FRDCT-002/12-16			
	FRDCT-003/12-16			
	FRDCT-004/12-16			
	FRDCT-005/12-16			
8 (27 April 2017) [b]	FRDCT-007/04-17			
	FRDCT-008/04-17			
	FRDCT-009/04-17			
	FRDCT-010/04-17			

DDM = 1-O-n-Dodecyl-β-D Maltopyranoside.

a See Certificates of Analysis and Stability Summary.

b Samples of the 1st, 4th and 8th batches were analyzed for in-study confirmation of DDM content. See Formulations Analysis Report.

Methods

Doses:	0 (vehicle), 0.1, 0.3, 1.0, or 3.0 mg/animal/day
Frequency of dosing:	Once daily
Dose volume:	[redacted] µL/animal ([redacted] µL/nostril)
Route of administration:	Intranasal
Formulation/Vehicle:	Citric acid, monobasic potassium phosphate, dibasic sodium phosphate, [redacted] sodium chloride, and water.
Basis of dose selection:	Doses were selected based on previous studies of up to 26 weeks (also conducted at [redacted]) and based on recommendations by the FDA Carcinogenicity Assessment Committee.
Species/Strain:	Crl:CD(SD) rat
Number/Sex/Group:	55/sex/group
Age:	At dosing initiation: 6 to 7 weeks old
Animal housing:	Up to three animals of the same sex and group were housed together.
Paradigm for dietary restriction:	Animals had ad libitum access to SQC RAT Diet No. 1
Dual control employed:	Vehicle control only
Interim sacrifice:	None
Satellite groups:	None
Deviation from study protocol:	Minor deviations were noted, with no impact on study validity.

Observations and Results

Mortality

Animals were monitored twice daily.

Females administered DDM had survival rates similar to control, while males administered DDM had survival rates slightly higher than controls (see sponsor's table and figures).

Text Table 4.1: Incidence of Mortality

Sex	Males					Females				
Dose (mg/animal/day)	0	0.1	0.3	1	3	0	0.1	0.3	1	3
Total number of animals on study	55	55	55	55	55	55	55	55	55	55
Total number of decedent animals	36	27	26	19	27	35	37	36	34	33
Total number at terminal sacrifice [a]	19	28	29	36	28	20	18	19	21	22

a Final survival numbers taken from Day 685 (6th day of Week 98) for females and Day 708 (1st day of Week 102) for males.

Figure 8.1: Summary of Survival - Males

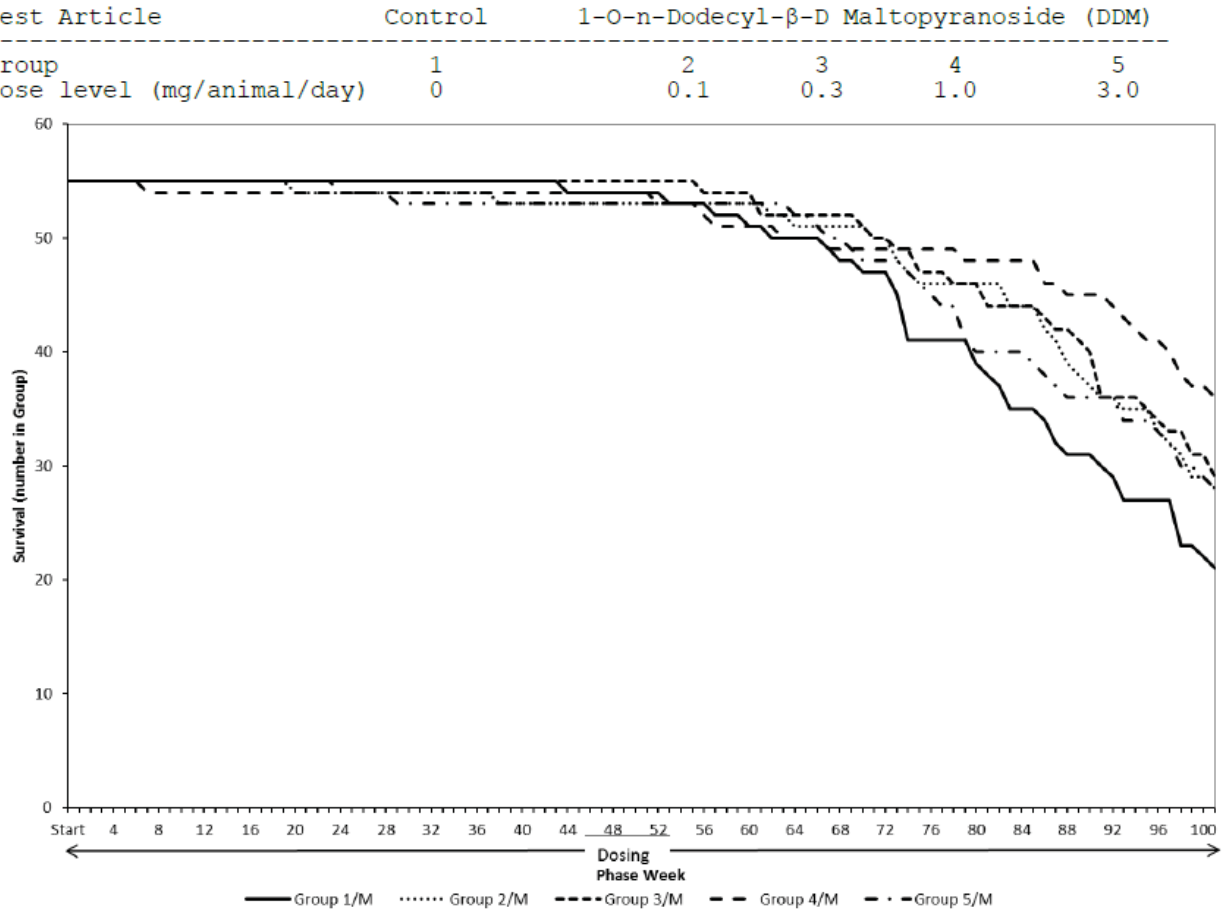
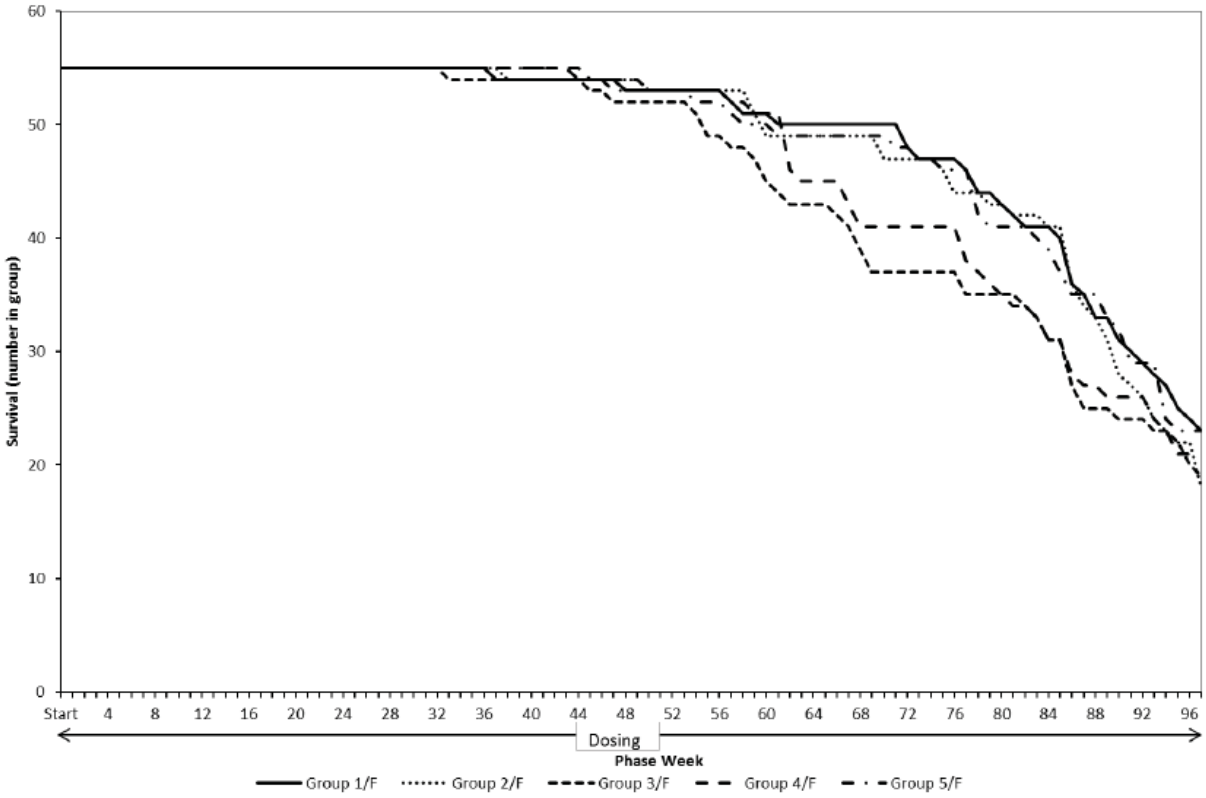


Figure 8.2: Summary of Survival - Females

Test Article	Control	1-O-n-Dodecyl-β-D Maltopyranoside (DDM)			
Group	1	2	3	4	5
Dose level (mg/animal/day)	0	0.1	0.3	1.0	3.0



Clinical Signs

Detailed physical examinations were made weekly.

There were no DDM-related findings.

Body Weights

Measurements were made weekly until Week 16, once every 4 weeks from Week 17 to 85, and then weekly from Week 86 until termination.

In males administered DDM, group mean body weights were 11 to 15% lower than control animals at the final weighing (Week 102), which was attributed to fewer control animals surviving to scheduled necropsy. There were no DDM-related differences in female animals.

Figure 8.3: Summary of Body Weight - Males

Test Article	Control	1-O-n-Dodecyl-β-D Maltopyranoside (DDM)			
Group	1	2	3	4	5
Dose level (mg/animal/day)	0	0.1	0.3	1.0	3.0

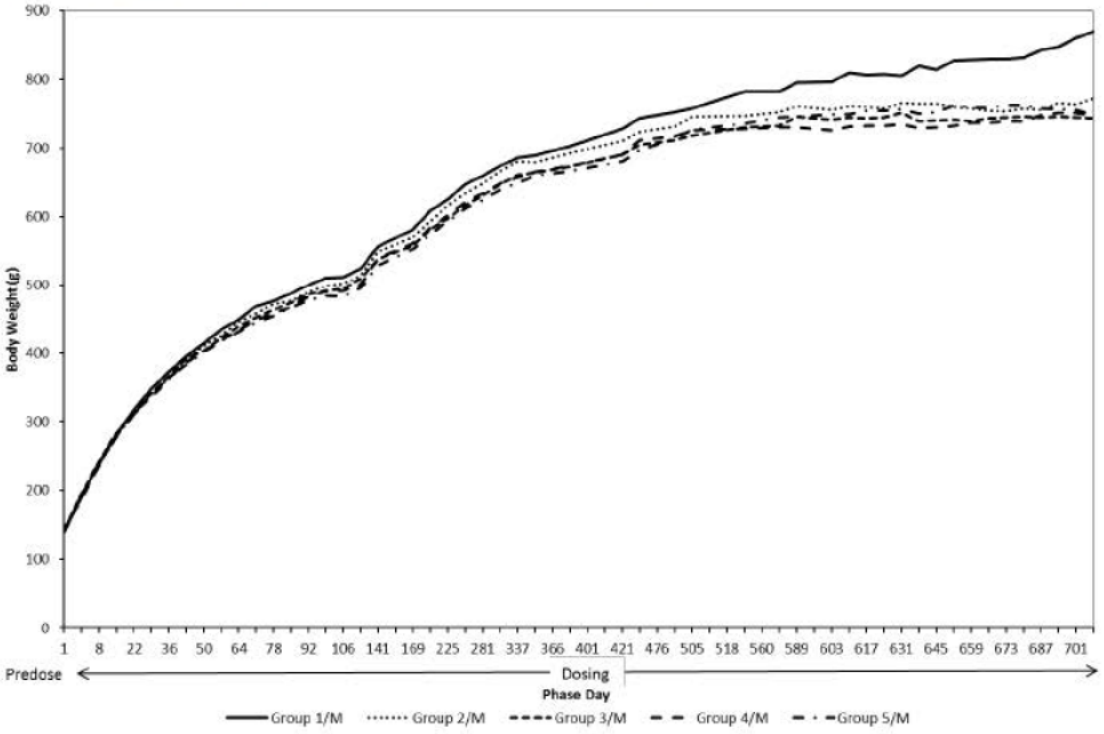
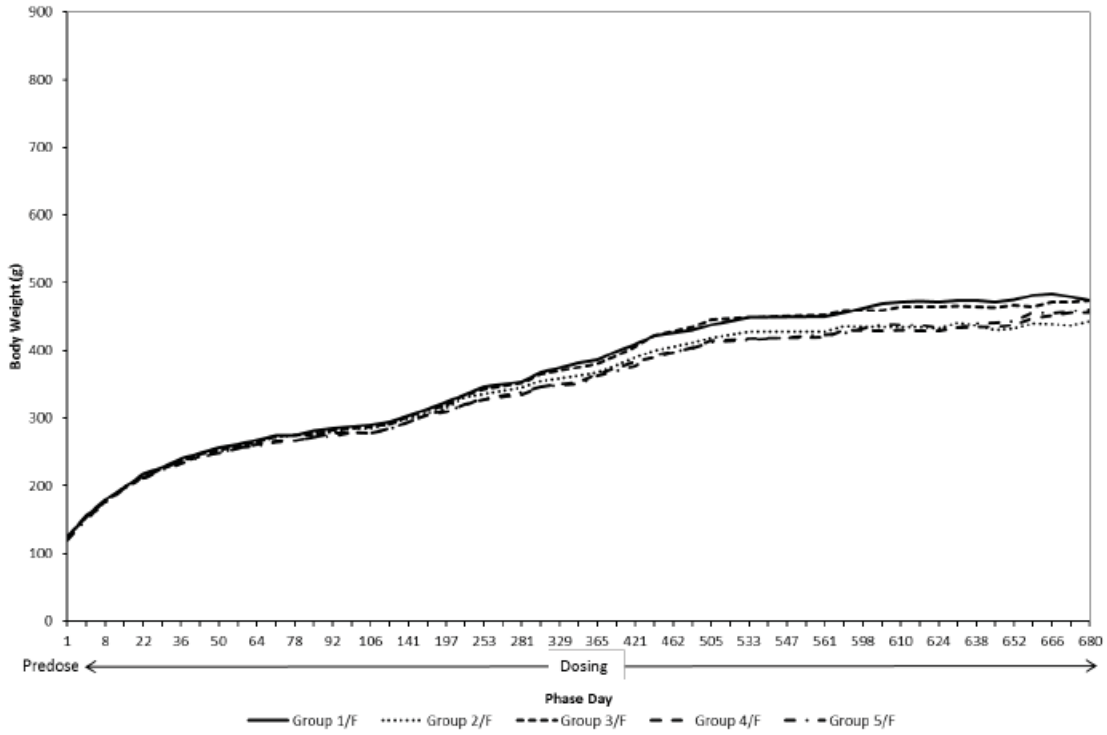


Figure 8.4: Summary of Body Weight - Females

Test Article	Control	1-O-n-Dodecyl-β-D Maltopyranoside (DDM)			
Group	1	2	3	4	5
Dose level (mg/animal/day)	0	0.1	0.3	1.0	3.0



Sponsor's figures

Food Consumption

Measured weekly

There were no DDM-related findings.

Ophthalmic examinations

Control and HD animals were examined during weeks 26, 52, 78, and 102.

There were no DDM-related findings.

Clinical chemistry

There were no DDM-related findings.

Gross Pathology

There were no DDM-related findings.

Histopathology

Complete battery: Yes

Peer Review: Yes

Signed pathology report: Yes

Neoplastic
The notable neoplastic lesions consisted of benign adrenal pheochromocytomas and benign dermal fibromas in ~10% of all DDM-dosed males and ~13% of HDM, respectively. In comparison, there were 0 and 2%, respectively, in the vehicle controls. There were also small increases (~4%) in malignant granulocytic leukemia in all male DDM groups, malignant sarcomas in the MDM and HDM, and malignant gliomas in the HDF. Statistical significance for both trend and pairwise comparison at the HD, was achieved in the benign dermal fibromas and the combined benign dermal fibroma + malignant sarcoma NOS.

Neoplastic Lesions – Males (n=55)							
Tissue	**Findings**	**mg/day**					
		Vehicle	**0.1**	**0.3**	**1.0**	**3.0**	**HC n=717**
Adrenal	Benign Pheochromocytoma	0	6	3	5	5	**104**
		-	10.91%* P=0.0285	5.45 %	9.09%* P=0.0048	9.09%* P=0.0331	**14.50% (^Range : 9.32 to 22.31%)**
	Malignant Pheochromocytoma	0	1	0	2	1	**19**
		-	1.82%	-	3.64%	1.82%	**2.65% (^Range : 1.01 to 6.15%)**
	Benign + Malignant pheochromocytoma	0	7	3	7	6	**123**
		-	12.73%* P=0.0117	5.45 %	12.73%* P=0.0158	10.91%* P=0.0188	**17.15%**
Haemolymph o-reticular system	Malignant-Granulocytic Leukemia	0	1	2	2	2	**-**
Skin/Subcutis	Malignant Sarcoma NOS	0	0	0	2	2	**12**
		-	-	-	3.64%	3.64%	**1.68% (^Range : 0 to 3.33%)**
	Benign Dermal fibroma	1	2	2	2	7	**56**
		1.82%* P=0.0049 (trend)	3.64%	3.64 %	3.64%	12.73%	**7.82% (^Range : 4.62 to 15%)**
	Benign Dermal fibroma + Malignant Sarcoma NOS	**1**	**2**	**2**	**4**	**4**	**68**
		0.9%* <0.001 (trend)	1.82%	1.82 %	5.45%	8.20%	**9.5%**

Neoplastic Lesions – Females (n=55)							
Tissue	Findings	mg/day					
		Vehicle	0.1	0.3	1.0	3.0	HC n=720
Brain	Malignant Glioma	0	0	0	0	2	5
		-	-	-	-	3.64	0.69% (^Range : 0 to 2%)
HC= Historical Control - collected from 104-week carcinogenicity studies conducted at the same testing facility ((b) (4)) in SD rats during the 7-year period (2007 to 2013) by different routes of administration without any diet restrictions. ^= Range (Minimum to Maximum) across individual studies calculated from the (b) (4) (b) (4). *= Statistically significant							

Non Neoplastic
In the nasal cavity, there was DDM-related minimal or slight squamous cell metaplasia in the transitional and/or respiratory epithelium.

Text Table 4.6: Incidence of Selected Findings; Upper Respiratory Tract - All Animals

		Males					Females				
		1M	2M	3M	4M	5M	1F	2F	3F	4F	5F
Tissue and finding	Level (mg/animal/day)	0	0.1	0.3	1	3	0	0.1	0.3	1	3
Nasal cavity	No. examined:	55	55	55	55	54	55	54	54	55	55
Squamous cell metaplasia, transitional epithelium	Grade -	52	22	8	4	4	35	7	1	3	1
	1	3	31	20	19	7	20	33	18	11	8
	2	-	2	27	32	43	-	14	35	41	46
Squamous cell metaplasia, respiratory epithelium	Grade -	54	53	45	42	44	55	53	44	38	24
	1	1	2	10	10	9	-	1	9	14	28
	2	-	-	-	3	1	-	-	1	3	3

Sponsor's table

In the liver, there was an increase in minimal to moderate bile duct hyperplasia in all DDM groups, compared to control animals. In the uterus, there was a minor non dose-related increase in squamous cell metaplasia and hyperplasia and a dose-related increase in squamous cysts.

Findings in the liver and uterus (n=55)										
Tissue	Male mg/day					Female mg/day				
	vehicle	0.1	0.3	1.0	3.0	vehicle	0.1	0.3	1.0	3.0
Liver: Bile duct - Hyperplasia	9	14	15	23	20	8	10	10	10	13
Uterus: Squamous - Cell Hyperplasia	-	-	-	-	-	9	18	7	14	17
Cell Metaplasia	-	-	-	-	-	7	13	8	14	10
Cyst	-	-	-	-	-	0	0	0	1	2

In the adrenal gland, there were minimal to moderate dose-related increases in medullary hyperplasia in males.

Adrenal Findings - at terminal kill										
Sex	Male					Female				
mg/day	vehicle	0.1	0.3	1.0	3.0	vehicle	0.1	0.3	1.0	3.0
Number of animals	19	28	29	36	28	20	18	19	21	22
Adrenal: Medullary hyperplasia	3	4	3	7	6	0	0	2	0	0

Toxicokinetics

None

Dosing Solution Analysis

All samples were within ± (b) (4) % of nominal.

9 Reproductive and Developmental Toxicology

9.1 Fertility and Early Embryonic Development

DMF# (b) (4)

Study title: Dodecyl Maltoside: Pilot investigation of the tolerance by continuous intravenous (24 hours per day) infusion in the pregnant Wistar rat.

Study no.: AA99567

Study report location: EDR

Conducting laboratory and location: (b) (4)

Date of study initiation: February 15, 2011

GLP compliance: Yes

QA statement: Yes

Drug, lot #, and % purity:

Drug	Lot #	% Purity
Control	-	-
DDM	P21/148/010	99.6

Key Study Findings: The HD was the NOAEL

Methods

Doses:	0 and 30 mg/kg/day
Frequency of dosing:	Daily, from day 6 to 17 of gestation (continuous infusion for 24 h).
Dose volume:	(b) (4) mL/hour
Route of administration:	Intravenous
Formulation/Vehicle:	Sterile physiological saline ((b) (4) % NaCl)
Species/Strain:	Rat/Wistar
Number/Sex/Group:	8/females/group
Satellite groups:	None
Study design:	Females were mated by the supplier and received by the testing facility on gestation day 0.
Deviation from study protocol:	Minor deviations were noted, with no impact on study integrity.

Observations and Results

Mortality

Animals were monitored twice daily.

There were no animal deaths prior to necropsy.

Clinical Signs

Observations were made twice daily.

There were no DDM-related findings.

Body Weight

Animal weights were recorded on gestation days 0, 6, 9, 12, 15, 18, and 20.

There were no DDM-related findings.

Food Consumption

Recordings were made during the following gestation day intervals: 0 to 6, 6 to 9, 9 to 12, 12 to 15, 15 to 18, and 18 to 20.

There were no DDM-related findings.

Toxicokinetics

Not assessed.

Dosing Solution Analysis

All samples were within ± (b) (4) % of nominal.

Necropsy

There were no DDM-related findings.

Fertility Parameters (pregnancy incidence, preimplantation data, post-implantation data, fetal body weight, fetal examinations and observations, soft tissue findings, skeletal observations)

There were no DDM-related findings.

11 Integrated Summary and Safety Evaluation

Introduction

Dr. Reddy's Laboratories Limited (DRL) has developed an intranasal (IN) formulation of sumatriptan, a 5-$HT_{1B/1D}$ receptor agonist, for the acute treatment of migraine with or without aura. The formulation is intended to improve the PK of sumatriptan by reducing T_{max}, compared to Imitrex nasal spray, by including 1-O-n dodecyl-β-D-maltopyranoside (DDM), [redacted]. For sumatriptan, DRL is relying on the findings of safety and efficacy of Imitrex subcutaneous injection (NDA-020080) via the 505(b)(2) pathway. For DDM, an unqualified excipient, safety is supported by an LOA to DMF [redacted] and the submitted nonclinical studies by DRL.

Pharmacology

Safety pharmacology studies were conducted in rat (6/males/group) testing single intranasal doses of 0 (+DDM), 5, or 15 mg sumatriptan with [redacted] mg [redacted]%) DDM. Collectively these studies assessed the central nervous (neurobehavioral assessment), respiratory, and gastrointestinal systems. There were no drug- or excipient-related neurobehavioral findings; respiratory assessments showed non dose-related increases in mean tidal volume at the MD and HD; gastrointestinal findings consisted of a slight delay (~11%) in mean intestinal transit and a ≤17% reduction in gastric emptying. Because none of the respiratory or gastrointestinal system findings were considered adverse, the NOAEL for these studies was the HD.

DMF [redacted]

Cardiovascular assessments were made in conscious telemetered dogs (4/males/group) testing single intranasal doses of 0 (+DDM), 15, 30, or 45 mg sumatriptan with [redacted]% DDM. Each animal received all doses, with a washout period of 6 days between doses. There were no drug-related findings; however, the positive control (moxifloxacin) increased QTc, as expected. The NOAEL was the HD. Sumatriptan was detected at 30 min in all animals dosed with DFP-02; however, no excipient (DDM) was detected. The plasma sumatriptan levels were highly variable.

Pharmacokinetics

Validation and determination of DDM and sumatriptan levels in rat, dog, and monkey plasma were made using liquid chromatography coupled with tandem mass spectrometric detection (LC-MS/MS). In monkey, information on the upper and lower limits of quantification could not be located in the submission.

In monkeys (4/sex/group), the PK following IN administration of DDM ([redacted]%, [redacted] mg/kg) and sumatriptan [redacted] mg/kg) and IV administration of DDM ([redacted]%, [redacted] mg/kg) on Days 1 and 8 was assessed using a crossover design. There were no sex differences in the PK data. For sumatriptan, T_{max} and half-life were ~ 5 min and 2.3 hours, respectively. For DDM, T_{max} and half-life were 0.5 (IN) and 0.6 (IN and IV) hours, respectively, and bioavailability (IN) was ~3.9%.

In rats, an IN PK study was conducted to assess 2 DFN-02 formulations. Eight animals/sex/group were used in the study; however, blood samples from 2 animals were pooled to give 4/sex/group. The PK of the DFN-02 to be marketed [redacted] and prototype DFN-02 [redacted] formulations were as

formulation produced sumatriptan and DDM C_{max} and AUC values that were comparable to the prototype formulation. The addition of DDM increased sumatriptan C_{max} and AUC values ~7- and 1.4-fold, respectively, and reduced T_{max} by between ~4 and 13 minutes. Sumatriptan C_{max} and AUC values were similar between sexes (F/M ranged from (b) (4) to (b) (4)). The to-be-marketed formulation was used in the subchronic and chronic toxicity studies (see study duration table in the **Toxicology** section).

In the DDM manufacture assessment, 12 rats/sex/group were used to assess the PK of A: (b) (4) manufactured by (b) (4) (b) (4) B: (b) (4) manufactured by (b) (4), or C: (b) (4) Sumatriptan and DDM exposure (C_{max} and AUC) values were generally higher in group A, compared to group B, with A/B exposure ratios ranging from (b) (4) to (b) (4). Sumatriptan exposure in group A and B were higher than group C. Based on these data DDM manufactured by (b) (4) (group A) was used in the subsequent studies.

DMF (b) (4)

The metabolic profile and tissue distribution of DDM following a single IN administration to male albino rats was assessed. DDM was rapidly metabolized to approximately 20 metabolites; one of the major metabolites was lauric acid. Autoradiograph tissue distribution studies showed the highest concentrations of radioactivity in the nasal mucosa at between 5 and 30 min post dose, with significant distribution to the stomach and intestine. In other tissues, exposure was very low, except for the liver and kidney. DDM was primarily excreted in the urine. C_{max} and $AUC_{0\text{-}24h}$ were highest in the liver at 37800 ng equiv/g and 306000 h*ng equiv/g, respectively. Half-life was approximately 8 hours in blood and plasma and 6 hours in the liver.

Toxicology

Intranasal administration of DDM was assessed in acute, subchronic, and chronic toxicology studies conducted in Sprague-Dawley rat and Beagle dog. In both species, the most common finding was minimal to slight squamous metaplasia of the transitional and/or respiratory epithelium, which was observed at all DDM dose levels. Additionally, squamous epithelial hyperplasia in the nares was observed in the 13-week rat study. These findings nearly completely reversed by the end of the recovery periods. A Pathology Working Group (PWG) review was conducted to assess the potential impact of these findings on humans. The PWG considered whether these findings were adaptive or adverse, if they would be expected to reverse following cessation of dosing, and if they could progress to neoplastic changes. The PWG determined that the changes were not adverse and unlikely to lead to neoplasia with continued treatment.

In rat, atrophy of the olfactory epithelium was observed in some animals at 10 mg DDM/day only. The NOAEL was the DDM HD in all toxicity studies in both species. An assessment of embryofetal development was deemed unnecessary at the End of Phase 2 meeting because the circulating levels of DDM in patients were very low (below AUC (b) (4) ng•hr/mL).

DMF (b) (4)

However, a pilot study assessing the tolerance of DDM by continuous intravenous infusion in pregnant Wistar rats was submitted, which showed no DMM-related findings.

The TK assessments in the general toxicity studies showed no sex-related differences in exposure (C_{max} and AUC) in either species. DDM decreased the T_{max} (1- to 50-fold) and increased C_{max} (3- to 25-fold) of sumatriptan compared to sumatriptan alone. DDM exposure (C_{max} and AUC) generally increased approximately dose proportionally, except at the HD in rats, at which it increased less than dose proportionally. Repeat administration of DDM, sumatriptan, and DFN-02 did not result in systemic accumulation of DDM or sumatriptan. In both species DDM concentrations were low and cleared rapidly within 4 to 8 hours post-dose.

DDM Toxicology Study Dosing		
Test Article	mg/kg/day	
	Rat	Dog
Vehicle (-)DDM	0	0
LD + DMM	0.1	1.2
MD + DDM	0.3	10
HD + DDM	10	40
Sumatriptan	30	90
Sumatriptan + DDM	30+0.3	90+1.2

DDM Toxicity Study Duration	#/sex/group	
	Rat	Dog
Acute, 4-week	10	3
Subchronic, 13-week	10	3
Chronic, 26-week	15	-
Chronic, 39-week	-	4

Genotoxicity

DMF (b) (4)

The genotoxicity package consisted of *in vitro* Ames and chromosome aberration assays and an *in vivo* rat micronucleus assay; all conducted under OECD guidelines. All of these tests were negative.

Carcinogenicity

In a 104-week carcinogenicity study in rat (55/sex/group), DDM was administered intranasally at daily doses of 0 (vehicle), 0.1, 0.3, 1.0, or 3.0 mg/day. A survival analysis conducted by the CDER Office of Biometrics revealed no DDM-related increase in mortality. Histopathology evaluation conducted on a complete battery of tissues revealed no statistically significant increase in neoplasms according to CDER criteria.

There were non-neoplastic DDM-related findings consisting of minimal or slight squamous cell metaplasia in the transitional and/or respiratory epithelium of the nasal cavity in both sexes, minimal to moderate bile duct hyperplasia in the liver, in both sexes, minor non-dose-related increases in squamous cell metaplasia and hyperplasia, a dose-related increase in squamous cysts in the uterus, and minimal to moderate

dose-related increases in medullary hyperplasia in the adrenal gland in males. Additionally, males administered DDM had slightly lower mean body weights (11 to 15%) than control animals at Week 102.

Overall, the study findings indicate that DDM is not tumorigenic.

Summary

DNF-2 did not have any adverse effects in safety pharmacology or general toxicology studies and was negative in a 104-week carcinogenicity study. The nonclinical NDA package supports approval.

Safety Margins for Sumatriptan Based on nasal surface area (mg/cm²)				
Animal Study	**Duration**	**NOAEL**	**Margin**	**Findings**
Rat Toxicology	26-Week	HD = 30 mg (2.143 mg/cm²)	11x	Dose-related minimal to moderate squamous cell metaplasia of the respiratory epithelium and atrophy of the olfactory epithelium was observed in the nasal cavity, which partially resolved during the recovery period.
Dog Toxicology	39-Week	HD = 90 mg (0.407 mg/cm²)	2x	Minimal to slight squamous cell metaplasia in the respiratory epithelium of the nasal cavity and nasopharyngeal ducts.
Max human dose (b) (4)				

Safety Margins for DDM Based on nasal surface area (mg/cm²)				
Animal Study	**Duration**	**NOAEL**	**Margin**	**Findings**
Rat Toxicology	4-week	HD = 10 mg (0.714 mg/cm²)	191x	Minimal squamous cell metaplasia of the respiratory tract
Rat Toxicology	13-week	HD = 10 mg (0.714 mg/cm²)	191x	Minor squamous cell hyperplasia in males
Rat Toxicology	26-Week	HD = 10 mg (0.714 mg/cm²)	191x	Squamous cell metaplasia of the respiratory epithelium and atrophy of the olfactory epithelium was observed in the nasal cavity
Rat Carcinogenicity	104-Week	HD = 3 mg (0.214 mg/cm²)	57x	The data indicate that DDM is not tumorigenic
Dog Toxicology	4-week	HD = 40 mg (0.645 mg/cm²)	172x	Sneezing, sniffing, nose rubbing, nose licking, head shaking, and salivation. Minimal squamous metaplasia of the respiratory epithelium in the nasal passages
Dog Toxicology	13-week	HD = 40 mg (0.645 mg/cm²)	172x	Salivation
Dog Toxicology	39-Week	HD = 40 mg (0.645 mg/cm²)	172x	Minimal to slight squamous cell metaplasia in the respiratory epithelium of the nasal cavity and nasopharyngeal ducts
Max human dose: (b) (4)				

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