

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

211243Orig1s000

PRODUCT QUALITY REVIEW(S)

Recommendation: Approval

**NDA 211243
Review #1**

Drug Name/Dosage Form	Spravato (Esketamine) Nasal Spray
Strength	28mg
Route of Administration	Intranasal
Rx/OTC Dispensed	Rx
Applicant	Janssen Pharmaceuticals, Inc.

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
0000	09/04/2018	All
0010	10/17/2018	Micro
0019	11/21/2018	CDRH
0024	12/06/2018	Micro
0026	12/14/2018	Drug Substance
0029	12/18/2018	Micro
0031	12/20/2018	Process, Environmental Assessment
0032	12/31/2018	Drug Product
0034	01/09/2019	CDRH
0036	01/16/2019	Process
0039	02/01/2019	Drug Product

Quality Review Team

DISCIPLINE	PRIMARY REVIEWER	SECONDARY REVIEWER
Drug Substance	Rohit Tiwari	Su Tran
Drug Product	Stephanie Emory	Wendy Wilson-Lee
Process	Christina Capacci-Daniel	Ying Zhang
Microbiology	Jonathan Burgos	Elizabeth Bearr
Facility	Christina Capacci-Daniel	Ying Zhang
Environmental	James Laurenson	Ranaan Bloom
CDRH	Kathleen Fitzgerald	Alan Stevens
RBPM	Teshara Bouie	
ATL	David Claffey	

Quality Review Data Sheet

[IQA Review Guide Reference](#)

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status
(b) (4)	Type II		(b) (4)	Acceptable
	Type II		Acceptable	
	Type I		Acceptable	
	Type I		Acceptable	

B. Other Documents: *IND, RLD, or sister applications*

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
Referenced INDs	IND 58634 IND 114345 (b) (4)	Ketamine Injection Esketamine nasal spray (b) (4)

2. CONSULTS

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
CDRH	Complete	Acceptable	24 JAN 2019	Kathleen Fitzgerald

Executive Summary

I. Recommendations and Conclusion on Approvability

Recommend **approval** from a product quality perspective.

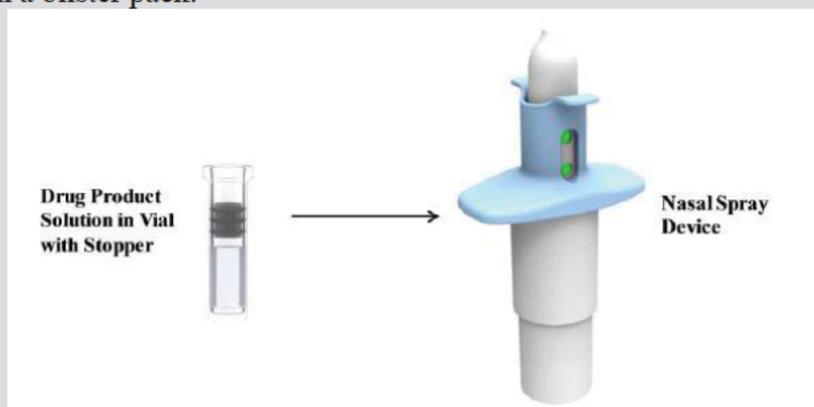
II. Summary of Quality Assessments

A. Product Overview

This application proposes the marketing of SPRAVATO (esketamine) nasal spray for the treatment of treatment-resistant depression (TRD) in adults.

The drug substance, esketamine hydrochloride is the S-enantiomer of ketamine. Racemic ketamine hydrochloride injection has been marketed as an anesthetic agent for several decades. Nasal administration was chosen for this product because it bypasses first-pass metabolism and is more convenient and less invasive than a typical IV ketamine administration.

Use of a 28 mg-strength drug/device combination product is proposed. Each device delivers two 14 mg-strength doses of esketamine. The labeled strength is based on esketamine base. Each device contains a solution of (b) (4) esketamine hydrochloride (equivalent to 32 (b) (4) mg of esketamine base). This represents a (b) (4) % overfill. Excipients include EDTA (b) (4), citric acid monohydrate (b) (4) Sodium hydroxide (b) (4) pH 4.5. The solution is contained within a (b) (4) glass vial with a rubber stopper within the nasal spray device. Each device is packaged in a blister pack.



The nasal spray device is a manually operated, disposable, single-use device that is designed to deliver two consecutive sprays, one to each nostril. Under the supervision of an HCP, the patient manually activates the device by pushing on the plunger with the thumb to deliver a spray. Thus, a single device delivers a total of 0.2 mL, or 32.3 mg of esketamine hydrochloride, equivalent to 28 mg of esketamine free base. Successful administration of each spray is indicated by each of two dots in the indicator window

changing color from green to white. The device does not require priming before use. Doses of up to 84 mg are proposed in the labeling. This would require the use of (b) (4) devices, with a 5-minute rest between use of each device. Labeling includes a Patient Information Sheet and Instructions for Use.

All excipients are compendial, and the primary container and device are constructed of commonly used materials for nasal spray products. The proposed commercial formulation (G005) was used in all Phase 2 and Phase 3 studies. The solution has higher osmolality (~1050 mOsm/kg) compared to typical nasal solution (600 mOsm/kg). However, this formulation was used in all clinical studies. Primary stability data supported the proposed expiry of 24 months at USP controlled room temperature.

2	 Total Number of Comparability Protocols
---	--

Proposed Indication(s) including Intended Patient Population	Treatment of Treatment-Resistant Depression in Adults	
Duration of Treatment	Induction Phase (weeks 1-4) Two treatment sessions/week: Starting Day 1 dose*: 56 mg Subsequent doses: 56 mg or 84 mg	Maintenance Phase Weeks 5-8: 56 mg or 84 mg once weekly From Week 9: 56 mg or 84 mg every 2 weeks or once weekly**
Maximum Daily Dose	84 mg (four devices)	
Alternative Methods of Administration	<i>None.</i>	

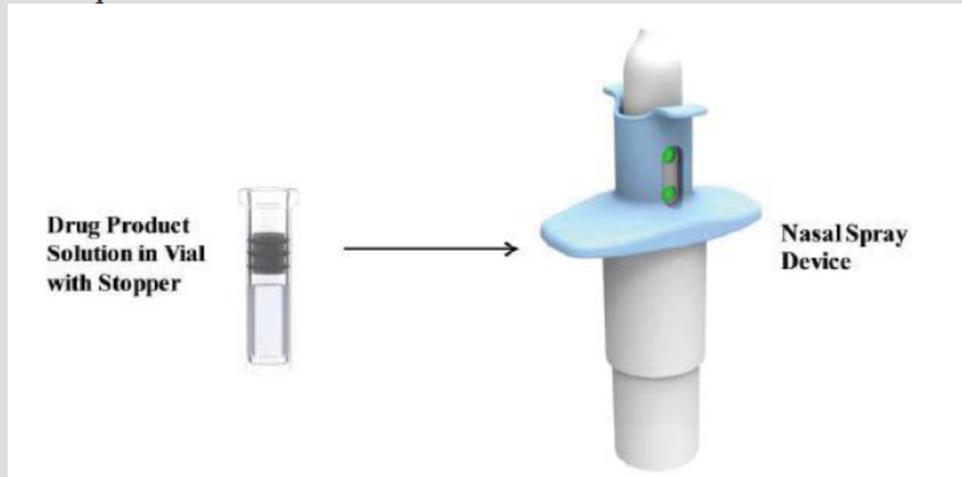
* Patients ≥65 years Day 1 starting dose is 28 mg
 ** Lowest frequency to maintain remission/response

B. Quality Assessment Overview

DRUG SUBSTANCE: The drug substance, esketamine hydrochloride, is white crystalline solid, consistently manufactured as a single (b) (4) It is the S-enantiomer ketamine. The manufacturing process involves (b) (4) starting material (b) (4) The applicant provided adequate (b) (4) data for all the impurities originated from the starting materials as per ICH Q11. This application proposes to employ drug substance manufactured by both the applicant and by (b) (4) Both sources were found acceptable and data adequately demonstrate their comparability.

The drug substance specification, analytical methods and their validation for esketamine HCl were found to be acceptable. The process derived impurities Impurity A, Impurity B, Impurity C are controlled to (b) (4)%, each. The R-enantiomer of the drug substance (Impurity D) has a NMT (b) (4)% limit. The proposed (b) (4)-month retest period was found acceptable.

DRUG PRODUCT: Use of a single 28 mg-strength drug product drug/device combination product is proposed. Each device delivers two 14 mg-strength doses of esketamine. The drug product strength is based on esketamine base. Each device contains a solution of (b) (4) mg esketamine hydrochloride (equivalent to 32 (b) (4) mg of esketamine base). This represents a (b) (4) % overfill. Excipients include EDTA (b) (4) (b) (4), citric acid monohydrate (b) (4). Sodium hydroxide (b) (4) pH 4.5. The solution is contained within a (b) (4) glass vial with a rubber stopper within the nasal spray device. Each device is packaged in a blister pack.



All excipients are compendial, and the primary container and device are constructed of commonly used materials for nasal spray products. (b) (4)

The proposed commercial formulation (G005) was used in all subsequent studies.

The solution has higher osmolality (~1050 mOsm/kg) compared to typical nasal solution (600 mOsm/kg). However, this formulation was used in all clinical studies.

The drug product, vials, and device were appropriately evaluated for elemental impurities and extractables/leachables. No significant risks were identified. The product is well-controlled by a combination of specifications for the filled vials and pre-assembled devices. No drug-product specific impurities or degradation products were identified, and no significant changes are observed on stability. The product was found to be stable across a range of long-term storage conditions from refrigerated (5°) to intermediate/high humidity (30°C/75%RH), as well as accelerated and stress conditions, including light exposure. Primary stability data supported the proposed expiry of 24 months at USP controlled room temperature.

Extractable and leachable studies were performed on the primary container closure (vial, stopper) and the device components that come in contact with the solution after

actuation (cannula, spray pin, and actuator). The results demonstrate that leachables do not present a significant safety risk.

The drug product specification is typical of a nasal spray device. Actuation force is not included in the release testing but stability data found no significant changes in batches through the 24 month expiry period.

Spray content uniformity, spray pattern, droplet size distribution and microbial purity are part of the drug product release and stability specification.

The claim for an exclusion from an environmental assessment was found acceptable.

Manufacturing: The drug product is manufactured (b) (4)

Adequate process development data were provided and the control strategy was found to be acceptable. The drug product manufacturing facility has experience with several similar marketed devices.

The proposed comparability protocol (CP) for (b) (4) vial filling and stoppering line was found to be acceptable; the completed CP for a second filling line will be reported in the Annual Report.

Microbiology: The drug product solution is sterile (b) (4)

the drug product vials. This was found to be acceptable by the Microbiology review team as the product is not designed to be sterile and had adequate microbial controls. The application was found acceptable from a microbiology perspective.

Device: The CDRH review found device performance acceptable, no issues with biocompatibility of the patient contacting components and found the drug product release specification acceptable from a device perspective.

Note: a biopharmaceutics review was not carried out on this product as the drug substance is in solution.

C. Special Product Quality Labeling Recommendations (NDA only)

None.

D. Final Risk Assessment (see Attachment)



David
Claffey

Digitally signed by David Claffey

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MICROBIOLOGY

[IQA Review Guide Reference](#)

Product Background:

NDA: 211243

Drug Product Name/Strength: SPRAVATO™
(Esketamine)

Route of Administration: Intranasal

Applicant Name: Janssen Pharmaceuticals, Inc.
1125 Trenton-Harbourton Road
Titusville, NJ 08560

Manufacturing Site: (b) (4)

Method of Sterilization:

Review Recommendation: Adequate

Theme (ANDA only): N/A

Justification (ANDA only): N/A

Review Summary:

List Submissions Being Reviewed:

Submit	Received	Review Request	Assigned to Reviewer
09/04/2028	09/04/2028	N/A	09/25/2018
10/17/2018			10/17/2018
12/06/2018			12/06/2018
12/18/2018			12/18/2018

Highlight Key Outstanding Issues from Last Cycle: N/A

Remarks: This NDA was submitted in E-CTD format.

Concise Description Outstanding Issues Remaining:

Supporting Documents: N/A

List Number of Comparability Protocols (ANDA only): N/A

S Drug Substance

N/A

Note to Reviewer: As instructed by the review team lead, the Microbiology Product Quality review was performed by evaluating information presented in Module 2.3 (Quality Overall Summary). When necessary, information within Module 3.2.P (Drug Product) was reviewed. For consistency, the established IQA Sections remained unchanged.

P.1 Description of the Composition of the Drug Product

(Information Located at: Sequence 0001 [09/04/2018], Section 2.3.P.1, Description and Composition of the Drug Product, Page 1; Section 2.3.P.3, Manufacture, Page 7/9)

SPRAVATO is a non-sterile spray solution. It will be packaged in a 28 mg/Vial (b) (4) configuration filled in (b) (4) glass vials (b) (4) (b) (4) single-use nasal spray device. See table below for drug product composition.

Ingredient	Quality Standard	Function	Quantity, mg/Device
Esketamine HCl	Company Specification	API	(b) (4)
Citric Acid Monohydrate	USP	(b) (4)	
Disodium Edetate			
Sodium Hydroxide	NF		
Water for Injection	USP		
Nasal Spray Device (including container closure of (b) (4) glass vial and rubber stopper)	Company Specification	Nasal Spray Delivery Device	1 Device

Reviewer's Assessment: The information provided by the applicant was adequate.

Acceptable

P.2 Pharmaceutical Development

N/A

P.2.5 Microbiological Attributes

N/A

Container/Closure and Package Integrity

N/A

Antimicrobial Effectiveness Testing

N/A

P.3 Manufacture

(b) (4)

(b) (4)

A.2.1 Materials of Biological Origin

N/A

A.2.2 Testing at Appropriate Stages of Production

N/A

A.2.3. Viral Testing of Unprocessed Bulk

N/A

A. 2.4 Viral Clearance Studies

N/A

R Regional Information

Executed Batch Records

(Information Located at: Sequence 0002 [03/26/2018], Section 3.2.R, Regional Information, Batch Records DP 161185, Batch Records DP 161191, and Batch Records DP 161192)

Executed lot #(s): Executed batch record summaries were available for exhibit batches 161185, 161891, and 161892. The batches were generated according to the proposed manufacturing parameters.

Reviewer's Assessment: The information provided by the applicant was adequate.

Acceptable

Comparability Protocols

N/A

2. REVIEW OF COMMON TECHNICAL DOCUMENT – QUALITY (CTD-Q) MODULE 1

2.A. Package Insert

(Information Located at: Sequence 0001 [09/04/2018], Section 1.14.1.3, Draft Labeling Text)

SPRAVATO™ is supplied in a single-use spray device containing a total of 0.2 mL of non-sterile esketamine hydrochloride solution. The proposed volume is equivalent to 28 mg of esketamine and covers the delivery of two nasal sprays, one for each nostril. Three different presentations of SPRAVATO are available, ranging from a carton containing one device (28 mg total dose) to a carton containing three individually packed devices (84 mg total dose). While excursions are permitted from 15-30°C, it is recommended that SPRAVATO is stored at 20-25°C. The proposed starting adult dose is 56 mg. Depending on the efficacy and tolerability to the drug product, the proposed dose can be increase up to a weekly or biweekly dose of 84 mg SPRAVATO. (b) (4)

Reviewer's Assessment: The information provided by the applicant was adequate.

Acceptable

Post-Approval Commitments:

N/A

Lifecycle Management Considerations

N/A

List of Deficiencies: N/A

Primary Microbiology Reviewer Name and Date:

Jonathan Burgos, Ph.D.
21 December, 2018

Secondary Reviewer Name and Date (and Secondary Summary, as needed):

Elizabeth Berr, Ph.D.
21 December, 2018



Jonathan
Burgos

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Elizabeth
Barr

Digitally signed by Elizabeth Barr
Date: 12/21/2018 02:04:21PM
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OFFICE OF DEVICE EVALUATIONDIVISION OF ANESTHESIOLOGY, GENERAL HOSPITAL,
RESPIRATORY, INFECTION CONTROL, AND DENTAL DEVICES**GENERAL HOSPITAL DEVICES BRANCH
INTERCENTER CONSULT MEMORANDUM**

Date	January 24, 2019
To	Hiren Patel, RPM, CDER/OND/ODEI/DPP
Requesting Division	CDER/OND/ODEI/DPP
From	Kathleen Fitzgerald CDRH/ODE/DAGRID/GHDB
Through (Team Lead)	Sarah Mollo, ICC Team Lead CDRH/ODE/DAGRID/GHDB
Through (Branch Chief)	CDR Alan Stevens CDRH/ODE/DAGRRID/GHDB
Subject	Consult for Submission NDA211243 ICCR2018-03519 ICC1800728
Recommendation	Device Constituents Parts of the Combination Product are Approvable

Digital Signature Concurrence Table

Reviewer	
Team Lead	
Branch Chief	

1. Submission Overview

Table 1. Submission Information	
ICCR # (Lead)	ICCR2018-03519
ICCR SharePoint Link	http://sharepoint.fda.gov/orgs/OSMP/ocp/ICRR/Lists/ICRR%20Forms/Item/displayifs.aspx?List=337aa2e9%2D7692%2D4a76%2Dada9%2Dae967ad4a69b&ID=3846&Web=703664f2%2D33ef%2D4c9f%2Da6f2%2De1f658e187f9
ICC tracking # (Lead)	ICC1800728
Submission Number	NDA 211243
Sponsor	Janssen Pharmaceuticals Inc
Drug/Biologic	Esketamine (Spravato)
Indications for Use	Treatment Resistant Depression
Device Constituent	Nasal Spray
Related Files	None

Table 2. Review Team				
CDER/CBER Lead Review Division	CDER/OND/ODEI/DPP			
Submission RPM	Hiren Patel			
Lead Device Reviewer	Kathleen Fitzgerald			
The CDRH review is being managed under ICC #: ICC1800728				
Below is a list of the Discipline Specific ICCR#, ICC# and CON#. The CON# are under ICC800728 in CTS.				
Discipline Specific Consults	Reviewer Name (Center/Office/Division/Branch)	ICCR #	ICC #	CON #
Biocompatibility	Jacqueline Gertz	ICCR2018-03527	ICC800728	CON1822636
Compliance	Isabel Tejero	ICCR2018-03519	ICC800728	CON1822278

Table 3. Important Dates	
Interactive Review Goal Dates	
1st round of Information Requests	October 2018
2nd Round of Information Requests	December 2018
Final Discipline Specific Memos Due	12-20-2018
Final Lead Device Review Memo Due	2-11-2018

Interim Due Dates	Meeting Date	Due Date
Filing	11-3-2018	
74-Day Letter	11-17-2018	
Mid-Cycle	12-15-2018	
Primary Review	2-11-2019	
Internal Meeting	N/A	
Safety Meeting	N/A	
Sponsor Meeting	N/A	
Written Feedback Due	N/A	

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2. PURPOSE/BACKGROUND

2.1. Scope

Purpose:

The goal of this memo is to provide a recommendation of the approvability of the device constituent of the combination product. This review will cover the following review areas:

- Device performance
- Biocompatibility of the patient contacting components
- Release specifications for the device constituent

This review will not cover the following review areas:

- Compatibility of the drug with the device materials
- Biocompatibility fluid path assessment, reviewed by CDER
- Human factors

CDER's consult request (9-11-2018): Review of the nasal spray device.

2.2. Prior Interactions

None

2.2.1. Related Files

2.3. Indications for Use

Combination Product	Indications for Use
Esketamine (Spravato)	Treatment Resistant Depression
Nasal Spray Device	Delivery of Drug Product

3. ADMINISTRATIVE

3.1. Documents Reviewed

Document Title	Date - Version	Location
NDA 211243	0001, 9-4-2018	GSR
NDA 211243	0034, 1-9-2019	GSR

4. DEVICE DESCRIPTION AND PERFORMANCE REQUIREMENTS

The following information was taken from Section 4 of Technical Summary Device Parts, under 3.2.R.2 in GSR.

The nasal spray device is a manually operated, disposable, single-use device that is designed to deliver two consecutive sprays, one to each nostril. Under the supervision of an HCP, the patient manually activates the device by holding the device in one hand, placing the tip into the first nostril until the nose rest touches the skin between the nostrils, and pushing on the plunger with the thumb to deliver a spray. Switching hands, the patient then places the tip into the second nostril until the nose rest touches the skin between the nostrils, and again pushes on the plunger to deliver the second spray. Thus, a single device delivers a total of 0.2 mL, or 32.3 mg of esketamine hydrochloride or 28 mg of esketamine free base. Successful administration of each spray is indicated by each of two dots in the indicator window changing color from green to white. The features of the nasal spray device are illustrated in [Figure 2](#).

Figure 2: Nasal Spray Device Features

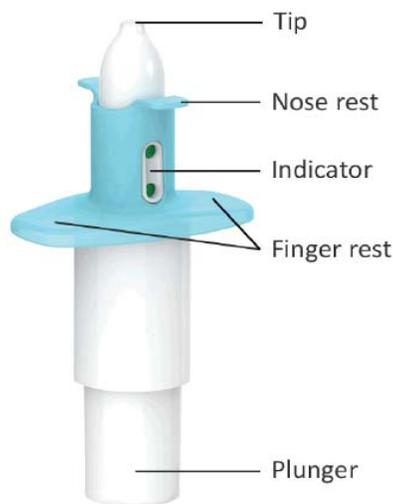
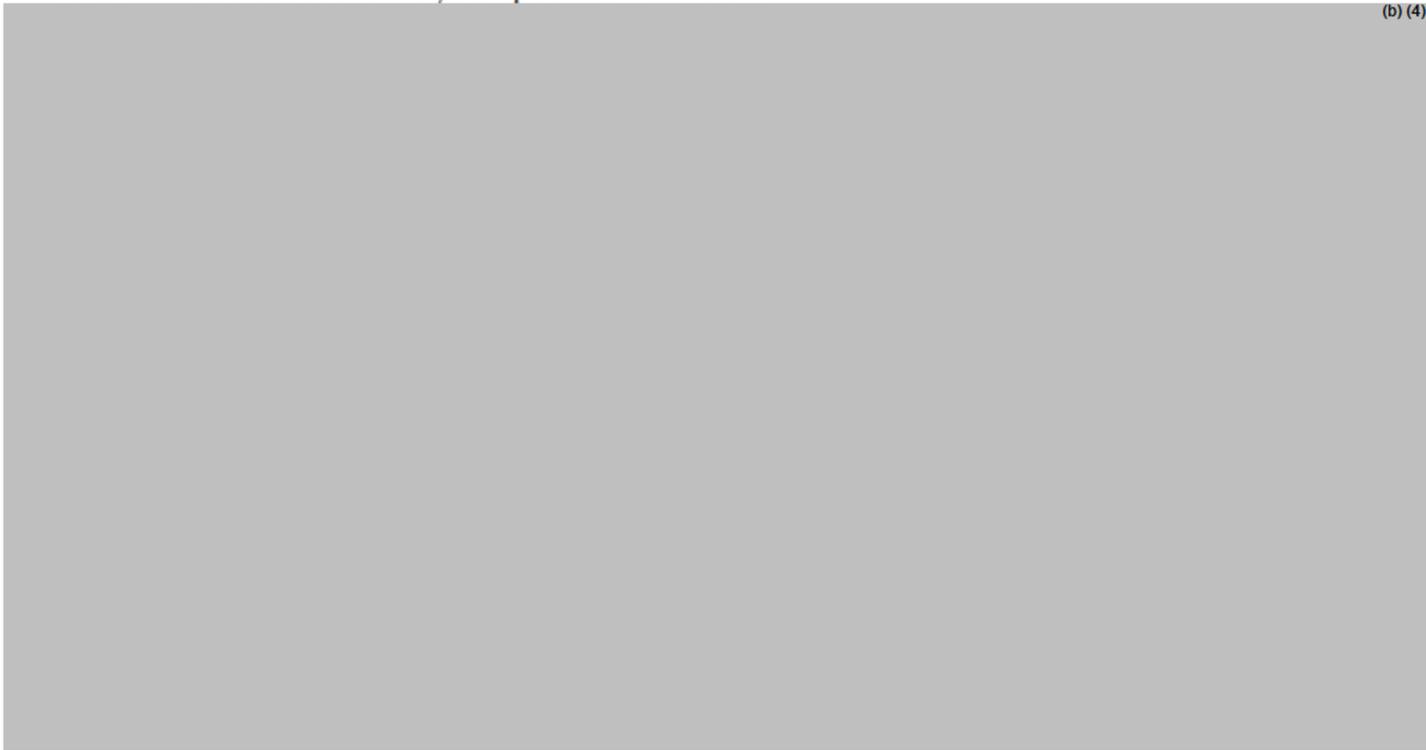


Table 2: Actuator Subassembly Components and Materials

(b) (4)



4 Page(s) have been Withheld in Full as b4 (CCI/TS) immediately following this page



5.1.1. Design Control Documentation Check

Design Control Requirement*	Signed/Dated Document Present		Submission Location
	Yes	No	
Design Requirements Specifications included in the NDA / BLA by the Combination Product Developer	X		3.2.P.5.1 in sequence 0001
Design Verification Data included in the NDA / BLA or adequately cross-referenced to a master file.	X		3.2.R in sequence 0001 and 0034
Risk Analysis supplied in the NDA / BLA by the Combination Product Developer	X		3.2.R.2 in sequence 0001 and 0034
Validation Data	X		3.2.R.2 in sequence 0001 and 0034
<ul style="list-style-type: none"> • Human factors • Clinical data 	X		
Traceability Documentation	X		3.2.R.2 in sequence 0001 and 0034

Table 24: Traceability Matrix for Nasal Spray Device Essential Performance Requirements

Essential Performance Requirement	Specification	Verification	Validation	Aging/ Stability (Y/N)	Shipping/ Transportation (Y/N)	Lot Release Testing (Y/N)
Manual Operation	See Section 3.2.P.5.1., Specifications	See Section 3.2.P.8.1, Stability Summary and Conclusion See Section 6.4 for results of Simulated Distribution Testing See Section 3.2.P.5.4 for Lot Release Testing	See Human Factors Study Validation Results, Section 10	Yes	Yes	Yes
Spray Content Uniformity by Weight	See Section 3.2.P.5.1., Specifications	See Section 3.2.P.8.1, Stability Summary and Conclusion See Section 6.4 for results of Simulated Distribution Testing See Section 3.2.P.5.4 for Lot Release Testing	Parameter validated via Design Verification; see also usability testing results in Human Factors Study Results, Section 10	Yes	Yes	Yes
Spray Pattern	See Section 3.2.R, Medical Device, Key Performance Requirements, Table 3 and 3.2.P.5.1., Specifications	See Section 3.2.R, Section 6.2 Functional Stability See 3.2.R., Section 6.4 for results of Simulated Distribution Testing See Section 3.2.P.5.4 for Lot Release Testing	Parameter validated via Design Verification	Yes	Yes	Yes

Table 24: Traceability Matrix for Nasal Spray Device Essential Performance Requirements

Essential Performance Requirement	Specification	Verification	Validation	Aging/Stability (Y/N)	Shipping/Transportation (Y/N)	Lot Release Testing (Y/N)
Droplet Size Distribution	See Section 3.2.R, Medical Device, Key Performance Requirements, Table 3 and 3.2.P.5.1., Specifications	See Section 3.2.P.8.1, Stability Summary and Conclusion See 3.2.R., Section 6.4 for results of Simulated Distribution Testing See Section 3.2.P.5.4 for Lot Release Testing	Parameter validated via Design Verification	Yes	Yes	Yes
Actuation Force	See Section 3.2.R, Medical Device, Key Performance Requirements, Table 3	See Section 3.2.R, Section 6.2 Functional Stability See 3.2.R., Key Performance Requirement Design Verification Report, DS-TEC-127742 See 3.2.R., Section 6.4 for results of Simulated Distribution Testing	Parameter validated via Design Verification	Yes	Yes	No

5.1.2. Design Control Review

6. DESIGN VERIFICATION AND VALIDATION REVIEW

6.1. Summary of Design V&V Attributes

Design Verification / Validation Attributes	Yes	No	N/A
Validation of essential requirements covered by clinical and human factors testing	X		
To-be-marketed device was used in the pivotal clinical trial			
Verification methods relevant to specific use conditions as described in design documents and labeling	X		
Device reliability is acceptable to support the indications for use (i.e. emergency use combination product may require separate reliability study)	X		
Traceability demonstrated for specifications to performance data	X		

Discipline -Specific Design Verification / Validation adequately addressed*						
	Consult needed			Consultant	Attributes Acceptable	
	Yes	No	N/A		Yes	No
Engineering (Materials, Mechanical, General)		X			X	
Biocompatibility	X			Jacqueline Gertz	X	
Sterility			X			
Software / Cybersecurity			X			
Electrical Safety / EMC			X			
Human Factors			X	Reviewed by DMEPA		

*Other discipline specific consults may be necessary based on product characteristics

Standards / Guidance Conformance		YES	NO	N/A
Conformance to Standards	ISO 11608-1:2014 – Needle based injection systems – Requirements and Test Methods			X
	ISO 11608-2:2012 – Needles			X
	ISO 11068-4:2006 – Electronic and Electromechanical Pen Injectors			X
	ISO 11608-5:2012 – Automated Functions			X
Adherence to FDA Guidance	Infusion Pumps Total Product Life Cycle – Guidance for Industry and FDA Staff (2014)			X
	Guidance for Industry and FDA Staff – Medical Devices with Sharps Injury Prevention Features (2005)			X
	Guidance for Industry and FDA Staff – Intravascular Administration Sets Premarket Notification Submissions (2008)			X
	Guidance for Industry and FDA Staff: Technical Considerations for Pen, Jet, and Related Injectors Intended for Use with Drugs and Biological Products (2013)			X
	Guidance for Industry Nasal Spray and Inhalation Solution,	X		

	Suspension, and Spray Drug Products — Chemistry, Manufacturing, and Controls Documentation (2002)			
	Guidance for Industry and FDA Staff: Current Good Manufacturing Practice Requirements for Combination Products (2017)	X		
	Mobile Medical Applications Guidance for Industry and Food and Drug Administration Staff (2015)			X

*This table does NOT include discipline specific Guidance / Standards that may be applicable to the review

The following table identifies any standards or relevant FDA guidance documents not listed in the above table that might be referenced by the sponsor or determined to be relevant by the CDRH / ODE reviewer in the course of the design review.

Reference Standard / Guidance	Description / Extent of FDA Recognition	Documentation Adequate	
		Yes	No
Referenced standards not listed in Table above	ISO 14971-Application of risk management to medical devices	X	
Reference FDA guidance not listed in Table above			

6.2. Design Validation Review

Design Validation Attributes	Yes	No	N/A
Phase I/II/III Study utilized the to-be-marketed device	X		
Bioequivalence Study utilized to-be-marketed device	X		
Simulated Actual Use Study utilized to-be-marketed device	X		

ICC800728

NDA 211243, Spravato, Nasal Spray

Janssen Pharmaceuticals Inc

Key Performance Requirement	Acceptance Criteria	Test Method	Sample Requirements
Spray Pattern	(b) (4)		
Droplet Size Distribution*			
Spray Content Uniformity by Weight			

(b) (4)

	<p>(b) (4)</p>
<p>Minimum and Maximum Actuation Force</p>	

<p>Device Manually Operated: The combination product is manually operated to deliver the content by pressing the plunger base toward the flange until it stops.</p>	<p>(b) (4)</p>
<p>Content Delivered through two manual actuations: The content of the device is delivered through two manual actuations, or sprays.</p>	
<p>Integrated indicator: Integrated spray indicator to indicate device is full, partially use, and empty</p>	

6.3. Design Verification Review

Table 8: Key Performance Requirements verified at (b) (4)

Requirement	Results	Pass/Fail
Spray pattern	(b) (4)	Pass
Droplet Size Distribution		Pass
Spray content uniformity by weight		Pass
Actuation Force		Pass

Requirement	Results	Pass/Fail
	(b) (4)	
Device Manually Operated Content Delivered through two manual actuations	All devices were tested for manual operation and content delivered through two manual actuations and meet the acceptance criteria.	Pass
Integrated indicator	All devices tested met the integrated indicator acceptance criteria.	Pass

N/A = not applicable due to one-sided limit.

Functional Stability testing:

Table 7: Functional Stability Results – Accelerated Conditions (40 °C/75RH)

Test	Timepoint (days) ^a						
	26 [3M]	53 [6M]	80 [9M]	105 [12M]	157 [18M]	210 [24M]	315 [36M]
	[Real-Time Equivalent in months (M)]						
	Spray Pattern – Dmin (mm)						
Samples	20	20	20	20	20	20	20
Mean	34	34	32	32	35	33	TBD
SD	2.4	2.4	2.1	1.8	3	2.4	TBD
Min	31	31	28	28	29	30	TBD
Max	40	39	35	36	42	38	TBD
Result	Pass	Pass	Pass	Pass	Pass	Pass	TBD
	Spray Pattern – Dmax (mm)						
Samples	20	20	20	20	20	20	20
Mean	43	43	42	42	43	42	TBD
SD	3.3	3.0	2.5	2.4	4	3.3	TBD
Min	39	39	37	38	38	37	TBD
Max	49	50	48	46	53	50	TBD
Result	Pass	Pass	Pass	Pass	Pass	Pass	TBD
	Spray Pattern – Ovality Ratio						
Samples	20	20	20	20	20	20	20
Mean	1.3	1.3	1.3	1.3	1.2	1.3	TBD
SD	0.05	0.08	0.10	0.1	0.1	0.05	TBD
Min	1.2	1.2	1.2	1.2	1.2	1.2	TBD
Max	1.4	1.4	1.6	1.6	1.4	1.4	TBD
Result	Pass	Pass	Pass	Pass	Pass	Pass	TBD
	Actuation Force (Maximum ^b) (N)						
Samples	20	20	20	20	20	20	20
Mean	43	42	41	42	41	43	TBD
SD	2.4	1.9	2.6	2.2	2.2	2.3	TBD
Min	38	38	37	38	36	38	TBD
Max	51	45	48	48	49	45	TBD
Result	Pass	Pass	Pass	Pass	Pass	Pass	TBD

^a For t = 0 results, see Design Verification Results, DS-TEC-127742

^b Only maximum actuation force evaluated because minimum actuation force is not stability-indicating

Table 8: Functional Stability Results – Zone 4 Condition (30 °C/75%RH)

Test	Time Points (months) ^a							
	1	3	6	9	12	18	24	36
Spray Pattern Dmin (mm)								
Samples	20	20	20	20	20	20	20	20
Mean	34	32	34	36	TBD	TBD	TBD	TBD
SD	2.1	3	2.6	2.3	TBD	TBD	TBD	TBD
Min	30	26	30	33	TBD	TBD	TBD	TBD
Max	37	37	39	42	TBD	TBD	TBD	TBD
Result	Pass	Pass	Pass	Pass	TBD	TBD	TBD	TBD
Spray Pattern Dmax (mm)								
Samples	20	20	20	20	20	20	20	20
Mean	44	42	42	45	TBD	TBD	TBD	TBD
SD	3.3	3.8	2.4	3.1	TBD	TBD	TBD	TBD
Min	39	38	39	41	TBD	TBD	TBD	TBD
Max	51	49	48	52	TBD	TBD	TBD	TBD
Result	Pass	Pass	Pass	Pass	TBD	TBD	TBD	TBD
Spray Pattern Ovality Ratio								
Samples	20	20	20	20	20	20	20	20
Mean	1.3	1.3	1.3	1.3	TBD	TBD	TBD	TBD
SD	0.06	0.1	0.1	0.05	TBD	TBD	TBD	TBD
Min	1.2	1.2	1.2	1.1	TBD	TBD	TBD	TBD
Max	1.4	1.6	1.4	1.3	TBD	TBD	TBD	TBD
Result	Pass	Pass	Pass	Pass	TBD	TBD	TBD	TBD
Actuation Force (Maximum)^b (N)								
Samples	20	20	20	20	20	20	20	20
Mean	45	43	42	40	TBD	TBD	TBD	TBD
SD	3.1	2.5	3.0	2.2	TBD	TBD	TBD	TBD
Min	39	39	38	38	TBD	TBD	TBD	TBD
Max	52	47	51	45	TBD	TBD	TBD	TBD
Result	Pass	Pass	Pass	Pass	TBD	TBD	TBD	TBD

^a For t = 0 results, see Design Verification Results, DS-TEC-127742

^b Only maximum actuation force evaluated because minimum actuation force is not stability-indicating

Table 9: Functional Stability Results – Normal (25 °C/40%RH) and Cold Storage (5 °C) Conditions

Test	Time Points (months) ^a							
	25 °C/40%RH				5 °C			
	6	12	24	36	6	12	24	36
Spray Pattern Dmin (mm)								
Samples	20	TBD	TBD	TBD	20	TBD	TBD	TBD
Mean	33	TBD	TBD	TBD	30	TBD	TBD	TBD
SD	1.7	TBD	TBD	TBD	1.7	TBD	TBD	TBD
Min	31	TBD	TBD	TBD	27	TBD	TBD	TBD
Max	36	TBD	TBD	TBD	33	TBD	TBD	TBD
Result	Pass	TBD	TBD	TBD	Pass	TBD	TBD	TBD
Spray Pattern Dmax (mm)								
Samples	20	TBD	TBD	TBD	20	TBD	TBD	TBD
Mean	41	TBD	TBD	TBD	38	TBD	TBD	TBD
SD	1.4	TBD	TBD	TBD	1.9	TBD	TBD	TBD
Min	37	TBD	TBD	TBD	35	TBD	TBD	TBD
Max	45	TBD	TBD	TBD	41	TBD	TBD	TBD
Result	Pass	TBD	TBD	TBD	Pass	TBD	TBD	TBD
Spray Pattern Ovality Ratio								
Samples	20	TBD	TBD	TBD	20	TBD	TBD	TBD
Mean	1.3	TBD	TBD	TBD	1.3	TBD	TBD	TBD
SD	0.1	TBD	TBD	TBD	0.1	TBD	TBD	TBD
Min	1.1	TBD	TBD	TBD	1.2	TBD	TBD	TBD
Max	1.4	TBD	TBD	TBD	1.5	TBD	TBD	TBD
Result	Pass	TBD	TBD	TBD	Pass	TBD	TBD	TBD
Actuation Force (Maximum ^b) (N)								
Samples	20	TBD	TBD	TBD	20	TBD	TBD	TBD
Mean	43	TBD	TBD	TBD	44	TBD	TBD	TBD
SD	2.2	TBD	TBD	TBD	2.8	TBD	TBD	TBD
Min	39	TBD	TBD	TBD	39	TBD	TBD	TBD
Max	49	TBD	TBD	TBD	51	TBD	TBD	TBD
Result	Pass	TBD	TBD	TBD	Pass	TBD	TBD	TBD

Nasal sprays were stored for two days at -20 °C followed by two days at 60 °C (1 cycle). Five cycles were executed. Storage condition between the cycles was 25 °C/60%RH (controlled room temperature). Following cyclic temperature variations, the functionality of the combination product was verified.

Table 10: Results of Stress Temperature Cyclic Study

Requirement	Results				Pass/Fail
	Unit #	% Target Weight			
Spray Content	1	100			
Uniformity by Weight (n = 10)	2	100			
	3	98			
	4	98			
	5	101			Pass
	6	102			
	7	99			
	8	98			
	9	99			
	10	101			
		Mean (n=10)	100		
Spray Pattern (n = 5)	Attribute	Dmin (mm)	Dmax (mm)	Ovality Ratio	
	Mean (x)	32.7	42.8	1.3	
	SD (s)	1.8	1.1	0.1	Pass
	Min	30.9	41.3	1.2	
	Max	35.0	44.1	1.4	
Droplet Size Distribution (n = 5)	Attribute	Dv(10) (µm)	Dv(50) (µm)	Dv(90) (µm)	%vol ≤10.0 µm
	Mean (x)	24.8	40.0	64.0	0.3
	SD (s)	2.9	1.4	3.3	0.6
	Min	20.4	38.5	61.0	0.0
	Max	28.5	41.7	68.7	1.5
Actuation Force (Maximum) (n = 5)	Attribute	Force (N)			
	Mean (x)	44			
	SD (s)	4.6			Pass
	Min	37			
	Max	49			

Table 11: Simulated Distribution Conditions

Test	Description
Schedule A Manual Handling	The samples are exposed to a series of six (6) free fall impacts per ASTM D4169. Drop height is determined by test sample weight.
Schedule F Loose Load Vibration	The samples are exposed to repetitive shocks using a vertical linear vibration system with a fixed displacement of one (1) inch. Dwell time is distributed 50% along normal vertical shipping axis and the remaining 50% evenly along all other possible shipping orientations. Total test duration = forty (40) minutes.
Schedule I Low Pressure (High Altitude)	The samples are exposed to a pressure equivalent of 14,000 ft. at ambient lab conditions, for a period of one (1) hour
Schedule E Vehicle Vibration	The samples are exposed to random vibration input. Dwell time is distributed among all possible shipping orientations. Total test duration = one hundred eighty (180) minutes of vibration input; sixty (60) minute Truck Profile followed by one hundred twenty (120) minute Air Profile.
Schedule A Manual Handling	The samples are exposed to the final series of six (6) free fall impacts per ASTM D4169. Drop height is determined by test sample weight

Table 12: Simulated Distribution Test Results – Intermediate Distribution (in WIP Trays)

Requirement	Results				Pass/Fail	
Manual Operation (n = 60)	Both dots on the indicator are green before actuation. Plunger base can be pressed towards the flange. After first actuation the lower dot is white the other one remains green. After second actuation both dots are white. If both dots are white, a third actuation of the device is not possible. With both actuations the content of the device is delivered in 2 sprays.				Pass	
Spray content uniformity by weight (n = 10)	Unit #	% Target Weight			Pass	
	1	99				
	2	97				
	3	100				
	4	99				
	5	99				
	6	100				
	7	100				
	8	99				
	9	99				
	10	98				
	Mean (n = 10)	99				
Spray pattern (n = 20)	Attribute	Dmin (mm)	Dmax (mm)	Ovality Ratio	Pass	
	Mean (x)	50	62	1.2		
	SD (s)	5.9	7.0	0.06		
	Min	38	52	1.2		
	Max	60	82	1.4		
Droplet Size Distribution (n = 20)	Attribute	Dv(10) (µm)	Dv(50) (µm)	Dv(90) (µm)	%vol ≤10.0 µm	Pass
	Mean (x)	21	36	61	1	
	SD (s)	1.3	1.3	2.8	0.5	
	Min	18	33	56	0	
	Max	24	38	67	2	
Actuation Force (n = 20)	Attribute	Maximum Actuation Force (N)			Pass	
	Mean (x)	41				
	SD (s)	1.8				
	Min	38				
	Max	45				

Table 13: Simulated Distribution Test Results – Final Distribution (in Secondary Packaging)

Requirement	Results				Pass/Fail	
Spray content uniformity by weight (n = 10)	Unit #	% Target Weight			Pass	
	1	99				
	2	99				
	3	100				
	4	98				
	5	100				
	6	100				
	7	97				
	8	98				
	9	99				
	10	97				
Mean (n = 10)		99				
Spray pattern (n = 20)	Attribute	Dmin (mm)	Dmax (mm)	Ovality Ratio	Pass	
	Mean (x)	43	51	1.2		
	SD (s)	4.3	4.9	0.06		
	Min	35	43	1.1		
	Max	49	59	1.4		
Droplet Size Distribution (n = 20)	Attribute	Dv(10) (µm)	Dv(50) (µm)	Dv(90) (µm)	%vol ≤10.0 µm	Pass
	Mean (x)	22	38	63	1	
	SD (s)	1.7	1.5	2.3	0.6	
	Min	20	36	59	0	
	Max	27	42	70	2	
Actuation Force (n = 20)	Attribute	Maximum Actuation Force (N)			Pass	
	Mean (x)	41				
	SD (s)	2.3				
	Min	36				
	Max	45				

Table 14: Drop Testing Results

Attribute	Volume Delivered in µL (% of Nominal Volume)	Result
Mean	199 (99.5%)	Pass
Minimum	195 (97.5%)	Pass
Maximum	204 (102%)	Pass

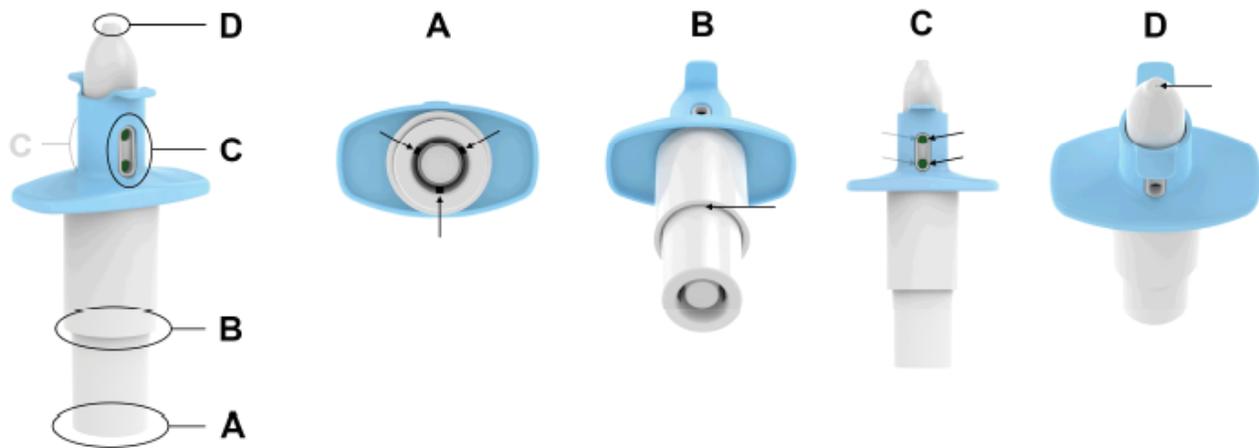
Reviewer's Comments: The verification and validation testing cover all essential performance requirements and the test results are acceptable.

7. DISCIPLINE SPECIFIC SUB-CONSULTED REVIEW

7.1. Discipline 1 Biocompatibility, reviewed by Jacqueline Gertz

Biocompatibility testing of the nasal spray device was conducted by an independent test laboratory in accordance with ISO 10993-1, Biological Evaluation of Medical Devices. Per the ISO standard, cytotoxicity, sensitization, and irritation/intracutaneous reactivity testing were performed in-line with classification as a skin contacting surface device having limited contact duration (<24 hours). Per ISO 10993-12, samples tested represented the commercial device in that they were constructed of the same materials and were manufactured and assembled using commercially representative processes. For each test, a single preparation of one test article and each of the controls were subjected to the extraction conditions as described below. The test article was not subdivided; portals to the inside of the device (indicated in Figure 10 below) were sealed with medical grade silicone and allowed to cure for at least 72 hours to ensure that only surfaces of the test article potentially in direct contact with the user were assessed.

Figure 10: Points of Ingress Sealed During Biocompatibility Testing



- A: Plunger bottom
- B: Actuator attachment
- C: Indicator
- D: Device tip

Type/duration of contact

Nasal Spray components are classified as:

Actuator tip – included in CDER’s review of fluid path E&L

Contact type: Mucosal membrane

Contact Duration: prolonged duration

Everything else – included in test article here

Contact type: intact skin

Contact duration: prolonged

Cytotoxicity – MEM Elution (ISO 10993-5)

The extraction ratio was appropriate for the article type.

-
- 3 cm²/mL (>0.5mm thick)

The extraction vehicle was MEM culture medium with 5-10% serum to include polar and non-polar components.

The extraction conditions are appropriate, the duration is at least as long as the device duration of use.

-
- 37C for 72 hours

The extracts were:

- Clear.
- Not diluted
- Not filtered
- Not pH adjusted
- Used within 24 hours.

Negative and positive control groups were included.

Positive control: powder free latex gloves

Negative control: high density polyethylene

The test system is L-929 mouse fibroblast monolayer.

The cells were incubated with the test article extract at 37C for 48 hours.

The following scale was used, and the results were not more than 2 = noncytotoxic

- 0: discrete intracytoplasmic granules and no lysis
- 1: occasional lysed cells (0-20% cells rounded, loose)
- 2: no extensive cell lysis (20-50% cells rounded)
- 3: 50-70% lysis (50-70% cells rounded)
- 4: nearly complete destruction of cell layer (>70% lysis)

No cytotoxicity or cell lysis was noted in any of the test wells. No pH shift was observed at 48 hours. The reagent control, negative control and the positive control performed as anticipated. The individual reactivity grades are presented in Appendix 1.

There were no deviations.

Results:

- No cell abnormalities were reported. Control scores were as expected (negative is negative, positive is positive).
-

Recommendation: Non-cytotoxic, acceptable.

Sensitization – Guinea Pig Maximization (ISO 10993-10)

The extraction ratio was appropriate for the article type.

- 3 cm²/mL (>0.5mm thick)

The extraction vehicle(s) included:

- Polar (saline)
- Non-polar (vegetable, sesame, or cotton seed oil).
-

The extraction conditions are appropriate, the duration is at least as long as the device duration of use.

- 50C for 72 hours

The extracts were (select all that apply):

- clear.
- not diluted,
- Not filtered
- Not pH adjusted
- used within 24 hours.

A historical positive control was conducted within 3 months of this test. The positive control is either DNCB (0.1-0.9%), formaldehyde, Mercaptobenzothiazole, Hexyl cinnamic aldehyde, or Benzocaine.

Control date: 05/10/2017-06/5/2017

Test date: 8/22/2017- 9/16/2018

The negative control is the extraction vehicle without test materials.

The test system includes at least 10 test and 5 control animals. Males and/or females that are not pregnant.

3 pairs of intradermal injections were given on the backs of the animals:

- 2 x 0.1 mL of 1:1 FCA/vehicle
- 2 x 0.1 mL of test extract/control vehicle
- 2 x 0.1 mL of 1:1 mix of the test extract/control vehicle and 1:1 FCA/vehicle

On day 6 after injection the injection sites were clipped and treated with 10% SLS in petroleum jelly and any remaining SLS was removed prior to induction II treatment

On day 7 after injection 2 x 4 cm filter paper patches were saturated with 0.3mL test extract or control vehicle and applied to the injection area for 48 hours. After 48 hours the patches were removed.

14 days after removal of the patches the right and left flanks of each animal were clipped, and 2 x 2 cm patches were saturated with test extract or control vehicle and applied for 24 hours.

The sites were assessed 24 and 48 hours after the last round of patches were removed.

There were no deviations.

The animals appeared normal and there were no deaths.

The Magnusson and Klingman score was <1 for all of the polar and non-polar extracts (non-sensitizer)

Recommendation: Non- sensitizing, acceptable.

Irritation – Intracutaneous Irritation (ISO 10993-10)

The extraction ratio was appropriate for the article type.

-
- 3 cm²/mL (>0.5mm thick)

The extraction vehicle(s) included:

-
- Polar (saline)
- Non-polar (vegetable, sesame, or cotton seed oil).
-

The extraction conditions are appropriate, the duration is at least as long as the device duration of use.

- 50°C for 72 hours

The extracts were (select all that apply):

- clear.
- not diluted,
- Not filtered
- Not pH adjusted
- used within 24 hours.

The negative control is the extraction vehicle without test materials.

The test system includes at least 3 rabbits

Intracutaneous injections were given along the spine on one side of the back:

- 5 x 0.2 mL doses of one test extract
- 5 x 0.2 mL doses of the control vehicle
- Similar injections of the other test article and control vehicle should be injected along the other side of the back.

The animals were assessed at 24, 48, and 72 hours.

All Erythema and edema grades were totaled separately for each test article and vehicle control, and the total was divided by 15 (3 scoring periods x 5 injections sites) in each animal. To determine the overall score for each test article versus each corresponding vehicle control, the scores of each animal were added and divided by the total number of animals.

There were Deviations that were determined to be acceptable

Per the protocol, the test article extraction conditions were to be 50°C for 72 (±2) hours. During extraction, the incubator was out of temperature tolerance for 1 hour and 3 minutes and dropped to a temperature of 47°C. The extractions were extracted for a total of 73 hours; therefore, the extractions were prepared at 50°C for the required minimum of 70 hours, although discontinuous. The temperature excursion had no impact on the validity of the test.

The animals:

- Appeared normal and there were no deaths.

The erythema and edema scores were calculated using the following formula:

To calculate the score of a test sample or blank on each individual animal, divide each of the totals by 15 (3 scoring time points × 5 test or blank sample injection sites). To determine the overall mean score for each test sample and each corresponding blank, add the scores for the three animals and divide by three. The final test sample score can be obtained by subtracting the score of the blank from the test sample score. The requirements of the test are met if the final test sample score is 1.0 or less.

The final test sample score was ≤ 1 , non-irritant

Recommendation: Non-irritant, acceptable

The final finished device is used for the biocompatibility testing. This is acceptable. All entry points have been sealed with silicone to extract fluid entry into the fluid path. This is acceptable because we will only be reviewing the mucosal membrane contacting components here. The fluid path is reviewed by CDER/CMC separately, this includes the actuator tip, which is the only portion that would contact the mucosal membrane. Defer to CDER regarding acceptability of the extractables and leachables testing of the actuator tip.

7.2. Discipline 2 Compliance facilities review by Isabel Tejero

Email sent on 9-25-2018 Isabel stated:

Based on the risk assessment of the device constituent part, CDRH does not need to conduct a compliance evaluation of the application.

This assessment pertains exclusively to the Compliance Review:

- Desk review of 21 CFR 820 call-outs, and
- Evaluation of manufacturing facilities to determine the need for inspections associated with this application.

The decision for not conducting a device compliance review for this application is independent from the technical review of the device constituent part done by our pre-market colleagues.

8. RISK ANALYSIS

8.1. Risk Analysis Attributes

Risk Analysis Attributes	Yes	No	N/A
Risk analysis conducted on the combination product	X		
Hazards adequately identified (e.g. FMEA, FTA, post-market data, etc.)	X		
Mitigations are adequate to reduce risk to health	X		
Version history demonstrates risk management throughout design / development activities	X		

8.2. Summary of Risk Analysis

Severity classifications used in the risk assessment are provided in [Table 20](#). ISO 14971 directs the device developer to consider and list any and all potential events, no matter how unlikely, and to assess them for the worst-case outcomes, no matter how unlikely. This exercise establishes design priorities for

device development and is followed by an assessment of how those hazards have been addressed in device design activities including mitigation of these hazards by design, manufacturing, and labeling using a FMEA approach including the likelihood of an event. Verification activities are conducted for design, manufacturing, and labeling activities associated with each hazard.

Table 20: Severity Classifications for Assessment of Risks, as well as Failure Modes, that Result in Harm to an Individual

Classification	Rating	Description
Catastrophic	10	Life-threatening injury/illness (death has or could occur). Threat to life that requires immediate professional medical intervention.
Critical	8	Serious injury/illness that resulted in, or can be reasonably expected to result in, permanent/irreversible impairment of body function or permanent damage to a body structure.
		<u>or</u>
		Serious injury/illness that necessitates significant medical or surgical intervention to preclude permanent injury.
Marginal	5	Injury/illness that may be significant, but is temporary or reversible (a medical condition that would likely resolve itself or where medical treatment may be necessary).
Minimal	3	Injury/illness that is transient and minor, and that does not require medical intervention.
Negligible	1	No adverse health consequences, illness or injury.

The overall results of the clinical studies are reported in Module 5.3 Clinical Study Reports. No adverse events were related to the nasal spray device; however, some complaints related to the device were received during clinical studies. Complaints from 2,997 Phase 3 study subjects (total of 110,664 devices used) were analyzed to determine root cause and identification of any hazards that might need to be considered in the use-related risk analysis.

The overall complaint rate among these study subjects was 0.15% and complaints were considered to be one of two categories:

‘Use Error’: device was functioning properly but the user’s action or or lack of action while using the device led to a different result than that intended or expected

‘Device Complaint’: device does not function properly due to design or manufacturing issues

Complaints in the second category (‘Device Complaint’) received during clinical studies have been addressed with the commercial device design (see Table 4 in Section 5.4 for key design changes) and assembly process controls (see Section 8.2) to mitigate or reduce device-related issues. None of the complaints resulted in any study subject receiving more than the prescribed dose. Complaints which resulted in subjects receiving a partial dose of medication are not considered to have had an impact on the safety and efficacy outcomes of the study. Nevertheless, these complaints were analyzed to determine root cause and identification of any hazards that might need to be considered in the use-related risk analysis. A list of complaints, rate of their occurrence, root cause, and mitigations for both Phase 3 studies and for commercial product are described in Table 21.

Table 21: Reported Clinical Study Complaints Related to Nasal Spray Device

#	Reported Complaint	Number of Devices Used/Overall Complaint Rate (ppm ^a)	Root Cause	Mitigation Implemented During Phase 3 Studies	Mitigation for Commercial Use
Use Error					
1	Second spray never administered	32/289	All occurrences at one site at which staff only instructed patients to deliver one spray per device.	Site staff no longer oversee administration and the site coordinator was retrained.	As described in Section 10.1, instructions on the required number of devices and sprays per device are explained in the IFU.
2	Both sprays during a single actuation	3/27	User perception; most likely that the patient did not feel the second spray. May have occurred if patient had pressed directly on the bottom surface of the container holder but not likely as the container holder is recessed from (not flush with) the bottom of the plunger.	Emphasis on how patients should hold the device correctly included in new training video and investigator meetings.	Recommendations on how to hold the device are emphasized through graphics and text in the IFU.
4	Misinterpretation of the Indicator	1/9	Site staff checked the status of the device with the accessory indicator <i>before and after</i> the first spray (rather than just after the first spray, as instructed). In this instance, after the first spray, the indicator pin was higher than expected, therefore the site staff incorrectly interpreted the first spray as incomplete. Subsequently a second actuation was performed into the same nostril. After the second actuation the device was checked with the accessory indicator and it correctly communicated that the device was empty. In this case, the full device contents were delivered but into the same nostril.	Once this site staff learned how to use the accessory indicator correctly, no further issues were reported.	As the commercial product has an integrated "dot" indicator with instructions about how to use and interpret the dots, the need to interpret this particular accessory indicator is eliminated.
#	Reported Complaint	Number of Devices Used/Overall Complaint Rate (ppm ^a)	Root Cause	Mitigation Implemented During Phase 3 Studies	Mitigation for Commercial Use
(Continued)					
5	Accidental Actuation	4/36	Accidental actuation outside the nostril occurred occasionally during handling of the device.	None required; low rate of occurrence	As described in Table 4 in Section 5.4., the minimum actuation force for the commercial device is slightly higher than that used in the Phase 3 studies, so the likelihood of accidental actuation has been reduced
Device Complaints					
6	False Reading by the Accessory Indicator	62/560	The pin on the accessory indicator was falsely indicating that the device had not delivered both sprays because the indicator pin was slightly raised as a result of the patient pushing the device with enough force to cause the plunger legs to buckle and advance past the stopping position. When the spring reset after the first spray, the buckled plunger legs then pulled the container holder downward resulting in the indicator pin only partially advancing, thus falsely indicating that both sprays had not been delivered.	Phase 3 study sites were retrained on the appropriate pushing force required	The ancillary pin indicator used with the Phase 3 design was replaced in the commercial design with an integrated (dot) indicator utilizing existing components of the device. As noted in Table 4 of Section 5.4, the profile of the plunger legs of the commercial device was modified to accommodate a change to the spring and to improve robustness of manufacturability. This change did not impact spray performance and resulted in an elimination of incidences of leg buckling previously observed in usability studies and engineering development.

#	Reported Complaint	Number of Devices Used/Overall Complaint Rate (ppm ^a)	Root Cause	Mitigation Implemented During Phase 3 Studies	Mitigation for Commercial Use
(Continued)					
7	Difficulty delivery 2 nd spray	26/235	As communicated 18 August 2016 (IND 114,345, SN0165), a small number of nasal spray devices used in these clinical studies, containing either esketamine or placebo, could not complete the actuation of the second of two sprays because incorrect parameter settings on assembly equipment resulted in incorrect engagement of the container holder and the centerpiece for those devices.	The clinical impact of a patient receiving a device assembled with the incorrect parameters was evaluated and determined to have minimal patient risk if no special action was taken. Supplemental instructions were disseminated to investigators explaining how to use the accessory indicator (dose gauge) to complete dose delivery of the product in the event that the investigator and/or patient encountered a device that cannot complete delivery of the second spray.	As described in Section 8.2., in the commercial assembly process, a specification for critical process parameters and 100% inspection of those parameters have mitigated the risk of incorrect positioning of the centerpiece and container holder.
8	Difficulty delivering sprays	21/189	Issue due to an off-center cannula which pierces the side wall rather than the septum of the stopper during the first, second, or both actuations, more likely if the patient was pushing the plunger at an angle.	None required as the medication could be delivered following multiple attempts to actuate the device.	As described in Table 4 of Section 5.4, the cannula design used in the commercial devices is self-centering and misalignment would not likely occur.
9	No sprays delivered after multiple attempts to actuate device	3/27	Under x-ray analysis, these devices were found to have cannulas that were inverted, blunt, or too short. If a cannula is too short, it cannot pierce the stopper septum and thus no liquid is released from the vial.	None required; occurrence very low	Issue has been mitigated in the component supplier's assembly process

^a ppm = parts per million

Reviewer's Comments: Device Design changes were made from the phase 3 device to commercial use due to device malfunctions/failures and use errors. These failures and use errors could result in incorrect drug dosage administration. The described device malfunctions/use errors occurred during actual use in a much larger patient population (phase 3 trial) as compared to the Human factors validation study with the redesigned to be marketed device. IR#2 asked the Sponsor to address this. In their response they stated that the current redesigned combination product continues to be used in the ongoing phase 3 clinical trial and approximately 10,000 redesigned/current devices have been used with minimal complaints or malfunctions.

9. LABELING

Device label:



Blister label

(b) (4)



Patient instructions for use. The patient administers the dose to self under the supervision of a healthcare professional.

(b) (4)



(b) (4)



Reviewer's comments: The instructions for use are adequate for how to use the device

10.DESIGN TRANSFER ACTIVITIES – RELEASE SPECIFICATION

The following release specifications are included for the device constituent within eCTD Module 3.2.P.5:

User Requirement	Specification (Design Requirement)
The device shall deliver the target dose	The combination product is manually operated to deliver the content by pressing the plunger base toward the flange until it stops. The content of the device is delivered through two manual actuations, or sprays.
The combination product shall be visually different before and after use such that the patient and HCP can distinguish between a used and an unused product.	An integrated visual indicator shall indicate if the device is full, has some content remaining, or is empty.
The device shall deliver the target dose	Spray Content Uniformity ^a <div style="background-color: #cccccc; height: 200px; width: 100%;"></div> (b) (4)
The device shall allow delivery of the drug product into the nasal cavity	<u>Spray Pattern</u> <ul style="list-style-type: none"> • Dmin (shortest diameter of oval shape) (b) (4) mm • Dmax (longest diameter of oval shape) (b) (4) mm • Ovality ratio \leq (b) (4)
The device shall allow delivery of the drug product into the nasal cavity	<u>Droplet Size Distribution</u> <ul style="list-style-type: none"> • <div style="background-color: #cccccc; height: 150px; width: 100%;"></div> (b) (4)
The device shall fit into and be operated by one hand and shall have no discriminating features that would favor/compel use by either the right or left hand.	<u>Actuation Force</u> <ul style="list-style-type: none"> • Maximum actuation force (b) (4) N • Minimum actuation force (b) (4) N

^a Refer to combination product specification, 3.2.P.5.1.

Reviewer's comments: The release specifications are adequate.

11.INTERACTIVE REVIEW

Agency Information Request #1 (sent on 12/20/2018) - ADEQUATE

You have provided a traceability matrix on page 51 of 3.2.R.2 for device performance requirements. The traceability matrix is missing some of the essential performance requirements. Please include the following additional essential performance requirements for a nasal spray device:

- *Pump Delivery (Spray Weight)*
- *Spray Pattern and Plume Geometry Shape*
- *Droplet / Particle Size Distribution*
- *Activation Force*

Sponsor Response (received on 01/09/2019)

The Applicant included the overall essential performance requirements (EPRs) (performance requirements having the potential to influence the intended dosing of the drug product) for the nasal spray device in Section 11 of 3.2.R.2. These EPRs, also specified in release testing, were the same as those noted in the minutes for the Type B pre-NDA meeting on March 14, 2018, proposed by Janssen in the pre-NDA Briefing Book for FDA concurrence. These included the ability to deliver a full dose through two manual actuations of the device and spray content uniformity/pump delivery.

As requested, the EPR traceability matrix in 3.2.R.2. has been updated with the above parameters ([Table 1](#)). Note that these parameters were included in the “key” performance requirements in Section 5.3 of 3.2.R.2. Verification results for these requirements were included in the design verification report, DS-TEC-127742, in 3.2.R.2.

The above parameters were addressed in the NDA as follows:

Pump Delivery (Spray Weight): For the single-use esketamine nasal spray device, spray weight is measured (spray content uniformity by weight), which was already defined as an EPR and is a drug product release and stability specification.

Spray Pattern and Plume Geometry Shape: Spray pattern, including plume geometry shape (ovality), is a technical design requirement that was verified as reported in 3.2.R., Medical Device, Section 6, is also a drug product release specification, and stability was monitored during development.

Droplet/Particle Size Distribution: Droplet size distribution is a technical design requirement that was verified as reported in 3.2.R., Medical Device, Section 6 and is also a drug product release and stability specification.

Activation Force: The ability to deliver the drug product solution by manually applying force to actuate the device is an essential performance requirement and a drug product release and stability specification (Device Manual Operation). If the force required to actuate the device is too high, the user would not be able to push the plunger to deliver the spray and the Manual Operation of Device test would fail when tested at release and stability. In addition to the Manual Operation of Device test, described in 3.2.P.5.2 test method DS-TMD-24003, actuation force characterization testing has been conducted throughout development, including stability studies, and shown to remain consistent and within specified criterion (Figure 1-Figure 3). For the esketamine nasal spray device, the force to actuate the delivery

device is controlled by the design of the device components (e.g. cannula, spring, tolerance between interacting components).

As noted above, we have enclosed an updated 3.2.R.2 section including the added parameters in the EPR traceability matrix table (Section 11, Table 24). The table also indicates where the design criteria and test results can be located, and whether these parameters are controlled by design (dimensions and materials) and design verification testing or are confirmed as release tests and undergo stability testing due to the potential to be impacted by the assembly process or aging during shelf life.

Reviewer Comments – The sponsor’s response is adequate. Deficiency resolved.

Agency Information Request #2 (sent on 12/10/2018) - ADEQUATE

There were several changes in device design from the phase 3 trial to marketing device as noted in section 9 of 3.2.R.2. Device Design changes were made from the phase 3 device to commercial use due to device malfunctions/failures and use errors. These failures and use errors could result in incorrect drug dosage administration. The described device malfunctions/use errors occurred during actual use in a much larger patient population (phase 3 trial) as compared to the Human factors validation study with the redesigned to be marketed device. Please explain how you have determined device performance reliability, such as device spray delivery and dose accuracy, during actual use based on the comparison of number of subjects who used the redesigned device in the Human Factors validation study compared to the phase 3 trial.

Sponsor Response (received on 01/09/2019)

The device malfunctions and use errors reported as complaints during the Phase 3 clinical studies (Table 2) have all been appropriately addressed by either mitigations implemented as a direct result of the complaint, such as Instructions for Use (IFU) or manufacturing process changes, or as a result of device design changes (Table 3) that had been implemented prior to receiving the complaints.

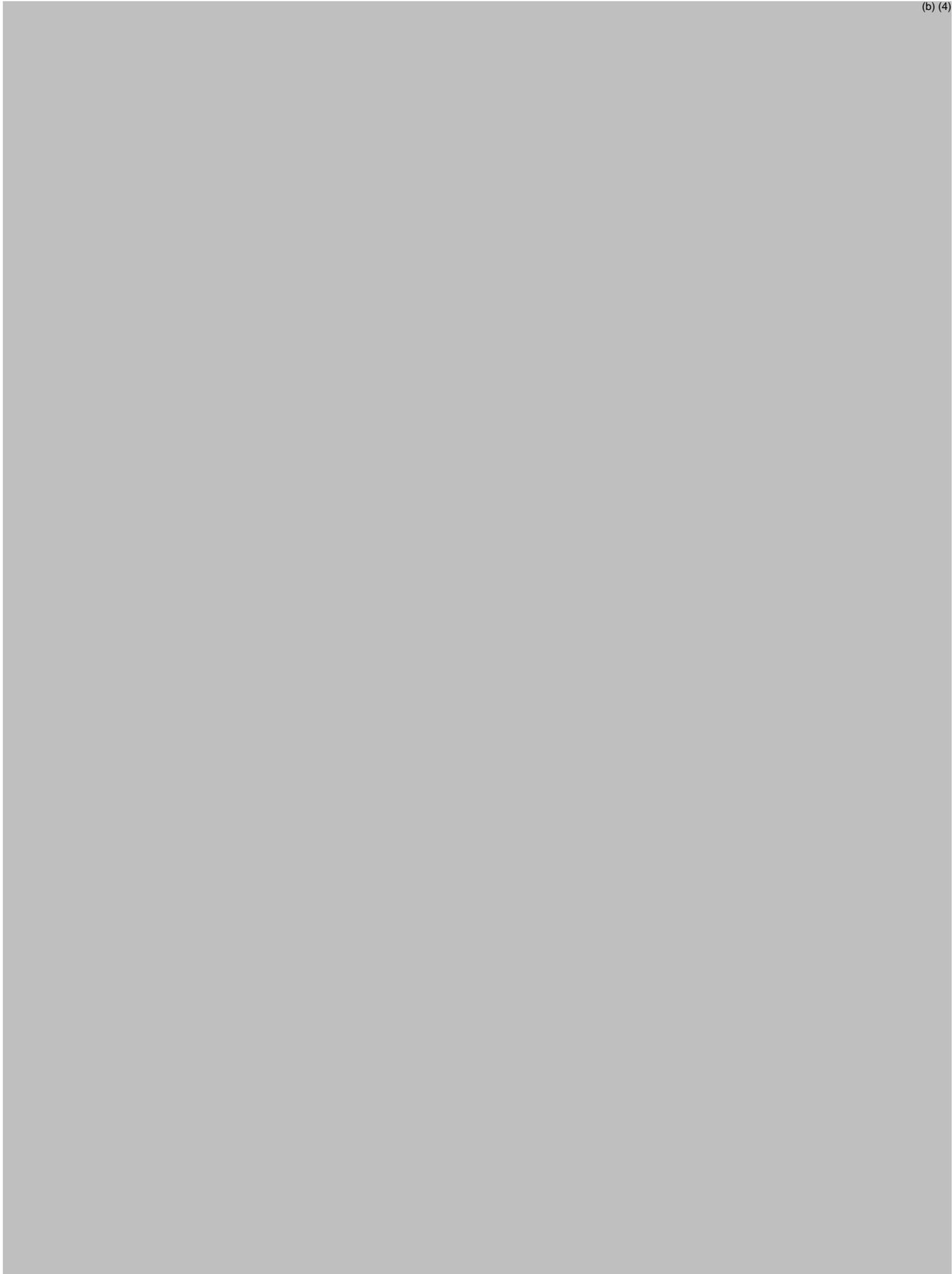
Results of Design Verification and the summative Human Factors study demonstrated that the redesigned proposed commercial device, incorporating all the changes described above, met user requirements. In addition, the redesigned proposed commercial device is being used in ongoing Phase 3 clinical studies; more than 10,000 devices have been used thus far and minimal complaints related to device performance reliability have been reported.

Table 2: Phase 3 Study Complaints (based on Table 21 in 3.2.R.) and Mitigations

Reported Complaints	Root Cause Mitigations
1. Second spray never administered	IFU change, Device design change
2. Both sprays during a single actuation	IFU change, Device design change
3. Misinterpretation of the Indicator	Device design change
4. Accidental Actuation	Device design change
5. False Reading by the Accessory Indicator	Device design change
6. Difficulty delivery 2 nd spray	Combination product assembly change
7. Difficulty delivering sprays	Device design change
8. No sprays delivered after multiple attempts to actuate device	Component assembly change

ICC800728
NDA 211243, Spravato, Nasal Spray
Janssen Pharmaceuticals Inc

(b) (4)



ICC800728

NDA 211243, Spravato, Nasal Spray

Janssen Pharmaceuticals Inc

Reviewer Comments – The Sponsor’s response is adequate. The Sponsor states the redesigned combination product is currently being used in the ongoing phase 3 clinical trial with 10, 000 devices having been used thus far with minimal malfunctions or complaints. Deficiency resolved.

12.OUTSTANDING DEFICIENCIES

None

13.RECOMMENDATION

Device Constituents Parts of the Combination Product are Approvable

14.APPENDIX

CDRH Biocompatibility Consult memo.



Memorandum: Biocompatibility Consult

To: Kathleen Fitzgerald, Lead Reviewer, GHDB/DAGRID/ODE/CDRH

From: Jacqueline Gertz, Ph.D., GHDB/DAGRID/ODE/CDRH

Date: December 17, 2018

Subject: NDA211243/ICC1800728/CON1822636

Device: Nasal Spray

Sponsor: Janssen Research and Development

Recommendation: No additional information needed, Sponsor has satisfied the Biocompatibility requirements.

Of note: quotes from the Sponsor are written in *italics*, comments to be directed to the Sponsor are in **bold**.

I. Scope of Consult Request

- Biocompatibility of Patient contacting components
 - Review of biocompatibility testing

II. Background

This device was custom designed for delivery of Esketamine

III. Indications for Use

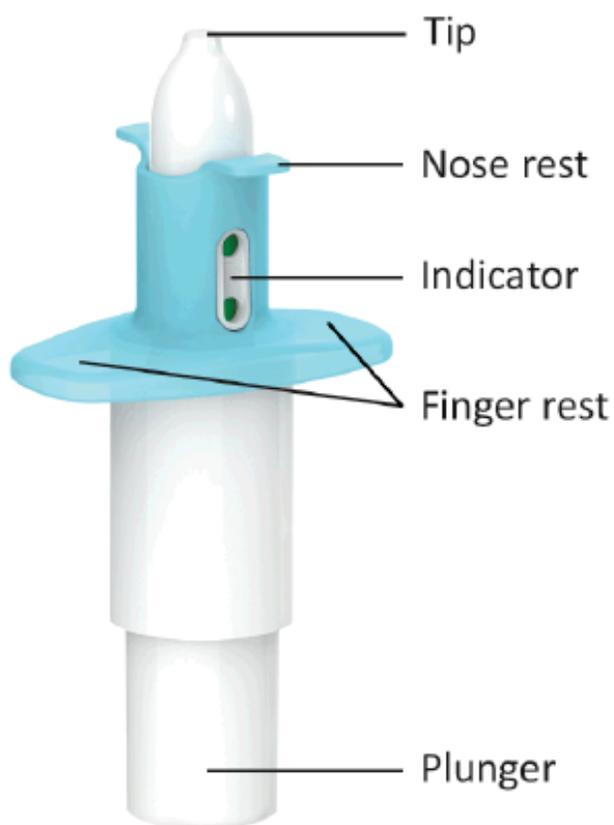
- Treatment of treatment resistant depression

IV. Device Description

The following device description was provided in the 3.2.R.2 Medical Device Information, Introduction section:

The drug-device combination product to be marketed by the Applicant is a single-use nasal spray device (may also be referred to in reference documents as Intranasal Single-Use Device or Intranasal Dual Spray Device) assembled with a filled and stoppered vial containing the esketamine drug product solution. As described in the Instructions for Use (Module 1), the product is ready to use once removed from its secondary packaging. Patients self-administer the drug using this nasal spray device under the supervision of a Healthcare Professional (HCP) in a healthcare setting. [Figure 1](#) presents a picture of a representative to-be-marketed combination product.

The nasal spray device is a manually operated, disposable, single-use device that is designed to deliver two consecutive sprays, one to each nostril. Under the supervision of an HCP, the patient manually activates the device by holding the device in one hand, placing the tip into the first nostril until the nose rest touches the skin between the nostrils, and pushing on the plunger with the thumb to deliver a spray. Switching hands, the patient then places the tip into the second nostril until the nose rest touches the skin between the nostrils, and again pushes on the plunger to deliver the second spray. Thus, a single device delivers a total of 0.2 mL, or 32.3 mg of esketamine hydrochloride or 28 mg of esketamine free base. Successful administration of each spray is indicated by each of two dots in the indicator window changing color from green to white. The features of the nasal spray device are illustrated in [Figure 2](#).



Current Usage/Marketing History

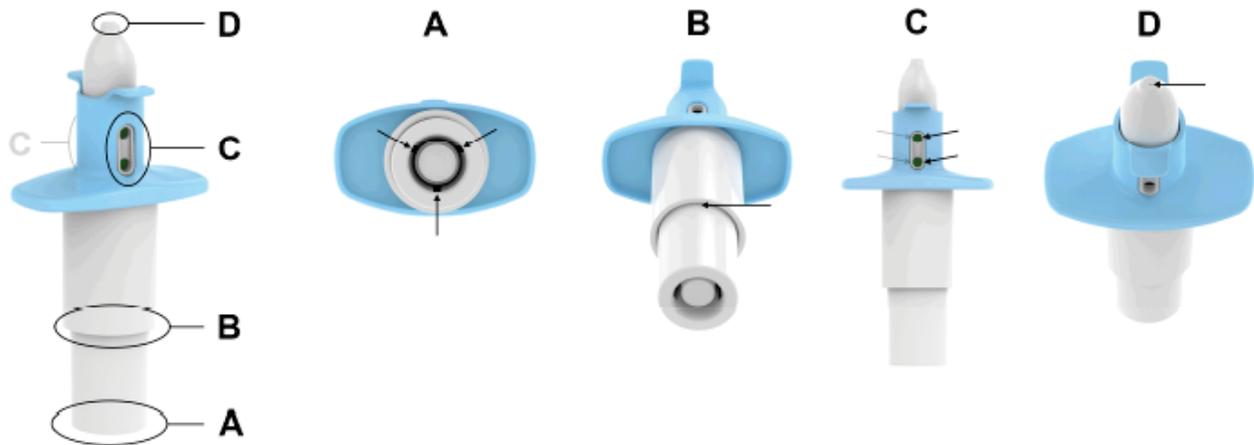
The nasal spray device used to deliver esketamine has been custom-designed for use with esketamine patients and is not a marketed medical device.

V. Biocompatibility Summary

The following information was included in the Biocompatibility section of 3.2.R.2 Medical Device Information document:

Biocompatibility testing of the nasal spray device was conducted by an independent test laboratory in accordance with ISO 10993-1, Biological Evaluation of Medical Devices. Per the ISO standard, cytotoxicity, sensitization, and irritation/intracutaneous reactivity testing were performed in-line with classification as a skin contacting surface device having limited contact duration (<24 hours). Per ISO 10993-12, samples tested represented the commercial device in that they were constructed of the same materials and were manufactured and assembled using commercially representative processes. For each test, a single preparation of one test article and each of the controls were subjected to the extraction conditions as described below. The test article was not subdivided; portals to the inside of the device (indicated in Figure 10 below) were sealed with medical grade silicone and allowed to cure for at least 72 hours to ensure that only surfaces of the test article potentially in direct contact with the user were assessed.

Figure 10: Points of Ingress Sealed During Biocompatibility Testing



- A: Plunger bottom
- B: Actuator attachment
- C: Indicator
- D: Device tip

Type/duration of contact

Nasal Spray components are classified as:

Actuator tip – included in CDER’s review of fluid path E&L

Contact type: Mucosal membrane

Contact Duration: prolonged duration

Everything else – included in test article here

Contact type: intact skin

Contact duration: prolonged

Reviewer Comments

Discussion with Sarah:

Nozzle is mucosal membrane

The fluid path would be blood path indirect - CMC will be looking at E&L for fluid path, including tox risk assessment

No particulate testing for nasal sprays

Repeated use = prolonged

Material mediated pyrogenicity for sterile devices only – if the fluid path is sterile, request it. Don't request it for oral.

Per ISO 10993 guidance – attachment A:

Only the intact skin components are reviewed here. The nozzle tip that would contact the mucosal membrane is reviewed as part of CDER's review of extractables and leachables.

A device with intact skin prolonged duration requires:

- Cytotoxicity
- Sensitization
- Irritation or Intracutaneous reactivity

The final finished device is used for the biocompatibility testing. This is acceptable. All entry points have been sealed with silicone to extract fluid entry into the fluid path. This is acceptable because we will only be reviewing the mucosal membrane contacting components here. The fluid path is reviewed by CDER/CMC separately, this includes the actuator tip, which is the only portion that would contact the mucosal membrane. Defer to CDER regarding acceptability of the extractables and leachables testing of the actuator tip.

Cytotoxicity – MEM Elution (ISO 10993-5)

The extraction ratio was appropriate for the article type.

- 3 cm²/mL (>0.5mm thick)

The extraction vehicle was MEM culture medium with 5-10% serum to include polar and non-polar components.

The extraction conditions are appropriate, the duration is at least as long as the device duration of use.

- 37C for 72 hours

The extracts were:

- Clear.
- Not diluted
- Not filtered
- Not pH adjusted
- Used within 24 hours.

Negative and positive control groups were included.

Interoffice Memorandum – (continued)

Positive control: powder free latex gloves

Negative control: high density polyethylene

The test system is L-929 mouse fibroblast monolayer.

The cells were incubated with the test article extract at 37C for 48 hours.

The following scale was used, and the results were not more than 2 = noncytotoxic

- 0: discrete intracytoplasmic granules and no lysis
- 1: occasional lysed cells (0-20% cells rounded, loose)
- 2: no extensive cell lysis (20-50% cells rounded)
- 3: 50-70% lysis (50-70% cells rounded)
- 4: nearly complete destruction of cell layer (>70% lysis)

No cytotoxicity or cell lysis was noted in any of the test wells. No pH shift was observed at 48 hours. The reagent control, negative control and the positive control performed as anticipated. The individual reactivity grades are presented in Appendix 1.

There were no deviations.

Results:

- No cell abnormalities were reported. Control scores were as expected (negative is negative, positive is positive).

Recommendation: Non-cytotoxic, acceptable.

Sensitization – Guinea Pig Maximization (ISO 10993-10)

The extraction ratio was appropriate for the article type.

- 3 cm²/mL (>0.5mm thick)

The extraction vehicle(s) included:

- Polar (saline)
- Non-polar (vegetable, sesame, or cotton seed oil).

The extraction conditions are appropriate, the duration is at least as long as the device duration of use.

- 50C for 72 hours

The extracts were (select all that apply):

- clear.
- not diluted,
- Not filtered
- Not pH adjusted
- used within 24 hours.

Interoffice Memorandum – (continued)

A historical positive control was conducted within 3 months of this test. The positive control is either DNCB (0.1-0.9%), formaldehyde, Mercaptobenzothiazole, Hexyl cinnamic aldehyde, or Benzocaine.

Control date: 05/10/2017-06/5/2017

Test date: 8/22/2017- 9/16/2018

The negative control is the extraction vehicle without test materials.

The test system includes at least 10 test and 5 control animals. Males and/or females that are not pregnant.

3 pairs of intradermal injections were given on the backs of the animals:

- 2 x 0.1 mL of 1:1 FCA/vehicle
- 2 x 0.1 mL of test extract/control vehicle
- 2 x 0.1 mL of 1:1 mix of the test extract/control vehicle and 1:1 FCA/vehicle

On day 6 after injection the injection sites were clipped and treated with 10% SLS in petroleum jelly and any remaining SLS was removed prior to induction II treatment

On day 7 after injection 2 x 4 cm filter paper patches were saturated with 0.3mL test extract or control vehicle and applied to the injection area for 48 hours. After 48 hours the patches were removed.

14 days after removal of the patches the right and left flanks of each animal were clipped, and 2 x 2 cm patches were saturated with test extract or control vehicle and applied for 24 hours.

The sites were assessed 24 and 48 hours after the last round of patches were removed.

There were no deviations.

The animals appeared normal and there were no deaths.

The Magnusson and Klingman score was <1 for all of the polar and non-polar extracts (non-sensitizer)

Recommendation: Non- sensitizing, acceptable.

Irritation – Intracutaneous Irritation (ISO 10993-10)

The extraction ratio was appropriate for the article type.

- 3 cm²/mL (>0.5mm thick)

The extraction vehicle(s) included:

- Polar (saline)
- Non-polar (vegetable, sesame, or cotton seed oil).

The extraction conditions are appropriate, the duration is at least as long as the device duration of use.

Interoffice Memorandum – (continued)

- 50°C for 72 hours

The extracts were (select all that apply):

- clear.
- not diluted,
- Not filtered
- Not pH adjusted
- used within 24 hours.

The negative control is the extraction vehicle without test materials.

The test system includes at least 3 rabbits

Intracutaneous injections were given along the spine on one side of the back:

- 5 x 0.2 mL doses of one test extract
- 5 x 0.2 mL doses of the control vehicle
- Similar injections of the other test article and control vehicle should be injected along the other side of the back.

The animals were assessed at 24, 48, and 72 hours.

All Erythema and edema grades were totaled separately for each test article and vehicle control, and the total was divided by 15 (3 scoring periods x 5 injections sites) in each animal. To determine the overall score for each test article versus each corresponding vehicle control, the scores of each animal were added and divided by the total number of animals.

There were Deviations that were determined to be acceptable

Per the protocol, the test article extraction conditions were to be 50°C for 72 (±2) hours. During extraction, the incubator was out of temperature tolerance for 1 hour and 3 minutes and dropped to a temperature of 47°C. The extractions were extracted for a total of 73 hours; therefore, the extractions were prepared at 50°C for the required minimum of 70 hours, although discontinuous. The temperature excursion had no impact on the validity of the test.

The animals:

- Appeared normal and there were no deaths.

The erythema and edema scores were calculated using the following formula:

To calculate the score of a test sample or blank on each individual animal, divide each of the totals by 15 (3 scoring time points × 5 test or blank sample injection sites). To determine the overall mean score for each test sample and each corresponding blank, add the scores for the three animals and divide by three. The final test sample score can be obtained by subtracting the score of the blank from the test sample score. The requirements of the test are met if the final test sample score is 1.0 or less.

The final test sample score was ≤ 1 , non-irritant

Recommendation: Non-irritant, acceptable.

Reviewer Comments

The testing is acceptable. There are no deficiencies.

VI. Recommendation

The testing is acceptable.

Digital Signature Concurrence Table	
Consultant Reviewer	



David
Claffey

Digitally signed by David Claffey
Date: 2/11/2019 05:53:19PM
GUID: 508da71e00029e20b201195abff380c2