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APPLICATION NUMBER:

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NON-CLINICAL REVIEW(S)

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

PHARMACOLOGY/TOXICOLOGY NDA/BLA ASSESSMENT AND EVALUATION

Application number: 208157

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Applicant's letter date: 08/22/2018

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Product: Human Insulin in 0.9% Sodium Chloride

Indication: To improve glycemic control in patients with
diabetes mellitus

Applicant: Celerity Pharmaceuticals LLC

Review Division: Division of Metabolism and Endocrinology
Products (DMEP)

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1 Executive Summary

1.1 Introduction

Celerity Pharmaceuticals, LLC (the Applicant) seeks marketing approval of Human Insulin Injection (rDNA origin; 1U/ml) in an isotonic solution (0.9% NaCl) for the intravenous treatment of diabetes mellitus in the hospital setting. The Applicant seeks to rely on FDA's previous findings of safety and effectiveness for the U.S.-approved, Orange Book-listed drug (LD) Novolin R injection marketed by Novo Nordisk (NDA 019938), via the 505(b)(2) approval pathway. Unlike the LD, Human Insulin Injection is intended to provide a ready-to-use IV bag convenience formulation for the hospital setting, which may reduce handling and dosing errors. The insulin drug substances in Human Insulin Injection contains recombinant human insulin produced in a *Pichia pastoris* yeast expression system. The LD drug substance is produced recombinantly in *Saccharomyces cerevisiae* yeast.

1.2 Brief Discussion of Nonclinical Findings

The toxicological profile of recombinant human insulin is well established. The dose-limiting toxicity with insulin in animals is hypoglycemia, a relatively insensitive endpoint for comparing two insulins of the same sequence. In vitro assessments are more sensitive than animal toxicity studies for evaluating comparative differences in toxicological profiles of insulin. To establish a scientific "bridge" between Human Insulin Injection and the LD, the Applicant conducted in vitro functional assays comparing the activities of the two insulins (e.g., insulin and IGF-1 receptor binding and activation, in vitro metabolism and mitogenic activity). The impurity profile of Human Insulin Injection, which differs from that of the LD, was qualified in a two-week "bridging" toxicity study with comparison to the LD (diluted in saline) for intravenous administration.

Human Insulin Injection was compared directly to the LD, or to insulin drug substance extracted from the LD, using an in vitro battery of tests. Extraction followed by reconstitution in saline was performed for head-to-head comparisons in the following assays: 1) binding affinity of insulin and insulin-like growth factor-1 receptors, 2) metabolic activation, and 3) mitogenic activity. For the insulin receptors binding affinity, the Applicant used the IR-B (the long-form receptor present in adult tissues) and did not evaluate IR-A (the short-form receptor present in fetal tissues and some cancer cells). This product is intended for use in the hospital and emergency room settings as a ready-to-use IV bag convenience formulation (i.e., for short-term use), and therefore binding affinity and phosphorylation assays using the IR-A receptor would be necessary to support chronic use. Because insulin toxicity is related to the pharmacological activity of insulin itself, and because Human Insulin Injection contains only insulin, sodium chloride and sodium phosphate, extraction of the LD drug substance to remove excipients does not impact the safety assessment. The results of nonclinical studies comparing the insulin from Human Insulin Injection and the LD do not indicate meaningful differences between the two active ingredients as tested in in vitro insulin and IGF-1 receptor binding/activation, metabolism and mitogenicity assays.

Human Insulin Injection differs from the listed drug with respect to levels of (b)(4) impurities. Therefore, a two-week repeat-dose rat toxicity study with a 2-week recovery period was conducted with continuous intravenous infusion of 0.2 U/kg/hr Human Insulin Injection

containing (b) (4) impurities or 0.2 U/kg/hr diluted LD in order to qualify the safety of (b) (4) impurities. This study did not demonstrate any meaningful safety issues with (b) (4) impurities compared to Human Insulin Injection with low levels of impurities or to the LD.

1.3 Recommendations

1.3.1 Approvability

Pharmacology/Toxicology recommends approval of this NDA for Human Insulin Injection.

1.3.2 Additional Non-Clinical Recommendations

None

1.3.3 Labeling

From a nonclinical perspective, product labeling should be identical to the PLLR-compliant labeling for the LD (Novolin R, NDA 019938), with the exception of the product trade names.

2 Drug Information

2.1 Drug

CAS Registry Number(s): 11061-68-0

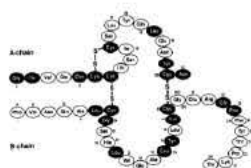
Generic Name: Insulin Human

Proprietary Name of Drug Product: MYXREDLIN™

Chemical Name: Insulin Human, USP

Molecular Formula/Molecular Weight: C₂₅₇H₃₈₃N₆₅O₇₇S₆/5807.57

Structure or Biochemical Description: Insulin Human, USP is a two-chain peptide hormone consisting of 51 amino acids. The A-chain is composed of 21 amino acids and the B-chain is composed of 30 amino acids.



Pharmacologic Class: Short-acting human insulin

2.2 Relevant INDs, NDAs, BLAs and DMFs

NDA 019-938, Novo Nordisk (Novolin R)

IND 124943, Celerity Pharmaceuticals (Human Insulin Injection)

DMF (b) (4), (b) (4) (insulin drug substance manufactured from *Pichia pastoris*).

DMF 006344, Baxter (Galaxy IV bag)

2.3 Drug Formulation

Human Insulin Injection is a premixed solution of recombinant human insulin formulated in a (1 U/mL) solution of 0.9% sodium chloride, 0.29 mg/mL monobasic sodium phosphate, monohydrate, 0.412 mg/mL dibasic sodium phosphate, anhydrous, and water, pH 6.5-7.2, in a 100 mL plastic Galaxy PL 2501 container (ready for injection). Galaxy is Baxter's proprietary IV bag that encompasses the manufacturing of sterile SVP injections in (b) (4) plastic containers (DMF 006344). Several approved products are delivered in the GALAXY containers, including Azactam, Ceftriaxone, and Nafcillin. The drug substance, human insulin, is manufactured from a yeast (*Pichia pastoris*) by (b) (4) (b) (4); DMF (b) (4). According to the Applicant, "The protein is a simple polypeptide consisting of 51 amino acids containing two chains (Chains A and B) linked with two inter and one intra disulfide linkages (molecular weight = 5.8 KD). The amino acid sequence is identical to the endogenous human insulin and contains no (b) (4)." .

Table 1: Composition of the Drug Product

Component	Concentration	Dose (100 Units/100 mL ^b)
Insulin Human, USP ^a	1.00 Units/mL	100 Units
Sodium Chloride, USP	9.0 g/L	0.9 g
Monobasic Sodium Phosphate, Monohydrate, USP ^c	0.290 g/L	0.029 g
Dibasic Sodium Phosphate, Anhydrous, USP ^c	0.412 g/L	0.0412 g
Water for Injection, USP	QS	

USP = United States Pharmacopeia; QS = Quantity Sufficient

^a The amount required for batch manufacture is calculated based on the assay value of the drug substance.

^b Labeled volume: 100 mL. Fill volume: (b) (4) mL.

^c Total phosphate is (b) (4). The ratio of (b) (4) was chosen to achieve a target pH of (b) (4). The product pH limits are 6.5 – 7.2.

Applicant's Table

Table 2: Comparison Celerity's Human Insulin Injection to Novolin®R

Applicant	Novo Nordisk [Reference Listed Drug]	Human Insulin Injection (Proposed Drug)
Product	NOVOLIN R is a sterile human insulin injectable solution stored in 10 mL glass vials	Human Insulin Injection is a sterile premixed human insulin injectable solution stored in a 100 mL GALAXY plastic bag
Active Ingredient	Human Insulin, USP	Human Insulin, USP
Total Drug Content	1000 U (100 U/mL in 10 mL glass vial)	100 U (1 U/mL in a 100 mL bag)
Container Closure	Single-use glass vial. When administered intravenously, polypropylene infusion bags should be used. Can be used with the following infusion fluids:	Single-use plastic bag (GALAXY),
Tonicity Agent	0.9% sodium chloride, 5% dextrose, or 10% dextrose with 40 mmol/L potassium chloride	Premixed with 0.9% w/v Sodium Chloride, USP 900 mg/100 mL (9 mg/mL)
Other Inactive Ingredients	Zinc Chloride approximately 70 mcg/10 mL (approximately 7 mcg/mL) Glycerol 160 mg/10 mL (16 mg/mL) Metacresol 30 mg/10 mL (3 mg/mL) pH Adjusted with Sodium Hydroxide and/or Hydrochloric Acid	Sodium Chloride, USP 900 mg/100 mL (9 mg/mL)-also listed as a tonicity agent Monobasic Sodium Phosphate, Monohydrate, USP 29.6 mg/100 mL (0.296 mg/mL) Dibasic Sodium Phosphate, Anhydrous, USP 41.2 mg/100 mL (0.412 mg/mL) pH Adjusted with Sodium Hydroxide, NF and/or Hydrochloric Acid, NF
Volume	Water for Injection, USP 10 mL glass vial	Water for Injection, USP 100 mL GALAXY plastic bag
Concentration	100 U/mL	1 U/mL
Dosage Form	Injectable; sterile solution (should be used in infusion systems using polypropylene infusion bags)	Injectable; sterile solution (premixed for intravenous infusion)
Route of Administration	Injection: IV infusion or subcutaneous	Injection: IV infusion
Dosing Regimen	Total daily insulin requirements vary and are usually between 0.05 and 1.0 units/kg/day.	Total daily insulin requirements vary and are usually between 0.05 and 1.0 units/kg/day.
Marketing Status	OTC	Prescription (Rx)
Host Cell Expression System	<i>Saccharomyces cerevisiae</i> (baker's yeast)	<i>Pichia pastoris</i> (yeast)

Applicant's Table

The Applicant conducted several studies to evaluate the similarity between the new drug product and that of the LD. These studies were related to both the CMC and nonclinical functional characteristics of the drug substances. The table below presents samples that were used for those studies.

Table 3: List of Samples - Tested at (b) (4)

Sample Type	Lot Number	Sample ID Abbreviation	Manufacturer	Manufacturing Date	Age at Time of Testing
Drug Substance	(b) (4) 15002402	(b) (4) 15002402	(b) (4)	July 2015	4 Months
Drug Substance	(b) (4) 15002500	(b) (4) 15002500	(b) (4)	August 2015	4 Months
Drug Substance	(b) (4) 15002681	(b) (4) 15002681	(b) (4)	August 2015	4 Months
Novolin® R Vehicle 100 U/mL	NB28973-066	Novolin R Matrix	NA ^a	July 2016	2 Months
Drug Substance (Novolin® R Vehicle), 100 U/mL	RD150902A	DS1-Novolin R vehicle	NA ^a	July 2016	2 Months
Drug Substance (Novolin® R Vehicle), 100 U/mL	RD150902B	DS2-Novolin R vehicle	NA ^a	July 2016	2 Months
Drug Substance (Novolin® R Vehicle), 100 U/mL	RD150902C	DS3-Novolin R vehicle	NA ^a	July 2016	2 Months
Drug Substance (Novolin® R Vehicle) Diluted in 0.9% Saline, 1 U/mL	NA ^a	DS1-Novolin R vehicle (diluted)	NA ^a	NA ^a	NA ^a
Drug Substance (Novolin® R Vehicle) Diluted in 0.9% Saline, 1 U/mL	NA ^a	DS2-Novolin R vehicle (diluted)	NA ^a	NA ^a	NA ^a
Drug Substance (Novolin® R Vehicle) Diluted in 0.9% Saline, 1 U/mL	NA ^a	DS3-Novolin R vehicle (diluted)	NA ^a	NA ^a	NA ^a
Drug Product, 1 U/mL	78221	DP 1	Baxter	20 June 2016	3 Weeks
Drug Product, 1 U/mL	78222	DP 2	Baxter	22 June 2016	3 Weeks
Drug Product, 1 U/mL	78223	DP 3	Baxter	23 June 2016	3 Weeks
Drug Product, 1 U/mL	NC080916	DP 4	Baxter	27 October 2016	3 Weeks
Novolin® R (RLD) US-Approved	EZF0278	Novolin R 1	Novo Nordisk	Expiry Date: August 2017	NA

Sample Type	Lot Number	Sample ID Abbreviation	Manufacturer	Manufacturing Date	Age at Time of Testing
Novolin® R (RLD) US-Approved	EZF0444	Novolin R 2	Novo Nordisk	Expiry Date: September 2017	NA
Novolin® R (RLD) US-Approved	EZF0488	Novolin R 3	Novo Nordisk	Expiry Date: October 2017	NA
Novolin® R (RLD) US-approved Diluted in 0.9% Saline, 1 U/mL	EZF0278	Novolin R 1 Diluted	NA	NA	NA
Novolin® R (RLD) US-approved Diluted in 0.9% Saline, 1 U/mL	EZF0444	Novolin R 2 Diluted	NA	NA	NA
Novolin® R (RLD) US-approved Diluted in 0.9% Saline, 1 U/mL	EZF0488	Novolin R 3 Diluted	NA	NA	NA
USP Human Insulin Reference Standard	R032L0	USP Ref Std	NA	NA	NA

NA = Not Applicable

^a Lot prepared at Baxter; (b) (4) drug substance lots (b) (4) 15002402, (b) (4) 15002500, and (b) (4) 15002681 were prepared at a concentration of 100 U/mL in the Novolin® R vehicle to produce lots RD150902A, RD150902B, and RD150902C, respectively. Drug substance in Novolin® R vehicle was diluted at the time of analysis.

Applicant's Table

2.4 Comments on Novel Excipients

There are no novel excipients in the Applicant's Human Insulin Injection product. All excipients are considered safe based on their inclusion in the Agency's Inactive Ingredient Database (IID) list of approved products that produce similar or greater exposures to each excipient, for chronic administration, and in comparable patient populations.

2.5 Comments on Impurities/Degradants of Concern

For information regarding the quality of ingredients and container, the Applicant referred to two DMFs. DMF (b) (4) (b) (4) was referenced for Human Insulin - Bulk (rDNA origin) and DMF 006344 (Baxter Healthcare Corporation) was referenced for the Galaxy Container Closure System. Letters of authorization for these two DMFs were submitted.

Two insulin degradants (b) (4) and (b) (4) were identified for Human Insulin Injection. While the concentrations of these (b) (4) impurities were below the USP limit of (b) (4) for (b) (4) and other related compounds, the Applicant conducted a two-week rat toxicity study with continuous intravenous infusion to evaluate the toxicity of (b) (4) impurities at levels of (b) (4)%. The findings of this study (reviewed in Section 6.2) suggested no safety issues related to impurities. The table below presents potential impurities for the new DP.

Table 4: Potential Process/Degradation Impurities

Impurity	IUPAC Chemical Name	Code #	Process/Degradation Impurity	Source Mechanism
(b) (4)	N/A	N/A	Degradation Product	(b) (4)
	N/A	N/A	Degradation Product	
	N/A	N/A	Degradation Product	
	N/A	N/A	Degradation Product	
	N/A	N/A	Degradation Product	(b) (4)
	N/A	N/A	Process Impurity	
	N/A	N/A	Process Impurity	

N/A = Not Applicable

Applicant's Table

2.6 Proposed Clinical Population and Dosing Regimen

- Adults and children with diabetes mellitus
- The daily dosage of (b) (4) (based on individual blood glucose monitoring) will be delivered via intravenous infusion

2.7 Regulatory Background

- On March 23, 2015, a Type B pre-IND meeting was requested, and written responses were granted. A Type B pre-IND meeting briefing package was received on April 22, 2015.
- See below for nonclinical-related questions (PT/ PIND memo in DARRTS, 05/04/2015):

Celerity Question #2

Celerity proposes the use of the 505(b)(2) regulatory pathway, referencing preclinical safety data and certain clinical safety data from the US-approved Novolin R.

Does the Agency agree that the proposed 505(b)(2) NDA marketing application pathway is appropriate?

FDA Pharm/Tox Response: "It is recommended that a nonclinical GLP compliant bridging toxicity study, with TK assessment, comparing Celerity's product with US-approved Novolin R® is completed, to support a 505(b)(2) pathway. For a 505(b)(2) pathway, it is your responsibility to not only establish that it is scientifically appropriate to rely, in part, upon the Agency's finding of safety and effectiveness for Novolin R® to support approval, but also to identify what data you would like to reference to support your Human Insulin Injection.

The final decision about the adequacy of your nonclinical development program cannot be determined until the review of your bridging toxicity study and CMC characterization of your impurities. If there is a difference in the impurity profiles (i.e. impurity, degradant, leachable) between your product and the listed drug, additional nonclinical studies may be required to assess these impurities."

- From March – May 2016 via emails, the Applicant requested FDA review and feedback for Celerity's toxicology study design. The Agency provided responses on the draft protocol.
- On March 31, 2017, the IND 124943 for Human Insulin in 0.9% Sodium Chloride Injection 1 U/mL (100 U/100 mL) was submitted. There were no toxicity issues identified and the pharm/tox 30-day safety review was finalized on 04/26/2017.

3 Studies Submitted

3.1 Studies Reviewed

- 2-Week Toxicity and Toxicokinetic Continuous Intravenous Infusion Study with Insulin in Rats with a 2-Week Recovery Phase (8337290)

- Radioligand binding Experiments to evaluate similarity of the test Insulin batches with Novolin (R) as reference standard for binding to Insulin Receptors expressed in HepG2 cells (001)
- Insulin mediated Glucose Uptake assay to evaluate similarity of the test Insulin batches with Novolin (R) as reference standard on pre-differentiated adipocytes (3T3-L1)
- Affinity and Kinetics of Insulin Binding to IGFR-1 by (b) (4) Comparability of Insulin DS and Novolin (001)
- Mitogenic Potency Similarity assessment between test Insulin batches and Novolin (R) as reference on 3T3-A31 cells using a fluorimetric bioassay

3.2 Studies Not Reviewed

None

3.3 Previous Reviews Referenced

Pharm/Tox PIND 124943 memo in DARRTS (05/04/2015)

Pharm/Tox IND 124943 review in DARRTS (04/26/2017)

4 Pharmacology

Human Insulin Injection contains a polypeptide hormone with identical sequence to native human insulin and is produced by rDNA technology using yeast. In general, insulins (including that in the proposed Regular Human Insulin product) bind to insulin receptors (on muscle and adipocytes) and lower blood glucose by enabling the cellular uptake of glucose and inhibiting the output of glucose from the liver.

4.1 Primary Pharmacology

4.1 Primary Pharmacology

The Applicant conducted several pharmacology studies to evaluate the similarity between the insulin in Human Insulin Injection and either the LD drug substance or insulin extracted insulin from LD. These studies evaluated insulin and IGF-1 receptor binding and activation, glucose uptake, and mitogenic potential. These studies were initially reviewed under IND 124943 (in DARRTS 04/26/2017).

Study Title: Radioligand binding Experiments to evaluate similarity of the test Insulin batches with Novolin (R) as reference standard for binding to Insulin Receptors expressed in HepG2 cells.

Key Study Findings:

- Both insulins bind to and activate the insulin receptor with similar affinity
- Both insulins bind the IGF-1 receptor with ~1000-fold lower affinity compared to the insulin receptor

The binding efficiency of different insulin batches were conducted on human hepatocarcinoma cells (HepG2) with expressing insulin growth factor 1(IGF-1) and insulin receptors (IRs). To

detect IC_{50} , GraphPad Prism Version 5.0 (One Site Competition Model) was used. HepG2 cells were selected to evaluate an increase in the binding time of insulin to IR, and increased activation of IGF-1R (HepG2 cells expressing IGF-I receptors and IRs). The competitive binding study (binding of a single concentration of radio labeled 125I recombinant human Insulin) was conducted with various concentrations of unlabeled drug substances and the LD (in triplicates). Moreover, insulin was extracted from the LD and formulated in the new DP matrix. According to the Applicant "To have the matrix matched to that of the Insulin batches in the comparability study, the extraction procedure mentioned below was performed to recover the Drug Substance (insulin) from Drug Product (Novolin) and get it in formulation buffer (b) (4). So that the excipients of Novolin R are not interfering in the binding assay".

The findings of this study showed that the mean IC_{50} values and concentration response curves were considered comparable for the binding efficiency of different batches of the new DP on HepG2 cells to the LD for the same receptor as summarized in the Applicant's figure and tables below:

Figure 1: One Site Competition Curves of Novolin R (EZFO324) compared with Insulin Batches (b) (4) 15002500 and (b) (4) 15002402. (Compiled representation of three studies (N=3; n=3))

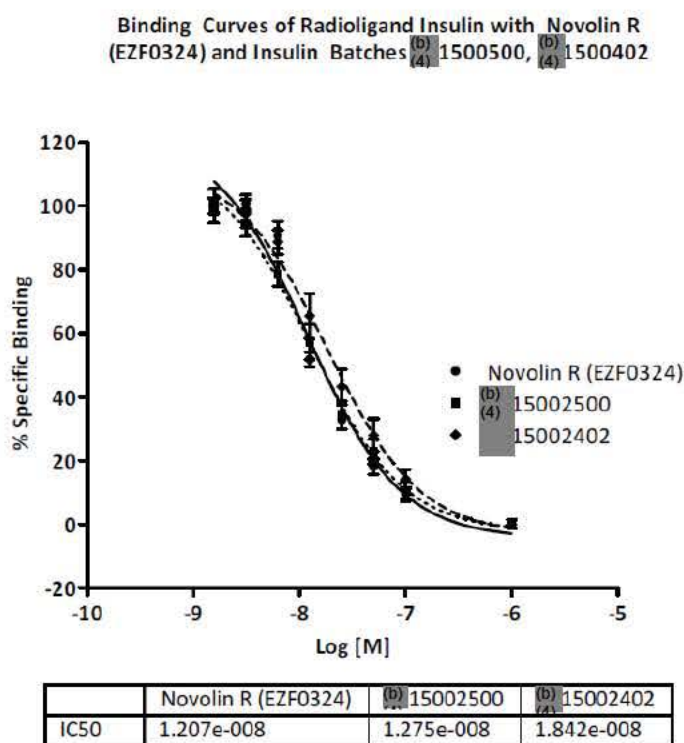


Table 5: IC₅₀ values of the Insulin test batches and the excipient free Novolin R lots with their 95% Confidence Interval.

STUDY	SAMPLE		IC ₅₀ (M)	95% CI for IC ₅₀ (M)
STUDY-1	Insulin Batches	(b) (4) 15002500	1.025E-08	6.897e-009 to 1.522e-008
		(b) (4) 15002402	1.838E-08	1.213e-008 to 2.786e-008
		(b) (4) 15002681	9.914E-09	6.530e-009 to 1.505e-008
	Novolin R Lots	EZF0324	1.362E-08	7.162e-009 to 2.589e-008
		EZF0324	1.107E-08	8.460e-009 to 1.449e-008
		EZF0324	1.232E-08	8.856e-009 to 1.714e-008
		EZF0488	8.595E-09	6.097e-009 to 1.212e-008
		DZF0495	9.225E-09	6.652e-009 to 1.280e-008
STUDY-2	Insulin Batches	(b) (4) 15002500	7.891E-09	5.247e-009 to 1.187e-008
		(b) (4) 15002402	8.651E-09	5.357e-009 to 1.397e-008
		(b) (4) 15002681	1.647E-08	9.723e-009 to 2.792e-008
	Novolin R Lots	EZF0324	1.216E-08	8.191e-009 to 1.806e-008
		EZF0324	1.921E-08	1.360e-008 to 2.715e-008
		EZF0324	1.999E-08	1.366e-008 to 2.925e-008
		EZF0488	1.546E-08	1.032e-008 to 2.318e-008
		DZF0495	1.672E-08	1.049e-008 to 2.666e-008
STUDY-3	Insulin Batches	(b) (4) 15002500	2.807E-08	1.831e-008 to 4.301e-008
		(b) (4) 15002402	3.644E-08	2.469e-008 to 5.380e-008
		(b) (4) 15002681	3.842E-08	2.459e-008 to 6.004e-008
	Novolin R Lots	EZF0324	9.776E-09	6.953e-009 to 1.375e-008
		EZF0324	1.284E-08	8.983e-009 to 1.835e-008
		EZF0324	1.472E-08	1.041e-008 to 2.083e-008
		EZF0488	2.473E-08	1.706e-008 to 3.584e-008
		DZF0495	2.769E-08	1.817e-008 to 4.220e-008

Sample	Potency Ratio	95% Confidence Interval	RCI
(b) (4) 15002500	0.866	0.68762 - 1.08360	79.42% - 125.15% (45.73%)
(b) (4) 15002402	0.780	0.63865 - 0.94489	81.90% - 121.17% (39.27%)
(b) (4) 15002681	0.834	0.70152 - 0.98896	84.11% - 118.57% (34.46%)
Novolin (EZF0488)	1.033	0.89219 - 1.19706	86.35% - 115.85% (29.51%)
Novolin (DZF0495)	0.964	0.83343 - 1.11440	86.47% - 115.62% (29.15%)
Novolin (EZF0324)*	Reference standard		

The Applicant noted that “The Parallel Line Analysis using PLA 3.0 and subsequent estimation of relative potency at 95% confidence interval, demonstrates that all three test batches were similar to Novolin R lots”.

Table 6: Relative Potency - Insulin Drug Product and Novolin® R

Relative Potency of the Insulin Batches and the Novolin® R Lots with their 95% Confidence Interval

Sample	Potency Ratio	95% Confidence Interval	RCI (Relative Confidence Interval)
(b) (4) 5002500	0.866	0.68762 - 1.08360	79.42% - 125.15% (45.73%)
(b) (4) 5002402	0.780	0.63865 - 0.94489	81.90% - 121.17% (39.27%)
(b) (4) 5002681	0.834	0.70152 - 0.98896	84.11% - 118.57% (34.46%)
Novolin® R (EZF0488)	1.033	0.89219 - 1.19706	86.35% - 115.85% (29.51%)
Novolin® R (DZF0495)	0.964	0.83343 - 1.11440	86.47% - 115.62% (29.15%)
Novolin® R (EZF0324) ^a	Reference standard		

^a Novolin® R (EZF0324) was used as a reference batch to compare the drug substance batches and the other two lots of Novolin® R. Hence the potency ratio of Novolin® R (EZF0324) is not captured.

***Note:** Novolin R (EZF0324) was used as a reference batch to compare the Drug Substance batches and the other two lots of Novolin R. Hence the potency ratio of Novolin R (EZF0324) is not captured.

Applicant's table

Study Title: Affinity and Kinetics of Insulin Binding to IGFR-1 by (b) (4) Comparability of Insulin DS and Novolin

Key Study Findings

- The affinity binding values to IGF-1 receptor were comparable for both Human Insulin Injection drug substance drug substance (b) (4) and the LD (Novolin® R).

The affinity binding of the LD and matrix matched insulin-DP substance (b) (4) to IGFR-1 receptor was conducted via a (b) (4) analysis. According to the Applicant, "Parameters such as on-rate, off-rate and affinities were calculated based on the standard computational tools".

To conduct the IGF-1 receptor binding study, the insulin drug substance was tested in the LD matrix. According to the Applicant "In order to maintain uniformity between Novolin and Insulin DS, the latter was formulated in the condition as Novolin. This was done to minimize differences in deduced parameter due to matrix effect as well as refractive index mismatch". Differences were reported when the new DP formulation was used.

The results of this study show similarity in binding affinity to the IGF-1 receptor for both the insulin drug substance (b) (4), ranging from 1.2 µM to 1.5 µM and the LD (ranging from 1.5 µM to 1.6 µM) as summarized in the Applicant table and figure below:

Table 7: Affinity Comparison - Novolin and Insulin-Drug Substance (b) (4)

Affinity Comparison of Novolin and Insulin-Drug Substance (b) (4) Batches

Cycle Number	Novolin (EZFO324) μM	Novolin (EZFO488) μM	Novolin (EZFO495) μM	Insulin-DS (b) (4) 15002681) μM	Insulin-DS (b) (4) 15002402) μM	Insulin-DS (b) (4) 15002500) μM
1	1.43E-06	1.21E-06	1.28E-06	9.46E-07	1.27E-06	1.32E-06
2	1.52E-06	1.57E-06	1.45E-06	1.22E-06	1.31E-06	1.38E-06
3	1.71E-06	1.54E-06	1.55E-06	1.27E-06	1.48E-06	1.55E-06
4	1.68E-06	1.74E-06	1.67E-06	1.40E-06	1.66E-06	1.34E-06
5	1.78E-06	1.79E-06	1.72E-06	1.53E-06	1.85E-06	2.26E-06
Average	1.62E-06	1.57E-06	1.53E-06	1.27E-06	1.51E-06	1.57E-06
Std Dev	1.42E-07	2.31E-07	1.79E-07	2.19E-07	2.45E-07	3.97E-07
% RSD	9%	15%	12%	17%	16%	25%

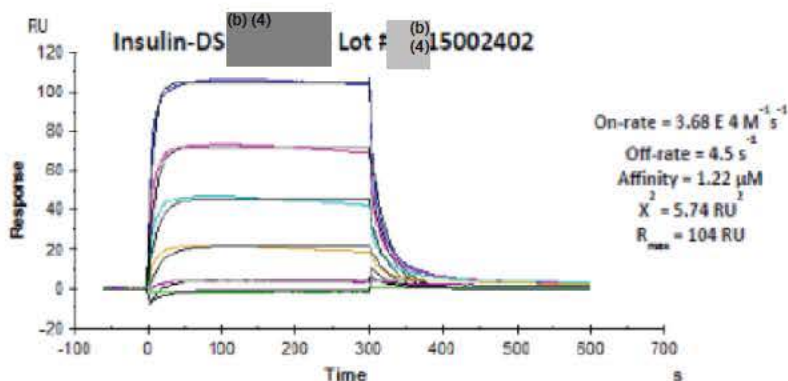
DS = Drug Substance

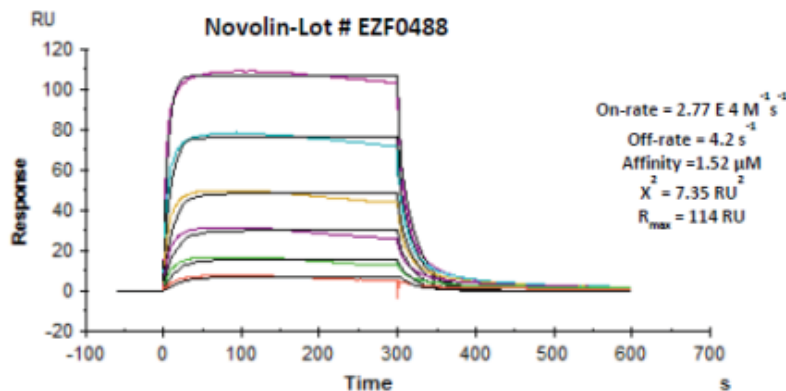
Table 8: The Affinity comparison of all the batches along with the Confidence Interval.

Sample Name	Average	Std Dev	Confidence Interval
Novolin (EZFO324)	1.62E-06	1.42E-07	1.49 E-06-1.75 E-06
Novolin (EZFO488)	1.57E-06	2.31E-07	1.36 E-06-1.78 E-06
Novolin (EZFO495)	1.53E-06	1.79E-07	1.37 E-06-1.69 E-06
Insulin-DS (b) (4) 15002681)	1.27E-06	2.19E-07	1.07 E-06-1.47 E-06
Insulin-DS (b) (4) 15002402)	1.51E-06	2.45E-07	1.29 E-06-1.73 E-06
Insulin-DS (b) (4) 15002500)	1.57E-06	3.97E-07	1.22 E-06-1.92 E-06

Figure 2: Comparison Binding to IGF-1 Receptor

Comparison of BIAcore Association and Dissociation Kinetics of Insulin Drug Substance (b) (4) and Novolin Binding to IGF-1 Receptor (Representative Cycle)





Study Title: Mitogenic Potency Similarity assessment between test Insulin batches and Novolin (R) as reference on 3T3-A31 cells using a fluorimetric bioassay

Key Study Findings

- The mitogenic potency of different batches of drug substances was comparable to the different lots of the LD.

The mitogenic potency of different batches of Human Insulin Injection and insulin extracted from the LD were performed in three independent studies in 3T3-A31 cells (Mouse fibroblast). According to the Applicant “During the method development Novolin formulation buffer as well as Celerity proposed Drug Product excipients ^{(b) (4)}) were tried and did not provide a good dose dependent Growth Stimulation Ratio (%GSR). Good results were obtained with dilution in saline which is the diluent that is used for diluting per package insert for Novolin®. To have the formulation buffer matrix matched to that of the reference standard (Novolin R) the three batches of Drug Substance were dissolved in in 10ml of Novolin formulation buffer for a concentration corresponding to 100U/ml. For the assay purpose 100U/ml of Novolin R and Drug Substances were further diluted in saline (0.9% NaCl) to a concentration of 1U/ml.”

Moreover, the Applicant noted that “The % GSR (growth stimulation ratio) obtained from the triplicates of each reference Novolin® R and matrix matched DS from all three runs were plotted on to SoftMax Pro 5.4.1 for the individual and combined analysis. The relative potencies of the insulin batches were calculated by determining parallelism between the standard and test drug by selecting the Parallel Line analysis mode with fixed weightage for all points and subsequent estimation of relative potencies at 95% confidence interval using SoftMax Pro 5.4.1”.

The findings of this study suggested that insulin samples and its analog bind and activate its related receptors with sub-nanomolar affinity. Insulin and its analog also bind to the structurally related IGF-1 receptor as summarized in the Applicant’s table and figures below:

Figure 3: Combined Analysis - Three Independent Studies

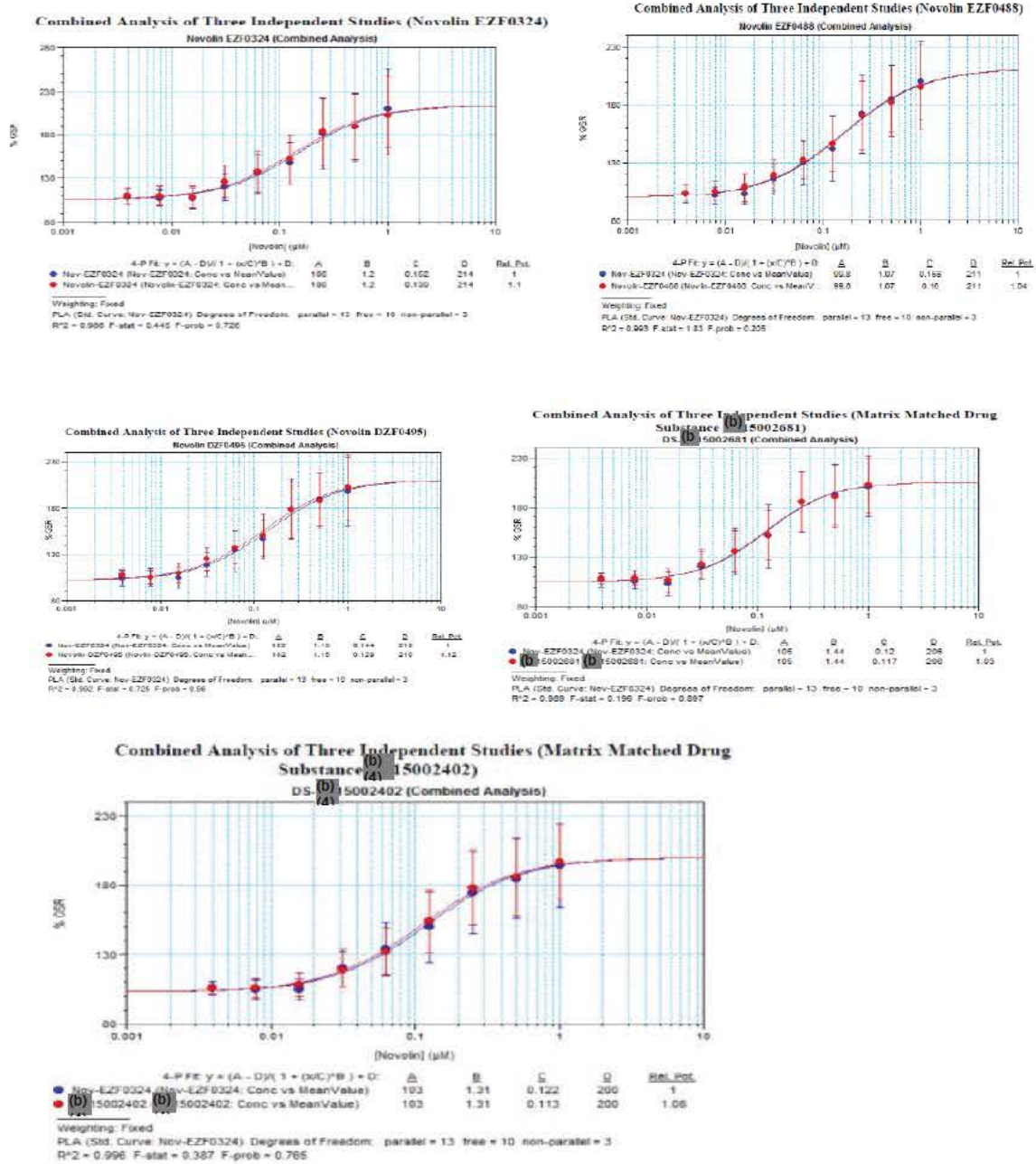


Table 9: Relative Potencies - Three Independent Studies

Sample	Relative Potency ^a						
	Study-1	Study-2	Study-3	%CV	Combined Analysis	CI-Low	CI-High
(b) (4) 15002500	1.14	1.13	1.08	2.9	1.12	0.891	1.348
(b) (4) 15002402	1.02	1.14	1.08	5.6	1.08	0.926	1.236
(b) (4) 15002681	1.06	1.09	0.972	5.9	1.03	0.788	1.263
Novolin-EZF0324	0.998	1.13	1.08	6.2	1.1	0.809	1.386
Novolin-EZF0488	1.09	1.04	1.06	2.4	1.04	0.852	1.23
Novolin-DZF0495	1.14	1.17	1.06	5.1	1.12	0.895	1.348

^a Compiled analysis of the data from three independent runs.

Study Title: Insulin mediated Glucose Uptake assay to evaluate similarity of the test Insulin batches with Novolin (R) as reference standard on pre-differentiated adipocytes (3T3-L1)

Key Study Findings

- The glucose uptake assay showed similar metabolic activity for both Human Insulin Injection and insulin extracted the LD.

The study was designed to use a fluorescence-based enzymatic assay to illustrate the similarity in metabolic activity of three batches of Human Insulin Injection prepared from (b) (4) drug substances (b) (4) 15002500, (b) (4) 15002402, and (b) (4) 15002681) to the LD batches (EZF0324, EZF0488, and DZF0495) in 3T3-L1 Cells. According to the Applicant "The RFUs (Relative fluorescence units) were exported to the template created in SoftMax Pro 5.4.1. The Parallel Line Analysis and the graphs were plotted using SoftMax Pro 5.4.1. The relative potency was calculated for the samples using Novolin® R (EZF0324) as reference at 95% confidence interval using SoftMax Pro 5.4.1".

Moreover, insulin was extracted from the LD batches and formulated in the new Human Insulin Injection matrix. Again, according to the Applicant "To evaluate the metabolic activity of Insulin alone in the absence of excipients, the extraction of insulin from Novolin® R was performed using Amicon Ultra-15 Centrifugal Filter Units of 3KDa with Ultracel-3 membrane tubes to get the insulin in formulation buffer (b) (4). Hence the excipients of Novolin® R do not interfere in this metabolic assay".

The results of three independent studies with different batches of the LD (Novolin® R) and the new DP suggested comparability in glucose uptake with both formulations as summarized in figures below from the Applicant:

Figure 4: Combined Analysis of Three Independent Studies

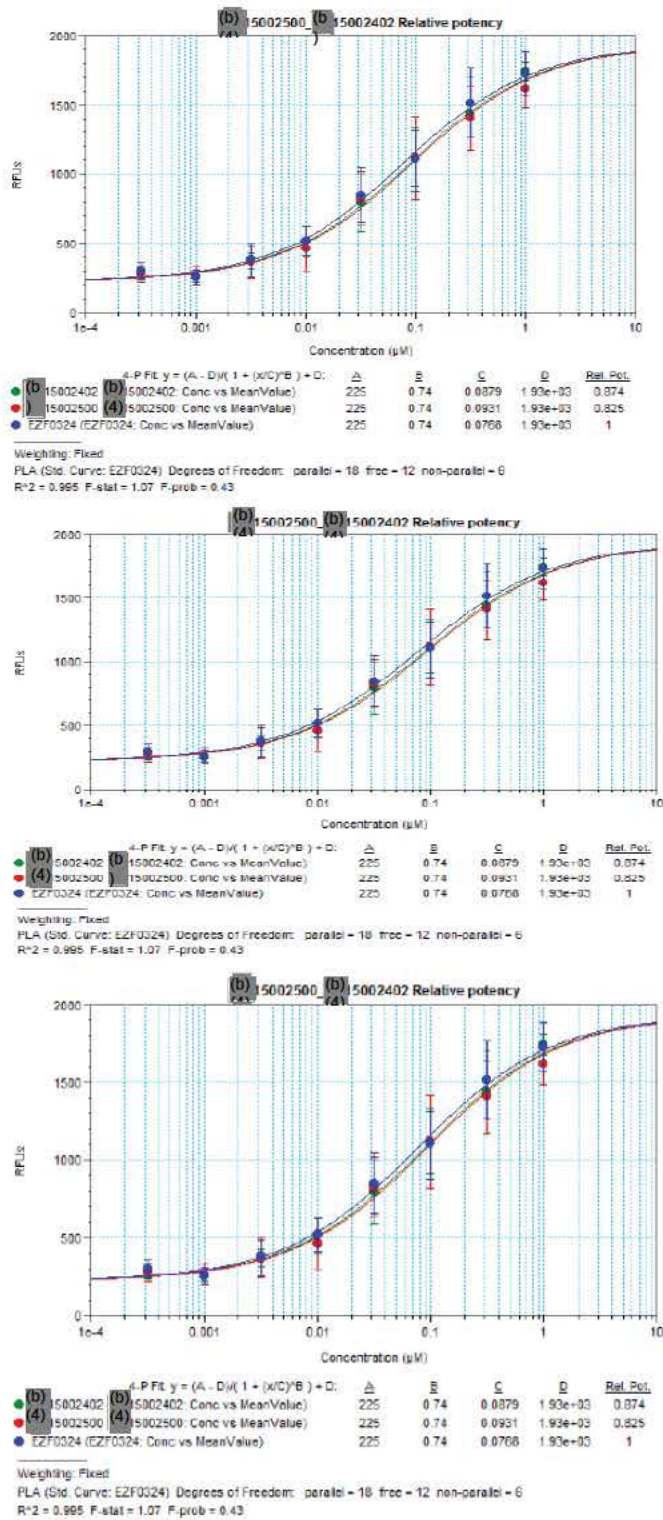


Table 10: Glucose Uptake - Relative Potency Results

Sample	Relative Potency					
	Study-1	Study-2	Study-3	Combined Analysis	CI-Low	CI-High
(b) (4) 15002500	1.410	0.792	0.615	0.825	0.640	1.010
(b) (4) 15002402	1.010	1.090	0.700	0.874	0.678	1.069
(b) (4) 15002681	1.310	1.370	0.934	1.120	0.909	1.332
Novolin-EZF0488	0.745	1.040	1.060	1.000	0.782	1.223
Novolin-DZF0495	1.050	0.896	0.742	0.899	0.702	1.097
Novolin-EZF0324 ^a	Reference Standard					

^a Novolin[®] R (EZF0324) was used as a reference batch to compare the drug product batches and the other two lots of Novolin[®] R. Hence the potency ratio of Novolin[®] R (EZF0324) is not captured.

4.2 Secondary Pharmacology

No secondary pharmacology studies were conducted.

4.3 Safety Pharmacology

No safety pharmacology studies were conducted.

5 Pharmacokinetics/ADME/Toxicokinetics

5.1 PK/ADME

No PK/TK or ADME studies were conducted.

6 General Toxicology

6.1 Single-Dose Toxicity

No single-dose toxicity studies were conducted.

6.2 Repeat-Dose Toxicity

A 2-week repeat-dose toxicity study with 2-week recovery phase was conducted to determine the toxicity of (b) (4) impurities ((b) (4) -degradation products) in human insulin with continuous intravenous infusion to rats.

Study title: 2-Week Toxicity and Toxicokinetic Continuous Intravenous Infusion Study with Insulin in Rats with a 2-Week Recovery Phase	
Study no.:	8337290
Study report location:	eCTD
Conducting laboratory and location:	(b) (4)
Date of study initiation:	11 July 2017
GLP compliance:	Yes
QA statement:	Yes

Drug, lot #, and % purity:	Human Insulin (rDNA origin) Injection; Batch #: NC080916; Purity: see under section "Dosing Solution Analysis".
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Key Study Findings: In 2-week rat study with continuous intravenous infusion, no safety issues were reported in the new DP with levels of (b) (4) impurities.

Methods	
Doses:	See Table below
Frequency of dosing:	Continuous intravenous infusion
Route of administration:	Intravenous infusion (by catheter implanted into a femoral vein)
Dose volume:	4.8 mL/kg/day (0.2 mL/kg/hr) except for females weighing less than 250 g (0.05 mL/kg/hr from day 6 onwards). Novolin® R (1 U/mL by diluted with sterile saline (0.9% sodium chloride injection, USP)
Formulation/Vehicle:	Sterile saline (0.9% sodium chloride injection, USP)
Species/Strain:	CrI:CD(SD) rats
Number/Sex/Group:	15/sex/group
Age:	10 to 11 weeks
Weight:	Males: 306 to 414 g; Females: 206 to 261 g
Deviation from study protocol:	Did not affect the results

Table 11: Experimental Design

Group ^a	No. of Animals		Nominal Insulin Dose Level ^b (U/kg/hour)	Target (b) (4) Concentration ^c (%)
	Male ^d	Female ^d		
1 (Control)	15	15	0	Not applicable
2 (Novolin® R)	15	15	0.2	*
3 (Low)	15	15	0.2	2
4 (Mid)	15	15	0.2	5
5 (High)	15	15	0.2	10

^a Group 1 received saline control article only.

^b Nominal insulin concentration for Groups 2 through 5 was 1.0 U/mL.

^c % (w/w) of (b) (4) and (b) (4) degradants relative to insulin.

^d The lowest numbered 10 animals/sex/group were designated for terminal sacrifice and the highest numbered five animals/sex/group were designated for toxicokinetic sampling and a 14-day recovery evaluation (survival permitting).

^e The (b) (4) concentration was measured in formulated dosing samples (i.e., a target concentration did not apply to this group).

Applicant's Table

Note: Insulin containing graded concentrations of (b) (4) and (b) (4) degradants was administered to animals in Groups 3, 4, and 5.

Observations and Results

Mortality

Mortality in 4 animals was not considered drug-related because no significant macroscopic/microscopic observations were noted in these animals. The table below presents the cause of death for each animal:

Table 12: Cause of Death

Mortality		
Groups	Female / cause of death	Male /cause of death
1 (Control)	1 (due to blood sampling)	-----
2 (LD)	1 (due to animal's response to the catheter)	-----
3 (DP, Low)	-----	1 (due to blood sampling)
4 (DP, Mid)	-----	-----
5 (DP, High)	1 (due to blood sampling)	-----

Clinical Signs

Unremarkable

Body Weights

Unremarkable

Feed Consumption

Unremarkable

Hematology

Unremarkable

Clinical Chemistry

- Clinical chemistry analyses on samples showed expected pharmacologic action of insulin by lower glucose concentration (on Day 10) in 0.2 U/kg/h insulin treated animals alone or with $\geq$ (b) (4).
- In treated males (0.2 U/kg/h insulin + (b) (4), group 5), statistically significant increases in the level of aspartate aminotransferase (ALT), alanine aminotransferase (AST), and alkaline phosphatase (ALP) compared to control saline group were reported. These changes were not correlated with any macroscopic or microscopic observations, and were not of a biologically significant magnitude (see table below):

Table 13: Clinical Chemistry Significant Changes

Groups/Males	ALT (U/L)		AST (U/L)		ALP (U/L)	
	Dosing	Recovery	Dosing	Recovery	Dosing	Recovery
1 (Control)	4.2±0.51	3.9±0.31	109±12.3	103±15.8	123±26.3	103±15.8
2 (LD)	4.0±0.13	4.0±0.31	127±25.5*	95±13.4	136±25.6	95±13.4
3 (DP, Low)	4.0±0.19	4.4±0.05*	111±11.1	118±25.1	127±1.5	118±25.1
4 (DP, Mid)	4.1±0.26	4.3±0.11*	115±15.4	104±10.8	95±12.7	104±10.8
5 (DP, High)	4.0±0.23	4.1±0.29	128±15.3*	97±13.0	156±26*	123±19.8

Urinalysis

No (b) (4) - and/or nominal insulin- related urinalysis effects were observed.

Gross Pathology

Unremarkable

Organ Weights

Unremarkable

Histopathology**Adequate Battery**

Yes (only tissues from all animals in Groups 1, 2, and 5 were analyzed).

Peer Review

Peer review was not noted in the study report.

Histological Findings

No significant microscopic observational differences were reported in different treated groups. Chronic-active inflammation was reported at the catheter and infusion sites of animals from all groups.

Dosing Solution Analysis

According to the Applicant “The analysis results for the pre-study samples indicate that the degraded products were successfully produced with attainment of an approximate (b) (4) and (b) (4) concentration of (b) (4) degradation products for Groups 3, 4 and 5, respectively. Analysis results from Day 1 and Day 14 indicated that the concentrations of HIIDP and (b) (4) degradation products remained consistent as stored and used through the dosing phase, including the sample shipments”.

Table 14:Dosing Solution Analysis

3.2.1 Test Article

Test Article ^a	Storage	Batch No.	Expiration Date	Purity
Human Insulin (rDNA origin) Injection, 1 U/mL in a 100 mL plastic bag, formulated in 0.9% sodium chloride.	In a refrigerator, set to maintain 2 to 8°C	NC080916	b	c
a The test article was provided with various target concentrations of (b) (4) degradants (b) (4) % (w/w) of (b) (4) and (b) (4) degradants, relative to insulin.				
b The test article was provided at the following stability time points at 25°C: 10 days (Group 3), 7 weeks (Group 4), or 17 weeks (Group 5).				
c See Certificates of Analysis for (b) (4) (b) (4) and (b) (4) content.				

Applicant's Table

Table 15: Mean Concentrations of Human Insulin in Rat - Days 2 and 14

Group	Insulin Dose (U/kg/hr)	Sex	Day 2 Time After Dose (hr)			Day 14 Time After Dose (hr)		
			1	6	12	1	6	12
Group 1 Saline	0	M	0 ± 0	0 ± 0	8.56 ± 19.1	0 ± 0	0 ± 0	0 ± 0
		F	0 ± 0	0 ± 0	0 ± 0	0 ± 0	0 ± 0 ^a	0 ± 0 ^a
Group 2 Novolin R	0.2	M	728 ± 405	1010 ± 1050	663 ± 356	431 ± 321	1170 ± 1860	15.2 ± 34
		F	436 ± 411	275 ± 202	926 ± 934	604 ± 428	830 ± 725	6.27 ± 14
Group 3 Human Insulin, (b) (4) imp.	0.2	M	619 ± 186	768 ± 223	882 ± 195	709 ± 213	980 ± 558 ^a	53.6 ± 87.5 ^a
		F	358 ± 392	606 ± 428	618 ± 425	358 ± 164	862 ± 478	14.3 ± 19.9
Group 4 Human Insulin, (b) (4) imp.	0.2	M	411 ± 50.9	481 ± 117	887 ± 669	483 ± 136	467 ± 73.2	0 ± 0
		F	138 ± 176 ^a	518 ± 584	606 ± 584	1530 ± 2210	1740 ± 2680	42.8 ± 54.9
Group 5 Human Insulin, (b) (4) imp.	0.2	M	619 ± 253	777 ± 163	866 ± 222 ^a	733 ± 383	989 ± 371	0 ± 0
		F	977 ± 919	1820 ± 2150	1350 ± 935 ^a	1380 ± 1610	1290 ± 835	0 ± 0

M = Male; F = Female

Notes: All means (± SD) represent values of n=5 animals, except where noted (^a, n=4).**Applicant's Table****7 Genetic Toxicology**

No genetic toxicology studies were performed.

Human insulin is not mutagenic in the following *in vitro* tests: The chromosomal aberration assay in human lymphocytes, the micronucleus assay in mouse polychromatic erythrocytes, and the mutation frequency assay in Chinese hamster cells.

8 Carcinogenicity

No carcinogenicity studies were performed.

Standard 2-year carcinogenicity studies in animals have not been performed to evaluate the carcinogenic potential of human insulin.

9 Reproductive and Developmental Toxicology

No reproductive studies were performed.

No reproductive toxicity studies have been performed with human insulin. Standard reproduction and teratology studies in animals, including fertility assessments have not been conducted with human insulin.

11 Integrated Summary and Safety Evaluation

The Applicant seeks approval of Human Insulin Injection (rDNA origin; 1U/ml in 0.9% NaCl) for the treatment of diabetes mellitus under the 505(b)(2) NDA approval pathway.

For the development of Human Insulin Injection, the Applicant relies on the Agency's previous findings of safety and effectiveness for previously the U.S.-approved, Orange Book-listed drugs (LD) Novolin® R Injection marketed by Novo Nordisk (NDA 019938). Novolin® R was approved in 1991 and its safety profile is well-known. Celerity's Human Insulin (rDNA origin) Injection is a ready-to-use (1 U/mL) premixed solution of recombinant human insulin manufactured from a yeast (*Pichia pastoris*) expression system. Both Human Insulin Injection and the LD will be administered at the same dose specified in the labeling for Novolin® R's indication for intravenous administration.

In the body, insulin binds to the insulin receptors on various tissues and regulates levels of blood glucose. Insulin can cause hypoglycemia if administered in excess amounts.

To establish a scientific "bridge" between the Human Insulin Injection and the LD, the Applicant conducted a pharmacokinetic (PK)/pharmacodynamic (PD) bioequivalence (study report #: CEL-HI-200) to compare the pharmacokinetics of the two formulations, establish the required bioequivalence determination, investigate the CMC properties and functional characteristics (affinities, activities) of the two formulations, and performed a two week "bridging" toxicity study (study report #: 8337290) to qualify the impurity profile of Human Insulin Injection.

Nonclinical pharmacology studies were designed to compare different batches of Human Insulin Injection to the different batches of the LD (or to insulin extracted from the LD). The following were conducted: 1) Assessment of binding affinity/activation of the insulin and IGF-1 receptors; 2) determining metabolic activation; and 3) evaluating mitogenicity. For the insulin receptors binding affinity assay, the Applicant evaluated the binding affinity for the IR-B (the long form receptor in adult tissues for the metabolic actions) and did not evaluate IR-A (the short form receptor in fetal and prenatal period for the mitogenic actions). Because the Celerity's product is intended to use in the hospital and emergency room with a ready-to-use IV bag convenience formulation (not for the chronic use), the binding affinity to the IR-A receptor is not needed. The Applicant noted that for some of the in vitro pharmacology studies, insulin was extracted from the LD and formulated in the Human Insulin Injection buffer because excipients of the LD

confounded results of these studies. Human Insulin Injection has none of the LD's excipients, and contains only sodium chloride buffered with sodium phosphate; therefore, there is no safety concerns for the excipients of Human Insulin Injection. Concern for Human Insulin Injection is primarily related to the active ingredient (insulin), but the results of nonclinical studies suggest no safety concerns and the insulin in Human Insulin Injection was comparable to insulin in the LD in the in vitro battery of assays.

A two-week repeat-dose toxicity study with a 2-week recovery was conducted with continuous intravenous infusion in rats with 0.2 U/kg/hr containing (b) (4) impurities to qualify the (b) (4) impurities. The results of this study showed no additional safety issues with (b) (4) impurities in Human Insulin Injection. Therefore, impurities of the new DP were identified within established acceptable limits.

The carcinogenic potential of insulin has not been evaluated with animal studies, because the insulin sequence is identical to that of the endogenous human hormone. In the Pharm/Tox review of the LD (NDA 019938), it is indicated that the insulin in the LD was not mutagenic in the following in vitro tests: the chromosomal aberration assay in human lymphocytes; the micronucleus assay in mouse polychromatic erythrocytes; and the mutation frequency assay in Chinese hamster cells, and that no animal studies have been conducted to determine the effect of insulin on fertility or reproduction.

Concerning the immunogenicity of the new DP, the Applicant provided literature to justify that there is low immunogenicity risk for recombinant human insulin in both humans and animal models. According to the Applicant, "the protein is a simple polypeptide consisting of 51 amino acids containing two chains (Chains A and B) linked with two inter and one intra-chain disulfide linkages (molecular weight = 5.8 KD). The amino acid sequence is identical to the endogenous human insulin and contains no (b) (4) thereby not introducing any neoepitopes or modifications that might stimulate an immune response". Animal studies are not considered predictive of adaptive immune responses in humans; results of immunogenicity assessments in animals are useful for animal study interpretation.

In summary, to establish similarity between Human Insulin Injection and the U.S. approved LD, Novolin R, the Applicant conducted a PK/PD bioequivalence study, a series of CMC, nonclinical pharmacology assays and a 2-week "bridging" toxicity study to qualify impurities. Pharmacology studies suggest affinities and activities of insulin in Human Insulin Injection is comparable to that of the LD. No significant safety signals were reported in the 2-week bridging nonclinical toxicity study in rats with excess impurities.

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/s/

PARVANEH ESPANDIARI
04/29/2019 01:16:43 PM

CALVIN L ELMORE
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I concur.

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

PHARMACOLOGY/TOXICOLOGY IND REVIEW AND EVALUATION

Application number: 124943
Review number: 1
Supporting document/s: SDN 5
PDUFA review deadline date: April 30, 2017
CDER stamp date: 03/31/2017
Product: Human Insulin in 0.9% Sodium Chloride Injection
1 U/mL (100 U/100 mL)
Indication: To improve glycemic control in patients with
diabetes mellitus
Therapeutic area: Endocrinology, Diabetes, and Metabolism
Sponsor: Celerity Pharmaceuticals LLC
Review Division: Division of Metabolism and Endocrinology
Products (DMEP)
Reviewer: Parvaneh Espandiari, Ph.D.
Supervisor/Team Leader: C. Lee Elmore, Ph.D.
Division Director: Jean-Marc Guettier, M.D.C.M.
Project Manager: CappellLynch, Callie

Template Version: August 29, 2016

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1 Executive Summary

1.1 Introduction

Celerity Pharmaceuticals, LLC (Celerity or “the Sponsor”) is developing Human Insulin Injection (rDNA origin; 1U/ml in 0.9% NaCl) for improving glycemic control in patient with diabetes mellitus. Human Insulin Injection is a polypeptide hormone structurally identical to native human insulin and is produced by rDNA technology using yeast. The Sponsor plans to submit a 505(b)(2) NDA with reliance on the FDA’s previous findings of the safety and efficacy approved Orange book-listed drug (LD) Novolin® R Injection (Nordisk; NDA# 019938).

The Sponsor proposes a Phase 1 BE clinical study with both Celerity’s drug product and the LD to evaluate the similarity of PK/PD profiles of these two formulations along with the safety and tolerability of Human Insulin Injection. Both the Sponsor’s drug product and the LD will be administered at the same dose and method that is written in the labeling for Novolin® R. Also, this rate of infusion for the proposed clinical study has previously been used in other clinical glucose clamp studies with no safety issues.

1.2 Brief Discussion of Nonclinical Findings

In addition to CMC characterization (e.g., release testing, impurity, stability, etc.), the functional characteristics of insulin (e.g., binding affinity to insulin receptors; binding affinity to insulin growth factor-1 receptor; metabolic activity; and mitogenic activity) were evaluated in in vitro nonclinical studies. The findings of these studies indicate a high degree of similarity between Celerity’s drug product and the putative LD (Novolin® R).

Based on prior Agency advice, the Sponsor submitted the experimental outline for a proposed 4-week “bridging” rat toxicity study for Agency feedback. The study’s design is acceptable from the Agency’s perspective; however, if conducted, a 4-week recovery period should be added to the study to assess the reversibility of any adverse effects observed during the treatment phase.

1.3 Internal Comments

While the in vitro characterization of Human Insulin Injection appears to indicate a robust similarity compared to Novolin R, Human Insulin Injection is produced recombinantly in a different strain of yeast compared to Novolin R. Concerns related to differences in immunogenicity risk cannot be adequately predicted based on nonclinical animal models and should be evaluated clinically.

1.4 Recommendations

Pharm/Tox recommends that the proposed Phase I clinical study is reasonably safe to proceed.

1.4.1 Clinical Study (ies) Safe to Proceed: Y

1.4.2 If Not Safe to Proceed

Nonclinical deficiencies

[Click here to enter text.](#)

Nonclinical information needed to resolve deficiencies

[Click here to enter text.](#)

1.4.3 Additional Recommendation(s) (Non-hold comments/advice to sponsor) if any.

The overall experimental design of the proposed bridging 4-week rat toxicity study appears reasonable, except we recommend including a recovery period of sufficient duration to assess reversibility of any adverse effects observed at the end of the dosing phase. Based on evolving Agency approaches to the nonclinical safety evaluation of recombinant human insulin products, a complete in vitro battery of similarity studies (i.e., studies establishing similarity via evaluation of receptor binding affinity, receptor activation, metabolic activity, and mitogenic potential) with comparison of your product to the listed drug (US-approved Novolin R) may be adequate from a nonclinical point of view to support a marketing application. I.e., should in vitro studies be deemed to have established sufficient similarity between your human insulin product and the listed drug (in addition to adequate CMC and clinical assessments), the in vivo bridging 4 week rat toxicity study may not be warranted. Final determination of acceptability remains a review issue. Any impurities, degradants and/or residual solvents exceeding qualification thresholds per Agency guidance may require additional nonclinical studies. Any changes to your formulation (e.g., changes in excipients) you might make prior to marketing may also require additional nonclinical studies.

2 Drug Information

2.1 Drug

Code Name(s):

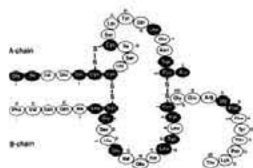
CAS Registry Number(s): 11061-68-0

Generic Name: Insulin Human

Chemical Name: Not applicable

Molecular Formula/Molecular Weight: C₂₅₇H₃₈₃N₆₅O₇₇S₆/5807.57

Structure or Biochemical Description: Insulin Human, USP is a two-chain peptide hormone consisting of 51 amino acids. The A-chain is composed of 21 amino acids and the B-chain is composed of 30 amino acids.



Pharmacologic Class: Human insulin

2.2 Relevant INDs, NDAs, BLAs and DMFs

NDA# 019-938 (Novolin R[®])

2.3 Drug Formulation

The Celerity's drug product is a premixed solution of recombinant human insulin formulated (1 U/mL) in a solution of 0.9% sodium chloride, 0.29 mg/mL monobasic sodium phosphate, monohydrate, 0.412 mg/mL dibasic sodium phosphate, anhydrous, and water in a 100 mL plastic Galaxy PL 2501 container (ready for injection). Galaxy is Baxter's proprietary IV bag that encompasses the manufacturing of sterile SVP injections in (b) (4) plastic containers (DMF#6344). Several approved products are delivered in the GALAXY containers, including Azactam, Ceftriaxone, and Nafcillin.

The drug substance, human insulin, is manufactured from a yeast (*Pichia pastoris*) by (b) (4) (b) (4); DMF# (b) (4). According to the Sponsor, "The protein is a simple polypeptide consisting of 51 amino acids containing two chains (Chains A and B) linked with two inter and one intra disulfide linkages (molecular weight = 5.8 KD). The amino acid sequence is identical to the endogenous human insulin and contains no (b) (4)". See Sponsor's tables below:

Table 1: Human Insulin Injection Formulation

Component	Quality Standard	Component Quantity
		Per mL
Insulin Human	USP	1 U/mL
Sodium Chloride	USP	9.0 mg/mL
Monobasic Sodium Phosphate, Monohydrate	USP	0.29 mg/mL
Dibasic Sodium Phosphate, Anhydrous	USP	0.412 mg/mL
Hydrochloric Acid ^a	NF	pH adjustment
Sodium Hydroxide ^a	NF	pH adjustment
Water for Injection	USP	QS

USP = United States Pharmacopeia; NF = National Formulary; QS = Quantity Sufficient
Added as a 1N solution, if necessary, for pH adjustment.

Table 2: Drug substance specification

Description	(b) (4) or practically (b) (4) crystals.
Solubility	Soluble in solutions of (b) (4) and (b) (4)
Identification A. By RT Comparison B. By Peptide mapping	A. Retention time of sample and standard in assay chromatogram should be comparable. B. Test chromatogram should be consistent with reference chromatogram
Bioidentity	It meets the requirements of the Bioidentity test.
Loss on drying	NMT (b) (4)
Related compounds (b) (4)	(b) (4) - NMT (b) (4)
Other related compounds	Other related compounds - NMT (b) (4)
Limit of high molecular weight proteins	Total impurities NMT (b) (4)
(b) (4)	NMT (b) (4) w/w
Assay* (Content of Human insulin + (b) (4)) (b) (4)	NLT (b) (4) USP Human insulin units in each mg
Bacterial endotoxins	NMT (b) (4) USP endotoxins unit in each mg.
Microbial limits	
Total bacterial count	NMT (b) (4) cfu per g.
Host cell derived proteins	NMT (b) (4) ppm
Host cell DNA content	NMT (b) (4) pg / (b) (4) mg
Residual Solvents: (b) (4)	NMT (b) (4) ppm NMT (b) (4) ppm NMT (b) (4) ppm NMT (b) (4) ppm
Content of (b) (4) (b) (4)	NMT (b) (4) ppm
Microbial Limits:	
Total Yeasts and Molds Count	NMT (b) (4) CFU/g

* - On (b) (4)

Note: Each 0.0347 mg of Human Insulin is equivalent to 1 IU of Human Insulin.

Table 3: Comparison Celerity's Human Insulin Injection to Novolin R

Applicant	Novo Nordisk [Reference Listed Drug]	Human Insulin Injection (Proposed Drug)
Product	NOVOLIN R is a sterile human insulin injectable solution stored in 10 mL glass vials	Human Insulin Injection is a sterile premixed human insulin injectable solution stored in a 100 mL GALAXY plastic bag
Active Ingredient	Human Insulin, USP	Human Insulin, USP
Total Drug Content	1000 U (100 U/mL in 10 mL glass vial)	100 U (1 U/mL in a 100 mL bag)
Container Closure	Single-use glass vial. When administered intravenously, polypropylene infusion bags should be used.	Single-use plastic bag (GALAXY),
Tonicity Agent	Can be used with the following infusion fluids: 0.9% sodium chloride, 5% dextrose, or 10% dextrose with 40 mmol/L potassium chloride	Premixed with 0.9% w/v Sodium Chloride, USP 900 mg/100 mL (9 mg/mL)
Other Inactive Ingredients	Zinc Chloride approximately 70 mcg/10 mL (approximately 7 mcg/mL) Glycerol 160 mg/10 mL (16 mg/mL) Metacresol 30 mg/10 mL (3 mg/mL) pH Adjusted with Sodium Hydroxide and/or Hydrochloric Acid Water for Injection, USP	Sodium Chloride, USP 900 mg/100 mL (9 mg/mL)-also listed as a tonicity agent Monobasic Sodium Phosphate, Monohydrate, USP 29.0 mg/100 mL (0.290 mg/mL) Dibasic Sodium Phosphate, Anhydrous, USP 41.2 mg/100 mL (0.412 mg/mL) pH Adjusted with Sodium Hydroxide, NF and/or Hydrochloric Acid, NF Water for Injection, USP
Volume	10 mL glass vial	100 mL GALAXY plastic bag
Concentration	100 U/mL	1 U/mL
Dosage Form	Injectable; sterile solution (should be used in infusion systems using polypropylene infusion bags)	Injectable; sterile solution (premixed for intravenous infusion)
Route of Administration	Injection: IV infusion or subcutaneous	Injection: IV infusion
Dosing Regimen	Total daily insulin requirements vary and are usually between 0.05 and 1.0 units/kg/day.	Total daily insulin requirements vary and are usually between 0.05 and 1.0 units/kg/day.
Marketing Status	OTC	Prescription (Rx)
Host Cell Expression System	Saccharomyces cerevisiae (baker's yeast)	Pichia pastoris (yeast)

Table 4: Drug Excipients

Component	Baxter Batch Number	Manufacturer Batch Number
Insulin Human, USP	RD160912	(b) (4) 16003436
Sodium Chloride, USP	RD21625003	RI16211052
Monobasic Sodium Phosphate, Monohydrate, USP	RD160829	0000133199
Dibasic Sodium Phosphate, Anhydrous, USP	RD160829	0000132437
Hydrochloric Acid, NF	N/A	N/A
Sodium Hydroxide, NF	N/A	N/A
Water for Injection, USP	RD161026	

USP = United States Pharmacopeia; NF = National Formulary; N/A = Not Applicable

To submit NDA with the 505(b)(2) regulatory pathway, the Sponsor conducted several studies to evaluate the similarity between Celerity's drug product and the LD (Novolin®R). These studies were related to the CMC description and functional characteristics.

Results of studies for amino acid analysis, N-terminal sequencing, peptide mapping, circular dichroism, SDS-PAGE, imaged capillary isoelectric focusing (icIEF), micro flow imaging (MFI), differential scanning calorimetry (DSC), analytical ultracentrifuge sedimentation velocity (AUC), nuclear magnetic resonance (NMR), and mass spectrometry suggested that (b) (4) insulin that formulated into Celerity's drug product (Human Insulin Injection) is similar to the LD (Novolin®R).

Moreover, findings from studies related to pH, appearance, high molecular weight proteins, osmolality, and impurity profile (comparisons using RP-uPLC and SEC) suggested similarity between (b) (4) insulin and the LD (Novolin®R). Furthermore, several in vitro assays were conducted related to insulin receptor binding, mitogenic potential, glucose uptake, and IGF-1 receptor binding (reviewed under section 4. 2, Secondary Pharmacology). The table below from the Sponsor shows samples that were used for the above studies:

Table 5: List of Samples - Tested at (b) (4)

Sample Type	Lot Number	Sample ID Abbreviation	Manufacturer	Manufacturing Date	Age at Time of Testing
Drug Substance	(b) (4) 15002402	(b) (4) 15002402	(b) (4)	July 2015	4 Months
Drug Substance	(b) (4) 15002500	(b) (4) 15002500	(b) (4)	August 2015	4 Months
Drug Substance	(b) (4) 15002681	(b) (4) 15002681	(b) (4)	August 2015	4 Months
Novolin® R Vehicle 100 U/mL	NB28973:066	Novolin R Matrix	NA ^a	July 2016	2 Months
Drug Substance (Novolin® R Vehicle), 100 U/mL	RD150902A	DS1-Novolin R vehicle	NA ^a	July 2016	2 Months
Drug Substance (Novolin® R Vehicle), 100 U/mL	RD150902B	DS2-Novolin R vehicle	NA ^a	July 2016	2 Months
Drug Substance (Novolin® R Vehicle), 100 U/mL	RD150902C	DS3-Novolin R vehicle	NA ^a	July 2016	2 Months
Drug Substance (Novolin® R Vehicle) Diluted in 0.9% Saline, 1 U/mL	NA ^a	DS1-Novolin R vehicle (diluted)	NA ^a	NA ^a	NA ^a
Drug Substance (Novolin® R Vehicle) Diluted in 0.9% Saline, 1 U/mL	NA ^a	DS2-Novolin R vehicle (diluted)	NA ^a	NA ^a	NA ^a
Drug Substance (Novolin® R Vehicle) Diluted in 0.9% Saline, 1 U/mL	NA ^a	DS3-Novolin R vehicle (diluted)	NA ^a	NA ^a	NA ^a
Drug Product, 1 U/mL	78221	DP 1	Baxter	20 June 2016	3 Weeks
Drug Product, 1 U/mL	78222	DP 2	Baxter	22 June 2016	3 Weeks
Drug Product, 1 U/mL	78223	DP 3	Baxter	23 June 2016	3 Weeks
Drug Product, 1 U/mL	NC080916	DP 4	Baxter	27 October 2016	3 Weeks
Novolin® R (RLD) US-Approved	EZF0278	Novolin R 1	Novo Nordisk	Expiry Date: August 2017	NA

Sample Type	Lot Number	Sample ID Abbreviation	Manufacturer	Manufacturing Date	Age at Time of Testing
Novolin® R (RLD) US-Approved	EZF0444	Novolin R 2	Novo Nordisk	Expiry Date: September 2017	NA
Novolin® R (RLD) US-Approved	EZF0488	Novolin R 3	Novo Nordisk	Expiry Date: October 2017	NA
Novolin® R (RLD) US-approved Diluted in 0.9% Saline, 1 U/mL	EZF0278	Novolin R 1 Diluted	NA	NA	NA
Novolin® R (RLD) US-approved Diluted in 0.9% Saline, 1 U/mL	EZF0444	Novolin R 2 Diluted	NA	NA	NA
Novolin® R (RLD) US-approved Diluted in 0.9% Saline, 1 U/mL	EZF0488	Novolin R 3 Diluted	NA	NA	NA
USP Human Insulin Reference Standard	R032L0	USP Ref Std	NA	NA	NA

NA = Not Applicable

* Lot prepared at Baxter; (b) (4) drug substance lots (b) (4) 15002402, (b) (4) 15002500, and (b) (4) 15002681 were prepared at a concentration of 100 U/mL in the Novolin® R vehicle to produce lots RD150902A, RD150902B, and RD150902C, respectively. Drug substance in Novolin® R vehicle was diluted at the time of analysis.

2.4 Comments on Novel Excipients

No novel excipient is used in the Celerity's Human Insulin Injection.

2.5 Comments on Impurities/Degradants of Concern

For information regarding the quality of ingredients and container, the sponsor referred to two DMFs in the following:

- DMF #: (b) (4) (holder, (b) (4)) for Human Insulin- Bulk (rDNA origin)
- DMF #: 6344 (holder, Baxter Healthcare Corporation) for the Galaxy Container Closure System

Letters of authorization for these two DMFs were submitted. In regard to the impurity profile comparisons, the Sponsor noted that "The results indicate that (b) (4) drug substance, Human Insulin Injection drug product, Novolin® R, and USP human insulin reference standard are similar". Moreover, the Sponsor reported that (b) (4) and (b) (4) have similar biological potency as the parent human insulin and the two compounds are not immunogenic.

The Sponsor submitted reports for the all (b) (4) studies. The results of these studies showed an increase from (b) (4) to (b) (4) over the 30 day period at 5°C storage and from (b) (4) to (b) (4) over the 30 day period at 25°C. According to the Sponsor, "The Sum of All (b) (4) results remain within the proposed Sum of All (b) (4) specification (NMT (b) (4))".

2.6 Proposed Clinical Protocol First in human: N

Phase: Phase I Trial

Study Title: A Double-Blind, Randomized, Crossover, Euglycemic Glucose Clamp Trial to Test for Bioequivalence between Celerity's Premixed Human Insulin (rDNA origin) Injection 1 USP unit/mL in 0.9% Sodium Chloride and Novolin® R in Healthy Subjects

Study ID: CEL-HI-200

Doses: Celerity's drug product (Human Insulin in 0.9% Sodium Chloride Injection) is in 100 mL PL 2501 Galaxy bags (100 U/100 mL). For the BE clinical study, subjects will be injected with a constant rate of 1.0 mU/kg/min of Celerity's drug product and/or the LD (Novolin®R) for 6 hours (total dose of 0.36 U/kg).

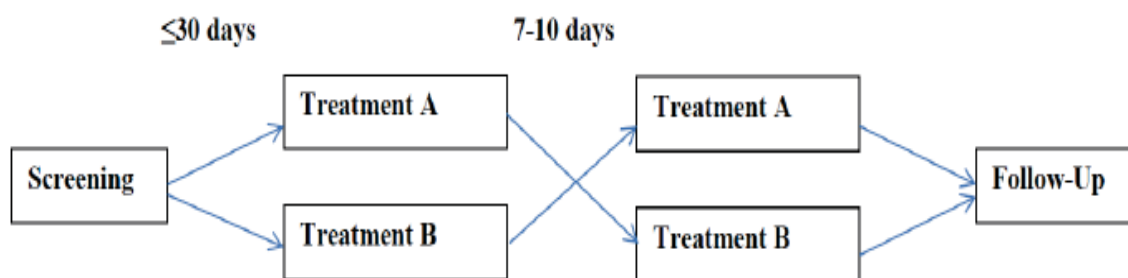
Study Participants

75 healthy male subjects

Protocol Summary

The proposed clinical study is a PK/PD bioequivalence clinical study (a single center, blinded, randomized, active control, two way cross over glucose clamp) in 75 healthy male subjects comparing the pharmacologic profile of Celerity's proposed Human Insulin Injection in 0.9% Sodium Chloride to the LD (Novolin®R). According to the Sponsor, "Each subject will undergo a screening visit, followed by 2 treatment periods, each consisting of an in-house stay, with 1 euglycemic clamp procedure. The washout period between Treatment Periods 1 and 2 will be 7-10 days". See figure below from the Sponsor:

Figure 1: Study Schematic



- Treatment A: Celerity's product Injection (1 U/mL) [100 U/100 mL], infusion bag 100 mL.
- Treatment B: Regular human insulin (i.e., Novolin®R 100 U/mL), vials 10.0 mL. For IV infusion, human (regular) insulin is diluted in 0.9% sodium chloride to an equivalent 1 U/mL concentration.

Study Synopsis

Safety and Efficacy of intended use of Intradermal Infusion, US	
Study Title	Safety and efficacy of ID insulin delivery
Study Type	Non-inferiority ID vs SC insulin delivery with respect to glucose control assessed by HbA1c (non-inferiority margin 0.4%), open label Two-arm parallel design ID vs SC insulin delivery, repeated measure design change from baseline to the end of the study period (24 weeks)
Study Population	Adult Subjects with Type 1 Diabetes on CSII
Inclusion criteria	Baseline HbA1c $\leq 7.5\%$ Existing HbA1c value within past 6 month within 0.5% of the baseline HbA1c Documented SMBG values (minimum of avg. 4 per day) No severe hypoglycemic events during past 6 months Minimum of 1 year on pump therapy
Number of Subjects and Study Sites	Up to 3 sites, Total N = 140 subjects, 70 subjects SC, 70 subjects ID Subjects will be added to accommodate attrition
Study Duration	After Baseline assessment / randomization SC or ID 24 weeks intended use (A1C at baseline, 12 weeks and 24 weeks of intended use)
Study Objectives	To demonstrate safe and effective glucose control with ID insulin infusion during intended use conditions
Primary Endpoint	Change from baseline in HbA1c at 24 weeks powered using a non-inferiority margin of 0.4% for a six month randomized treatment period with either SC or ID insulin infusion
Secondary Endpoints	- HbA1c at 12 weeks - Average glucose values, SMBG - Average insulin use (pump downloads) - Occurrence of hypo-/hyper-glycemic events (SMBM, self-reported) - ID vs SC set lifetime (pump downloads) - Occurrence of catheter occlusion rate (self-reported, pump downloads) - Human factor assessment by patient questionnaire about wearability comfort, ease of use, preference (pain assessment, location documentation e.g., abdomen, arm, thigh, back) - Assessment of infusion site reaction by site observation - AE reporting - Antibody profile at baseline and 24 weeks
Sample size and statistics	Based on previous studies it is estimated that the HbA1c standard deviation between subjects after 24 weeks is 1.1, and the correlation to baseline is 70%. Assuming no difference in glycemic control between ID and SC delivery methods, one-sided non-inferiority test with alpha = 0.05 and margin of 0.4%, the study has 91% power to conclude that ID delivery is non-inferior to SC delivery. Additional subjects may be recruited to account for attrition.

Inclusion criteria:Baseline HbA1c $\leq 7.5\%$ Previous HbA1c value within past 6 months $\pm 0.5\%$ of the baseline HbA1c

Documented SMBG values (minimum of avg. 4 per day)

No severe hypoglycemic events during past 6 months

Minimum of 1 year on pump therapy

Major Analyses planned: The change in HbA1c from baseline will be estimated using an ANCOVA model, with end-of-study HbA1c as response and baseline HbA1c as

Safety Measures: According to the Sponsor, “Safety assessments will occur throughout the duration of the trial, including monitoring of adverse events (AEs), clinical laboratory tests (chemistry, hematology and urinalysis), vital signs measurements (blood pressure, heart rate, respiratory rate, and aural temperature), 12-lead electrocardiograms (ECGs) and physical examinations”.

Sponsor’s Maximum Recommended Human Dose

According to the Sponsor, “The concentration of Human Insulin in 0.9% Sodium Chloride Injection is 1 USP unit of human insulin (rDNA origin)/mL”.

2.7 Previous Clinical Experience

Previous clinical experience: N

If yes, Phase: [Choose an item.](#)

2.8 Regulatory Background

On March 23, 2015, a pre-IND Type B meeting was requested and written responses were granted. See below for nonclinical- related questions (PT/ PIND memo in DARRTS, 05/04/2015):

Celerity Question #2

Celerity proposes the use of the 505(b)(2) regulatory pathway, referencing preclinical safety data and certain clinical safety data from the US-approved Novolin R.

Does the Agency agree that the proposed 505(b)(2) NDA marketing application pathway is appropriate?

FDA Pharm/Tox Response:

“It is recommended that a nonclinical GLP compliant bridging toxicity study, with TK assessment, comparing Celerity’s product with US-approved Novolin R® is completed, to support a 505(b)(2) pathway. For a 505(b)(2) pathway, it is your responsibility to not only establish that it is scientifically appropriate to rely, in part, upon the Agency’s finding of safety and effectiveness for Novolin R® to support approval, but also to identify what data you would like to reference to support your Human Insulin Injection. The final decision about the adequacy of your nonclinical development program cannot be determined until the review of your bridging toxicity study and CMC characterization of your impurities. If there is a difference in the impurity profiles (i.e. impurity, degradant, leachable) between your product and the listed drug, additional nonclinical studies may be required to assess these impurities.”

3 Studies Submitted

3.1 Studies Reviewed

No animal studies were conducted. Several in vitro assays were conducted in the following: Insulin receptor binding, Mitogenic potential, Glucose uptake, Insulin Growth Factor-1 (iGFR) receptor binding of the drug substance to Novolin® R in vitro studies.

3.3 Previous Reviews Referenced

Pharm/Tox PIND 124943 memo in DARRTS (05/04/2015)

4 Pharmacology

Human Insulin Injection is a polypeptide hormone structurally identical to native human insulin and is produced by rDNA technology using yeast. In the body, insulin binds to insulin receptors on muscle and adipocytes and reduces blood glucose by enabling the cellular uptake of glucose.

4.1 Primary Pharmacology (IR binding/activation) and Secondary (IGF-1R binding/activation and mitogenicity)

Several in vitro studies (mitogenic potential, glucose uptake, and insulin growth factor-1, iGFR, receptor binding) were conducted with Celerity's drug product and the LD (Novolin® R). Findings of these studies suggested that Celerity's drug product and the LD (Novolin® R) have similar functional characteristics. The results of these studies are summarized below:

Study Title: Insulin Receptor Binding Assay

Key Study Findings

- Insulin and its analogues bind and activate the insulin receptor with high affinity
- Insulin binds with the structurally related Insulin Growth Factor 1 (IGF-1) with ~1000 fold lower affinity than insulin receptor.

Methods: The binding efficiency of different insulin batches were conducted on human hepatocarcinoma cells (HepG2) with expressing insulin growth factor 1 (IGF-1) and insulin receptors (IRs). Therefore, IC₅₀ determination was performed using GraphPad Prism Version 5.0 (One Site Competition Model). HepG2 cells were chosen to evaluate both major mechanisms: (1) an increase in the binding time of insulin to IR; and (2) increased activation of IGF-1R. The competitive binding study (binding of a single concentration of radio labeled I¹²⁵ recombinant human Insulin) was conducted with various concentrations of unlabeled drug substances and the LD (in triplicates).

Results: Findings of this study suggested that the binding efficiency of different batches of the drug product on HepG2 cells is similar to the LD (Novolin® R) for the same receptor. See the Sponsor's table and figures below:

Table 6: Insulin Receptor Binding Assay – Samples

Sample Number	Sample Name	Batch/Lot Number	Expiry	Concentration
1	Insulin Human	(b) (4) 15002500	Jul, 2019	1U/mL
2	Insulin Human	(b) (4) 15002402	Jul, 2019	1U/mL
3	Insulin Human	(b) (4) 15002681	Jun, 2019	1U/mL
4	Novolin® R	EZF0324 ^a	Oct, 2017	100U/mL
5	Novolin® R	EZF0488	Nov, 2017	100U/mL
6	Novolin® R	DZF0495	Dec, 2016	100U/mL

^a Novolin® R (EZF0324) was used as a reference batch to compare the Drug Product prepared from (b) (4) Drug Substance batches and the other two lots of Novolin® R.

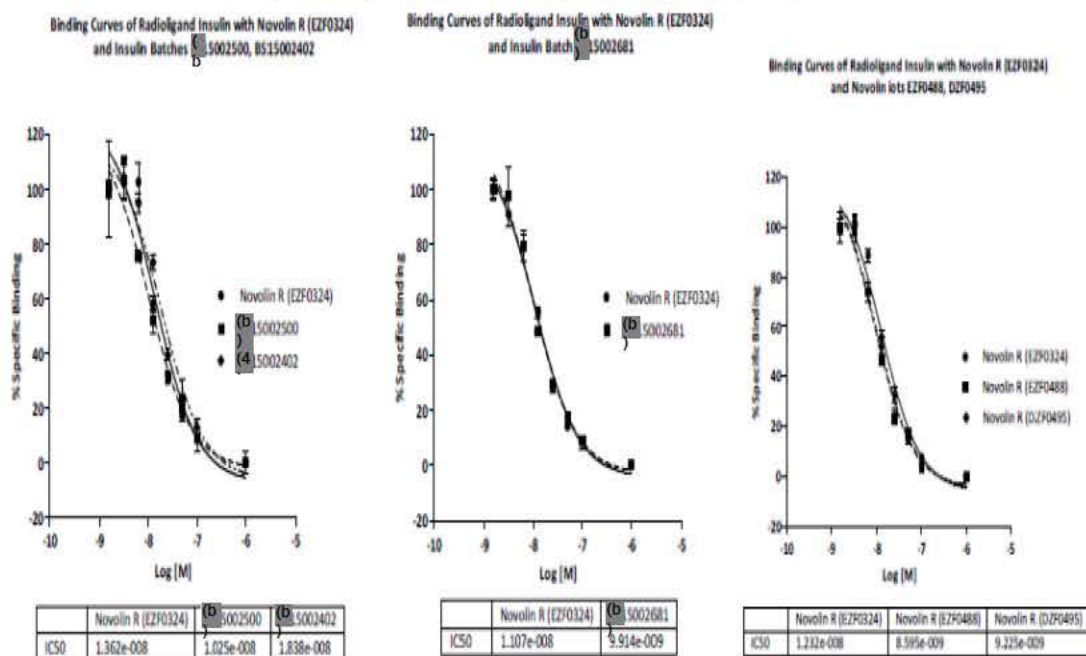
The figures below compare different batches of insulin drug products ((b) (4) 15002500, (b) (4) 15002402, (b) (4) 15002681) to different lots numbers of the LD (Novolin® R) (EZF0488, DZF0495):

Figure 2: One Site Competition Curves - Novolin® R and Insulin Drug Product

Study-1 (N1) One Site Competition Curves of Novolin® R (EZF0324)

Compared with Insulin Drug Product Batches: (b) (4) 15002500, (b) (4) 15002402,

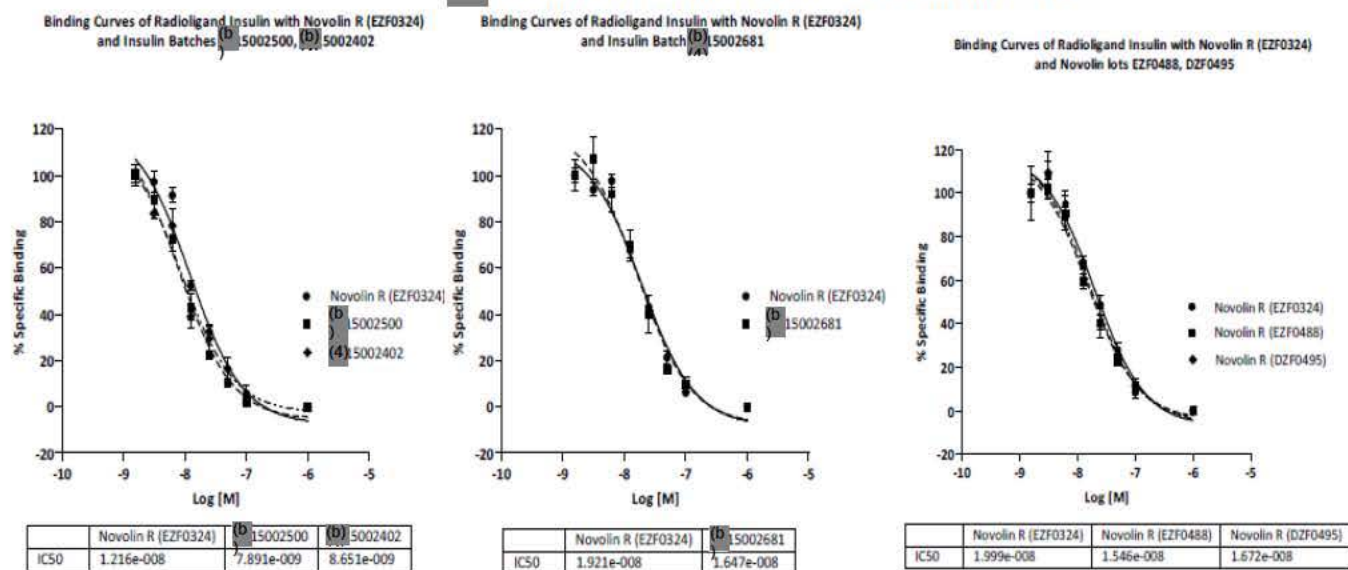
(b) (4) 15002681, and Novolin® R Lots: EZF0488 and DZF0495



Note: All doses in triplicates.

Figure 3: One Site Competition Curves - Novolin® R and Insulin Drug Product

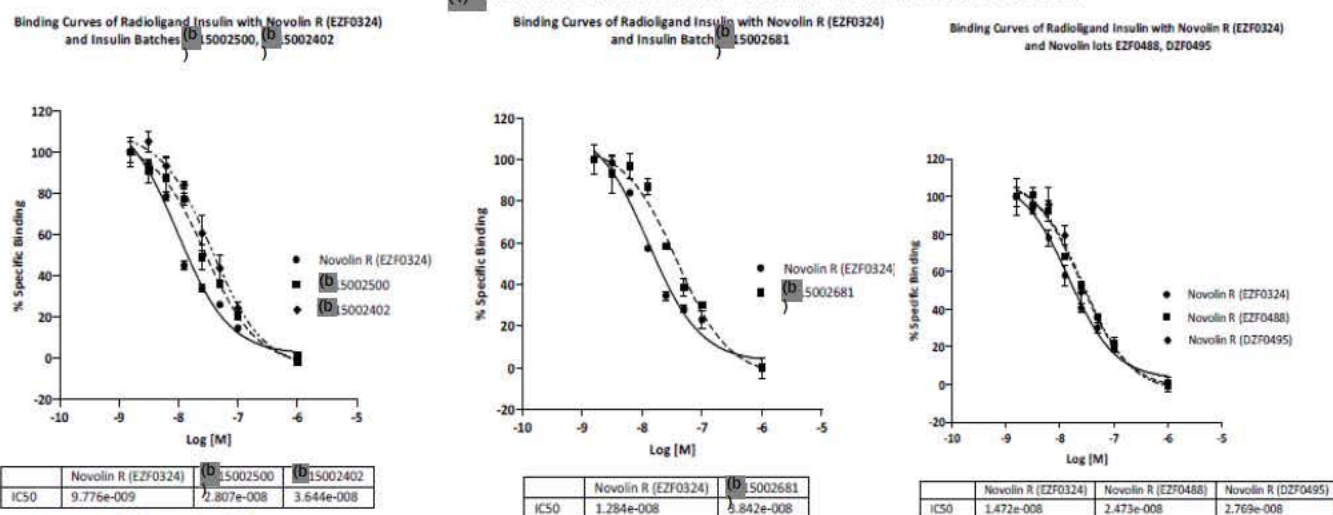
Study-2 (N2) One Site Competition Curves of Novolin® R EZF0324
 Compared with Insulin Drug Product Batches: (b) (4) 15002500, (b) (4) 15002402, and
 (b) (4) 15002681 and Novolin® R Lots: EZF0488 and DZF0495



Note: All doses in triplicates.

Figure 4: One Site Competition Curves - Novolin® and Insulin Drug Product

Study-3 (N3) One Site Competition Curves of Novolin® R EZF0324
 Compared with Insulin Drug Product Batches: (b) (4) 15002500, (b) (4) 15002402, and
 (b) (4) 15002681 and Novolin® R Lots: EZF0488 and DZF0495

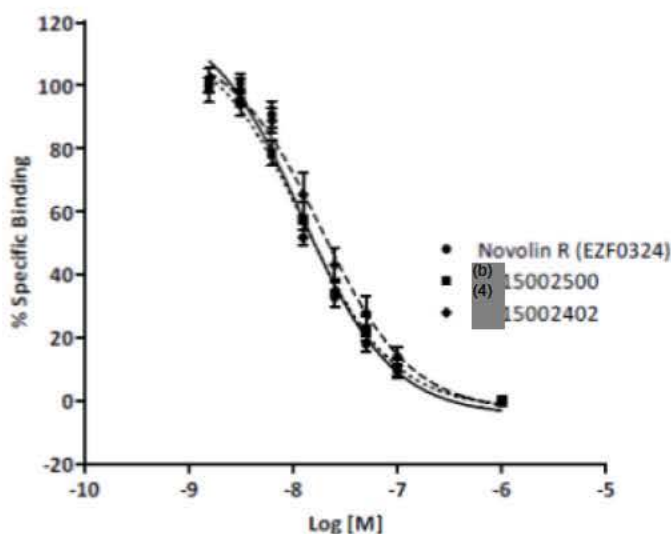


Note: All doses in triplicates.

Figure 5: One Site Competition Curves - Novolin® and Insulin Drug Product

One Site Competition Curves of Novolin® R (EZF0324) Compared with Insulin Drug Product Batches (b) (4) 15002500 and (b) (4) 15002402

Binding Curves of Radioligand Insulin with Novolin R (EZF0324) and Insulin Batches (b) (4) 1500500, (b) (4) 1500402



	Novolin R (EZF0324)	(b) (4) 15002500	(b) (4) 15002402
IC50	1.207e-008	1.275e-008	1.842e-008

Note: Compiled representation of three studies (N=3; n=3)

The table below from the Sponsor shows the linearity of the bioassay with different concentrations of insulin drug products and the LD (Novolin®R):

Table 7: Relative Potency - Insulin Drug Product and Novolin® R

Relative Potency of the Insulin Batches and the Novolin® R Lots with their 95% Confidence Interval

Sample	Potency Ratio	95% Confidence Interval	RCI (Relative Confidence Interval)
(b) (4) 15002500	0.866	0.68762 - 1.08360	79.42% - 125.15% (45.73%)
(b) (4) 15002402	0.780	0.63865 - 0.94489	81.90% - 121.17% (39.27%)
(b) (4) 15002681	0.834	0.70152 - 0.98896	84.11% - 118.57% (34.46%)
Novolin® R (EZF0488)	1.033	0.89219 - 1.19706	86.35% - 115.85% (29.51%)
Novolin® R (DZF0495)	0.964	0.83343 - 1.11440	86.47% - 115.62% (29.15%)
Novolin® R (EZF0324) ^a	Reference standard		

^a Novolin® R (EZF0324) was used as a reference batch to compare the drug substance batches and the other two lots of Novolin® R. Hence the potency ratio of Novolin® R (EZF0324) is not captured.

Study Title: Mitogenic Potential

Key Study Findings

The mitogenic potency of different batches of drug substances was comparable to the different lots of the LD (Novolin®R).

Methods: In three independent studies, the mitogenic potential of different batches of human insulin was compared to the LD (Novolin® R) on 3T3-A31 cells (Mouse fibroblast) using Cell Titer Blue. According to the Sponsor "During the method development Novolin formulation buffer as well as Celerity proposed Drug Product excipients (b) (4)) were tried and did not provide a good dose dependent Growth Stimulation Ratio (%GSR). Good results were obtained with dilution in saline which is the diluent that is used for diluting per package insert for Novolin®. The % GSR (growth stimulation ratio) obtained from the triplicates of each reference Novolin® R and matrix matched DS from all three runs were plotted on to SoftMax Pro 5.4.1 for the individual and combined analysis. The relative potencies of the insulin batches were calculated by determining parallelism between the standard and test drug by selecting the Parallel Line analysis mode with fixed weightage for all points and subsequent estimation of relative potencies at 95% confidence interval using SoftMax Pro 5.4.1".

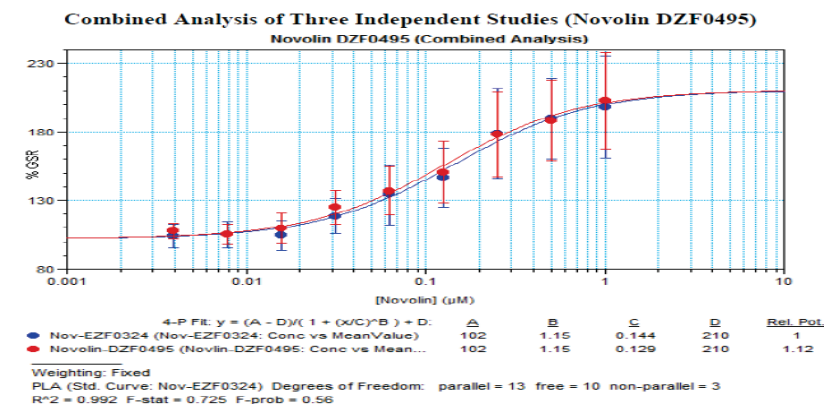
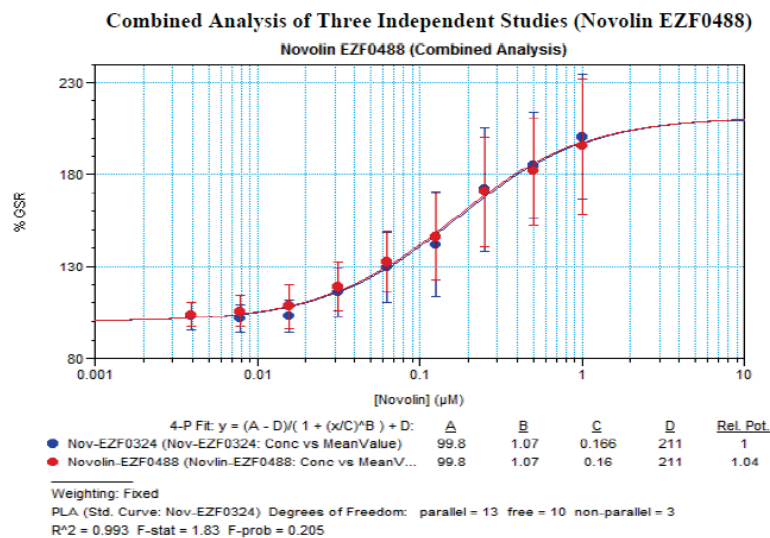
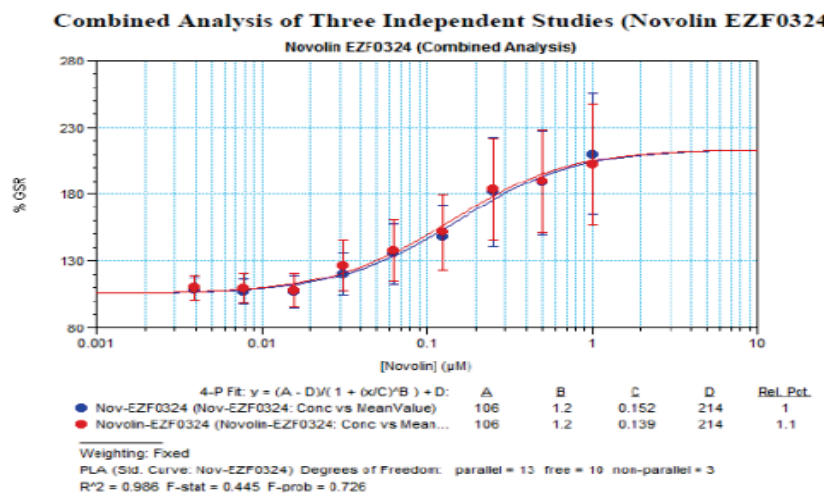
Results: The findings of this study suggested that insulin samples and its analogues bind and activate its related receptors with sub-nanomolar affinity. Insulin and its analogues also bind to the structurally related insulin growth factor (see table below for samples that were tested):

Table 25: Mitogenic Potential - Samples

Sample Number	Sample Name	Batch/Lot Number	Expiry	Concentration
1	Insulin Human	(b) (4) 15002500	Jul, 2019	1 U/mL
2	Insulin Human	(b) (4) 15002402	Jul, 2019	1 U/mL
3	Insulin Human	(b) (4) 15002681	Jun, 2019	1 U/mL
4	Novolin® R	EZF0324 ^a	Oct, 2017	100 U/mL
5	Novolin® R	EZF0488	Nov, 2017	100 U/mL
6	Novolin® R	DZF0495	Dec, 2016	100 U/mL

^a Novolin® R (EZF0324) was used as a reference batch to compare the drug substance batches matrix matched to Novolin® R and the other two lots of Novolin® R.

Figures below (from the Sponsor) show the similarity of matrix matched drug substances in comparison with the Novolin® R (EZF0324) as reference standard:

Figure 6: Combined Analysis - Three Independent Studies

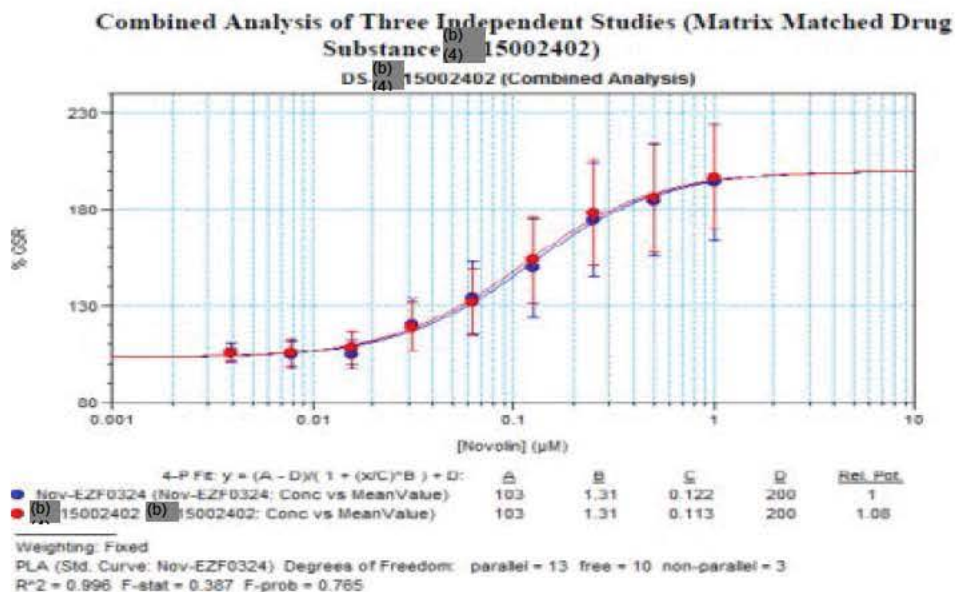
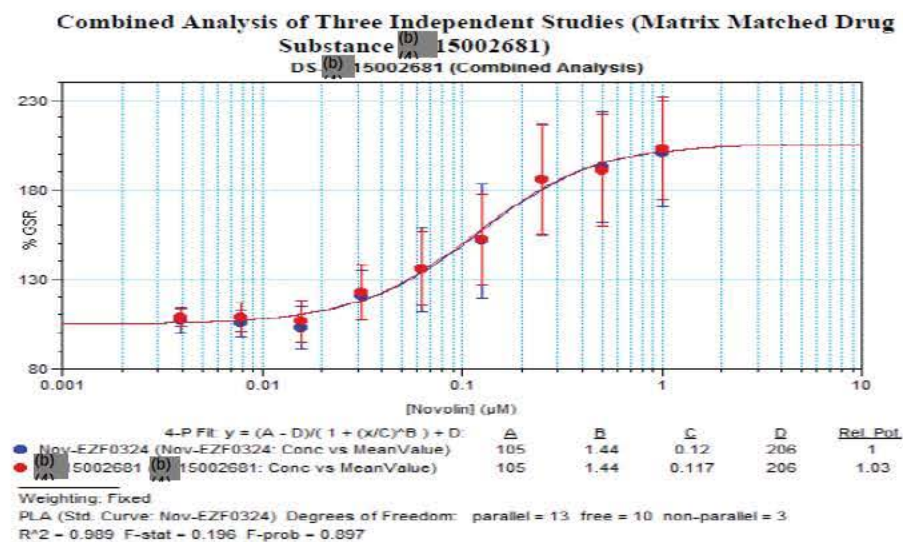


Table 8: Relative Potencies - Three Independent Studies

Sample	Relative Potency ^a						
	Study-1	Study-2	Study-3	%CV	Combined Analysis	CI-Low	CI-High
(b) (4) 15002500	1.14	1.13	1.08	2.9	1.12	0.891	1.348
(b) (4) 15002402	1.02	1.14	1.08	5.6	1.08	0.926	1.236
(b) (4) 15002681	1.06	1.09	0.972	5.9	1.03	0.788	1.263
Novolin-EZF0324	0.998	1.13	1.08	6.2	1.1	0.809	1.386
Novolin-EZF0488	1.09	1.04	1.06	2.4	1.04	0.852	1.23
Novolin-DZF0495	1.14	1.17	1.06	5.1	1.12	0.895	1.348

^a Compiled analysis of the data from three independent runs.

Study Title: Glucose Uptake Assay**Key Study Findings**

The glucose uptake was similar for both drug products and the LD (Novolin® R).

Methods: According to the Sponsor, *“This similarity study used a fluorescence based enzymatic assay to illustrate the similarity in metabolic activity of three batches of drug product prepared from (b) (4) drug substances (b) (4) 15002500, (b) (4) 15002402, and (b) (4) 15002681) to Novolin® R lots (EZF0324, EZF0488, and DZF0495) on 3T3-L1 Cells. The metabolic activity was analyzed using the Parallel Line Analysis with fixed weightage for all points and subsequent estimation of relative potencies at 95% confidence interval using SoftMax Pro 5.4.1”.*

Results: The results of three independent studies with different batches of the LD (Novolin® R) and Celerity’s drug product suggested comparability in glucose uptake with these two formulations. The table below from the Sponsor shows samples that were used for this study:

Table 9: Glucose Uptake Assay - Samples

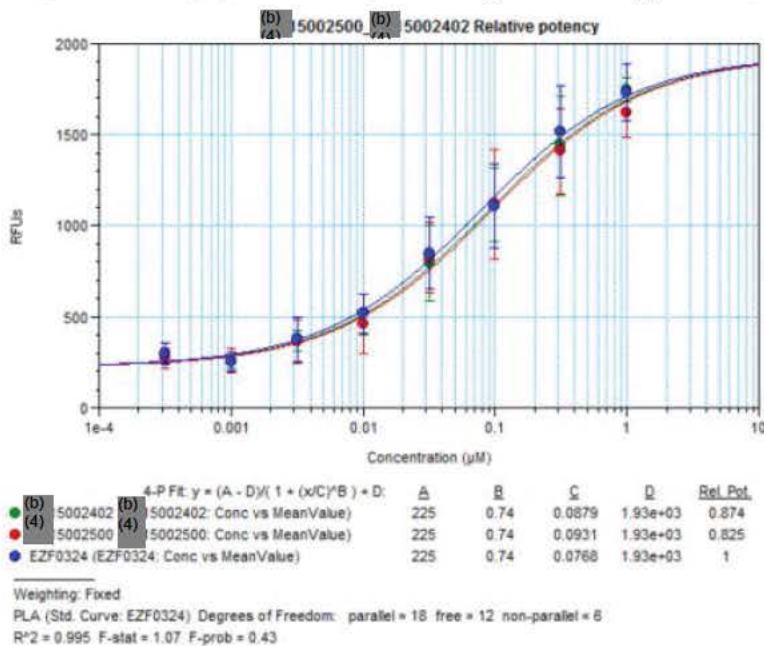
Sample Number	Sample Name	Batch/Lot Number	Expiry	Concentration
1	Insulin	(b) (4) 5002500	Jul, 2019	1 U/mL
2	Insulin	(b) (4) 5002402	Jul, 2019	1 U/mL
3	Insulin	(b) (4) 5002681	Jun, 2019	1 U/mL
4	Novolin® R	EZF0324 ^a	Oct, 2017	100 U/mL
5	Novolin® R	EZF0488	Nov, 2017	100 U/mL
6	Novolin® R	DZF0495	Dec, 2016	100 U/mL

^a Novolin® R (EZF0324) was used as a reference batch to compare the Celerity drug product batches and the other two lots of Novolin® R.

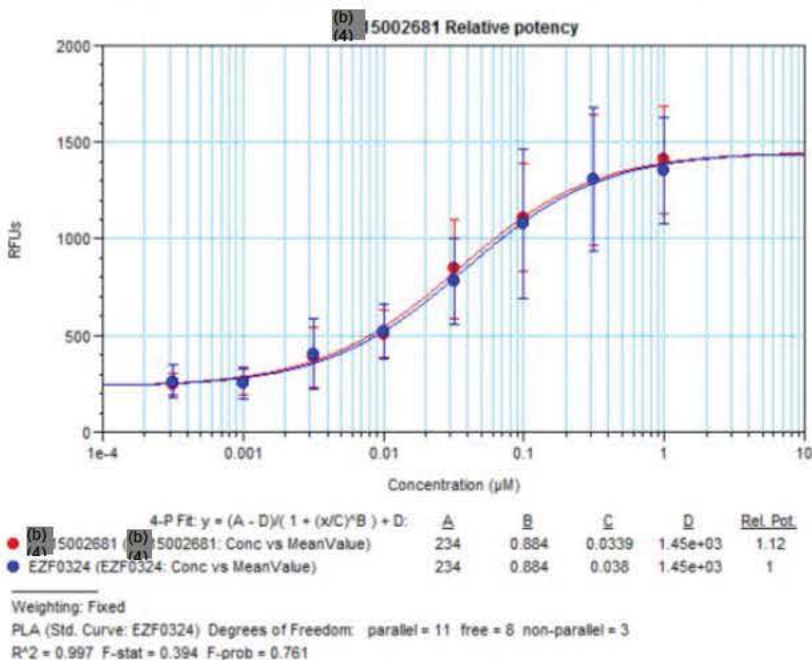
According to the Sponsor *“The RFUs (Relative fluorescence units) were exported to the template created in SoftMax Pro 5.4.1. The Parallel Line Analysis and the graphs were plotted using SoftMax Pro 5.4.1. The relative potency was calculated for the samples using Novolin® R (EZF0324) as reference at 95% confidence interval using SoftMax Pro 5.4.1” (see figures below from the Sponsor):*

Figure 7: Combined Analysis - Three Independent Studies

Similarity Study: Combined Analysis of Three Independent Studies
(Drug Product Lots prepared from Drug Substance (b) (4) 15002500 and (b) (4) 15002402)

**Figure 47: Similarity Study: Combined Analysis of Three Independent Studies (Novolin® R Lots: EZF0324, EZF0488, and DZF0495)**

Similarity Study: Combined Analysis of Three Independent Studies
(Drug Product prepared from Drug Substance (b) (4) 15002681)



Similarity Study: Combined Analysis of Three Independent Studies (Novolin® R Lots: EZF0324, EZF0488, and DZF0495)

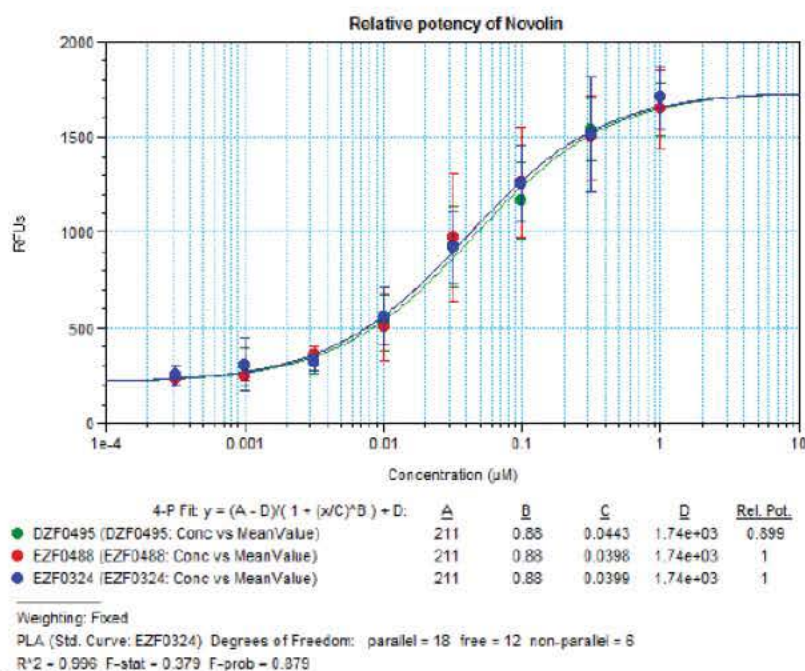


Table 10: Glucose Uptake - Relative Potency Results

Sample	Relative Potency					
	Study-1	Study-2	Study-3	Combined Analysis	CI-Low	CI-High
(b) (4) 15002500	1.410	0.792	0.615	0.825	0.640	1.010
(b) (4) 15002402	1.010	1.090	0.700	0.874	0.678	1.069
(b) (4) 15002681	1.310	1.370	0.934	1.120	0.909	1.332
Novolin-EZF0488	0.745	1.040	1.060	1.000	0.782	1.223
Novolin-DZF0495	1.050	0.896	0.742	0.899	0.702	1.097
Novolin-EZF0324 ^a	Reference Standard					

^a Novolin® R (EZF0324) was used as a reference batch to compare the drug product batches and the other two lots of Novolin® R. Hence the potency ratio of Novolin® R (EZF0324) is not captured.

Study Title: Insulin Growth Factor-1 (IGF-1) Receptor Binding Assay

Key Study Findings

The affinity binding values to IGF-1 receptor were comparable for both human insulin drug substance ((b) (4)) and the LD (Novolin® R).

Methods

The (b) (4) analysis was carried to determine the binding of Novolin and matrix matched insulin-drug substance (b) (4) to IGFR-1 receptor. According to the Sponsor, "Parameters such as on-rate, off-rate and affinities were calculated based on the standard computational tools". See table below from the Sponsor for samples that were tested for this study:

Table 11: Insulin Growth Factor-1- Sample

Sample Number	Sample Name	Batch/Lot Number	Expiry	Concentration
1	Novolin® R	EZF0324	Oct, 2017	100 U/mL
2	Novolin® R	EZF0488	Nov, 2017	100 U/mL
3	Novolin® R	DZF0495	Dec, 2016	100 U/mL
4	Insulin Human Drug Substance (b) (4)	(b) (4) 15002500	Jul, 2019	NA
5	Insulin Human Drug Substance (b) (4)	(b) (4) 15002402	Jul, 2019	NA
6	Insulin Human Drug Substance (b) (4)	(b) (4) 15002681	Jun, 2019	NA

NA = Not Applicable

Results:

The results of this study shows similarity in binding affinity to the IGF-1 receptor for both the insulin drug substance (b) (4) and Novolin (see the Sponsor's table and figures below):

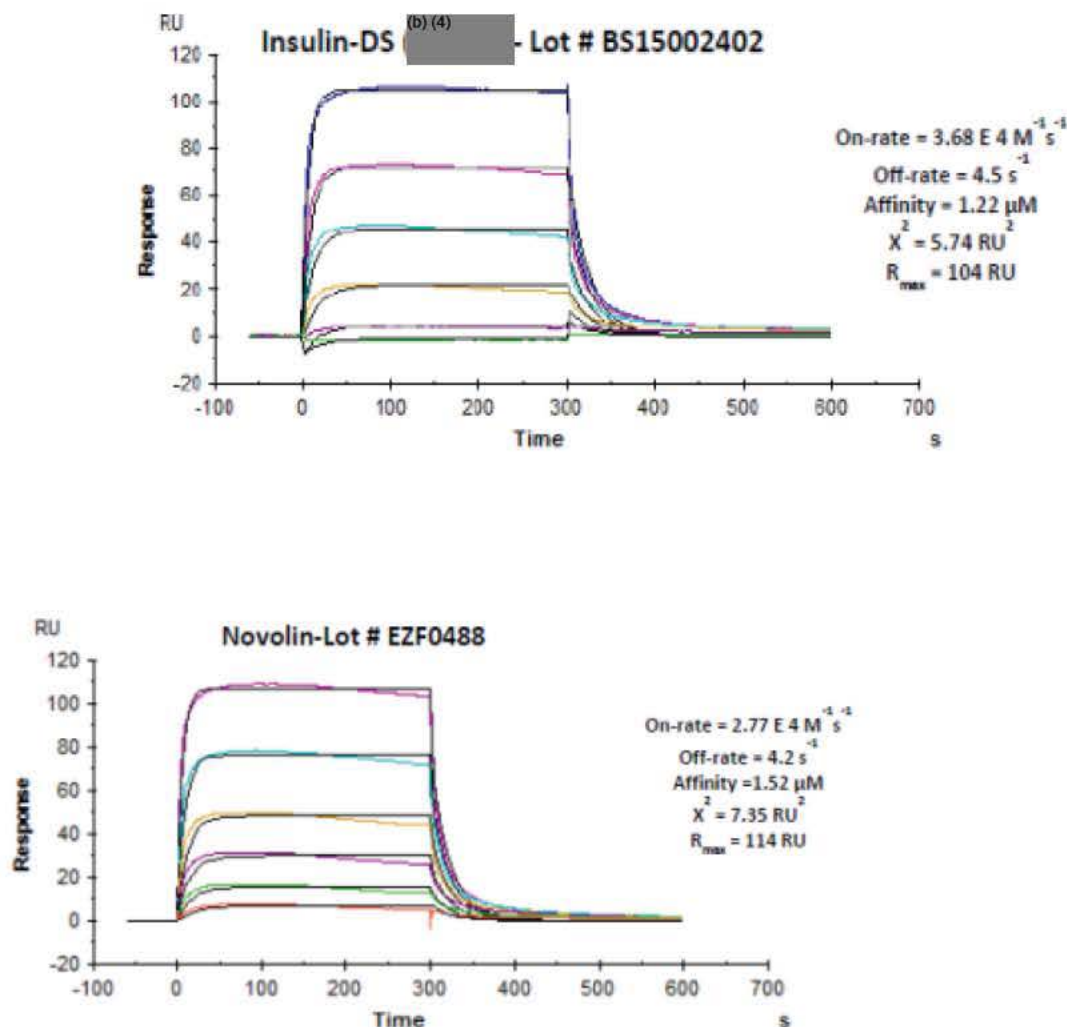
Table 12: Affinity Comparison - Novolin and Insulin-Drug Substance (b) (4)

Affinity Comparison of Novolin and Insulin-Drug Substance (b) (4) Batches

Cycle Number	Novolin (EZF0324) μ M	Novolin (EZF0488) μ M	Novolin (EZF0495) μ M	Insulin-DS (b) (4) 15002681 μ M	Insulin-DS (b) (4) 15002402 μ M	Insulin-DS (b) (4) 15002500 μ M
1	1.43E-06	1.21E-06	1.28E-06	9.46E-07	1.27E-06	1.32E-06
2	1.52E-06	1.57E-06	1.45E-06	1.22E-06	1.31E-06	1.38E-06
3	1.71E-06	1.54E-06	1.55E-06	1.27E-06	1.48E-06	1.55E-06
4	1.68E-06	1.74E-06	1.67E-06	1.40E-06	1.66E-06	1.34E-06
5	1.78E-06	1.79E-06	1.72E-06	1.53E-06	1.85E-06	2.26E-06
Average	1.62E-06	1.57E-06	1.53E-06	1.27E-06	1.51E-06	1.57E-06
Std Dev	1.42E-07	2.31E-07	1.79E-07	2.19E-07	2.45E-07	3.97E-07
% RSD	9%	15%	12%	17%	16%	25%

DS = Drug Substance

Figure 8: Comparison Binding to IGF-1 Receptor - (b) (4) Association and Comparison of (b) (4) Association and Dissociation Kinetics of Insulin Drug Substance (b) (4) and Novolin Binding to IGF-1 Receptor (Representative Cycle)



11 Integrated Summary and Safety Evaluation

The Sponsor is developing Human Insulin Injection (rDNA origin; 1 U/ml in 0.9% NaCl) for improving glycemic control in patients with diabetes mellitus. Human Insulin Injection is a polypeptide hormone structurally identical to native human insulin and is produced by rDNA technology using yeast.

The Sponsor plans to submit a 505(b)(2) NDA with approved Orange book- LD drug Novolin®R Injection (Nordisk; NDA# 019938). The Sponsor **plans to** rely on the FDA's previous findings of the safety and efficacy of Novolin®R for approval Human Insulin Injection. Novolin® R was approved in 1991 and its safety profile is well-known.

Celerity's Human Insulin (rDNA origin) Injection and LD (Novolin® R) will be administered at the same dose and method that is written in the labeling for Novolin® R. To support the 505(b)(2) NDA application, based on the Agency's recommendation, the Sponsor will conduct a GLP 4-week rat "bridge" toxicity study with both Celerity's drug product and the LD as well as a Phase 1 clinical bioequivalence (BE) study to evaluate the similarity of PK/PD profiles of these two formulations along with the safety and tolerability of Human Insulin Injection.

With the "bridge" GLP repeat-dose toxicity study in rats, (b) (4) degradants of the Sponsor's drug formulation will be determined along with similarity in TK data, pharmacologic profiles, and toxicity of Human Insulin Injection to the LD. The Sponsor submitted the experimental design for this 4-week nonclinical rat study to receive the Agency's recommendation. This study is acceptable; however, a 4-week recovery period should be added to the study design. This clinical study is designed with the infusion rate of 1.0 mU/kg/min (total of 0.36 U). This rate of infusion with human insulin has been used previously in other clinical glucose clamp studies with no safety issues. In addition, the Sponsor conducted several *in vitro* studies to demonstrate the similarity in the CMC description and functional characteristics between their product and the LD. These studies were: amino acid analysis, N-terminal sequencing, peptide mapping, circular dichroism, SDS-PAGE, imaged capillary isoelectric focusing (icIEF), micro flow imaging (MFI), differential scanning calorimetry (DSC), analytical ultracentrifuge sedimentation velocity (AUC), nuclear magnetic resonance (NMR), and mass spectrometry. Findings of these studies suggested that (b) (4) insulin that formulated into Human Insulin Injection drug product is similar to the LD (Novolin® R).

Moreover, results from studies related to pH, appearance, high molecular weight proteins, osmolality, and impurity profile (comparisons using RP-uPLC and SEC) suggested similarity between these two formulations (b) (4) drug substance, Human Insulin Injection drug product and the LD, Novolin® R).

To support the proposed clinical study, nonclinical studies consisted of several *in vitro* assays related to insulin receptor binding, mitogenic potential, glucose uptake, IGF-1 receptor binding. Findings of these studies also suggested similarity in functional characteristics between Celerity's drug product and the LD.

Regarding to the immunogenicity of the drug product, the sponsor submitted literature to support the low immunogenicity risk for recombinant Human Insulin in humans and low immunogenicity potential in animal models.

It appears that the Sponsor conducted most of the required nonclinical *in vitro* battery of studies (except for the metabolic activity, lipogenicity in cell culture) to support a 505(b)(2) NDA submission. Therefore, there may be less need for a 4-week "bridging" toxicity study if these studies are acceptable.

In summary, human insulin injection (based on recombinant DNA technology) has been in the U.S. market since 1980 for treatment of severe hyperglycemia and/or to improve

glycemic control in adults and children. The proposed clinical study is designed with the infusion rate of 1.0 mU/kg/min (total of 0.36 U/kg); this rate of infusion has been used previously in other clinical glucose clamp studies with no safety issues. Therefore, there are no safety concerns for the proposed clinical study.

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/s/

PARVANEH ESPANDIARI
04/26/2017

CALVIN L ELMORE
04/26/2017



DEPARTMENT OF HEALTH & HUMAN SERVICES
Food and Drug Administration

Memorandum

Date: May 4, 2015

From: Miyun Tsai-Turton; Pharmacology/Toxicology Reviewer; DMEP

Subject: **Written Response for PIND 124943 Human Insulin Injection
1U/ml in 0.9% Sodium/Celerity Pharmaceuticals, LLC**

Background

The sponsor is developing Human Insulin Injection (rDNA origin; 1U/ml in 0.9% NaCl). It is a polypeptide hormone structurally identical to native human insulin and is produced by rDNA technology using yeast. The drug substance, human insulin, is manufactured by (b) (4); DMF# (b) (4). This drug product is a pre-mixed, sterile nonpyrogenic solution packaged in Baxter's plastic bag suitable for IV use, which intends to provide convenience in the hospital setting. GALAXY is Baxter's proprietary IV bag that encompasses the manufacturing of sterile SVP injections in (b) (4) plastic containers (DMF#6344). Several approved products are delivered in the GALAXY containers, including Azactam, Ceftriaxone, and Nafcillin.

Human Insulin Injection will be submitted following the 505(b)(2) using Novolin R® Injection packaged in a 10 ml glass vial (Novo Nordisk; NDA# 019938) as their listed drug.

Comparison of Novolin R and Celerity's Human Insulin Injection

Applicant	Novo Nordisk [Reference Listed Drug]	Human Insulin Injection (Proposed Drug)
Product	NOVOLIN R is a sterile human insulin injectable solution stored in 10 mL glass vials	Human Insulin Injection is a sterile premixed human insulin injectable solution stored in a 100 mL GALAXY plastic bag
Active Ingredient	Human Insulin, USP	Human Insulin, USP
Total Drug Content	1000 U (100 U/mL in 10 mL glass vial)	100 U (1 U/mL in a 100 mL bag)
Container Closure	Single-use glass vial. When administered intravenously, polypropylene infusion bags should be used.	Single-use plastic bag (GALAXY),
Tonicity Agent	Can be used with the following infusion fluids: 0.9% sodium chloride, 5% dextrose, or 10% dextrose with 40 mmol/L potassium chloride	Premixed with 0.9% w/v Sodium Chloride, USP 900 mg/100 mL (9 mg/mL)
Other Inactive Ingredients	Zinc Chloride approximately 70 mcg/10 mL (approximately 7 mcg/mL) Glycerol 160 mg/10 mL (16 mg/mL) Metacresol 30 mg/10 mL (3 mg/mL) pH Adjusted with Sodium Hydroxide and/or Hydrochloric Acid Water for Injection, USP	Sodium Chloride, USP 900 mg/100 mL (9 mg/mL)-also listed as a tonicity agent Monobasic Sodium Phosphate, Monohydrate, USP 29.0 mg/100 mL (0.290 mg/mL) Dibasic Sodium Phosphate, Anhydrous, USP 41.2 mg/100 mL (0.412 mg/mL) pH Adjusted with Sodium Hydroxide, NF and/or Hydrochloric Acid, NF Water for Injection, USP
Volume	10 mL glass vial	100 mL GALAXY plastic bag
Concentration	100 U/mL	1 U/mL
Dosage Form	Injectable; sterile solution (should be used in infusion systems using polypropylene infusion bags)	Injectable; sterile solution (premixed for intravenous infusion)
Route of Administration	Injection: IV infusion or subcutaneous	Injection: IV infusion
Dosing Regimen	Total daily insulin requirements vary and are usually between 0.05 and 1.0 units/kg/day.	Total daily insulin requirements vary and are usually between 0.05 and 1.0 units/kg/day.
Marketing Status	OTC	Prescription (Rx)
Host Cell Expression System	Saccharomyces cerevisiae (baker's yeast)	Pichia pastoris (yeast)

Clinical Development

The sponsor plans to conduct a PK/PD bioequivalence clinical study with approximately 40 healthy male subjects. This will be a single center, blinded, randomized, active controlled, two-way cross over study comparing the pharmacologic profile of Celerity's proposed Human Insulin (rDNA origin) Injection 1U/mL (100 U/100 mL) in 0.9% Sodium Chloride to an on-site preparation of Novolin R® 100 U/mL (Regular, Human Insulin (rDNA origin) USP) diluted per approved labeling in 0.9% Sodium Chloride to an equivalent 1 U/mL

concentration. The hyperinsulinemic-euglycemic time-action profile clamp will be used as the platform to characterize PD profiles.

Nonclinical Development

No in vivo study is planned except in vitro studies (e.g. receptor binding, Mitogenic and metabolic activity). The sponsor provided the following reasons:

- Preliminary comparability assessment showed similarity (e.g. release testing, impurity, and stability) between Human Insulin Injection to Novolin R®.
- No novel excipient is used in the Human Insulin Injection.
- The drug substance, (b) (4) insulin, meets USP specifications.
- (b) (4)
- Published literature on Novolin R (b) (4) revealed no safety concern associated with this form of insulin.

Impurity

(b) (4) and (b) (4) are expected degradation products of insulin preparation. They have similar biological potency as the parent human insulin and are not immunogenic. These were also seen in preparations of Novolin R®. Therefore, the sponsor currently has no plan to conduct any study to qualify these (b) (4) degradants.

Reviewer's Comment

(b) (4)

The comparator product to be used in a nonclinical bridging study should be a US-approved drug in order to qualify any differences in impurities or degradants with the product, and provide scientific justification for reliance on the US listed drug for nonclinical safety and efficacy.

Celerity's Human Insulin Injection (in a pre-mixed IV bag) has a different source of drug substance (b) (4) insulin) and inactive ingredients when compared to Novolin R® (in a glass vial). Since a different device is used to deliver insulin (a plastic bag versus a glass vial), CDRH is likely to request a biocompatibility study that can establish safety of any of the components that interface with the insulin.

Celerity plans a 505(b)(2) submission referencing Novolin R®. However, the host cell expression system for (b) (4) insulin (yeast *pichia pastoris*) differs from the Novolin R (*baker's yeast, saccharomyces cerevisiae*) and therefore the impurity profile may also differ. Any novel impurities will need to be characterized and perhaps qualified in accordance with CMC guidelines and Guidance

documents ICH Q3A and Q3B.

Therefore, one 28-day bridging toxicity study, comparing Celerity's product directly with US-approved Novolin R®, should be conducted. If there is a difference in their impurity/degradant profile, more nonclinical studies may be required to further address or qualify any impurity issues of your final drug product.

Celerity's Questions & FDA's Response

There is no nonclinical question. However, we have comments for the sponsor which can be added under Question 2.

Pharm/Tox comments for Question 2

Celerity Question #2

Celerity proposes the use of the 505(b)(2) regulatory pathway, referencing preclinical safety data and certain clinical safety data from the US-approved Novolin R.

Does the Agency agree that the proposed 505(b)(2) NDA marketing application pathway is appropriate?

FDA Pharm/Tox Response:

It is recommended that a nonclinical GLP compliant bridging toxicity study, with TK assessment, comparing Celerity's product with US-approved Novolin R® is completed, to support a 505(b)(2) pathway. For a 505(b)(2) pathway, it is your responsibility to not only establish that it is scientifically appropriate to rely, in part, upon the Agency's finding of safety and effectiveness for Novolin R® to support approval, but also to identify what data you would like to reference to support your Human Insulin Injection.

The final decision about the adequacy of your nonclinical development program cannot be determined until the review of your bridging toxicity study and CMC characterization of your impurities. If there is a difference in the impurity profiles (i.e. impurity, degradant, leachable) between your product and the listed drug, additional nonclinical studies may be required to assess these impurities.

Appendix

Drug substance specification

Drug Substance Specifications Insulin Human

Description	(b) (4) or practically (b) (4) crystals.
Solubility	Soluble in solutions of (b) (4) and (b) (4)
Identification	
A. By RT Comparison	A. Retention time of sample and standard in assay chromatogram should be comparable.
B. By Peptide mapping	B. Test chromatogram should be consistent with reference chromatogram
Bioidentity	It meets the requirements of the Bioidentity test.
Loss on drying	NMT (b) (4)
Related compounds (b) (4)	(b) (4) - NMT (b) (4)
Other related compounds	Other related compounds - NMT (b) (4)
Limit of high molecular weight proteins	Total impurities NMT (b) (4)
(b) (4)	NMT (b) (4) w/w
Assay*	
(Content of Human insulin + (b) (4) (b) (4))	NLT (b) (4) USP Human insulin units in each mg
Bacterial endotoxins	NMT (b) (4) USP endotoxins unit in each mg.
Microbial limits	
Total bacterial count	NMT (b) (4) cfu per g.
Host cell derived proteins	NMT (b) (4) ppm
Host cell DNA content	NMT (b) (4) pg/ 3.5 mg
Residual Solvents: (b) (4)	NMT (b) (4) ppm NMT (b) (4) ppm NMT (b) (4) ppm NMT (b) (4) ppm
Content of (b) (4)	NMT (b) (4) ppm
Microbial Limits:	
Total Yeasts and Molds Count	NMT (b) (4) CFU/g
* - On (b) (4)	

Note: Each 0.0347 mg of Human Insulin is equivalent to 1 IU of Human Insulin.

Primary endpoints: Change from baseline in HbA1c at 24 weeks powered using a non-inferiority margin of 0.4% for a six month randomized treatment period with either SC or ID insulin infusion

Secondary endpoints: are to be determined and would include items such as:

- HbA1c at 12 weeks
- Average glucose values, SMBG
- Average insulin dosing (pump downloads)
- Occurrence of hypo- /hyper-glycemic events (SMBM, self-reported)
- ID vs SC set lifetime (pump downloads; self-reported)
- Occurrence of catheter occlusion rate (self-reported, pump downloads)
- Human factor assessment by patient questionnaire about wearability comfort, ease of use, preference (pain assessment, location documentation e.g., abdomen, arm, thigh, back)
- Assessment of Infusion site reaction by site observation
- AE reporting
- Antibody profile at baseline and 24 weeks

Inclusion criteria:

Baseline HbA1c $\leq 7.5\%$

Previous HbA1c value within past 6 months $\pm 0.5\%$ of the baseline HbA1c

Documented SMBG values (minimum of avg. 4 per day)

No severe hypoglycemic events during past 6 months

Minimum of 1 year on pump therapy

Major Analyses planned: The change in HbA1c from baseline will be estimated using an ANCOVA model, with end-of-study HbA1c as response and baseline HbA1c as

covariate. A non-inferiority test will be applied to the estimated difference between ID and SC delivery methods (non-inferiority margin = 0.4%).

Study Synopsis

Safety and Efficacy of intended use of Intradermal Infusion, US	
Study Title	Safety and efficacy of ID insulin delivery
Study Type	Non-inferiority ID vs SC insulin delivery with respect to glucose control assessed by HbA1c (non-inferiority margin 0.4%) , open label Two-arm parallel design ID vs SC insulin delivery, repeated measure design change from baseline to the end of the study period (24 weeks)
Study Population	Adult Subjects with Type 1 Diabetes on CSII
Inclusion criteria	Baseline HbA1c $\leq$ 7.5% Existing HbA1c value within past 6 month within 0.5% of the baseline HbA1c Documented SMBG values (minimum of avg. 4 per day) No severe hypoglycemic events during past 6 months Minimum of 1 year on pump therapy
Number of Subjects and Study Sites	Up to 3 sites, Total N = 140 subjects, 70 subjects SC, 70 subjects ID Subjects will be added to accommodate attrition
Study Duration	After Baseline assessment / randomization SC or ID 24 weeks intended use (A1C at baseline, 12 weeks and 24 weeks of intended use)
Study Objectives	To demonstrate safe and effective glucose control with ID insulin infusion during intended use conditions
Primary Endpoint	Change from baseline in HbA1c at 24 weeks powered using a non-inferiority margin of 0.4% for a six month randomized treatment period with either SC or ID insulin infusion
Secondary Endpoints	- HbA1c at 12 weeks - Average glucose values, SMBG - Average insulin use (pump downloads) - Occurrence of hypo- /hyper-glycemic events (SMBM, self-reported) - ID vs SC set lifetime (pump downloads) - Occurrence of catheter occlusion rate (self-reported, pump downloads) - Human factor assessment by patient questionnaire about wearability comfort, ease of use, preference (pain assessment, location documentation e.g., abdomen, arm, thigh, back) - Assessment of Infusion site reaction by site observation - AE reporting - Antibody profile at baseline and 24 weeks
Sample size and statistics	Based on previous studies it is estimated that the HbA1c standard deviation between subjects after 24 weeks is 1.1, and the correlation to baseline is 70%. Assuming no difference in glycemic control between ID and SC delivery methods, one-sided non-inferiority test with alpha = 0.05 and margin of 0.4%, the study has 91% power to conclude that ID delivery is non-inferior to SC delivery. Additional subjects may be recruited to account for attrition.

Proposed drug product specifications

Proposed Finished Product Release Specifications

Test	Method	Limits
Visual Inspection	USP <1>	(b) (4)
Identification (HPLC)	TBD	
Identification Spectral match by PDA	TBD	
HPLC Assay by RP-uPLC (Assay includes (b) (4))	TBD	
Related Substances (HPLC)	TBD	
High Molecular Weight Proteins (HMWP) by SEC	TBD	
pH <791>	USP <791>	
Weight Loss	TBD	
Osmolality	USP <785>	
Particulate Matter, USP <788>	USP <788>	
Bacterial Endotoxins, USP <85>	USP <85>	
Leachable (CE228 by GC)	TBD	
Sterility USP <71>	USP <71>	

USP = United States Pharmacopeia; TBD = to be determined; HPLC = High Performance Liquid Chromatography; PDA = photodiode array; RP-uPLC = Reverse Phase Ultra Performance Liquid Chromatography; NMT = not more than; EU = Endotoxin Unit(s); GC = Gas Chromatography

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/s/

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05/04/2015

STEPHANIE J QUINN
05/04/2015