CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

210913Orig1s000

CLINICAL PHARMACOLOGY REVIEW(S)

CLINICAL PHARMACOLOGY REVIEW

NDA	208157
Link to EDR	\\CDSESUB1\evsprod\NDA208157\0000 (original submission) \\CDSESUB1\evsprod\NDA208157\0004 (resubmission)
Submission Date(s)	Aug 22, 2018
Submission Type	505(b)(2)
Brand Name	Myxredlin
Generic Name	Regular Human Insulin in 0.9% Sodium Chloride Injection
Dosage Form and Strength	Solution
Route of Administration	Intravenous infusion
Proposed Indication	To improve glycemic control in adults and children with diabetes mellitus
Applicant	Celerity Pharmaceuticals LLC
Associated IND	124943
Clinical Pharmacology Reviewer	Tao Liu, Ph.D.
Clinical Pharmacology Team Leader	Manoj Khurana, Ph.D.
OCP Division	Division of Clinical Pharmacology 2
OND Division	Division of Metabolism and Endocrinology Products

TABLE OF CONTENTS

List of Tables

List of Figures

1 Executive Summary

1.1 Recommendation

Celerity Pharmaceuticals, LLC (hereafter referred to as Celerity) has submitted NDA 208157 under Section 505(b)(2) of the FD&C Act, seeking marketing approval for regular human insulin product, presented as a diluted insulin solution formulated at a concentration of 1 USP unit(U)/mL in 0.9% sodium chloride that is ready-to-use for improving glycemic control in adults and children with diabetes mellitus. The applicant references Novolin® R (NDA 019938) as the reference listed drug (RLD) for regular human insulin.

The Office of Clinical Pharmacology (OCP) has reviewed the NDA 208157 and has found the application approvable from a clinical pharmacology perspective.

1.2 Post-Market Requirements and Commitments

None

2 Question Based Review

Celerity has submitted NDA 208157 seeking marketing approval for improving glycemic control in adults and children with diabetes mellitus. NDA 208157 is reviewed under 505(b)(2) pathway. The RLD is Novolin® R (NDA 019938).

Novolin® R was approved under NDA 019938 for improving glycemic control in adults and children with diabetes mellitus. The dosage and timing of Novolin® R must be individualized. For intravenous administration, Novolin® R should be used at concentrations from 0.05 to 1.0 U/mL in infusion systems using polypropylene infusion bags. Novolin® R is stable in 0.9% sodium chloride, 5% dextrose, or 10% dextrose with 40 mmol/L potassium chloride.

In support of this NDA, the applicant conducted one clinical pharmacology study titled "*A Double-Blind, Randomized, Crossover, Euglycemic Glucose Clamp Study to Test for Bioequivalence between Celerity's Premixed Regular 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). The objectives of this clinical pharmacology study were to:

1) To assess and compare the pharmacokinetic (PK) profile of Celerity's premixed Human Insulin (rDNA origin) Injection to an equivalent dose of the commercially available reference product Novolin® R, administered by intravenous (IV) infusion for 6 hours with an 8-hour blood sampling period.
2) To assess and compare the pharmacodynamic (PD) profile of Celerity's premixed Human Insulin (rDNA origin) Injection to an equivalent dose of the commercially available reference product Novolin® R, administered by intravenous (IV) infusion for 6 hours with an 8-hour blood sampling period.

Note that a study design, statistical analysis, and criterion similar to that used for typical bioequivalence assessment is used for comparison of primary PK and PD parameters towards similarity claims in this application. However, since intravenous delivery is 100% bioavailable, this is scientifically, a comparison of the following at steady state:

- pharmacokinetic characteristics of Myxredlin after intravenous infusion at a pre-specified fixed rate over a fixed duration to evaluate if on average, the systemic insulin concentrations achieved at steady state are similar to those achieved with reference insulin infusion, including whether the steady insulin concentrations are achieved at similar time and decline in similar manner as reference after stopping the IV infusion (which are a function of two fundamental PK characteristics of the active ingredient - clearance and volume of distribution), and
- the pharmacodynamic effect of Myxredlin or reference insulin on glucose reduction for which, glucose infusion rate works as a surrogate in the euglycemic clamp study, is evaluated with a similar approach

The bioequivalence criteria applied towards the primary PK/PD parameters is simply a reflection of the Agency's general approach in accepting no clinically meaningful difference between the two comparisons and is consistent with the current applicable guidance.

2.1 What are the highlights of the formulations of the test and reference drug products

Celerity's premixed regular human insulin (rDNA origin) injection is a diluted insulin solution formulated at a concentration of 1 USP unit(U)/mL in 0.9% sodium chloride that is ready-to-use. A comparison between Celerity's premixed regular human insulin (rDNA origin) injection and RLD Novolin® R is given in Table 1.

Table 1 Summary of Product Information

Product	Celerity's premixed Regular Human Insulin (rDNA origin) Injection	Novolin® R
Manufacturer	(b) (4) (b) (4) (b) (4)	Novo Nordisk A/S, Bagsvaerd, Denmark
Strength	1 U/mL	100 U/mL
Assayed Potency	(b) (4)	[redacted]
Dosage Form	IV	IV, 1 mL diluted into 0.9% NaCl for 1U/mL final concentration

(source: adapted from 2.7.1 Summary of Biopharmaceutic Studies and Associated Analytical Methods Table 1)

2.2 General Attributes of the Drug

2.2.1 What are the proposed mechanism of action and therapeutic indications?

The primary activity of insulin, including MYXREDLIN is the regulation of glucose metabolism. Insulins lower blood glucose by stimulating peripheral glucose uptake, especially by skeletal muscle and fat, and by inhibiting hepatic glucose production. Insulin inhibits lipolysis and proteolysis, and enhances protein synthesis.

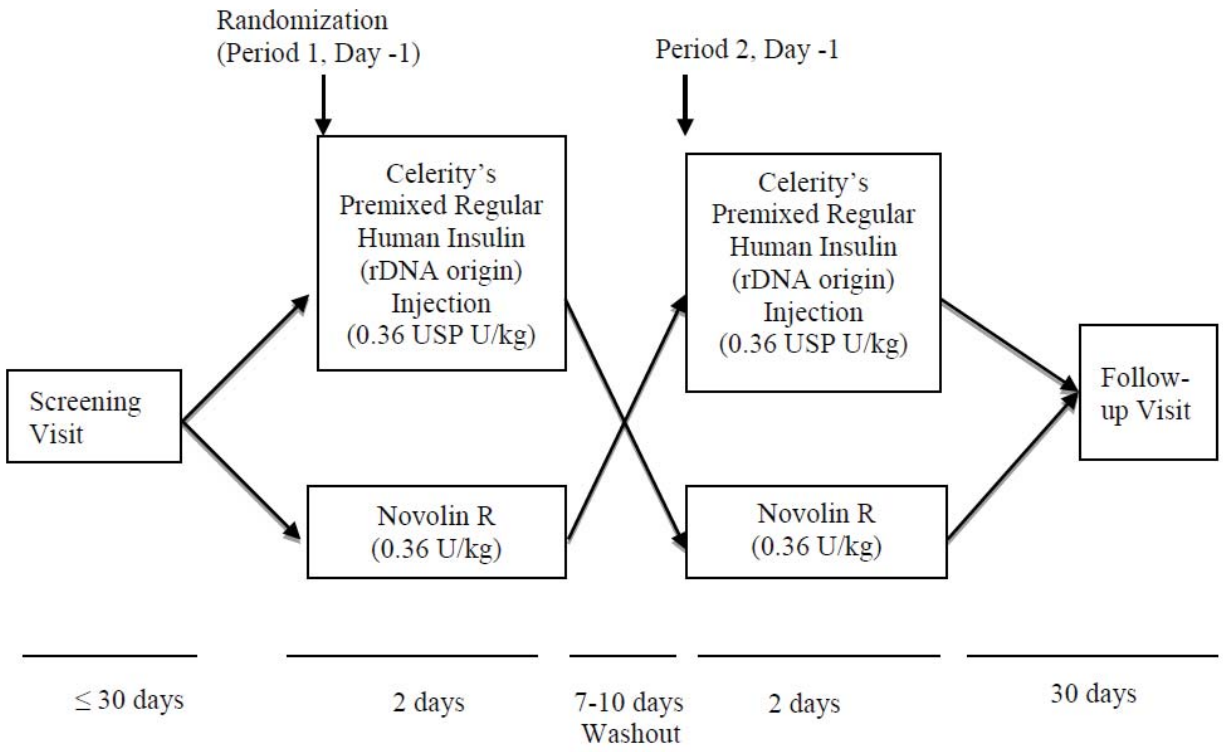
2.2.2 What are the proposed dosage and routes of administration?

Myxredlin is to be administered intravenously under medical supervision. Dose should be individualized based on metabolic needs, blood glucose monitoring results, and glycemic control goal.

2.3 General Clinical Pharmacology

2.3.1 What are the key design features of the pivotal PK/PD bridging study?

Study CEL-HI-200 is a double-blind, randomized, 2-way crossover, euglycemic glucose clamp study to test for PK and PD similarity between Celerity's premixed regular human insulin (rDNA origin) injection 1 USP unit/mL in 0.9% sodium chloride and Novolin® R in healthy subjects. The study design is shown in Figure 1.



(source: Figure 9-1 in Final Clinical Study Report Version 1.0 17 April 2018)

Figure 1 Study Design for CEL-HI-200

Subjects received a constant rate of either Celerity's premixed human insulin injection or the reference product Novolin® R infusion of 1.0 mU/kg/min for 6 hours, resulting in a total dose of 0.36 U/kg trial product. Following the start of the infusion, blood glucose concentration was clamped at a target blood glucose concentration which is 9 mg/dL (0.5 mmol/L) below the individual fasting blood glucose level of the subject by means of an intravenous infusion of 20 % glucose (i.e., target blood glucose level is determined individually for each subject by mean fasting glucose level minus 9 mg/dL).

For the clamp procedure, up to four venous catheters were inserted into peripheral veins for blood sampling and IV infusions. Subjects were connected to a Biostator®, (MTB Medizintechnik, Amstetten, Germany) for at least 1 hour prior to administration of study drug. A low dose heparin solution (10,000 Units heparin/100 mL saline) was infused into the double lumen catheter to prevent blood clotting in the system. This arm remained under a heating pad throughout the clamp. The heating of the peripheral arm or hand resulted in an arterialization of the venous blood, due to a reflexive opening of arterio-venous shunts.

Blood glucose concentration were determined 60 minutes prior to dosing at the following time points relative to dosing: -60, -30, -20 and -10 minutes with an YSI 2300 STAT or equivalent YSI Glucose Analyzer (Yellow Springs Instruments, Yellow Springs, USA). The average of three blood glucose readings from -30 to -10 minutes (i.e., -30, -20 and -10 minutes) was used to determine the individual subject's fasting blood glucose level for each dosing visit.

2.3.2 What are the primary PK and PD endpoints?

PK endpoint:

• The area under the insulin concentration-time curve at steady state PK, measured from 300-360 minutes ($AUC_{INS\text{-}SS\ 300\text{-}360\ min}$).

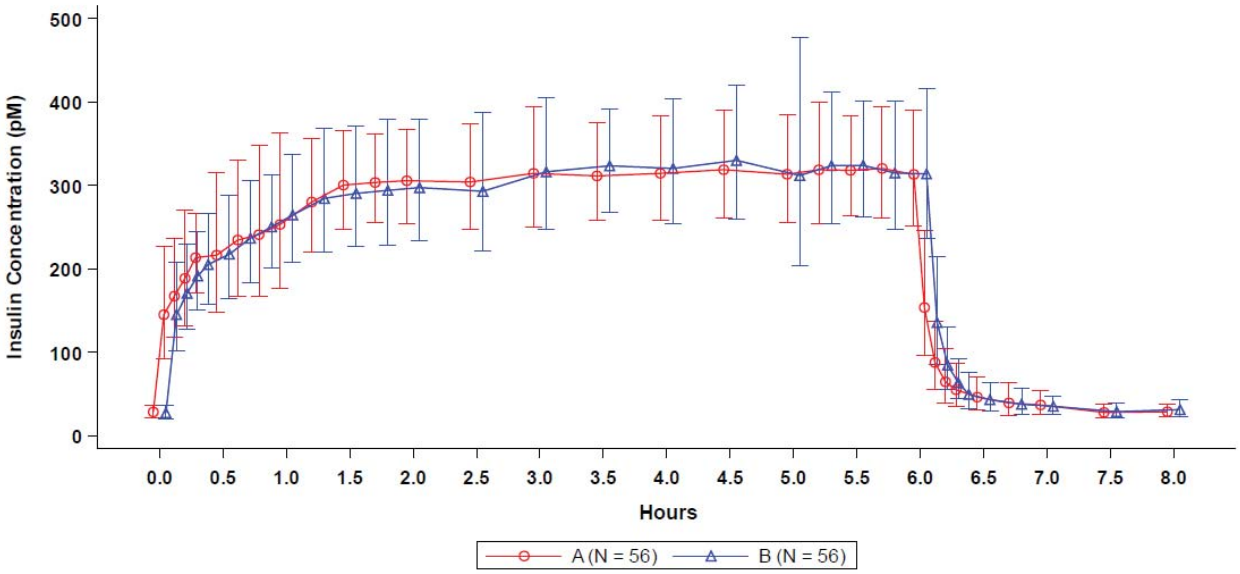
PD endpoint:

• The area under the GIR-time curve at steady state from 300-360 minutes ($AUC_{GIR\text{-}SS\ 300\text{-}360\ min}$).

2.3.3 What are the key PK and PD characteristics?

PK:

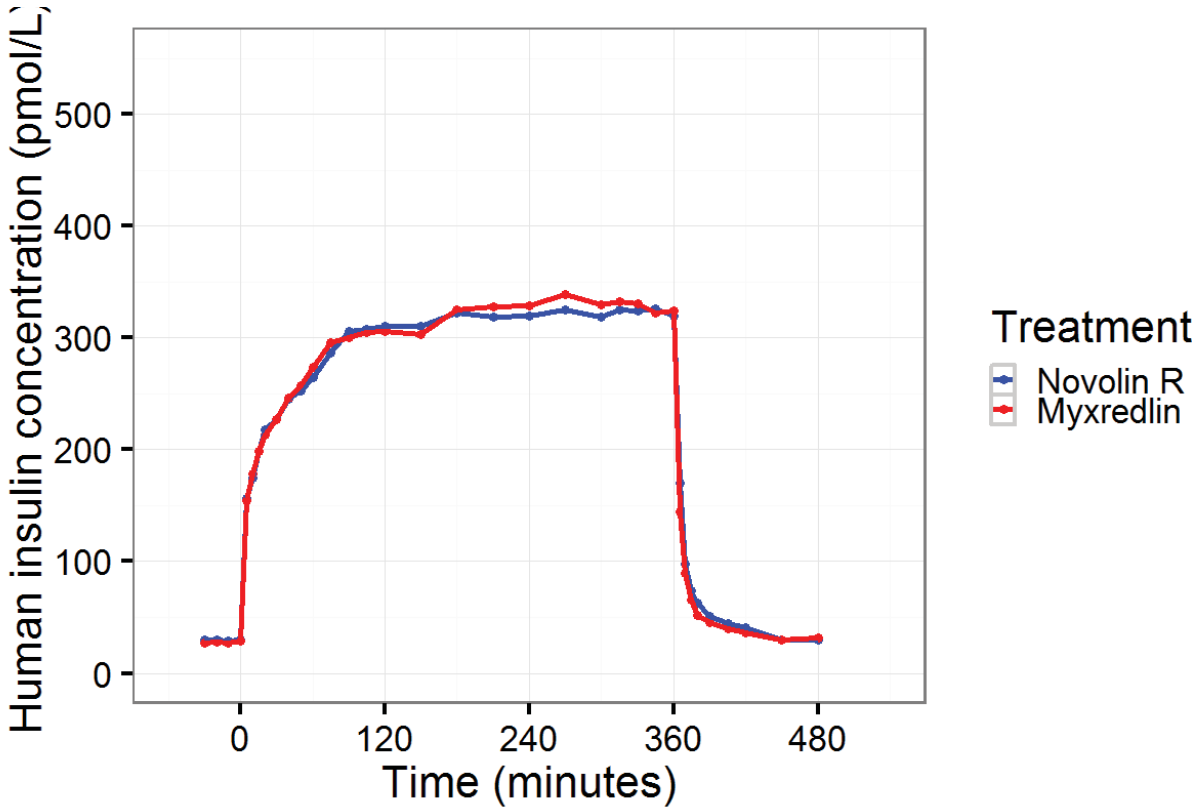
After intravenous infusion of 1.0 mU/kg/min for 6 hours, the insulin concentration time profile was similar between the two treatment groups (Figure 2). Plasma insulin concentration reached to steady state at approximately 1.5 hours, and then remained stable afterwards until the end of IV infusion. Plasma insulin concentration returned to baseline level roughly about 1.5 hours after end of IV infusion.



Treatment A = Infusion of Celerity's Premixed Regular Human Insulin (rDNA origin) Injection;
Treatment B = Infusion of Novolin R
(source: Figure 11-1 in Final Clinical Study Report Version 1.0 17 April 2018)

Figure 2 Plot of the Geometric Mean (± SD) of the Serum Insulin Concentration (pM) Over Time by Treatment for the PK Population in CEL-HI-200

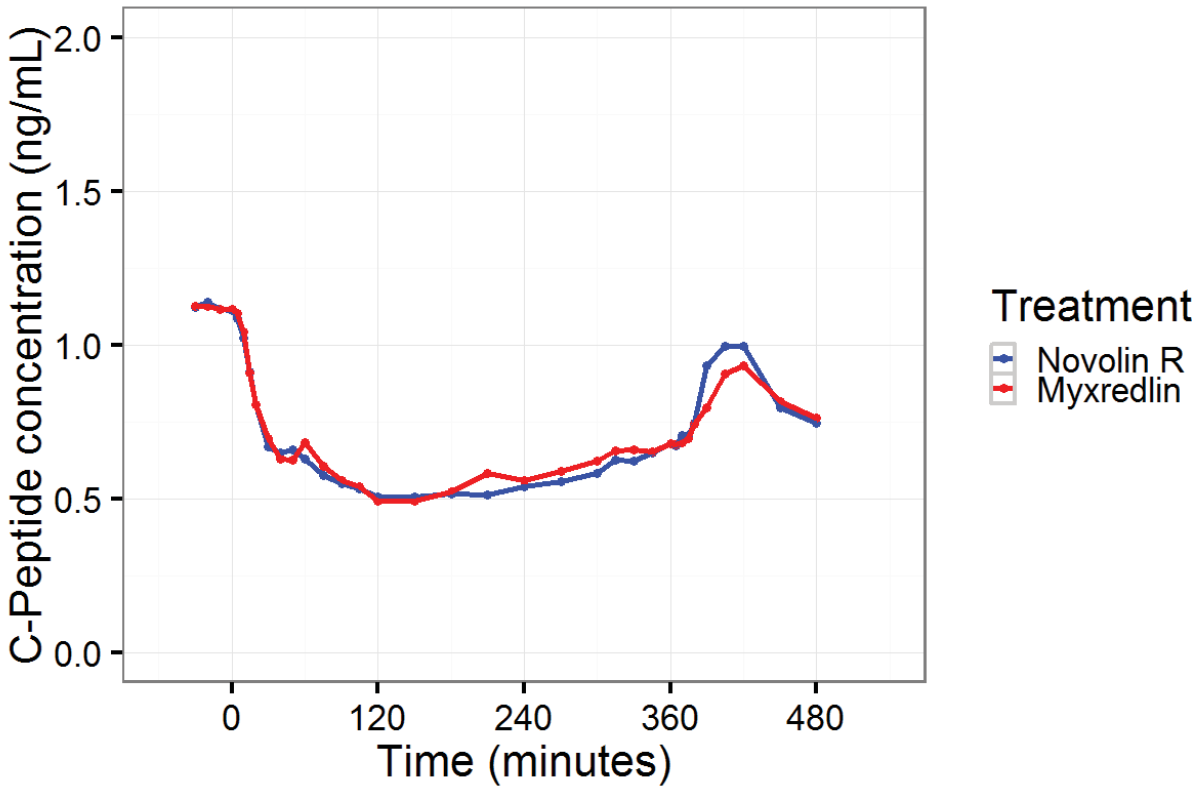
Reviewer's assessment:
The applicant's Figure above was drawn apparently with an offset to visually distinguish the curves from the two treatments, which are otherwise overlapping on average. The reviewer reproduced Figure 2 with arithmetic mean using the data submitted by the applicant (Figure 3). Both Figure 2 and Figure 3 suggested similar PK profile for Novolin R and Myxredlin.



(reviewer's assessment, data source: adpc.xpt)

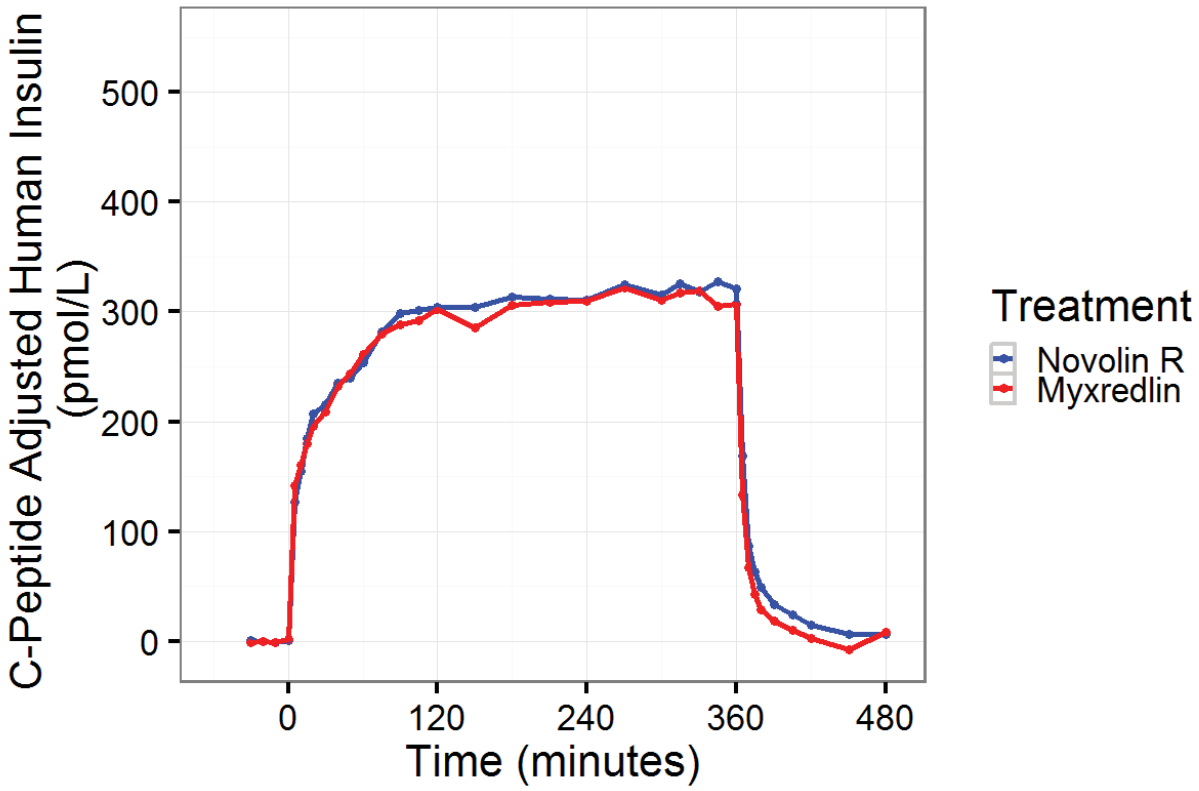
Figure 3 Plot of Arithmetic Mean of Serum Insulin Concentration (pmol/L) Over Time by Treatment

In addition, the C-peptide concentration time profile was also consistent between the two treatment groups (Figure 4), which suggested that on average, the endogenous insulin change during the clamp duration was similar between the two treatment groups. Therefore, after adjusting the endogenous insulin, the C-peptide adjusted human insulin concentration time profile was also similar between the two products (Figure 5). Further, the decrease from baseline in C-peptide also indicates that clamp quality was optimal in ensuring minimal confounding by endogenous insulin to both PK and PD data.



(reviewer's assessment, data source: adpc.xpt)

Figure 4 Plot of the Arithmetic Mean of C-peptide Concentration (ng/mL) Over Time by Treatment



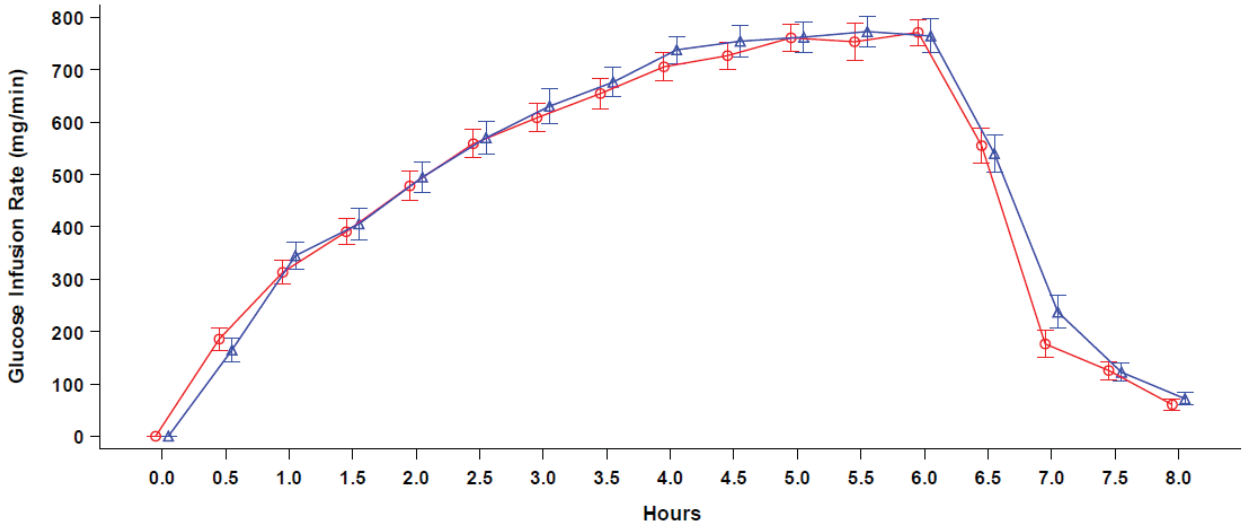
(reviewer's assessment, data source: adpc.xpt)

Figure 5 Plot of the Arithmetic Mean of C-peptide Adjusted Human Insulin Concentration (pmol/L) Over Time by Treatment

In summary, the concentration time profile of human insulin was similar between the Celerity's product and RLD Novolin R after IV infusion.

PD:

After infusion of 1.0 mU/kg/min for 6 hours, the glucose infusion rate time profile was similar between the two treatment groups (Figure 6). Glucose infusion rate gradually increased from baseline and reached to steady state at approximately 4.5 hours, and then remained stable afterwards until the end of IV infusion. GIR tended to return to baseline level roughly about 2 hours after end of IV infusion.



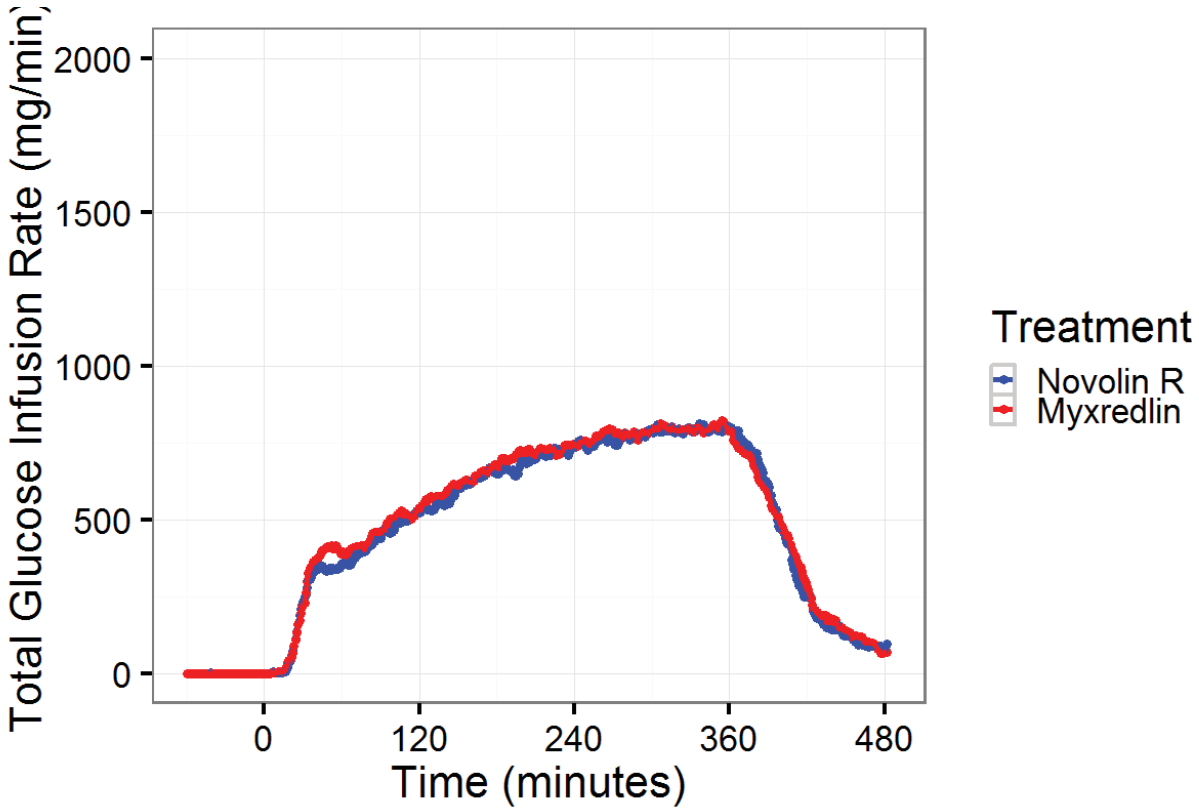
Treatment A = Infusion of Celerity's Premixed Regular Human Insulin (rDNA origin) Injection; Treatment B = Infusion of Novolin R

(source: Figure 11-2 in Final Clinical Study Report Version 1.0 17 April 2018)

Figure 6 Plot of the Geometric Mean (± SE) GIR (mg/minute) Over Time by Treatment for the PD Population in CEL-HI-200

Reviewers' assessment

The applicant's Figure above was drawn apparently with an offset to visually distinguish the curves from the two treatments, which are otherwise overlapping on average. In addition, Figure 6, which was generated by the applicant, include GIR data at every half an hour. By including GIR at each minute in the study, the average GIR time profiles are given in Figure 7. No difference was apparent between the two treatment groups.



(reviewer's assessment, data source: adpd.xtp)

Figure 7 Plot of Arithmetic Mean of Glucose Infusion Rate (GIR) (mg/minute) Over Time by Treatment

After infusion of 1.0 mU/kg/min for 6 hours, the blood glucose concentration time profile (Figure 8) was similar between the two treatment groups. In response to insulin infusion, the blood glucose concentration profile could be divided into three stages: 1) The blood glucose concentration dropped immediately right after the starting of insulin infusion, 2) and then triggered the glucose infusion at round 30 minutes to bring the blood glucose infusion back to the previously specified level, 3) after the end of insulin infusion, blood glucose increased towards the baseline level and triggered the release of endogenous insulin (also suggested by Figure 4). The blood glucose concentration time profile was similar between the two products at each stage.

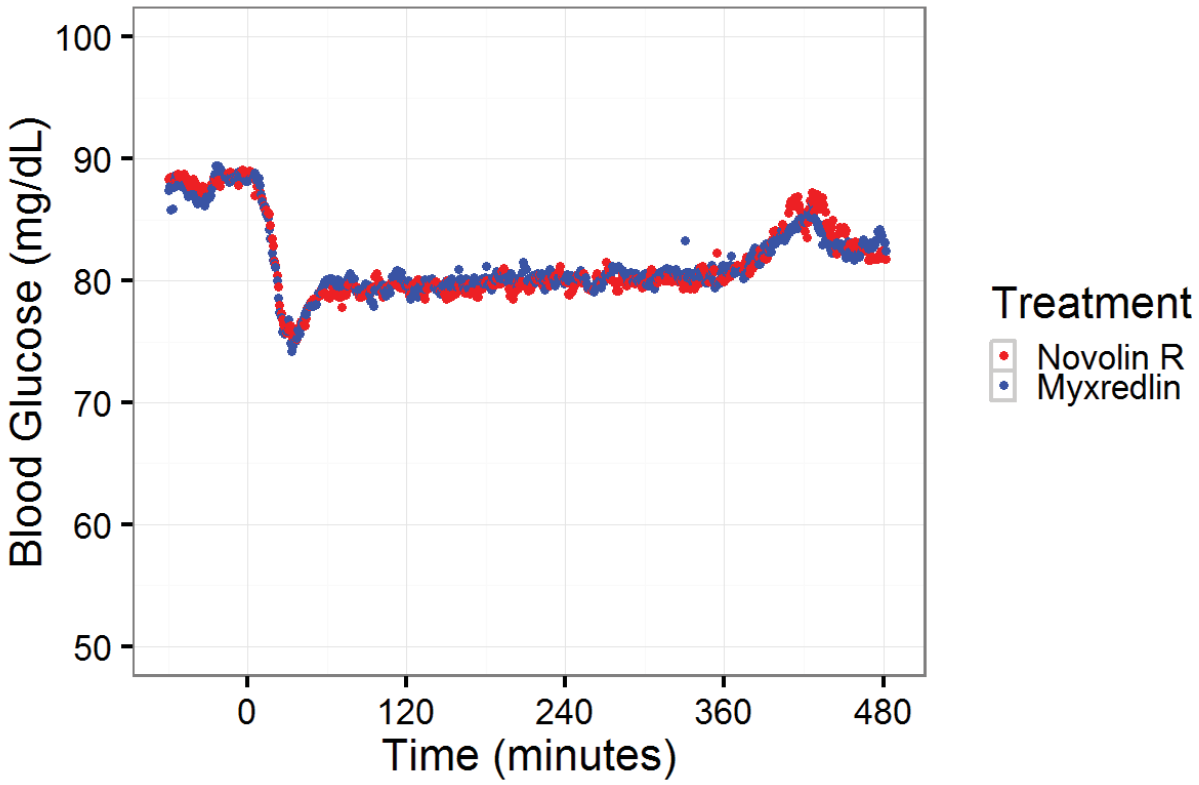


Figure 8 Plot of Arithmetic Mean of Blood Glucose Over Time by Treatment

In summary, the PD profile of Myxredlin (reflected by GIR and supported by blood glucose) is similar to Novolin R.

2.3.4 What are the major findings in primary PK endpoint?

The comparison for primary PK endpoint $AUC_{INS\text{-}ss\ 300\text{-}360\ min}$ is given in Table 2. The PK parameters were similar between the two products, and the statistical analysis results of primary PK parameters, which met the pre-specified criteria for geometric mean ratios and 90%CI to be within 80-125%, also suggested that the PK profile was similar between the two products.

Table 2 Comparing $AUC_{INS\text{-}ss\ 300\text{-}360\ min}$ between Celerity's Premixed Regular Human Insulin (rDNA origin) Injection and Novolin R for the PK Population in CEL-HI-200

Parameter	Statistic	Celerity's Insulin[1] (N=56)	Novolin R (N=56)	Ratio (SE)[3]	90% CI for Ratio[3]
$AUC_{INS\text{-}ss\ 300\text{-}360\ min}$ (pM*min)	Geometric LS Mean (SE)[2]	19097.3 (514.34)	19266.5 (518.44)	1.0 (0.02)	0.96, 1.03
$AUC_{INS\text{-}ss\ 300\text{-}360\ min}$ (pM*min) (C-peptide corrected)	Geometric LS Mean (SE)[2]	18423.4 (493.99)	18585.5 (497.92)	1.0 (0.02)	0.96, 1.02
Source Data: Table 14.2.2.2 and 14.2.2.2.s 1 – Celerity's Premixed Regular Human Insulin (rDNA origin) Injection 2 – Geometric Mean = exp(Mean(log(X))). SE of Geometric Mean = Geometric Mean * SE of Mean(log(X)). 3 – Compared to Novolin R					

(source: Table 11-1 in Final Clinical Study Report Version 1.0 17 April 2018)

2.3.5 What are the major findings in primary PD endpoint?

The comparison for primary PD endpoint $AUC_{GIR\text{-}ss\ 300\text{-}360}$ is given in Table 3. The PD parameter was similar between the products, and the statistical analysis results also suggested that the PD profile was similar between the two products.

Table 3 Comparing $AUC_{GIR\text{-}ss\ 300\text{-}360\ min}$ between Celerity's Premixed Regular Human Insulin (rDNA origin) Injection and Novolin R for the PD Population in CEL-HI-200

Parameter	Statistic	Celerity's Insulin[1] (N=56)	Novolin R (N=56)	Ratio (SE)[3]	90% CI for Ratio[3]	95% CI for Ratio[3]
$AUC_{GIR\text{-}ss\ 300\text{-}360\ min}$ (mg)	Geometric LS Mean (SE)[2]	46461.9 (1424.53)	46543.0 (1425.55)	1.0 (0.03)	0.96, 1.04	0.95, 1.05
Source Data: Table 14.2.6.2 1 – Celerity's Premixed Regular Human Insulin (rDNA origin) Injection 2 – Geometric Mean = exp(Mean(log(X))). SE of Geometric Mean = Geometric Mean * SE of Mean(log(X)). 3 – Compared to Novolin R						

(source: Table 11-2 in Final Clinical Study Report Version 1.0 17 April 2018)

2.4 Intrinsic Factors

Not applicable.

2.5 Analytical Section

2.5.1 What bioanalytical methods are used to assess concentrations of insulin?

The bioanalytical method for human insulin in human serum is summarized in Table 4 below. Based on reported validation parameters, this method is considered adequate for quantitation of human insulin.

Table 4 Summary of Human Insulin Bioanalytical Method

Analyte	Human Insulin			
Matrix	Human Serum			
Anticoagulant	N/AP			
Method SOP number	SM3-393B / SM3-393 C			
Assay method	Enzyme-linked immunosorbent assay (ELISA)			
Sample volume	2 x 75 µL (duplicate determination)			
Minimum required dilution	no pre-dilution			
Analytical range	20 pM – 600 pM			
Regression model	4-PL (Watson: auto-estimate), weighting $1/y^2$			
Precision and Accuracy		**Precision (%)**	**Mean Bias (%)**	**Total Error**
Between-runs	LLOQ-QC (20.8 pM)	7.8	-1.4	9.2
	LQC (55.0 pM)	5.8/138.3[a]	-0.5/31.5[a]	6.3/169.8[a]
	MQC (235 pM)	5.2	-1.7	6.9
	HQC (420 pM)	6.4/15.8[b]	-0.2/2.1[b]	6.6/17.9[b]
	ULOQ-QC (600 pM)	5.8	-3.8	9.6
	DQC (1200 pM)	4.8	5.8	10.6
Precision and Accuracy		**Precision (%)**	**Mean Bias (%)**	**Total Error**
Intra-run (first P&A run ZZ50158_V5)	LLOQ-QC (20.8 pM)	3.2	1.9	5.1
	LQC (55.0 pM)	2.6/154.4[b]	2.2/230.9[b]	4.8/385.3[b]
	MQC (235 pM)	0.8	0.4	1.2
	HQC (420 pM)	2.9	2.6	5.5
	ULOQ-QC (600 pM)	0.6	-1.2	1.8
	DQC (1200 pM)	2.5	7.5	10.0
Selectivity in human serum	Within acceptance: (b) (4)% at LLOQ Criteria passed			
Dilution linearity	Within acceptance (up to (b) (4))			
Parallelism	Within acceptance			
Hemolysis ((b) (4)%)	Criteria passed at LQC and HQC level of (b) (4)% hemolysis			
Stability	QC samples were assessed after frozen storage at -20°C and -80°C independently at the LQC and HQC level. STD samples were assested after frozen storage at -20°C at the STD1 and STD8 level			
	in human serum (LQC and HQC)		In surrogate matrix (STD1 and STD8)	
Freeze/Thaw	7 cycles		7 cycles	
Benchtop (RT)	43 h		43 h	
Longterm-Stability	(b) (4) days (after storage at -20°C and -80°C)		(b) (4) days (after storage at -20°C)	
Longterm-Stability for WS3	up to 19 days at -20°C			

[a] left value with two outliers excluded, right value with two outliers included in statistics
[b] left value with one outlier excluded, right value with outlier included in statistics

2.5.2 What bioanalytical methods are used to assess concentrations of C-peptide?

The bioanalytical method for C-peptide in human serum is summarized in Table 5 below. Based on reported validation parameters, this method is considered adequate for quantitation of human insulin.

Table 5 Summary of C-peptide Bioanalytical Method

Analyte	Human C-Peptide			
Matrix	Human serum			
Anticoagulant	N/AP			
Method SOP	SM3-390B			
Assay method	Enzyme-linked immunosorbent assay (ELISA)			
Sample volume	2 x 50 µL (duplicate determination)			
Minimum required dilution	no pre-dilution			
Analytical range	0.15 ng/mL – 5.00 ng/mL			
Regression model	4-PL (Watson: auto-estimate), weighting $1/y^2$			
Precision and accuracy		**Precision (%CV)**	**Mean Bias (%)**	**Total Error (%)**
Between-runs	LLOQ (0.1675 ng/mL)	5.9	1.1	7.0
	LQC (0.4500 ng/mL)	14.8	-1.0	15.9
	MQC (2.000 ng/mL)	11.3	-1.6	12.9
	HQC (3.500 ng/mL)	4.4	-3.0	7.5
	ULOQ (5.000 ng/mL)	7.5	-11.5	19.0
	DQC (10.00 ng/mL)	4.0	3.8	7.8
Intra-run (first P&A run ZZ51294_V09)	LLOQ (0.1675 ng/mL)	3.0	4.8	7.8
	LQC (0.4500 ng/mL)	1.5	1.3	2.8
	MQC (2.000 ng/mL)	2.7	1.2	3.9
	HQC (3.500 ng/mL)	1.3	0.8	2.1
	ULOQ (5.000 ng/mL)	3.7	-8.7	12.4
	DQC (10.00 ng/mL)	1.4	3.2	4.6
Selectivity	10 individuals, including 2 lipemic, tested unspiked and spiked to (b) (4) ng/mL: 10/10 within acceptance criteria			
Hemolysis	(b) (4) % hemolysis tested in LQC and HQC samples 18/18 samples within aceeptance criteria: no effect found with up to (b) (4) % hemolysis			
Dilution linearity / hook effect	Dilution factors: (b) (4) In all cases, 5/5 duplicates within acceptance criteria No hook effect observed up to (b) (4) g/mL			
Parallelism	3 individual matrices, diluted (b) (4) 15/15 duplicates within acceptance criteria			
Stress test:	32/32 Blank samples < LLOQ ; 32/32 DQC samples >ULOQ No stress effect observed			
Stability in human serum:	Samples: HQC and LQC Storage temperature: -20°C and -80°C Long term stability: (b) (4) days Short term stability: 36 h RT Freeze/Thaw: 6 cycles All samples within acceptance criteria			
Stability in other matrices:	Samples: STD 1 and STD8 (2x charcoal stripped serum) Storage temperature: -20°C and -80°C Stability: (b) (4) days and 1 F/T cycle All samples within acceptance criteria		Samples: WS1 and WS 4 (0.1% BSA buffer) Storage temperature: -20°C and -80°C Stability (b) (4) days and 1 F/T cycle 23/24 samples within acceptance criteria	

2.6 Office of Study Integrity and Surveillance Inspection

2.6.1 Clinical site

The Office of Study Integrity and Surveillance (OSIS) arranged an inspection of ProSciento, Inc., Chula Vista, CA. No objectionable conditions were observed, and Form FDA 483 was not issued at the close-out of the inspection. The final inspection classification for the inspected site is No Action Indicated (NAI) (see OSIS memo by Dr. Sripal Reddy Mada in DARRTS dated 05/08/2019).

Base on the inspectional findings, the data from the audited study CEL-HI-200 (NDA 208157) are reliable to support a regulatory decision.

2.6.2 Bioanalytical site

OSIS inspected the analytical portion (Studies CA19891-01 (Regular Human Insulin) and CA19891-02 (Human C-peptide)) of the clinical Study CEL-HI-200 (NDA 208157, Regular Human Insulin) conducted at (b) (4) .

No objectionable conditions were observed, and Form FDA 483 was not issued at the inspection close-out. The final inspection classification is NAI (see OSIS memo by Dr. Li-Hong Yeh in DARRTS dated 02/21/2019).

Based on OSIS's review of the inspectional findings, the analytical data from the audited studies are reliable to support a regulatory decision.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

TAO LIU
05/15/2019 10:09:22 AM

MANOJ KHURANA
05/15/2019 12:01:53 PM