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ORIGINAL ARTICLE

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Pharmacokinetic and pharmacodynamic bioequivalence between regular human insulin (rDNA origin) in 0.9% sodium chloride ready-to-use infusion 1 U/mL and 100 U/mL concentrate diluted to 1 U/mL in healthy males

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Abstract

Aim: To show pharmacokinetic (PK) and pharmacodynamic (PD) bioequivalence between Myxredlin, a novel, ready-to-use regular human insulin 1 U/mL formulation (BAX-HI), and Novolin R 100 U/mL concentrate diluted to 1 U/mL (NOVO-HI).

Materials and Methods: This phase 1, double-blind, randomized, two-way crossover study compared the PK and PD properties of BAX-HI and NOVO-HI. A total of 58 healthy males received 0.36 U/kg of each study drug, administered intravenously over a 6-hour period, concurrent with an 8-hour euglycaemic clamp at two treatment periods separated by a washout period of 7-10 days. The primary PK endpoint was the area under the insulin concentration-time curve at steady state (SS) measured from 300 to 360 minutes ($AUC_{INS\text{-}SS\ 300\text{-}360\ min}$). The primary PD endpoint was the area under the glucose infusion rate-time curve at SS measured from 300 to 360 minutes ($AUC_{GIR\text{-}SS\ 300\text{-}360\ min}$).

Results: All subjects completed the first treatment period and 54 subjects completed both treatment periods. Bioequivalence between BAX-HI and NOVO-HI was shown for the primary endpoints as the 90% confidence interval (CI) of the geometric least-squares (LS) mean ratio for $AUC_{INS\text{-}SS\ 300\text{-}360\ min}$, and the 90% CI and 95% CI of the geometric LS mean ratio for $AUC_{GIR\text{-}SS\ 300\text{-}360\ min}$ were entirely contained within the prespecified limits of 80%-125%. Safety profiles were comparable for both study drugs and there were no serious adverse events.

Conclusions: The study showed bioequivalence between BAX-HI and NOVO-HI in terms of PK and PD characteristics in healthy males.

KEYWORDS

biosimilar insulin, insulin therapy, pharmacodynamics, pharmacokinetics, phase I-II study

1 | INTRODUCTION

For most hospitalized diabetes patients with hyperglycaemia, the current American Diabetes Association guidelines recommend insulin as the primary therapy.[1] Insulin is the preferred treatment modality in the hospital setting because it is the most potent agent to lower blood glucose, is rapidly effective, and is easily titrated. In the critical care setting, moderate glycaemic goals that seek to control glucose while avoiding hypoglycaemia are preferred for the majority of hospitalized patients.[2] Intravenous (IV) administration of insulin has been shown to accomplish adequate control of blood glucose levels with smaller insulin doses.[3]

Despite the long history of usage and well-defined benefits of insulin treatment for hyperglycaemia, insulin is considered a high-alert medication by the Institute for Safe Medication Practices (ISMP) because of the risk of harm to patients that can accompany errors in prescribing, transcribing, or dosing.[4] There are multiple accepted routes for insulin administration (e.g. subcutaneous, inhaled, oral, or IV).[5] IV infusion is the preferred route of delivery in critical care, labour and delivery, and perioperative inpatient settings, as the rapid onset and short duration of action associated with IV infusion allow for matching insulin requirements to rapidly changing glucose levels.[6] In acutely ill cardiac patients, therapy with IV insulin was shown to be safer and more effective than subcutaneous insulin.[7,8]

The American Society of Health-System Pharmacists and ISMP recommend a standardized concentration of 1 U/mL for IV insulin.[9] There are several marketed insulin products in vials approved for IV use (e.g. insulin human [regular], insulin aspart, insulin lispro, insulin glulisine); however, to achieve a solution of 1 U/mL, these concentrated solutions (e.g. 100 U/mL) require dilution on site prior to administration, which introduces the opportunity for preparation errors and subsequent dosing errors. A ready-to-use insulin formulation, such as Myxredlin, a novel, ready-to-use regular human insulin 1 U/mL formulation (referred to herein as BAX-HI), offers the benefit of a reduction of the common errors associated with dilution of concentrated insulin solutions.[10]

Here we report the results of a two-way crossover, pharmacokinetic/pharmacodynamic (PK/PD) bioequivalence study of BAX-HI for IV administration, versus Novolin R, a regular human insulin (rDNA origin) 100 U/mL concentrate, diluted to 1 U/mL in 0.9% sodium chloride (referred to herein as NOVO-HI). Safety and tolerability outcomes were also evaluated.

2 | MATERIALS AND METHODS

2.1 | Materials

A ready-to-use insulin for IV infusion was developed for use in the hospital and emergency room setting using the Galaxy technology platform. BAX-HI is a dilute recombinant human insulin solution (Myxredlin, Baxter Healthcare Corporation) formulated at a concentration of 1 U/mL in 0.9% sodium chloride, 0.29 mg/mL monobasic sodium phosphate, monohydrate, 0.412 mg/mL dibasic sodium phosphate, anhydrous, and water for infusion. The active substance, human insulin, is manufactured from a yeast (*Pichia pastoris*) expression system by an established method based on rDNA technology. The amino acid sequence and structure is identical to endogenous human insulin and contains no foreign glycosylation, thus no neoepitopes or modifications are introduced that might stimulate an immune response.

The reference drug is Novolin R (regular human insulin [RHI] [rDNA origin] USP; Novo Nordisk Medical, Bagsvaerd, Denmark). Human insulin in Novolin R is manufactured utilizing a yeast (*Saccharomyces cerevisiae*) as the production organism. Novolin R differs from BAX-HI in that it is provided as a more concentrated formulation for subcutaneous or IV use (100 U/mL), is fortified with zinc chloride, and contains the excipients metacresol and glycerol. Novolin R was supplied in 10-mL vials at a concentration of 100 U/mL and diluted to a concentration of 1 U/mL in 0.9% sodium chloride for IV infusion (NOVO-HI).

2.2 | Study design

This was a phase 1, double-blind, randomized, two-way crossover, euglycaemic glucose clamp study conducted from 22 May to 21 October 2017. The study was conducted in accordance with the International Council for Harmonisation Good Clinical Practice guidelines, the Declaration of Helsinki, and other applicable regulations. The protocol was approved by the Institutional Review Board and all participants provided written informed consent.

Subjects were randomized 1:1 to one of two sequences, receiving BAX-HI and NOVO-HI, based on their order of entry into the study, using a randomization list.

The study consisted of a screening visit, two treatment periods separated by a washout period of 7-10 days, and a follow-up visit 30 days after the last clamp. During each treatment period, subjects checked into a clinic for a 2-day in-house stay. Subjects were fasted for 10 hours or longer prior to initiation of the 8-hour euglycaemic clamp procedure. Four venous catheters were inserted into peripheral veins for collection of blood samples and infusions. Subjects were connected to a fully automated clamp device (Biostator, MTB Medizintechnik, Amstetten, Germany) for at least 1 hour prior to drug administration. The study drugs were administered intravenously in a blinded manner concurrent with the clamp procedure starting at time 0 and continuing over a 6-hour period (1.0 mU/kg/min resulting in a total dose of 0.36 U/kg). The duration of study drug infusion ensured that steady state (SS) conditions were reached during the last 60 minutes (between 300 and 360 minutes) of the procedure. Following the start of the infusion, blood glucose concentration was clamped at a target blood glucose concentration of 9 mg/dL (0.5 mmol/L) below the individual fasting blood glucose level of the subject by means of an IV infusion of 20% glucose. The glucose infusion rate (GIR) required to keep blood glucose at target level (±10%) was recorded during the entire clamp period and data were used to

calculate PD variables. The glucose clamp continued until 8 hours after the start of the study drug infusion. The subjects remained fasting and in a supine or semisupine position during the entire glucose clamp and received a standardized meal at the end of the clamp procedure.

Predose sampling was taken within 5 minutes before dosing. A 3-mL sample of blood was taken at each study time point by venous catheter. Serum insulin was quantified using a commercially available enzyme-linked immunosorbent assay (ELISA; Mercodia Insulin ELISA Kit). Blood samples to determine serum insulin concentration were obtained at prespecified intervals. C-peptide was measured, using a sandwich ELISA assay, in parallel to insulin concentrations to detect potential changes in endogenous insulin secretion and enable a correction for endogenous insulin secretion, if necessary. Additional plasma glucose (Figure S1) and C-peptide (Figure S2) samples were obtained throughout the clamp procedure to provide increased clarity in the interpretation of the results.

The PD effects of BAX-HI were measured during the 8-hour euglycaemic clamp procedure using the Biostator device. The blood glucose measurements of the Biostator device were recalibrated at regular intervals (approximately every 30 minutes) by blood glucose measurements performed with the YSI 2300 STAT glucose analyser during the clamp procedure.

Safety and tolerability of the investigational products were assessed by collecting the incidence and severity of adverse events (AEs), incidence of clinical laboratory abnormalities, and change from baseline in vital signs and in 12-lead ECG variables.

Eligible subjects were healthy males aged 18-50 years with no history of diabetes or RHI use, a fasting HbA1c of less than 5.6%, a body mass index of 18 to 27 kg/m^2, and a minimum weight of 50 kg. Subjects were not allergic or hypersensitive to insulin, and concurrent use of drugs that could interfere with glucose or insulin metabolism was not allowed. Subjects must have been non-smokers for 12 months or longer.

2.3 | Study endpoints

The primary PK endpoint was the area under the insulin concentration-time curve (AUC), measured from 300 to 360 minutes ($AUC_{INS\text{-}SS\ 300\text{-}360\ min}$). The primary PD endpoint was the area under the GIR-time curve at SS measured from 300 to 360 minutes ($AUC_{GIR\text{-}SS\ 300\text{-}360\ min}$).

Secondary PK endpoints were maximum insulin concentration (C_{max}), time to reach C_{max} (T_{max}), apparent terminal half-life ($T_{1/2}$), and total and incremental AUC_{INS} (i.e. $AUC_{INS\ 0\text{-}6\ hours}$, $AUC_{INS\ 0\text{-}8\ hours}$, $AUC_{INS\ 6\text{-}8\ hours}$).

Secondary PD endpoints were maximum GIR (GIR_{max}), total and incremental AUC_{GIR} (i.e. $AUC_{GIR\ 0\text{-}5\ hours}$, $AUC_{GIR\ 0\text{-}6\ hours}$, $AUC_{GIR\ 0\text{-}8\ hours}$, $AUC_{GIR\ 6\text{-}8\ hours}$), time to reach GIR_{max} ($T_{GIR\ max}$), and time to onset of action (defined as the start of IV glucose infusion during the clamp).

Safety endpoints were incidence of AEs, clinical laboratory abnormalities, clinical findings on physical examination, and change from baseline in vital signs and 12-lead ECG variables.

2.4 | Statistical methods

The primary PK and PD endpoints were calculated using raw, log-transformed data, and analysed in a mixed-effects model with treatment (two levels), sequence (two levels) and period (two levels) as fixed effects, and subject-within-sequence as a random effect. The least squares (LS) geometric means of the two treatments were calculated and the associated 95% confidence intervals (CIs) were constructed. In addition, the LS mean differences between BAX-HI and NOVO-HI were also calculated and the associated 90% CI was constructed. The LS treatment means and the 95% CIs were exponentiated to obtain the LS geometric means of the treatment and the 95% CIs at the original scales. The LS mean treatment difference and 90% CI were exponentiated to the original scale to yield the LS geometric mean ratio between BAX-HI and NOVO-HI and the associated 90% CI (for the PD endpoint, the 95% CI was also calculated). The intrasubject variability and coefficient of variation (CV)% were calculated from the same model. Bioequivalence was established if the 90% CI for the ratio of the LS geometric means for BAX-HI/NOVO-HI for the PK and PD variables fell within the 80%-125% range.

Safety and tolerability of BAX-HI and NOVO-HI were assessed by collection and review of AEs, physical examination, vital signs, ECGs and laboratory variables (chemistry, haematology, and urinalysis). All safety data were tabulated and summarized.

Based on the assumptions that intraindividual CVs of the PK and PD variables were of a maximum of 30% and that BAX-HI was not more than ±5% different than NOVO-HI, a minimum sample size of 52 subjects in a crossover design was determined to show bioequivalence with 90%.

3 | RESULTS

3.1 | Patient disposition and baseline characteristics

Of the 58 enrolled subjects, 54 completed the study. Subjects were randomized into one of two possible treatment sequences (AB or BA; treatment A = infusion of BAX-HI; treatment B = infusion of NOVO-HI). All subjects completed the first treatment period, and four subjects (two in each treatment sequence) were discontinued from the study prior to completing the second treatment period. The reasons for discontinuation were an AE (abnormal ECG junctional rhythm reported between treatment periods which was consistent with ECGs before treatment and deemed by the investigator to be not related to study-drug administration), withdrawal by the Investigator because of an IV-line error during the euglycaemic clamp in treatment period 2 that impacted data integrity, consent withdrawal, and withdrawal by the Investigator as the subject may have been unblinded to the study drug administered. All discontinued subjects were included in the safety, PK, and PD populations. None of the included subjects had relevant medical histories reported. Patient baseline characteristics are presented in Table 1.

3.2 | PK endpoints

The PK profiles of both BAX-HI and NOVO-HI were characterized by a rapid increase in the serum concentration of insulin at the start of the infusion and were similar throughout the procedure. Notably, once the infusion ended, a rapid return to baseline insulin concentrations was observed with both BAX-HI and NOVO-HI (Figure 1). PK bioequivalence was shown between BAX-HI and NOVO-HI as the 90% CI of the geometric LS mean ratio for $AUC_{INS\text{-}SS\ 300\text{-}360\ min}$ was entirely contained within the prespecified limits of 80%-125% (Table 2). No differences were observed between BAX-HI and NOVO-HI in terms of the total and incremental AUC_{INS} at the analysed time points.

A sensitivity analysis using C-peptide corrected serum insulin data was conducted and the results were consistent with the primary and secondary PK bioequivalence endpoint analyses.

TABLE 1 Demographics and baseline characteristics

Characteristics	All subjects (N = 58)
Male, n (%)	58 (100)
Age, y, mean (SD) [range]	32.9 (7.86) [19-50]
Race:	
White, n (%)	45 (77.6)
Asian, n (%)	3 (5.2)
Black or African American, n (%)	6 (10.3)
Native Hawaiian or other Pacific islander, n (%)	1 (1.7)
Multiple races, n (%)	2 (3.4)
Other, n (%)	1 (1.7)
Ethnicity:	
Hispanic or Latino, n (%)	25 (43.1)
Not Hispanic or Latino, n (%)	33 (56.9)
Weight, kg, mean (SD) [range]	75.3 (9.18) [57.4-96.1]
Height, cm, mean (SD) [range]	177 (6.93) [161-190]
Body mass index, kg/m^2, mean (SD) [range]	23.9 (2.49) [18.2-27.8]

Baseline variables prior to infusion of BAX-HI or NOVO-HI	BAX-HI (N = 56)	NOVO-HI (N = 56)
Insulin, pM, geometric mean (SE)	28.6 (1.33)	27.7 (1.39)
C-peptide, ng/mL, geometric mean (SE)	0.99 (0.06)	1.00 (0.06)
Glucose mg/dL, geometric mean (SE)	88.5 (0.76)	88.0 (0.69)

Abbreviations: pM, picomoles/L; SD, standard deviation; SE, standard error.

3.3 | PD endpoints

The results show PD bioequivalence between BAX-HI and NOVO-HI as the 90% CI and 95% CI of the geometric mean ratio for $AUC_{GIR\text{-}SS\ 300\text{-}360\ min}$ were entirely contained within the prespecified limits of 80%-125% (Table 3). The geometric mean (SD) GIR over time was similar between BAX-HI and NOVO-HI. Both study drugs were characterized by a rapid onset of action and similar TGIR max. A rapid return to baseline GIR levels was observed with both BAX-HI and NOVO-HI following the end of the IV insulin infusion and within the PD sampling period (Figure 2). One subject was highly insulin sensitive and presented a very robust response to both insulins, which resulted in a higher than expected GIRmax value. However, this was still within the expected normal variation. Because the same subject was notably more sensitive to both insulin formulations, the variability (geometric CV%) of GIRmax was still comparable between insulins (19.3% for BAX-HI and 21.2% for NOVO-HI). No differences were found between BAX-HI and NOVO-HI in terms of the total and incremental AUC_{GIR} at the analysed time points. Taken together, the results of the PD analyses were comparable between BAX-HI and NOVO-HI.

3.4 | Safety

Overall, 15 AEs were recorded in 10 of 58 subjects (17.2%) during the study. Five AEs were reported in five subjects (8.9%) after treatment

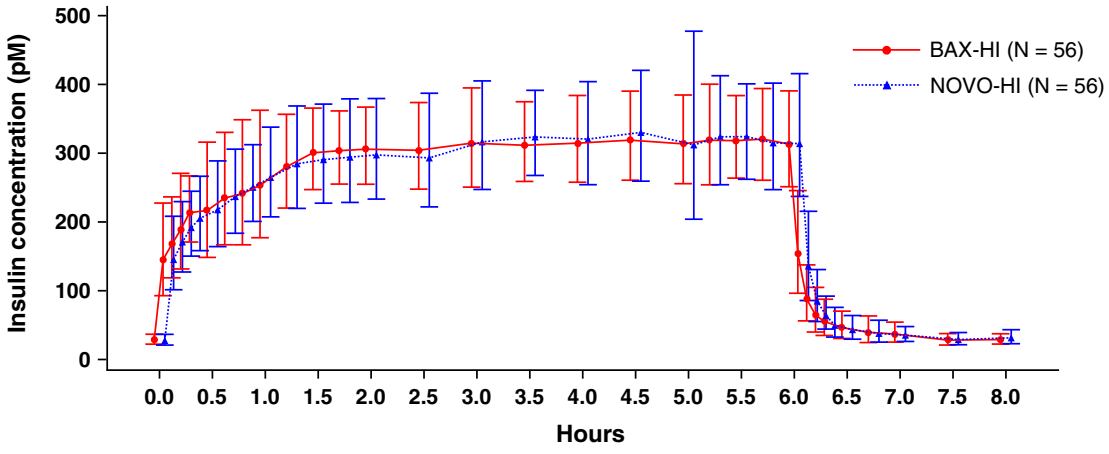

FIGURE 1 Geometric mean (SD) insulin concentration (pM) over time. BAX-HI and NOVO-HI were infused over a 6.0-hour period with initial infusion at 0.0 hours, concurrent with an 8.0-hour euglycaemic clamp procedure. pM, picomoles/L

TABLE 2 Pharmacokinetic variables for BAX-HI and NOVO-HI

Variable	Statistic	BAX-HI (N = 56)	NOVO-HI (N = 56)	Ratio	90% CI
Primary analysis					
$AUC_{INS\ SS\ 300\text{-}360\ min}$	Geometric LS mean (SE)	19 097 (514)	19 267 (518)	1.0 (0.02)	0.96, 1.03
C_{max} (pM)	Geometric LS mean (SE)	368 (9.27)	373 (9.39)	0.99 (0.02)	0.96, 1.02
$T_{1/2}$ (min)	Mean (SD)	68.2 (79.5)	59.4 (37.5)	–	–
T_{max} (min)	Median [range]	270 [30-360]	270 [75-360]	–	–
Sensitivity analysis: C-peptide corrected values					
$AUC_{INS\ SS\ 300\text{-}360\ min}$	Geometric LS mean (SE)	18 423 (494)	18 586 (498)	1.0 (0.02)	0.96, 1.02
C_{max} (pM)	Geometric LS mean (SE)	357 (8.96)	362 (9.09)	0.99 (0.02)	0.96 (1.02)
$T_{1/2}$ (min)	Mean (SD)	24.0 (9.93)	25.54 (9.07)	–	–
T_{max} (min)	Median [range]	240 [30-360]	270 [75-360]	–	–

Abbreviations: CI, confidence interval; INS, insulin; LS, least squares; max, maximum; min, minute; pM, picomoles/L; SD, standard deviation; SE, standard error; SS, steady state.

TABLE 3 Pharmacodynamic variables for BAX-HI and NOVO-HI

Variable	Statistics	BAX-HI (N = 56)	NOVO-HI (N = 56)	Ratio	90% CI	95% CI
$AUC_{GIR\ SS\ 300\text{-}360\ min}$	Geometric LS mean (SE)	46 462 (1425)	46 543 (1426)	1.0 (0.03)	(0.96, 1.04)	(0.95, 1.05)
GIR_{max} (mg/min)	Mean (SD)	1029 (210)	1029 (227)	–	–	–
T_{GIRmax} (min)	Median [range]	301 [65-383]	290 [49-388]	–	–	–
Time to onset of action (min)	Median [range]	21.0 [5-35]	19.0 [5-33]	–	–	–

Abbreviations: GIR, glucose infusion rate; LS, least squares; max, maximum; min, minute; SD, standard deviation; SE, standard error; SS, steady state.

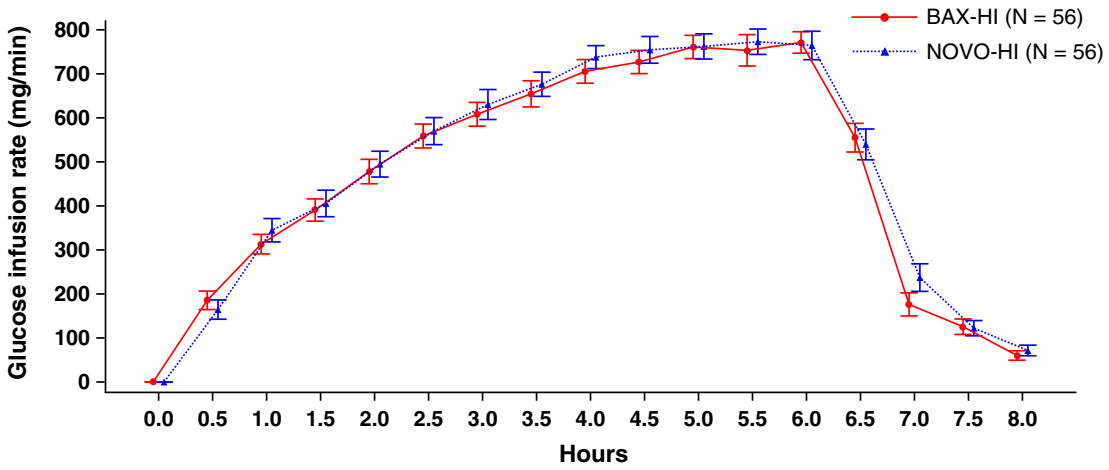

FIGURE 2 Geometric mean (SD) glucose infusion rate (mg/min) over time for BAX-HI and NOVO-HI. Glucose was infused over a 6.0-hour period with initial infusion at 0.0 hours, concurrent with an 8.0-hour euglycaemic clamp procedure

with BAX-HI (n = 56), and 10 AEs were reported in five subjects (8.9%) after treatment with NOVO-HI (n = 56). All the reported AEs were mild in nature. There were no serious AEs or deaths. None of the AEs were classified as related to BAX-HI. Four AEs were classified as related to NOVO-HI infusion and included abdominal discomfort, nausea, headache, and hyperhidrosis. There were no episodes of hypoglycaemia. Two subjects had abnormal, clinically significant 12-lead ECG findings; neither was considered drug-related.

There were no clinically meaningful changes in vital signs, clinical laboratory evaluations, or physical examination findings.

4 | DISCUSSION

In the current study, PK and PD bioequivalence of BAX-HI to NOVO-HI was shown in healthy male subjects who received IV infusions of

1.0 mU/kg/min of the study drugs over a period of 6 hours (total insulin dose of 0.36 U/kg). This dose was anticipated to provide a robust and meaningful metabolic response after insulin administration in healthy subjects. The dose was within the ranges used in other clinical glucose clamp studies in healthy subjects, and there have been no safety issues observed at this dose level.[11,12]

A two-way crossover design was appropriate for this bioequivalence study as each subject acted as his own control, eliminating any influence of intersubject variability in insulin sensitivity on the study results.[13] The euglycaemic glucose clamp is widely regarded as the gold standard in assessing insulin sensitivity and is widely used in the evaluation of insulin activity.[14] Healthy subjects are generally recommended in bioequivalence studies when use of the test product in this population is safe to reduce variability in response that is not caused by the study product.[15] Selection of healthy subjects for this insulin bioequivalence study also ensured that the assessments were not biased by diabetes-related factors (e.g. individually varying degrees of insulin resistance), which could amplify non-product–related variability in a comparative study.

Further, female subjects were excluded in this study to eliminate the possible variability in insulin sensitivity during the female menstrual cycle.[16] Therefore, healthy, male subjects were selected to represent the most homogenous and insulin-sensitive study population for the detection of differences in insulin response to the study treatments and provide confidence that the bioequivalence result for BAX-HI compared with NOVO-HI is applicable to the intended patient population.

The primary PK analysis of serum insulin concentration data showed that the two study treatments were bioequivalent as the geometric LS mean ratio of the $AUC_{INS\text{-}SS\ 300\text{-}360\ min}$ variable was 100%, and the geometric 90% CI ratio (96%-103%) was contained within the prespecified limits (80%-125%) for determination of bioequivalence. C-peptide concentrations were comparable between BAX-HI and NOVO-HI and showed that insulin production was suppressed as expected during clamp and drug infusion (data not shown). In addition, a sensitivity analysis using C-peptide corrected insulin concentration data was performed to account for the possibility of endogenous insulin secretion during the PK sampling period, confirming the bioequivalence of BAX-HI to NOVO-HI. Both study drugs resulted in a rapid increase in serum insulin concentration following their administration, a rapid decrease following cessation of the insulin infusion, and a return to predose levels within the PK sampling period. There were no substantial differences in the other PK variables measured. In addition, secondary endpoint analyses, although not used to determine bioequivalence, supported the conclusion of bioequivalence.

The PD analysis further supported the conclusion of bioequivalence of the two study treatments. Both insulins had a rapid onset of action (approximately 20 minutes) and GIR increased concurrently with insulin concentration, as expected. The geometric LS mean ratio for the primary PD endpoint, $AUC_{GIR\text{-}SS\ 300\text{-}360\ min}$, was 100%, and the 95% CI ratio was 95%-105%, which was completely contained within the prespecified limits (80%-125%) for establishing bioequivalence. No significant differences were noted between BAX-HI and NOVO-HI in any of the measured PD variables.

This study is the first-in-human display of PK/PD bioequivalence between a ready-to-use formulation of insulin designed for IV use in the hospital and other acute care settings and a concentrated insulin solution diluted prior to use.[17] Novolin R was chosen as the reference drug in this study because it is produced in yeast using rDNA technology (as is BAX-HI) and there are no other approved ready-to-use insulin solutions for IV infusion.[18] Although other PK/PD profile studies have previously been conducted, insulin bioavailability differs when administered via alternative routes of administration, thus an appropriate comparison of the current study and published data cannot be performed.

It should be noted that insulin has been used to control hyperglycaemia for many years, however, it is still considered a high-alert medication.[19] The ISMP defines high-alert medications as those bearing a heightened risk of causing significant patient harm when used in error.[20] Compounding of products may lead to errors because of factors such as the components/diluents, the compounding equipment, and the compounding technique used.[20] Manufacturer-prepared ready-to-use products are considered to be intrinsically more consistent than compounded products.[20] Several publications have described the wide variability in concentration present in compounded pharmaceutical products.[21-23] The highest variability in concentrations ranged from −78% to +210% of the desired concentration and up to 65% of the compounded infusions with a concentration greater than 10% different from the desired concentration.[24] Automatic insulin delivery systems are devices used for continuous subcutaneous insulin infusion that automatically adjust insulin delivery via a pump.[25] While automatic insulin delivery systems allow for standardized dosing of insulin, not all hospital settings have access to them. A ready-to-use 1 U/mL insulin formulation, such as BAX-HI, provides the benefit of stable, consistent, and predictable insulin dosing with each administration, in the absence of automated delivery systems, and eliminates the risk of compounding errors.

Compounding has also been shown to increase the risk of microbial contamination of the final product.[10] Utilization of sterile manufactured, ready-to-use products, such as BAX-HI, reduces the risk of potential contamination or mixing errors enhancing patient safety, and the use of these products is recommended when they are available.[26,27]

There were no significant safety findings in either treatment group. Both BAX-HI and NOVO-HI were generally well tolerated; the type and frequency of AEs reported were consistent with other insulin products.[11,28,29]

Hyperglycaemia in the critical care setting increases both mortality and disease-specific morbidity in hospitalized patients and requires patient-tailored and situation-tailored insulin therapy.[30] Patients with newly identified hyperglycaemia may be at the highest risk. Treatment of newly detected hyperglycaemia in a hospitalized patient must be highly accurate and precisely monitored as glucose levels may change rapidly and sometimes unpredictably. While hypoglycaemia is typically

the most common adverse reaction in the treatment of hyperglycaemia postinsulin administration,[31] the use of the glucose clamp technique in this study allowed for avoidance of hypoglycaemia in all patients.

In conclusion, this study showed PK and PD bioequivalence of Myxredlin, a ready-to-use human insulin 1 U/mL formulation (or BAX-HI), and Novolin R 100 U/mL concentrate diluted to 1 U/mL (NOVO-HI). Insulin concentration or activity in this study population were not affected by the differences in excipients and insulin source. Overall, BAX-HI was well tolerated and the safety profile is expected to be equivalent to other insulin products administered intravenously. The results of this study support the use of BAX-HI as a ready-to-use insulin for IV infusion that is bioequivalent to NOVO-HI.

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CONFLICT OF INTEREST

MHo is an employee, member of the board of directors, and shareholder at ProSciento, Inc. LP, AH, and AW are employees of Baxter Healthcare Corporation and own stock in the company. MHe is an employee at ProSciento and owns stock options in the company. All remaining authors have nothing to disclose.

AUTHOR CONTRIBUTIONS

All the authors made substantial contributions to the interpretation of data for the manuscript, drafted and critically revised the manuscript. All the authors are responsible for the integrity of the work as a whole.

PEER REVIEW

The peer review history for this article is available at https://publons.com/publon/10.1111/dom.14520.

DATA AVAILABILITY STATEMENT

Deidentified individual participant data (including data dictionaries) in addition to the study protocol, the statistical analysis plan, and the informed consent form, will be made available upon request to researchers who provide a methodologically sound proposal for use in achieving the goals of the approved proposal. Proposals should be submitted tolucas_peterson@baxter.com.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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