Clinical trial results:
A Randomised, Open, Parallel-group Phase III Biosimilarity Study to Assess the Long-term Safety, Focusing on Immunogenicity, of Rechon Insulin Human Soluble in Type 1 Diabetic Patients.

Summary

EudraCT number	2016-004691-22
Trial protocol	DE PL
Global end of trial date	17 December 2019

Results information

Result version number	v1 (current)
This version publication date	27 November 2020
First version publication date	27 November 2020

Trial information

Trial identification

Sponsor protocol code	RCT-004

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Rechon Life Science AB
Sponsor organisation address	Soldattorpsvägen 5, Limhamn, Sweden, SE-216 10
Public contact	Clinical Development, Rechon Life Science AB, info@rechon.se
Scientific contact	Clinical Development, Rechon Life Science AB, info@rechon.se

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	17 December 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	17 December 2019
Global end of trial reached?	Yes
Global end of trial date	17 December 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To asses the long-term safety of Rechon Human Insulin Soluble as compared to Humulin® Regular in terms of immunogenicity and insulin tolerance.

Protection of trial subjects:

All patients received written and verbal information regarding the study. The given information emphasised that participation in the study was voluntary and that the patient could withdraw from the study at any time and for any reason. All patients were given the opportunity to ask questions about the study and were given sufficient time to decide whether they would participate in the study.

Before any study-related procedures, the informed consent form (ICF) was signed and personally dated by the patient and by the person who conducted the informed consent discussion.

Participation in the study was not judged to pose any risk for the patients. The individual patients participating in the study gained benefit from regular health checkups during the study. Additionally, by their participation they supported the development of new insulins to be put on the market. Rechon Insulin Human Soluble has been developed to compete with the innovator product on the market, thereby increasing the availability of insulin products for diabetic patients. Europe’s healthcare systems will benefit from the cost relief and the increased patient access to the life enhancing treatments that biosimilar products will bring.

Background therapy:

N/A

Evidence for comparator:

The insulin substance used in Humulin® Regular, the reference product, is a recombinant human insulin with a molecular weight of 5,808 kDa. The molecule consists of two chains interconnected by two disulfide bonds. The insulin substance is synthesised in a non-disease producing strain of E.coli that has been genetically altered by the addition of the human gene for insulin production. The insulin is produced by Eli Lilly and Company.

Humulin® Regular is a fast acting solution. The IMP was manufactured by Eli Lilly and Company.

Humulin® Regular was provided in 3 mL cartridges to be used in the insulin pen Humapen Savvio. The pen was intended for use with the Humulin® products.

The Sponsor (Rechon Life Science AB) is developing the fast-acting insulin Rechon Insulin Human Soluble as a biosimilar to the fast-acting insulin Humulin® Regular and the intermediate-acting insulin Rechon Insulin Human Isophane as a biosimilar to Humulin® NPH.

At the initiation of this clinical study, RCT-004, both pre-clinical studies and three clinical trials had been performed on the Rechon drug substance and on these two formulations of Rechon insulin, which were compared to their respective Humulin® reference products.

Actual start date of recruitment	20 December 2017
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 323
Country: Number of subjects enrolled	Germany: 8
Worldwide total number of subjects	331
EEA total number of subjects	331

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	303
From 65 to 84 years	28
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

In this study, 370 patients were screened for participation, and as 39 patients (10.5%) were screening failures, 331 patients (89.5%) were randomized to treatment with either Rechon Insulin (164 patients) or Humulin Regular (167 patients).

Pre-assignment

Screening details:

Male or female patients 18-75 years, with BMI 18.0-32.0 kg/m2 and diagnosed with type 1 diabetes mellitus (T1DM) for at least two years. They should have ongoing daily treatment with insulin for at least 12 months, below or equal to 1.2 U/kg/day and HbA1c below or equal to 94 mmol/mol.

Period 1

Period 1 title	Overall period (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

Patients and Investigators were not blinded to study treatment in this study. It was not possible to completely blind the study since the cartridges differed in colour of the plunger, lined-seal and metal cap of the cartridges. The primary variable in the study was anti-insulin antibody, which was analysed by Wieslab AB, Malmö, Sweden. Laboratory staff doing the laboratory analyses were blinded to treatment.

Arms

Are arms mutually exclusive?	Yes
Arm title	Rechon Insulin Human Soluble

Arm description:

Patients received either Rechon Insulin Human Soluble or Humulin® Regular in a randomised way. The IMP was administered at home by the patients themselves. Dosing was individualised and adjusted based on blood glucose levels for each patient.

Arm type	Experimental
Investigational medicinal product name	Rechon Insulin Human Soluble
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Patients received either Rechon Insulin Human Soluble or Humulin® Regular in a randomised way. The IMPs were administered at home by the patients themselves. Dosing was individualised and adjusted based on blood glucose levels for each patient.

Rechon Insulin Human Soluble was provided in 3 mL cartridges to be used in the insulin pen (YpsoPen Twist) manufactured by Ypsomed AG, Switzerland. The pen is documented for use with Rechon insulin products and is CE marked.

Before a meal, fast acting insulins (e.g. Rechon Insulin Human Soluble or) are taken to be able to utilise the carbohydrates in the food and prevent blood glucose levels to rise. The more carbohydrates the food contains, the more insulin is needed. Many fast acting insulins reach the blood after approximately 15 minutes and are effective for 3-4 hours.

Arm title	Humulin® Regular

Arm description:

Patients received either Rechon Insulin Human Soluble or Humulin® Regular in a randomised way. The IMP was administered at home by the patients themselves. Dosing was individualised and adjusted

based on blood glucose levels for each patient.

Arm type	Reference product
Investigational medicinal product name	Humulin® Regular
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Patients received either Rechon Insulin Human Soluble or Humulin® Regular in a randomised way. The IMPs were administered at home by the patients themselves. Dosing was individualised and adjusted based on blood glucose levels for each patient.

Before a meal, fast acting insulins (e.g. Rechon Insulin Human Soluble or) are taken to be able to utilise the carbohydrates in the food and prevent blood glucose levels to rise. The more carbohydrates the food contains, the more insulin is needed. Many fast acting insulins reach the blood after approximately 15 minutes and are effective for 3-4 hours. Humulin® Regular has a somewhat slower onset of the effect and is effective for a longer time. Humulin® Regular is taken around 30 minutes before each meal.

Number of subjects in period 1	Rechon Insulin Human Soluble	Humulin® Regular
Started	164	167
Completed	152	152
Not completed	12	15
Consent withdrawn by subject	8	9
Physician decision	2	-
Adverse event, non-fatal	2	3
Pregnancy	-	1
Lost to follow-up	-	1
Protocol deviation	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Rechon Insulin Human Soluble
Reporting group description:	
Patients received either Rechon Insulin Human Soluble or Humulin® Regular in a randomised way. The IMP was administered at home by the patients themselves. Dosing was individualised and adjusted based on blood glucose levels for each patient.	
Reporting group title	Humulin® Regular
Reporting group description:	
Patients received either Rechon Insulin Human Soluble or Humulin® Regular in a randomised way. The IMP was administered at home by the patients themselves. Dosing was individualised and adjusted based on blood glucose levels for each patient.	

Reporting group values	Rechon Insulin Human Soluble	Humulin® Regular	Total
Number of subjects	164	167	331
Age categorical			
Patients 18-75 years, both inclusively, could be included in the study.			
Units: Subjects			
Adults (18-64 years)	149	154	303
From 65-84 years	15	13	28
Age continuous			
In the safety set, the mean age was similar in both treatment groups, 46.2 years in the Rechon Insulin group and 45.5 years in the Humulin Regular group. The demographic characteristics in the PPS were similar to those in the safety set, where the overall mean age in the PPS was 45.9 years. Baseline characteristics have only been summarized for the safety set for respective reporting group and total, wherefore the Humulin reporting group is based on 164 patients, i.e. not 167.			
Units: years			
arithmetic mean	46.2	45.5	
standard deviation	± 13.8	± 13.2	-
Gender categorical			
Both male and female patients were included in the study. The demographics were similar in the treatment groups, both in the safety set and the PPS, apart from a skewed gender distribution in the Humulin Regular group where only approximately 40% of the patients were female.			
Units: Subjects			
Female	86	67	153
Male	78	100	178
Race			
Information of race (White, Black, Asian, Other) were collected at screening. The vast majority of patients were White in both treatment groups, 99.4% of the patients (n=163) in the Rechon Insulin group and 100% of the patients (n=164) in the Humulin Regular group.			
Units: Subjects			
White	163	167	330
White, Other	1	0	1

Subject analysis sets

Subject analysis set title	Safety set
Subject analysis set type	Safety analysis

Subject analysis set description:

All randomised patients who took at least 1 dose of the study drug.

In total, 0.9% of the patients (n=3), all randomised to treatment with Humulin Regular, were excluded from the safety set.

Subject analysis set title	Per protocol set
Subject analysis set type	Sub-group analysis

Subject analysis set description:

The PPS was defined for each study visit to consist of all randomised patients who completed the study up to the specific visit and were deemed to have no major protocol deviations that could interfere with the objectives of this study. The visit-specific PPS are sub-sets of the safety set.

3.3% of the patients (n=11) had at least some data that was excluded from the PPS on a per-visit basis.

For the primary endpoint, PPS was the primary analysis population.

Reporting group values	Safety set	Per protocol set	
Number of subjects	328	320	
Age categorical			
Patients 18-75 years, both inclusively, could be included in the study.			
Units: Subjects			
Adults (18-64 years)	300	293	
From 65-84 years	28	27	
Age continuous			
In the safety set, the mean age was similar in both treatment groups, 46.2 years in the Rechon Insulin group and 45.5 years in the Humulin Regular group. The demographic characteristics in the PPS were similar to those in the safety set, where the overall mean age in the PPS was 45.9 years. Baseline characteristics have only been summarized for the safety set for respective reporting group and total, wherefore the Humulin reporting group is based on 164 patients, i.e. not 167.			
Units: years			
arithmetic mean	45.9		
standard deviation	± 13.0	±	
Gender categorical			
Both male and female patients were included in the study. The demographics were similar in the treatment groups, both in the safety set and the PPS, apart from a skewed gender distribution in the Humulin Regular group where only approximately 40% of the patients were female.			
Units: Subjects			
Female	151	149	
Male	177	171	
Race			
Information of race (White, Black, Asian, Other) were collected at screening. The vast majority of patients were White in both treatment groups, 99.4% of the patients (n=163) in the Rechon Insulin group and 100% of the patients (n=164) in the Humulin Regular group.			
Units: Subjects			
White	328	320	
White, Other	0	0	

End points

End points reporting groups

Reporting group title	Rechon Insulin Human Soluble

Reporting group description:

Patients received either Rechon Insulin Human Soluble or Humulin® Regular in a randomised way. The IMP was administered at home by the patients themselves. Dosing was individualised and adjusted based on blood glucose levels for each patient.

Reporting group title	Humulin® Regular

Reporting group description:

Patients received either Rechon Insulin Human Soluble or Humulin® Regular in a randomised way. The IMP was administered at home by the patients themselves. Dosing was individualised and adjusted based on blood glucose levels for each patient.

Subject analysis set title	Safety set
Subject analysis set type	Safety analysis

Subject analysis set description:

All randomised patients who took at least 1 dose of the study drug.

In total, 0.9% of the patients (n=3), all randomised to treatment with Humulin Regular, were excluded from the safety set.

Subject analysis set title	Per protocol set
Subject analysis set type	Sub-group analysis

Subject analysis set description:

The PPS was defined for each study visit to consist of all randomised patients who completed the study up to the specific visit and were deemed to have no major protocol deviations that could interfere with the objectives of this study. The visit-specific PPS are sub-sets of the safety set.

3.3% of the patients (n=11) had at least some data that was excluded from the PPS on a per-visit basis.

For the primary endpoint, PPS was the primary analysis population.

Primary: Anti-Insulin Binding Antibodies (PPS)

End point title	Anti-Insulin Binding Antibodies (PPS)

End point description:

The primary endpoint of this study was to evaluate the proportion of patients having binding antibodies against human insulin. Since it was expected that a large proportion of patients would have anti-insulin antibodies already at baseline, the primary analysis assessed shift from negative at baseline to positive at subsequent visits. For the primary endpoint, PPS was the primary analysis population.

In the PPS, fewer patients were positive for anti-insulin antibodies at baseline in the Rechon Insulin group (4.3% of the patients [n=7]) as compared to the Humulin Regular group (7.4% of the patients [n=12]) with only small changes over time. At Visit 5, the difference between the groups was 8.0 percent units more positive patients in the Humulin Regular group than in the Rechon Insulin group (95% CI: -13.3, -2.7).

End point type	Primary

End point timeframe:

From Visit 2, Day 1 to Visit 5, Day 180.

End point values	Rechon Insulin Human Soluble	Humulin® Regular		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	164[1]	164[2]		
Units: Number of patients with non-missing data				
Visit 2 - Positive	7	12		
Visit 2 - Negative	156	151		
Visit 3 - Positive	6	12		
Visit 3 - Negative	152	146		
Visit 4 - Positive	5	11		
Visit 4 - Negative	149	143		
Visit 5 - Positive	3	15		
Visit 5 - Negative	147	135		

Notes:

[1] - Visit 2, n=163
Visit 3, n=158
Visit 4, n=154
Visit 5, n=150
[2] - Visit 2, n=163
Visit 3, n=158
Visit 4, n=154
Visit 5, n=150

Statistical analyses

Statistical analysis title	Odds Ratio for Testing Positive for Anti-Insulin A

Statistical analysis description:

A sensitivity analysis using logistic regression in the safety set shows a trend for patients in the Humulin Regular group to have a higher probability of being positive for anti-insulin binding antibodies at Visit 3 and Visit 4, compared to patients treated with Rechon Insulin. At Visit 5, the difference in probability of being positive for anti-insulin antibodies was statistically significant (p-value 0.0152) in favour of the Rechon Insulin treatment.

Comparison groups	Rechon Insulin Human Soluble v Humulin® Regular
Number of subjects included in analysis	328
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.6434 [3]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)

Notes:

[3] - Visit 3, P=0.6434
Visit 4, P=0.4903
Visit 5, P=0.0152

Primary: Testing Positive for Anti-Insulin Antibodies (Safety Set)

End point title	Testing Positive for Anti-Insulin Antibodies (Safety Set)[4]

End point description:

A sensitivity analysis using logistic regression in the safety set shows a trend for patients in the Humulin Regular group to have a higher probability of being positive for anti-insulin binding antibodies at Visit 3 and Visit 4, compared to patients treated with Rechon Insulin. At Visit 5, the difference in probability of being positive for anti-insulin antibodies was statistically significant (p-value 0.0152) in favour of the Rechon Insulin treatment.

End point type	Primary

End point timeframe:

Visit 3 - Visit 5.

Notes:

[4] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Presented under the primary end point Anti-Insulin Binding Antibodies.

End point values	Safety set			
Subject group type	Subject analysis set			
Number of subjects analysed	328			
Units: odds ratio				
number (confidence interval 95%)				
Visit 3	0.817 (0.347 to 1.922)			
Visit 4	0.759 (0.344 to 1.671)			
Visit 5	0.320 (0.128 to 0.803)			

Statistical analyses

No statistical analyses for this end point

Secondary: Total Daily Insulin dose (Safety Set)

End point title	Total Daily Insulin dose (Safety Set)

End point description:

In the safety set, the median total daily insulin dose at baseline was 0.645 IU/kg in the Rechon Insulin group and 0.665 IU/kg in the Humulin Regular group. The median total daily dose changed from baseline by 0.026 IU/kg in the Rechon Insulin group and by 0.027 IU/kg in the Humulin Regular group at Visit 5.

End point type	Secondary

End point timeframe:

Visit 2 to visit 5.

End point values	Rechon Insulin Human Soluble	Humulin® Regular		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	164[5]	164[6]		
Units: IU/kg				
arithmetic mean (standard deviation)				
Visit 2 - Derived value	0.685 (± 0.208)	0.678 (± 0.198)		
Visit 3 - Change from baseline	0.035 (± 0.100)	0.022 (± 0.086)		
Visit 4 - Change from baseline	0.035 (± 0.111)	0.026 (± 0.099)		
Visit 5 - Change from baseline	0.035 (± 0.114)	0.036 (± 0.108)		

Notes:

[5] - Visit 2, n=148
Visit 3, n=143
Visit 4, n=137
Visit 5, n=134

[6] - Visit 2, n=156
Visit 3, n=152
Visit 4, n=144
Visit 5, n=139

Statistical analyses

No statistical analyses for this end point

Secondary: Daily Basal Insulin Dose (Safety Set)

End point title	Daily Basal Insulin Dose (Safety Set)

End point description:

In the safety set, the median basal insulin dose at baseline was 0.260 IU/kg in the Rechon Insulin group and 0.246 IU/kg in the Humulin Regular group. The change from
baseline at Visit 5 was -0.002 IU/kg in the Rechon Insulin group and 0.001 IU/kg in the Humulin Regular group.

End point type	Secondary

End point timeframe:

Visit 2 to Visit 5.

End point values	Rechon Insulin Human Soluble	Humulin® Regular		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	164[7]	164[8]		
Units: IU/kg				
arithmetic mean (standard deviation)				
Visit 2 - Derived value	0.267 (± 0.116)	0.264 (± 0.104)		
Visit 5 - Change from baseline	-0.002 (± 0.046)	0.007 (± 0.066)		

Notes:

[7] - Visit 2, n=153
Visit 5, n=140
[8] - Visit 2, n=158
Visit 5, n=143

Statistical analyses

No statistical analyses for this end point

Secondary: Daily Bolus Insulin Dose (Safety Set)

End point title	Daily Bolus Insulin Dose (Safety Set)

End point description:

In the safety set, the median bolus insulin dose at baseline was 0.396 IU/kg in the Rechon Insulin group and 0.386 IU/kg in the Humulin Regular group and the change from baseline at Visit 5 was 0.032 IU/kg in the Rechon Insulin group and 0.023 IU/kg in the Humulin Regular group.

End point type	Secondary

End point timeframe:

Visit 2 to Visit 5.

End point values	Rechon Insulin Human Soluble	Humulin® Regular		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	164[9]	164[10]		
Units: IU/kg				
arithmetic mean (standard deviation)				
Visit 2 - Derived value	0.425 (± 0.165)	0.418 (± 0.163)		
Visit 5 - Change from baseline	0.035 (± 0.096)	0.029 (± 0.105)		

Notes:

[9] - Visit 2, n=157
Visit 5, n=141
[10] - Visit 2, n=160
Visit 5, n=143

Statistical analyses

No statistical analyses for this end point

Secondary: Total Daily Insulin Dose at Baseline - Intermediate-acting insulin (Safety Set)

End point title	Total Daily Insulin Dose at Baseline - Intermediate-acting insulin (Safety Set)

End point description:

In the safety set, there were approximately 10-times more patients that had long/ultralong-acting basal insulin at baseline compared to patients that had intermediate-acting insulin. For patients with intermediate-acting basal insulin at baseline, the median total daily insulin dose was 0.652 IU/kg in the Rechon Insulin group and 0.606 IU/kg in the humulin Regular group, which at Visit 5 had changed by 0.027 IU/kg and 0.029 IU/kg, respectively. For patients with long/ultralong-acting basal insulin at baseline, the median total daily insulin dose was 0.641 IU/kg in the Rechon Insulin group and 0.665 IU/kg in the Humulin Regular group, which at Visit 5 had changed by 0.023 IU/kg and 0.027 IU/kg, respectively.

End point type	Secondary

End point timeframe:

Visit 2 to Visit 5.

End point values	Rechon Insulin Human Soluble	Humulin® Regular		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	164[11]	164[12]		
Units: IU/kg				
arithmetic mean (standard deviation)				
Visit 2 - Derived value	0.703 (± 0.191)	0.656 (± 0.190)		
Visit 5 - Change from baseline	0.038 (± 0.094)	0.007 (± 0.092)		

Notes:

[11] - Visit 2, n=14
Visit 5, n=12

[12] - Visit 2, n=10
Visit 5, n=10

Statistical analyses

No statistical analyses for this end point

Secondary: Total Daily Insulin Dose at Baseline - Long/ultralong-acting insulin (Safety Set)

End point title	Total Daily Insulin Dose at Baseline - Long/ultralong-acting insulin (Safety Set)

End point description:

In the safety set, there were approximately 10-times more patients that had long/ultralongacting basal insulin at baseline compared to patients that had intermediate-acting insulin. For patients with intermediate-acting basal insulin at baseline, the median total daily insulin dose was 0.652 IU/kg in the Rechon Insulin group and 0.606 IU/kg in the Humulin Regular group, which at Visit 5 had changed by 0.027 IU/kg and 0.029 IU/kg, respectively. For patients with long/ultralong-acting basal insulin at baseline, the median total daily insulin dose was 0.641 IU/kg in the Rechon Insulin group and 0.665 IU/kg in the Humulin Regular group, which at Visit 5 had changed by 0.023 IU/kg and 0.027 IU/kg, respectively.

End point type	Secondary

End point timeframe:

Visit 2 to Visit 5.

End point values	Rechon Insulin Human Soluble	Humulin® Regular		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	164[13]	164[14]		
Units: IU/kg				
arithmetic mean (standard deviation)				
Visit 2 - Derived value	0.682 (± 0.212)	0.679 (± 0.202)		
Visit 5 - Change from baseline	0.031 (± 0.115)	0.038 (± 0.111)		

Notes:

[13] - Visit 2, n=131
Visit 5, n=119
[14] - Visit 2, n=142
Visit 5, n=126

Statistical analyses

No statistical analyses for this end point

Secondary: Daily Bolus Insulin Dose at Baseline - Intermediate-acting insulin (Safety Set)

End point title	Daily Bolus Insulin Dose at Baseline - Intermediate-acting insulin (Safety Set)

End point description:

For patients in the safety set with intermediate-acting basal insulin at baseline, the median daily bolus dose was 0.432 IU/kg in the Rechon Insulin group and 0.422 IU/kg in the Humulin Regular group, which

at Visit 5 had changed by 0.031 IU/kg and 0.019 IU/kg, respectively. For patients with long/ultralong-acting basal insulin at baseline, the median daily bolus dose was 0.391 IU/kg in the Rechon Insulin group and 0.383 IU/kg in the Humulin Regular group, which at Visit 5 had changed by 0.032 IU/kg and 0.025 IU/kg, respectively.

End point type	Secondary

End point timeframe:

Visit 2 to Visit 5

End point values	Rechon Insulin Human Soluble	Humulin® Regular		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	164[15]	164[16]		
Units: IU/kg				
arithmetic mean (standard deviation)				
Visit 2 - Derived value	0.446 (± 0.153)	0.422 (± 0.142)		
Visit 5 - Change from baseline	0.042 (± 0.098)	0.006 (± 0.075)		

Notes:

[15] - Visit 2, n=14
Visit 5, n=12
[16] - Visit 2, n=10
Visit 5, n=10

Statistical analyses

No statistical analyses for this end point

Secondary: Daily Bolus Insulin Dose at Baseline - Long/ultralong-acting insulin (Safety Set)

End point title	Daily Bolus Insulin Dose at Baseline - Long/ultralong-acting insulin (Safety Set)

End point description:

For patients in the safety set with intermediate-acting basal insulin at baseline, the median daily bolus dose was 0.432 IU/kg in the Rechon Insulin group and 0.422 IU/kg in the Humulin Regular group, which at Visit 5 had changed by 0.031 IU/kg and 0.019 IU/kg, respectively. For patients with long/ultralong-acting basal insulin at baseline, the median daily bolus dose was 0.391 IU/kg in the Rechon Insulin group and 0.383 IU/kg in the Humulin Regular group, which at Visit 5 had changed by 0.032 IU/kg and 0.025 IU/kg, respectively.

End point type	Secondary

End point timeframe:

Visit 2 to Visit 5.

End point values	Rechon Insulin Human Soluble	Humulin® Regular		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	164[17]	164[18]		
Units: IU/kg				
arithmetic mean (standard deviation)				
Visit 2 - Derived value	0.420 (± 0.161)	0.413 (± 0.156)		

Visit 5 - Change from baseline	0.034 (± 0.096)	0.034 (± 0.105)		

Notes:

[17] - Visit 2, n=131
Visit 5, n=119
[18] - Visit 2, n=142
Visit 5, n=126

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical Chemistry Assessments at Baseline and Absolute Change at Visit 5

End point title	Clinical Chemistry Assessments at Baseline and Absolute Change at Visit 5

End point description:

For clinical chemistry and haematology parameters, there were no apparent trends for the assessed values to change over time from Visit 2 to Visit 5. The assessed values and absolute change from baseline were similar between the treatment groups.

End point type	Secondary

End point timeframe:

Visit 2 to Visit 5.

End point values	Rechon Insulin Human Soluble	Humulin® Regular		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	164	164[19]		
Units: U/L				
arithmetic mean (standard deviation)				
Alkaline phosphatase - Visit 2	82.1 (± 22.7)	81.1 (± 25.2)		
Alkaline phosphatase - Change at Visit 5	2.06 (± 17.3)	1.32 (± 17.6)		
Alanine aminotransferase - Visit 2	28.8 (± 12.5)	28.8 (± 15.0)		
Alanine aminotransferase - Change at Visit 5	0.0993 (± 12.1)	2.66 (± 19.3)		
Aspartate aminotransferase - Visit 2	24.4 (± 20.2)	24.1 (± 9.96)		
Aspartate aminotransferase - Change at Visit 5	0.828 (± 15.0)	1.89 (± 13.2)		
Gamma glutamyltransferase - Visit 2	23.1 (± 19.3)	31.8 (± 37.3)		
Gamma glutamyltransferase - Change at Visit 5	2.25 (± 14.6)	2.06 (± 31.7)		

Notes:

[19] - Safety set

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical Chemistry Assessments at Baseline and Absolute Change at Visit 5

End point title	Clinical Chemistry Assessments at Baseline and Absolute Change at Visit 5

End point description:

For clinical chemistry and haematology parameters, there were no apparent trends for the assessed values to change over time from Visit 2 to Visit 5. The assessed values and absolute change from baseline were similar between the treatment groups.

End point type	Secondary

End point timeframe:

Visit 2 to Visit 5.

End point values	Rechon Insulin Human Soluble	Humulin® Regular		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	164	164[20]		
Units: mg/dl				
arithmetic mean (standard deviation)				
Total bilirubin - Visit 2	0.633 (± 0.311)	0.667 (± 0.302)		
Total bilirubin - Change at Visit 5	0.0100 (± 0.244)	0.0161 (± 0.245)		
Creatinine - Visit 2	0.859 (± 0.149)	0.910 (± 0.286)		
Creatinine - Change at Visit 5	0.0168 (± 0.106)	-0.0001 (± 0.147)		
C-reactive protein - Visit 2	0.286 (± 0.416)	0.386 (± 0.820)		
C-reactive protein - Change at Visit 5	0.0564 (± 0.543)	-0.0793 (± 0.761)		
Glucose in NaF blood - Visit 2	183 (± 74.7)	186 (± 86.1)		
Glucose in NaF blood - Change at Visit 5	24.3 (± 92.1)	5.73 (± 105)		

Notes:

[20] - Safety set

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical Chemistry Assessments at Baseline and Absolute Change at Visit 5

End point title	Clinical Chemistry Assessments at Baseline and Absolute Change at Visit 5

End point description:

For clinical chemistry and haematology parameters, there were no apparent trends for the assessed values to change over time from Visit 2 to Visit 5. The assessed values and absolute change from baseline were similar between the treatment groups.

End point type	Secondary

End point timeframe:

Visit 2 to Visit 5.

End point values	Rechon Insulin Human Soluble	Humulin® Regular		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	164	164[21]		
Units: mmol/L				
arithmetic mean (standard deviation)				
Potassium - Visit 2	4.46 (± 0.434)	4.41 (± 0.418)		
Potassium - Change at Visit 5	0.0000 (± 0.436)	0.0171 (± 0.450)		
Sodium - Visit 2	140 (± 3.76)	139 (± 3.04)		
Sodium - Change at Visit 5	-0.809 (± 3.96)	-0.368 (± 5.44)		

Notes:

[21] - Safety set

Statistical analyses

No statistical analyses for this end point

Secondary: Haematology Assessments at Baseline and Absolute Change at Visit 5

End point title	Haematology Assessments at Baseline and Absolute Change at Visit 5

End point description:

For clinical chemistry and haematology parameters, there were no apparent trends for the assessed values to change over time from Visit 2 to Visit 5. The assessed values and absolute change from baseline were similar between the treatment groups.

End point type	Secondary

End point timeframe:

From visit 2 to Visit 5

End point values	Rechon Insulin Human Soluble	Humulin® Regular		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	164	164[22]		
Units: various				
arithmetic mean (standard deviation)				
Haematocrit (%) - Visit 2	43.9 (± 3.94)	44.1 (± 4.69)		
Haematocrit (%) - Change at Visit 5	0.513 (± 3.30)	0.899 (± 4.36)		
Haemoglobin (g/dL) - Visit 2	14.1 (± 1.37)	14.3 (± 1.63)		
Haemoglobin (g/dL) - Change at Visit 5	-0.146 (± 0.621)	0.0457 (± 1.23)		
Platelets (10^3/uL) - Visit 2	259 (± 66.6)	250 (± 70.7)		
Platelets (10^3/uL) - Change at Visit 5	9.20 (± 53.7)	15.1 (± 52.6)		
Erythrocytes (/pL) - Visit 2	4.76 (± 0.466)	4.76 (± 0.510)		
Erythrocytes (/pL) - Change at Visit 5	-0.0285 (± 0.214)	0.0351 (± 0.382)		
Leukocytes (/nL) - Visit 2	6.14 (± 1.73)	6.13 (± 1.97)		
Leukocytes (/nL) - Change at Visit 5	0.0695 (± 1.49)	0.212 (± 1.44)		

Haemoglobin A1c (mmol/mol Hb) - Visit 2	62.6 (± 12.7)	63.8 (± 13.4)		
Haemoglobin A1c (mmol/mol Hb) - Change at Visit 5	1.44 (± 6.99)	0.739 (± 9.37)		

Notes:

[22] - Safety set

Statistical analyses

No statistical analyses for this end point

Secondary: Level of circulating Antibodies

End point title	Level of circulating Antibodies

End point description:

Blood samples for analysing levels of total circulating immunoglobulin E (IgE) antibodies were taken at Visit 2, Visit 3, Visit 4 and Visit 5. The analysis was performed by Synlab, Munich.

At baseline, the IgE levels were 35.0 kU/I in the Rechon Insulin group and 37.8 kU/I in the Humulin Regular group, with a change of 0.1 kU/I and 0.8 kU/I compared to the IgE levels at Visit 5 for the treatment groups, respectively.

End point type	Secondary

End point timeframe:

Visit 2 to Visit 5

End point values	Rechon Insulin Human Soluble	Humulin® Regular		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	164[23]	164[24]		
Units: kU/l				
median (inter-quartile range (Q1-Q3))				
Visit 2	35.0 (13.8 to 95.6)	37.8 (17.2 to 95.8)		
Visit 3	34.8 (12.4 to 102)	36.1 (17.1 to 94.2)		
Vsiit 3 - Change from baseline	0.00 (-2.40 to 2.60)	-0.700 (-4.50 to 3.35)		
Visit 4	37.3 (12.0 to 98.8)	43.2 (18.0 to 96.3)		
Visit 4 - Change from baseline	-0.450 (-4.20 to 4.50)	0.800 (-4.60 to 5.80)		
Visit 5	36.6 (12.8 to 98.6)	44.9 (18.4 to 103)		
Visit 5 - Change from baseline	0.100 (-3.55 to 8.35)	0.800 (-5.30 to 8.75)		

Notes:

[23] - Visit 2, n=164
Visit 3, n=159
Visit 4, n=154
Visit 5, n=152

[24] - Safety set
Visit 2, n=164
Visit 3, n=160
Visit 4, n=155
Visit 5, n=152

Statistical analyses

Statistical analysis title	Circulating IgE Antibodies (ANCOVA) (Safety Set)

Statistical analysis description:

An ANCOVA assessment did not detect a statistically significant difference between the treatment groups in change from baseline (p-value 0.745 at Visit 5).

Comparison groups	Rechon Insulin Human Soluble v Humulin® Regular
Number of subjects included in analysis	328
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.492 [25]
Method	ANCOVA

Notes:

[25] - Visit 3, P= 0.492
Visit 4, P= 0.394
Visit 5, P= 0.745

Secondary: Partial Correlation Analysis of Circulating IgE Antibodies (Safety Set)

End point title	Partial Correlation Analysis of Circulating IgE Antibodies (Safety Set)

End point description:

Partial Spearman correlations were performed where the change in anti-insulin antibody levels was compared to:
- change from baseline in HbA1c;
- change from baseline in body weight;
- level of fasting glucose; and
- total insulin dose.

At Visit 3, there was a moderate, statistically significant correlation in change from baseline in HbA1c in the Humulin Regular group (0.3630, p-value <0.0001) and a weak positive correlation in total insulin dose in the Rechon Insulin group (0.1980, p-value 0.0186). In addition, there was a statistically significant weak negative correlation in change from baseline in body weight at Visit 5 in the Rechon Insulin group (-0.1970, p-value 0.0220).

End point type	Secondary

End point timeframe:

From Baseline to Visit 5.

End point values	Rechon Insulin Human Soluble	Humulin® Regular		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	164	164[26]		
Units: various				
number (not applicable)				
Change from baseline in HbA1c (mmol/mol Hb) - V3	0.0857	0.3630		
Change from baseline in HbA1c (mmol/mol Hb) - V4	0.689	0.0849		
Change from baseline in HbA1c (mmol/mol Hb) - V5	0.987	0.0574		
Change from baseline in body weight (kg) - V3	-0.0212	-0.0330		
Change from baseline in body weight (kg) - V4	-0.1105	-0.1329		
Change from baseline in body weight (kg) - V5	-0.1970	-0.0033		
Fasting glucose (mg/dL) - V3	-0.0546	-0.0404		

Fasting glucose (mg/dL) - V4	-0.0327	0.0637		
Fasting glucose (mg/dL) - V5	0.0545	0.0989		
Total insulin dose (IU/kg) - V3	0.1980	0.0089		
Total insulin dose (IU/kg) - V4	0.1592	0.0124		
Total insulin dose (IU/kg) - V5	0.1167	-0.0654		

Notes:

[26] - Safety set

Statistical analyses

Statistical analysis title	Partial Correlation Analysis - HbA1c

Statistical analysis description:

At Visit 3, there was a moderate, statistically significant correlation in change from baseline in HbA1c in the Humulin Regular group (0.3630, p-value <0.0001) and a weak positive correlation in total insulin dose in the Rechon Insulin group (0.1980, p-value 0.0186).

Comparison groups	Rechon Insulin Human Soluble v Humulin® Regular
Number of subjects included in analysis	328
Analysis specification	Pre-specified
Analysis type	other[27]
P-value	= 0.3125 [28]
Method	Spearman correlation

Notes:

[27] - Correlation

[28] - Rechon insulin, Visit 3, P=0.3125
Humulin Regular, Visit 3, P=0.3630
Rechon insulin, Visit 4, P=0.4239
Humulin Regular, Visit 4, P=0.3118
Rechon insulin, Visit 5, P=0.2548
Humulin Regular, Visit 5, P=0.5040

Statistical analysis title	Partial Correlation Analysis - Body weight

Statistical analysis description:

At Visit 3, there was a moderate, statistically significant correlation in change from baseline in HbA1c in the Humulin Regular group (0.3630, p-value <0.0001) and a weak positive correlation in total insulin dose in the Rechon Insulin group (0.1980, p-value 0.0186).

Comparison groups	Rechon Insulin Human Soluble v Humulin® Regular
Number of subjects included in analysis	328
Analysis specification	Pre-specified
Analysis type	other[29]
P-value	= 0.8033 [30]
Method	Spearman correlation

Notes:

[29] - Correlation

[30] - Rechon insulin, Visit 3, P=0.8033
Humulin Regular, Visit 3, P=0.6925
Rechon insulin, Visit 4, P=0.1987
Humulin Regular, Visit 4, P=0.1124
Rechon insulin, Visit 5, P=0.0220
Humulin Regular, Visit 5, P=0.9690

Statistical analysis title	Partial Correlation Analysis - Fasting glucose

Statistical analysis description:

At Visit 3, there was a moderate, statistically significant correlation in change from baseline in HbA1c in the Humulin Regular group (0.3630, p-value <0.0001) and a weak positive correlation in total insulin dose in the Rechon Insulin group (0.1980, p-value 0.0186).

Comparison groups	Rechon Insulin Human Soluble v Humulin® Regular

Number of subjects included in analysis	328
Analysis specification	Pre-specified
Analysis type	other[31]
P-value	= 0.5201 [32]
Method	Spearman correlation

Notes:

[31] - Correlation

[32] - Rechon insulin, Visit 3, P=0.5201
Humulin Regular, Visit 3, P=0.6279
Rechon insulin, Visit 4, P=0.7043
Humulin Regular, Visit 4, P=0.4483
Rechon insulin, Visit 5, P=0.5303
Humulin Regular, Visit 5, P=0.2483

Statistical analysis title	Partial Correlation Analysis - Total insulin dose

Statistical analysis description:

At Visit 3, there was a moderate, statistically significant correlation in change from baseline in HbA1c in the Humulin Regular group (0.3630, p-value <0.0001) and a weak positive correlation in total insulin dose in the Rechon Insulin group (0.1980, p-value 0.0186).

Comparison groups	Rechon Insulin Human Soluble v Humulin® Regular
Number of subjects included in analysis	328
Analysis specification	Pre-specified
Analysis type	other[33]
P-value	= 0.0186 [34]
Method	Spearman correlation

Notes:

[33] - Correlation

[34] - Rechon insulin, Visit 3, P=0.0186
Humulin Regular, Visit 3, P=0.9147
Rechon insulin, Visit 4, P=0.0631
Humulin Regular, Visit 4, P=0.8832
Rechon insulin, Visit 5, P=0.1776
Humulin Regular, Visit 5, P=0.4461

Secondary: Spearman Correlation of Circulating IgE Antibodies versus Body Weight, Fasting Blood Glucose, HbA1c, and Insulin Dose at Visit 5 (Safety Set)

End point title	Spearman Correlation of Circulating IgE Antibodies versus Body Weight, Fasting Blood Glucose, HbA1c, and Insulin Dose at Visit 5 (Safety Set)

End point description:

The clinical relevance of antibody formation was evaluated using Spearman correlations between change from baseline in anti-insulin antibody levels and change from baseline in glucose response as HbA1c, fasting plasma glucose, insulin dose and weight change.

Based on the results from the Spearman correlation analyses, it is not possible to conclude if there is any specific relationship between antibody formation and change from baseline in HbA1c, change from baseline in body weight, fasting glucose or total insulin dose.

End point type	Secondary

End point timeframe:

Visit 5

End point values	Rechon Insulin Human Soluble	Humulin® Regular		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	164	164[35]		
Units: correlation rank				
number (not applicable)				
Body weight	-0.1539	-0.0322		
Fasting blood glucose	0.0092	0.0960		
Glycosylated A1c	0.1141	0.0752		
Insulin dose	0.1004	-0.0747		

Notes:

[35] - Safety set

Statistical analyses

No statistical analyses for this end point

Secondary: Assessment of Hypoglycaemic Episodes According to ADA Criteria (Safety Set)

End point title	Assessment of Hypoglycaemic Episodes According to ADA Criteria (Safety Set)

End point description:

All hypoglycaemic episodes were summarised by severity according to ADA-defined categories 1-5 and in total.

All hypoglycaemic episodes were presented, including number of and percent of patients with at least one episode, number of episodes and rate (as number of events per patient year of exposure).

Hypoglycaemic episodes occurred overall at a significantly higher rate (1.20 [1.14-1.27], p-value <0.0001) in the Rechon Insulin group (2700 episodes) than in the Humulin Regular group (2217 episodes).

With the exception of the overall rate ratio for hypoglycaemic episodes, that was slightly higher in the Rechon Insulin group, no clinically meaningful changes were detected compared to treatment with Humulin Regular.

End point type	Secondary

End point timeframe:

After first exposure of randomised treatment and no later than 1 day after last exposure to randomised treatment.

End point values	Rechon Insulin Human Soluble	Humulin® Regular		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	164	164[36]		
Units: Numbers of events				
All hypoglycaemic events	2700	2217		
1. Severe hypoglycaemia	3	3		
2. Documented symptomatic hypoglycaemia	2003	1764		
3. Asymptomatic hypoglycaemia	582	401		
4. Probable symptomatic hypoglycaemia	11	5		
5. Relative hypoglycaemia	101	41		

Notes:
[36] - Safety set

Statistical analyses

Statistical analysis title	Hypoglycaemic Episodes: Gen. Linear Regression

Statistical analysis description:

A generalised linear regression model with number of episodes as response (using a log-link function in accordance with a Poisson regression) and including treatment group and country as factors and exposure time as offset was applied to estimate the treatment rate ratio with a 95% CI.

Comparison groups	Rechon Insulin Human Soluble v Humulin® Regular
Number of subjects included in analysis	328
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	< 0.0001
Method	Regression, Linear
Parameter estimate	Rate ratio
Point estimate	1.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.14
upper limit	1.27

Secondary: Assessment of Hypoglycaemic Episodes According to ADA Criteria (Safety Set)

End point title	Assessment of Hypoglycaemic Episodes According to ADA Criteria (Safety Set)

End point description:

All hypoglycaemic episodes were summarised by severity according to ADA-defined categories 1-5 and in total.

All hypoglycaemic episodes were presented, including number of and percent of patients with at least one episode, number of episodes and rate (as number of events per patient year of exposure).

Hypoglycaemic episodes occurred overall at a significantly higher rate (1.20 [1.14-1.27], p-value <0.0001) in the Rechon Insulin group (2700 episodes) than in the Humulin Regular group (2217 episodes).

With the exception of the overall rate ratio for hypoglycaemic episodes, that was slightly higher in the Rechon Insulin group, no clinically meaningful changes were detected compared to treatment with Humulin Regular.

End point type	Secondary

End point timeframe:

After first exposure of randomised treatment and no later than 1 day after last exposure to randomised treatment.

End point values	Rechon Insulin Human Soluble	Humulin® Regular		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	164	164		
Units: No of patients with at least one event				
All hypoglycaemic events	109	117		
1. Severe hypoglycaemia	3	3		
2. Documented symptomatic hypoglycaemia	101	110		
3. Asymptomatic hypoglycaemia	40	40		
4. Probable symptomatic hypoglycaemia	3	2		
5. Relative hypoglycaemia	23	14		

Statistical analyses

No statistical analyses for this end point

Secondary: Hypersensitivity (Safety Set)

End point title	Hypersensitivity (Safety Set)

End point description:

The patients were asked to complete a paper diary with doses of administered insulin during one week after Visit 2 and during one week before Visit 3, 4 and 5 and to register local and systemic hypersensitivity reactions and hypoglycaemic episodes daily.

Local and systemic hypersensitivity reactions were reported by 3.7% of patients (n=6) in each of the treatment groups.

The 13 incidents in the Rechon Insulin and the 6 incidents in the Humulin Regular group that were recorded by the patients in the diary and judged by the Investigators either as not an AESI, an AESI not related to treatment or an AESI related to treatment

End point type	Secondary

End point timeframe:

Visit 2 to Visit 5

End point values	Rechon Insulin Human Soluble	Humulin® Regular		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	164	164[37]		
Units: Numbers of events and patients				
Number of hypersensitivity events	13	6		
Number of patients with at least one event	6	6		

Notes:

[37] - Safety set

Statistical analyses

No statistical analyses for this end point

Secondary: Systolic Blood Pressure

End point title	Systolic Blood Pressure

End point description:

Supine systolic and diastolic blood pressure (mmHg) were taken after 5 minutes lying down.

Assessments of blood pressure and pulse showed similar results in both treatment groups and over time.

End point type	Secondary

End point timeframe:

Visit 1 to Visit 5

End point values	Rechon Insulin Human Soluble	Humulin® Regular		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	164[38]	164[39]		
Units: mmHg				
arithmetic mean (standard deviation)				
Visit 1	129.6 (± 15.4)	129.8 (± 17.9)		
Visit 5 - Change from baseline	-1.1 (± 12.7)	-0.5 (± 12.4)		

Notes:

[38] - Visit 1, n=164
Visit 5, n=152
[39] - Visit 1, n=164 (Safety set)
Visit 5, n=152

Statistical analyses

No statistical analyses for this end point

Secondary: Diastolic Blood Pressure

End point title	Diastolic Blood Pressure

End point description:

Supine systolic and diastolic blood pressure (mmHg) were taken after 5 minutes lying down.

Assessments of blood pressure and pulse showed similar results in both treatment groups and over time.

End point type	Secondary

End point timeframe:

Visit 1 to Visit 5

End point values	Rechon Insulin Human Soluble	Humulin® Regular		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	164[40]	164[41]		
Units: mmHg				
arithmetic mean (standard deviation)				
Visit 1	78.6 (± 9.2)	78.1 (± 8.4)		
Visit 5 - Change from baseline	-0.6 (± 8.8)	-0.2 (± 7.4)		

Notes:

[40] - Visit 1, n=164
Visit 5, n=152
[41] - Visit 1, n=164 (Safety set)
Visit 5, n=152

Statistical analyses

No statistical analyses for this end point

Secondary: Pulse

End point title	Pulse

End point description:

Supine systolic and diastolic blood pressure (mmHg) were taken after 5 minutes lying down.

Assessments of blood pressure and pulse showed similar results in both treatment groups and over time.

End point type	Secondary

End point timeframe:

Visit 1 to Visit 5

End point values	Rechon Insulin Human Soluble	Humulin® Regular		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	164[42]	164[43]		
Units: beats/min				
arithmetic mean (standard deviation)				
Visit 1	74.0 (± 9.9)	73.6 (± 8.8)		
Visit 5 - Change from baseline	0.1 (± 8.9)	1.5 (± 9.1)		

Notes:

[42] - Visit 1, n=164
Visit 5, n=152
[43] - Visit 1, n=164 (Safety set)
Visit 5, n=152

Statistical analyses

No statistical analyses for this end point

Secondary: Physical examination

End point title	Physical examination

End point description:

Standard physical examinations included assessments of the general condition, heart, lungs and

abdomen.

The physical examinations showed similar results between groups, with only 3 cases of CS abnormal findings that were noted at baseline, which all were due to the patients' general condition and not related to the study treatment.

End point type	Secondary
End point timeframe:	
From Visit 1 to Visit 5.	

End point values	Rechon Insulin Human Soluble	Humulin® Regular		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	164[44]	164[45]		
Units: Number of patients				
V1, General Condition - Normal	160	160		
V1, General Condition - Abnormal NCS	4	4		
V2, General Condition - Normal	158	160		
V2, General Condition - Abnormal NCS	6	4		
V3, General Condition - Normal	155	155		
V3, General Condition - Abnormal NCS	5	5		
V3, General Condition - Abnormal CS	1	0		
V4, General Condition - Normal	153	151		
V4, General Condition - Abnormal NCS	2	3		
V4, General Condition - Abnormal CS	0	1		
V5, General Condition - Normal	145	149		
V5, General Condition - Abnormal NCS	6	3		
V5, General Condition - Abnormal CS	1	0		
V1, Abdomen - Normal	156	160		
V1, Abdomen - Abnormal NCS	8	4		
V2, Abdomen - Normal	158	160		
V2, Abdomen - Abnormal NCS	6	4		
V3, Abdomen - Normal	154	156		
V3, Abdomen - Abnormal NCS	7	4		
V4, Abdomen - Normal	150	152		
V4, Abdomen - Abnormal NCS	5	3		
V5, Abdomen - Normal	145	149		
V5, Abdomen - Abnormal NCS	7	3		
V1, Lungs - Normal	163	163		
V1, Lungs - Abnormal NCS	1	1		
V2, Lungs - Normal	162	163		
V2, Lungs - Abnormal NCS	2	1		
V3, Lungs - Normal	159	160		
V3, Lungs - Abnormal NCS	2	0		
V4, Lungs - Normal	154	155		
V4, Lungs - Abnormal NCS	1	0		
V5, Lungs - Normal	149	151		
V5, Lungs - Abnormal NCS	3	1		
V1, Heart - Normal	163	161		
V1, Heart - Abnormal NCS	1	3		
V2, Heart - Normal	164	163		

V2, Heart - Abnormal NCS	0	1		
V3, Heart - Normal	161	160		
V3, Heart - Abnormal NCS	0	0		
V4, Heart - Normal	154	155		
V4, Heart - Abnormal NCS	1	0		
V5, Heart - Normal	150	152		
V5, Heart - Abnormal NCS	2	0		

Notes:

[44] - Visit 1, n=164
Visit 2, n=164
Visit 3, n=161
Visit 4, n=155
Visit 5, n=152
[45] - Visit 1, n=164 (Safety set)
Visit 2, n=164
Visit 3, n=160
Visit 4, n=155
Visit 5, n=152

Statistical analyses

No statistical analyses for this end point

Secondary: Injection site reactions (Safety Set)

End point title	Injection site reactions (Safety Set)

End point description:

There were only a few cases of AESI of injection site reactions and thus no trends were seen for a different distribution between treatment groups for injection site erythema, injection site pain, injection site pruritus and injection site rash.

End point type	Secondary

End point timeframe:

From first dose of IMP to completion of Visit 5.

End point values	Rechon Insulin Human Soluble	Humulin® Regular	Safety set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	164	164[46]	328	
Units: Number of patients and events				
Injection site erythema - No of events	1	1	2	
Inj. site erythema - No of patients with event	1	1	2	
Injection site pain - No of events	0	1	1	
Injection site pain - No of patients with event	0	1	1	
Injection site pruritus - No of events	1	1	2	
Inj. site pruritus - No of patients with event	1	1	2	
Injection site rash - No of events	2	0	2	
Injection site rash - No of patients with event	2	0	2	

Notes:

[46] - Safety set

Statistical analyses

No statistical analyses for this end point

Secondary: Creatinine Assessments (Safety Set)

End point title	Creatinine Assessments (Safety Set)

End point description:

Overall, the laboratory assessments showed similar results between the treatment groups without clear tendencies to change over time, including creatinine, indicating a stable diabetic condition over time irrespective of treatment.

The creatinine level at baseline was 0.859 mg/dL in the Rechon Insulin group and 0.910 mg/dL in the Humulin Regular group, which at Visit 5 had changed by 0.0168 mg/dL and -0.0001 mg/dL, respectively.

End point type	Secondary

End point timeframe:

Visit 2 to Visit 5.

End point values	Rechon Insulin Human Soluble	Humulin® Regular		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	164[47]	164[48]		
Units: mg/dL				
arithmetic mean (standard deviation)				
Visit 2	0.859 (± 0.149)	0.910 (± 0.286)		
Visit 3	0.876 (± 0.172)	0.0214 (± 0.100)		
Visit 3 - Change from baseline	0.892 (± 0.247)	-0.0134 (± 0.123)		
Visit 4	0.875 (± 0.168)	0.0213 (± 0.101)		
Visit 4 - Change from baseline	0.915 (± 0.266)	0.0066 (± 0.131)		
Visit 5	0.870 (± 0.164)	0.0168 (± 0.106)		
Visit 5 - Change from baseline	0.911 (± 0.284)	-0.0001 (± 0.147)		

Notes:

[47] - Visit 2, n=163
Visit 3, n=159
Visit 4, n=154
Visit 5, n=152
[48] - Visit 2, n=164 (Safety set)
Visit 3, n=158
Visit 4, n=153
Visit 5, n=152

Statistical analyses

No statistical analyses for this end point

Secondary: Clinically Significant Laboratory Values: Urinalysis (Safety Set)

End point title	Clinically Significant Laboratory Values: Urinalysis (Safety Set)

End point description:

As expected from the patient population, the urinalysis parameter most commonly assessed as CS abnormal was glucose in urine. This was reported for slightly more patients in the Rechon Insulin group than in the Humulin Regular group; for 7 patients on 10 occasions in the Rechon Insulin group and by 3 patients on 5 occasions in the Humulin Regular group. Out of these in total 15 cases of CS abnormal glucose in urine, 1 case was reported as an AE which was unrelated to treatment with Humulin Regular. All other cases were reported as medical history.

End point type	Secondary

End point timeframe:

From Visit 1 to Visit 5.

End point values	Rechon Insulin Human Soluble	Humulin® Regular		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	164	164[49]		
Units: Number of patients with CS values				
Visit 1 - Glucose in urine	4	1		
Visit 2 - Glucose in urine	3	2		
Visit 3 - Glucose in urine	1	1		
Visit 4 - Glucose in urine	1	1		
Visit 5 - Glucose in urine	1	0		
Visit 1 - Protein in urine	1	0		
Visit 2 - Protein in urine	0	0		
Visit 3 - Protein in urine	0	0		
Visit 4 - Protein in urine	0	0		
Visit 5 - Protein in urine	0	0		
Visit 1 - Erythrocytes in urine	1	0		
Visit 2 - Erythrocytes in urine	0	0		
Visit 3 - Erythrocytes in urine	0	0		
Visit 4 - Erythrocytes in urine	1	0		
Visit 5 - Erythrocytes in urine	0	0		
Visit 1 - Leukocytes in urine	1	0		
Visit 2 - Leukocytes in urine	0	1		
Visit 3 - Leukocytes in urine	0	0		
Visit 4 - Leukocytes in urine	0	0		
Visit 5 - Leukocytes in urine	0	0		

Notes:

[49] - Safety set

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first dose of IMP until the completion of Visit 5.

Adverse event reporting additional description:

Detailed information on each AE was recorded in the eCRF. Any AE that was ongoing at the time when the patient left the study was to be followed up until the AE was resolved or the Investigator decided that the AE was stable and did not need further follow-up.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.1

Reporting groups

Reporting group title	Rechon Insulin Human Soluble

Reporting group description:

Patients received either Rechon Insulin Human Soluble or Humulin® Regular in a randomised way. The IMP was administered at home by the patients themselves. Dosing was individualised and adjusted based on blood glucose levels for each patient.

In total, 0.9% of the patients (n=3), all randomised to treatment with Humulin Regular, were excluded from the safety set.

Reporting group title	Humulin® Regular

Reporting group description:

Patients received either Rechon Insulin Human Soluble or Humulin® Regular in a randomised way. The IMP was administered at home by the patients themselves. Dosing was individualised and adjusted based on blood glucose levels for each patient.

Serious adverse events	Rechon Insulin Human Soluble	Humulin® Regular	
Total subjects affected by serious adverse events			
subjects affected / exposed	9 / 164 (5.49%)	9 / 164 (5.49%)	
number of deaths (all causes)	0	2	
number of deaths resulting from adverse events	0	2	
Injury, poisoning and procedural complications			
Muscle rupture			
subjects affected / exposed	1 / 164 (0.61%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper limb fracture			
subjects affected / exposed	0 / 164 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			

Iliac artery occlusion			
subjects affected / exposed	0 / 164 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Bradycardia			
subjects affected / exposed	0 / 164 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Gastric haemorrhage			
subjects affected / exposed	0 / 164 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Psychiatric disorders			
Completed suicide			
subjects affected / exposed	0 / 164 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Infections and infestations			
Appendicitis			
subjects affected / exposed	1 / 164 (0.61%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic foot infection			
subjects affected / exposed	0 / 164 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	1 / 164 (0.61%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			

subjects affected / exposed	1 / 164 (0.61%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hypoglycaemia			
subjects affected / exposed	5 / 164 (3.05%)	3 / 164 (1.83%)	
occurrences causally related to treatment / all	3 / 5	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ketoacidosis			
subjects affected / exposed	1 / 164 (0.61%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 1.2 %

Non-serious adverse events	Rechon Insulin Human Soluble	Humulin® Regular	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	32 / 164 (19.51%)	12 / 164 (7.32%)	
Nervous system disorders			
Headache			
subjects affected / exposed	3 / 164 (1.83%)	1 / 164 (0.61%)	
occurrences (all)	3	1	
General disorders and administration site conditions			
Injection site rash			
subjects affected / exposed	2 / 164 (1.22%)	0 / 164 (0.00%)	
occurrences (all)	2	0	
Peripheral swelling			
subjects affected / exposed	2 / 164 (1.22%)	0 / 164 (0.00%)	
occurrences (all)	2	0	
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	0 / 164 (0.00%)	2 / 164 (1.22%)	
occurrences (all)	0	2	
Nausea			

subjects affected / exposed	2 / 164 (1.22%)	1 / 164 (0.61%)	
occurrences (all)	2	1	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	3 / 164 (1.83%)	0 / 164 (0.00%)	
occurrences (all)	3	0	
Infections and infestations			
Bronchitis			
subjects affected / exposed	2 / 164 (1.22%)	1 / 164 (0.61%)	
occurrences (all)	2	1	
Nasopharyngitis			
subjects affected / exposed	2 / 164 (1.22%)	2 / 164 (1.22%)	
occurrences (all)	2	2	
Rhinitis			
subjects affected / exposed	2 / 164 (1.22%)	0 / 164 (0.00%)	
occurrences (all)	2	0	
Sinusitis			
subjects affected / exposed	2 / 164 (1.22%)	0 / 164 (0.00%)	
occurrences (all)	2	0	
Urinary tract infection			
subjects affected / exposed	4 / 164 (2.44%)	2 / 164 (1.22%)	
occurrences (all)	4	2	
Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	3 / 164 (1.83%)	0 / 164 (0.00%)	
occurrences (all)	3	0	
Hypoglycaemia			
subjects affected / exposed	5 / 164 (3.05%)	3 / 164 (1.83%)	
occurrences (all)	5	3	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
05 December 2017	Prior to this amendment, there were two local versions of the CSP; version 3.0 that was approved only in Poland and version 4.0 that was approved only in Germany. This substantial amendment was made to combine information in the two local CSP versions into a single global version of the CSP. This substantial amendment included: - Addition of a withdrawal criterion regarding pregnancy - Updated information on origin of source data and medical records - Correction to the list of references This substantial amendment rendered the global CSP version 5.0.
25 June 2018	The analysis method for the primary variable was changed to a 3-tiered approach with a new method of analysis and procedure for the detection of antibodies against insulin. A clarification was made for the re-check of eligibility criteria, where laboratory safety assessments were to be performed. Exclusion criteria regarding definition of hypoglycaemic episodes and patient life expectancy were updated. Definition and reporting procedure for suspected unexpected serious adverse reactions (SUSARs), as well as clarification of follow-up of patients with ongoing AEs at database lock was added. In addition, clarification of when hypoglycaemic events should be reported as an AE was made. A sample size adjustment was added to avoid a decrease in sample size due to dropout and the planned study start and end dates were updated. Information regarding data protection was updated in light of new GDPR legislation. Minor administrative and editorial changes were made. This substantial amendment rendered the CSP version 6.0.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

N/A

Notes: