Clinical Study Synopsis

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<table>
<thead>
<tr>
<th><strong>Date of study report:</strong></th>
<th>09 Jan 2015</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Study title:</strong></td>
<td>A prospective multi-centre, non-randomized, open-label, non-interventional study to evaluate the safety, efficacy and injection compliance of Scilin N, Scilin R or Scilin M30 in Chinese Type 2 diabetes mellitus (T2DM)</td>
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<tr>
<td><strong>Sponsor's study number:</strong></td>
<td>16372(SL1210CN)</td>
</tr>
<tr>
<td><strong>NCT number:</strong></td>
<td>01588639</td>
</tr>
<tr>
<td><strong>EudraCT number:</strong></td>
<td>Not Applicable</td>
</tr>
<tr>
<td><strong>Sponsor:</strong></td>
<td>Bayer HealthCare</td>
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<tr>
<td><strong>Clinical phase:</strong></td>
<td>IV (Non-interventional study)</td>
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<tr>
<td><strong>Study objectives:</strong></td>
<td>PRIMARY OBJECTIVE(S): To evaluate the safety of recombinant human insulin-SciLin® N, SciLin® R and SciLin® M30 (alone or in combination) in subjects with type 2 diabetes in routine clinical practice. SECONDARY OBJECTIVE(S): To investigate the clinical effectiveness and injection compliance of recombinant human insulin-SciLin® N, SciLin® R and SciLin® M30 (alone or in combination) in subjects with type 2 diabetes in routine clinical practice.</td>
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<tr>
<td><strong>Test drug:</strong></td>
<td>Recombinant Human Insulin Injection (SciLin® R, BAY81-9924), Protamine Recombinant Human Insulin Injection (SciLin® N, BAY81-9924), Isophane Protamine Recombinant Human Insulin Injection (Pre-mixed 30/70) (SciLin® 30, BAY81-9924)</td>
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<tr>
<td><strong>Name of active ingredient(s):</strong></td>
<td>Recombinant Human Insulin</td>
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<tr>
<td><strong>Dose:</strong></td>
<td>A physician may determine the injected dose based on a patient’s actual requirement.</td>
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<tr>
<td><strong>Route of administration:</strong></td>
<td></td>
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<tr>
<td><strong>Duration of treatment:</strong></td>
<td>12-week</td>
</tr>
<tr>
<td><strong>Reference drug:</strong></td>
<td>Not Applicable</td>
</tr>
<tr>
<td><strong>Indication:</strong></td>
<td>Diabetes patients requiring treatment with insulin.</td>
</tr>
</tbody>
</table>
**Diagnosis and main criteria for inclusion:**

**INCLUSION CRITERIA:**
Subjects who were treated with SciLin® N, SciLin® R and SciLin® M30 (alone or in combination) were eligible to be included in the study based on physicians’ clinical judgment.

**EXCLUSION CRITERIA:**
Subjects with one of the conditions listed below were excluded:
- Women who were pregnant, breast feeding or had the intention of becoming pregnant within the next 3 months
- Subjects who had to be treated with other insulins simultaneously
- Subjects who were participating in other diabetes clinical studies at the same time

**Study design:** A prospective, multi-center, open-label, non-interventional study

**Methodology:**
This was a prospective, multi-center, open-label, non-interventional, 12-week study in subjects with type 2 diabetes mellitus who were treated with recombinant human insulin-SciLin® N, SciLin® R and SciLin® M30 (alone or in combination) in routine clinical practice. The term study insulin was used in this protocol for these drugs and combinations.

**Study center(s):** 62 investigational sites in China.

**Publication(s) based on the study (references):**
None at the time of report creation

**Study period:**
- **Study Start Date:** 29 Aug 2012
- **Study Completion Date:** 30 Oct 2013

**Early termination:** Not Applicable

**Number of subjects:**
- **Planned:** 3000
- **Analyzed:** 2683
Criteria for evaluation

**PRIMARY:**
Occurrence rate of serious adverse drug reactions (also including severe hypoglycaemic events) from baseline to final visit.

*Severe hypoglycaemic events: Severe central nervous system symptoms due to hypoglycemia, can’t be handled by the subjects themselves, and with one of the following characteristics:
*• Plasma glucose <70mg/dL (3.9mmol / L);
• Intravenous injection of glucagon, or intravenous glucose, the symptoms relief or disappear.

**SECONDARY:**
1) Other safety outcomes
• Occurrence rate of overall hypoglycaemic events from baseline to final visit
• Occurrence rate of nocturnal hypoglycaemic events from baseline to final visit
• Occurrence rate of adverse drug reactions from baseline to final visit
2) Effectiveness outcomes
Change in following parameters at 12 week (the final visit) compared to baseline:
• Ratio of reaching HbA1c target
• FPG
• PPG (after breakfast/lunch/supper)
• Body weight
• Insulin dosage
• Blood pressure
• Lipids (low-density lipoprotein C [LDL-C], high-density lipoprotein C [HDL-C]; total cholesterol, and triglyceride)
3) Injection compliance
• Comparison the injection time between doctors’ advice and patients’ actual practice
• Number and ratio of missing Injections
4) Others
• The distribution of medical insurance type
• Ratio of self-payment
• Score of insulin satisfaction questionnaire
Statistical methods: Statistical analysis was performed using statistical analysis software SAS (version 9.2). In principle, descriptive statistics were used. Continuous variables were described with N, mean, SD, median, min, and max. Categorical variables were described with frequency and percentage. The AEs were coded according to the 16.1 version of the MedDRA.

Primary objective(s): The number of patients and the 95%CI of occurrence rate of primary outcome (SADR plus severe hypoglycemia events) were used for analysis.

Secondary objective(s):
Other safety outcomes:
The frequency and percentage of subjects with any ADRs, ADRs leading to discontinuation, hypoglycemic events were summarized.

Effectiveness outcomes:
For all quantitative effectiveness parameters above, description statistics were used by subgroup (e.g. HbA1c based stratified analysis, treatment based stratified analysis) and total. The ratio of reaching HbA1c target was summarized with percentage by subgroup and total. The dosage of insulin during the whole study was also described by visit.

Substantial protocol changes: The study was conducted according to final Study Protocol from date June 28th, 2012, and included no substantial amendments.

Subject disposition and baseline
Of 2683 subjects who accepted the treatment of SciLin, there were 1469 males (54.75%) and 1214 females (45.25%). The mean age was 55.43 years old, the mean BMI was 24.64 kg/m2, the mean body weight was 67.67 kg, the average systolic blood pressure was 130.14 mmHg, and the average diastolic blood pressure was 80.24 mmHg.

80.20% of the enrolled subjects had been diagnosed with type 2 diabetes with a mean diabetic duration of 75.01 months. 51.73% of the subjects had already developed diabetic complications or comorbidities at baseline. The diabetic complications included diabetic neuropathy (19.53%), diabetic retinopathy (11.03%), diabetic nephropathy (7.60%), etc. The comorbidities mainly referred to hypertension (21.51%), coronary heart disease (5.93%), hyperlipidemia (5.29%), etc. The percentage of subjects who received the treatment of antihypertensive drugs, lipid-lowering drugs and aspirin were 22.62%, 9.65% and 8.95%, respectively.

Only 1.53% of the subjects accepted insulin treatment within one month before the recruitment. Among the subjects who received oral antidiabetic drugs (OADs) at baseline, Metformin, alpha-glucosidase inhibitor and sulfonylureas were the most commonly used drugs. The main reason for initiation of SciLin was to improve glucose control. Other reasons included attenuating glycemic fluctuation, increasing satisfaction, reducing the risk of hypoglycemia, etc.
Results Summary — Safety:

Primary safety measures: The primary outcome incidence during study was 0.26%. After 12-week treatment of SciLin in 2683 Chinese T2DM subjects, no SADR were observed, 0.26% reported severe hypoglycemia events (95%CI: 0.10%, 0.54%).

Other safety measures: The incidence of overall hypoglycemia of all the subjects was 18.32%, while that of daily and nocturnal hypoglycemia was 14.21% and 7.10%, respectively.

The incidence of the adverse drug reactions excluding hypoglycemia was 1.49%. The incidence of the adverse drug reactions that led to drop out cases was 0.04%. There was no serious adverse reaction.

Results Summary — Effectiveness:

Among all subjects, the mean reduction levels of effectiveness variables were as follows: HbA1c by 2.34%, FPG by 4.35mmol/L, 2h PPG (after breakfast) by 6.27mmol/L, 2h PPG (after lunch) by 5.68mmol/L, and 2h PPG (after supper) by 5.18mmol/L. 41.40% of subjects achieved the target of HbA1c<7% after 12-week of treatment, while the target of HbA1c≤6.5% was achieved by 23.11% of subjects.

The mean total daily insulin doses were 28.71±10.46 IU at baseline, reaching 29.61±10.51 IU at the end of the trial after 12-week treatment. The mean daily dose (per weight) was 0.43±0.16 IU/Kg at baseline, while that on the final visit was 0.44±0.16 IU/Kg.

The blood pressure decreased slightly after treatment, and the serum profiles were improved significantly. The body weight gained 0.12 kg of all the subjects from baseline to end of study. After 12-week treatment, LDL-C, TC and TG had statistically significant decreases compared with the baseline (P<0.0001), and HDL-C increased significantly (P<0.0001).

Results Summary — Others:

26.17% of the subjects injected insulin with the same inject-meal-interval based on their physicians’ advice. The average times of missing injection was 3.09, and the average rate of missing injection was 1.69%. 98.15% of the subjects (n=2546) showed a good injection compliance of 80%~120%.

The number of the subjects covered by the medical insurance for urban workers, medical insurance for urban residents, new rural cooperative medical system (NCMS), commercial insurance and other medical insurance were 1271 (47.37%), 582 (21.69%), 591 (22.03%), 1 (0.04%), and 12 (0.45%), respectively, while 226 subjects did not have medical insurance (8.42%). Among the insured subjects, the self-paid ratio of the urban workers, the urban residents and the NCMS subjects were 48.61%, 67.19% and 78.92% respectively, while that of other insured subjects was up to 99.04%.

According to the medical advice, 82.74% of the subjects received the monotherapy of SciLin M30 as the initiation. Most of the subjects maintained the initiated insulin regimen at the final visit, while 26.3% of the subjects who initiated with combined treatment of Scilin N/R switched to Scilin M30.
As suggested by the questionnaire, most of the subjects believed that the blood glucose can be controlled effectively by SciLin, which was also easy to use, and satisfied with diabetes education. However, there were still 1/3 subjects who expressed concerns about the side effects and complications of the insulin treatment.

**Overall conclusions**

Both the 12-week monotherapy and the combined therapy of SciLin can significantly improve blood glucose control. SciLin M30 regimen is the most commonly used initial human insulin regimen of type 2 diabetes mellitus subjects in this study. After 12-week treatment of SciLin in 2683 Chinese T2DM subjects, no SADR were observed. This study shows a low incidence of severe hypoglycemia, a good compliance of injection and a high satisfaction of treatment.