Clinical Trial Study Synopsis: SKP1052

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Name of sponsor: Skyepharma AG	
Name of finished product: SKP-1052 Modified –Release Tablets	
Name of active ingredient: Terbutaline sulphate	
Study title: Randomised, single-blind, placebo controlled, four-period four-treatment cross-over design, proof of concept study to compare the pharmacodynamic, safety and pharmacokinetics of one single administration of SKP-1052 versus immediate-release terbutaline and placebo tablets in stable Type 1 Diabetes Mellitus Patients	
Investigators: Dr. Tim Heise (Principal Investigator)	
Study center: Profil Institut für Stoffwechselforschung GmbH, Hellersbergstraße 9, D-41460 Neuss, Germany	
Publication (reference): Unpublished	
Studied period (years): Date First Subject First Visit: 25 February 2011 Date Last Subject Last Visit: 06 May 2011	**Phase of development:** Phase IIa
Study objectives: The primary objective of this study was to assess the pharmacodynamic (PD) effects of SKP-1052 and immediate-release terbutaline on nocturnal glucose levels based on mean nadir blood glucose at 0-10 hours post-dose.	
Methodology / Study Design: Each subject received placebo, 2.5 mg and 5 mg of SKP-1052, and 5 mg of immediate-release terbutaline. The sequence in which the treatments were administered was determined by the randomisation schedule. Subjects were requested to maintain their standard insulin regimen and their self-monitoring of blood glucose throughout the study. Subjects participated in 6 clinical visits consisting of 1 screening visit, 4 treatment visits (Visits 1-4) including one overnight stay per treatment visit, and one follow-up visit. The 4 treatment visits were separated by 7-14-day wash-out periods. Within 21 days before the first dosing visit and after having given written informed consent, potential study participants underwent screening examinations to assess eligibility for inclusion	

in the trial and entered the experimental intervention phase of the study. On Day 1 of each of the 4 treatment visits, subjects' blood glucose levels were clamped to a target level of 90 mg/dL by means of a variable intravenous insulin aspart or glucose infusion, followed by a standardised meal and subsequent blood glucose level stabilisation with individually determined insulin glargine doses. One hour prior to dosing with the investigational product, the insulin infusion rate was continuously decreased and finally stopped. At pre-defined time points before and after dosing on Day 1 and 2, blood samples for pharmacokinetic, pharmacodynamic and safety assessments were taken including determination of lactate, cortisol, glucagon, catecholamines and serum potassium concentrations. Hourly vital signs recording, continuous ECG monitoring and treatment of hypoglycaemic episodes with blood sugar levels of <50 mg/dL with carbohydrate intake was performed during treatment visits. This was followed by a full safety assessment at the follow-up visit (4-10 days after the last treatment).

Number of subjects:

Planned: 28 subjects to be enrolled in order to get 25 evaluable subjects

Enrolled: 30 subjects

Completed: 28 subjects

Diagnosis

Type 1 diabetes mellitus

Main inclusion criteria:

Daily use of insulin therapy for at least one year, male or female subject, age 18-50 years, HbA1c <8.5%, insulin pump therapy or multiple basal-bolus regimen with the long-basal insulin given once daily or twice daily, or basal long lasting analogue with a bolus insulin pre-meal 3 times a day or premixed insulin when one dose is given at bedtime for at least 1 month and not anticipating a change prior to the subject's completion of the study, normal values for TSH, FT3 and FT4, able to read, understand and sign the informed consent and willing and able to comply with study requirements.

Main exclusion criteria:
Concomitant diseases as defined in the protocol, clinically significant abnormal safety or laboratory tests at screening, inadequate contraceptive measures, severe hypoglycaemia in last 3 months, hypersensitivity to terbutaline, history of HIV, hepatitis B or hepatitis C, treatment with non-allowed medications (as defined in the protocol), blood loss >500 mL in last 3 months, significant history of alcoholism or drug/chemical abuse, or positive alcohol breath test at screening, intake of other study drug in last 90 days.

Test product, dose and mode of administration, batch number:

Description: SKP-1052 tablets (modified-release terbutaline)

Manufacturer: SkyePharma AG

Dose and schedule of administration: Single dose of 2.5 mg and 5 mg at two different occasions

Mode of administration: oral

Batch numbers: S10E39P (2.5 mg tablets) and S10E40P (5 mg tablets)

Comparator / reference therapy:

Description: Bricanyl® tablets (immediate-release terbutaline)

Manufacturer: AstraZeneca, UK

Dose and schedule of administration: Single dose of 5 mg

Mode of administration: oral

Batch number: GT049

Description: Placebo tablets for modified-release SKP-1052

Manufacturer: SkyePharma AG,

Dose and schedule of administration: Single dose

Mode of administration: oral

Batch number: S10E37P

Duration of treatment:

Four single dose administrations, separated from each other by a 7-14 days wash-out period.

Criteria for evaluation:

Efficacy:

Primary pharmacodynamic (PD) endpoint:
- Mean nadir blood glucose concentration 0-10 h post-dose (BGn 0-10h).

Secondary PD endpoints:
- Individual blood glucose level at each time point
- Mean blood glucose concentration during overnight sampling (BGmean)
- Time spent with nocturnal blood glucose levels <63 mg/dL (3.5 mmol/L) 0-10h post-dose (TG<63mg/dL 0-10h)
- Morning blood glucose concentration at 10h post-dose (BGmorning)

Safety:

Safety endpoints:
- Number of adverse events/serious adverse events
- Incidence, severity, relatedness and severity of treatment emergent adverse events
- Vital signs
- ECG
- Laboratory assessments
- Physical examinations

Pharmacokinetics:

Pharmacokinetic (PK) endpoints:
- Observed maximum drug plasma concentration (Cmax) normalised for dose
- Area under the curve from dosing to the last measurable drug plasma concentration (AUC0-tlast) normalised for dose
- Area under the curve from dosing to infinity (AUC0-∞) normalised for dose
- Time at Cmax (Tmax)
- Area under the drug plasma concentration curve from dosing to the time of the last significant (>LLOQ) drug plasma concentration (AUC0-tn) normalised for dose

Statistical methods:

Phoenix WinNonlin 6 was employed for all PK calculations and PK/PD correlations, and the SAS® System for Windows (Version 9.2) statistical software for all other statistical calculations. The statistical analysis of the primary PD endpoint BGn 0-10h and secondary PD endpoint $T_{<63mg/dL}$ 0-10h employed a non-parametric Wilcoxon's Signed Rank test with determination of

the point estimate and the corresponding 95% confidence interval of Hodges and Lehmann. For analysis of differences between each pair of the 4 treatments, the median of differences between treatments was estimated. The analysis of the secondary PD endpoints BGmean and BGmorning employed a mixed linear effect model (Analysis of variance (ANOVA)) with log transformed variables as response variables, sequence, period and treatment as fixed factors, and subject within sequence as a random factor. For analysis of differences between each pair of the 4 treatments the geometric least square means (LS-means) of ratios of treatments were estimated together with the corresponding two-sided 95% confidence intervals. The number of hypoglycaemic events, subjects treated with carbohydrates per treatment arm and differences between treatments were compared using Exact Chi-Square test for equal proportions (events) and Fisher's Exact test (subjects) with a 5% level of significance. Dose-normalised PK endpoints and dose proportionality were analysed statistically according to the same parametric model employed for PD parameters (ANOVA). PD parameters were also analysed post-hoc in the time interval 2-10 h or in subjects without carbohydrate treatment. For the PK endpoints, the 90% confidence interval was evaluated against the range (0.80; 1.25) and for assessment of dose-proportionality, the 90 and 95% confidence intervals were evaluated against the range (0.75; 1.33). The level of significance was set to 5% for PD parameters and to 10% for PK parameters. PK/PD relationship was assessed with a classical hysteresis graph of the terbutaline concentrations or PK parameters vs. various PD markers and hypoglycaemic events, and a number of link-models were tested to for fit. All efficacy endpoints were also analysed descriptively. Safety endpoints except for frequency of hypoglycaemic events were analysed solely by descriptive methods.

Summary results:

In total, 55 subjects were screened, and 30 type 1 diabetic subjects (26 males and 4 females; mean (±SD) age 35±8.3 years, HbA1c 7.6±0.57%, plasma glucose 8.4±3.44 mmol/L) were randomised to 1 of the 4 treatment sequences and exposed to the trial medication. Twenty-eight (28) subjects completed the study according to the protocol. One subject was withdrawn after treatment with placebo after an SAE and another subject after treatment with 2.5 and 5 mg SKP-1052 due to withdrawal of consent.

Efficacy:

Primary pharmacodynamic endpoint:

BGn 0-10h of Bricanyl® was statistically significantly higher compared to 2.5 mg SKP-1052 and placebo (p=0.0239 and 0.0276, respectively). Treatment with 5 mg SKP-1052 led to slightly higher BGn 0-10h compared to placebo which approached but did not reach statistical significance (p=0.0719). However, when the 2-hour lag-time for SKP-1052 was deducted (2-10h), both the 5 mg SKP-1052 and the 5 mg Bricanyl® formulation raised BGn with statistical significance compared to placebo (5 mg SKP: p=0.0406; 5 mg Bricanyl®: p<0.0001), and the difference between Bricanyl® and 2.5 mg SKP-1052 remained significant (p<0.0001). No further significant differences between treatments were observed.

Secondary pharmacodynamic endpoints:

Treatment with either of the 5 mg terbutaline formulations led to 20-29% higher mean blood glucose concentrations (BGmean 0-10h; mean±SD of Bricanyl®: 128.98±49.23 mg/dL; SKP-1052: 120.58±44.37 mg/dL) compared to 2.5 mg SKP-1052 (100.83±32.32 mg/dL) or placebo (100.03±35.19 mg/dL) and reached statistical significance. No significant difference between the 2 doses of SKP-1052 or between 2.5 mg SKP-1052 and placebo was observed. However, when the 2-hour lag-time for SKP-1052 was deducted (2-10 hour interval), both the 5 mg SKP and Bricanyl® formulation displayed similar and statistically significant effects compared to placebo. SKP-1052 2.5 mg exhibited a modest but statistically not significant increase compared to placebo.

Mean (±SD) time spent with blood glucose concentrations below 63 mg/dL (0-10 h post-dose) was lowest after treatment with Bricanyl® (52.2±84.8 min), followed by corresponding values for 5 mg SKP-1052 (73.8±84.4 min), 2.5 mg SKP-1052 (96.6±110.0 min) and placebo

(106.6±107.0 min). For Bricanyl® compared to placebo or 2.5 mg SKP-1052, the non-parametric analysis showed a statistically significant difference with p=0.0028 and p=0.0134, respectively. No further differences between treatments reached statistical significance.

Mean (±SD) morning blood glucose concentrations (BGmorning at 10h post-dose) after treatment with Bricanyl® or 5 mg-SKP-1052 was higher (142.5±70.0 and 144.2±72.9 mg/dL) than values obtained after 2.5 mg SKP-1052 or placebo treatment (111.3.±56.4 and 113.1±56.8 mg/dL, respectively), and reached statistical significance. No significant difference in BGmorning concentrations after treatment with 5 mg SKP-1052 compared to Bricanyl® or after treatment with 2.5 mg SKP-1052 compared to placebo was observed.

Safety:

A total of 12 subjects (41.4%) experienced at least one AE (0-24 h post-dose) after study drug administration. Five (5) subjects (17.2%) experienced at least one AE after 5 mg SKP-1052, 4 subjects (14.3%) after 5 mg immediate-release terbutaline (Bricanyl®), and 5 subjects (17.2%) after placebo (not including hypoglycaemic events). The total number of AEs was 18, and the respective numbers were 5, 7 and 6. No AE occurred after treatment with 2.5 mg SKP-1052. Except for 1 AE, all AEs were non-serious. The serious AE (ventricular tachycardia) experienced after dosing with placebo led to the subject's premature withdrawal from the study. The majority of AEs were of mild intensity, and there was no AE with intensity rated as severe. Headache and hyperhidrosis were the most frequently reported AEs occurring in 1 (3.4%) and 2 (6.9%) subject(s) treated with 5 mg SKP-1052, in 3 (10.7%) and 1 (3.6%) subject(s) treated with Bricanyl®, and in 3 (10.3%) subjects following treatment with placebo (only headache). A total of 5 AEs in 3 subjects (1 after dosing with SKP-1052) were evaluated as possibly related to the study medication. Among hypoglycaemic events collected over a time period from 0-10 h post-dose, only 1 event was symptomatic and of moderate intensity.

Relative numbers of subjects with hypoglycaemic events (0-10h post-dose) after dosing with immediate release-terbutaline (Bricanyl®) or 2.5 or 5 mg SKP-1052 were lower (25.0%, 34.5% and 41.4%, respectively), compared to subjects receiving placebo (51.7%). All AEs had the outcome resolved.

Treatment with either of the 5 mg terbutaline formulations led to a statistically significantly lower number of hypoglycaemic events 0-10h post-dose (10 with Bricanyl® and 16 with SKP-1052) that had to be treated with carbohydrates, compared to placebo (33 events; 5 mg SKP-1052 vs. placebo: p=0.0213; 5 mg Bricanyl® vs. placebo: p=0.0006). When instead the numbers of subjects that experienced nocturnal hypoglycaemic episodes and required carbohydrate intake were compared, only the comparison of effects after dosing with Bricanyl® (7 subjects) vs. placebo (15 subjects) approached but did not reach statistical significance (p=0.0570).

There were no clinically significant findings or changes in laboratory, physical examination or ECG results. In 1 subject, pulse (heart) rate after treatment with 5 mg Bricanyl® was above normal reference ranges and accompanied with palpitations.

Pharmacokinetics:

<u>Pharmacokinetic endpoints:</u>

With regard to the 90% confidence interval, all dose-normalised geometric LS-mean of ratios of treatments for AUC0-∞, AUC0-tn and Cmax from the statistical comparison of 2.5 or 5 mg SKP-1052 vs. Bricanyl® were within the range 0.80 and 1.25 and thus could be considered bioequivalent.

When dose-normalised AUC0-tlast, AUC0-∞ and Cmax of both SKP-1052 strengths were compared, the 90% and 95% confidence intervals of the LS-mean of ratios resided all between the range 0.75 and 1.33, indicating that there was no influence on the terbutaline absorption when different doses of SKP-1052 were administered. Furthermore, the difference in mean AUC between dose-normalised 2.5 and 5 mg SKP-1052 did not exceed 25%. Therefore, regarding the two strengths, dose-proportionality of SKP-1052 pharmacokinetics can be concluded.

A difference in tmax of about 2 hours between SKP-1052 and Bricanyl® confirmed the expected profile of the Geoclock™ SKP formulations.

Post-hoc evaluations:

PD parameters were-reanalysed in subjects that did not require oral carbohydrate treatment for hypoglycaemia, but, given the low sample size in this subset, no more distinct treatment differences could be identified. Re-analysis of PD parameters in the time interval 2-10 hours, after deduction of the lag-time of SKP-1052, led to slightly more pronounced effects for 5 mg SKP-1052 that were comparable to those of Bricanyl®.
The PK/PD relationship was also tested for correlation between the number of hypoglycaemic events and the main PK parameters Cmax or AUC0-tlast. Visual inspection of the scatter plot revealed that increasing concentrations of terbutaline were accompanied by a decrease in the number of hypoglycaemic events. At high concentrations of Cmax >about 7 ng/mL and AUC0-tlast >about 35 ng/*h/mL no hypoglycaemic events were observed, while low terbutaline absorption data showed a relatively high variability in the number of hypoglycaemic events. Blood glucose concentrations were also normalised for placebo values and plotted against the main PK parameters. However, no further mathematical PK/PD correlation could be identified.

Conclusions:

Administration of single doses of 5 mg SKP-1052 or 5 mg immediate-release terbutaline (Bricanyl®) led to a slightly higher mean nadir blood glucose concentration 0-10 hours post-dose when compared to 2.5 mg SKP-1052 and placebo. When the lag-time for SKP-1052 was deducted, the effects of both 5 mg SKP-1052 and Bricanyl® on nadir blood glucose concentrations (2-10 hours) reached statistical significance when compared to placebo.

Treatment with either 5 mg SKP-1052 or Bricanyl® led to statistically significantly higher mean blood glucose concentrations (0-10 or 2-10 hours post-dose) when compared to treatment with 2.5 mg SKP-1052 and placebo. Mild effects on mean blood glucose were observed for SKP-1052 2.5 mg versus placebo but the difference did not reach statistical significance. Similar findings were observed for BG mean after subtracting the placebo effect, where the 3 treatments showed greater values than placebo.

After treatment with 5 mg SKP-1052 or Bricanyl® , time with nocturnal blood glucose levels <63 mg/dL (0-10 hours or 2-10 hours post-dose) was reduced when compared to placebo, but reached statistical significance only for Bricanyl®. Both 5 mg SKP-1052 and Bricanyl® increased morning blood glucose levels to a similar extent when compared to 2.5 mg SKP-1052 and placebo. Based on the dose-normalised values for the main PK parameters AUC0-∞, AUC0-tn and Cmax, SKP-1052 was found to be bioequivalent to Bricanyl®.

The expected lag-time was confirmed for both SKP-1052 formulations with a delay of drug release of 2 hours. Mean time to maximum terbutaline concentration (tmax) was about 2 hours longer after treatment with SKP-1052 compared to Bricanyl®.
Both doses of SKP-1052 displayed comparable and dose-proportional absorption characteristics. Both treatments had positive effects on nocturnal blood glucose levels and number of hypoglycaemic events in comparison to placebo without obvious differences between the two 5 mg terbutaline formulations. Doses of 2.5 mg SKP-1052 had small pharmacodynamic effects but did not reach statistical significance vs. placebo.
Treatment with SKP-1052 was well tolerated and safe, based on number of AEs/SAEs, laboratory examinations, ECGs and other safety assessments. Cardiac AEs only included palpitations and tachycardia with the immediate-release formulation. One serious adverse event (non-sustained ventricular tachycardia with 6 beats) was reported, which was resolved and occurred in a placebo treated subject.

The total number and proportion of subjects with AEs (without hypoglycaemic events) was similar after treatment with Bricanyl®, 5 mg SKP-1052 and placebo, while no AE (without hypoglycaemic events) was reported after single doses of SKP-1052 2.5mg.
Administration of single doses of either 5 mg SKP-1052 or Bricanyl® led to a significantly lower number of hypoglycaemic events requiring treatment with carbohydrates, when compared to placebo. SKP-1052 2.5 mg led also to a reduction of hypoglycaemic events but the difference to placebo did not reach statistical significance.