SYNOPSIS OF RESEARCH REPORT [redacted] (PROTOCOL BP21572)

COMPANY: NAME OF FINISHED PRODUCT: NAME OF ACTIVE SUBSTANCE(S):	(FOR NATIONAL AUTHORITY USE ONLY)

TITLE OF THE STUDY / REPORT No. / DATE OF REPORT	BP21572 - A randomized, double-blind, placebo controlled, parallel group study to investigate the effect of taspoglutide on gastric emptying measured by a paracetamol test after single dose and after multiple doses in patients with type 2 diabetes. Report No. [redacted] August 2010		
INVESTIGATORS / CENTERS AND COUNTRIES	– [redacted] Germany – [redacted] Germany – [redacted] UK		
PUBLICATION (REFERENCE)	N/A		
PERIOD OF TRIAL	Dec 2, 2008 to July 27, 2009	CLINICAL PHASE	I
OBJECTIVES	**1. Primary Objective:** • To evaluate the effect of taspoglutide on gastric emptying (as assessed by the pharmacokinetics of paracetamol) after first and multiple dose of taspoglutide **2. Secondary Objectives:** • To explore the relationship between plasma taspoglutide concentrations and gastric emptying (as measured by the pharmacokinetics of paracetamol) • To assess the safety and tolerability of taspoglutide and placebo (diluent) • To assess the effect of taspoglutide on renal function parameters after single and multiple dose of taspoglutide • To assess the multiple dose pharmacokinetics of taspoglutide • To assess the effect of taspoglutide on fasting plasma glucose and HbA1c		
STUDY DESIGN	Multiple-center, randomized, double-blind, placebo controlled, parallel group study		

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NUMBER OF SUBJECTS	60 type 2 diabetic patients
DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION	Male and female patients with type 2 diabetes; aged 18 to 75 years inclusive
TRIAL DRUG / STROKE (BATCH) No.	Taspoglutide 10 mg: [redacted] Taspoglutide 20 mg: [redacted] Paracetamol [redacted]
DOSE / ROUTE / REGIMEN / DURATION	Taspoglutide at doses of 10 mg, 20 mg or placebo was administered weekly for 12 weeks by subcutaneous injection in the abdomen. Each patient received one of the following treatments: **Treatment A** – 10 mg taspoglutide on Days 1, 8, 15, 22, 29, 36, 43, 50, 57, 64, 71, and 78. **Treatment B** – 10 mg taspoglutide on Days 1, 8, 15, and 22, – 20 mg taspoglutide on Days 29, 36, 43, 50, 57, 64, 71, and 78. **Treatment C1** – 10 mg matching taspoglutide placebo on Days 1, 8, 15, 22, 29, 36, 43, 50, 57, 64, 71, and 78. **Treatment C2** – 10 mg matching taspoglutide placebo on Days 1, 8, 15, and 22, – 20 mg matching taspoglutide placebo on Days 29, 36, 43, 50, 57, 64, 71, and 78. 1.5 g paracetamol on Days 1, 29, and 78 (paracetamol was administered as solution at the end of the standardized meal six hours after the taspoglutide/taspoglutide placebo administration. 1.5 g paracetamol on Days -1, 5, 33, and 82 (paracetamol was administered as solution at the end of the standardized meal in the morning.

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PLACEBO / STROKE (BATCH) No.	Taspoglutide Placebo 10 mg: [redacted] Taspoglutide Placebo 20 mg: [redacted]
DOSE / ROUTE / REGIMEN / DURATION	Taspoglutide placebo 10 mg/20 mg was administered weekly for 12 weeks by subcutaneous injection in the abdomen.
CRITERIA FOR EVALUATION	
PHARMACOKINETICS:	<u>Primary PK parameters:</u> • Paracetamol: $AUC_{0-\infty}$, C_{max}, t_{max}. • Taspoglutide: C_{max} (week 1, 3, 5, 8 and 12), AUC_{0-7d} (week 1, 3, 5, 8 and 12). <u>Secondary PK parameters:</u> • Paracetamol: AUC_{0-3h}, AUC_{0-last}, $t_{1/2\beta,}$ Cl/F. • Taspoglutide: t_{max} (week 1, 3, 5, 8 and 12), C_{trough}, $t_{1/2\beta}$ (only assessed after the last dose administration), Cl/F (only assessed after the last dose administration).
PHARMACODYNAMICS:	FPG, HbA1c and body weight.
SAFETY:	Adverse events, vital signs, physical examination, clinical laboratory tests, ECGs, ant-taspoglutide antibodies.
STATISTICAL METHODS	The primary parameters for the analysis of the effect of taspoglutide on gastric emptying were T_{max}, $\log(AUC_{0-\infty})$ and $\log(C_{max})$ of paracetamol. For the parameters $\log(AUC_{0-\infty})$ and $\log(C_{max})$, an analysis of variance model with fixed effects for Day (seven levels [-1, 1, 5, 29, 33, 78, and 82]), treatment (three levels), and their interaction, as well as random patient effects was used. From the model, geometric mean ratios comparing the paracetamol exposures on Days 1 to 82 with Day -1 were estimated per treatment arm and the results for treatments A and B compared to those of treatment C. Estimates for the relative differences with their 90% confidence intervals were reported.

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METHODOLOGY:

A screening examination was performed between 28 and 3 days before the start of the study. Patients were admitted to the clinic the morning of Days -2, 4, 28, 32, 77, and 81. Drug treatment was administered as described above. Patients remained in the clinic until Days 2, 6, 30, 34, 79, and 83 respectively. Patients were then required to return to the unit for dosing on Days 8, 15, 22, 36, 43, 50, 57, 64, and 71 and for additional ambulatory visits on Days 3, 16, 17, 19, 31, 51, 52, 54, 80, 84, 85, 92, and 99. The safety follow-up was scheduled between Days 106 and 112. A physical examination was performed at screening, and at the follow-up visit. Height and waist/hip circumference were recorded at screening only, weight at screening, pre-dose on Days 1, 29, 57, 85 and at follow-up. Safety laboratory tests (hematology, biochemistry, and urinalysis) were carried out fasted at screening, on Day -1, at pre-dose on Day 29, at follow-up and at random during the other visits. Measurements of blood pressure, pulse rate and ECGs were taken at screening, on Day -1, on Days 1, 29, 50, 78 (pre-dose) and at follow-up visit. Blood samples for determination of plasma concentrations of anti-taspoglutide antibodies and its characterization were collected at screening, at pre-dose of Days 22, 57, 78 and at follow-up.

PHARMACOKINETIC RESULTS:

Paracetamol

On taspoglutide dosing days at peak concentrations of taspoglutide (Days 1, 29 and 78) mean paracetamol C_{max} was decreased by up to 32% and 41% compared to baseline (Day -1) after treatments A and B, respectively. Median paracetamol t_{max} was prolonged by up to 0.75 and 1.12 hours, respectively. Mean paracetamol $AUC_{0-\infty}$ was unchanged or slightly decreased by up to 12% and 13%, respectively. At trough concentrations of taspoglutide (Days 5, 33 and 82) mean C_{max} and $AUC_{0-\infty}$ of paracetamol appeared to be slightly affected ($\leq$ 11%). This applied for both active treatments. The median t_{max} of paracetamol was slightly delayed by up to 0.75 hours.

Statistical Analysis of Paracetamol

A 18 to 45% mean decrease in the ratio of C_{max} and a 0.5 to 1.1 hour mean increase in the difference of t_{max} of paracetamol was observed at taspoglutide peak concentrations (Days 1, 29 and 78) comparing data from treatments A and B to data from treatment C. For the estimated ratios of AUC_{inf} and AUC_{last} of paracetamol no or a slight change (0 to -22%) was measured on all days for both active treatments compared to placebo.Trough concentrations of taspoglutide (Days 5, 33 and 82) did not cause a statistical significant change in C_{max}, AUC_{inf} and AUC_{last} of paracetamol comparing patients on taspoglutide (treatments A and B) versus placebo (treatment C). For the estimated difference in t_{max} of paracetamol a slight delay by 0.1 to 0.6 hours was detected.

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Taspoglutide

During treatment A (taspoglutide 10 mg from week 1 to 12), taspoglutide median trough concentrations showed an initial increase up to week 4, followed by a decline during weeks 5 to 6. As of week 6 until end of treatment schedule (week 12) median trough were at the same level. During treatment B (taspoglutide 10 mg dose from week 1 to 4, 20 mg from week 5 to 12), again, the median trough concentrations showed an initial increases for both the 10 mg and the 20 mg doses, followed by a decline starting as of weeks 6. From week 7 on until end of treatment schedule (week 12) median trough concentrations were at the same level.

PHARMACODYNAMIC RESULTS:

Treatment with taspoglutide resulted in a reduction of fasting plasma glucose in both active treatment groups compared to the placebo group. Reductions in fasting plasma glucose were apparent for both active treatment groups after one week and maximum reductions were achieved within 3-4 weeks. Thereafter, the reductions were maintained over the treatment period of 12 weeks.

Treatment with taspoglutide over 12 weeks resulted in reductions in HbA1c levels in both active treatment groups compared to the placebo group. Mean change from baseline in HbA1c was approximately -0.5% on Day 29, -0.8% on Day 57 for both treatment groups and -0.8% and -0.7% on Day 85 for treatments A and B, respectively (compared with -0.1% on Days 29 and 85 and -0.4% on Day 57 for the placebo group).

Body weight loss was recorded for both active treatment groups at all post-dose assessments. Mean body weight was decreased on Day 29 by 1.2 and 1.0 kg , on Day 57 by 1.6 and 2.1 kg and on Day 85 by 1.6 and 1.9 kg for treatment groups A and B, respectively. In contrast the mean body weight of the placebo group remained unchanged or slightly decreased (up to -0.6 kg on Day 59) during the study conduct.

SAFETY RESULTS:

Taspoglutide was safe and well tolerated. The higher incidence of AEs in the taspoglutide groups was mainly due to the known injection site reactions and gastrointestinal events. These AEs were dose-dependent and transient in nature. Two serious adverse events of severe intensity (pancreatitis and acromioclavicular separation) were reported during the study. These adverse events were considered as unrelated or remotely related to trial treatment. There were no clinically significant changes in laboratory parameters including renal function parameters, vital signs or in ECG characteristics. There was a maximum increase in the mean heart rate values of 3, 7 and 8 bpm in Week 8 Day 50 compared to baseline under placebo and taspoglutide treatments A and B, respectively. At the follow-up visit a confirmed positive anti-taspoglutide antibody result was detected in a total of 9 patients.

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CONCLUSIONS:

- Administration of taspoglutide caused a delayed gastric emptying as measured by pharmacokinetics of paracetamol. Paracetamol absorption was slowed when paracetamol was administered in combination with taspoglutide as detected by a prolonged median paracetamol t_{max} of up to 1.1 hour. Overall paracetamol exposure ($AUC_{0-\infty}$) was unchanged or slightly affected (up to -13%). The effect on gastric emptying was mainly observed on taspoglutide dosing days at peak concentrations of taspoglutide resulting in a decreased mean paracetamol C_{max} by up to 41% compared to baseline.
- A decrease in change from baseline for C_{max}, AUC_{0-3h}, $AUC_{0-\infty}$ and AUC_{last} and an increase in t_{max} of paracetamol after administration of taspoglutide was observed. These changes appeared to be more prominent at taspoglutide peak concentrations compared to trough concentrations and the effect seemed to diminish over time suggesting possible tolerance to taspoglutide on gastric emptying.
- The pharmacokinetic parameters of taspoglutide for the first eight weeks showed patterns comparable to those observed in previous studies. For both treatment groups an initial increase of median trough concentrations was seen in the first four to six weeks. This was followed by a decline of the trough levels over the next one to two weeks. From this point on median trough levels remained at the same level.
- Treatment with taspoglutide resulted in a reduction of fasting plasma glucose and HbA1c in both active treatment groups compared to placebo.
- The multiple once weekly administration of taspoglutide was safe and overall well tolerated. There were no clinically significant changes in laboratory parameters, vital signs or in ECG characteristics. There were no clinically significant changes in any parameter for assessing the effect of taspoglutide on renal function.