CLINICAL TRIAL PROTOCOL

Trial ID: DPP4-Hypo

DPP-4 inhibition with sitagliptin and the risk for hypoglycaemia in the fasting state in subjects with type 2 diabetes treated to fasting plasma glucose targets with insulin glargine and metformin

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List of Abbreviations

AE	Adverse event
ALT/GPT	Alanine aminotransferase
AMG	Arzneimittelgesetz
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
APTT	Activated partial thromboplastin time
AST/GOT	Aspartate aminotransferase
BMI	Body mass index
CGM	Continuous glucose monitoring
CK	Creatine kinase
CKMB	Creatine kinase isoform MB
CRF	Case report form
DPP	Dipeptidyl peptidase
ECG	Electrocardiogram
EMA	European Medicine Agency
EOT	End of text
EPAR	European public assessment report
EU	European Union
FAS	Full analysis set
FPG	Fasting plasma glucose
FSFV	First subject first visit
FSH	Follicle stimulating hormone
GCP	Good clinical practice
GIP	Glucose-dependent insulinotropic peptide
GLP-1	Glucagon-like peptide 1
HbA1C	N-(1-deoxy)-fructosyl-haemoglobin
HDL	High-density lipoprotein
HEENT	Head, ears, eyes, nose, throat
HIV	Human immunodeficiency virus
HR	Heart rate
ICH	International conference on harmonisation
ICMJE	International Committee of Medical Journal Editors
ID	Identifier
IEC	Independent ethics committee
IMP	Investigational medicinal product
INR	International normalised ratio
IRB	Institutional review board

IU	International unit
LDH	Lactic dehydrogenase
LDL	Low-density lipoprotein
LSLV	Last subject last visit
MCH	Mean corpuscular haemoglobin
MCHC	Mean corpuscular haemoglobin concentration
MCV	Mean corpuscular volume
MSD	Merck Sharp & Dohme
NIMP	Non-investigational medicinal product
OAD	Oral antidiabetic drug
OGT	Oral glucose test
PD	Pharmacodynamic
PG	Plasma glucose
PPP	Per-Protocol Population
SAE	Serious adverse event
SAP	Statistical analysis plan
SAS	Statistical Analysis System
SIV	Site initiation visit
SMPG	Self monitoring of plasma glucose
SmPC	Summary of Product Characteristics
SOP	Standard operating procedure
SUSAR	Suspected Unexpected Serious Adverse Reactions
TIF	Trial investigator file
TZD	Thiazolidinedione
U	Units
β-HCG	Beta-human chorionic gonadotropin
γ-GT	Gamma-glutamyltransferase

1 Synopsis

Name of Sponsor: Profil	**Trial ID:** DPP4-Hypo
Title of the trial: DPP-4 inhibition with sitagliptin and the risk for hypoglycaemia in the fasting state in subjects with type 2 diabetes treated to fasting plasma glucose targets with insulin glargine and metformin	
Trial design: Single center, randomised, double blind, two-way, placebo controlled, crossover design	
Clinical phase of development: Phase 2	
Trial centre: Profil Institut für Stoffwechselforschung GmbH, Hellersbergstraße 9, 41460 Neuss, Germany	
Principal Investigator: Dr. Christoph Kapitza, Profil Institut für Stoffwechselforschung GmbH, Hellersbergstraße 9, 41460 Neuss, Germany	
Planned trial start (First Subject First Visit): 11/2017	**Planned trial end (Last Subject Last Visit):** 05/2019
Trial population: Subjects with diabetes mellitus type 2, treated with basal insulin glargine and metformin	
Key Objectives: It is the purpose of the present trial to test the influence of DPP-4 inhibition (comparing sitagliptin 100 mg per day versus placebo in a cross-over design) on (a) the risk to develop hypoglycemia and on (b) hormonal responses and recovery from hypoglycemia in the case that they occur **Hypothesis:** Sitagliptin, through its effects on sensitizing α-cell sensitivity to glucose, can initiate counter-regulatory glucagon responses at higher glycemic thresholds, thus reducing the number of clinically apparent hypoglycemic episodes, and/or ameliorating the severity of hypoglycemic episodes in the case that they should occur. The endpoints have defined such that consequences of this hypothesis can be measured.	
Key Endpoints: **Primary Endpoint(s):** • The difference between sitagliptin and placebo treatment regarding the number of hypoglycaemic episodes characterized by a plasma glucose nadir of ≤ 70 mg/dl (i.e. in *chemical* hypoglycaemic episodes) occurring during the in-house period. **Secondary Endpoints:** • The difference between sitagliptin and placebo treatment regarding the number of any (confirmed or not) symptomatic hypoglycaemic episodes or regarding asymptomatic hypoglycaemia occurring during the in-house period. • The time spent at an interstitial (plasma-calibrated) glucose concentration ≤ 70 mg/dl as determined by CGM. • The concentration of counter-regulatory hormones (first of all, glucagon) at times when plasma glucose is ≤ 70 mg/dl, as well as 30 and 60 min later will be compared between sitagliptin and placebo treatment. • The rise in glucose between the index time point and 30 and 60 min later (taking into account any compensatory oral carbohydrate administration). **Exploratory Endpoints:**	

- the above-mentioned parameters broken down to specific periods of the supervised fast:
  (a) 8 a.m. to 4 p.m. (8 hours following oral glucose, day 1)
  (b) 4 p.m. to 8 a.m. (fasting period of day 1)
  (c) 8 a.m. to 1 p.m. (5 hours following the lipid meal on day 2, release of incretin hormones expected)
  (d) 1 p.m. to 4 p.m. (period following exercise on day 2)
  (e) 4 p.m. to 8 a.m. (fasting period day 2)
  (f) 8 a.m. to 1 p.m. (oral glucose and exercise day 3).
- the time spent at an interstitial glucose concentration ≥ 180 mg/dl as determined by CGM ("hyperglycaemia")
- the (relative) difference between sitagliptin and placebo treatment regarding the number of any self-reported hypoglycaemic episodes during the insulin titration period.
- Characterization of the insulin titration algorithm (e.g., number of subjects reaching titration goal, reduction in fasting plasma glucose, duration of titration, number of hypoglycaemic episodes, change in insulin daily dose).
- Comparison of venous and capillary blood glucose values (applicable for venous plasma glucose values < 90 mg/dL as well as for all hypoglycemia-related measurements)

Safety:

- AEs, excluding hypoglycaemic episodes
- Vital signs
- ECG
- Safety laboratory parameters

Key inclusion and key exclusion criteria:

Inclusion:

- Male or female subject with diabetes mellitus type 2.
- Age between 18 and 64 years, both inclusive.
- HbA1c <= 8.5%.
- Stable treatment with insulin glargine (any dose) and metformin (>= 1500 mg/day or at highest tolerated dose) for at least 3 months prior to inclusion into the trial with or without additional oral glucose-lowering agents (except thiazolidinediones).
- Considered generally healthy (apart from diabetes mellitus type 2 and associated conditions such as hypertension, hyperlipidaemia and hyperuricaemia) upon completion of medical history, physical examination, vital signs, ECG and analysis of laboratory safety variables, as judged by the Investigator.

Exclusion:

- Known or suspected hypersensitivity to sitagliptin or related products.
- More than one episode of severe hypoglycaemia with seizure, coma or requiring medical assistance of another person during the past 6 months or hypoglycaemic unawareness as judged by the Investigator.
- Current or previous treatment (less than 3 months prior to screening) with insulin products other than insulin glargine and/or with GLP-1 receptor agonists and/or with thiazolidinediones.
- Unwillingness to wash-off any oral glucose-lowering agents other than metformin.

Sample size:

Twenty (20) subjects are planned to be randomized in the trial.

IMPs:

- Sitagliptin 50 mg coated tablets (Januvia®, Merck Sharp & Dohme Ltd., UK) to be taken orally at a dose of 100 mg/day
- Matching placebo tablets
- Insulin glargine (for in-house days)
- OGT solution

Duration of treatment:
The treatment consists of sitagliptin 100 mg/day or placebo taken together with a morning dose of metformin during two treatment periods. At the end of each treatment period a 54 hour inpatient period is performed. The duration of each treatment period is planned to be between 1 and 16 weeks. At the discretion of the investigator the treatment period may be increased up to a maximum of 24 weeks.

Assessments:
All subjects will undergo outpatient insulin titration (insulin glargine injected at bedtime and metformin will be continued) during each treatment period (either sitagliptin 100 mg/day or matching placebo), aiming at finding the insulin dose that, under these conditions, takes individual fasting plasma glucose to a range of 80-120 mg/dl for at least one week (with at least 4 out of 7 fasting glucose concentrations falling into this range). Once these conditions are met, insulin dose is not changed further, and subjects are invited to an inpatient supervised visit (within the following 7 days) with 54-h monitoring for episodes of hypoglycemia while continuing the same glucose-lowering treatment.
Subjects will be admitted to the investigational site the night before beginning a supervised fast. An indwelling venous cannula will be placed into a distal forearm vein for blood sampling. A standardised dinner will be served at approximately 19:00 h. From 10 hours before starting an oral glucose tolerance test the following morning, only carbohydrate- and calorie-free drinks (mineral water, unsweetened tea) are allowed. Baseline venous plasma glucose (PG) samples will be taken on day 1, shortly before IMP (sitagliptin or matching placebo) administration. At day 1, at approximately 08:00 h, a standard oral glucose load will be administered (75 g OGT, Roche). Subjects will be fasting for 24 hours from then on. In the evening of day 1, the insulin glargine dose will be increased by 10 % (to 110 % of the results of titration) to further increase the risk of hypoglycaemia. On day 2, at approximately 08:00 h, subjects will receive a mixed high lipid meal (to support release of gastro-intestinal peptides like GLP-1 and GIP). Subjects will be fasting for another 24 hours from then on. Approximately 3 hours later (at approximately 11:00 h), subjects will undergo a 30 min bicycle ergometer test at a workload taking them to a pulse > 120/min (approximately 75 Watt to start with, increasing every 5 min until this pulse rate is achieved). In the evening of day 2, the insulin glargine dose will be increased by 20 % (to 120 % of the results of titration) to further increase the risk of hypoglycaemia. On day 3, another oral glucose tolerance test (75 g) will be administered at approximately 08:00 h, with an additional bicycle ergometer test following 3 h later, at the time when reactive hypoglycaemia may be expected following the oral glucose load. On day 3 at approximately 13:00h the experimental procedures are completed and subjects are offered an *ad libitum* lunch before they will be discharged.
Blood samples. Blood will be drawn to characterize the plasma glucose responses to fasting while injecting basal insulin, including the detection of any hypoglycaemic episodes. During the in-house period, when low plasma glucose values are provoked by interventions like exercise or when low plasma glucose values are less likely, samples will be analyzed for glucose, insulin glargine, C-peptide (to detect reductions in insulin secretion in response to low plasma glucose) and counter-regulatory hormones (glucagon, cortisol, growth hormone, epinephrine, norepinephrine, prolactin).
Continuous measurement of interstitial glucose concentrations (CGM). For the full duration of the 3-day experiment (starting early enough to complete calibration before the supervised fast is initiated), glucose will be determined continuously.

Statistical method(s):
The number of hypoglycemic episodes (primary endpoint and secondary endpoints; varying definitions of hypoglycemia) will be compared between sitagliptin and placebo treatment by Fisher's exact test. Time spent at an interstitial glucose concentration will be analyzed by ANOVA, with the experimental condition (sitagliptin vs. placebo), sequence and period as fixed independent variables, subject within sequence as random effect, and the time spent at an interstitial glucose concentration during the 54 h inpatient observation periods as dependent variable.

In case of hypoglycemic episodes, plasma glucose, insulin, C-peptide and counter-regulatory hormones will be analysed at the time point of first detecting symptoms or a low plasma glucose (whatever triggers the detection) and 30 as well as 60 min thereafter, to determine the activity of the counter-regulatory response. Counter-regulatory hormones will be analyzed by ANOVA with the experimental condition (sitagliptin vs. placebo), time point (index time point, 30min and 60 min later) and their interaction, sequence and period as fixed independent variables, subject within sequence as random effect, and the counter-regulatory hormones as dependent variable. The rise in counter-regulatory hormones will be analyzed by ANCOVA with the experimental condition (sitagliptin vs. placebo), time point (30min and 60 min later) and their interaction, sequence and period as fixed independent variables, baseline counter-regulatory hormones (index timepoint) as covariate, subject within sequence as random effect, and the rise in counter-regulatory hormones (change from index timepoint) as dependent variable.

Sample size calculation. It is assumed that the protocol will provoke an average of 2 confirmed episodes of hypoglycaemia per 48 hours with the administration of placebo. A reduction by 30% due to sitagliptin would be of clinical significance. As the relevant information needed for a sample size calculation is not available no formal sample size calculation was performed for the primary objective. The sample size calculation is based on one of the secondary objectives, the comparison of the time spent at an interstitial glucose concentration $\leq$ 70 mg/dL. Assuming a variability of 40% for placebo and sitagliptin in this trial and assuming a 25% reduction in the secondary endpoint with sitagliptin compared to placebo, there will be an approximate 85% power to detect a statistically significance difference ($p<0.05$) with 18 completers. However, due to the uncertain variability 20 patients will be randomised into the study.

2 Schematic Trial Overview

2.1 Chronological Structure of the Trial

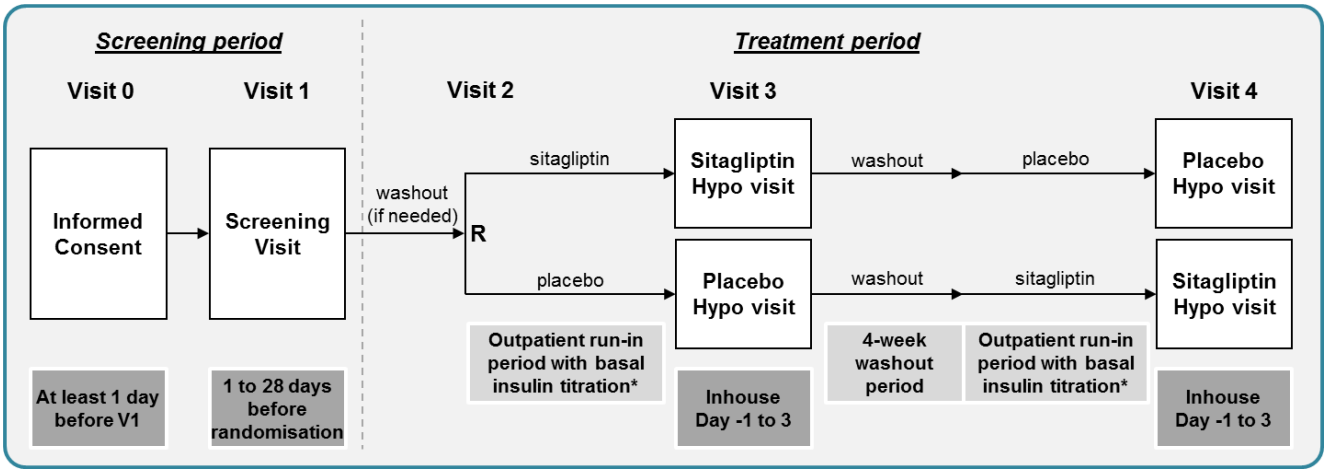

Figure 1 **Schematic overview of the chronological structure of the trial.**
R = Randomisation at V2. Before V2 oral glucose-lowering agents other than metformin (will be continued) and thiazolidinediones (TZDs; subject is excluded) will be washed out for approximately 1 week.
*Duration of the run-in periods will be approximately 1 to 16 weeks. At the discretion of the Investigator the duration of the run-in period may be increased to 24 weeks to achieve target fasting plasma glucose concentrations.
After V3, the subject will wash off IMP (sitagliptin or matching placebo) and resume their pre-trial insulin dose and OAD therapy. Any additional oral glucose lowering agents will be washed out for approximately 1 week prior to starting the second run-in period.

2.2 Trial Flow Chart

The trial flow chart is the master representation of the trial schedule. In case of (apparent) inconsistencies in the trial protocol the information provided here is the binding one.

Table 1 Trial Flow Chart

Trial Period	**Screening Period**		**Treatment Period**		
Visit no.	**0**	**1**	**2**	**Outpatient**	**3 and 4**
	Informed Consent	**Screening**	**Randomisation**	**Run-in and Insulin titration**	**Inhouse Visits**
Timing	At least 1 day before V1	At least 1 day before V2		1-24 weeks between V2-V3, between V3-V4[1]	Day -1 to 3
In-house Visit					X
Telephone contacts				X	
Informed consent	X	X[2]			
Fasting		X			
Inclusion/exclusion criteria		X	X[3]		
Demographic data		X			
Smoking and alcohol consumption habits		X			
Concomitant illness and medical history		X	X		
Current diabetes therapy		X			
Diagnosis of diabetes		X			
Weight, height, BMI		X			X (weight only)
Waist circumference		X			
Alcohol breath test		X			X
Physical examination		X			X
Vital signs		X			X
12-lead ECG		X			X
Haematology		X			X
Biochemistry		X			X
Coagulation		X			
Urinalysis		X			
Infectious serology		X			
HbA1c		X			
Fasting plasma glucose[4]		X		X	X
Pregnancy test (females only)[5]		X			X
FSH test (females only)[5]		X			
Drug screen		X			
Handout diary and glucometer		X[8]	X[8]		X[6]
Washout of OADs			X[7]	X[7]	
Randomisation			X		
Handout IMP			X		X (V3 only)

Trial Period	**Screening Period**		**Treatment Period**		
Visit no.	**0**	**1**	**2**	**Outpatient**	**3 and 4**
	Informed Consent	**Screening**	**Randomisation**	**Run-in and Insulin titration**	**Inhouse Visits**
Timing	At least 1 day before V1	At least 1 day before V2		1-24 weeks between V2-V3, between V3-V4[1]	Day -1 to 3
In-house Visit					X
Telephone contacts				X	
IMP administration				X	X
Insulin glargine titration				X	
Check of diary (also by telephone)				X	X
Inhouse visit exclusion and withdrawal criteria					X
CGM					X
Standardised food intake					X
Exercise bouts					X
Blood sampling for glucose					X
Blood sampling for insulin, C-peptide, glucagon and other counter-regulatory hormones					X
Adverse events				X	X
Concomitant medication		X	X	X	X

[1] The run-in and insulin titration period between V3 and V4 is preceded by a minimum 4-week washout period starting after V3 (see Figure 1)
[2] Check that informed consent has been signed and dated
[3] Confirm subject eligibility
[4] At V1, V3 and V4 fasting plasma glucose will be measured with a laboratory method at the trial site. During the outpatient periods, subjects will use a glucometer for self-monitoring of plasma glucose.
[5] Pregnancy test / FSH test in women will be performed according to Section 8.8.2
[6] At V3 a diary for the second run-in period will be provided
[7] OADs in addition to metformin need to washed out for approximately 1 week before V2 (start of first insulin titration period) and before starting the second insulin titration period.
8 If a washout of OADs is necessary, subjects will receive the glucometer and diary at the screening visit. After eligibility is confirmed subjetcts will be called to start with the washout period. If subjects do not need to washout medication, diary and glucometer will be handed out at visit 2.

2.3 Assessment Schedules

The figure and table below give a detailed overview of the timing of assessments performed at Visits 3 and 4.

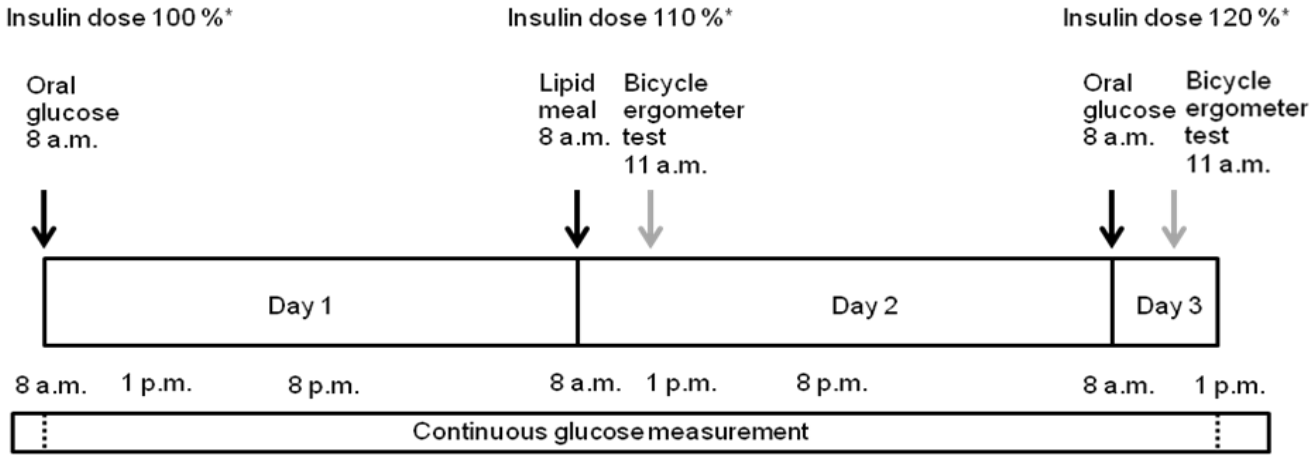

Figure 2 **Schematical representation of the assessment schedule.** All times are approximate. Sampling of plasma glucose, insulin, C-peptide, glucagon and other counter-regulatory hormones will be performed according to table 2.

*: relative to the results of outpatient titration

Table 2 Assessment Schedule for Visits 3 and 4

Approx. hour (hh:mm)[1]	Nominal timing[1]	Activity	Plasma glucose, insulin, C-peptide, glucagon and other counter-regulatory hormones[2]	Other
18:00	**Day -1**	Subject arrives at the trial site – check of inhouse visit exclusion and withdrawal criteria.		Vital signs, weight, alcohol breath test, pregnancy test, ECG, physical exam[3]
18:15		Insert and initiate CGM sensor	X (CGM calibration)	
19:00		Subject is served a standardised meal		
		Insulin glargine dose administration – dose is 100% relative to the outpatient titrated dose		
22:00	-10 h	START 10-hour overnight fasting period		
07:50	**Day 1** -10 min		X	
07:55	-5 min		X	
08:00	0 min	START oral glucose load (75g) followed by START 24-hour fasting period Metformin intake IMP intake		
09:00	1 h		X	
10:00	2 h		X	
11:00	3 h		X	
12:00	4 h		X	
13:00	5 h		X	
16:00	8 h		X	
20:00	12 h		X	
		Insulin glargine dose administration – dose is 110% relative to the outpatient titrated dose		
00:00	**Day 2** 16 h		X	
04:00	20 h		X	
07:55	23h 55 min		X	
08:00	24 h	START lipid meal intake followed by START 24-hour fasting period Metformin intake IMP intake		
09:00	25 h		X	
10:00	26 h		X	
11:00	27 h	START exercise activity	X	

Approx. hour (hh:mm)[1]	Nominal timing[1]	Activity	Plasma glucose, insulin, C-peptide, glucagon and other counter-regulatory hormones[2]	Other
11:30	27 h 30 min	STOP exercise activity		
12:00	28 h		X	
13:00	29 h		X	
16:00	32 h		X	
20:00	36 h		X	
		Insulin glargine dose administration – dose is 120% relative to the outpatient titrated dose		
00:00	**Day 3** 40 h		X	
04:00	44 h		X	
07:55	47 h 55 min		X	
08:00	48 h	START oral glucose load (75g) Metformin intake IMP intake		
09:00	49 h		X	
10:00	50 h		X	
11:00	51 h	START exercise activity	X	
11:30	51 h 30 min	STOP exercise activity		
12:00	52 h		X	
13:00	53 h		X	
		Subject is served food of his/her choice and can leave the site at the discretion of the Investigator after a short medical examination		Vital signs, physical exam, ECG, safety lab[4]

[1] All times are approximate and are given as a guidance for the activity schedule only. The time window for all blood sampling is ±5 minutes.

[2] Blood samples for the evaluation of plasma glucose, insulin, C-peptide, glucagon and counter-regulatory hormones are taken (i) at the nominal times indicated; (ii) immediately after a plasma glucose value of ≤ 70 mg/dL has been measured if not already sampled simultaneously (±5 minutes) and 30 and 60 minutes thereafter; (iii) at the time subject reports symptoms of hypoglycaemia and 30 and 60 minutes thereafter if the measured plasma glucose value is ≤ 90 mg/dL.

[3] Before meal

[4]Before discharge

3 Introduction

In some clinical trials examining the effect of DPP-4 inhibitors used as additional therapy together with long-acting insulin preparations like insulin glargine, the DPP-4 inhibitor led to an improvement in HbA_{1c} without increasing the risk for hypoglycaemic episodes (1-4). In some studies, the risk for hypoglycaemic episodes was even lowered by the use of a DPP-4 inhibitor (1, 2). Since DPP-4 inhibitors are thought to act through stimulating GLP-1, which leads to a suppression of glucagon from pancreatic endocrine α-cells (5), a potential α-cell sensitization to changes in ambient glycaemia has been hypothesized, leading to better suppression of glucagon secretion in the case of hyperglycaemia, but on the other hand an augmented counter-regulatory glucagon response in the case of hypoglycaemia (6, 7). This could prevent hypoglycaemia altogether by initiating counter-regulation early enough to avoid low plasma glucose, or it could lead to improved and more rapid recovery from hypoglycaemic episodes, producing less symptoms with milder reductions in plasma glucose concentrations. Clinically, this may result in episodes of relatively low plasma glucose that are not even noticed as hypoglycaemia. This hypothesis is based on experimental results which rely on the hyperinsulinaemic, hypoglycaemic clamp technique (8, 9), which – in a highly artificial manner – uses relatively high doses of intravenous insulin to drive a fall in plasma glucose, while at the same time controlling the reduction in glucose concentrations by intravenously infusing glucose guided by repeated measurements of plasma glucose. High insulin concentrations (as used under these circumstances) alone may have the potential to alter counter-regulatory responses (10). Certainly, the conditions of hyperinsulinaemic, hypoglycaemic clamps do not entirely reflect those of hypoglycaemic episodes in subjects with type 2 diabetes treated with basal insulin plus oral glucose-lowering agents (11-13). Here, it can be expected that hypoglycaemia is not due to excessive insulin concentrations, but rather to slight imbalances between insulin levels and requirements, as a consequence of variances in insulin absorption from day to day, for example. The risk of hypoglycaemia in real life will be highest during periods of fasting and during vulnerable periods following meals, when reactive hypoglycaemia is most likely to occur approximately 3-5 h after nutrient ingestion.

3.1 Background Information on Investigational Medicinal Product (IMP) Sitagliptin

The information below is included in the European public assessment report (EPAR) for sitagliptin (Januvia®). The full EPAR for Januvia can be found on the European Medicine Agency (EMA) website: www.http://www.ema.europa.eu/ema/. Please refer to this document, including the Summary of product characteristics (SmPC, Annex 1 of the EPAR) for further details.

3.1.1 Description

- Januvia® is an approved drug for the treatment of type 2 diabetes in adults and contains sitagliptin phosphate monohydrate as active ingredient.

- Januvia® is a member of a class of oral anti-hyperglycaemic agents called dipeptidyl peptidase 4 (DPP-4) inhibitors. The improvement in glycaemic control observed with this medicinal product may be mediated by enhancing the levels of active incretin hormones. Incretin hormones, including glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), are released by the intestine throughout the day, and levels are increased in response to a meal. The incretins are part of an endogenous system involved in the physiologic regulation of glucose homeostasis. When blood glucose concentrations are normal or elevated, GLP-1 and GIP increase insulin synthesis and release from pancreatic beta cells by intracellular signaling pathways involving cyclic AMP.

- Treatment with GLP-1 or with DPP-4 inhibitors in animal models of type 2 diabetes has been demonstrated to improve beta cell responsiveness to glucose and stimulate insulin biosynthesis and release. With higher insulin levels, tissue glucose uptake is enhanced. In addition, GLP-1 lowers glucagon secretion from pancreatic alpha cells. Decreased glucagon concentrations, along with higher insulin levels, lead to reduced hepatic glucose production, resulting in a decrease in blood glucose levels. The effects of GLP-1 and GIP are glucose-dependent such that when blood glucose concentrations are low, stimulation of insulin release and suppression of glucagon secretion by GLP-1 are not observed. For both GLP-1 and GIP, stimulation of insulin release is enhanced as glucose rises above normal concentrations. Further, GLP-1 does not impair the normal glucagon response to hypoglycaemia. The activity of GLP-1 and GIP is limited by the DPP-4 enzyme, which rapidly hydrolyzes the incretin hormones to produce inactive products. Sitagliptin prevents the hydrolysis of incretin hormones by DPP-4, thereby increasing plasma concentrations of the active forms of GLP-1 and GIP. By enhancing active incretin levels, sitagliptin increases insulin release and decreases glucagon levels in a glucose-dependent manner.

- In patients with type 2 diabetes with hyperglycaemia, these changes in insulin and glucagon levels lead to lower haemoglobin A1c (HbA1c) and lower fasting and postprandial glucose concentrations. The glucose-dependent mechanism of sitagliptin is distinct from the mechanism of sulphonylureas, which increase insulin secretion even when glucose levels are low and can lead to hypoglycaemia in patients with type 2 diabetes and in normal subjects. Sitagliptin is a potent and highly selective inhibitor of the enzyme DPP-4 and does not inhibit the closely-related enzymes DPP-8 or DPP-9 at therapeutic concentrations. In a two-day study in healthy subjects, sitagliptin alone increased active GLP-1 concentrations,

whereas metformin alone increased active and total GLP-1 concentrations to similar extents. Co-administration of sitagliptin and metformin had an additive effect on active GLP-1 concentrations. Sitagliptin, but not metformin, increased active GIP concentrations.

- Januvia® is approved as monotherapy and in combination therapy, including as add-on to insulin therapy (with or without metformin).

3.1.2 Non-clinical Findings

- In vitro studies performed suggest that the risk for clinically meaningful interactions by co-administered medicinal products is low.

- Renal and liver toxicity were observed in rodents at systemic exposure values 58 times the human exposure level, while the no-effect level was found at 19 times the human exposure level. Incisor teeth abnormalities were observed in rats at exposure levels 67 times the clinical exposure level; the no-effect level for this finding was 58-fold based on the 14-week rat study. The relevance of these findings for humans is unknown. Transient treatment-related physical signs, some of which suggest neural toxicity, such as open-mouth breathing, salivation, white foamy emesis, ataxia, trembling, decreased activity, and/or hunched posture were observed in dogs at exposure levels approximately 23 times the clinical exposure level. In addition, very slight to slight skeletal muscle degeneration was also observed histologically at doses resulting in systemic exposure levels of approximately 23 times the human exposure level. A no-effect level for these findings was found at an exposure 6-fold the clinical exposure level. Sitagliptin has not been demonstrated to be genotoxic in preclinical studies. Sitagliptin was not carcinogenic in mice. In rats, there was an increased incidence of hepatic adenomas and carcinomas at systemic exposure levels 58 times the human exposure level. Since hepatotoxicity has been shown to correlate with induction of hepatic neoplasia in rats, this increased incidence of hepatic tumours in rats was likely secondary to chronic hepatic toxicity at this high dose. Because of the high safety margin (19-fold at this no-effect level), these neoplastic changes are not considered relevant for the situation in humans. No adverse effects upon fertility were observed in male and female rats given sitagliptin prior to and throughout mating. In a pre-/postnatal development study performed in rats sitagliptin showed no adverse effects. Reproductive toxicity studies showed a slight treatment-related increased incidence of foetal rib malformations (absent, hypoplastic and wavy ribs) in the offspring of rats at systemic exposure levels more than 29 times the human exposure levels. Maternal toxicity was seen in rabbits at more than 29 times the human exposure levels. Because of the high safety margins, these findings do not suggest a relevant risk for human reproduction. Sitagliptin is secreted in considerable amounts into the milk of lactating rats (milk/plasma ratio: 4:1).

3.1.3 Clinical Findings

- A 24-week placebo-controlled study was designed to evaluate the efficacy and safety of sitagliptin (100 mg once daily) added to insulin (at a stable dose for at least 10 weeks) with or without metformin (at least 1,500 mg). In patients taking pre-mixed insulin, the mean daily dose was 70.9 U/day. In patients taking non-pre-mixed (intermediate/long-acting) insulin, the mean daily dose was 44.3 U/day. The addition of sitagliptin to insulin provided significant improvements in glycaemic parameters. There was no meaningful change from baseline in body weight in either group.

- A 24-week placebo-controlled study involving 660 patients was designed to evaluate the insulin-sparing efficacy and safety of sitagliptin (100 mg once daily) added to insulin glargine with or without metformin (at least 1,500 mg) during intensification of insulin therapy. Baseline HbA1c was 8.74 % and baseline insulin dose was 37 IU/day. Patients were instructed to titrate their insulin glargine dose based on fingerstick fasting glucose values. At Week 24, the increase in daily insulin dose was 19 IU/day in patients treated with sitagliptin and 24 IU/day in patients treated with placebo. The reduction in HbA1c in patients treated with sitagliptin and insulin (with or without metformin) was -1.31 % compared to -0.87 % in patients treated with placebo and insulin (with or without metformin), a difference of -0.45 % [95 % CI: -0.60, -0.29]. The incidence of hypoglycaemia was 25.2 % in patients treated with sitagliptin and insulin (with or without metformin) and 36.8 % in patients treated with placebo and insulin (with or without metformin). The difference was mainly due to a higher percentage of patients in the placebo group experiencing 3 or more episodes of hypoglycaemia (9.4 vs. 19.1 %). There was no difference in the incidence of severe hypoglycaemia.

3.2 Rationale for the Trial

It is hypothesized that sitagliptin, through its effects on sensitizing α-cell sensitivity to glucose, can initiate counter-regulatory glucagon responses at higher glycemic thresholds, thus reducing the number of clinically apparent hypoglycemic episodes, and/or ameliorating the severity of hypoglycemic episodes in the case that they should occur. This trial is designed such that consequences of this hypothesis can be measured and this important research question can be answered.

4 Objectives and Endpoints

The hypothesis tested in this trial is that sitagliptin reduces the number of hypoglycaemic episodes in patients with type 2 diabetes treated to target with basal insulin glargine and metformin, when measures are taken to increase the risk for such episodes (fasting, increases in insulin dosage, lipid load to increase incretin hormone release, exercise). The hypothesis that sitagliptin improves recovery from such episodes will also be examined.

4.1 Objectives

Key objectives:

It is the purpose of the present trial to test the influence of DPP-4 inhibition (comparing sitagliptin 100 mg per day versus placebo in a cross-over design) on:
(a) the risk to develop hypoglycemia and on
(b) hormonal responses and recovery from hypoglycemia in the case that they occur.

4.2 Endpoints

Primary endpoint:

The difference between sitagliptin and placebo treatment regarding the number of hypoglycaemic episodes characterized by a plasma glucose nadir of ≤ 70 mg/dl (i.e. in *chemical* hypoglycaemic episodes) occurring during the in-house period.

Secondary endpoints:

- The difference between sitagliptin and placebo treatment regarding the number of any (confirmed or not) symptomatic hypoglycaemic episodes or regarding asymptomatic hypoglycaemia occurring during the in-house period.
- The time spent at an interstitial (plasma-calibrated) glucose concentration ≤ 70 mg/dl as determined by CGM.
- The concentration of counter-regulatory hormones (first of all, glucagon) at times when plasma glucose is ≤ 70 mg/dl, as well as 30 and 60 min later will be compared between sitagliptin and placebo treatment.
- The rise in glucose between the index time point and 30 and 60 min later (taking into account any compensatory oral carbohydrate administration).

Exploratory endpoint(s):

- the above-mentioned parameters broken down to specific periods of the supervised fast:

(a) 8 a.m. to 4 p.m. (8 hours following oral glucose, day 1)
(b) 4 p.m. to 8 a.m. (fasting period of day 1)
(c) 8 a.m. to 1 p.m. (5 hours following the lipid meal on day 2, release of incretin hormones expected)
(d) 1 p.m. to 4 p.m. (period following exercise on day 2)
(e) 4 p.m. to 8 a.m. (fasting period day 2)
(f) 8 a.m. to 1 p.m. (oral glucose and exercise day 3).

- the time spent at an interstitial glucose concentration ≥ 180 mg/dl as determined by CGM ("hyperglycaemia")
- the (relative) difference between sitagliptin and placebo treatment regarding the number of any self-reported hypoglycaemic episodes during the insulin titration period.
- Characterization of the insulin titration algorithm (e.g., number of subjects reaching titration goal, reduction in fasting plasma glucose, duration of titration, number of hypoglycaemic episodes, change in insulin daily dose).
- Comparison of venous and capillary blood glucose values (applicable for venous plasma glucose values < 90 mg/dL as well as for all hypoglycemia-related measurements)

Safety endpoints:

- AEs, excluding hypoglycaemic episodes
- Vital signs
- ECG
- Safety laboratory parameters

5 Trial Design

5.1 Type of Trial

This is a postmarketing phase 2 trial. The trial is designed as single centre, randomised, double blind, two-way treatment, placebo controlled crossover trial in subjects with type 2 diabetes mellitus treated to fasting plasma glucose targets with insulin glargine and metformin.

A schematic trial overview is given in Section 2, **Figure 1**.

5.2 Randomisation

This is a randomised trial. Assignment of treatment sequence will take place at the trial site. There will be two randomisation groups.

The randomisation list will be provided by Profil. A subject will only be randomised if he/she complies with all inclusion/exclusion and inhouse visit exclusion criteria. Randomisation should occur as close as possible to the first administration of IMP. When a subject is randomised in the trial, he/she must always be assigned to the lowest available randomisation number available from the randomisation list. Twenty (20) subjects are planned to be randomised in this trial. The drop-out rate is expected to be 20% or less. Replacement of drop-outs will be performed at the discretion of the sponsor.

Randomisation numbers will be as follows:

- Randomisation numbers starting with 101, 102, 103…
- Corresponding randomisation numbers for replacements: 201, 202, 203…

Replacement subjects must always be assigned to the same sequence as the subject they replace (please see Section 6.6).

5.3 Blinding and Code Breaking Procedures

This is a double-blind randomised trial. Except for the unblinded persons involved in the preparation of the IMP (these persons are not involved in any other trial activities), everyone involved in the trial will be blinded until completion of the trial and the final data review.

Treatment assignment will be kept strictly confidential and accessible only to authorised persons until documented un-blinding. Sealed codes with treatment assignment will, however, be readily available to the blinded personnel in case of an emergency.

One set of sealed codes with the subject randomisation number containing information about the treatment at each visit will be prepared for each subject. The set will be kept at the trial site in the office of the physician on duty (during the entire trial period) and is to be used in case of code break need.

The code for a particular subject may be broken in a medical emergency if knowing the identity of the treatment allocation would influence the treatment of the subject. Whenever a code is broken, the person breaking the code must record the time, date and reason as well as his/her initials in the source documents and on the code envelope. The breaking of blinded codes in case of medical emergency for one subject should not unblind the trial personnel to the treatment information of other subjects. The person performing the unblinding should inform as few people as possible about the result of the unblinding. All persons unblinded for a specific subject should be documented.

If the trial site needs to break the code, the medical monitor should, if possible, be contacted prior to breaking the code. In all cases, the medical monitor and trial monitor must be notified within 24 hours after the code has been broken.

All codes (whether broken or not) must be kept throughout the trial period. The codes kept at the trial site will be checked by the monitor and the close-out visit report should confirm adequate documentation of any code breaks (if applicable).

5.4 Treatment of Subjects

This is an experimental trial in which each subject will receive anti-diabetes medication at doses and routes approved for the treatment of their disease. Before starting treatment with IMP and basal insulin titration, subjects who are taking oral glucose lowering agents other than metformin will need to wash-out the additional medication for approximately 1 week. During two treatment periods, all subjects will undergo outpatient insulin titration (insulin glargine injected at bedtime and metformin will be continued). The IMP (sitagliptin/placebo) will be administered once daily together with a morning dose of metformin during or immediately after food intake in the morning The run-in insulin titration period aims at finding the insulin dose that, under these conditions, takes individual fasting plasma glucose to a range of 80-120 mg/dL for at least one week (with at least 4 out of 7 fasting glucose concentrations falling into this range). Once these conditions are met, insulin dose is not changed further, and subjects are invited to an inpatient supervised visit (within the following 7 days) during which insulin glargine, metformin and sitagliptin/placebo treatment is

continued. The insulin glargine dose will be increased by 10 % (to 110 % of the titration dose) in the evening of Day 1 and increased by 20% (to 120 % of the titration dose) in the evening of Day 2.

After the first treatment period, subjects will be asked to resume their pre-trial insulin dose and OAD therapy. IMP will be washed off for 4 weeks before starting the second treatment and run-in period. Subjects taking oral glucose lowering agents other than metformin will need to wash off the additional medication for approximately 1 week before starting the second treatment and run-in period.

5.5 Duration

Planned date for FSFV: 11-2017

Planned date for LSLV: 05-2019

The end of the clinical trial is defined as LSLV.

Actual time-lines may vary.

The total trial duration for a subject will be about 7 to 53 weeks.

5.6 Stopping Rules

No specific stopping rules in addition to section 6.5 and 14.4 are applicable for this trial.

5.7 Rationale for the Trial Design and Treatment

A crossover design is chosen in order to reduce variability and increase the power as each subject acts as its own control. The total number of subjects needed with a crossover design is decreased as compared to a parallel group design.

Randomisation and blinding is used in order to avoid bias introduced through an association between allocation order of IMP and subject characteristics.

A dose of sitagliptin 100 mg/day was chosen as a dose within the clinically relevant range for the treatment of diabetes mellitus type 2. The insulin glargine dose is individually titrated to a fasting plasma glucose target level of 80 – 120 mg/dL and increased at the inpatient visits under medical supervision to increase the risk of hypoglycaemic episodes at the inhouse visits.

A minimum 4-week wash-out period between Visit 3 and Visit 4 is introduced to ensure a sufficient wash-out period from previous sitagliptin dosing to avoid any carry-over effect.

6 Trial Population

6.1 Number of Subjects to be Studied

Planned number of subjects to be screened: 48

Planned number of subjects to be randomised: 20 (dropout rate of 20% or less)

6.2 Inclusion Criteria

1. Signed and dated informed consent obtained before any trial-related activities. (Trial-related activities are any procedures that would not have been performed during normal management of the subject).
2. Male or female subject with diabetes mellitus type 2.
3. Age between 18 and 64 years, both inclusive.
4. HbA1c <= 8.5%.
5. Total insulin dose of < 1.2 U/kg/day.
6. Diabetes duration of at least 12 months.
7. Stable treatment with insulin glargine (any dose) and metformin (>= 1500 mg/day or at highest tolerated dose) for at least 3 months prior to inclusion into the trial with or without additional oral glucose-lowering agents (except thiazolidinediones).
8. Considered generally healthy (apart from diabetes mellitus type 2 and associated conditions such as hypertension, hyperlipidaemia and hyperuricaemia) upon completion of medical history, physical examination, vital signs, ECG and analysis of laboratory safety variables, as judged by the Investigator.

6.3 Exclusion Criteria

1. Known or suspected hypersensitivity to sitagliptin or related products.
2. Previous participation in this trial. Participation is defined as randomised.
3. Receipt of any medicinal product in clinical development within 30 days before randomisation in this trial.
4. History of multiple and/or severe allergies to drugs or foods or a history of severe anaphylactic reaction.

5. Any history or presence of clinically relevant cardiovascular, pulmonary, respiratory, gastrointestinal, hepatic, renal, metabolic, endocrinological (with the exception of conditions associated with diabetes mellitus), haematological, dermatological, neurological, osteomuscular, articular, psychiatric, systemic, ocular, gynaecologic (if female), or infectious disease, or signs of acute illness as judged by the Investigator.
6. Any serious systemic infectious disease during four weeks prior to screening, as judged by the Investigator.
7. Proliferative retinopathy or maculopathy, based on a recent (< 1.5years) ophthalmologic examination and/or severe neuropathy, in particular autonomic neuropathy, as judged by the Investigator.
8. More than one episode of severe hypoglycaemia with seizure, coma or requiring medical assistance of another person during the past 6 months or hypoglycaemic unawareness as judged by the Investigator.
9. Current or previous treatment (less than 3 months prior to screening) with insulin products other than insulin glargine and/or with GLP-1 receptor agonists and/or with thiazolidinediones.
10. Unwillingness to wash-off any oral glucose-lowering agents other than metformin.
11. Significant history of alcoholism or drug abuse as judged by the Investigator or consuming more than 24 grams of alcohol per day for male subjects or 12 grams per day (on average) for female subjects.
12. A positive result in the alcohol and/or urine drug screen at the screening visit.
13. Subject who is not able or willing to refrain from smoking and use of nicotine substitute products during the inpatient period.
14. Positive to the screening test for Hepatitis Bs antigen or Hepatitis C antibodies and/or a positive result to the test for HIV-1/2 antibodies or HIV-1 antigen.
15. Any medication (prescription and non-prescription drugs) intake planned within 7 days before start of IMP administration period that is known to influence BG levels or insulin secretion at the discretion of the investigator. Stable dose therapy with blood pressure lowering medication, thyroid hormones, cholesterol-lowering or uricostatic drugs will be allowed.
16. Blood donation or blood loss of more than 500 mL within the 3 months prior to screening.
17. Mental incapacity, unwillingness or language barriers precluding adequate understanding or co-operation.
18. Females of childbearing potential who are pregnant, breast-feeding or intend to become pregnant or are not using highly effective contraceptive methods (highly effective contraceptive

methods are considered those with a failure rate less than 1% undesired pregnancies per year including surgical sterilisation, hormonal intrauterine devices (coil), oral hormonal contraceptives, sexual abstinence or a surgically sterilised partner). Sexual abstinence is considered as a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of the study. The reliability of sexual abstinence needs to be evaluted in relation to the preferred and usual lifestyle of the subject.

Females who are postmenopausal can participate in the study without using adequate contraceptive methods. Postmenopausal is defined as women aged <52 years and being amenorrheic for more than one year with serum FSH level > 40 IU/L or aged >= 52 years and being amenorrheic for less than one year and with serum FSH level > 40 IU/L or aged >=52 years being amenorrheic for more than one year.

6.4 Inhouse visit Exclusion Criteria

Subjects who fulfil one or more of the inhouse visit exclusion criteria (see below) will be excluded from participation in the inhouse Visits 3 or 4. The inhouse visit may be rescheduled at the discretion of the Investigator.

1. Consumption of alcohol within the last 24 hours prior to admission or a positive result of the breath alcohol test.

2. Strenuous exercise within the last 48 hours prior to admission.

3. Any medical condition or AE that could interfere with glucose metabolism, as judged by the Investigator.

4. Any use of prescription or non-prescription medication according to exclusion criterion no. 15.

6.5 Withdrawal Criteria

1. Subjects have the right to withdraw from the trial at any time for any reason.

2. The subject may be withdrawn from the trial at the discretion of the Investigator if judged non-compliant with trial procedures or due to a safety concern.

3. If a protocol violation or concurrent illness occurs, which, in the clinical judgement of the Investigator, may invalidate the trial by interfering pharmacokinetically or pharmacodynamically with the IMPs, the subject will be withdrawn by the Investigator.

4. Adverse event (AE): Subject reports symptoms, which are considered unacceptable by the subject and/or the Investigator. An AE form will be completed and the subject will be withdrawn from the trial.

5. More than one episode of severe hypoglycaemia with seizure, coma or requiring medical assistance of another person during the treatment period.

6. If a hypersensitivity reaction is suspected, Januvia® should be discontinued.

7. If bullous pemphigoid is suspected, Januvia® should be discontinued.

8. Pregnancy or intention to becoming pregnant.

The date and reason of withdrawal will be entered on the end of trial page of the CRF. The end of trial form will be completed for all prematurely withdrawn subjects.

6.6 Subject Replacement

A total of 20 subjects are planned to be randomised in the trial according to the sample size calculation (see Section 13.1). To account for drop-outs (a drop-out is defined as a subject leaving the trial after randomisation), drop-out subjects may be replaced at the discretion of the sponsor. A replacement subject will be assigned to the same treatment sequence as the subject being replaced.

6.7 Rationale for Trial Population

Sitagliptin is an approved glucose lowering agent for adult patients with type 2 diabetes. This trial is therefore performed in adult patients with type 2 diabetes.

Subjects with a background therapy of metformin and insulin glargine will be recruited to test the hypothesis that additional therapy with sitagliptin may improve the risk to develop hypoglyacemia in this patient population. Treatment with additional oral glucose lowering agents (except TZDs will be allowed to facilitate recruitment, but any oral diabetes therapy other than metformin and IMP should be discontinued throughout the entire trial duration to ensure the same background therapy in all participants.

Since insulin glargine doses will be titrated to target as part of the protocol, baseline HbA1c of subjects may range from well-controlled to moderately controlled (8.5 %). For each subject, its daily metformin dose should be at least 1500 mg/day or at its highest tolerated dose level to ensure a homogeneously treated trial population.

Both male and female subjects will be allowed to participate in the trial, but pregnant females or females who intend to become pregnant are not allowed to participate in the trial due to the risks associated with the induction of hypoglycaemic episodes.

7 Trial Materials

7.1 Investigational Medicinal Products (IMPs)

The IMPs listed in Table 3 will be used in this trial:

IMPs	Kind of IMP	Strength	Pharmaceutical dosage form	Dose per administration	Route of administration
Januvia® (sitagliptin)	IMP to be tested	50 mg	Film-coated tablet	2 tablets (100 mg)	oral
Matching placebo	IMP for comparison	-	Film-coated tablet	2 tablets	oral
Lantus® (insulin glargine)	Challenging agent	100 U/mL	Solution for injection	-	subcutaneous injection
OGT solution (glucose)	Challenging agent	75 g glucose/~300 mL	Liquid solution	75 g glucose	oral

Table 3: Specification of Investigational medicinal products (IMPs) used in the trial

Manufacturer of sitagliptin and matching placebo tablets is MSD and will be provided by MSD. Sitagliptin and matching placebo are referred to as "IMP" in this document if not stated otherwise.

Sitagliptin (Januvia® 50mg) received market authorisation in the EU in 2007 for the control of blood glucose levels in patients with type 2 diabetes.

For further information please refer to the SmPC for Januvia® 50 mg.

On in-house days Lantus® (insulin glargine) will be used as a challenging agent to provoke hypoglycaemic episodes. For this purpose it will be sourced from the German market and will be used from its original packaging (Lantus 100 U/mL Solostar ready-to-use pen). On outpatient days subjects will use their own insulin glargine. Here, insulin glargine is not used as challenging agent and consequently not regarded as IMP.

The OGT in this trial is performed to provoke reactive hypoglycemia. Therefore, the glucose solution is defined as challenging agent. The OGT solution will be sourced from the German market (manufacturer: Roche) and will be used from its original packaging.

Metformin may be provided by the investigational site as non-investigational medicinal product (NIMP) to those patients who have to discontinue their usual metformin combination product to washout any other oral glucose lowering agent. NIMP will be sourced from the German market and will be used from its original packaging.

7.2 Packaging and Labelling of Investigational Medicinal Product (sitagliptin and placebo)

IMP (sitagliptin and matching placebo) is provided by MSD in blinded dosing bottles.

Enough investigational medicinal products will be packed for the scheduled number of subjects. A buffer volume of IMPs will be provided in case of replacement of withdrawn subjects or damaged IMPs.

7.2.1 Storage and Drug Accountability of Investigational Medicinal Product

All IMPs will be stored and handled in accordance with the manufacturer instructions.

All used, partly used and unused IMP/packaging must be kept by the Investigator in an access-controlled room.

For the IMP, the Investigator must keep an accurate record of all IMPs received and the products used for each subject in a Drug Accountability Record. Storage locations, batch numbers and expiry dates are also documented in this form.

The drug accountability has to be performed in a timely manner.

7.2.2 Dispensing of Investigational Medicinal Product(s)

No IMPs may be dispensed to any person not enrolled in the trial.

Any dispensing of IMP to an individual subject and return of IMP will be documented by the Investigator.

Upon completion of the trial, the Sponsor will be responsible for destruction of IMP (used, partially used or unused) and destruction must be documented in the trial investigator file (TIF).

7.3 Retention Samples

No retention samples will be kept for this trial.

7.4 Preparation and Application of IMP (sitagliptin and placebo)

IMP (sitagliptin and matching placebo) is provided in dosing bottles. Two IMP tablets from the dosing bottle are to be taken daily together with the morning metformin dose.

8 Visits and Assessments

8.1 Visit Procedures

Please refer to the information given in Section 2 for a general overview of the trial visits and the visit assessments and procedures. The following sections describe details of the visit assessments and procedures.

The Investigator must keep a subject screening and identification log.

8.2 Visit 0 – Informed Consent Visit

Prior to any trial-related activities, potential subjects will be provided with oral and written information about the trial course, the employed IMPs and the visit procedures. The subjects will be fully informed of their responsibilities and their rights while participating in the trial as well as of the possible risks and potential benefits of participation in the trial. They have the opportunity to discuss all open questions and will have ample time to consider participation. Subjects who wish to participate in the trial will be asked to personally date and sign an informed consent form prior to any trial-related activities. Trial-related activities are any procedures that would not have been performed during normal management of the subject (including e.g. fasting for screening). Likewise, the Investigator must also personally date and sign the informed consent form prior to any trial related activities. All subjects will be provided with a copy of their own signed and dated informed consent form.

8.3 Visit 1 – Screening Visit

A rescheduling of the screening visit (within 1–7 days) is allowed once in case subjects have failed to be fasting.

Subjects will receive a screening number in ascending order starting with 001.

Screened subjects who do not meet or comply with all inclusion and exclusion criteria are excluded (screening failures), and their data will be recorded on a screening failure form. The reason for exclusion must be recorded on the screening failure form. Detailed information about which data will be entered into the trial database will be described in the trial specific data management plan.

Re-screening of screening failures is generally not allowed according to Profil's SOPs. Re-assessment of laboratory parameters will be allowed once if handling issues, damaged samples, or haemolysed samples may have confounded the measurement results.

Eligible or potentially eligible subjects (lab results pending) will be provided with a Subject Identification Card (ID card), stating that the subject is participating in the trial and whom to contact (site address, Investigator name and telephone number). The subjects should be instructed to return the ID card to the Investigator at the last visit or to destroy the card after the last visit.

If a washout of OADs is necessary, subjects will receive the glucometer, test strips and a diary to record amongst others daily fasting plasma glucose self-measurements during the washout before the randomisation visit.

Before leaving the site, subjects are offered a breakfast.

8.4 Visit 2 – Randomisation Visit

Results from the screening visit (including laboratory safety parameters) must be available before subjects can be invited to return to the trial site for the randomisation visit and assessed to be acceptable by the Investigator. These results must be verified by the signing and dating of test results by the Investigator. The Investigator should document if out of range results are clinically significant.

Subjects taking oral anti-diabetes medication other than metformin will need to washout the additional medication for approximately 1 week before the randomisation visit.

After the eligibility for trial participation has been confirmed, subjects will be randomised to receive first either sitagliptin or placebo (see Section 5.2).

Subjects will be provided with IMP (sitagliptin or matching placebo) for the insulin titration period, a blood glucose meter and test strips (if not already handed out at the screening visit), as well as a diary (see Section 8.4.1) to record amongst others daily fasting plasma glucose self-measurements during the insulin titration period before the inhouse visit. The correct storage and administration of IMP, the correct usage of the glucometer will be explained and instructions on how to fill out the diary will be given.

The investigator will inform the subject on the starting basal insulin glargine dose for the insulin titration period and how to change their daily basal insulin dose based on the daily fasting plasma glucose levels according to a titration algorithm. Subjects who are used to take their insulin glargine dose in the morning or divided over two doses will be instructed how to change their therapy for evening dosing. Subjects are informed about the symptoms of hypoglycaemia and about appropriate methods to treat hypoglycaemia.

8.4.1 Insulin titration period

Subjects will start an insulin titration period, aiming at finding the basal insulin dose that takes individual fasting plasma glucose to a range of 80-120 mg/dL for at least one week (with at least 4

out of 7 fasting glucose concentrations falling into this range). A guideline for the insulin titration can be found in Appendix 1: Insulin titration guideline. Titration of insulin glargine is planned every 3-4 days based upon the lowest measured plasma glucose value since the last titration step. The trial physician may change the recommend insulin change by this guideline after reviewing the plasma glucose concentrations, any safety concerns from the subject and any other feedback (e.g., narrative from the subject).

Subjects will be asked to record the following information in their diary (all data will be transferred to CRF):

- daily fasting plasma glucose; date, time and value
- daily insulin glargine dose; date and dose
- any change in concomitant medication; start/stop date, description
- adverse events; start/stop date and time, description
- hypoglycaemic episodes; start/stop date and time, glucose value, treatment

Regular telephone calls (e.g. twice weekly) with the subject will be planned during this period to evaluate the recorded fasting plasma glucose levels in the diary and supervise the dose titration. At the discretion of the investigator or at the request of the subject, the subject may visit the trial site for an unscheduled visit for personal review (by a trial physician) and consultation on the subject's insulin titration and/or to receive more IMP (sitagliptin or matching placebo) or NIMP when needed. Once the fasting plasma glucose is in the range of 80-120 mg/dL for 4 out of the last 7 days, the insulin dose is not changed further and subjects are invited to the supervised inhouse visit (within the following 7 days) and are instructed to comply with the dosing day exclusion criteria (Section 6.4). Subjects will be reminded to take all medication (insulin glargine, metformin and IMP) with them to the trial site.

After reaching the above defined glucose range for 4 out of 7 days, subjects will continue with the documentation of fasting plasma glucose values until the inhouse visit takes place. If it is not possible to schedule the inhouse visit within the following 7 days, plasma glucose values have to be reconsidered and the titration period may be extended.

8.5 Visit 3 and 4 – Inhouse visits

Please refer to the assessment schedule in Section 2.3 for the procedures and timing of assessments at the inhouse visits.

Day -1

Patients will be admitted to the trial site in the evening before first dosing (no fasting requirement). After a check of inhouse visit exclusion and withdrawal criteria and the subject diary, eligible subjects will continue with the visit procedures. A CGM sensor will be inserted and initiated. An

indwelling venous cannula placed into a distal forearm vein will be used for frequent blood sampling (plasma glucose, insulin, C-peptide, glucagon and other counter-regulatory hormones (see Table 2); hypoglycemia-related blood sampling will start at Day -1). A standardised dinner will be served (approximately at 19:00 hours) and subjects take their titrated dose of insulin glargine at their usual time in the evening. After 22:00 hours, approximately ten hours before dosing, only carbohydrate-free and calorie-free drinks (e.g., water, unsweetened tea) are allowed.

Day 1

At approximately 08:00 hours, a standard oral glucose load will be administered (75 g OGT, Roche). Subjects will take their daily morning metformin dose together with two tablets of IMP (sitagliptin or placebo, depending on randomisation). Subjects will be fasting for 24 hours from then on. In the evening of Day 1, the insulin glargine dose will be increased by 10% (to 110% of the results of titration) to further increase the risk of hypoglycaemia.

Day 2

On day 2, at approximately 08:00 hours, subjects will receive a mixed high lipid meal (see Appendix 2: Mixed high lipid meal examples) to support release of gastro-intestinal peptides like GLP-1 and GIP. Subjects will take their daily morning metformin dose together with two tablets of IMP (sitagliptin or matching placebo) and be fasting for another period of 24 hours from then on. Approximately 3 hours after the lipid meal, subjects will undergo a 30 min bicycle ergometer test at a workload taking them to a pulse > 120/min (approximately 75 Watt to start with, increasing the workload every 5 min until this pulse rate is achieved). The pulse rate of > 120/min should be kept until the end of the test. In the evening of day 2, the insulin glargine dose will be further increased by 10% (to 120% of the results of titration) to further increase the risk of hypoglycaemia.

Day 3

On day 3, another standard oral glucose load (75 g) will be administered at approximately 08:00 hours. Subjects will take their daily morning metformin dose together with two tablets of IMP. Another bicycle ergometer test, under the same conditions as on Day 2, is performed at approximately 11:00 hours, the time when reactive hypoglycaemia may be expected following the oral glucose load. At approximately 13:00 hours on this day, the sampling period stops and subjects are offered food of their choice. After a short medical examination (vital signs, ECG, physical examination, safety lab), subjects can leave the site at the discretion of the Investigator. The subject may be released from the trial site if the Investigator does not have any safety concerns based on the last safety blood glucose value and the general condition of the subject. However, at the discretion of the Investigator or per request by the subject, the subject may stay at the trial site for a longer period.

Before discharge from the clinic, the subject is provided with a diary for the second titration and treatment period, test strips for the glucose meter (if needed) and IMP (sitagliptin or matching placebo) for the second treatment period.

8.5.1 Washout and insulin titration period

After completion of Visit 3, a minimum 4-week washout period starts. During the washout period, subjects continue taking their daily metformin and insulin glargine dose (at the pre-trial dose level) and should resume their pre-trial oral anti-diabetes medication. Any additional anti-diabetic oral medication has to be discontinued at least one week before the start of the insulin titration period. The insulin titration period will be conducted as described in Section 8.4.1.

8.6 Assessment of Treatment Compliance

Treatment compliance will be checked by comparing the number of dispensed and returned tablets for each subject. Subjects for which treatment compliance is estimated to be less than 50%, will be withdrawn. Inhouse administrations will be supervised and recorded in the CRF.

8.7 Assessments for Pharmacodynamics

8.7.1 Hypoglycaemic episodes

Hypoglycaemia is defined as a:

(a) symptomatic hypoglycaemic episode, symptoms typical for hypoglycaemia are experienced by the subject, irrespective of the plasma glucose concentration;

(b) confirmed symptomatic hypoglycaemic episode, if in addition to the experienced hypoglycaemia symptoms plasma glucose is determined to be ≤ 70 mg/dL;

(c) chemical hypoglycaemic episode, if a plasma glucose ≤ 70 mg/dL is determined, irrespective of the presence of hypoglycaemia symptoms;

(d) asymptomatic episode, if a plasma glucose ≤ 70 mg/dL is measured in the absence of symptoms typical for hypoglycaemia.

One hypoglycaemic episode can be a combination of the above. E.g., if both symptoms and a fasting plasma glucose level ≤ 70 mg/dL are recorded, the hypoglycaemic episode can be defined as (a), (b) and (c). An episode continuously characterized by hypoglycaemia symptoms or plasma glucose levels ≤ 70 mg/dL will be counted as one episode. Newly appearing symptoms after some time (approximately 30 minutes) without symptoms and with plasma glucose levels > 70 mg/dL or

plasma glucose levels ≤ 70 mg/dL after two consecutive measurements > 70 mg/dL will be counted as a new episode.

Each time plasma glucose is ≤ 70 mg/dL, 100 mL juice or dextrose tablets (equivalent to 10 g of rapidly absorbable carbohydrate) will be given by mouth. Repeat plasma glucose measurement will be made in 10 minute intervals until two consecutive measurements are above 70 mg/dL.

During the outpatient period, plasma glucose measurements to confirm hypoglycemia are performed by the subject (SMPG) and recorded in the diary. During the in-house visits, plasma glucose measurements are performed by trained staff on a laboratory analyser (see Section 8.7.2).

The following information should be recorded for each hypoglyceamic episode:

-Start / Stop date and time of episode (symptoms, plasma glucose measurement ≤ 70 mg/dL)
-Plasma glucose value at start of episode and for repeat measurements
-Symptoms (yes / no, if yes, description of all symptoms)
-Treatment (to be ticked for every glucose measurement)

8.7.2 Plasma glucose, Insulin, C-peptide, glucagon and (other) counter-regulatory hormones

Venous blood samples taken for the analysis of glucose concentration will be analysed at the trial site using the Super GL glucose analyzer (Dr Müller Gerätebau GmbH, Freital, Germany). The device can be programmed to measure the plasma glucose content of each sample. In case of venous plasma glucose measurements < 90 mg/dL as well as for all hypoglycemia-related measurements, glucose will be additionally measured in capillary blood (e.g., fingerstick; also analysed with the Super GL). In that case, the capillary measurement value will be used to trigger any subsequent sampling and for analysis of trial related endpoints.

Insulin, C-peptide, glucagon and other counter-regulatory hormone concentrations (cortisol, human growth hormone, adrenaline, noradrenaline, prolactin) will be determined by the PD laboratory.

Blood samples for the evaluation of plasma glucose, insulin, C-peptide, glucagon other counter-regulatory hormones are taken (i) at the times indicated in Table 2; (ii) immediately after a plasma glucose value of ≤ 70 mg/dL has been measured if not already sampled simultaneously and 30 and 60 minutes thereafter; (iii) at the time subject reports symptoms of hypoglycaemia and the measured plasma glucose value is ≤ 90 mg/dL, as well as 30 and 60 minutes thereafter.

8.7.3 Continuous glucose monitoring (CGM)

Subjects will use a CGM system during the inhouse visit to evaluate the time spent at low glucose, target glucose and high glucose ranges. A commercially available sensor system (e.g., Dexcom G5; the same system will be used in all trial subjects) will be inserted and started upon subject arrival on Day -1 of the inhouse visit. The system will be calibrated according to the manufacturing instructions with the exception that plasma glucose values from venous samples may be used. The CGM data will not be blinded and a low sensor glucose alert will be programmed to warn subjects for glucose readings below or equal to 70 mg/dL. Subjects should inform study staff of each alert, as these may trigger an additional laboratory plasma glucose measurement (if this hypoglycemic episode was not detected previously). The sensor will be removed before discharge on Day 3.

8.8 Assessments for Safety

8.8.1 Clinical Assessments

Adverse events

Adverse events (AEs) will be recorded in accordance with the procedures described in Section 9. Any clinically significant worsening since baseline of a previous finding must be reported as an AE.

During each contact with the trial site staff (site visits and telephone contacts) the subject must be asked about changes of their health status. This must be documented in the subject's medical record.

Concomitant illness and medical history

A concomitant illness is any illness that is present prior start of the trial (i.e. prior to randomisation).

Medical history is an account of medical events that the subject has experienced in the past.

- Concomitant illnesses present at the start of the trial will be recorded in the CRF prior to randomisation.
- Relevant medical conditions/illnesses in the past will be recorded in the CRF at screening.

The information collected for concomitant illness and medical history should include diagnosis, date of onset, date of resolution or continuation.

Any change to a concomitant illness should be recorded during the trial, including end date, if applicable. A clinically significant worsening of a concomitant illness must be reported according to Section 9.

Physical examination

An examination of the following body systems will be performed:

- Head, ears, eyes, nose, throat (HEENT), incl. thyroid gland
- Heart, lung, chest
- Abdomen
- Skin and mucosae
- Musculoskeletal system
- Nervous system
- Lymph node
- Other findings

At the screening visit, any abnormality will be recorded and described in the CRF including the Investigator's assessment of clinical significance ('abnormal, not clinically significant' or 'abnormal, clinically significant'). Clinically significant findings at the screening visit should be recorded as concomitant illness.

At subsequent visits, any clinically significant deterioration of a pre-existing condition as well as any new clinically significant findings will be recorded as AEs.

Vital signs

An examination of the following vital signs will be performed:

- Diastolic and systolic blood pressure (mmHg) are measured after at least 5 min rest in a supine position. At the screening visit blood pressure is measured in both arms. The blood pressure from the arm with the higher systolic value is transcribed into the CRF and this arm is used for all subsequent measurements of the subject's blood pressure in this trial.
- Pulse (beats per min) measured after at least 5 min rest in a supine position.
- Body temperature, tympanic (^{o}C).

In addition to the pre-specified assessments in sections 2.2 and 2.3, blood pressure and pulse may be assessed at any time during the trial at the discretion of the Investigator. Additional measurements will not be recorded in the CRF.

Electrocardiogram

A standard 12-lead electrocardiogram (ECG) will be performed.

ECG parameters (Heart rate, PQ, QRS, QT, QTcB) and any abnormality will be recorded and described in the CRF including the Investigator's assessment of clinical significance ('abnormal, not clinically significant' or 'abnormal, clinically significant'). Clinically significant findings at the screening visit should be recorded as concomitant illness.

At subsequent visits, any clinically significant deterioration of a pre-existing condition as well as any new clinically significant findings will be recorded as AEs.

Plasma glucose for safety

During the trial, plasma glucose levels will be monitored at the trial site by a laboratory method (Super GL Glucose Analyzer; Dr. Müller Gerätebau GmbH, Freital, Germany) for pharmacodynamic analysis and safety. At the discretion of the Investigator additional plasma glucose measurements may be made when there is a suspicion of a hypoglycaemic (e.g. triggered by a CGM alert) or hyperglycaemic episode. All plasma glucose measurements will be recorded in the CRF, also if they are not related to a hypoglycaemic episode.

Treatment of hypoglycaemic episodes is described in Section 8.7.1.

8.8.2 Laboratory Assessments

The safety parameters that will be determined at the safety laboratory are listed in Table 4.

The safety laboratory will perform a first check on their values for safety parameters and flag any values outside the reference range. The Investigator must evaluate all results outside the reference range (clinically significant or not clinically significant). Before the Investigator starts the trial (i.e. obtains informed consent from the first subject), the laboratory reference ranges must be available in the Investigator's Trial File. The results provided by the safety laboratory will be part of the trial database.

Table 4 Routine laboratory safety tests

Haematology

Haematocrit
Haemoglobin
Erythrocytes
Mean corpuscular volume (MCV)
Mean corpuscular haemoglobin (MCH)
Mean corpuscular haemoglobin concentration (MCHC)
Thrombocytes (platelets)
Leucocytes
Neutrophile granulocytes (total count and relative)
Lymphocytes (total count and relative)
Monocytes (total count and relative)
Eosinophile granulocytes (total count and relative)
Basophile granulocytes (total count and relative)

Biochemistry

Sodium
Potassium
Calcium
Chloride
Phosphate
Creatinine
Urea
AST (aspartate aminotransferase, GOT)
ALT (alanine aminotransferase, GPT)
Total cholesterol
Low-density lipoprotein (LDL) cholesterol
Uric acid
Total protein
Albumin
Total bilirubin
Creatine kinase*
Alkaline phosphatase
Gamma-glutamyltransferase (γ-GT)
Lactic dehydrogenase (LDH)
High-density lipoprotein (HDL) cholesterol
Triglycerides

Coagulation (screening only)

International normalised ratio (INR)
Activated partial thromboplastin time (APTT)

Urinalysis[#] (screening only)

Protein
Glucose
Erythrocytes
Leucocytes
pH
Ketones

Infectious serology (screening only)

Hepatitis B surface antigen
Hepatitis C antibodies
HIV-1/2 combi

Other

HbA1c (screening only)
serum β-HCG (females only; screening only)
serum FSH (post-menopausal females only; screening only)

[#] In case of specific abnormalities in the urinalysis a urine sediment assessment will be performed.
[*] If CK is outside normal range CKMB will be analysed. If CKMB is elevated, Troponin T will be analysed.

Pregnancy test

For all female participants, a pregnancy test will be performed at the safety laboratory on a blood (serum) sample obtained at the screening visit and at Visits 3 and 4 from a urine sample at the trial site. The pregnancy test will be performed according to local regulation.

For women aged < 52 years and being amenorrheic for more than one year or aged ≥ 52 years and being amenorrheic for less than one year a serum FSH will be performed at the screening visit to confirm the postmenopausal state. Postmenopausal is defined as women aged < 52 years and being amenorrheic for more than one year with serum FSH level > 40 IU/L or aged ≥ 52 years and being amenorrheic for less than one year and with serum FSH level > 40 IU/L or aged ≥ 52 years being amenorrheic for more than one year.

8.9 Other Assessments and Dietary Requirements

Demography

- Age
- Sex
- Race

Concomitant medication

A **concomitant medication** is any medication, other than the IMPs and current diabetes treatment (including oral glucose-lowering agents that need to be washed out), which is taken during the trial, including insulin titration and washout periods.

Details of any concomitant medication must be recorded at trial entry (i.e. at screening). Any changes in concomitant medication must be recorded at each visit as they occur. The information collected for each concomitant medication includes (at a minimum) trade name or generic name, indication, start date and stop date or continuation. A change in medication due to an AE must be recorded and reported according to section 9. If the change in medication influences the subject's eligibility to continue in the trial, the Sponsor and monitor must be informed.

Diagnosis of diabetes and current diabetes treatment

- Date of diagnosis of diabetes
- Current diabetes treatment [start date, product name(s), dose(s)]

Body measurements

- Height (cm or m), without shoes

- Body weight (kg), only wearing underwear
- Body mass index (kg/m^2) calculated by the Investigator based on height and body weight (body weight/height^2)

Alcohol breath test

An alcohol breath test will be performed using an alcohol meter (‰) by standard procedures at the trial site.

Screening for drugs of abuse

At the screening visit, a urine quick test for the presence of drugs of abuse (e.g. amphetamine, barbiturates, benzodiazepines, cannabis, cocaine, methadone, methamphetamine, opiates, phencyclidine and tricyclic antidepressants) will be performed at the trial site from at least 5 mL fresh mid-stream urine using a stick.

Fasting

Fasting is defined as abstinence from food and beverage consumption (other than water) for at least 10 hours. Intake of rapidly absorbable carbohydrates (not more than 20 g carbohydrate) will be allowed if necessary to prevent hypoglycaemia.

Subjects should arrive fasting prior to screening and will undergo multiple fasting periods at the inhouse visits.

Dietary Requirements

No specific nutritional regimen is required during the outpatient periods of the trial.

During the inpatient periods, specific dietary restrictions apply. During the inpatient periods, consumption of foods or drinks other than those served at the clinical unit is prohibited.

8.10 Volume of Blood Sampled during Trial

The total volume of blood sampled from each subject during the trial depends on the amount of additional samples taken in conjuction with hypoglycemic episodes.

For each inhouse visit (Visit 3 and 4), the blood volume of the planned samples adds up to approximate 150 mL blood per subject. Each hypoglycaemic episode will trigger 2 or 3 additional blood samples of approximately 7.5 mL each.

Additional blood samples may be drawn at the discretion of the Investigator (e.g. glucose for safety).

If blood loss for a subject is expected to exceed 500 mL during a 3-month period, the Investigator should confirm that there are no medical concerns (based on a laboratory hemoglobin measurement) before blood sampling is continued.

Blood samples storage

All blood samples taken will be destroyed at the latest after finalisation of the clinical trial report.

9 Adverse Events

9.1 Definitions

Adverse Event (AE)

An AE is any untoward medical occurrence in a trial subject after randomisation (Visit 2) and which does not necessarily have a causal relationship with the IMP. An AE can therefore be any unfavourable and unintended sign (for example, an abnormal laboratory finding), symptom, or disease documented during the clinical trial, whether or not considered related to the experimental procedures or IMPs.

AEs include:

- A clinically significant worsening of a concomitant illness.
- A clinical laboratory abnormality which is clinically significant, i.e. any abnormality that suggests a disease and/or organ toxicity and is of a severity that requires active management. Active management includes active treatment or further investigations, for example change of medicine dose or more frequent follow-up due to the abnormality.

The following should **not** be recorded as AEs, if recorded at screening (on Screening Form or CRF):

- Pre-planned procedure, unless the condition for which the procedure was planned has worsened from the first trial related activity after the subject has signed the informed consent.
- Pre-existing conditions found as a result of screening procedures (pre-existing conditions should be reported as medical history or concomitant illness).

Serious Adverse Event (SAE)

A SAE is any untoward medical occurrence that:

- results in death
- is life-threatening
- requires inpatient hospitalisation or prolongation of existing hospitalisation,
- results in persistent or significant disability or incapacity,
- is a congenital anomaly or birth defect,

or events that may require intervention to prevent one of the above listed outcomes.

Suspected Unexpected Serious Adverse Reactions (SUSAR)

An AE, fulfilling one of the criteria of seriousness and being assessed as related to IMP application (all IMPs according to **Table 3**), the nature or severity of which is not consistent with the applicable reference document.

Intensity of an Adverse Event

The maximum intensity (severity) of all AEs must be assessed by the Investigator and documented. Severity should be graded when the AE outcome is known:

Mild: A type of adverse event that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.

Moderate: A type of adverse event that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant.

Severe: A type of adverse event that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

A 'severe' reaction does not necessarily deem the AE as 'serious' and a SAE may not be 'severe' in nature.

Causality relationship to IMP

The causality of each AE should be assessed by the Investigator according to the following classification:

Probable: Good reason and sufficient documentation to assume a causal relationship.

Possible: A causal relationship is conceivable and cannot be dismissed.

Unlikely: The event is most likely related to aetiology other than the trial product.

Outcome of an Adverse Event

The outcome of all AEs must be assessed by the Investigator and documented by his/her staff. The following definitions should be used:

Recovered/resolved: The subject has fully recovered, or by medical or surgical treatment the condition has returned to the level observed at the first trial-related activity after the subject signed the informed consent.

Recovering/resolving: The condition is improving and the subject is expected to recover from the event. This term is only applicable if the subject has completed the trial.

Recovered/resolved with sequelae: The subject has recovered from the condition, but with lasting effect due to a disease, injury, treatment or procedure. If a sequela meets an SAE criterion, the AE must be reported as an SAE.

Not recovered/ not resolved: The condition of the subject has not improved and the symptoms are unchanged, or the outcome is not known.

Fatal: This term is only applicable if the subject died from a condition related to the reported AE. Outcomes of other reported AEs in a subject before he/she died should be assessed as "recovered/resolved", "recovering/resolving", "recovered/ resolved with sequelae" or "not recovered/not resolved". An AE with fatal outcome must be reported as an SAE.

Unknown: This term is only applicable if the subject is lost to follow-up.

9.2 Collection, Recording and Reporting of Adverse Events

All events meeting the definition of an AE must be collected and reported from the randomisation visit until the end of Visit 4 (post-treatment follow-up may be performed to assess the outcome of the AE). At each contact with the site (visit or telephone) the subject must be asked about AEs. All AEs, either observed by the Investigator or reported by the subject, must be recorded by the Investigator and evaluated.

The Investigator should record the diagnosis, if possible. If no diagnosis can be made the Investigator should record each sign and symptom as individual AEs.

All AEs must be recorded by the Investigator. One single Adverse Event Form must be used per AE from start to resolution. For SAEs, the Serious Adverse Event Form must also be completed.

AE information should include the following:

- Date and time of onset and resolution
- Date of Investigator's first information on the (S)AE (not to be recorded in the CRF)
- Seriousness
- Severity
- Causal relationship with IMP
- Interruption or withdrawal of treatment and other measures taken
- Outcome

All AEs are coded; details are described in the trial specific Data Management Plan.

The Investigator / Sponsor must report initial information in writing (fax or email) on all SAEs to the responsible medical monitor of the trial immediately (within 24 hours) after obtaining knowledge about the event.

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The Sponsor must inform the Competent Authorities and IRBs/IECs in accordance with the local requirements in force and ICH guideline for GCP. The trial monitor must be informed accordingly.

9.3 Follow-up of Adverse Events

Follow-up procedures may be different based on the nature (diagnosis, severity, seriousness) of the AE and will follow Profil's SOP on (S)AE Handling and Reporting.

Follow-up actions for all SAEs will be determined after internal review and/or sponsor review.

The follow up information should only include new (updated and/or additional) information that reflects the situation at the time of the Investigator's signature.

Follow-up information on (S)AEs will be updated using the (S)AE Form. If a non-serious event becomes serious during the follow-up the AE Form and SAE Form have to be used and reporting timelines follow those of a SAE.

The Investigator must forward follow-up information on SAEs and if previously non-serious AEs become SAEs to the medical monitor (contact details are given in section 9.2).

9.4 Hypoglycaemia

The aim of this trial is provoke hypoglycaemic episodes during the medically supervised, inhouse visits. Hypoglycaemic episodes are considered pharmacodynamic responses to the treatment administered and experimental procedures. Hypoglycaemic episodes will therefore not be regarded as adverse events in this trial and documented separately as efficacy parameter.

However, should a hypoglycaemic episode be considered severe, such an event will be regarded as SAE and should be recorded on an AE / SAE form.

Severe hypoglycaemia (major hypoglycaemia): A hypoglycaemic event requiring assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions. These events may be associated with sufficient hypoglycaemia to induce seizure or coma. Plasma or blood glucose measurements may not be available during such an event, but neurological recovery attributable to the restoration of plasma glucose to normal is considered sufficient evidence that the event was induced by a low plasma glucose concentration.

Any severe hypoglycaemic episode will be accompanied by a narrative giving qualitative descriptions of timing of the episodes in relation to drug exposure, time of onset, time after last drug administration, time after meal, severity, duration, outcome of hypoglycaemia, dose of treatment.

9.5 Pregnancy

Female subjects must be instructed to notify the Investigator immediately if they become pregnant or if they suspect to be pregnant during the trial. The Sponsor has a responsibility to monitor the outcome of all pregnancies reported during the clinical trial.

The Investigator must report all information on pregnancies, including AEs in the subject, the foetus, and newborn infant/ toddler. The pregnancy report must be forwarded to the Sponsor preferably electronically as PDF or by fax.

The Investigator must follow the pregnancy until the pregnancy outcome and the newborn infant(s) until the age of 1 month. The Investigator must collect information on the pregnancy and pregnancy complications as well as the pregnancy outcome including the health of the newborn infant(s) on the pregnancy forms.

The following must be collected:

- Initial information of the pregnancy.
- Information on the outcome of the pregnancy - including the health status of the newborn infant at the age of 1 month.
- All AEs in connection with the pregnancy and pregnancy outcome must be reported on the pregnancy forms. It must be clear in the description if the event occurs in the subject, the foetus or the newborn infant.
- All SAEs in connection with the pregnancy and pregnancy outcome must be reported on the pregnancy forms following the same timelines as required for other SAEs (see Section 9.2). It must be clear in the description if the event occurs in the subject, the foetus or the newborn infant.

The SAEs that must be reported including abnormal outcome - such as congenital anomalies, foetal death and termination of pregnancy (spontaneous or elective abortion), including any anomalies of the foetus observed at gross examination or during autopsy - as well as other pregnancy complications (ectopic pregnancy) fulfilling the criteria of an SAE.

9.6 Precautions

Normal precautions taken for a human trial, including the provision of emergency equipment, will be taken during this trial. Qualified and well-trained physicians and medical staff will instruct the subjects. During a subject's participation in the trial, the Investigator should ensure that adequate medical care is provided to the subjects for any AEs, including clinically significant laboratory values related to the trial. The Investigator should inform the subject when medical care is needed for intercurrent illnesses of which the Investigator becomes aware.

For further information on safety precautions for sitagliptin, please refer to the current version of the SmPC for Januvia® respectively.

10 Risk-Benefit Assessment

Potential Risks

Trial subjects will have been informed by the Investigator of the potential risks of sitagliptin treatment and other trial-related procedures before they enter the trial.

Treatment with sitagliptin can result in undesired effects or complaints. Undesired effects and complaints which have been observed are listed below (please also refer to the SmPC for Januvia®).

After adding sitagliptin to metformin:

Common (may affect up to 1 in 10 people): low blood sugar, nausea, flatulence, vomiting
Uncommon (may affect up to 1 in 100 people): stomach ache, diarrhoea, constipation, drowsiness
Some patients have experienced different types of stomach discomfort when starting the combination of sitagliptin and metformin together (frequency is common).

Some patients have experienced the following side effects while taking sitagliptin in combination with insulin (with or without metformin):

Common: flu
Uncommon: dry mouth

Some patients have experienced the following side effects while taking sitagliptin alone in clinical studies, or during post-approval use alone and/or with other diabetes medicines:

Common: low blood sugar, headache, upper respiratory infection, stuffy or runny nose and sore throat, osteoarthritis, arm or leg pain
Uncommon: dizziness, constipation, itching

Frequency not known: kidney problems (sometimes requiring dialysis), vomiting, joint pain, muscle pain, back pain, interstitial lung disease

Subjects that are required to washout oral anti-diabetes medication before starting the insulin titration period may temporarily experience more pronounced fluctuations of their plasma glucose levels, with a tendency to elevated glucose levels. As the washout period is relatively short (1 week) and is followed by an intensification of their diabetes treatment thereafter, this risk is considered low.

Trial-related risks are mainly associated with an increased risk of hypoglycaemia due to therapy intensification with basal insulin titration. The add-on of sitagliptin is hypothesized not to increase and potentially reduce the risk of hypoglycaemia. Testing this hypothesis is the objective of the current trial. To minimise the risk of (severe) hypoglycaemia during the insulin titration period subjects will be educated on the symptoms of hypoglycaemia and how to act in case of hypoglycaemia. Subjects will receive a blood glucose meter and test strips for self-measurement of

plasma glucose levels during the outpatient periods. The insulin titration scheme used aims to bring the subject's fasting plasma glucose level down into a normal range in a safe manner. The insulin titration scheme has been adopted in a previous study at the Ruhr-University Bochum (unpublished data), during which basal insulin titration was performed under inhouse conditions in 16 subjects with type 2 diabetes. The basal insulin dose was changed under medical supervision on a daily basis. At the end of the titration period, all subjects achieved FPG levels below 120 mg/dL without any episodes of symptomatic hypoglycaemia. The lowest measured FPG concentration in the study was 72 mg/dL, demonstrating both efficacy and safety of this insulin titration algorithm.The insulin titration is supervised by medical staff during regular telephone calls and the research physician may adjust the insulin titration on an individual basis for safety reasons. Procedures during the inhouse visits are designed to increase the risk of hypoglycaemia. To minimise the risk of severe hypoglycaemia during the inhouse period, CGM technology to detect low glucose levels in real-time will be used in addition to regular and frequent plasma glucose checks at times the risk of hypoglycaemia is expected to be highest. Medical supervision and emergency equipment will be available at all times inhouse.

Other risks of trial procedures are associated with insertion of intravenous catheters for regular venous blood sampling. These risks are minimal, because the blood sampling techniques have been used as standard procedure for a long time in human research subjects.

The long inhouse fasting periods may be regarded as unpleasant with a strong feeling of hunger. There is a risk of gastro-intestinal problems with the consumption of the high-fat meal on Day 2.

Potential Benefits

Subjects will receive a thorough medical examination at the start of the trial. The insulin titration will provide valuable information to the subject on how to adjust their daily basal insulin dose after the trial to improve their metabolic control. The trial subjects are a target population for improved diabetes treatment with a DPP-4 inhibitor. The results of the trial may possibly contribute to the improved treatment of patients with type 2 diabetes taking sitagliptin in addition to basal insulin and metformin.

Risk-Benefit Assessment

The overall residual risk for subjects participating in this trial is believed to be acceptable.

While mitigation strategies implemented in the protocol reduce the potential risks of treatment and trial-related procedures, most notably hypoglycaemia, the findings of this trial may reveal information that can substantially improve medical care for persons with diabetes type 2.

11 Data Management

Data Management is the responsibility of Profil Institut für Stoffwechselforschung GmbH, Neuss Germany.

The complete Data Management process will be described in detail and agreed on in the Data Management Plan for this trial.

11.1 Case Report Forms (CRFs)

The Data Management Department of Profil Institut für Stoffwechselforschung GmbH will provide the CRFs. All further information regarding the CRFs and the data flow will be described and agreed on in the Data Management Plan.

12 Monitoring Procedures

The monitoring procedures for this trial are described in detail in the Monitoring Manual. The objectives of the monitoring procedures are to ensure that (i) the safety and rights of the trial subjects are respected, (ii) that accurate, valid and complete data are collected, and (iii) that the trial is conducted in accordance with the trial protocol, the principles of GCP and local legislation.

The monitor must be given direct access to the TIF and source documents (original documents, data and records). Direct access includes permission to examine, analyse, verify and reproduce any record(s) and report(s) that are important to evaluation of the clinical trial.

Key tasks of the monitor include to verify the presence of informed consent, the adherence to the inclusion/exclusion criteria, the documentation of SAEs, and the recording of all safety and efficacy variables. The monitor will also confirm the completeness of patient records, the adherence to the protocol and the progress in subject enrolment.

Because no information that could reveal the identity of subjects may ever be removed from the trial site, the monitor will visit the site at regular intervals to perform these monitoring tasks. Other contact between the Investigator and monitor will be maintained as required through telephone calls and e-mail. The Investigator and/or key members of staff involved in the trial must be available to assist the monitor during all visits.

Site Initiation Visit

During the Site Initiation Visit (SIV) the Sponsor and/or monitor will review information on the IMP, the protocol, the CRFs and other key aspects of the trial with the Investigator and the key members of staff involved in the trial. The topics of the SIV are documented in a SIV report made available to the Investigator. Sponsor's documentation on the SIV (e.g. power point presentation) should be filed by the Investigator.

Source Data Verification

Details on source data verification are specified in the Monitoring Manual.

13 Statistical Considerations

Profil Institut für Stoffwechselforschung GmbH, Neuss, Germany, will be responsible for the statistical analysis. The statistical planning and conduct of analyses of the data from this trial will follow the principles defined in relevant ICH guidelines. A general description of the statistical methods to be used is given in this chapter, specific details will be provided in the Statistical Analysis Plan (SAP), which will be prepared before data base lock. All statistical analyses will be performed using SAS® (SAS Institute Inc., Cary, North Carolina, United States of America [USA]), version 9.4 or later.

13.1 Sample Size Calculation

It is assumed that the protocol will provoke an average of 2 confirmed episodes of hypoglycaemia per 48 hours with the administration of placebo. A reduction by 30% due to sitagliptin would be of clinical significance.

As the relevant information needed for a sample size calculation is not available no formal sample size calculation was performed for the primary objective. The sample size calculation is based on one of the secondary objectives, the comparison of the time spent at an interstitial glucose concentration ≤ 70 mg/dL. Assuming a variability of 40% for placebo and sitagliptin in this trial and assuming a 25% reduction in the secondary endpoint with sitagliptin compared to placebo, there will be an approximate 85% power to detect a statistically significance difference ($p<0.05$) with 18 completers. However, due to the uncertain variability 20 subjects are planned to be randomised into the study.

13.2 Selection of Subjects for Analyses

The following analysis sets are defined in accordance with the ICH-E9 guidance (14):

Full Analysis Set (FAS):
is based on the intention-to-treat principle and includes all randomised subjects. In exceptional cases subjects from the FAS may be excluded (will be decided in the DBR meeting). In such cases the exclusion will be justified and documented. Subjects will contribute to the evaluation ‘as randomized’.

Per-Protocol Population (PPP):
includes all subjects of the FAS who completed the trial without any major protocol violations. Subjects in the PPP will contribute to the evaluation ‘as treated’.

Safety Analysis Set:
includes all subjects receiving at least one dose of the investigational product or its comparator. Subjects in the safety set will contribute to the evaluation 'as treated'.

Analyses of PD endpoints will be based on the FAS (and PPP if necessary). The analysis of the safety endpoints will be based on the Safety Analysis Set.

Before data are released for statistical analysis, a blinded review of all data will take place to identify protocol deviations that may potentially affect the results. This review will be performed without revealing which IMP the subjects are assigned to. The blinding of the IMPs will be maintained for everyone involved in allocating subjects to the analysis sets until data are released for statistical analysis. Furthermore, outliers will be identified by data review according to ICH-E9 (14), using a fake randomisation. In addition, protocol deviations, which may potentially affect the results, will be identified and it will be evaluated if subjects and/or data should be excluded from the analysis.

Obviously erroneous data points may be excluded from the analyses or re-analysed (in case of e.g. serum concentrations). The decision to re-analyse or exclude data points from the statistical analysis is the joint responsibility of the Sponsor, the Scientific Consultants and the Trial Statistician.

The subjects or observations to be excluded and the reason for their exclusion will be documented and signed by those responsible prior to database release. The documentation will be stored together with the remaining trial documentation. The subjects and observations excluded from analysis sets, and the reason for this, will be described in the clinical trial report.

13.3 Statistical Methods

The hypothesis that will be investigated in this trial is that sitagliptin reduces the number of hypoglycaemic episodes in patients with type 2 diabetes treated to target with basal insulin glargine and metformin, when measures are taken to increase the risk for such episodes (fasting, increases in insulin dosage, lipid load to increase incretin hormone release, exercise). The hypothesis that sitagliptin improves recovery from such episodes will also be examined.

The primary analysis is aimed to demonstrate a reduction of 30% in the number of hypoglycaemic episodes with sitagliptin compared to placebo during the experimental procedures. Unless otherwise stated, all formal tests of hypothesis will be conducted at the two-sided 5% level of significance. No alpha adjustment will be done.

All analyses, listings, tables and plots will be performed using all available data unless otherwise stated. In general missing data will not be replaced, and obviously erroneous data points will be excluded from the analyses or re-analysed (as described in section 13.2).
In general, descriptive statistics will be performed for all endpoints. Categorical data will be presented using counts and percentages, whilst continuous variables will be presented using the mean, geometric mean, standard deviation, coefficient of variances, minimum, median, maximum and the number of subjects with evaluable data.

Data from clinical assessments will be presented in summary tables and in individual subject listings. Data will be summarized with respect to demographic and other baseline characteristics, efficacy and safety observations and other measurements.

Individual subject listings will be sorted by randomization number, treatment group, and, if applicable, visit and/or time. Summary tables will be presented by treatment group.

13.3.1 Analysis of the Primary Efficacy Endpoint(s)

The number of hypoglycemic episodes (primary endpoint and secondary endpoints; varying definitions of hypoglycemia) will be compared between sitagliptin and placebo treatment by Fisher's exact test.

13.3.2 Analysis of the Secondary Efficacy Endpoints

Time spent at an interstitial glucose concentration will be analyzed by ANOVA, with the experimental condition (sitagliptin vs. placebo), sequence and period as fixed independent variable and subject within sequence as random effect, and the time spent at an interstitial glucose concentration during the 54 h inpatient observation periods as dependent variable.

In case of hypoglycemic episodes, plasma glucose, insulin, C-peptide and counter-regulatory hormones will be analysed at the time point of first detecting symptoms or a low plasma glucose (whatever triggers the detection) and 30 as well as 60 min thereafter, to determine the activity of the counter-regulatory response. Counter-regulatory hormones will be analyzed by ANOVA with the experimental condition (sitagliptin vs. placebo), time point (index time point, 30min and 60 min later) and their interaction, sequence and period as fixed independent variables, subject within sequence as random effect, and the counter-regulatory hormones as dependent variable. The rise in counter-regulatory hormones will be analyzed by ANCOVA with the experimental condition (sitagliptin vs. placebo), time point (30 min and 60 min later) and their interaction, sequence and period as fixed independent variables, baseline counter-regulatory hormones (index timepoint) as covariate, subject within sequence as random effect, and the rise in counter-regulatory hormones (change from index timepoint) as dependent variable.

All other parameters determined from blood samples or continuous glucose measurements will be compared between sitagliptin and placebo treatment by ANCOVA for repeated measures across all standard time points for drawing blood for the parameter in question, using the mean baseline concentration of the parameter as a covariate (exploratory endpoints).

13.3.3 Safety Criteria

The following variables will be evaluated according to treatment for safety purposes:

Adverse events
All AEs will be coded.

Hypoglycaemic episodes
Severe hypoglycaemia, documented symptomatic hypoglycaemia and asymptomatic hypoglycaemia will be fully reported. The number of episodes and the percentage of exposed subjects having at least one episode will be provided.

Laboratory safety assessments
Laboratory assessments (biochemistry (incl. lipids), haematology, coagulation and urinalysis) will be summarised. A listing of abnormal values will be presented in an end of text (EOT) listing.

Physical examination
A frequency table will show the number and percentage of physical examinations. Changes to physical examination from screening to end of trial will be recorded as AEs if the Investigator judges these as being clinically significant.

Vital signs
Vital signs will be summarised by descriptive statistics by treatment/time point.

ECG
Numeric data (HR, QRS etc) will be summarised by descriptive statistics. Qualitative ECG data will be summarised in a frequency table. Abnormal individual evaluations will be listed together with the Investigator's comments. Changes to ECG from screening to end of trial will be recorded as AEs if the Investigator judges these as being clinically significant.

13.4 Interim Analysis

No interim analysis is planned.

14 Independent Ethics Committee and Competent Authority

The trial will be conducted according to Profil's written instructions (SOPs, working instructions or process descriptions). Content and definitions of Profil's written instructions are based on the following relevant binding documents and standards

- the German Drug Law (AMG)
- the German GCP ordinance (GCP-Verordnung)
- the Declaration of Helsinki
- the International Conference on Harmonisation Good Clinical Practice (ICH GCP)

The trial will be conducted in accordance with the above mentioned standards.

14.1 Independent Ethics Committee

Written favourable opinion must be obtained from the responsible independent ethics committee (IEC) prior to commencement of the trial. Clinical trial submission and reporting requirements before, during and after completion of the trial will be performed in accordance with national law and local regulations.

All amendments that affect subject safety or the trial integrity (substantial amendments) must not be implemented before favourable opinion has been obtained, unless necessary to eliminate hazards to the subjects. Non-substantial amendments do not require favourable opinion by the IEC but the respective IEC will be notified according to local requirements.

The Sponsor and Investigator must approve any amendment in writing before its implementation.

The Sponsor must maintain an accurate and complete record of all submissions made to the IEC. The records should be filed in the Sponsor's Trial Master File.

14.2 Informed Consent Process for Subjects

In obtaining and documenting informed consent, the Investigator must comply with the applicable regulatory requirement(s) and adhere to the ICH GCP guideline (15) and the requirements in the Declaration of Helsinki (16).

Prior to any trial-related activity, the Investigator must give the subject oral and written information in a form that the subject can read and understand about all aspects of the trial that are relevant to the subject's decision to participate. The subject will be given ample time to decide whether or not to participate in the trial.

The subject must be informed that his/her personal trial-related data will be used in accordance with the local data protection law. The level of disclosure must also be explained to the subject.

The subject must be informed that his/her medical records may be examined by authorised monitors or Clinical Quality Assurance auditors appointed by the Sponsor, by appropriate IEC members, and by inspectors from regulatory authorities.

A voluntary, personally signed and dated Informed Consent Form must be obtained from the subject prior to any trial-related activity. The Informed Consent Form must also be signed and dated by the physician who conducted the informed consent procedure. All subjects will be provided with a copy of their own signed and dated informed consent form and with any additional subject information.

The responsibility for taking informed consent must remain with that of a research physician.

If information becomes available that may be relevant to the subject's willingness to continue participating in the trial, the Investigator must inform the subject in a timely manner, and a revised written informed consent must be obtained.

Should a protocol amendment become necessary, the Informed Consent Form may need to be revised to reflect the changes to the protocol. It is the responsibility of the Sponsor to ensure that an amended consent form is reviewed and has received favourable opinion from IEC, and the Investigator has to ensure that the amended consent form is signed by all subjects subsequently entered in the trial and those currently in the trial, if affected by the amendment.

14.3 Competent Authority

An implicit or explicit approval must be obtained from the Competent Authority prior to commencement of the trial. Clinical trial submission and reporting requirements before, during and after completion of the trial will be performed in accordance with national law and local regulations.

An implicit or explicit approval will also be mandatory before implementation of substantial changes. Non-substantial amendments do not require approval from the Competent Authority but will be notified according to local requirements.

The Sponsor and Investigator must approve the amendment in writing before its implementation.

The Sponsor must maintain an accurate and complete record of all submissions made to the Competent Authority. The records should be filed in the Sponsor's Trial Master File.

14.4 Premature Termination of the Trial

The Sponsor, Investigator or a pertinent regulatory authority may decide to stop the trial or part of the trial at any time but agreement on procedures to be followed must be obtained.

Conditions that may warrant termination of the clinical trial include, but are not limited to:

- Safety or administrative reasons.
- The discovery of an unexpected, relevant, or unacceptable risk to the subjects enrolled in the clinical trial.
- A decision of the Sponsor to suspend or discontinue investigation of the IMP.

If a trial is prematurely terminated or suspended, the Investigator should promptly inform the subjects and assure appropriate therapy and follow-up. Furthermore, the Sponsor should promptly inform the IEC and provide a detailed written explanation. The pertinent regulatory authorities should be informed according to national regulations.

If after the termination of the trial the risk/benefit analysis has changed, the new evaluation should be provided to the IEC in case it will have an impact on the planned follow-up of the subjects who have participated in the trial. Necessary actions needed to protect the subjects should be described.

15 Administrative Matters

15.1 Deviations from the Protocol

A deviation from the protocol is in general an unplanned non-compliance with the protocol that is not implemented or intended as a systematic change. The Investigator, or person designated by the Investigator, should document and explain any deviation from the protocol and inform the Sponsor and/or monitor. The deviation must be evaluated for its root cause and classification (important/non-important). Corrections (if possible) and/or corrective/preventive actions are to be documented and implemented. The documentation must be kept in the Trial Investigator File and the Sponsor's Trial Master File. Each deviation is listed in a deviation log.

15.2 Essential Documents

Essential Documents, as outlined in ICH GCP Chapter 8, are those documents that individually and collectively permit evaluation of the conduct of a trial and the quality of the data produced. These documents serve to demonstrate the compliance of the Investigator, Sponsor, and monitor with the standards of GCP and with all applicable regulatory requirements.

Essential Documents also serve a number of other important purposes. Filing essential documents at the Investigator/institution and Sponsor sites in a timely manner can greatly assist in the successful management of a trial by the Investigator, Sponsor, and monitor. These documents are also the ones that are usually audited by the Sponsor's independent audit function and inspected by the regulatory authority(ies) as part of the process to confirm the validity of the trial conduct and the integrity of data collected.

Trial files should be established at the beginning of the trial, both at the Investigators' site (Trial Investigator File) and at the Sponsor office (Trial Master File). The Sponsor will nominate a person or a group of persons independent from the Project Team responsible for study overview and TMF maintenance. A final close-out of a trial can only be done when the monitor has reviewed both Investigator/institution and Sponsor files and confirmed that all necessary documents are in the appropriate files.

15.3 Responsibilities

The term Investigator as used in this study protocol defines the person responsible for the conduct of the clinical trial at a trial site. As the trial is conducted by a team of individuals at the trial site,

the investigator is the responsible leader of the team and may also be called the Principal Investigator.

The Investigator is accountable for the conduct of the trial according to the approved protocol, ICH-GCP (15) and Declaration of Helsinki (16). For responsibilities delegated, the Investigator should maintain a list of appropriately qualified persons to whom he has delegated specified significant trial-related duties. The Principal Investigator will discuss and approve the protocol and review and sign the Integrated Clinical Trial Report.

The Investigator will take all necessary technical and organisational safety measures to prevent accidental or wrongful destruction, loss or deterioration of data. The Investigator will prevent any unauthorised access to data or any other processing of data against applicable law.

15.4 Reports and Publications

The Principal Investigator of the trial will review and sign the clinical trial report on behalf of Profil Institut für Stoffwechselforschung GmbH. A summary of the final clinical trial report will be submitted to the IEC and Competent Authority.

According to the Declaration of Helsinki (16) Investigators and Sponsors ‘have ethical obligations with regard to the publication and dissemination of the results of research’.

The trial design and results may be published as one or more original research manuscripts / abstracts and presented at a scientific meeting. The Investigator and Sponsor reserve the right to review any proposed presentation of the results of this trial before they are submitted for publication. Authorship on any publication(s) resulting from this clinical trial will be assigned according to the recommendations of the International Committee of Medicinal Journal Editors (ICMJE) (17).

Participating subjects will not be identified by name in any published reports about the clinical trial.

15.5 Audits and Inspections

In the event of an audit, representatives of the Sponsor or designee, or national and international regulatory authorities may request access to all trial records for inspection and copying. Such access must be stated in the informed consent form signed by the patient.

15.6 Retention of Clinical Trial Documentation

A subject's medical file will be mainted by the trial sites according to local regulations.

The trial sites will archive the documentation pertaining to the trial in an archive after completion or discontinuation of the trial if not otherwise notified. Trial sites should not destroy any documents without prior permission from the Sponsor.

The documentation includes all the raw data generated during the clinical trial, the TIF and a copy of the clinical report. The documents will be retained for a period of at least 15 years at archives by the trial sites, or their sub-contractor.

The Sponsor will maintain the documentation pertaining to the trial in accordance with national regulations.

Appendix 1: Insulin titration guideline

Table: Insulin titration standards with „learning“ algorithm on the basis of percentage instead of absolute dose changes. Not only the actual fasting plasma glucose value is considered but also fasting glucose changes after the last dose adjustment will be incorporated in the consideration of the new dose adaptation.

Fasting plasma glucose	Range [mg/dL]	Decrease in fasting plasma glucose after last insulin dose adjustment [mg/dL]	Change in insulin dose [%]
1	< 70	-	- 15
2	70-89	-	-5
3	90-110	-	0
4	111-130	-	+ 10
5	131-150	< 15	+ 25
		15-30	+ 15
		> 31	+ 10
		No information available*	+ 10
6	151-170	< 20	+ 30
		20-40	+ 20
		> 41	+ 10
		No information available*	+ 15
7	171-190	< 25	+ 35
		25-50	+ 25
		> 51	+ 15
		No information available*	+ 20
8	191 -250	< 30	+ 40
		30-60	+ 30
		> 61	+ 20
		No information available*	+ 20
9	> 250	< 35	+ 45
		35-70	+ 35
		> 71	+ 25
		No information available*	+ 25

*e.g., at the beginning of titration and in case of missing information

Appendix 2: Mixed high lipid meal examples

DPP4-Hypo, lipid meal 1 (standard option)

Amount	Ingredient	kcal	Protein g	Fat g	Carbs g
	Lipid meal				
	Frittata with bacon and avocado:				
10 Grams	Bacon	35	1,4	3,2	0,1
20 Grams	Chicken egg white	9	2,2	0,0	0,1
30 Grams	Chicken egg yolk	106	4,8	9,6	0,1
23 Grams	Olive oil	203	0,0	23,0	0,0
90 Grams	Avocado	212	1,7	21,1	0,4
	Salt, Pepper				
	Shake:				
80 Grams	Coconut milk creamy	144	1,3	12,2	1,8
50 Grams	Cream 30% Fat	152	1,2	15,9	1,6
30 Grams	Raspberries (frozen)	12	0,4	0,1	1,4
15 Grams	Sunflower oil	133	0,0	15,0	0,0
	Sweetener				
	Total	**1006**	**13,0**	**100,2**	**5,5**

DPP4-Hypo, lipid meal 2 (vegetarian option)

Amount	Ingredient	kcal	Protein g	Fat g	Carbs g
	Lipid meal				
150 Grams	Avocado	353	2,8	35,3	0,6
4 Grams	Olive oil	35	0,0	4,0	0,0
	Salt, Pepper				
	Shake:				
80 Grams	Coconut milk creamy	144	1,3	12,2	1,8
50 Grams	Cream 30% Fat	152	1,2	15,9	1,6
30 Grams	Raspberries (frozen)	12	0,4	0,1	1,4
15 Grams	Sunflower oil	133	0,0	15,0	0,0
	Sweetener				
	Garnish with nuts:				
25 Grams	Walnuts	181	4,0	17,6	1,5
	Total	**1010**	**9,7**	**100,2**	**6,9**

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