

## Clinical Trial Protocol

Doc. No.: c02204602-03

<b>EudraCT No.:</b>	2014-000904-88	
<b>BI Trial No.:</b>	1218.149	
<b>BI Investigational Product(s):</b>	Tradjenta®, Trajenta®, Trayenta®, Trazenta®, linagliptin	
<b>Title:</b>	A 24 week randomized, double-blind, placebo-controlled, parallel group, efficacy and safety trial of once daily linagliptin, 5 milligrams orally, as add on to basal insulin in elderly Type 2 Diabetes Mellitus patients with insufficient glycaemic control	
<b>Clinical Phase:</b>	IV	
<b>Trial Clinical Monitor:</b>	[REDACTED]	
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<b>Co-ordinating Investigator:</b>	[REDACTED]	
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<b>Status:</b>	<b>Final Protocol (Revised Protocol based on global amendment 1)</b>	
<b>Version and Date:</b>	<b>Version: 2.0</b>	<b>Date: 15 May 2014 Original Protocol 16 October 2015 Revised Protocol</b>
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## CLINICAL TRIAL PROTOCOL SYNOPSIS

<b>Name of company:</b> Boehringer Ingelheim(BI)		<b>Tabulated Trial Protocol</b>	
<b>Name of finished product:</b> Tradjenta®, Trajenta®, Trayenta®, Trazenta®			
<b>Name of active ingredient:</b> linagliptin			
<b>Protocol date:</b> 15 May 2014	<b>Trial number:</b> 1218.149		<b>Revision date:</b> 16 October 2015
<b>Title of trial:</b>	A 24 week randomized, double-blind, placebo-controlled, parallel group, efficacy and safety trial of once daily linagliptin, 5 milligrams orally, as add on to basal insulin in elderly Type 2 Diabetes Mellitus patients with insufficient glycaemic control		
<b>Co-ordinating Investigator:</b>	[REDACTED]		
<b>Trial sites:</b>	A multi-centre trial to be conducted in multiple countries		
<b>Clinical phase:</b>	Phase IV		
<b>Objectives:</b>	To investigate the efficacy, safety, and tolerability of linagliptin 5 milligrams (mg) once a day (q.d.) compared to placebo as add-on therapy for 24 weeks to stable basal insulin treatment in elderly ( $\geq 60$ years old) patients with Type 2 Diabetes Mellitus (T2DM) with insufficient glycaemic control		
<b>Methodology:</b>	Randomised, double-blind, multi-national, placebo-controlled, parallel design comparison as add-on therapy to a stable background of basal insulin, metformin (optional), and/or alpha-glucosidase inhibitors (optional) over 24 weeks.		
<b>No. of patients:</b>			
<b>total entered:</b>	Entered (into the double-blind treatment period): approximately <b>300</b>		
<b>each treatment:</b>	1:1 allocation ratio per treatment arm [i.e., <b>150</b> patients assigned to linagliptin 5mg q.d. and <b>150</b> patients assigned to placebo matching linagliptin 5 mg q.d.]		
<b>Diagnosis:</b>	Elderly ( $\geq 60$ years old) T2DM patients with glycated (or glycosylated) haemoglobin (HbA <sub>1c</sub> ) levels of <b>7.0%</b> to 10.0% at Screen who are on a stable background antidiabetic therapy of basal insulin, metformin (optional), and/or alpha-glucosidase inhibitor (optional).		
<b>Main criteria for inclusion:</b>	T2DM patients who are <b>60</b> years of age or older: <ul style="list-style-type: none"> <li>• with HbA<sub>1c</sub> levels of <b>7.0%</b> to 10.0% at Screen</li> <li>• taking stable doses of basal insulin at least 4 weeks prior to randomisation, and metformin (optional) and/or alpha-glucosidase inhibitor (optional) at least 12 weeks prior to randomization</li> <li>• with a Body Mass Index (BMI) of less than or equal to 45 kilograms per meters squared (<math>\leq 45 \text{ kg/m}^2</math>)</li> </ul>		

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<b>Name of active ingredient:</b> linagliptin			
<b>Protocol date:</b> 15 May 2014	<b>Trial number:</b> 1218.149		<b>Revision date:</b> 16 October 2015
<b>Test product(s):</b>	linagliptin tablet		
<b>dose:</b>	5 mg (tablet strength)		
<b>mode of admin.:</b>	by mouth (p.o.) each morning		
<b>Comparator products:</b>	placebo tablet (matching linagliptin)		
<b>dose:</b>	Not Applicable (N/A)		
<b>mode of admin.:</b>	p.o.		
<b>Duration of treatment:</b>	A one week Screen period with no study medication, leading into a one week placebo Run-In period, followed by a double-blind treatment period for 24 weeks, and a one week post-treatment period with no study medication.		
<b>Criteria for efficacy:</b>	<p>The primary endpoint is the change from baseline in HbA<sub>1c</sub> after 24 weeks of treatment.</p> <p>Secondary endpoints are the following:</p> <ul style="list-style-type: none"> <li>• <b>Proportion of patients experiencing at least one confirmed hypoglycaemic event during 24 weeks of treatment.</b></li> <li>• Proportion of patients with HbA<sub>1c</sub> on treatment &lt;8.0% after 24 weeks of treatment</li> <li>• Proportion of patients with HbA<sub>1c</sub> on treatment &lt;7.0% after 24 weeks of treatment</li> <li>• Proportion of patients with HbA<sub>1c</sub> lowering by at least 0.5% after 24 weeks of treatment</li> <li>• Change from baseline in Fasting Plasma Glucose (FPG) after 24 weeks of treatment</li> </ul>		
<b>Criteria for safety:</b>	Adverse events (including relevant new or worsening pre-existing conditions) and hypoglycaemic events		
<b>Statistical methods:</b>	Restricted maximum likelihood estimation based on mixed-effect model for repeated measures analysis will be used to obtain adjusted means for the treatment effects. This model will include treatment, baseline insulin dose, and week as discrete fixed effects, baseline HbA <sub>1c</sub> as a continuous fixed effect, interaction between week and treatment, and interaction between week and baseline HbA <sub>1c</sub> . The primary treatment comparisons will be the contrast between treatments at Week 24.		

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## FLOW CHART

	Screen	Run-In	Treatment					Post-Treatment
Visit	1	2	3	4	5	6	98	99
Week	-2	-1	1	6	12	18	24	25
Day	-14	-7	1	43	85	127	169	176
Visit Duration to Next Visit (days)	7	7	42	42	42	42	7	N/A
Maximum Visit Window (in days) <sup>A</sup>	-7	-7	0	+/-7	+/-7	+/-7	+/-7	N/A
Informed Consent <sup>A</sup>	X							
Patient Health Questionnaire (9 item) <sup>B</sup>	X							
Mental Status Examination <sup>B</sup>	X							
Medical History <sup>B</sup>	X							
Demographics <sup>B</sup>	X							
Inclusion/Exclusion Criteria Checks <sup>B</sup>	X	X	X					
Blood Pressure and Pulse <sup>B</sup>	X	X	X	X	X	X	X	X
Height and BMI <sup>A</sup>	X							
Weight <sup>A</sup>	X		X				X	
Physical Examination <sup>B</sup>	X						X	
12-Lead ECG <sup>C</sup>	X		X				X	
FPG <sup>D</sup>			X	X	X	X	X	
HbA <sub>1c</sub>	X		X	X	X	X	X	
[REDACTED]								
Laboratory Tests (urine and blood) <sup>B, F</sup>	X	X	X	X	X	X	X	X
Lipid Panel			X				X	
[REDACTED]								
HbGM and eDiary	X	X	X	X	X	X	X	X
Diet / Exercise Counseling <sup>I</sup>	X	X	X	X	X	X	X	
Adverse Events <sup>B, J</sup>	X	X	X	X	X	X	X	X
Concomitant Therapy <sup>B</sup>	X	X	X	X	X	X	X	X
Interactive Response Technology Use <sup>K</sup>	X	X	X	X	X	X	X	X
Dispense Study Medication <sup>L</sup>		X	X	X	X	X		
Randomisation			X					
Study Medication Compliance Check			X	X	X	X	X	
Conclusion of Patient Participation <sup>M</sup>								X

A The duration of the Screen Visit or Run-In Visit (each visit) must be 7 days in duration but no fewer provided that all evaluations, including laboratory and ECG results as well as any applicable medical information are available at the trial site, and the patient meets the inclusion and exclusion criteria. The allowed visit window for the Screen Visit or Run-In Visit (each visit) includes an additional 1 to 7 days. Therefore, the maximum duration of the Screen Visit or Run-In Visit (each visit) is a total of 14 days.

If a visit window (+/- 7 days: i.e., 1 day to 7 days) is used after randomisation, the patient should be returned to the original trial schedule by the next visit (i.e., the number of visit window days used must be subtracted from the upcoming visit). This procedure ensures that all patients complete: the treatment period at approximately Day 169 and the Post-Treatment Visit at approximately Day 176. The visit window between Visits 98 and 99 will not be allowed once trial enrolment has been achieved (sufficient patients screened to randomise **300 with 100 from Japan**); the Clinical Monitor Local (CML) will inform trial sites when trial enrolment is complete.

B Functional reviews (Patient Health Questionnaire and Saint Louis University Mental Status Examination) will be completed first to assess the functional ability, mental health, and cognitive ability of potential patients. For the Screen Visit: the screening evaluations (except for the Patient Health Questionnaire, Saint Louis University Mental Status Examination, and HbA<sub>1c</sub> which must be completed in this order immediately after informed consent) may be completed on separate days as long as the results are obtained within the allowed days for the visit.

C In the event of any cardiac symptoms (i.e., suspicion of heart rhythm disorders or cardiac ischemia) at Visit 1, Visit 3 and/or Visit 98, an additional follow-up ECG will be collected and recorded after that particular visit.

D Fasting blood samples (no food and/or drink except for water 10 hours prior to visit) via central lab. Starting at Visit 3, if hyperglycaemia is noted, repeat FPG via central lab.

[REDACTED]

F Exception: For the Screen Visit only, patients do not have to be fasting.

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[REDACTED]

- H Instruction on how to use the Home Blood Glucose Monitoring (HBGM) device will be conducted at Visit 1 and the device will be given to the patient. The patient should be instructed to monitor their blood glucose 4 times daily (before breakfast after overnight fasting, before lunch, before dinner, and before bedtime) using the HBGM device beginning that day with the closest monitoring time point. The patient will also answer meal, exercise, and symptom questions on the eDiary and upload their glucose values to the eDiary daily. The patient will be instructed to monitor their blood glucose once or twice weekly during sleeping hours if the patient gets up. During the trial participation, additional HBGM monitoring should be completed if the patient has hypo- or hyperglycaemia-related symptoms.
- I Diet and exercise counseling by a diet specialist or trained staff member. Counseling should be based on local diet recommendations. At all other visits, patients should be reminded about the importance of following the recommended diet and exercise plan.
- J The only adverse events that are required to be reported for patients who screen fail before Visit 2 are serious adverse events (SAEs).

[REDACTED]

- M The criteria for discontinuing patients from the trial participation are included in [Section 3.3.4.1](#).

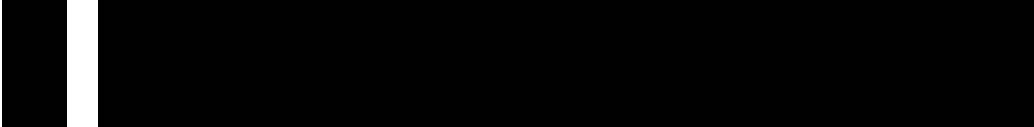


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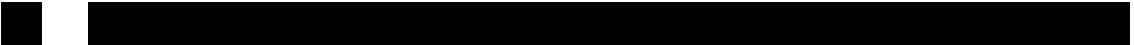
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HBGM	Home Blood Glucose Monitoring
HDL	High Density Lipoprotein
█	█
ICH	International Conference on Harmonisation
i.e.	id est (that is)
IEC	Independent Ethics Committee
█	█
Inc.	Incorporated
INR	International Normalized Ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology
ISF	Investigator Site File
ITT	intention to treat
kg/m <sup>2</sup>	kilograms per meters squared
LDH	Lactate Dehydrogenase
LDL	Low Density Lipoprotein
LOCF	last observation carried forward
MedDRA	Medical Dictionary for Drug Regulatory Activities
mg	milligrams
mg/dL	milligrams per deciliter
mmol/L	millimoles per Liter
mmol/mol	millimoles per mole
MMRM	Mixed Model Repeated Measures
N/A	not applicable
NCF	Non-completer's considered failures
NGSP	National Glycohaemoglobin Standardisation Program
OC	Observed Cases
OPU	Operating Unit
█	█
█	█
█	█
p.o.	per os (oral)
PPS	Per Protocol Set
█	█
q.d.	quaque die (once a day)
RDC	Remote Data Capture

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REP	residual effect period
█	█
SAE	Serious Adverse Event
SGLT2	sodium glucose co-transporter 2
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SOP	Standard Operating Procedure
STEMI	ST Elevation Myocardial Infarction
SUSAR	Serious Unexpected Suspected Adverse Reaction
T2DM	Type 2 Diabetes Mellitus
TCM	Trial Clinical Monitor
TDMAP	Trial Data Management and Analysis Plan
TMF	Trial Master File
TS	treated set
TSAP	Trial Statistical Analysis Plan
ULN	upper limit of normal

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## 1. INTRODUCTION

### 1.1 MEDICAL BACKGROUND

T2DM accounts for 90% to 95% of all cases of diabetes and is an increasingly prevalent disease with over 300 million people estimated to be affected worldwide ([R09-4240](#)). The rate of obesity is increasing, with a parallel increase in the rate of T2DM ([R14-0447](#)). The high frequency of complications leads to a significant reduction of life expectancy ([R09-4241](#)). Because of hyperglycaemia induced microvascular complications, diabetes is currently the most frequent cause of adult-onset loss of vision, renal failure, and amputation in the Industrialised World and is additionally associated with a two to five fold increase in cardiovascular disease risk.

#### *Emerging treatment for T2DM*

With the chronic progression of T2DM in many patients, a declining glycaemic control over time can become evident despite adequate diet, exercise, and therapies with oral antihyperglycaemic agents. Within a few years, treatment intensification is required because of a progressive loss of beta cells and the diminishing secretory capacity of the remaining cells, resulting in secondary drug failure and the necessity to institute insulin therapy in many patients. In most cases, insulin resistance cannot be compensated by an adequately increased insulin secretion, ultimately leading to increased fasting and postprandial glucose concentrations. Currently available antidiabetic agents are not sufficient to maintain long term glycaemic control. Management of diabetes in the elderly population is complicated by these age-related changes ([P13-00432](#)).

Traditional insulin secretagogues, such as the sulphonylurea drugs, increase insulin secretion in a non-glucose-dependent manner and carry an increased risk for hypoglycaemia. Additionally, it is unclear whether such a glucose independent stimulation of insulin secretion accelerates the loss in beta cell function.

An improved understanding of the interaction between gut related hormones and the endocrine system has led to the incretin concept and, based on this concept, to the development of a new class of antidiabetic agents. The incretin effect is a phenomenon where the glucose-stimulated insulin secretion is augmented by intestinally derived peptides, which are released in the presence of glucose or nutrients in the gut. Glucagon-like peptide-1 (GLP-1) is an important member of the incretin hormone family. Importantly, the actions of GLP-1 depend on the actual glucose concentration. GLP-1's stimulation of insulin secretion ceases when glucose concentrations fall below 55 milligrams per deciLiter (mg/dL). Therefore, elevation of GLP-1 levels bears little to no risk of hypoglycaemia.

GLP-1 is almost instantaneously inactivated by the enzyme dipeptidyl-peptidase IV (DPP-4) explaining its short half-life of only a few minutes. Postprandial GLP-1 secretion has been reported to be attenuated in T2DM which may partially explain the increased postprandial glucose excursions. Therefore, a prolongation of the half-life of GLP-1 may be seen as a therapy which restores the lack of GLP-secretion. Besides its stimulatory effects on insulin secretion, GLP-1 has been shown to inhibit glucagon secretion, to delay gastric emptying, to induce satiety, and, in animal models, to maintain long-term beta cell function. Especially the maintenance of beta cell function is of interest, because loss of beta cell function has been

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identified as a major contributor to the deterioration of long term glycaemic control in T2DM.

DPP-4 is an enzyme widely expressed in many tissues including kidney, liver, intestine, lymphocytes and vascular endothelial cells. In addition, a significant level of DPP-4 activity is also observed in plasma, which likely originates from multiple tissues that express the enzyme. DPP-4 is thought to play an important role in the degradation of a number of peptides, thus regulating their half-life. However, physiological evidence for the role of DPP-4 in this process is only available for a few DPP-4 substrates, e.g., GLP-1 and glucose-dependent insulintropic peptide (GIP), both of which exert glucose-dependent insulintropic actions and thereby contribute to the maintenance of post-meal glycaemic control. DPP-4 knock out rodents exhibit improved glycaemic control and are resistant to diet induced obesity, indicating a physiological role of this enzyme in glucose homeostasis and body weight regulation.

A newer class of antihyperglycaemic agent, DPP-4 inhibitors, acting on the GLP-1 axis, targets pancreatic islet dysfunction, in particular gut-derived incretin hormones. DPP-4 inhibitors have some characteristics which may be of particular value in older patients. DPP-4 inhibitors can be taken orally, are weight neutral, well tolerated and have a lower risk of hypoglycaemia compared with insulin and sulphonylureas ([P12-06615](#)). Indeed, the American Diabetes Association and European Association for the Study of Diabetes position statement specifically describe the advantage of DPP-4 inhibitors as rarely having severe side effects as opposed to the other treatment options ([P12-05315](#)). In a recent observational trial evaluating the tolerability and safety of DPP-4 inhibitors for the treatment of older people has shown that patients prescribed DPP-4 inhibitors had evidence of improved glycaemic control in addition to a lower rate of documented hypoglycaemia (3% vs. 8%) than the non-DPP4 inhibitor treated group ([R14-0340](#)).

A strong scientific rationale suggests that DPP-4 inhibitors can prevent or counteract hypoglycaemia. This is especially important for the management of insulin-treated patients since the limiting factor in this population is iatrogenic hypoglycaemia. The insulintropic effects of incretins are glucose-dependent and decline as postprandial serum glucose levels return to normal ranges. The incretin GIP increases glucagon levels during fasting and hypoglycaemic conditions, while potentiating glucose-induced insulin secretion during hyperglycaemia ([P13-14398](#)). The DPP-4 inhibitors have been studied in large clinical trials, as add-ons to insulin. For vildagliptin, sitagliptin and saxagliptin, an improved glycaemic control was shown when added to ongoing insulin therapy. All three DPP-4 inhibitors were generally well tolerated in patients with T2DM ([R14-0340](#)). The results of these trials suggest that concomitant treatment with DPP-4 and insulin is effective for achieving better glycaemic control in patients with T2DM while improving the safety and tolerability of the antihyperglycaemic treatment.

#### *Management of elderly T2DM patients*

T2DM is up to five times more prevalent in elderly patients (65 years of age and older) compared to patients who are younger ([R14-0340](#)). Additionally, up to one in five elderly patients have T2DM while a similar proportion may have undiagnosed T2DM ([R14-0183](#)).

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Furthermore, diabetes in the elderly is metabolically distinct from diabetes in middle aged patients ([R04-1263](#), [R09-5797](#)).

Glucose-lowering treatment of elderly patients with T2DM is generally deemed necessary to alleviate symptoms associated with hyperglycaemia and risk reduction of the long-term complications. Although the general goal for patients with T2DM of a HbA<sub>1c</sub> level of 7.0% or less may be reasonable for some elderly patients, recent guidelines stress individualizing this target to balance potential benefit and risk of treatment for elderly patients at high risk of hypoglycaemia or complications from hypoglycaemia, as long as acutely symptomatic hyperglycaemia is avoided ([R14-0344](#)).

Higher glucose levels may contribute to an increase risk of dementia through several potential mechanisms, including acute and chronic hyperglycaemia, insulin resistance, and increased microvascular disease of the central nervous system ([R12-1338](#), [R14-0250](#), [R14-0436](#), [R14-0435](#), [R14-0434](#), [R14-0437](#)). This link of hyperglycaemia to an increase risk of dementia may speak against generally higher targets for HbA<sub>1c</sub> in the elderly population. Moreover, the general concern about stricter HbA<sub>1c</sub> control is largely based on trials that used glucose-lowering drugs with relatively high risk of hypoglycaemia. Thus, hypoglycaemia has been shown to increase the risk for dementia and is associated with increased cardiovascular risk in patients with T2DM. This illustrates the dilemma of poor health outcomes with either hyperglycaemia or hypoglycaemia in older adults with T2DM. This burden may be alleviated by using pharmacotherapies that could achieve relevant improvements in glycaemic control with low risk of hypoglycaemia or other adverse effects.

Elderly patients with T2DM generally have a reduced ability to tolerate the adverse effects of medication, compared with younger patients ([R09-6092](#)). Over time, most patients with T2DM experience progressive beta cell dysfunction and will require insulin therapy, usually in combination with oral agents, for satisfactory glycaemic control ([P13-14398](#)). Insulin treatment can improve and maintain glycaemic control, preventing long-term complications in T2DM. Basal insulin is becoming an important option when initiating insulin therapy in T2DM patients who require insulin ([R14-0360](#)). Many elderly patients are prescribed insulin along with other antidiabetic medications for glycaemic control, which increases the risk of hypoglycaemia ([P13-00432](#)).

Many glucose-lowering drugs have potential disadvantages for elderly patients, particularly a risk for hypoglycaemia (sulfonylureas, insulin), fractures (thiazolidinediones), contraindication, or dose adjustments for renal impairment for most oral and injectable agents ([P13-00432](#)). Additionally, efficacy of glucose lowering can be affected by disease duration, because of deterioration over time in pancreatic beta cell function. Therefore, safety is an important consideration for treatment, especially avoidance of iatrogenic hypoglycaemia, which occurs frequently in elderly patients and can have severe consequences. Renal impairment is also very common in elderly with T2DM, increasing their risk for hypoglycaemia and complicating treatment strategies ([P13-00432](#), [R14-0183](#)).

Of particular importance is that hypoglycaemia had the third highest incidence of nonfatal complications in 70 year old and older T2DM patients, with the highest rates in patients who had T2DM for 10 years or more ([R14-0002](#)). Eventually, the initiation of insulin therapy is

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necessary in order to maintain glycaemic control. Insulin accounts for a significant number of hypoglycaemic events in the elderly American population each year and SAEs, reported to the United States Food and Drug Administration (FDA), related to its use have been steadily rising in recent years ([P07-11112](#), [P11-14211](#)). Additionally, sulfonylureas, insulin, and metformin (possibly used in combination with each other or other antidiabetic medications) trigger a large proportion of drug-related emergency room visits and hospitalizations in the United States ([R14-0002](#)).

There is a significant variation in T2DM prevalence and associated mortality rates between different geographic areas ([P08-11948](#)). There is a disproportionate burden of this disease among some racial and ethnic populations, especially those at the low end of the socioeconomic spectrum and/or residing in developing countries.

Clinical trials contribute toward reducing health disparities through improved knowledge about treatment among diverse populations. Minorities are significantly underrepresented in clinical trials, with non-participation frequently related to recruitment barriers. The limited generalisability of trial results led the National Institutes of Health to develop guidelines ensuring that funded clinical research would generate information about the effects of the study intervention on both genders and diverse racial (and ethnic) groups ([R13-2759](#)). Even with such guidelines in place, literature suggests significant barriers to successful recruitment of minority patients into clinical trials, including cultural beliefs regarding illness and disease, mistrust of the health care system, and differences in health beliefs and practices. Solutions lie in exploring new venues to reach minority populations and to create strategies aimed at recruiting and retaining these patients. Greater diversity in clinical trial samples allows for broader generalization of trial results, increased minority access to trials, improved standards of care, decreased disparities in disease treatment and outcomes, and improved external validity supported by a more representative sample ([R13-2759](#)).

Despite assuming a disproportional burden of disease and consumption of prescription drugs as well as therapies, these older patients have been vastly underrepresented in clinical trials, thereby restricting treatments' generalizability, efficacy and safety ([R14-0182](#)). A recent analysis has shown that only 0.6% of interventional trials in T2DM specifically targeted this age group, 31% excluded patients older than 65 years, and almost all excluded those older than 75 years ([R14-0345](#)). In addition, elderly patients, defined as 65 years of age and older, by the American Geriatric Society, have frequently been excluded from those major clinical trials used to develop practice guidelines due to age-related complications ([R10-5452](#)). Based on patients' health status and risk factors, these complications include but are not limited to comorbid conditions, polypharmacy, renal insufficiency, increase fall risk, visual impairment, and cognitive impairment and age-related decrease in pancreatic-islet function ([P14-00552](#)). As noted, although there are numerous evidence-based guidelines, few guidelines are specifically targeted toward the needs of these patients.

**As a result of the extreme difficulty with recruiting this population, the global protocol amendment 1 expanded the definition of elderly population beginning at age 60 and reduced the lower limit of HbA<sub>1c</sub> to match the trials that were used for this trial's hypothesis.**

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## 1.2 DRUG PROFILE

[REDACTED]

Linagliptin is a potent inhibitor of DPP-4 and prolongs the half-life of endogenous GLP-1. Unlike the other DPP-4 inhibitors, linagliptin, given in a once-daily, single-dose 5 mg regimen is excreted mainly by non-renal pathways and dose adjustment is not needed for renal impairment or any other factor ([P12-05699](#)). Linagliptin also has minimal drug interactions ([P12-05699](#)). [REDACTED]

Treatment with 5 mg linagliptin, once daily, has been shown to be well-tolerated and results in clinically meaningful and statistically significant reductions in HbA<sub>1c</sub>, FPG, and postprandial glucose [REDACTED]. There was a consistent pattern in the improvement in HbA<sub>1c</sub> when linagliptin was used in patients with different background therapies. Linagliptin 5 mg has also been shown to give sustained efficacy over 52 weeks in T2DM patients with severe renal impairment. Additionally, linagliptin 5 mg has demonstrated clinically relevant efficacy for elderly and African American T2DM patients ([P10-14001](#), [P11-02847](#), [P11-06845](#), [P11-09378](#), [P11-12477](#), [P13-09565](#), [REDACTED])

[REDACTED]

[REDACTED] To date, in Phase III trials in patients with T2DM, linagliptin elicited meaningful glucose-lowering effects and was well tolerated with little intrinsic risk for hypoglycaemia ([P10-14001](#), [P11-02847](#), [P11-06845](#), [P11-09378](#), [P11-12477](#)).

[REDACTED]

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Overall, it has been shown that linagliptin is an effective and safe add-on therapy to insulin in patients with T2DM. This combination therapy was also shown to be safe and effective in vulnerable, elderly T2DM patients and in T2DM patients with renal impairment ([P13-14398](#)).

Recently, in a randomised, placebo-controlled clinical trial that included 241 patients, who were 70 years of age and older, with inadequate glycaemic control on stable backgrounds of metformin and/or sulphonylurea and/or basal insulin, linagliptin was shown to be safe and effective in this patient population ([P13-09565](#)). A subset from a pooled analysis of two Phase III trials consisting of 247 patients, 70 years of age and older, who received linagliptin or placebo showed adding linagliptin to basal insulin appeared to decrease the risk of hypoglycaemia despite significant reduction in HbA<sub>1c</sub> and no relevant reductions in insulin dose ([P13-07824](#)). In summary, linagliptin has been shown to be effective and safe as an add-on therapy that can help patients on basal insulin to improve their blood sugar control without weight gain or additional risk of hypoglycaemia.

Symptoms that could be attributed to hypoglycaemia as well as plasma glucose levels will be closely monitored in this current trial. Glycaemic goals in elderly patients and interventions to achieve such goals must take into account the clinical status of individual patients, in particular, avoidance of hypoglycaemia which can have a profound impact on health and quality of life in elderly patients.

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## 2. RATIONALE, OBJECTIVES, AND BENEFIT - RISK ASSESSMENT

### 2.1 RATIONALE FOR PERFORMING THE TRIAL

The rationale for conducting this trial in an elderly population on a stable background therapy of basal insulin is:

- to further establish the adverse event profile of linagliptin,
- to achieve improved glycaemic control without increasing adverse events,
- to assess the occurrence of hypoglycaemia, and
- to collect additional data in this population.

### 2.2 TRIAL OBJECTIVES

The objective of this trial is to investigate the efficacy, safety, and tolerability of linagliptin 5 mg given orally once daily compared to placebo as add-on therapy for 24 weeks to stable basal insulin treatment in elderly patients, **60** years of age and older, with T2DM with insufficient glycaemic control (i.e., HbA<sub>1c</sub> of **7.0%** to 10%). Stable background therapy of metformin and/or alpha-glucosidase inhibitors is also allowed.

In addition, this trial will assess if linagliptin reduces the risk of hypoglycaemia when added to background basal insulin therapy. The treatment duration of this trial (24 weeks) will enable assessment of the clinically relevant endpoint of a decrease in HbA<sub>1c</sub>, a well-accepted measurement of chronic glycaemic control.

For a description of the endpoints chosen and statistical analyses to assess these objectives, refer to [Section 5](#) and [7](#).

### 2.3 BENEFIT - RISK ASSESSMENT

Potential general benefits for patients in this trial irrespective of the investigational medication received are: improvements in glycaemic control, regular diet and exercise counseling, as well as general medical benefit from careful and close monitoring by medical personnel, and HBGM during the trial.

General risk associated with participating is related to trial specific procedures such as blood sampling that can be associated with bruising and pain. The amount of blood taken during the whole course of the trial is not believed to be excessive and is associated with the standard of care for the patients.

#### *One week Run-In Period Risk*

Trial designs with a one-week placebo Run-In Period are well-established for T2DM trials. The patients will be maintained on stable antidiabetic therapy during the one-week Run-In

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Period and continue regular monitoring of blood glucose with a HBGM device. Thus, the risk of the one-week placebo treatment in this trial is considered to be minimal.

#### *Background Therapy and Study Medication Specific Risk*

Basal insulin is the stable background therapy in this trial. Patients are administered basal insulin and not short-acting insulin because there are fewer injections, lower risk of hypoglycaemia, and basal insulin covers postprandial peaks. Weight gain, hypoglycaemia, allergic reactions, injection site reaction, lipodystrophy, pruritus, and rash are the most common side effects noted with basal insulin. All patients will have received basal insulin and these events mainly occur shortly after insulin initiation (at least allergic reactions). For safety reasons, the basal insulin dose can always be modified by investigators.

Metformin, a typical background medication, is a drug that has been on the market for a long time, is widely used as a first line therapy, and therefore believed to be well characterized in terms of risk profile. Metformin can however cause lactic acidosis to develop, which is relatively infrequent and more likely to occur in patients who have kidney or liver disease, excessive alcohol use, X-ray or scanning procedures that require an injectable iodinated contrast drug, surgery, or a serious infection ([R10-5341](#), [R10-5537](#)). Patients may be taking metformin as part of their stable background therapy. With all these conditions being excluded and the monitoring throughout the trial, this risk will be minimal for patients taking linagliptin and metformin.

Alpha-glucosidase inhibitors (such as acarbose) may be used as background medication and decrease the absorption of carbohydrates from the digestive tract, thereby lowering the post-meal glucose levels. Alpha-glucosidase inhibitors are used to establish greater glycaemic control over hyperglycaemia in T2DM, particularly with regard to postprandial hyperglycaemia. Alpha-glucosidase inhibitors may be used as monotherapy in conjunction with an appropriate diabetic diet and exercise, or they may be used in conjunction with other anti-diabetic drugs. Alpha-glucosidase inhibitors commonly are associated with gastrointestinal side effects such as flatulence, bloating, nausea, vomiting, and diarrhoea.

Angioedema, urticaria and rash are listed as side effects for linagliptin (with any background, [R11-2588](#)). For the fixed dose combination of linagliptin plus metformin, the identified side effects correspond to the observed side effects of metformin (i.e., decreased appetite, diarrhoea, nausea, vomiting, and pruritus) plus the events for linagliptin on all backgrounds (nasopharyngitis, cough, hypersensitivity and pancreatitis as well as angioedema, urticaria, and rash). Furthermore, longer term safety data have not shown any further safety trends to date.

As with all drugs, the potential for hypersensitivity and allergic reactions has to be taken into consideration when linagliptin is administered. Other risks to the patients are the risks inherent to any clinical trial such as unexpected adverse clinical or laboratory events. Safety will be ensured by monitoring the patients for adverse events (AEs) both clinically and by laboratory testing. If any investigator should have a clinical concern, the safety of the patients will be of paramount importance.

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Approximately half of the patients participating in this trial may derive a direct benefit from being treated with an active compound and not a placebo. Patients who are not adequately controlled (whether in the blinded placebo or active compound group), as evidenced by FPG or blood glucose values (by HBGM device), will have adjustments to their background therapy or receive rescue therapy (according to [Section 4.2.1](#)) to ensure their safety.

Rescue therapy will be permitted in case of hyperglycaemia during the randomised treatment period if the defined criteria are met (refer to Section 4.2.1). The choice of rescue medication and its dosage according to Section 4.2.1 will be left to the discretion of the investigator and rescue medication will be taken in accordance with the local prescribing information of that respective medication. The use of rescue medication may be associated with relevant side effects, such as increase of hypoglycaemia risk, weight gain, etc.

#### *Alternative Therapies for T2DM*

There are several alternative therapies available for the treatment of T2DM (e.g., biguanides, sulphonylureas, thiazolidinediones, sodium glucose co-transporter 2 (SGLT2) inhibitors, metglitinides, alpha-glucosidase inhibitors, rapid acting or short acting insulin); however, these are not without side effects. Side effects in the elderly population with thiazolidinediones include fluid retention, fracture risk, and heart failure risk. Side effects in the elderly population with sulphonylureas and metglitinides include hypoglycaemia. In the context of advanced age and diminished renal functions, cases of prolonged and severe hypoglycaemia with sulphonylurea treatment have been reported. Side effects in the elderly population with alpha-glucosidase inhibitors include gastrointestinal side effects. Side effects in the elderly population with rapid acting or short acting insulin include several injections and hypoglycaemia.

Thus, given the above considerations, the benefit-risk assessment for the use of linagliptin for the treatment of T2DM in elderly patients to improve glycaemic control is considered favourable for the conduct of this trial.

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### 3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

#### 3.1 OVERALL TRIAL DESIGN AND PLAN

This randomised, double-blind, multi-national, placebo-controlled, parallel group trial will compare linagliptin 5 mg daily to placebo as add-on therapy to a stable background of basal insulin, metformin (optional), and/or alpha-glucosidase inhibitors (optional) over 24 weeks in elderly T2DM patients with insufficient glycaemic control.

In total, approximately **300 T2DM patients (100 from Japan)**, 60 years of age and older, with insufficient glycaemic control will enter (i.e., be randomised in) this trial. The randomised treatment will be provided in a double-blind design within the two treatment arms (each patient will receive either linagliptin as active treatment or placebo matching linagliptin).

Patients are enrolled into the trial once they have signed the informed consent. The Screen Period is one week in length. All patients meeting the inclusion and exclusion criteria will complete a one week placebo Run-In Period before randomisation.

Patients who successfully complete the Run-In Period and still meet the inclusion and exclusion criteria will be randomised into the 24 week treatment period of the trial in which they will receive either linagliptin 5 mg or placebo.

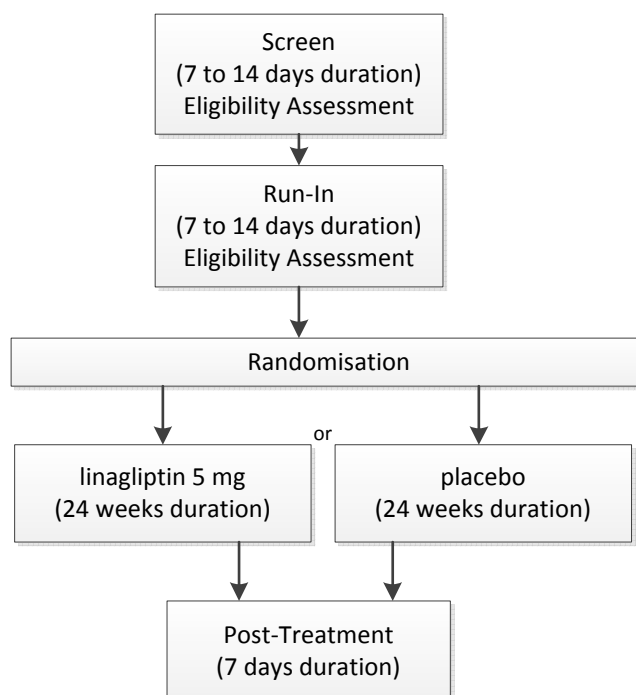


Figure 3.1: Trial Periods

All adverse events with an onset after the first dose of study medication up to a period of seven days after the last dose of study medication will be assigned to the treatment phase for

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evaluation. This includes adverse events that start before first study medication intake and deteriorate under treatment. Other adverse events will be assigned either to the screening, run-in, or follow-up phase as appropriate. All adverse events, including those persisting after trial completion at the Post-Treatment Visit (Visit 99), will be followed-up for up to 7 days. The investigative staff should confirm if continuing adverse events have resolved or have been sufficiently characterised.

The end of the trial is defined as “last patient out”, i.e., last visit completed by the last patient.

### 3.1.1 Administrative structure of the trial

The trial is sponsored by Boehringer Ingelheim Pharma GmbH & Co. KG.

BI will appoint a Trial Clinical Monitor (TCM), responsible for coordinating the activities required in order to manage the trial in accordance with applicable regulations and internal standard operating procedures (SOPs), directing the clinical trial team in the preparation, conduct, and reporting of the trial, order the materials as needed for the trial, ensures appropriate training and information of CML, Clinical Research Associates (CRAs), and investigators of participating countries.

Data Management and Statistical evaluation will be performed by BI according to BI SOPs. For these activities, a Trial Data Manager and a Trial Statistician will be appointed.

Tasks and functions assigned in order to organise, manage, and evaluate the trial will be defined according to BI SOPs. A list of responsible persons will be given in the Trial Master File (TMF) document.

The organisation of the trial in the participating countries will be done by the respective local BI organisation [Operating Unit (OPU)] or a by a Contract Research Organisation with which the responsibilities and tasks will have been agreed and a written contract filed before initiation of the clinical trial. In each OPU participating in this trial, a CML will be appointed responsible for coordinating the activities required in order to manage the trial in accordance with applicable regulations and internal SOPs in the countries covered by the respective BI OPU.

A Co-ordinating Investigator will be nominated to coordinate investigators at different trial sites participating in this multicentre trial. Tasks and responsibilities for the Co-ordinating Investigator will be defined in a contract filed before initiation of the trial.

Documents on participating (Principal) investigators and other important participants, especially their curricula vitae, will be filed in the TMF.

A BI preferred central laboratory, ECG, and IRT provider will be selected to provide services for laboratory sample handling and analyses, ECG interpretation, and for study medication logistics, respectively as required for this protocol.

The eDiary and HBGM device will be provided by a BI preferred provider.

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Details on handling of the trial supplies including responsible institutions are given in [Section 4](#) of this protocol.

The Investigator Site File (ISF) will be kept in printed version at the trial sites as far as required by local regulation and BI SOP. A copy of the ISF documents will be kept as an electronic TMF document according to BI SOPs.

Based on the known safety profile, therapeutic window, and tolerability of linagliptin, a Data Monitoring Committee is not required for this trial.

#### Clinical Event Committees:

Independent, blinded, external committees will be managed by BI's third party preferred provider and set up for adjudication of pancreatic, cerebrovascular, and cardiovascular events. Details on the composition of each of the committees, their respective procedures and interaction will be provided in separate Clinical Event Committee (CEC) charters that will be filed in the TMF.

### **3.2 DISCUSSION OF TRIAL DESIGN, INCLUDING THE CHOICE OF CONTROL GROUPS**

Due to its mechanism of action and the low risk for hypoglycaemia induction, DPP-4 inhibitors like linagliptin should provide additional efficacy alongside manageable tolerability and safety in elderly patients when added to background antidiabetic therapy consisting of basal insulin, metformin (optional), and/or alpha-glucosidase inhibitors (optional).

Elderly patients with T2DM who have insufficient glycaemic control will enter the trial and receive either double-blind linagliptin or placebo. The placebo-controlled design is considered ethically acceptable on the basis of the benefit and risk assessment, as defined in [Section 2.3](#); appropriate criteria for patient discontinuation, ability to adjust or change permitted antidiabetic therapy to maintain, or obtain sufficient level of glycaemic control, as defined in [Section 4.2.1](#); and relevant local and regional guidelines for optimized standard of care.

The randomised treatment period is planned for 24 weeks because the primary efficacy endpoint of HbA<sub>1c</sub> has been shown to reflect glycaemic control over the preceding 12 weeks and this period should allow sufficient time to demonstrate changes in the incidence of hypoglycaemia events. The 1-week Post-Treatment period is considered to be sufficient, as previous trials with linagliptin have shown that the pharmacodynamic effect of linagliptin only extends to about 7 days after the last dose.

The permitted background antidiabetic therapy will not be provided as part of the clinical trial supplies, unless required by local laws and regulations.

The rationale for dose and dose-interval selection is described in [Section 4.1.3](#).

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### 3.3 SELECTION OF TRIAL POPULATION

This is an international trial in which approximately **300 patients (100 patients from Japan)** will be randomised to treatment (**150 patients to each treatment group**).

It is expected that at least 4 to 8 patients should be enrolled (or screened) at each trial site. If enrolment is delayed, additional trial sites may be recruited.

The IRT system will permit each trial site to randomise up to 30 patients. The TCM may allow the randomisation of additional patients after a careful assessment of potential bias due to the patient distribution across trial sites. Permission for a trial site to randomise more than 30 patients must be obtained from the TCM in writing, via the Clinical Monitor Local at BI, in order to increase the number of patients allowed to be randomised at the trial site.

Screening of patients for this trial is competitive (i.e., when a sufficient number of patients have been screened and/or randomised to study medication, screening of patients for the trial will end at all trial sites). **It is possible that recruitment for countries may be stopped while recruitment in Japan continues in order to achieve the required 100 patients randomized in Japan.** Investigators will be notified when a sufficient number of patients have been screened and of the date on which screening will finish. The date that screening may end could be within a 24 hour period of time depending on enrolment numbers. Therefore, investigators may need to contact patients in order to cancel planned screening visits. The investigators will not be allowed to recruit additional patients for this trial after the date that screening has ended. Patients who have completed Screen procedures prior to notification of the termination of recruitment will be allowed to continue in the trial if they meet all entry criteria and are able to follow the visit schedule specified in this protocol.

Patient eligibility will be assessed by a complete medical history, which may be obtained by the investigator verbally from the patient during a trial site visit but is required to be documented in a source document by the investigator (including past medical records of **at least 1 year**), physical examination, and laboratory tests as described in this protocol. Judgement of the clinical relevance of a concomitant disease is at the discretion of the investigator. Conditions under therapy are always clinically relevant.

A log of all patients included into the trial (i.e., having given informed consent) will be maintained in the ISF at the trial site irrespective of whether they have been treated with study medication or not.

#### 3.3.1 Main diagnosis for study entry

The trial will be conducted in elderly patients with T2DM on stable basal insulin, metformin (optional), and/or alpha-glucosidase inhibitors (optional) with insufficient glycaemic control, who may or may not be on a diet and exercise program per standard local clinical practice, prior to entry.

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### 3.3.2 Inclusion criteria

1. Patients must sign and date an Informed Consent consistent with International Conference on Harmonisation (ICH) / Good Clinical Practice (GCP) guidelines and local regulations prior to any evaluation and participation in the trial.
2. Male and female patients with a clinical diagnosis of T2DM, at the time of Informed Consent, who are:
  - a. **60** years of age or older at informed consent or Screen Visit,
  - b. taking stable doses of basal **or biosimilar basal** insulin [strictly inclusive of: insulin neutral protamine Hagedorn (NPH), **Humalog Basal® (a suspension of insulin lispro protamine)**, and isophane insulin; insulin degludec; insulin detemir; and insulin glargine] for at least 4 weeks prior to randomisation (Visit 3) with dose adjustments up to a maximum of +/- 20% of baseline being allowed,
  - c. may or may not be taking metformin immediate release or extended release [if the patient is taking metformin, stable dose must be maintained for at least 12 weeks without dose adjustments prior to randomisation (Visit 3)], and
  - d. may or may not be taking alpha-glucosidase inhibitors [acarbose, miglitol, and voglibose; if the patient is taking alpha-glucosidase inhibitors, stable dose must be maintained for at least 12 weeks without dose adjustments prior to randomisation (Visit 3)].
3. Patients must have an HbA<sub>1c</sub> of **7.0%** [**53** millimoles per mole (mmol/mol)] to 10.0% (86 mmol/mol) at the first visit (Screen).
4. Patients must have a BMI of 45 kg/m<sup>2</sup> or less at the Screen Visit.
5. In the investigator's opinion, patients must be reliable, compliant, and agree to cooperate with all planned future trial evaluations as explained in detail during the informed consent process and to be able to perform them.

### 3.3.3 Exclusion criteria

Patients with, who are, who have, or who have had:

1. Impaired cognitive ability as supported by the Saint Louis University Mental Status Examination ([R14-0995](#), [R14-0977](#), [R14-0992](#)), additional assessment if necessary (as described below), and verified by the investigator at Screen. Saint Louis University Mental Status Examination scores of **21 to 26** for those patients with high school education or **20 to 24** for those patients who did not complete a high school education indicate that the patient probably **has mild neurocognitive disorder and may be further evaluated as noted below**.

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The investigator may complete an additional assessment based on typical activities of daily living so that **mild neurocognitive disorder** can be ruled out if the investigator believes that a patient does not have **mild neurocognitive disorder** as supported by the score on the Saint Louis University Mental Status Examination. Patients with **dementia scores on this assessment of 1 to 20 with a high school education equivalent or 1 to 19 without a high school education equivalent must not proceed with further evaluations in the Screen Visit.**

Note: High school or upper secondary education (completing approximately 12 grade levels) equivalents may include the following examinations or certificates such as General Certificate of Education, Leaving Certificate, Reifezeugnis or Abitur, Apolyterion, Baccalaureate, Matura, Swiadectwo Dojrzalosci, Maturity, Studentereksamen, Ylioppilastutkintodistus or Studentbetyg, Diploma de Maturitate, Corso de Orientacion Universitaria, Senior High School Grad, Gymnasium, Higher Preparatory Examination, Higher Commercial Examination, Higher Technical Examination, Bachillerato, University Entrance Certificate, Senior Certificate, National Senior Certificate, Joint Matriculation Board Certificate, Advanced Level Exams, National Senior Certificate or Matric examination.

2. Depressed mood as supported by a score of 10 or more on the Patient Health Questionnaire ([R13-3779](#)) at the Screen Visit.
3. Type 1 Diabetes Mellitus as determined by past medical records and history.
4. Acute coronary syndrome [non-ST Elevation Myocardial Infarction (STEMI), **STEMI, and/or unstable angina pectoris**], stroke or transient ischemic attack within 3 months prior to Screen Visit.
5. Indication of liver disease determined during Screen and/or Run-In Period, defined by a serum level above 3 times the upper limit of normal (ULN) in any of the following: alanine aminotransferase [ALT or called serum glutamic pyruvic transaminase (SGPT)], aspartate aminotransferase [AST or serum glutamic oxaloacetic transaminase (SGOT)], or alkaline phosphatase. Gilbert-Meulengracht syndrome (also known as conjugated hyperbilirubinemia, constitutional hepatic dysfunction, or familial nonhemolytic jaundice) will be permitted.
6. Bariatric, gastric bypass, and other gastrointestinal procedures or surgeries (including all types of gastric banding, restriction, and/or LapBand®) with the objective of promoting weight loss within the past two years at Screen Visit.
7. Medical history of cancer (except for resected non-invasive basal or squamous cell carcinoma) and/or treatment for cancer within the last 5 years.
8. Blood dyscrasias or any disorders causing hemolysis or unstable red blood cells (e.g., malaria, babesiosis, haemolytic anaemia).
9. Treatment with GLP-1 analogues within 3 months prior to Informed Consent.

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10. Treatment with sulphonylureas, thiazolidinediones, **meglitinides, bromocriptine**, SGLT2 inhibitors, or DPP-4 inhibitors within 3 months prior to randomization (Visit 3).
11. Treatment with rapid acting or short acting insulin and/or pre-mixed insulin containing rapid acting or short acting insulin within 3 months prior to randomization (Visit 3).
12. Known hypersensitivity, allergy, or any contraindication to linagliptin or its excipients or the patients' background therapy (i.e., basal insulin, metformin, or alpha-glucosidase inhibitors) or placebo, according to local labels.
13. Treatment with anti-obesity drugs, including over-the-counter drugs such as Alli® (orlistat), 4 weeks prior to informed consent or any other treatment at the time of screening (i.e., surgery, aggressive diet regimen, etc.) leading to unstable body weight.
14. Current treatment with any drugs known to have significant effect on glucose metabolism, such as systemic steroids, at time of informed consent or change in dosage of thyroid hormones within 6 weeks prior to informed consent or any other uncontrolled endocrine disorder excluding T2DM.
15. Alcohol or drug abuse within the 3 months prior to informed consent that would interfere with trial participation or any ongoing condition leading to decreased compliance to trial procedures or study medication intake in the opinion of the investigator.
16. Participation in another trial with an investigational drug within 2 months prior to informed consent.
17. Psychological, familial, sociological, or geographical factors potentially hampering compliance with the protocol, visits, or trial procedures or any other clinical condition that would jeopardize patient safety while participating in this clinical trial in the opinion of the investigator.
18. Inability to commit to regular overnight fasting of at least 10 hours duration and attendance to trial site visits between 07:00 and 11:00 ante meridiem (a.m.).

NOTE: No protocol waivers will be granted for any reason during the trial. Patients who do not meet one or more of the entry criteria or discontinue before Visit 3 will not be randomised and will be screen failures. The primary reason for the screen failure will be recorded on the electronic case report form (eCRF).

If a protocol violation occurred in relation to inclusion or exclusion criteria and a patient was mistakenly randomized, the investigator will need to contact the CML to request permission for the patient to continue in the trial, document the reason for this protocol violation in the patient's medical records, and report the protocol violation to their Institutional Review Board (IRB) or Independent Ethics Committee (IEC).

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### 3.3.4 Removal of patients from therapy or assessments

#### 3.3.4.1 Removal of individual patients

##### Screen failures

Patients who do not meet one or more of the entry criteria or discontinue before Visit 3 will not be randomized and will be screen failures. The primary reason for the screen failure will be recorded on the eCRF. Patients who have screen failed in this trial are not permitted to be re-screened at a later time point.

##### Discontinuing or withdrawing patients from the trial

If a patient discontinues (drops out or withdraws) from this trial after randomization, the patient will not be replaced.

Patients have the right to withdraw from this trial at any time for any reason. The patients will be asked by the investigator to provide the specific reason for their withdrawal from the trial (e.g., moving out of the state or country, unable to drive to trial site, etc.) and this reason will be recorded on the eCRF.

Patients who discontinue from this trial are not allowed to re-enrol in this trial, including patients from other trial sites.

Patients will be discontinued from the trial for:

- significant non-compliance (If the patient fails to comply with the protocol (e.g., non-compliance with study medication or evaluations), a patient may be discontinued after discussion between investigator and sponsor),
- concomitant drugs that interfere with the medications being given in this trial,
- no longer being able to participate for other medical reasons (e.g., surgery, AEs, or other diseases),
- persistent hyperglycaemia that is uncontrolled with rescue medication as described in [Section 4.2.1](#) (In this case, the reason for discontinuation will be classified as “lack of efficacy”), and
- occurrence of hypoglycaemia that may put the patient at risk with continued participation (e.g., repeated hypoglycaemic episodes).
- If pancreatitis is suspected, the study medication should be stopped.

The investigator also has the right to withdraw patients from the trial because continuation of study medication or continuation of the follow up visits may not be in the best interest of the patient.

If necessary for patient safety, as determined by investigator, new antidiabetic medication regimen may be started the day after study medication discontinuation. The new antidiabetic medication must be recorded in eCRFs.

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It is understood by all concerned that an excessive rate of withdrawals can render the trial uninterpretable; therefore, unnecessary withdrawal of patients should be avoided. Should a patient decide to discontinue, all efforts by the investigator will be made to complete and report the last treatment visit evaluations (i.e., Visit 98) as thoroughly as possible.

If a patient discontinues from this trial, the patient should have the Visit 98 (the final assessment that is considered to be on-treatment or shortly thereafter) evaluations completed as soon after stopping study medication as possible. Additionally, the patient should have the Post-Treatment Visit (Visit 99) evaluations completed one week after Visit 98. The investigator or a staff member should contact the patient (or a responsible relative or designee) either by telephone to determine the primary reason for withdrawal from the trial if the patient refuses to return to the trial site. The primary reason for the withdrawal from the trial will be recorded on the Termination of Trial Medication eCRF. If the patient is dropped due to an adverse event, the Termination of Trial Medication form must agree with the adverse event eCRF. The reason for discontinuation will be included in the trial database and reported.

#### 3.3.4.2 Discontinuation of the trial by the sponsor

BI reserves the right to discontinue the trial overall or at a particular trial site at any time for the following reasons:

1. Failure to meet expected enrolment goals overall or at a particular trial site
2. Emergence of any efficacy/safety information that could significantly affect continuation of the trial and/or invalidate the earlier positive benefit-risk-assessment
3. Violation of GCP, this protocol, or the contract by a trial site or investigator, disturbing the appropriate conduct of the trial.

The investigator and/or the trial site will be reimbursed for reasonable expenses incurred in case of trial termination (except in case of the third reason).

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## 4. TREATMENTS

### 4.1 TREATMENTS TO BE ADMINISTERED

The study medication will be provided by Boehringer Ingelheim Pharma GmbH & Co. KG.

#### 4.1.1 Identity of BI investigational product and comparator product

The characteristics of the test products are below.

Substance:	linagliptin film-coated tablet 5 mg
Pharmaceutical form:	tablet
Source:	Boehringer Ingelheim Pharma GmbH & Co. KG
Unit Strength:	5 mg
Route of administration:	p.o., once daily

Substance:	placebo for linagliptin film-coated tablet 5 mg
Pharmaceutical form:	tablet
Source:	Boehringer Ingelheim Pharma GmbH & Co. KG
Unit Strength:	N/A
Route of administration:	p.o., once daily

#### 4.1.2 Method of assigning patients to treatment groups

When a patient is qualified for entry into the randomised, double-blind treatment period, treatment assignment will be by means of a third-party phone/web-based randomisation at Visit 3.

Patients will be randomly assigned to linagliptin film-coated tablet 5 mg or placebo for linagliptin film-coated tablet 5 mg in a 1:1 ratio. The randomisation will be stratified by HbA<sub>1c</sub> (< 8.5% vs. ≥ 8.5%) as determined from the blood sample taken at Visit 1 and insulin dose (< 40 international units total daily dose vs. ≥ 40 international units total daily dose) as determined at the beginning of the placebo run-in period (Visit 2). To ensure appropriate representation of patients with insulin doses of < 40 international units total daily dose as well as ≥ 40 international units total daily dose, the trial team will monitor the proportion of patients being recruited into these categories. The limitation of recruitment of a particular category may be arranged (on trial level and/or country level). For further details, refer to [Section 7.5](#).

Patient assignment to the treatment groups will be determined by a computer generated random sequence. IRT will be used to assign study medication. IRT handling details are described in the manual for IRT procedures, which is available in the ISF. Access to the randomisation code will be controlled and documented, for further details refer to [Sections 4.1.5.1](#) and [4.1.5.2](#).

The assigned medication numbers will be entered in the eCRF, and the corresponding study medication bottle should be given to the patient. Using this procedure, relevant parties will

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be blinded to the treatment group assignment.

#### 4.1.3 Selection of doses in the trial

The dose of 5 mg linagliptin was selected based on the results from previous dose ranging studies (refer to Investigator's Brochure, [U04-1767](#), current version) and represents the final marketed dose for linagliptin.

#### 4.1.4 Drug assignment and administration of doses for each patient

Patients will continue with the permitted antidiabetic therapy throughout the duration of the trial unless a medical emergency or another plausible reason (e.g., renal impairment, lactic acidosis, dose intolerance, hypoglycaemia, or hyperglycaemia) necessitate changes (at the discretion of the investigator). If a patient is taking antidiabetic therapy that includes metformin and is expected to be exposed to an iodine-containing contrast agent for a diagnostic or surgical procedure, metformin should be temporarily stopped before and after the administration of iodine-containing contrast agent according to the metformin prescribing information and regional or local guidelines.

Patients who qualify for double-blind treatment will be randomized to one of the dosage and treatment schedules described in Table 4.1.4: 1. The study medication for this trial will be dispensed in a double-blind manner. Each patient will receive a Run-In bottle at Visit 2 and be instructed to take placebo medication daily for one week. At Visit 3, patients who qualify based on inclusion and exclusion criteria will be randomised to one of the two dosage regimens, either linagliptin 5 mg daily or placebo matching linagliptin daily.

Dispensing of bottles for the double-blind treatment period will begin at Visit 3. Dispensing will occur on 4 occasions over a period of 24 weeks. For further details regarding packaging (e.g., number of tablets per bottle), refer to [Section 4.1.6](#).

Table 4.1.4: 1 Treatment group dosing schedule

Group 1: linagliptin 5 mg treatment group

Visit	Day	Treatment arm	Morning	Note
2	-7	placebo	○	Run-In Period
3 to 98	1 to 169	linagliptin 5 mg	●	Treatment Period: The last dose of study medication will be taken by the patient on the morning before Visit 98.

●: linagliptin 5 mg tablet; ○: placebo for linagliptin 5 mg tablet

Group 2: placebo for linagliptin 5 mg tablet treatment group

Visit	Day	Treatment arm	Morning	Note
2	-7	placebo	○	Run-In Period
3 to 98	1 to 169	placebo for linagliptin 5 mg	○	Treatment Period: The last dose of study medication will be taken by the patient on the morning before Visit 98.

○: placebo for linagliptin 5 mg tablet

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Administration of the study medication is once daily. Study medication can be taken with or without food. At Visit 2 and each subsequent clinic visit, the investigator will open the study medication bottle and administer the first dose of study medication to the patient after the safety laboratory tests and ECG, if applicable, have been completed.

At the beginning of the placebo Run-In Period (Visit 2), patients should be instructed to take 1 tablet with water in the morning. To ensure a dose interval of about 24 hours, the medication should be taken at the same time every morning. If a dose is missed by more than 12 hours, that dose should be skipped and the next dose should be taken as scheduled. No double doses should be taken and dose reductions are not permitted.

Patients should be instructed not to take their study medication and remain fasting on the morning of clinic visits. After the laboratory tests and ECG (if applicable at that particular visit) have been completed, the investigator will open the study medication bottle and administer the first dose of study medication to the patient. Patients who fail to follow this procedure should have the visit rescheduled as soon as possible, ideally on the following day. Visits will be routinely scheduled in the morning from 07:00 a.m. to 11:00 a.m., at approximately the same time of day for each visit. The actual date and time of administration of the study medication at the clinic visit will be recorded in the eCRF.

#### **4.1.5 Blinding and procedures for unblinding**

##### **4.1.5.1 Blinding**

This is a double-blind, placebo-controlled trial. After randomisation at Visit 3, all patients, members of the investigative staff, sponsor's Clinical Trial Team, and anyone involved in analysing or with an interest in this trial are to remain blinded to the randomisation treatment assignments until after the database is locked. The randomisation treatment assignments (code) will be kept secret by Clinical Trial Support until database lock.

During the trial conduct, a Clinical Safety Officer or representative from BI's Global Pharmacovigilance group will have access to the randomisation code for individual patients and would be able to unblind Serious Unexpected Suspected Adverse Reactions (SUSARs) for regulatory requirements to report these events. In such cases, access to the randomisation treatment assignments will only be provided to authorised Clinical Safety Officers or representatives of Global Pharmacovigilance.

Please refer to Section 4.1.5.2 for the procedure regarding unblinding the randomisation code for an individual patient in an emergency situation.

##### **4.1.5.2 Procedures for emergency unblinding**

An emergency unblinding process will allow the investigator to access an individual patient's treatment via IRT. This emergency unblinding process may only be initiated in emergency situations when the identity of the study medication must be known to the investigator in order to provide appropriate medical treatment or if required to assure safety of trial participants. The investigator will contact the sponsor to discuss the emergency situation as

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soon as possible. The reason for obtaining the emergency unblinding must be documented in the appropriate eCRF along with the date and the reason for unblinding the study medication.

#### **4.1.6 Packaging, labelling, and re-supply**

Study medication will be provided by the Department of Pharmaceutical Development of Boehringer Ingelheim Pharma GmbH & Co. KG, Biberach, Germany.

The study medication will consist of bottles labeled with the trial identification and medication number. After randomisation, each bottle will contain an appropriate number of linagliptin or placebo matching linagliptin tablets with two weeks reserve, for dosing until the next scheduled visit.

Study medication will be supplied on a per visit basis. Supply and re-supply will be managed by IRT.

For details of packaging and the description of the label, refer to the ISF.

#### **4.1.7 Storage conditions**

The study medication must be kept in its original packaging under the recommended storage conditions indicated on the label.

Trial sites must maintain a temperature log in the location that the study medication is being stored. The temperature must be recorded daily with temperature range (minimum and maximum temperatures) being collected for the week (i.e., thermometers must record and retain temperatures for 7 days so that temperatures can be retrieved and recorded for holidays and weekends). If the storage conditions are found to be outside the specified range, immediately contact the CRA and CML, as provided in the list of contacts in the ISF, in writing.

Following completion of the trial, all unused medication as well as bottles and containers must be returned to the Sponsor. Please refer to the detailed instructions on how to return the study medication in [Section 4](#) of the ISF. Receipt, usage, and return must be documented on the appropriate forms. An account must be provided for all discrepancies.

#### **4.1.8 Drug accountability**

Study medication, which will be provided by the Sponsor and/or an IRT vendor appointed by the Sponsor, must be kept in a secure, limited access storage area under the storage conditions defined by the sponsor. A temperature log must be maintained to make certain that the study medication is stored at the correct temperature.

The investigator, pharmacist, or study medication storage manager will receive the study medications delivered by the sponsor when the following requirements are fulfilled:

- approval of the trial protocol by the IRB or ethics committee,

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- availability of a signed and dated clinical trial contract between the sponsor and the principal investigator or trial site,
- approval/notification of the regulatory authority, e.g., competent authority (CA),
- availability of the curriculum vitae of the principal investigator,
- availability of a signed and dated clinical trial protocol (CTP) or immediately imminent signing of the CTP (in exceptional cases, medication could already be sent to the trial site, before its activation via IRT)
- availability of the proof of a medical licence for the principal investigator, and
- for the United States, availability of the FDA Form 1572.

The investigator, pharmacist, or study medication storage manager must maintain records of the study medication's delivery to the trial site, the inventory at the trial site, the use by each patient, and the return to the sponsor or alternative disposition of unused study medication.

These records will include dates, quantities, batch/serial numbers, expiry ('use by') dates, and the unique code numbers assigned to the study medication and patients in the trial. The investigator, pharmacist, or study medication storage manager will maintain records that document adequately that the patients were provided the doses specified by the CTP and reconcile all study medication received from the Sponsor. At the time of return to the Sponsor or appointed IRT vendor, the investigator, pharmacist, or study medication manager must verify that all unused or partially used study medication has been returned by the patients in the trial and that no remaining study medication is in the investigator's possession.

*The following text is only applicable for Japan:*

*The investigator, pharmacist, or study medication storage manager will receive the study medication delivered by the sponsor representative after IRB or ethics committee approval of the trial and completion of a clinical trial contract between the sponsor representative and the Head of Trial Site.*

*The investigator, pharmacist, or study medication storage manager should return the unused and collected study medication (including the empty boxes) to the sponsor after unblinding the trial.*

*In case study medication is returned before unblinding of the trial, the investigator, pharmacist, or study medication storage manager should seal the opened box (excluding empty boxes) for the patient, and before returning the unused and collected study medication (including the empty boxes) to the sponsor. When returning the study medication, the investigator, pharmacist, or study medication storage manager should exercise utmost caution to assure that the sponsor representative and other relevant trial staff members remain blinded to the patient's name on the package (box or label) of the study medication.*

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*Upon completion of the trial, the investigator, pharmacist, or study medication storage manager submits to the sponsor representative a copy of the study medication dispensing and return log. When submitting the copy, the investigator, pharmacist, or study medication storage manager should exercise caution to assure that the sponsor representative and other relevant trial staff members remain blind to the patient's name.*

## 4.2 CONCOMITANT THERAPY, RESTRICTIONS, AND RESCUE TREATMENT

### 4.2.1 Rescue medication, emergency procedures, and additional treatments

Patients should only take study medication and the permitted antidiabetic therapy of basal insulin, metformin (optional) and/or alpha-glucosidase inhibitor (optional) after randomisation (i.e., from Visit 3 to Visit 98) for the treatment of T2DM.

The patient's permitted antidiabetic therapy should not be increased or decreased by > 20% from stable baseline during the 7 day period from the Run-In Visit to randomisation (Visit 3).

After randomisation, investigators should review the patient's HBGM results electronically for hyperglycaemia and should **follow the permitted antidiabetic therapy criteria noted below** to achieve improved patient glycaemic control before taking any additional action **with rescue therapy**. Additionally, investigators should review the patient's HBGM and eDiary results electronically for hypoglycaemia and should adjust or decrease the patient's permitted antidiabetic therapy by electronic contact with the patient via the eDiary or recommend other medical advice (e.g., encouraging the patient not to skip meals, increasing carbohydrate intake if increasing exercise, etc.) to achieve improved or individualised patient glycaemic control before taking any additional action.

#### Criteria for Increasing, Adjusting, or Decreasing Permitted Antidiabetic Therapy

If the following FPG criteria are met and if further supported by HBGM results during the same time period, investigators may increase or adjust the patient's permitted antidiabetic therapy (i.e., the patient's background therapy of stable basal insulin prior to or after informed consent, and if applicable metformin and/or alpha-glucosidase inhibitor) for the treatment of hyperglycaemia ([R08-2669](#)):

#### Visit 3 to Visit 5

- The patient has a FPG level > 270 mg/dL [ $>15.0$  millimoles per Liter (mmol/L)] drawn by the study staff for the central lab after an overnight fast

#### Visit 5 to Visit 98

- The patient has a FPG level >240 mg/dL ( $>13.3$  mmol/L) drawn by the study staff for the central lab after an overnight fast

If the above criteria are met, the investigator should increase or adjust (e.g., by changing the timing of administration, etc.) the patient's permitted antidiabetic therapy to improve glycaemic control according to investigator's discretion and the changes should be documented in the eCRF.

If the patient is experiencing hypoglycaemia, the investigator should review the eDiary responses to diet and physical activity as well as the HBGM results to determine the

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appropriate approach to reduce occurrences of hypoglycaemia (e.g., encouraging the patient not to skip meals, increasing carbohydrate intake if increasing exercise, decreasing or adjusting the patient's permitted antidiabetic therapy).

**The following permitted antidiabetic therapy will be considered to be rescue therapy:**

- **For patients with a baseline daily insulin dose  $\leq 10$  units, any increase of basal insulin  $>50\%$  from baseline for  $> 7$  days duration**
- **For patients with a baseline daily insulin dose  $>10$  and  $\leq 20$  units, any increase of basal insulin  $>30\%$  from baseline for  $> 7$  days duration**
- **For patients with a baseline daily insulin dose  $> 20$  units, any increase of basal insulin  $>20\%$  from baseline for  $> 7$  days duration**
- **Any increase in metformin and/or alpha-glucosidase inhibitors (AGI) for  $\geq 1$  day**
- **Any introduction of a new antidiabetic therapy for  $\geq 1$  day.**

**Due to the elderly population and the inclusion of patients on very low daily insulin doses at baseline, this allows short term increases that may be required for reasons not associated with glycaemic control, e.g., medical procedures.**

Initiating Rescue Medication (i.e., additional medications)

Rescue medication cannot be initiated during the Run-In Period and would prohibit the randomisation of the patient.

If increasing or adjusting the patient's permitted antidiabetic therapy, as noted above, is unsuccessful in reducing the patient's FPG to 270 mg/dL or lower ( $\leq 15.0$  mmol/L) after an overnight fast following a dosage adjustment period of 6 weeks (i.e., occurring no earlier than Visit 4), the initiation of rescue medication is at the investigator's discretion, based on the patient's current clinical condition (e.g., ongoing illness, etc.).

Before the initiation of rescue therapy, a sample for FPG and HbA<sub>1c</sub> will be taken using the central laboratory. The HbA<sub>1c</sub> sample is not required if the HbA<sub>1c</sub> has been completed by the central laboratory within the last 4 weeks.

The choice of rescue medication and its dosage will be left to the discretion of the investigator. However, DPP-4 inhibitors and/or a GLP-1 agonist/analogue are not allowed to be used as rescue medication.

Rescue medication will not be provided as part of the clinical trial supplies, unless required by local laws and regulations. The rescue medication should be taken in accordance with the local prescribing information of that respective medication, taking into account potential contraindications.

If no further effect from the rescue medication is anticipated, in the investigator's clinical opinion, and/or the patient's hyper- or hypoglycaemia cannot be controlled, the patient should be discontinued from the trial as specified in [Section 3.3.4](#).

All concomitant (additional) and/or rescue medication will be recorded in the source documents and on the appropriate pages of the eCRF.

Any additional treatment, that does not qualify as a rescue medication, and is considered necessary for the patient's welfare may be given at the discretion of the investigator. Restrictions to additional treatment are described in [Section 4.2.2](#).

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There are no special emergency procedures to be followed.

#### 4.2.2 Restrictions

##### 4.2.2.1 Restrictions regarding concomitant treatment

The use of the following classes of antidiabetic medications will be prohibited during the course of the trial: sulphonylureas, thiazolidinediones, SGLT2 inhibitors, meglitinides, bromocriptine, GLP-1 analogues or DPP-4 inhibitors. The use of rescue medication for elevated FPG levels is noted in [Section 4.2.1](#).

Short-term use of rapid-acting insulin (e.g., in the event of hospitalisation) will be permitted based on clinical judgement of the investigator or treating physician. Prolongation of rapid-acting insulin treatment over more than 2 weeks vs. treatment discontinuation should be discussed on a case-by-case basis between the investigator and the CML or TCM. Refer to [Section 3.3.3](#) regarding the permitted use of antidiabetic agents.

Additionally, treatment with anti-obesity drugs [including over the counter preparations such as Alli®(orlistat)] or systemic steroids will be prohibited due to their influence on glucose metabolism. However, one off or short-term use (i.e., ≤ 1 week duration) of systemic steroids will be permitted as well as therapy with non-systemic steroids such as inhaled or local steroids. Furthermore, for patients taking thyroid hormones, any change in the dose should be avoided. If dose changes do occur, then they should be recorded in the source documents and in the eCRF.

No special contraindication for concomitant use with linagliptin is known based on the data from drug development to date (refer to [Section 1.2](#)).

For patients who are taking metformin as background therapy: If vascular administration of an iodine-containing contrast agent is required, patients should be informed to discontinue metformin 48 hours before the contrast agent is given and not to resume metformin administration until 48 hours after the vascular administration.

##### 4.2.2.2 Restrictions on diet and life style

At the first visit, patients will receive diet and exercise counseling by a diet specialist, trained staff member, physician, or investigator. This diet and exercise counseling will be reviewed at each subsequent visit. Documentation of diet and exercise counseling training of the applicable investigative staff is required to be maintained at the trial site. The counseling will be based on local diet recommendations. The patients will be reminded to follow the agreed diet and exercise plan at every visit. Patients may be provided with diet and exercise educational material (e.g., from national diabetes associations or national health authorities) relevant for the country/region by the trial site.

Patients also should not take part in another clinical trial involving an investigational medicinal product within the 2 months prior to Informed Consent and throughout this trial.

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### 4.3 TREATMENT COMPLIANCE

Patients will be asked to bring all study medication containers (with or without any remaining tablets) with them to each trial visit. The tablets will be counted by the investigator or study coordinator and compliance will be calculated according to the formula:

$$\text{Compliance(\%)} = \frac{\text{Number of tablets actually taken since last tablet count}}{\text{Number of tablets which should have been taken in the same period}} \times 100\%$$

During the Run-In Period, patients must have taken 80% to 120% of their prescribed study medication to be considered compliant. If a patient is non-compliant during the Run-In Period, the investigative staff will review the patient's correct daily dosage and counsel the patient on the importance of proper compliance. Extremely non-compliant (less than or equal to 50% compliant) patients should not be randomised at the discretion of the investigator.

At each visit, the investigative staff will assess medication compliance by counting the tablets remaining. Patients must have taken 80% to 120% of their prescribed study medication to be considered compliant. If a patient is non-compliant at any visit, the investigative staff should determine what the cause of the non-compliance is, will review the patient's correct daily dosage, and counsel the patient on the importance of proper compliance.

Patients who do not take any study medication for 10 consecutive days should not begin taking study medication at the next visit or re-start study medication and should be discontinued from the trial. The investigative staff should determine what the cause of the non-compliance is and bring the patient in for Visit 98 (last assessment considered to be on-treatment) as soon as possible. The patient should return one week later to complete Visit 99 (Post-Treatment Visit). Alternate antidiabetic therapy may be prescribed to patients being discontinued as necessary and any alternate antidiabetic therapy should be documented in the eCRFs.

If a patient has been non-compliant for two consecutive visits, the investigative staff should determine what the cause of the non-compliance is and contact the CML to discuss the patient's participation in the trial.

Patients who are extremely non-compliant (< 50% compliant) for two consecutive visits should be discontinued from study medication and the trial. The investigative staff should determine what the cause of the non-compliance is and bring the patient in for Visit 98 (last assessment considered to be on treatment) as soon as possible. The patient should return one week later to complete Visit 99 (Post Treatment Visit). Alternate antidiabetic therapy may be prescribed to patients being discontinued as necessary and any alternate antidiabetic therapy should be documented in the eCRFs.

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## 5. VARIABLES AND THEIR ASSESSMENT

### 5.1 EFFICACY - PHARMACODYNAMICS

Refer to the [Flow Chart](#) for a schedule of each efficacy observation in the trial.

#### 5.1.1 Endpoints of efficacy

The primary endpoint in this trial is the change from baseline in HbA<sub>1c</sub> after 24 weeks of treatment. Throughout the trial protocol, the term "baseline" refers to the last observation prior to the administration of any randomised study medication.

Secondary endpoints are the following:

- **Proportion of patients experiencing at least one confirmed hypoglycaemic event during 24 weeks of treatment. A confirmed hypoglycaemic event is defined as any symptomatic or asymptomatic event less than 54 mg/dL (< 3.0 mmol/L) as measured by the central laboratory (FPG) or HBGM device, any symptomatic event less than or equal to 70 mg/dL (3.9 mmol/L), and all events classified as "severe hypoglycaemia".**

**Severe hypoglycaemic episode: an event that requires the assistance of another person to actively administer carbohydrates or glucagon because the patient is unable to take the substance on his or her own.**

**Note: If another person hands the carbohydrate or glucagon to the patient without having to actively administer the substance because the patient is able to take the substance on his or her own, the hypoglycaemic episode does not qualify as severe.**

- Proportion of patients with HbA<sub>1c</sub> on treatment <8.0% after 24 weeks of treatment
- Proportion of patients with HbA<sub>1c</sub> on treatment <7.0% after 24 weeks of treatment
- Proportion of patients with HbA<sub>1c</sub> lowering by at least 0.5% after 24 weeks of treatment
- Change from baseline in FPG after 24 weeks of treatment

- [REDACTED]

- [REDACTED]

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*FPG:*

Blood samples for the determination of FPG will be taken after an overnight fast (at least 10 hours after the last meal) at the trial site and processed by central laboratory. The samples should be taken before breakfast and before study medication administration. The samples will be measured using validated assays by a central laboratory. Further details about sample handling and shipment will be located in the ISF (laboratory manual).

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

## 5.2 SAFETY

### 5.2.1 Endpoints of safety

- Incidence and intensity of Adverse Events (AEs)
- Withdrawal due to AEs

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- Incidence of hypoglycaemic events:
  - All investigator-reported hypoglycaemic events (with or without symptoms, with or without measured glucose)
  - Severe or symptomatic hypoglycaemic events
    - Severe or symptomatic events with measured glucose  $\leq 70$  mg/dL (3.9 mmol/L)
    - Severe or symptomatic events with measured glucose  $< 54$  mg/dL ( $< 3.0$  mmol/L)
  - Severe hypoglycaemic event or hypoglycaemic events (with or without symptoms) with measured glucose of  $\leq 70$  mg/dL (3.9 mmol/L)
  - Severe hypoglycaemic event or hypoglycaemic events (with or without symptoms) with measured glucose of  $< 54$  mg/dL ( $< 3.0$  mmol/L)

## 5.2.2 Assessment of adverse events

### 5.2.2.1 Definitions of adverse events

#### Adverse event

An adverse event (AE) is defined as any untoward medical occurrence, including an exacerbation of a pre-existing condition, in a patient in a clinical investigation who received a pharmaceutical product. The event does not necessarily have to have a causal relationship with this treatment.

#### Serious adverse event

A SAE is defined as any AE which results in death, is immediately life-threatening, results in persistent or significant disability / incapacity, requires or prolongs patient hospitalisation, is a congenital anomaly / birth defect, or is to be deemed serious for any other reason if it is an important medical event when based upon appropriate medical judgement which may jeopardise the patient and may require medical or surgical intervention to prevent one of the other outcomes listed in the above definitions.

*For Japan: An AE which possibly leads to disability will be reported as an SAE. Every new occurrence of cancer will be reported as a SAE regardless of the duration between discontinuation of the study medication and the occurrence of the cancer.*

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### Intensity of adverse event

The intensity of the AE should be judged based on the following:

Mild:	Awareness of sign(s) or symptom(s) which is/are easily tolerated
Moderate:	Enough discomfort to cause interference with usual activity
Severe:	Incapacitating or causing inability to work or to perform usual activities

### Causal relationship of adverse event

Medical judgment should be used to determine the relationship, considering all relevant factors, including pattern of reaction, temporal relationship, de-challenge or re-challenge, confounding factors such as concomitant medication, concomitant diseases and relevant history. Assessment of causal relationship should be recorded in the eCRF.

*For Japan: The reason for the decision on causal relationship needs to be provided in the eCRF.*

- Yes: There is a reasonable causal relationship between the investigational product administered and the AE.
- No: There is no reasonable causal relationship between the investigational product administered and the AE.

If a SAE is reported from a blinded trial, the causal relationship must be provided by the investigator for all potential trial drugs, i.e. the BI trial drug and for all other trial drugs (i.e., any active comparator or placebo according to the trial design).

### Worsening of the underlying disease or other pre-existing conditions

Worsening of the underlying disease or of other pre-existing conditions will be recorded as an AE or SAE (if SAE criteria are met) in the eCRF.

### Changes in vital signs, ECG, physical examination, and laboratory test results

Changes in vital signs, ECG, physical examination and laboratory test results will be recorded as an AE or SAE (if SAE criteria are met) in the eCRF, if they are judged clinically relevant by the investigator.

### Criteria for hypoglycaemic events

Every episode of FPG or blood glucose (by HBGM device) below **or equal to** 70 mg/dL (3.9 mmol/L) should be documented as a hypoglycaemic event in the eCRF with the respective time and date of occurrence.

Symptomatic, severe, and hypoglycaemias with FPG or blood glucose values < 54 mg/dL (< 3.0 mmol/L) should be documented as an AE of "hypoglycaemic event". Data related to these hypoglycaemic events [i.e., symptomatic, severe, and hypoglycaemias with FPG or blood glucose values < 54 mg/dL (< 3.0 mmol/L)] will be collected on a specific eCRF and included in the clinical trial report.

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In the case of hypoglycaemia that may put a patient at risk (for example, repeated symptomatic hypoglycaemia, or severe hypoglycaemia), appropriate adjustment of background therapy such as a dose reduction or time change should be initiated. Patients should be instructed to contact the trial site if they experience symptomatic hypoglycaemia.

#### Adverse Events of Special Interest

The following events are considered as Adverse Events of Special Interest (AESI):

- Hypersensitivity reactions such as angioedema, angioedema-like events, and anaphylaxis
- Skin lesions such as exfoliative rash, skin necrosis, or bullous dermatitis
- Hepatic events such as  $\geq 3$  fold ULN of AST and/or ALT in combination with an elevation of total bilirubin  $> 2$  fold ULN measured in the same blood draw sample, hepatitis, hepatic injury, jaundice and potential Hy's Law cases
- Renal adverse events such as acute renal failure
- Pancreatitis (refer to the ISF)
- Pancreatic cancer

Protocol-specified AESI (as identified by the investigator based on the above definitions for Adverse Events of Special Interest) can be classified as serious or non-serious but all these AESIs once identified by the investigator must be reported on an SAE form in an expedited manner similar to SAEs (within 24 hours of awareness), even if they do not meet any of the SAE seriousness criteria (refer to [Section 5.2.2.1](#) for details). Beyond of this, and for the purposes of ongoing pharmacovigilance activities by the sponsor, adverse events based on additional searches for coded preferred terms of adverse events captured in the trial database (such as Special MedDRA Queries and user defined searches) will be queried to verify with the investigator if the adverse event reported represent a suspected or diagnosed protocol-specified AESI. AESIs once identified by the investigator must be reported on an SAE form in an expedited manner similar to SAEs, even if they do not meet any of the SAE seriousness criteria.

These additional searches (summarised under the so called 'overview of protocol-specified AESIs and safety topics of interest ') may change according to active pharmacovigilance of linagliptin. The most up to date list of these searches will be included in the Remote Data Capture (RDC) system and changes will be communicated to all investigators.

#### 5.2.2.2 Adverse event and serious adverse event reporting

All adverse events, serious and non-serious, occurring during the course of the clinical trial (i.e., from signing the informed consent onwards through the last per protocol contact) will be collected, documented and reported to the sponsor by the investigator on the appropriate

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eCRFs / SAE reporting forms. Reporting will be done according to the specific definitions and instructions detailed in the ‘Adverse Event Reporting’ section of the ISF.

The residual effect period (REP), defined as the period of time after the last dose of medication when measurable drug levels or pharmacodynamic effects are still likely to be present, for linagliptin is 7 days. Therefore all events reported within 7 days of the last trial medication will be considered on-treatment. The follow-up period, defined as the period between the last medication and the last per protocol visit, is 7 days.

Reporting will be done according to the specific definitions and instructions detailed in the ‘Adverse Event Reporting’ section of the ISF.

For each adverse event, the investigator will provide the onset date, end date, intensity, treatment required, outcome, seriousness, and action taken with the investigational drug. The investigator will determine the relationship of the investigational drug to all AEs as defined in [Section 5.2.2.1](#).

The investigator does not need to actively monitor patients for adverse events once the clinical trial has ended. However, if the investigator becomes aware of an SAE(s) that occurred after the patient has completed the clinical trial (including any protocol required REP and / or follow-up period), it should be reported by the investigator to the sponsor if considered relevant by the investigator.

All AEs and/or SAEs, including those persisting after trial completion, must be followed up until they have resolved, have been sufficiently characterized, or no further information can be obtained.

If not stipulated differently in the ISF, the investigator must report the following events immediately (within 24 hours of awareness) to the sponsor: SAEs, AESIs, and non-serious AEs relevant to the reported SAE or AESI.

SAEs occurring in patients after having discontinued in the study due to screening failure and who did not receive any study medication, should only be reported if the investigator considers the SAE to be related to the screening procedure.

BI has set up a list of AEs which are defined to be always serious. In order to support the investigator with the identification of these “always SAEs”, if a non-serious AE is identified to be serious per BI definition, a query will be raised. The investigator must verify the description and seriousness of the event. If the event description is correct, the item “serious” needs to be ticked and an SAE has to be reported in expedited fashion following the same procedure as above.

The list of these always SAEs can be found in the RDC system.

With receipt of any further information to these events, a follow-up SAE report has to be provided. SAEs and non-serious AEs must include a causal relationship assessment made by the investigator.

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*For Japan: This information must be also reported immediately to the head of the trial site.*

The SAE form is to be forwarded to the defined unique entry point identified for the BI OPU (country-specific contact details will be provided in the ISF). This immediate report is required irrespective of whether the investigational product has been administered or not and irrespective of causal relationship. It also applies if new information to existing SAEs or AESIs becomes available.

### 5.2.3 Assessment of safety laboratory parameters

The blood sample at the Screen Visit may be taken with the patient in a fasted or non-fasted state. However, after the Screen Visit, all laboratory samples must be collected after a full overnight fast (nothing to eat or drink except water for at least 10 hours) and before study medication is administered to the patient as described in the [Flow Chart](#) and [Section 6](#).

All laboratory tests that will be performed during the trial are listed in Tables 5.2.3: 1 and [5.2.3: 2](#). The analysis of all laboratory tests will be performed by a central laboratory. The respective reference range and details regarding sample handling and shipment will be provided in the ISF (Laboratory Manual).

Laboratory tests and urinalysis will be performed for the visits as noted in the Flow Chart with the following exceptions:

- For the Screen Visit, only liver transaminases, alkaline phosphatase, serum creatinine, and urinalysis will be performed.
- The lipid panel will be performed for only Visit 3 and Visit 98

Table 5.2.3: 1 Haematology laboratory tests

---

#### Haematology

- Haematocrit
  - Haemoglobin - Reticulocyte Count (reflex test if Haemoglobin outside normal range)
  - Red Blood Cells/Erythrocytes
  - White Blood Cells/Leukocytes
  - Platelet Count/Thrombocytes
  - Differential Automatic (relative and absolute count):  
Neutrophils, Eosinophils, Basophils, Monocytes, Lymphocytes
- 

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Table 5.2.3: 1 (Cont.) Chemistry laboratory tests

<ul style="list-style-type: none"> <li>• Lipase</li> <li>• aspartate aminotransferase (AST, SGOT)</li> <li>• alanine aminotransferase (ALT, SGPT)</li> <li>• gamma-glutamyl-transferase (<math>\gamma</math>-GT)</li> <li>• Alkaline phosphatase</li> <li>• Lactic dehydrogenase (LDH)</li> <li>• Total bilirubin</li> <li>• Total Protein</li> <li>• Direct bilirubin, if total bilirubin is elevated</li> <li>• Albumin</li> <li>• Creatine kinase (CK)</li> <li>• Troponin T (reflex only for CK)</li> <li>• Potassium</li> <li>• activated partial thromboplastin time (aPTT)</li> <li>• fibrinogen</li> </ul>	<ul style="list-style-type: none"> <li>• Sodium</li> <li>• Creatinine</li> <li>• Urea (i.e., blood urea nitrogen)</li> <li>• Calcium</li> <li>• Chloride</li> <li>• Magnesium</li> <li>• Inorganic phosphorous</li> <li>• Uric acid</li> <li>• Cholesterol (total) *</li> <li>• High-Density Lipoprotein (HDL) cholesterol*</li> <li>• Low-Density Lipoprotein (LDL) cholesterol (calculated)*</li> <li>• Plasma triglycerides*</li> <li>• Glucose</li> </ul> <p style="text-align: right;"><b>* Visits 3 and 98 only</b></p>
--	---

If AST and/or ALT are increased  $\geq 3$  times ULN, follow-up laboratory tests of ALT, AST, total bilirubin (with differentiation of bilirubin in direct and indirect), with the addition of alkaline phosphate, creatine kinase (CK, CK isoenzyme MB if CK is elevated), amylase, lipase, and International Normalized Ratio (INR) blood samples must be collected as soon as possible (ideally within 48 to 72 hours of the pathologic test result). Further follow-up investigations shall be initiated depending on the patient's clinical course until the patient is recovered and/or a diagnosis was established.

Table 5.2.3: 2 Urinalysis

<ul style="list-style-type: none"> <li>• Albumin, Creatinine (spot urine: quantitative measurement)</li> <li>• Protein</li> <li>• Glucose</li> </ul>	<ul style="list-style-type: none"> <li>• Ketone</li> <li>• Leucocytes</li> <li>• Erythrocytes</li> </ul>
--	--

Albumin/creatinine ratio will be calculated at the central laboratory. Urine sediment will only be performed if there is a positive finding on the urinalysis.

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#### 5.2.4 Electrocardiogram

Twelve-lead ECGs will be recorded according to the [Flow Chart](#).

The 12-lead ECGs will be centrally analysed with interpretation by a cardiologist and assessed for pre-existing abnormalities. Patients with any pre-existing ECG abnormalities determined at the Screen Visit may be referred to a cardiologist and medically treated, as well as should be carefully monitored throughout the trial, as necessary. ECG abnormalities determined at the Screen Visit should be recorded on the baseline condition eCRF. After the 12-lead ECG is performed at the Screen Visit, any clinically relevant abnormal changes should be reported as AEs according to [Section 5.2.2.1](#).

Additional ECGs may be collected by the investigator for safety reasons.

#### 5.2.5 Assessment of other safety parameters

##### Physical examination

A physical examination (e.g., evaluation of the body and its functions using inspection, palpation, percussion, and auscultation) will be performed by the investigator according to the Flow Chart. Documentation of and findings from the physical examination must be part of the source documents available at the trial site.

##### Home Blood Glucose Monitoring

All patients will receive HBGM supplies at the Screen Visit to monitor their glucose levels at home each day. Instruction on the proper use of the glucometer will be provided by the study staff.

Each day: The patient should be instructed to complete 4 finger stick glucose measurements:

1. in a fasting state in the morning before breakfast (e.g., before 7 or 8 a.m.)
2. before lunch (e.g., 12 p.m.)
3. before dinner (e.g., 6 p.m.)
4. before bedtime (e.g., 8 or 9 p.m.)

It is not recommended that patients' skip meals but approximate times of glucose measuring have been provided above as general guidance.

Once or twice a week during typical hours of sleep (i.e., 10 p.m. to 5 a.m.):

The patient should be instructed to complete a finger stick glucose measurement when getting up to use the bathroom or any other reason for being awake during typical hours of sleep.

The patient should be instructed to also contact the trial site for advice if the results of a HBGM test reveal blood glucose value of  $\leq 70$  mg/dL (3.9 mmol/L) after an overnight fast.

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[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

#### 5.4 APPROPRIATENESS OF MEASUREMENTS

All measurements performed during this trial are standard measurements and will be performed in order to monitor efficacy and safety aspects in an appropriate way.

The scheduled measurements are appropriate to determine relevant drug-induced changes in blood pressure, pulse, standard laboratory values, and ECG specific to the efficacy of treatment of T2DM. The primary and secondary endpoints are standard, are widely used, and accepted for evaluation of safety and tolerability of oral antidiabetic drugs in respective pivotal Phase III trials.

#### 5.5 DRUG CONCENTRATION MEASUREMENTS AND PHARMACOKINETICS

The plasma concentration and pharmacokinetic analysis of linagliptin will not be performed in this trial.

[REDACTED]

[REDACTED]

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[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

## 5.7 PHARMACODYNAMICS

No additional pharmacodynamic parameters will be determined in this trial.

[REDACTED]

[REDACTED]

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## 6. INVESTIGATIONAL PLAN

### 6.1 VISIT SCHEDULE

All trial visits should be routinely scheduled in the morning, at approximately the same time of day (07:00 AM to 11:00 AM). If a patient mistakenly takes study medication on the morning of a visit before attending the clinic (excluding visits starting before randomisation) or comes in non-fasted where a fasting condition is required (all visits except Screen), the visit should be rescheduled for another day as soon as possible reminding the patient about the expected conditions. The rescheduled visit must take place within the allowed visit window (i.e., in less than 7 days) so that the patient has sufficient study medication.

All patients are to adhere to the visit schedule as specified in the [Flow Chart](#). If any visit has to be rescheduled, subsequent visits should follow the original visit date schedule. The study medication bottles contain sufficient medication to allow for these time windows.

### 6.2 DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS

#### 6.2.1 Screen and Run-In Periods

##### Screen

No trial procedures should begin until the patient has signed the informed consent for the trial.

Patients who have been on stable background therapy [i.e., basal insulin, metformin (optional), and/or alpha-glucosidase inhibitor (optional)] will have the Screen Visit performed.

The Screen Visit does not need to be performed fasting.

After a patient has signed the informed consent, the patient is enrolled in the trial and has begun screening. The patient should be recorded on the enrolment log and be registered in IRT as a screened patient.

Patients who are not eligible due to inclusion and exclusion criteria should be entered as a screen failure in IRT.

##### Run-In

Patients should be fasting (no food or drinks for at least 10 hours, only water is allowed).

Patients will be assigned and receive a placebo kit number through the IRT at this visit.

Patients who fail the Run-In Period following the Visit 2 evaluations should be entered as a screen failure in the IRT.

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## 6.2.2 Treatment period

Patients should not take study medication at home on the morning of trial visits during the treatment period.

The treatment period is from Visit 3 to Visit 98. Study medication will be dispensed to patients at each of these visits (except for Visit 98). Patients will be assigned a new medication number through IRT at each visit. Study medication will be administered by the investigator from a new bottle with the IRT-assigned medication number on the day of the visit.

### Treatment Period (Visits 3, 4, 5, 6, 98)

Visits should be performed fasting and as indicated in the [Flow Chart](#), and [Table 4.1.4: 1](#) and the respective protocol sections.




For Visit 98, patients will be entered in IRT as completing or discontinuing treatment.

### Premature discontinuation from the trial (between Visits 3 and 98)

If a patient prematurely discontinues from the 24-week treatment period, the patient must return to the trial site for both Visit 98 and Visit 99 (7 days after Visit 98), which will be performed.

The investigator may initiate any additional antidiabetic therapy based on his or her discretion no sooner than one day after discontinuing study medication.

The scheduled Visit 98 evaluations should be performed for patients who prematurely discontinued from the trial including the following:

- Blood pressure and pulse
- Weight
- Physical examination
- 12-lead ECG
- 
- 
- Collection of blood and urine samples for safety laboratory evaluation
- 
- eDiary
- Diet and exercise counseling

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- Study medication compliance
- Documentation of any adverse events
- Documentation of concomitant therapies

In addition, the patient will be instructed to return in one week for Visit 99 evaluations.

### 6.2.3 End of trial and follow-up period

Visits should be performed as indicated in the Flow Chart and in [Table 4.1.4: 1](#) and the respective protocol sections.

For Visit 99, patients will be entered in IRT as completing or discontinuing the trial.

#### Post-Treatment Period

Patients that complete the trial will take the last dose of study medication the day before Visit 98. The investigator may initiate any additional antidiabetic therapy based on his or her discretion no sooner than one day after Visit 98.

The following Visit 99 evaluations should be performed for all patients returning for this visit including those patients who prematurely discontinued from the trial:

- Blood pressure and pulse
- Collection of blood and urine samples for safety laboratory evaluation
- Return of the HBGM device for assessment of blood glucose levels
- Return of the eDiary
- Documentation of any adverse events
- Documentation of concomitant therapies

The end of the trial is defined as "last patient out", i.e., last visit completed by the last patient.

#### Premature discontinuation from the trial (between Visits 98 and 99)

If a patient discontinues after the 24-week treatment period, the patient should return to the trial site for Visit 99 (the Post-Treatment Visit that occurs 7 days after Visit 98), which will be performed as a trial visit.

The investigator may initiate any additional antidiabetic therapy based on his or her discretion no sooner than one day after discontinuing study medication.

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## 7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

### 7.1 STATISTICAL DESIGN - MODEL

The objective of the current trial is to investigate the efficacy, safety and tolerability of linagliptin compared to placebo given for 24 weeks as add-on therapy to a stable background of basal insulin, metformin (optional), and/or alpha-glucosidase inhibitors (optional) in elderly patients ( $\geq 60$  years of age) with T2DM and insufficient glycaemic control (i.e., HbA<sub>1c</sub> of 7.0% to 10%). It is planned to show superiority of linagliptin to placebo for the primary endpoint, the change from baseline in HbA<sub>1c</sub> (HbA<sub>1c</sub> after 24 weeks of treatment minus HbA<sub>1c</sub> at baseline), followed by a decrease in the proportion of patients experiencing at least one confirmed hypoglycaemic event during 24 weeks of treatment, in a hierarchical manner.

HbA<sub>1c</sub> will be measured in the unit of percent (%) at all clinical visits. A mixed model for repeated measures (MMRM) will be used to compare the change from baseline in HbA<sub>1c</sub> after 24 weeks of the treatments. The model will include treatment, baseline HbA<sub>1c</sub>, baseline insulin dose, week, week by baseline HbA<sub>1c</sub> interaction, and week by treatment interaction.

With regard to efficacy and safety endpoints, the term “baseline” refers to the last observed measurement prior to administration of any randomised study medication.

### 7.2 NULL AND ALTERNATIVE HYPOTHESES

The superiority of treatment with linagliptin to placebo will be tested for HbA<sub>1c</sub> change from baseline to Week 24 at the level of  $\alpha=0.05$  (two-sided).

The primary hypothesis can be written as follows:

$H_{0, 1}$ : Mean change from baseline in HbA<sub>1c</sub> after 24 weeks of treatment with linagliptin  
= Mean change from baseline in HbA<sub>1c</sub> after 24 weeks of treatment with placebo

$H_{1, 1}$ : Mean change from baseline in HbA<sub>1c</sub> after 24 weeks of treatment with linagliptin  
 $\neq$  Mean change from baseline in HbA<sub>1c</sub> after 24 weeks of treatment with placebo

This will be performed on the full analysis set (FAS).

### 7.3 PLANNED ANALYSES

The primary analysis will be performed on the FAS. The FAS will consist of all randomised patients who were treated with at least one dose of study medication, had a baseline and at least one on-treatment HbA<sub>1c</sub> measurement.

The FAS-completers set of patients is defined as all patients in the FAS who complete 24 weeks of treatment and have an HbA<sub>1c</sub> measurement after 24 weeks of treatment.

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[REDACTED] A protocol violation will be considered important if it can be expected to have a distorting influence on the assessment of the primary endpoint.

Important protocol violations include:

- Randomised study medication: incorrect study medication taken
- Severe violation of treatment compliance
- Severe violation of inclusion criteria
- Non-adherence to other specifications of the protocol that could bias the primary endpoint

Further details will be given in the Trial Statistical Analysis Plan (TSAP).

All patients treated with at least one dose of study medication (the Treated Set) will be included in the safety evaluation.

### 7.3.1 Primary analyses

The primary analysis will be performed on the FAS [observed cases (OC)]. Mean changes from baseline in HbA<sub>1c</sub> after 24 weeks of treatments will be analysed using a restricted maximum likelihood-based repeated measures approach. Analyses will include the fixed, categorical effects of baseline insulin dose, treatment, week, and treatment by week interaction, as well as the continuous, fixed covariates of baseline HbA<sub>1c</sub> and baseline HbA<sub>1c</sub> by week interaction. An unstructured (co)variance structure will be used to model the within patient measurements.

If this analysis fails to converge, the following covariance structures will be tested: Toeplitz, AR (1), and compound symmetry. The (co)variance structure converging to the best fit, as determined by Akaike's information criterion, will be used as the primary analysis. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom. Significance tests will be based on least-squares means using a two-sided  $\alpha = 0.05$  [two-sided 95% confidence intervals (CI)]. **The residuals are assumed to have a multivariate normal distribution with zero means and covariance matrix as mentioned above.** All analyses will be implemented using SAS®. The primary treatment comparisons will be the contrast between treatments at Week 24.

The statistical model will be:

HbA<sub>1c</sub> change from baseline = overall mean + baseline HbA<sub>1c</sub> + baseline insulin dose  
+ treatment + week + week by baseline HbA<sub>1c</sub> interaction  
+ week by treatment interaction + random error

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secondary and certain other endpoints (to be specified in TSAP) to obtain the odds ratio between treatment groups and its 95% CI and 2-sided p-value.

- [REDACTED]
- [REDACTED]

For these analyses, patients will be assigned to the treatment they were randomised to.

The analysis of endpoints related to questionnaires will be described in the TSAP.

### 7.3.3 Safety analyses

All safety data will be displayed and analysed using descriptive statistical methods. Depending on the character of the individual safety endpoint, the most appropriate way to summarize the results as frequency tables for categorical data or descriptive statistics for continuous data will be used. No formal inferential analysis is planned for safety comparison.

AEs will be coded using the Medical Dictionary for Drug Regulatory Activities (MedDRA) coding dictionary. All events with an onset after the first dose of study medication up to a period of seven days after the last dose of study medication will be assigned to the treatment phase for evaluation. This includes AEs that start before first study medication intake and deteriorate under treatment. Other AEs will be assigned either to the screening, run-in, or follow-up phase as appropriate. Safety analyses will be performed on the TS, with patients assigned to the treatment they were randomised to. Additional listings based on actual treatment at onset of AE will be produced for patients who receive incorrect treatment at any point throughout the trial.

Laboratory values taken after the first dose of randomised treatment up to a period of seven days after the last intake of treatment will be assigned to the treatment phase for evaluation. Laboratory values will be compared to their reference ranges and frequency tables will be provided for the number of patients within and outside the reference range.

Changes from baseline in blood pressure and pulse rate will be summarised by treatment group.

Further details on the safety analysis will be specified in the TSAP.

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#### 7.3.4 Interim analyses

No interim analysis is planned for this trial.

#### 7.3.5 Pharmacokinetic analyses

No pharmacokinetic sampling is planned for this trial.

#### 7.3.6 Pharmacodynamic analyses

No pharmacodynamic analysis is planned for this trial.

### 7.4 HANDLING OF MISSING DATA

#### 7.4.1 Efficacy endpoints

In the primary analysis, if a patient misses a visit, the missing data will not be imputed. The mixed effect model will handle missing data based on a likelihood method under the "missing at random assumption". Following the intention-to-treat (ITT) principle, every randomised patient with at least baseline and one on-treatment measurement will be included in the analysis.

If rescue therapy is initiated, HbA<sub>1c</sub> and FPG values after rescue will be set to missing and the missing data handled as above (OC or LOCF), according to the analysis strategy.

**For the analysis of hypoglycaemia endpoints, the available data of all patients in the TS will be analysed (OC approach) and no imputation performed.**

For binary endpoints including an HbA<sub>1c</sub> response criterion, non-completer's considered failures (NCF) approach will be used, i.e., patients who discontinue from the trial prematurely and have no Week 24 HbA<sub>1c</sub> value will be considered as non-responders.

Methods to handle any other exceptional cases will be considered before unblinding the data and will be applied in a manner consistent with other trials of this type. The evaluability of patients with deviations from the protocol likely to confound the treatment response will be decided prior to unblinding.

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#### 7.4.2 Safety and other endpoints

With respect to safety evaluations, it is not planned to impute missing values.

The handling of missing [REDACTED] as patient reported outcome measures data will be specified in the TSAP or a separate health economics analysis plan, as appropriate.

#### 7.5 RANDOMISATION

The sponsor will arrange for the randomisation as well as packaging and labelling of study medication. Eligible patients will be randomly assigned to one of the two treatment groups, with equal allocation of treatments. The randomisation list will be generated using a validated system, which involves a pseudo-random number generator so that the resulting treatment sequence will be both reproducible and non-predictable.

The randomisation will be stratified by HbA<sub>1c</sub> (< 8.5% vs. ≥ 8.5%) as determined from the blood sample taken at Visit 1 and insulin dose (< 40 international units total daily dose vs. ≥ 40 international units total daily dose) as determined at the beginning of the placebo run-in period (Visit 2). To ensure appropriate representation of patients with insulin doses of < 40 international units total daily dose as well as ≥ 40 international units total daily dose, the trial team will monitor the proportion of patients being recruited into these categories. The limitation of recruitment of a particular category may be arranged (on trial level and/or country level).

The allocation process will be performed at Visit 3 through IRT. However, the IRT allocation and randomization will not increase the study medication bottles at each trial site based on stratification.

Access to the code will be restricted to dedicated randomisation personnel and any exceptional access to the code (in case of an emergency) will be documented according to the sponsor's SOPs.

The trial will only be unblinded after all eCRF and electronic data have been entered into the trial database, after queries have been resolved, and after the database has been locked. Access to the codes will be controlled and documented by a signed confidentiality statement, which will be stored in the TMF.

Practical aspects of the treatment allocation process and methods to carry out blinding are detailed in [Sections 4.1.2](#) and [4.1.5](#), respectively.

#### 7.6 DETERMINATION OF SAMPLE SIZE

**This trial will be powered to detect differences between linagliptin and placebo in HbA<sub>1c</sub> change from baseline after 24 weeks.**

**A total of 300 patients will be randomised.**

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Based on pooled data from the 1218.36 and 1218.63 trials [REDACTED] assuming a standard deviation of 1.2% in both groups in the FAS with a 0.77% difference in HbA<sub>1c</sub> change from baseline in treatments, a number of 150 patients in each treatment arm will show superiority with a power >99%. This determination of power is based on a Student's t-test and a two-sided significance level of 5%.

Software package nQuery version 7.0 was used to derive the sample size.

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## 8. INFORMED CONSENT, DATA PROTECTION, TRIAL RECORDS

The trial will be carried out in compliance with the protocol, the principles laid down in the Declaration of Helsinki, in accordance with the ICH Harmonised Tripartite Guideline for GCP and relevant BI SOPs. Standard medical care (prophylactic, diagnostic and therapeutic procedures) remains in the responsibility of the treating physician of the patient.

The investigator should inform the sponsor immediately of any urgent safety measures taken to protect the study subjects against any immediate hazard, and also of any serious breaches of the protocol/ICH GCP.

*For Japan:*

*The investigator should inform the sponsor immediately of any urgent safety measures taken to protect the study subjects against any immediate hazard, and also of any serious breaches of the protocol, ICH GCP, and the Japanese GCP regulations (Ministry of Health and Welfare Ordinance No. 28, March 27, 1997).*

The rights of the investigator and of the sponsor with regard to publication of the results of this trial are described in the investigator contract. As a general rule, no trial results should be published prior to finalisation of the Clinical Trial Report.

*For countries with insurance cover requirements:*

*Insurance Cover: The terms and conditions of the insurance cover are made available to the investigator and the patients via documentation in the ISF.*

### 8.1 STUDY APPROVAL, PATIENT INFORMATION, AND INFORMED CONSENT

This trial will be initiated only after all required legal documentation has been reviewed and approved by the respective IRB or IEC and CA according to national and international regulations. The same applies for the implementation of changes introduced by amendments.

Prior to patient participation in the trial, written informed consent must be obtained from each patient (or the patient's legally accepted representative) according to ICH GCP and to the regulatory and legal requirements of the participating country. Each signature must be personally dated by each signatory and the informed consent and any additional patient-information form retained by the investigator as part of the trial records. A signed copy of the informed consent and any additional patient information must be given to each patient or the patient's legally accepted representative.

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

The patient must be informed that his / her medical records may be examined by authorised monitors (CML and/or CRA) or Clinical Quality Assurance auditors appointed by Boehringer

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Ingelheim, by appropriate IRB or IEC members, and by inspectors from regulatory authorities.

*For Japan:*

*The investigator must give a full explanation to trial patients including the items listed below in association with the use of the patient information form, which is prepared avoiding the use of technical terms and expressions. The patient is given sufficient time to consider participation in the trial. The investigator obtains written consent of the patient's own free will with the informed consent form after confirming that the patient understands the contents. The investigator must sign (or place a seal on) and date the informed consent form. If a trial collaborator has given a supplementary explanation, the trial collaborator also signs (or places a seal on) and dates the informed consent.*

*The following items need to be included:*

- 1. That the clinical trial is aimed at testing.*
- 2. Objectives of the trial.*
- 3. The name, title, and address of the investigator to contact.*
- 4. Trial procedures.*
- 5. Anticipated benefits of the investigational products and anticipated disadvantages to the patient.*
- 6. Matters concerning other therapeutic measures.*
- 7. Duration of participation in the clinical trial.*
- 8. That the patient may withdraw from the trial at any time.*
- 9. That patient's refusal of or withdrawal from participation in the trial does not cause any disadvantage to him or her.*
- 10. That the monitors, the auditors, and the IRB are given access to the relevant source documents on condition that confidentiality of the patient is fully secured.*
- 11. That privacy of the patient is kept.*
- 12. The office of the medical institution to contact in the event of trial-related injury.*
- 13. That necessary treatment is available to the patient in the event of trial-related injury.*
- 14. Matters concerning compensation in the event of any trial-related injury.*
- 15. The type of the IRB which is used for the reviews and deliberations on the matters such as appropriateness of conducting the clinical trial, the matters to be reviewed*

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*and deliberated by each IRB, and other matters concerning the IRBs involved in the clinical trial.*

*16. Other necessary matters concerning the clinical trial.*

## 8.2 DATA QUALITY ASSURANCE

The trial will be conducted according to the principles of GCP and the company SOPs.

The following steps will be taken to ensure accurate, consistent, complete, and reliable data:

- Use of techniques to achieve standardisation (e.g., investigator meetings, etc.)
- Use of techniques to achieve accuracy (e.g., global and local training sessions, etc.)
- Use of centralised evaluations (e.g., central laboratory, centralised review of ECGs, etc.)
- On-site monitoring and source data verification
- Equipment validation and calibration
- Auditing (in-house and on-site)
- Coding (e.g., MedDRA)
- Special data management procedures: The data management procedures to ensure the quality of the data are described in detail in the trial data management and analysis plan (TDMAP) available in the TMF.
- Establishing CECs to evaluate specific events (refer to [Section 3.1](#))
- Taking steps to maintain the blind (refer to [Section 4.1.5.1](#))
- Inter-laboratory standardisation methods: The samples will be analysed at a central laboratory or its affiliates having a NGSP Level I certificate.

The data management procedures to ensure the quality of the data are described in detail in the TDMAP available in TMF.

A quality assurance audit/inspection of this trial may be conducted by the sponsor or sponsor's designees or by IRBs or IECs or by regulatory authorities. The quality assurance auditor will have access to all medical records, the investigator's trial-related files and correspondence, and the informed consent documentation of this clinical trial.

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### 8.3 RECORDS

Case Report Forms (CRFs) for individual patients will be provided by the sponsor, via RDC. See [Section 4.1.5.2](#) for rules about emergency code breaks. For drug accountability, refer to [Section 4.1.8](#).

#### 8.3.1 Source documents

Source documents provide evidence for the existence of the patient and substantiate the integrity of the data collected. Source documents are filed at the investigator's trial site.

Data entered in the eCRFs that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the trial; also current medical records must be available.

For eCRFs, all data must be derived from source documents.

Additionally, the following source documents must be collected and filed at the investigator's trial site:

- ECG results (original or copies of printouts)
- Physical examinations (original documentation)
- HBGM results (printout from vendor at the end of the trial)

█ [REDACTED]

█ [REDACTED]

#### 8.3.2 Direct access to source data and documents

The investigator and/or institution will permit trial-related monitoring, audits, IRB or IEC review and regulatory inspection, providing direct access to all related source data / documents. eCRFs and all source documents, including progress notes and copies of laboratory and medical test results must be available at all times for review by the sponsor's clinical trial monitor, auditor and inspection by health authorities (e.g. FDA). The CRA or on-site monitor and auditor may review all eCRFs, and written informed consents. The accuracy of the data will be verified by reviewing the documents described in Section 8.3.1.

#### 8.3.3 Storage of records

*For Japan:*

*Trial sites:*

*The trial sites must retain the source documents and essential documents for a period defined by the Japanese GCP regulation and the sponsor's SOP.*

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*Sponsor:*

*The sponsor must retain the essential documents according to the sponsor's SOPs.*

*When it is no longer necessary for the trial site to retain the source documents and essential documents, the sponsor must notify the head of trial site.*

## **8.4 LISTEDNESS AND EXPEDITED REPORTING OF ADVERSE EVENTS**

### **8.4.1 Listedness**

To fulfil the regulatory requirements for expedited safety reporting, the sponsor evaluates whether a particular adverse event is "listed", i.e. is a known side effect of the drug or not. Therefore, a unique reference document for the evaluation of listedness needs to be provided. For Tradjenta®, Trajenta®, Trayenta®, and Trazenta®, this is the current version of the Investigator's Brochure [REDACTED]. The current version of this reference document is to be provided in the ISF. No AEs are classified as listed for matching placebo, study design, or invasive procedures.

### **8.4.2 Expedited reporting to health authorities and IECs/IRBs**

Expedited reporting of SAEs, e.g. suspected unexpected serious adverse reactions (SUSARs) to health authorities and IECs or IRBs, will be done according to local regulatory requirements. Further details regarding this reporting procedure are provided in the ISF.

## **8.5 STATEMENT OF CONFIDENTIALITY**

Individual patient medical information obtained as a result of this trial is considered confidential and disclosure to third parties is prohibited with the exceptions noted below. Patient confidentiality will be ensured by using patient identification code numbers.

Treatment data may be given to the patient's personal physician or to other appropriate medical personnel responsible for the patient's welfare. Data generated as a result of the trial need to be available for inspection on request by the participating physicians, the sponsor's representatives, by the IRB or IEC and the regulatory authorities (e.g., for EU: the CA).

## **8.6 COMPLETION OF TRIAL**

*For Japan:*

*When the trial is completed, the investigator should inform the head of the trial site of the completion in writing, and the head of the trial site should promptly inform the IRB and sponsor of the completion in writing.*

*For EU member states:*

*The EC and CA in each participating EU member state needs to be notified about the end of the trial (last patient/patient out, unless specified differently in [Section 6.2.3](#) of the CTP) or early termination of the trial.*

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## 8.7 PROTOCOL VIOLATIONS

*For Japan:*

*The investigator or sub-investigator should record all CTP violations. The investigator should provide and submit the sponsor and the head of the trial site the records of violations infringing the Japanese GCP or violations to eliminate an immediate hazard to trial subjects and for other medically inevitable reasons.*

## 8.8 COMPENSATION AVAILABLE TO THE PATIENT IN THE EVENT OF TRIAL RELATED INJURY

*For Japan:*

*In the event of health injury associated with this trial, the sponsor is responsible for compensation based on the contract signed by the trial site.*

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## 10. APPENDICES

### 10.1 INCLUSION OF ILLITERATE PATIENTS

#### 10.1.1 Home Blood Glucose Monitoring and eDiary

In the event of recruiting an illiterate patient, the following process should be followed with respect to HBGM as well as eDiary and documenting the results:

- At Screen, the person assisting the patient with this process (e.g., the patient's caregiver or relative) will attend the clinic together with the patient.
- The trial site staff should confirm that this individual will be present with the patient, whenever he/she is likely to need to perform HBGM and answer the eDiary questions.
- The trial site staff should then train both the patient and above-mentioned individual with respect to the correct use of the HBGM equipment during each period of the trial. This will include the use of the glucose meter itself and the test strips, lancet device and any control solutions. Furthermore, if whole blood referenced test strips are standard in the countries where illiterate patients are being recruited, the trial site staff must ensure that both the patient and the person assisting the patient with the HBGM, have understood that plasma referenced test strips are used in the trial, and that there may be differences in the results obtained via these two methods. A training letter is available to support this process.
- The trial site staff should also train both the patient and the above-mentioned individual with respect to the completion of the eDiary questions.

HGBM tests can be performed either by the patient him/herself, or by the person assisting the patient with this aspect of the trial. The person assisting the patient will need to obtain the answers to the eDiary questions from the patient and enter the patient's responses into the eDiary.

#### 10.1.2 Patient information and informed consent [REDACTED]

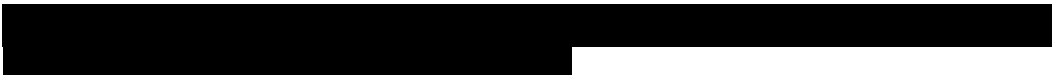
In the event of recruiting an illiterate patient, the following process should be followed with respect to patient information and informed consent:

- The designated trial site personnel performing the informed consent process will read the trial-approved patient information sheet and informed consent form to the patient, and explain the details of the trial, all in the presence of an impartial witness.
- This impartial witness must be literate, and can be the patient's relative or caregiver, or a member of staff employed by the clinic but not part of the immediate trial team. In addition, if there are any further local regulations with respect to the consent of illiterate patients, these should also be followed.

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- The requirements of the trial will be explained thoroughly and the patient will be given ample time to ask questions and consider his/her participation. If he/she wishes, the patient can take the patient information sheet and informed consent form home for further consideration.
- If patient agrees to take part in the trial, he/she would then return to the clinic for the consent process to be completed. The trial site designated personnel responsible for this process will confirm that the patient has no further questions in the presence of the same impartial witness (if the patient returns on another day). If a different impartial witness is present, the entire informed consent process must be repeated.
- Participating patients will provide a thumb impression or make a mark (or signature if the patient is able to sign him/herself) on the signature section of the informed consent form.
- The date of the patient's signature will be left blank as the patient is illiterate. However, if the patient is able, he/she will date the mark/signature personally.
- The impartial witness or the trial site designated personnel may write the name of the patient on the informed consent form.
- The impartial witness should enter his/her name, sign and personally date the witness section of the informed consent form. In countries where local data protection regulation permits it, the address or identification number of the impartial witness should also be entered. The signature then attests that the content of the patient information sheet and informed consent form was accurately explained to the patient, who apparently understood and freely gave consent to participate in the trial.
- The designated trial site personnel also signs and personally dates the informed consent form.
- 

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## 11. DESCRIPTION OF GLOBAL AMENDMENT

This is the original protocol.

<b>Number of global amendment</b>		1
<b>Date of CTP revision</b>		16 October 2015
<b>EudraCT number</b>		2014-000904-88
<b>BI Trial number</b>		1218.149
<b>BI Investigational Product</b>		Tradjenta®, Trajenta®, Trayenta®, Trazenta®, linagliptin
<b>Title of protocol</b>		A 24 week randomized, double-blind, placebo-controlled, parallel group, efficacy and safety trial of once daily linagliptin, 5 milligrams orally, as add on to basal insulin in elderly Type 2 Diabetes Mellitus patients with insufficient glycaemic control
<b>To be implemented only after approval of the IRB or IEC and/or Competent Authorities</b>		<input checked="" type="checkbox"/>
<b>To be implemented immediately in order to eliminate hazard – IRB or IEC and/or Competent Authority to be notified of change with request for approval</b>		<input type="checkbox"/>
<b>Can be implemented without IRB or IEC and/or Competent Authority approval as changes involve logistical or administrative aspects only</b>		<input type="checkbox"/>
<b>Section to be changed</b>		Title Page and Synopsis
<b>Description of change</b>		There was a change of Coordinating Investigator and a global amendment was added.
<b>Rationale for change</b>		The Coordinating Investigator discontinued from the trial and there was an addition of a global amendment due to recruitment difficulties.

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<b>Number of global amendment</b>		1
<b>Section to be changed</b>		Synopsis
<b>Description of change</b>		Decrease of: 1.) age to 60 years old, and 2.) lower limit of HbA <sub>1c</sub> to 7.0%; and the secondary endpoint of < 7.5% HbA <sub>1c</sub> was changed to < 7.0%.
<b>Rationale for change</b>		This trial was based on the data of two trials (1218.36 and 1218.63), which used a lower limit in age for one trial and HbA <sub>1c</sub> in both trials. As the inclusion criterion of HbA <sub>1c</sub> was decreased to 7.0%, the secondary endpoint for < 7.5% HbA <sub>1c</sub> was changed to < 7.0%.
<b>Section to be changed</b>		Synopsis and Flowchart
<b>Description of change</b>		Decrease sample size to 300 (150 per arm) based on the primary endpoint of HbA <sub>1c</sub> only, with 100 patients randomized required in Japan. The key secondary endpoint was changed to a secondary endpoint.
<b>Rationale for change</b>		Prescribing practices have changed in the past 5 years and recruitment has proved to be too difficult and slow to achieve the key secondary endpoint sample size requirement.
<b>Section to be changed</b>		Section 1.1
<b>Description of change</b>		An additional sentence was included regarding the rationale for the global protocol amendment.
<b>Rationale for change</b>		As a result of extreme difficulty with recruiting this population, the global protocol amendment expanded the definition of elderly population beginning at age 60.

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<b>Number of global amendment</b>		1
<b>Section to be changed</b>		Sections 2.2, 3.1, 3.3, and 3.3.2
<b>Description of change</b>		<p>Decrease of: 1.) age to 60 years old, 2.) lower limit of HbA<sub>1c</sub> to 7.0% (53 mmol/mol), and 3.) sample size to 300 (150 per arm) based on primary endpoint of HbA<sub>1c</sub> only, with 100 patients randomized from Japan per regulatory requirements.</p> <p>Section 3.3: A time period ‘of at least 1 year’ has been added to the medical history documentation requirement.</p> <p>Inclusion criterion 2b: The additions of ‘biosimilar’ basal insulin and Humalog Basal® (a suspension of insulin lispro protamine) have been included in order to expand the permitted basal insulins.</p>
<b>Rationale for change</b>		<p>This trial was based on the data of two trials (1218.36 and 1218.63), which used a lower limit of HbA<sub>1c</sub> of 7.0% and a lower limit in age for one trial. Prescribing practices have changed in the past 5 years and recruitment has proved to be too difficult and slow to achieve the key secondary endpoint sample size requirement.</p> <p>Section 3.3: Medical history documentation of at least 1 year is needed based on required medical follow up of a patient being on basal insulin.</p> <p>Inclusion criterion 2b: There are two newer basal insulins that can be used in this trial: ‘biosimilar’ basal insulin and Humalog Basal® (a suspension of insulin lispro protamine).</p>

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<b>Number of global amendment</b>		1
<b>Section to be changed</b>		Section 3.3.3
<b>Description of change</b>		Exclusion criterion number 1: Saint Louis University Mental Status Examination scores were further clarified for mild neurocognitive disorder. Exclusion criterion number 4: STEMI and/or unstable angina pectoris were added. Exclusion criterion number 10: The addition of meglitinides and bromocriptine were included into exclusion criterion as these were missing but were stated in Section 4.2.2.1 from the final protocol,
<b>Rationale for change</b>		Exclusion criterion number 1: Patients with Saint Louis University Mental Status Examination scores indicating dementia must not be evaluated further for the trial. Exclusion criterion number 4: Clarified to include STEMI and unstable angina pectoris for complete definition of acute coronary syndrome. Exclusion criterion number 10: The exclusion criterion must be consistent with Section 4.2.2.1 relating to prohibited concomitant medications,
<b>Section to be changed</b>		Section 4.2.1 - Permitted antidiabetic therapy
<b>Description of change</b>		3 <sup>rd</sup> paragraph: After randomisation, investigators should review the patient's HBGM results electronically for hyperglycaemia and should follow the permitted antidiabetic therapy criteria noted below to achieve improved patient glycaemic control before taking any additional action with rescue therapy.  Final paragraph: Clarification of permitted antidiabetic therapy that will be considered to be rescue therapy was included.
<b>Rationale for change</b>		Additions were provided to further clarify: the procedure for permitted antidiabetic therapy criteria related to the HBGM data (i.e., glucometer) and permitted antidiabetic therapy that will be considered to be rescue therapy.

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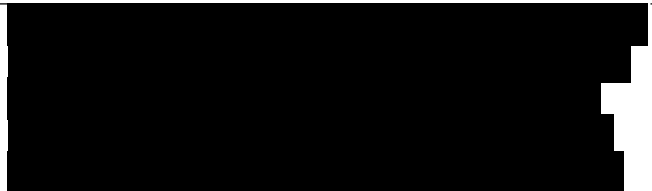






<b>Number of global amendment</b>		1
<b>Section to be changed</b>		Section 5.1.1
<b>Description of change</b>		The key secondary endpoint was removed and changed to a secondary endpoint. As the inclusion criterion of HbA <sub>1c</sub> was decreased to 7.0%, the secondary endpoint for HbA <sub>1c</sub> of 7.5% was changed to <7.0%. Added the word 'to' before 70 mg/dl.
<b>Rationale for change</b>		Prescribing practices have changed in the past 5 years and recruitment has proved to be too difficult and slow to achieve the key secondary endpoint sample size requirement. As the inclusion criterion of HbA <sub>1c</sub> was decreased to 7.0%, the secondary endpoint for HbA <sub>1c</sub> of 7.5% was changed to <7.0%. To further clarify definition of hypoglycaemia as less than or equal to 70 mg/dl.
<b>Section to be changed</b>		Sections 5.2.1, 5.2.2.1, and 5.2.5
<b>Description of change</b>		Symbol of ≤ added before 70 mg/dl and the AESI process was changed.
<b>Rationale for change</b>		To further clarify definition of hypoglycaemia as less than or equal to 70 mg/dl and the Sponsor's AESI process was updated and required additional clarification.
<b>Section to be changed</b>		Section 5.2.5 - <u>eDiary</u>
<b>Description of change</b>		The patient allowed recall period for completing a missed entry was changed to 12 hours.
<b>Rationale for change</b>		The original plan was to allow for a 24 hour recall period but was not possible with changes required for the functionality of the eDiary.

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<b>Number of global amendment</b>		1
<b>Section to be changed</b>		Section 5.3.3 – list number 1
<b>Description of change</b>		The pre-specified analyses will be performed at the end of the trial and the data will be reported separately from the clinical trial report.
<b>Rationale for change</b>		It was subsequently determined that the pre-specified analyses data would be reported separately from the clinical trial report.
<b>Section to be changed</b>		Section 5.3.3.1 – list numbers 1 and 2
		 
		 

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<b>Number of global amendment</b>	1
<b>Section to be changed</b>	Sections 7.1, 7.2, 7.3, 7.3.1, 7.3.7, 7.4.1, and 7.6
<b>Description of change</b>	<p>Decrease of age to 60 years old and lower limit of HbA<sub>1c</sub> to 7.0%. Changing the key secondary endpoint to a secondary endpoint and decreasing sample size to 300 (150 per arm) based on primary endpoint of HbA<sub>1c</sub> only.</p> <p>[REDACTED]</p>
<b>Rationale for change</b>	<p>This trial was based on the data of two trials (1218.36 and 1218.63), which used a lower limit in age for one trial and HbA<sub>1c</sub> in both trials. Prescribing practices have changed in the past 5 years and recruitment has proved to be too difficult and slow to achieve the key secondary endpoint sample size requirement.</p> <p>[REDACTED]</p>

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**APPROVAL / SIGNATURE PAGE****Document Number: c02204602****Technical Version Number:3.0****Document Name: clinical-trial-protocol**

**Title:** A randomized, double-blind, placebo-controlled, parallel group, efficacy and safety trial of linagliptin 5 milligrams taken once daily orally with basal insulin for 24 weeks in elderly Type 2 Diabetes Mellitus patients with insufficient glycaemic control

**Signatures (obtained electronically)**

<b>Meaning of Signature</b>	<b>Signed by</b>	<b>Date Signed</b>
Author-Trial Clinical Monitor	████████████████████	16 Oct 2015 23:20 CEST
Author-Trial Statistician	██████████	17 Oct 2015 00:57 CEST
Author-Trial Clinical Monitor	████████████████████	17 Oct 2015 03:18 CEST
Approval-Team Member Medicine	████████████████████	17 Oct 2015 13:36 CEST
Approval-Therapeutic Area ██████	████████████████████	19 Oct 2015 17:12 CEST

**(Continued) Signatures (obtained electronically)**

<b>Meaning of Signature</b>	<b>Signed by</b>	<b>Date Signed</b>
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