Boehringer Ingelheim

Clinical Trial Protocol

	Document Number:	**c11679959-03**
BI Trial No.:	1218.102	
BI Investigational Product:	Linagliptin (Trajenta)	
Title:	A phase III, randomised, double-blind, placebo-controlled, parallel group, efficacy and safety study of linagliptin, administered orally once daily, in combination with insulin therapy for 24 weeks in Chinese type 2 diabetes mellitus patients with insufficient glycaemic control	
Lay Title:	Linagliptin Add-on to Insulin Background Therapy	
Clinical Phase:	III	
Trial Clinical Monitor:	Phone: Fax:	
Coordinating Investigator:	Phone: Fax:	
Status:	Final Protocol (Revised Protocol (based on amendment 02))	
Version and Date:	**Version:** 3.0	**Date:** 28 Nov 2017

CLINICAL TRIAL PROTOCOL SYNOPSIS

Name of company:		**Boehringer Ingelheim**	
Name of finished product:		Linagliptin (Trajenta)	
Name of active ingredient:		Linagliptin (Trajenta)	
Protocol date: 04 Feb 2016	**Trial number:** 1218.102		**Revision date:** 28 Nov 2017

Title of trial:	A phase III, randomised, double-blind, placebo-controlled, parallel group, efficacy and safety study of linagliptin, administered orally once daily, in combination with insulin therapy for 24 weeks in Chinese type 2 diabetes mellitus patients with insufficient glycaemic control
Coordinating Investigator:	
Trial site:	Multi-centre trial conducted in China
Clinical phase:	Phase III
Objectives:	To evaluate the efficacy and safety of linagliptin 5 mg once a day (q.d.) compared to placebo when added on to insulin therapy alone or in combination with metformin in Chinese patients with type 2 diabetes mellitus with insufficient glycaemic control
Methodology:	A randomised, double-blind, placebo-controlled, parallel group design comparison, as add-on therapy to a stable background of insulin (basal insulin, premixed insulin) and metformin (optional) over 24 weeks
No. of patients:	
total entered:	206 patients
each treatment:	103 patients
Diagnosis :	Type 2 diabetes mellitus
Main criteria for inclusion:	Patients ≥ 18 years with type 2 diabetes mellitus Insufficient glycaemic control (HbA_{1C} ≥ 7.5 to ≤10.0%) Background therapy with subcutaneous insulin alone (basal insulin, premixed insulin) or in combination with metformin
Test product:	Linagliptin

Name of company:		**Boehringer Ingelheim**	
Name of finished product:		Linagliptin (Trajenta)	
Name of active ingredient:		Linagliptin (Trajenta)	
Protocol date: 04 Feb 2016	**Trial number:** 1218.102		**Revision date:** 28 Nov 2017

dose:	5mg once daily
mode of administration:	Tablets per os
Comparator products:	Placebo
dose:	Not applicable
mode of administration:	Tablets per os
Duration of treatment:	2-week placebo run-in 24 week double-blind treatment with either linagliptin 5 mg or placebo 1 week follow-up
Endpoints	The primary endpoint is the change from baseline in HbA_{1c} after 24 weeks of treatment. Secondary efficacy endpoints are the following: • Change from baseline in fasting plasma glucose (FPG) after 24 weeks of treatment • Change from baseline in 2-hour postprandial plasma glucose (PPG) after 24 weeks of treatment • Proportion of patients with HbA_{1c} on treatment <7.0% after 24 weeks of treatment • Proportion of patients with HbA_{1c} on treatment <6.5% after 24 weeks of treatment • Proportion of patients with HbA_{1c} lowering by at least 0.5% after 24 weeks of treatment Secondary safety endpoints are: • Incidence of investigator–reported hypoglycaemic events confirmed by a measured blood glucose ≤ 70 mg/dL

Name of company:		**Boehringer Ingelheim**	
Name of finished product:		Linagliptin (Trajenta)	
Name of active ingredient:		Linagliptin (Trajenta)	
Protocol date: 04 Feb 2016	**Trial number:** 1218.102		**Revision date:** 28 Nov 2017

	(≤ 3.9 mmol/L) • Incidence of severe hypoglycaemic events (requiring active assistance by another person, or fatal)
Safety criteria:	Adverse events (including relevant new or worsening pre-existing conditions) and AEs of Special Interest (AESI)
Statistical methods:	The primary analysis using a restricted maximum likelihood-based mixed model repeated measures approach is applied to compare the change in HbA_{1c} from baseline between treatments after 24 weeks of treatment. The statistical model will include 'treatment', 'type of insulin' and 'week' as fixed, categorical effects, 'baseline HbA_{1c}' as a continuous covariate, 'week by treatment interaction' and 'baseline HbA_{1c} by week interaction'.

FLOW CHART

Trial Period	**Screening**	**Placebo run-in period**	**Randomised treatment period**						**Follow -up period**
Visit	**1[A]**	**2**	**3**	**4**	**5**	**6**	**7**	**8(EOT)**	**9[B]**
Study week	**-3**	**-2**	**0**	**4**	**8**	**12**	**18**	**24**	**25**
Study day	**-21**	**-14**	**1**	**29**	**57**	**85**	**127**	**169**	**176**
Visit window (in days)	+/-7	-7	NA	+/-7	+/-7	+/-7	+/-7	+7	+7
Informed Consent	X								
Medical history / concomitant diagnoses	X								
Demographics	X[K]	X							
In-/Exclusion criteria	X	X	X						
Physical examination		X						X	
Vital signs	X	X	X	X	X	X	X	X	X
Height	X								
Weight	X		X					X	
Waist circumference			X					X	
Diet and exercise counselling [C]		X	X	X	X	X	X	X	
12-lead ECG[D]			X					X	
Pregnancy test [E]	X		X			X		X	
Glomerular filtration rate [M]	X		X			X		X	
Safety lab tests [F] (urine and blood)	X[G]	X	X			X		X	X
FPG		X	X	X	X	X	X	X	X
2-hour PPG test			X					X	
MTT test			X					X	
HbA_{1c}	X		X	X	X	X	X	X	
Lipid lab panel			X					X	
Home Blood Glucose Monitoring [H]		X	X	X	X	X	X	X	X

Trial Period	**Screening**	**Placebo run-in period**	**Randomised treatment period**						**Follow-up period**
Visit	**1[A]**	**2**	**3**	**4**	**5**	**6**	**7**	**8(EOT)**	**9[B]**
Study week	**-3**	**-2**	**0**	**4**	**8**	**12**	**18**	**24**	**25**
Adverse events	X	X[J]	X	X	X	X	X	X	X
Concomitant therapy	X	X	X	X	X	X	X	X	X
Dispense placebo run-in medication [I]		X							
Randomisation (via IRT)			X						
Dispense double-blind study medication [I]			X	X	X	X	X		
Medication compliance check			X	X	X	X	X	X	

A The screening procedures can be done on different days within the time window after inform consent signed.

B Visit 9 (Follow-up visit) is required as following:
(a) for patients that regularly completed treatment phase: phone visit to obtain adverse event information
(b) for prematurely discontinued patients: trial site visit to obtain vital signs, safety lab and adverse events etc.

C Diligent diet and exercise counselling by a diet specialist or delegated staff member at visit 2. Counselling is based on local diet recommendations. At all visits, patients should be reminded about the importance to follow the recommended diet and exercise plan.

D In addition to the visits indicated, ECG should be recorded in case of respective cardiac symptoms (indicating rhythm disorders or cardiac ischaemia)

E For female patients (local urine pregnancy test in women of child bearing potential)

F Fasting blood samples (full overnight fast (nothing to eat or drink except water for at least 10 hours))

G For the screening Visit 1, laboratory only includes liver transaminases, alkaline phosphatase, and serum creatinine. Patients do not have to be fasting.

H Instruction and training of the patient to use the device at Visit 2. Daily measurements during Run-in and Follow-up. During the treatment period a weekly test is recommended. During the whole trial participation, additional measurements should be done in case of hypo- or hyperglycaemia related symptoms.

I At all visits, the respective kit number has to be allocated to the patient via IRT.

J For patients that screen fail before Visit 2, only serious adverse events need to be reported

K Only screening relevant demographics (gender, date of birth, race and ethnicity) at visit 1. Smoking and alcohol status could be collected at visit 2.

M Calculated based on MDRD formula (Section 5.3.3)

TABLE OF CONTENTS

TITLE PAGE **1**
CLINICAL TRIAL PROTOCOL SYNOPSIS **2**
FLOW CHART **5**
TABLE OF CONTENTS **7**
ABBREVIATIONS **10**
1. INTRODUCTION **12**
1.1 MEDICAL BACKGROUND **12**
1.2 DRUG PROFILE **12**
2. RATIONALE, OBJECTIVES, AND BENEFIT - RISK ASSESSMENT **15**
2.1 RATIONALE FOR PERFORMING THE TRIAL **15**
2.2 TRIAL OBJECTIVES **15**
2.3 BENEFIT - RISK ASSESSMENT **15**
3. DESCRIPTION OF DESIGN AND TRIAL POPULATION **17**
3.1 OVERALL TRIAL DESIGN AND PLAN **17**
3.1.1 Administrative structure of the trial **18**
3.2 DISCUSSION OF TRIAL DESIGN, INCLUDING THE CHOICE OF CONTROL GROUP **19**
3.3 SELECTION OF TRIAL POPULATION **19**
3.3.1 Main diagnosis for trial entry **20**
3.3.2 Inclusion criteria **20**
3.3.3 Exclusion criteria **21**
3.3.4 Removal of patients from therapy or assessments **22**
3.3.4.1 Removal of individual patients 22
3.3.4.2 Discontinuation of the trial by the sponsor 23
4. TREATMENTS **24**
4.1 INVESTIGATIONAL TREATMENTS **24**
4.1.1 Identity of the Investigational Medicinal Products **24**
4.1.2 Selection of doses in the trial **24**
4.1.3 Method of assigning patients to treatment groups **24**
4.1.4 Drug assignment and administration of doses for each patient **25**
4.1.5 Blinding and procedures for unblinding **25**
4.1.5.1 Blinding 25
4.1.5.2 Unblinding and breaking the code 26
4.1.6 Packaging, labelling, and re-supply **26**
4.1.7 Storage conditions **26**
4.1.8 Drug accountability **27**
4.2 OTHER TREATMENTS, EMERGENCY PROCEDURES, RESTRICTIONS **27**
4.2.1 Other treatments and emergency procedures **27**

4.2.2 Restrictions 29
4.2.2.1 Restrictions regarding concomitant treatment 29
4.2.2.2 Restrictions on diet and life style 30
4.2.2.3 Restrictions regarding women of childbearing potential 30
4.3 TREATMENT COMPLIANCE 30

5. VARIABLES AND THEIR ASSESSMENT 32

5.1 TRIAL ENDPOINTS 32
5.1.1 Primary Endpoint 32
5.1.2 Secondary Endpoints 32

5.2 ASSESSMENT OF EFFICACY 33
5.3 ASSESSMENT OF SAFETY 34
5.3.1 Physical examination 34
5.3.2 Vital Signs 34
5.3.3 Safety laboratory parameters 34
5.3.4 Electrocardiogram 36
5.3.5 Other safety parameters 36
5.3.6 Assessment of adverse events 37
5.3.6.1 Definitions of AEs 37
5.3.6.2 Adverse event collection and reporting 40
5.3.7 Criteria for hypoglycaemic events 42

5.7 APPROPRIATENESS OF MEASUREMENTS 43

6. INVESTIGATIONAL PLAN 45

6.1 VISIT SCHEDULE 45
6.2 DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS 45
6.2.1 Screening and run-in period 45
6.2.2 Treatment period 46
6.2.3 Follow Up Period and Trial Completion 47

7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE 48

7.1 STATISTICAL DESIGN - MODEL 48
7.2 NULL AND ALTERNATIVE HYPOTHESES 48
7.3 PLANNED ANALYSES 48
7.3.1 Primary endpoint analyses 49
7.3.2 Secondary endpoint analyses 50

7.3.4 Safety analyses 51
7.3.5 Pharmacokinetic and pharmacodynamic analyses 51
7.4 INTERIM ANALYSES 51
7.5 HANDLING OF MISSING DATA 52
7.6 RANDOMISATION 52
7.7 DETERMINATION OF SAMPLE SIZE 53
8. INFORMED CONSENT, TRIAL RECORDS, DATA PROTECTION, PUBLICATION POLICY 54
8.1 TRIAL APPROVAL, PATIENT INFORMATION, INFORMED CONSENT 54
8.2 DATA QUALITY ASSURANCE 55
8.3 RECORDS 55
8.3.1 Source documents 55
8.3.2 Direct access to source data and documents 56
8.3.3 Storage period of records 56
8.4 EXPEDITED REPORTING OF ADVERSE EVENTS 56
8.5 STATEMENT OF CONFIDENTIALITY AND PATIENT PRIVACY 57
8.5.1 Collection, storage and future use of biological samples and corresponding data 57
8.6 TRIAL MILESTONES 57
9. REFERENCES 58
9.1 PUBLISHED REFERENCES 58
9.2 UNPUBLISHED REFERENCES 59
10. APPENDICES 60
11. DESCRIPTION OF GLOBAL AMENDMENT 61

ABBREVIATIONS

AE	Adverse Event
AESI	Adverse Events of Special Interest
ADA	American Diabetes Association
ALT	Alanine aminotransferase (or SGPT)
AMP	Auxiliary Medicinal Product
ANCOVA	Analysis of Covariance
AST	Aspartate aminotransferase (or SGOT)
BI	Boehringer Ingelheim
BIcMQs	Boehringer Ingelheim customized MedDRA Queries
BMI	Body Mass Index
BP	Blood Pressure
CA	Competent Authority
CEC	Clinical Event Committee
CI	Confidence Interval
CK	Creatine kinase
CML	Local Clinical Monitor
CRA	Clinical Research Associate
CRF/eCRF	Case Report Form/electronic Case Report Form
CRO	Clinical Research Organisation
CTMF	Clinical Trial Master File
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
DEDP	Drug exposure during pregnancy
DPP-4	Dipeptidyl-peptidase IV
EASD	European Association for the Study of Diabetes
ECG	Electrocardiogram
EOT	End of treatment
FAS	Full Analysis Set
FDA	Food and Drug Administration
FPG	Fasting plasma glucose
FPI	Fasting plasma insulin
FC	Flow chart
GCP	Good Clinical Practice
GFR	Glomerular filtration rate
GIP	Glucose-dependent insulinotropic peptide
GLP-1	Glucagon like peptide-1
HBA_{1c}	Glycosylated haemoglobin A1c
HBGM	Home Blood Glucose Monitoring
HDL	High Density Lipoprotein
IB	Investigator's Brochure
IEC	Independent Ethics Committee
ICH	International Conference on Harmonisation
IPV	important protocol violation

ISF	Investigator Site File
i.v.	intravenous
IRB	Institutional Review Board
IRT	Interactive Response Technology
ITT	Intention To Treat
LDH	Lactic dehydrogenase
LDL	Low Density Lipoprotein
MedDRA	Medical Dictionary for Drug Regulatory Activities
MTT	Meal Tolerance Test
NGSP	National Glycohemoglobin Standardization Program
NOAEL	No Observed Adverse Effect Level
OPU	Operative Unit
OC	observed case
PK	Pharmacokinetics
p.o.	per os (oral)
PPG	Post-prandial glucose
PPS	Per Protocol Set
q.d.	quaque die (once a day)
REP	Residual Effect Period
RDC	Remote Data Capture
SAE	Serious Adverse Event
s.c.	Subcutaneous
SFDA	State Food and Drug Administration
SGLT2	sodium glucose co-transporter 2
SMQs	Special MedDRA Queries
SOP	Standard Operating Procedure
SPC	Summary of Product Characteristics
STEMI	ST Segment Elevation Myocardial Infarction
SUSAR	Serious Unexpected Suspected Adverse Reaction
TCM	Trial Clinical Monitor
TDMAP	Trial Data Management and Analysis Plan
T2DM	Type 2 diabetes mellitus
TIA	Transient ischemic attack
TS	Treated set
t.i.d.	ter in die (3 times a day)
TMM	Team Member Medicine
TMW	Trial Medical Writer
TSAP	Trial Statistical Analysis Plan
ULN	upper limit of normal
WOCBP	women of childbearing potential

1. INTRODUCTION

1.1 MEDICAL BACKGROUND

Type 2 diabetes mellitus (T2DM) accounts for 90 to 95% of all cases of diabetes and is an increasingly prevalent disease with an estimated 180 million affected people worldwide. Its incidence is expected to double during the next 20 years. Complications induced by hyperglycaemia are currently the most frequent cause of adult-onset loss of vision, renal failure, and amputation in the Industrialized World. Diabetes is also associated with macrovascular complications with a 2- to 5-fold increase in cardiovascular disease risk. The high frequency of complications leads to a significant reduction of life expectancy.

Although several antidiabetic compounds have been developed to improve glucose control and attenuate the metabolic derangements that accompany uncontrolled T2DM, none of these compounds has been able to maintain long-term glycaemic control.

The improved understanding of the incretin effect has contributed to the development of a new class of antidiabetic agents. The incretin effect results from glucagon like peptide-1 (GLP-1) and glucose dependent insulinotropic peptide (GIP), two intestinal peptides, that are released in the presence of glucose or nutrients in the gut. GLP-1 stimulates insulin secretion, thereby augmenting glucose-stimulated insulin release. However, there is little risk of hypoglycaemia due to GLP-1 because GLP-1 activity decreases when glucose concentrations fall below 55 mg/dL. Normally, GLP-1 is almost instantaneously inactivated by the enzyme Dipeptidyl-peptidase IV (DPP-4) that is widely expressed in many tissues including kidney, liver, intestine, lymphocytes and vascular endothelial cells. Therefore, inhibiting DPP-4 would prolong the activity of GLP-1 for stimulating insulin secretion.

1.2 DRUG PROFILE

Linagliptin is a potent inhibitor of DPP-4 activity and prolongs the half-life of GLP-1. This has been shown in vitro, in various animal models, and in clinical trials. Linagliptin is an orally available compound with a low risk for hypoglycaemic episodes.

Linagliptin (BI 1356, Tradjenta®, Trayenta®, Trazenta®, Trajenta®), received its first worldwide marketing approval on 02 May 2011. Marketing approval in the meantime has been received in over 90 countries worldwide including Europe, US, China and other regions. Linagliptin is marketed as 5 mg film-coated tablets.

Clinical Pharmacokinetics
In earlier PK trials, linagliptin showed nonlinear PK in the therapeutic dose range, with a less than dose proportional increase in plasma concentrations. Clearance, volume of distribution, and amount excreted unchanged in urine increased with increasing doses, possibly due to nonlinear protein binding. Linagliptin was predominantly excreted unchanged in faeces. Renal excretion was considered to be a minor elimination pathway. No dose adjustment of linagliptin based on hepatic impairment, renal impairment, age, body mass index (BMI),

weight, gender, or race is considered necessary. Linagliptin showed no clinically relevant interaction with metformin, pioglitazone, glyburide or empagliflozin.

Clinical efficacy and safety
Treatment with 5 mg linagliptin qd has resulted in clinically meaningful and statistically significant reductions in HbA_{1c}, FPG, and postprandial glucose. There is a consistent pattern in the improvement in HbA_{1c} levels when linagliptin was used in patients with different background therapies. These findings demonstrate efficacy for up to 18 to 24 weeks duration for different background therapies and are further supported by trials of longer duration up to 104 weeks.

Overall, in phase III studies the overall incidence of adverse events (AEs), drug related AEs, AEs of severe intensity, AEs leading to discontinuation, and serious AEs (Serious Adverse Event, SAEs) were very similar across studies, with linagliptin being mostly comparable with placebo. For description of side effects of linagliptin refer to the current Investigator's Brochure (IB) [c01838725-16] and the local prescribing information of Trajenta® [R15-6052].

The growing safety evidence base for linagliptin, including completed Phase III and IV clinical trials, comprises patients treated with background therapies of metformin, sulphonylurea, empagliflozin, and insulin. 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].

The limited intrinsic risk for hypoglycaemia makes linagliptin especially interesting as an add-on to insulin. So far, the combination of linagliptin and insulin has been tested in three major clinical trials in different populations. 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_{1c} 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.

An analysis of two independent phase III studies, linagliptin monotherapy was shown to have a similar dose–exposure–response relationship in Japanese, Asian (non-Japanese) and White patients. Linagliptin treatment resulted in clinically relevant improvements in glycemic

control in all groups although the effect on HbA1c is more pronounced in Japanese and Asian (non-Japanese) patients. Overall, linagliptin 5 mg is a safe and effective treatment option in patients with type 2 diabetes regardless of race or ethnic backgrounds [P16-00852].

For a more detailed description of the linagliptin profile please refer to the current Investigator's Brochure (IB) [c01838725-16].

2. RATIONALE, OBJECTIVES, AND BENEFIT - RISK ASSESSMENT

2.1 RATIONALE FOR PERFORMING THE TRIAL

The rationale for conducting this trial in Chinese patients with T2DM on a stable background therapy of insulin is:

- to achieve improved glycaemic control,
- to assess the occurrence of hypoglycaemia, and
- to collect further data on efficacy and safety in patients treated with linagliptin in this population

2.2 TRIAL OBJECTIVES

The objective is to investigate the efficacy and safety of linagliptin (5 mg / once daily) compared to placebo for 24 weeks in Chinese patients with T2DM with insufficient glycaemic control (i.e., HbA_{1c} of 7.5% to 10%) on stable background therapy with insulin alone or in combination with metformin.

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 counselling, as well as general medical benefit from careful and close monitoring by medical personnel, and Home Blood Glucose Monitoring (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.

Two weeks Run-In Period Risk
Trial designs with a two-week placebo Run-In Period are well-established for T2DM trials. The patients will be maintained on stable antidiabetic therapy during the two-week Run-In Period and continue regular monitoring of blood glucose with a HBGM device. Thus, the risk of the two-week placebo treatment in this trial is considered to be minimal.

Background Therapy and Study Medication Specific Risk
Insulin is the stable background therapy in this trial. Patients are administered basal insulin or pre-mixed insulin and not short-acting insulin because there are fewer injections, lower risk of hypoglycaemia, and both kinds of insulin covers postprandial peaks. Weight gain,

hypoglycaemia, allergic reactions, injection site reaction, lipodystrophy, pruritus, and rash are the most common side effects noted with insulin. All patients will have received insulin and these events mainly occur shortly after insulin initiation (at least allergic reactions). For safety reasons, the insulin dose can always be modified by investigators.

For linagliptin, nasopharyngitis, cough, hypersensitivity and pancreatitis are listed side effects (independently of background therapy). For a background therapy of insulin in addition constipation is a listed ADR for linagliptin. In addition, based on post marketing experience, angioedema, urticaria and rash are listed as side effects for linagliptin [R15-6052]. Furthermore, longer term safety data have not shown any further safety trends to date. For additional information (on any further side effects of linagliptin beyond of the above described at time of protocol finalization) and for additional details, refer to the linagliptin Investigator Brochure [c01838725-16, current version] and the current version of the local prescribing information of Trajenta®.

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 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.

Patients who exceed the predefined limits for hyperglycaemia as determined by blood glucose values (section 4.2.1) during the randomised period will receive rescue therapy (according to Section 4.2.1) or have adjustments in their background therapy.

Alternative Therapies for T2DM

There are several alternative therapies available for the treatment of T2DM (e.g., sulphonylureas, thiazolidinediones, sodium glucose co-transporter 2 (SGLT2) inhibitors, meglitinides, alpha-glucosidase inhibitors, rapid acting or short acting insulin); however, these are not without side effects as described in local prescribing information for products in China.

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

3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN AND PLAN

This randomised, double-blind, multi-centre, and placebo-controlled, parallel group study compares linagliptin (5 mg) to placebo as add-on therapy to stable insulin alone (basal insulin, premixed insulin) or in combination with metformin.

In total, 206 patients with T2DM who meet the entry criteria are planned for inclusion in this trial. The randomised treatment will be double-blind between linagliptin and placebo, i.e. each patient will receive either active treatment or placebo matching linagliptin.

Patients pre-treated with insulin alone or insulin in combination with metformin are included in the study once they have signed the informed consent. Acceptable basal insulins could be insulin glargin, insulin detemir or NPH (neutral protamin hagedorn) insulin with duration of action up to 24 h; Furtheron, patients on pre-mixed insulins may be included up to a certain limit in accordance with the defined randomisation criteria (ref. to section 7.6 and the Investigator Site File (ISF) for further details). Acceptable pre-mixed insulins could be preparations with 25/75 or 30/70 ratio, with once or twice daily posology only. All patients suitable after screening will undergo a 2-week placebo run-in period before randomisation. Patients who successfully complete this period and who still meet the inclusion/exclusion criteria will be randomised (with an allocation of 1:1 and refer to section 7.6) to the 24 week randomised treatment period of the study in which they will receive either 5mg linagliptin or placebo. During the 24-week randomised treatment period, the background therapy described above should remain unchanged if at all possible.

The end of treatment (EOT) visit will be performed for all patients upon completion of 24-week treatment and for those who prematurely discontinue trial medication. The follow-up visit will be performed one week after EOT.

The patient participation is concluded when they have undergone last planned visit.
The time period for which AEs will still be considered on-treatment is 7 days following last intake of trial medication. After trial completion all AEs, including those persisting are followed-up for up to 30 days and it should be confirmed if they have resolved or sufficiently characterised.
The end of the trial is defined as “last patient out”, i.e. last visit completed by last patient.

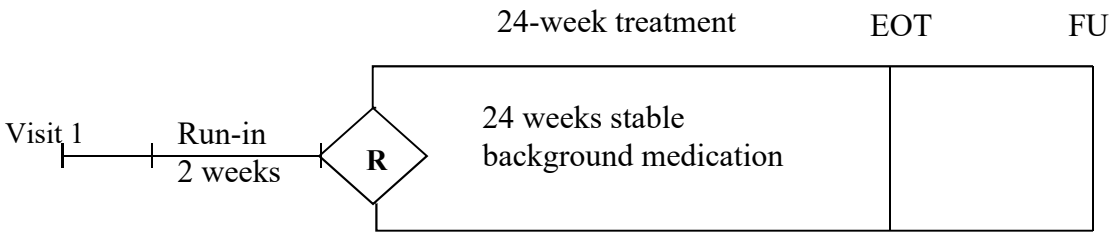

Figure 3.1:1 Treatment periods and treatment groups in the trial design

3.1.1 Administrative structure of the trial

The trial is sponsored by Boehringer Ingelheim (BI).

A Coordinating Investigator is responsible to coordinate Investigators at different centres participating in this multicentre trial. Tasks and responsibilities are defined in a contract.

Relevant documentation on the participating (Principal) Investigators and other important participants, including their curricula vitae, will be filed in ISF.

Boehringer Ingelheim has appointed a Trial Clinical Monitor, responsible for coordinating all required activities, in order to

- manage the trial in accordance with applicable regulations and internal Standard Operating Procedure (SOPs),
- direct the clinical trial team in the preparation, conduct, and reporting of the trial,
- ensure appropriate training and information of local clinical monitors (CML), Clinical Research Associates (CRAs), and Investigators of participating countries.

The organisation of the trial in the participating countries will be performed by the respective local or regional BI-organisation (Operating Unit, OPU) in accordance with applicable regulations and internal SOPs, or by a Contract Research Organisation (CRO) with which the responsibilities and tasks will have been agreed and a written contract filed before initiation of the clinical trial.

Data Management and Statistical Evaluation will be done by BI according to BI SOPs.

Tasks and functions assigned in order to organise, manage, and evaluate the trial are defined according to BI SOPs. A list of responsible persons and relevant local information can be found in the ISF.

A central laboratory service and an interactive response technology (IRT) vendor will be used in this trial. Details will be provided in IRT Manual and Central Laboratory Manual, available in ISF.

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

<u>Clinical Event Committee</u>

The study is set up with prospective centralized blinded adjudication of all cardio/cerebrovascular trigger events. The prospectively defined adjudication process will assess cardiac and neurological vascular events through an independent, blinded, external Clinical Event Committee (CEC). Details on the composition of the committee, its procedures and interactions are provided in a separate CEC charter.

Additionally, a separate independent, blinded, external committee will be set up for adjudication of pancreatic events. The adjudication process for pancreatic events will be clarified in a separate CEC charter.

3.2 DISCUSSION OF TRIAL DESIGN, INCLUDING THE CHOICE OF CONTROL GROUP

According to current guidelines (ADA, EASD), insulin therapy should be initiated immediately in patients newly diagnosed with T2DM with an HbA_{1c} >8.5% and as a second step in patients with insufficient glycaemic control despite treatment with oral antidiabetic agents [R10-5741]. Therefore, patients with current insulin therapy alone or combined with metformin represent an important proportion of the patient population with T2DM.

Due to its mechanism of action and the low risk for hypoglycaemia induction, DPP-4 inhibitors like linagliptin should provide additional efficacy in combination with the planned background therapy, especially in postprandial glucose control. The patients enter the study on the basis of insufficient glycaemic control despite standard treatment with insulin alone or combined with metformin. The placebo-controlled design is considered ethically acceptable on the basis of appropriate criteria for patient discontinuation and criteria for rescue therapy as defined in the relevant guidelines (e.g. FDA Guidance for Industry for developing drugs in diabetes [R08-2669]).

The study duration with stable background therapy is planned for 24 weeks because HbA_{1c} as the primary endpoint has been demonstrated to be a reflection of the glycaemic control over the preceding 12 weeks and a stable effect could be shown at 24 weeks [P13-12370]. The one week follow-up period is considered to be sufficient, as previous studies with linagliptin have shown that the pharmacodynamic effect of linagliptin only extends to about 7 days after the last dose.

3.3 SELECTION OF TRIAL POPULATION

Up to 400 patients will be screened for the trial in 20-30 investigational sites in China to ensure that 206 Chinese patients are randomised to trial treatment (103 to each treatment group) and complete the trial.

It is planned to have at least 90 randomised patients on both background of pre-mixed insulin and basal insulin, which will be handled through IRT and refer to section 7.6.

If the patient's background type distribution is not balanced as expected, the impact on the study conduct should be carefully considered. The sponsor should further monitor the recruitment of the trial with regard to the type of patient's background treatment.
The intent is to obtain a balanced mix of patients pre-treated with premixed insulin or basal insulin. As such the sponsor may cap specific patient populations.

It is expected that at least 5 patients should be randomised at each trial centre. Investigators who fail to screen at least one patient within the first 6 weeks of the site initiation may be excluded from further participation. If enrolment is delayed, additional centres may be recruited.

Permission to randomise more than 20 patients per site must be obtained from the Trial Clinical Monitor at Boehringer Ingelheim.

Screening of patients for this trial is competitive, i.e. screening for the trial will stop at all centres when such a number of patients has been screened that it is anticipated that a sufficient number of patients will be randomised to trial treatment. Investigators will be notified when the appropriate number of patients has been screened and screening is complete, and will not be allowed to recruit additional patients for this study. Patients who have completed Visit 1 procedures prior to notification of the termination of recruitment will be allowed to continue in the study, if they meet all entry criteria and they are able to follow the visit schedule specified in this protocol.

The check for patient eligibility will be based upon a complete medical history including a physical examination and clinical laboratory tests. 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 enrolled into the trial (i.e. who have signed informed consent) will be maintained in the ISF at the investigational site irrespective of whether they have been treated with investigational drug or not.

3.3.1 Main diagnosis for trial entry

The study will be performed in Chinese patients with T2DM who have insufficient glycaemic control despite diet and exercise and receiving insulin alone or in combination with metformin.

3.3.2 Inclusion criteria

1. Diagnosis of type 2 diabetes mellitus prior to informed consent.
2. Chinese male or female patients who are pre-treated with insulin alone or in combination with metformin:
   - With maximum insulin dose of ≤ 1 unit/kg/day. Acceptable basal insulins could be insulin glargin, insulin detemir or NPH (neutral protamin hagedorn) insulin with duration of action up to 24 h; acceptable pre-mixed insulins could be preparations with 25/75 or 30/70 ratio, with once or twice daily posology only. The total insulin dose should not be changed by more than 10% of the baseline value within the 12 weeks prior to randomisation (Visit 3). Both human insulin & insulin analogue are accepted.
   - If the patient is taking metformin, stable dose (at least 1500 mg daily) must be maintained for at least 12 weeks without dose adjustments prior to randomisation (Visit 3).
3. HbA_{1c} fulfills the following criteria: ≥ 7.5 % to ≤ 10.0 % at Visit 1.

4. Age ≥ 18 years at Visit 1.
5. BMI ≤ 45 kg/m^2 (Body Mass Index) at Visit 1.
6. Women of childbearing potential must be ready and able to use highly effective methods of birth control per ICH M3 (R2) that result in a low failure rate of less than 1% per year when used consistently and correctly. A list of contraception methods meeting these criteria is provided in the patient information.
   - A woman is considered of childbearing potential (WOCBP), i.e. fertile, following menarche and until becoming post-menopausal unless permanently sterile.
   - Permanent sterilisation methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy.
7. Signed and dated written informed consent by date of Visit 1 in accordance with ICH-GCP and local legislation

3.3.3 Exclusion criteria

1. Uncontrolled hyperglycaemia with a glucose level >240 mg/dl (>13.3 mmol/L) after an overnight fast during placebo run-in and confirmed by a second measurement (not on the same day).
2. Any other antidiabetic drug within 3 months prior to informed consent except those defined as background treatment via inclusion criterion 2.
3. Acute coronary syndrome (non-STEMI, STEMI and unstable angina pectoris), stroke or TIA within 3 months prior to informed consent.
4. Indication of liver disease, defined by serum levels of either ALT (SGPT), AST (SGOT), or alkaline phosphatase above 3 × upper limit of normal (ULN) as determined during screening and/or run-in phase.
5. Any contraindications to metformin according to the local label for those patients that enter the study with metformin therapy as provided in ISF.
6. Bariatric surgery within the past two years and other gastrointestinal surgeries that induce chronic malabsorption.
7. Medical history of cancer (except for basal cell carcinoma) and/or treatment for cancer within the last 5 years.
8. Blood dyscrasias or any disorders causing hemolysis or unstable Red Blood Cell (e.g. malaria, babesiosis, haemolytic anemia).
9. Known hypersensitivity or allergy to the investigational product or its recipients.
10. Treatment with anti-obesity drugs 3 months 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.
11. Current treatment with 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 except T2DM.
12. Women who are pregnant, nursing, or who plan to become pregnant while in the trial.

13. Alcohol or drug abuse within the 3 months prior to informed consent that would interfere with trial participation or any ongoing condition leading to a decreased compliance to study procedures or study drug intake in the opinion of the investigator.
14. Participation in another trial with an investigational drug within 2 months prior to informed consent or previous enrolment in this trial.
15. Any other clinical condition that would jeopardize patient's safety while participating in this clinical trial in the opinion of the investigator.

3.3.4 Removal of patients from therapy or assessments

3.3.4.1 Removal of individual patients

An excessive withdrawal rate can have a severe negative impact on the scientific value of the trial. Every effort should be made to keep patients in the trial as scheduled. This includes careful patient selection and appropriate explanation of the trial requirements and procedures prior to enrolment as well as an explanation of the consequences of premature withdrawal.

An individual patient is to be withdrawn from trial treatment if:

- The patient withdraws consent for trial treatment or trial participation, without the need to justify the decision.
- The patient needs to take concomitant drugs that interfere with the investigational product or other study medications.
- The patient can no longer be treated with trial medication for other medical reasons (such as surgery, adverse events, other diseases, or pregnancy).
- Introduction of rescue therapy due to hyperglycaemia as described in section 4.2.1 does not lead to sufficient treatment efficacy (rescue criteria still met). In this case, the reason for discontinuation will be classified as "lack of efficacy".
- Occurrence of hypoglycaemia that may put the patient at risk with continued participation (e.g. repeated hypoglycaemic episodes).
- If a patient becomes pregnant during the trial the investigational drug will be stopped, the patient will be discontinued from the trial and the patient will be followed up until birth or otherwise termination of the pregnancy.
- The patient has repeatedly shown to be non-compliant with important trial procedures and, in the opinion of both, the investigator and sponsor representative, is not willing or able to stick to the trial requirements in the future.

Given the patient's agreement, the patient will undergo the procedures for early treatment discontinuation and follow up as outlined in the Flow Chart (FC) and section 6.2.3.

For all patients the reason for withdrawal (e.g. adverse events) must be recorded in the CRF (case report form). These data will be included in the trial database and reported.

A patient can be discontinued after discussion between sponsor and investigator if eligibility criteria are being violated, or if the patient fails to comply with the protocol (e.g. non-attendance at study assessments).

Patients who drop out during the screening phase prior to randomisation (Visit 3) will be considered a screening failure. They have to be recorded as screening failure in eCRFs and no further follow-up is required.

Patients who discontinue or withdraw from the study after randomisation (Visit 3) will be considered as "early discontinuations" and the reason for premature discontinuation must be recorded in the eCRFs. The data will be included in the trial database and will be reported. If determined by investigator as necessary for patient safety, new antidiabetic medication regimen can be started immediately after discontinuation and must be recorded in eCRFs.

Patients who withdraw or discontinue from the trial after randomisation will not be replaced.

3.3.4.2 Discontinuation of the trial by the sponsor

Boehringer Ingelheim 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 invalidating the earlier positive benefit-risk-assessment that could significantly affect the continuation of the trial
3. Violation of GCP, the Clinical Trial Protocol (CTP), or the contract disturbing the appropriate conduct of the trial

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

4. TREATMENTS

4.1 INVESTIGATIONAL TREATMENTS

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

4.1.1 Identity of the Investigational Medicinal Products

The characteristics of the test product are below.
- Substance: linagliptin
- Pharmaceutical form: tablet
- Source: Boehringer Ingelheim Pharma GmbH & Co. KG
- Unit Strength: 5 mg
- Route of administration: p.o., once daily

The characteristics of the reference product are below.
- Substance: placebo matching linagliptin 5 mg
- Pharmaceutical form: tablet
- Source: Boehringer Ingelheim Pharma GmbH & Co. KG
- Unit Strength: NA
- Route of administration: p.o., once daily

4.1.2 Selection of doses in the trial

The doses of 5 mg linagliptin was selected based on the results from previous dose finding studies (please refer to the actual version of the Investigator's Brochure, [c01838725-16]) and represents the final to be marketed dose for linagliptin.

4.1.3 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. This will involve the use of interactive response technology (IRT). To facilitate the use of the IRT, the Investigator will receive an IRT manual including all necessary instructions for using the IRT. A copy of the manual will be available in the ISF.

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_{1c} (< 8.5% vs. ≥ 8.5%) as determined from the blood sample taken at Visit 1 and insulin type (basal insulin vs pre-mixed insulin). For further details please refer to Section 7.6.

Patient assignment to the treatment groups will be determined by a computer generated random sequence. Access to the randomisation code will be controlled and documented – for

further details please refer to Sections 4.1.5.1 and 4.1.5.2.

The assigned medication number will be entered in the eCRF, and the corresponding medication kit should be given to the patient. Using this procedure, relevant parties will be blinded to the treatment group assignment.

4.1.4 Drug assignment and administration of doses for each patient

Patients who qualify will be randomised to linagliptin 5 mg or placebo. Medication will be dispensed in a double-blind manner.

Patients will be assigned a placebo run-in kit at the beginning of the placebo run-in period (Visit 2), and dispensing will occur just once. Dispensing of kits for the double-blind treatment period will begin at Visit 3. Dispensing will occur on 5 occasions over a period of 24 weeks. For further details regarding packaging (e.g. number of tablets per pack) please refer to Section 4.1.6.

From the start of the placebo run-in period (Visit 2), patients should be instructed to take their trial medication once daily with water. To ensure a dose interval of about 24 hours, the medication should be taken at the same time every day. 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. Linagliptin can be taken with or without food.

Patients should be instructed not to take their trial medication on the morning of study visits as they will be dosed whilst in the trial site. Patients who fail to do so should have the visit rescheduled as soon as possible, ideally on the following day. Visits should be routinely scheduled in the morning, at approximately the same time of day (07:00 AM to 11:00 AM) for each visit. The actual date and time of administration of the medication at the trial visit will be recorded in the eCRF.

Patients will continue with their standard insulin with or without concomitant metformin therapy throughout the entire study.

4.1.5 Blinding and procedures for unblinding

4.1.5.1 Blinding

Patients, Investigators and everyone involved in trial conduct or analysis or with any other interest in this double-blind trial will remain blinded with regard to the randomised treatment assignments until after database lock.

The randomisation code will be kept secret by Clinical Trial Support at BI up to database lock. Please refer to Section 4.1.5.2 for the rules regarding breaking the code for an individual or for all patients in emergency situations.

4.1.5.2 Unblinding and breaking the code

Emergency unblinding will be available to the Investigator / Pharmacist / investigational drug storage manager via IRT. It must only be used in an emergency situation when the identity of the trial drug must be known to the Investigator in order to provide appropriate medical treatment or otherwise assure safety of trial participants. The reason for unblinding must be documented in the source documents and/or appropriate CRF page along with the date and the initials of the person who broke the code.

Due to the requirements to report Suspected Unexpected Serious Adverse Reactions (SUSARs), it may be necessary for a representative from Boehringer Ingelheim' s Pharmacovigilance group to access the randomisation code for individual patients during trial conduct. The access to the code will only be given to authorised Pharmacovigilance representatives and not be shared further.

4.1.6 Packaging, labelling, and re-supply

The investigational products will be provided by BI or a designated CRO. They will be packaged and labelled in accordance with the principles of Good Manufacturing Practice (GMP).

The study medication will consist of packs labelled with the trial identification and medication kit number. Each pack will contain an appropriate number of linagliptin tablets or matching linagliptin placebo with some reserve (see below), for dosing until the next scheduled visit.

The placebo run-in kit, assigned to all patients successfully completing Visit 2, will contain 21 tablets (i.e. sufficient supply for 2 weeks, with 1 week in reserve). Each double-blind treatment period kit will contain 42 tablets (i.e sufficient supply for 4 weeks, with 2 weeks in reserve). At Visit 3, 4 and 5, the patient will receive 1 treatment kit. At Visit 6 and 7, the patient will receive 2 treatment kits.

Re-supply to the sites will be managed via an IRT system, which will also monitor expiry dates of supplies available at the sites

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

4.1.7 Storage conditions

Drug supplies will be kept in their original packaging and in a secure limited access storage area according to the recommended storage conditions on the medication label. A temperature log must be maintained for documentation.

The minimum/maximum storage temperature must be measured and documented by the Investigator / pharmacist / investigational drug storage manager in accordance with BI (or designated CRO) SOPs.

4.1.8 Drug accountability

The Investigator / pharmacist / investigational drug storage manager will receive the investigational drugs delivered by the Sponsor when the following requirements are fulfilled:

- approval of the study protocol by the Institutional Review Board (IRB) / ethics committee
- availability of a signed and dated clinical trial contract between the sponsor and the head of the investigational site
- approval / notification of the regulatory authority, e.g. competent authority
- availability of the curriculum vitae of the Principal Investigator
- availability of a signed and dated clinical trial protocol
- if applicable, availability of the proof of a medical licence for the Principal Investigator

The Investigator < and/or > Pharmacist < and/or > investigational drug storage manager must maintain records of the product's delivery to the trial site, the inventory at the site, the use by each patient, and the return to the sponsor or warehouse / drug distribution centre or alternative disposal of unused products. If applicable, the sponsor or warehouse / drug distribution centre will maintain records of the disposal.

These records will include dates, quantities, batch/serial numbers, expiry ('use by') dates, and the unique code numbers assigned to the investigational product and trial patients. The Investigator / pharmacist / investigational drug storage manager will maintain records that document adequately that the patients were provided the doses specified by the CTP and reconcile all investigational products received from the Sponsor. At the time of return to the Sponsor / appointed CRO, the Investigator / pharmacist / investigational drug storage manager must verify that all unused or partially used drug supplies have been returned by the clinical trial patient and that no remaining supplies are in the Investigator's possession.

4.2 OTHER TREATMENTS, EMERGENCY PROCEDURES, RESTRICTIONS

4.2.1 Other treatments and emergency procedures

Throughout the duration of the trial, patients should continue to take insulin alone or in combination with metformin as background therapy.

Acceptable basal insulins could be insulin glargin, insulin detemir or NPH (neutral protamin hagedorn) insulin with duration of action up to 24 h; acceptable pre-mixed insulins could be preparations with 25/75 or 30/70 ratio, with once or twice daily posology only. The background medication of metformin should remain unchanged throughout the study. The total prescribed insulin dose should not be changed by more than 10% of the baseline value in the 24 weeks after randomisation. The background medication will not be provided as part of the clinical trial supplies.

The patients can take their background medication as they are used to, where it is suggested that basal insulin is always given in the evening. Morning dose of metformin/any permitted pre-mixed insulin and study medication should be taken after the visits blood sample taken, and the patients should have the same habits of dosing throughout the trial.

Hyperglycaemia

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 insulin prior to or after informed consent, and if applicable metformin) for the treatment of hyperglycaemia [R08-2669]:

Week	Visit	FPG level
Week 1-12	up to visit 6	>240 mg/dl (>13.3 mmol/l) after overnight fast
Week 12-24	after visit 6 until Visit 8	>200 mg/dl (>11.1 mmol/l) after overnight fast

To confirm the above results, meaning that there is a minimum of two measurements, at least one of which should be performed after an overnight fast at the investigational site, and on a different day to the initial measurement.

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.

The first choice of rescue therapy should be the adjustment of insulin therapy. Its dosage will be left to the discretion of the investigator. In very rare cases, adjustment of background therapy or addition of another oral anti-diabetic medication would be appropriate. Such cases should be discussed with the local clinical monitor or the Trial Clinical Monitor (TCM). Rescue therapy should be taken in accordance with the local prescribing information of the respective drug, taking into account potential contraindications.

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

- **For patients with a baseline daily insulin dose ≤10 units, any increase of insulin >50% from baseline for > 7 days duration**
- **For patients with a baseline daily insulin dose >10 and ≤20 units, any increase of insulin >30% from baseline for > 7 days duration**
- **For patients with a baseline daily insulin dose > 20 units, any increase of insulin >20% from baseline for > 7 days duration**
- **Any increase in metformin for ≥ 1 day**
- **Any introduction of a new antidiabetic therapy for ≥ 1 day.**

A FPG, HbA_{1c} sample should be taken before initiation of rescue therapy and sent to central lab for analysis. The HbA_{1c} sample is not required if a sample has been taken and sent to the central lab for analysis within the last 4 weeks.

Hypoglycaemia

If the patient is experiencing hypoglycaemia (criteria see section 5.3.7), the investigator should review the diary responses to diet and physical activity as well as the HBGM results to determine the 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).

In the case of hypoglycaemia that may put patient on risk (e.g. repeated symptomatic hypoglycaemia or severe hypoglycaemia), appropriate adjustment of anti-diabetic therapy such as a dose reduction / discontinuation of ongoing rescue medication or existing background therapy should be initiated. Reduction or discontinuation of ongoing rescue medication should be considered before a reduction in the dose of existing background therapy.

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

Any rescue medication will be recorded in the source documents and on the appropriate pages of the eCRF.

Rescue medication will not be provided as part of the clinical trial supplies.

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. Exceptions to this are the restrictions described in Section 4.2.2.

In this trial, the background therapy (i.e. insulin alone or in the combination with metformin) and the chosen rescue medications are considered as Auxiliary Medicinal Product (AMP). This means that in the event of SAEs, the Investigator will assess the causal relationship of the SAE to the AMPs. Further details regarding SAE reporting can be found in Section 5.3.6.

There are no special emergency procedures to be followed.

4.2.2 Restrictions

4.2.2.1 Restrictions regarding concomitant treatment

Short-term use of additional prandial/intravenous insulin will be permitted (only in the event of an emergency situation and/or hospitalisation) based on clinical judgement of the Investigator or treating physician. Prolongation of additional prandial/intravenous 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/TCM. Please also refer to Section 3.3.3 regarding the permitted use of antidiabetic agents pre-trial.

Additionally, treatment with anti-obesity drugs, herbal medications with antidiabetic effects or systemic steroids will be prohibited due to their influence on glucose metabolism. However, one off or short-term use (i.e. ≤ 1 week's 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.

For patients receiving metformin, in case a vascular administration of iodine containing contrast agent is required, metformin should be temporarily discontinued at the time of or before the contrast agent is given and resumed not earlier than 48 hours after administration.

4.2.2.2 Restrictions on diet and life style

At the beginning of the Run-in period, patients will receive diet and exercise counselling by a diet specialist or delegated staff member. The counselling will be based on local diet recommendations. The patients will be reminded to follow the agreed diet and exercise plan at every visit.

Patients also should not take part in another clinical trial involving an investigational medicinal product within 2 months prior to informed consent.

4.2.2.3 Restrictions regarding women of childbearing potential

Women of childbearing potential must use the contraception methods described in the patient information.

4.3 TREATMENT COMPLIANCE

Patients are requested to bring all remaining trial medication including empty package material with them when attending visits. The tablets will be counted by the investigator or designee and compliance will be calculated in a worksheet, which must be kept as a source document.

Based on tablets counts, treatment compliance will be calculated as the number of tablets taken, divided by the number of tablets which should have been taken according to the scheduled period, multiplied by 100. Compliance will be verified by the on-site monitor authorised by the sponsor.

$$\text{Treatment compliance (\%)} = \frac{\text{Number of tablets actually taken} \times 100}{\text{Number of tablets which should have been taken}}$$

Compliance during the placebo run-in period should be between 80% and 120%. If compliance is outside this range, the patient should be carefully interviewed and, if necessary, re-informed about the purpose and the conduct of the trial. Unreliable patients should not be randomised at the discretion of the Investigator.

Compliance during the double-blind treatment period should also be between 80% and 120%. Patients who are not compliant according to this definition should be carefully interviewed and re-informed about the purpose and the conduct of the trial.

5. VARIABLES AND THEIR ASSESSMENT

5.1 TRIAL ENDPOINTS

5.1.1 Primary Endpoint

The primary endpoint in this study is the change from baseline in HbA_{1c} after 24 weeks of treatment. Throughout the study protocol, the term "baseline" refers to the last observation prior to the randomised period.

5.1.2 Secondary Endpoints

Secondary efficacy endpoints are:

- Change from baseline in FPG after 24 weeks of treatment;
- Change from baseline in 2-hour PPG after 24 weeks of treatment
- Proportion of patients with HbA_{1c} on treatment <7.0% after 24 weeks of treatment
- Proportion of patients with HbA_{1c} on treatment <6.5% after 24 weeks of treatment
- Proportion of patients with HbA_{1c} lowering by at least 0.5% after 24 weeks of treatment

Secondary safety endpoints are:

- Incidence of investigator–reported hypoglycaemic events confirmed by a measured blood glucose ≤ 70 mg/dL (≤ 3.9 mmol/L)
- Incidence of severe hypoglycaemic events (requiring active assistance by another person, or fatal)

5.2 ASSESSMENT OF EFFICACY

HbA_{1c}
Blood samples for the determination of HbA_{1c} will be taken at all visits except Visit 2. The blood sample can be taken at any time during the visit. For the determination of HbA_{1c}, 3 mL of blood will be collected. The samples will be analysed at a central laboratory or its affiliates having a National Glycohemoglobin Standardization Program (NGSP) Level I certificate. Further details about sample handling, shipment, and assay procedures can be found in the Investigator's Site File (Lab manual).

Fasting plasma glucose (FPG)
Blood samples for the determination of FPG at the central laboratory will be taken after an overnight fast. The samples should be taken before breakfast and before trial drug administration. The samples will be measured at a central laboratory using validated assays. Further details about sample handling and shipment can be found in the ISF (Lab manual).

Meal Tolerance Test (MTT)
Meal Tolerance Test (MTT) will be performed using a standardised breakfast. MTT at Visit 3 would be performed before randomisation, i.e. without intake of trial medication during the MTT.

At Visit 3, after blood sample of FPG drawing, patients would have a standardised breakfast and intake metformin and/ or accepted pre-mixed insulin (if applicable), finished within 15 min, and PPG blood samples would be collected at time points 60 ±10 min and 120 ±10 min after the start of standardised breakfast. Study medication would only be taken after last PPG blood samples drawing, i.e. following randomisation.

At Visit 8, 30 min after blood sample of FPG drawing and administration of study medication, patients would have a standardised breakfast and intake metformin and/ or accepted pre-mixed insulin (if applicable), finished within 15 min, and PPG blood samples would be collected at time points 60 ±10 min and 120 ±10 min after the start of standardised breakfast.

Weight and Waist circumference
Weight measurements should always be done on the same scales for one patient. In order to get comparable body weight values, it should be performed in the following way:
- fasting (except for the screening visit),

- after the urine sampling (weight after bladder voiding),
- shoes and coat/jackets should be taken off
- pockets should be emptied of heavy objects (i.e. keys, coins etc)

Waist circumference measurements should be made around a patient's bare midriff, after the patient exhales while standing without shoes and with both feet touching and arms hanging freely. The measuring tape should be made of a material that is not easily stretched, such as fibreglass. The tape should be placed perpendicular to the long axis of the body and horizontal to the floor and applied with sufficient tension to conform to the measurement surface.

Waist circumference should be determined by measuring the midpoint between the lowest rib and the iliac crest.

5.3 ASSESSMENT OF SAFETY

5.3.1 Physical examination

At start of run-in and end of treatment, a complete physical examination will be performed by the investigator (see Flow chart). Documentation of, and findings from the physical examination, must be part of the source documents available at the site.

5.3.2 Vital Signs

Systolic and diastolic blood pressure as well as pulse rate (electronically or by palpation, count for 1 minute) will be measured after 5 minutes of rest in the seated position. All recordings should be made using the same blood pressure recording instrument on the same arm (see Flow chart).

5.3.3 Safety laboratory parameters

All safety laboratory samples (except at Visit 1) will be collected after a full overnight fast (nothing to eat or drink except water for at least 10 hours) and before background anti-diabetic therapies and investigational drug as described in the Flow Chart and Section 6. The blood sample at Visit 1 (screening visit) can be taken with the patient in a fasted or non-fasted state.
All parameters that will be determined during the trial conduct are listed in table 5.3.3: 1 and 5.3.3: 2. The analysis will be performed by a central laboratory. The respective reference range and details about sample handling and shipment will be provided in the ISF (Lab Manual).

Reduced safety lab panels excluding urinalysis are planned for the following visits:
- For the screening Visit 1, laboratory only includes liver transaminases, alkaline phosphatase, and serum creatinine.

- Lipid fractions will only be determined at baseline (V3) and end of treatment (V8)

Table 5.3.3: 1 Safety laboratory parameters – Haematology

- Haematocrit
- Haemoglobin
- Red Blood Cells (RBC)/Erythrocytes
- WBC/Leukocytes
- Platelet Count/Thrombocytes
- Differential Automatic (relative and absolute count):
- Neutrophils, Eosinophils, Basophils, Monocytes, Lymphocytes

Table 5.3.3: 2 Safety laboratory parameters – Clinical Chemistry

- Amylase
- Lipase
- AST (aspartate transaminase, SGOT)
- ALT (alanine transaminase, SGPT)
- γ-GT (gamma-glutamyl-transferase)
- Alkaline phosphatase
- Lactic dehydrogenase (LDH)
- Total bilirubin
- Direct bilirubin, if total bilirubin is elevated
- Total Protein
- Albumin
- Creatine kinase (CK)
- CK-MB, if CK is elevated
- Potassium
- Sodium
- Creatinine
- Urea
- Calcium
- Inorganic phosphorous
- Uric acid
- Cholesterol (total) *****
- HDL cholesterol*****
- LDL cholesterol*****
- Triglycerides*****
- Glucose

***** Visits 3,8 only

Table 5.3.3:3 Safety laboratory parameters – urine

- Albumin, Creatinine (spot urine –quantitative measurement)
- Protein
- Glucose
- Ketone
- Leucocytes
- Erythrocytes

The albumine/creatinine ratio will be calculated at the central lab. Urine sediment will only be done if there is a positive finding on the urinalysis.

The glomerular filtration rate (GFR) will be derived from serum creatinine* values based on the standard MDRD formula:

eGFR (ml/min/1.73 m^2) = 175 x [Screatinine (umol/L)/88.4]$^{-1.154}$ x [age]$^{-0.203}$ x [0.742 if patient is female] x [1.212 if patient is of African origin]

*: creatinine methods calibrated to an IDMS reference method

Pregnancy testing (urine) will be performed in female patients of child bearing potential only according to the timepoints indicated in the Flow chart.

5.3.4 Electrocardiogram

Printed paper traces from 12 lead ECGs (I, II, III, aVR, aVL, aVF, V1-V6) will be collected at baseline (visit 3) and at the end of the trial (visit 8) for all patients. In the event of any cardiac symptoms (i.e. suspicion of heart rhythm disorders or cardiac ischemia), an additional ECG will be recorded. All ECGs will be evaluated, (signed, dated and commented upon) by the treating physician/investigator and stored locally.
Any clinically relevant changes in the ECG will be reported as AEs. Any ECG abnormalities will be carefully monitored and if necessary the patient will be removed from the trial and medically treated.

5.3.5 Other safety parameters

Home Blood Glucose Monitoring

All patients will be provided with HBGM equipment and supplies for use at home during the 2-week Run-In periods. Instruction on the proper use of the HBGM will be provided by the study staff. The patient will be asked to record the results of the HBGM test on a HBGM Testing Log that will be included in the patients source document file. Only in the case of linked adverse events or of hypoglycaemia, the single HBGM values will be recorded in the CRF.

During Run-In and Follow-up, HBGM testing should be performed once daily in the fasted state and at any time the patient is symptomatic, i.e., experiences signs/symptoms of hyper- or hypoglycaemia. If during Run-in, results of a HBGM test reveal blood glucose >240 mg/dL (13.3 mmol/L) after an overnight fast, the patient should contact the site. The investigator should then decide about start of the randomised period or further patient participation in the trial based on fasted plasma glucose determinations according to the inclusion and exclusion criteria as outlined in Section 3.3.

During the randomised treatment period, HBGM testing is recommended to be done once weekly (more frequently if required by local authorities) and at any time the patient is symptomatic, i.e., experiences signs/symptoms of hyper- or hypoglycaemia. If during this period, results of a fasting HBGM test reveal blood glucose levels meeting rescue criteria (see Section 4.2.1), the patient should contact the site and the investigator should follow the instructions given in Section 4.2.1.

5.3.6 Assessment of adverse events

5.3.6.1 Definitions of AEs

Adverse event
An adverse event (AE) is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a medicinal product and which does not necessarily have to have a causal relationship with this treatment.

An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Adverse reaction
An adverse reaction is defined as a response to a medicinal product which is noxious and unintended. Response in this context means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility. Adverse reactions may arise from use of the product within or outside the terms of the marketing authorisation or from occupational exposure. Conditions of use outside the marketing authorization include off-label use, overdose, misuse, abuse and medication errors.

Serious adverse event
A serious adverse event (SAE) is defined as any AE which:

- results in death,
- is life-threatening, this refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if more severe.
- requires inpatient hospitalisation or
- prolongation of existing hospitalisation,
- results in persistent or significant disability or incapacity, or
- 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 judgment which may jeopardise the patient and may require medical or surgical intervention to prevent one of the other outcomes listed in the above definitions.

Medical and scientific judgement should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalisation but might jeopardise the patient or might require intervention to prevent one of the other outcomes listed above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation or development of dependency or abuse. Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.

AEs considered "Always Serious"

Cancers of new histology and exacerbations of existing cancer must be reported as a serious event regardless of the duration between discontinuation of the drug and the occurrence of the cancer.

In accordance with the European Medicines Agency initiative on Important Medical Events, Boehringer Ingelheim has set up a list of further AEs, which by their nature, can always be considered to be "serious" even though they may not have met the criteria of an SAE as given above.

The latest list of "Always Serious AEs" can be found in the Remote Data Capture (RDC) system. These events should always be reported as SAEs as described above.

Adverse events of special interest (AESIs)

The term AESI relates to any specific AE that has been identified at the project level as being of particular concern for prospective safety monitoring and safety assessment within this trial, e.g. the potential for AEs based on knowledge from other compounds in the same class. AESI need to be reported to the sponsor's Pharmacovigilance Department within the same timeframe that applies to SAE, please see above.

The following are considered as AESIs:

- Hypersensitivity reactions such as angioedema, angioedema-like events, and anaphylaxis
- Skin lesions such as exfoliative rash, skin necrosis, or bullous dermatitis
- *Hepatic injury as defined by the following alterations of hepatic laboratory parameters: ≥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

*These lab findings constitute a hepatic injury alert and the patients showing these lab abnormalities need to be followed up according to the "DILI checklist" provided via RDC. In case of clinical symptoms of hepatic injury (icterus, unexplained encephalopathy, unexplained coagulopathy, right upper quadrant abdominal pain, etc.) without lab results (ALT, AST, total bilirubin) available, the Investigator should make sure these parameters are analysed, if necessary in an unscheduled blood test. Should the results meet the criteria of hepatic injury alert, the procedures described in the DILI checklist should be followed.

Protocol-specified AESIs (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, even if they do not meet any of the SAE seriousness criteria.

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 (SMQs), and user defined

searches (Boehringer Ingelheim customized MedDRA Queries (BicMQs)) 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 defined 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 ISF/ RDC system and changes will be communicated to all investigators.

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

Mild:	Awareness of signs or symptoms that 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 AEs
The definition of an adverse reaction implies at least a reasonable possibility of a causal relationship between a suspected medicinal product and an adverse event. An adverse reaction, in contrast to an adverse event, is characterised by the fact that a causal relationship between a medicinal product and an occurrence is suspected.

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.

Arguments that may suggest that there is a reasonable possibility of a causal relationship could be:

- The event is consistent with the known pharmacology of the drug
- The event is known to be caused by or attributed to the drug class.
- A plausible time to onset of the event relative to the time of drug exposure.
- Evidence that the event is reproducible when the drug is re-introduced
- No medically sound alternative aetiologies that could explain the event (e.g. pre-existing or concomitant diseases, or co-medications).
- The event is typically drug-related and infrequent in the general population not exposed to drugs (e.g. Stevens-Johnson syndrome).
- An indication of dose-response (i.e. greater effect size if the dose is increased, smaller effect size if dose is diminished).

Arguments that may suggest that there is no reasonable possibility of a causal relationship could be:

- No plausible time to onset of the event relative to the time of drug exposure is evident (e.g. pre-treatment cases, diagnosis of cancer or chronic disease within days / weeks

of drug administration; an allergic reaction weeks after discontinuation of the drug concerned)
- Continuation of the event despite the withdrawal of the medication, taking into account the pharmacological properties of the compound (e.g. after 5 half-lives). Of note, this criterion may not be applicable to events whose time course is prolonged despite removing the original trigger.
- Additional arguments amongst those stated before, like alternative explanation (e.g. situations where other drugs or underlying diseases appear to provide a more likely explanation for the observed event than the drug concerned).
- Disappearance of the event even though the study drug treatment continues or remains unchanged.

5.3.6.2 Adverse event collection and reporting

AE <u>Collection</u>
The Investigator shall maintain and keep detailed records of all AEs in their patient files.
The following must be collected and documented on the appropriate CRF by the Investigator:
- From signing the informed consent onwards through the Residual Effect Period (REP), until individual patient's end of trial:
  -all AEs (serious and non-serious) and all AESIs.
  However, if an individual patient discontinues trial medication prematurely but stays in the trial (i.e. if further visits incl. telephone visits, or vital status assessments are planned) from then on and until the individual patient's end of the trial the Investigator must report related SAEs and related AESIs.
- After the individual patient's end of trial:
  the Investigator does not need to actively monitor the patient for AEs but should only report relevant SAEs and relevant AESIs of which the Investigator may become aware of.

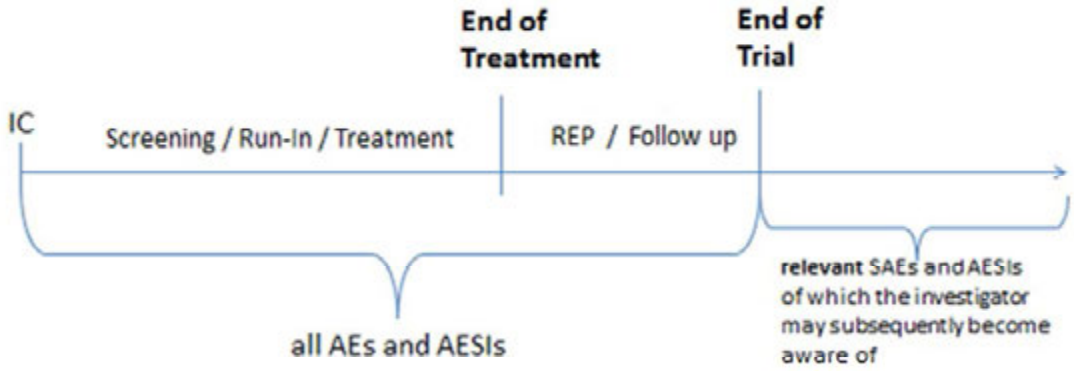

Figure 5.3.6.2: 1 Types of AEs to be reported according to the trial period

The REP is defined as 7 days after the last trial medication application. All AEs which occurred through the treatment phase and throughout the REP will be considered as on

treatment, please see section 7.3.4. Events which occurred after the REP will be considered as post treatment events.

AE reporting to sponsor and timelines
The Investigator must report SAEs, AESIs, and non-serious AEs which are relevant for the reported SAE or AESI, on the BI SAE form via fax immediately (within 24 hours) to the sponsor's unique entry point (country specific contact details will be provided in the ISF). The same timeline applies if follow-up information becomes available. In specific occasions the Investigator could inform the sponsor upfront via telephone. This does not replace the requirement to complete and fax the BI SAE form.
With receipt of any further information to these events, a follow-up SAE form has to be provided. For follow-up information the same rules and timeline apply as for initial information.

Information required
For each AE, the Investigator should provide the information requested on the appropriate CRF pages and the BI SAE form. The Investigator should determine the causal relationship to the trial medication and any possible interactions between the investigational drug and an AMP.

The following should also be recorded as an (S)AE in the CRF and SAE form (if applicable):

- Worsening of the underlying disease or of other pre-existing conditions
- Changes in vital signs, ECG, physical examination and laboratory test results, if they are judged clinically relevant by the Investigator.

If such abnormalities already pre-exist prior trial inclusion they will be considered as baseline conditions.

All (S)AEs, including those persisting after individual patient's end of trial must be followed up until they have resolved, have been sufficiently characterised, or no further information can be obtained.

Pregnancy
In rare cases pregnancy may occur in a clinical trial. Once a patient has been enrolled into this clinical trial and has taken trial medication, the Investigator must report immediately (within 24 hours) a potential drug exposure during pregnancy (DEDP) to the sponsor's unique entry point (country-specific contact details will be provided in the ISF). The Pregnancy Monitoring Form for Clinical Trials (Part A) should be used.

The outcome of the pregnancy associated with the drug exposure during pregnancy must be followed up and reported to the sponsor's unique entry point on the Pregnancy Monitoring Form for Clinical Trials (Part B).

The ISF will contain the Pregnancy Monitoring Form for Clinical Trials (Part A and B).

As pregnancy itself is not to be reported as an AE, in the absence of an accompanying SAE and/or AESI, only the Pregnancy Monitoring Form for Clinical Trials and not the SAE form

is to be completed. If there is an SAE and/or AESI associated with the pregnancy an SAE form must be completed in addition.

5.3.7 Criteria for hypoglycaemic events

Every episode of plasma glucose ⩽70 mg/dl (⩽3.9mmol/l) should be documented in the eCRF with the respective time and date of occurrence. Such hypoglycaemic events should be documented in the eCRF according to the following criteria:

- Asymptomatic hypoglycaemia: event not accompanied by typical symptoms of hypoglycaemia but with a measured plasma glucose concentration ⩽ 70 mg/dl (3.9 mmol/l)
- Documented symptomatic hypoglycaemia with glucose concentration ⩾ 54 mg/dl and ⩽70 mg/dl (⩾ 3.0 mmol/l and ⩽ 3.9 mmol/l): event accompanied by typical symptoms of hypoglycaemia
- Documented symptomatic hypoglycaemia with glucose concentration < 54 mg/dl (< 3.0 mmol/l): event accompanied by typical symptoms of hypoglycaemia
- Severe hypoglycaemic episode: Event requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions.

Note for severe hypoglycemia: 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.

Any hypoglycaemia with glucose values < 54 mg/dl (< 3.0 mmol/l) and all symptomatic or severe hypoglycaemia events should be documented as an adverse event of hypoglycemia.

Further details on documentation of hypoglycemia are provided on the respective eCRF pages.

5.7 APPROPRIATENESS OF MEASUREMENTS

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

The scheduled measurements are appropriate to see drug induced changes in vital signs, standard laboratory values, biomarkers specific to efficacy of treatment of T2DM, and ECG. The primary and secondary endpoints are standard and accepted for evaluation of safety and tolerability of an oral antidiabetic drug, and they are widely used in respective pivotal phase III studies.

Therefore, the appropriateness of all measurements applied in this trial is given.

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 trial medication on the morning of a visit before attending the trial site (excluding visits starting before randomisation) or comes in non-fasted where a fasting condition is required (all visits except screening), 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 in a short enough time-frame so that the patient has sufficient trial medication available.

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 trial medication packs contain sufficient medication to allow for these time windows.

6.2 DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS

6.2.1 Screening and run-in period

Screening Period

The screening visit is the only visit in this study that does not need to be done fasting.

No trial procedures should be done unless the patient has consented to taking part in the trial.

Once patients have consented, the patient is considered to be enrolled in the trial and have started screening. The patient should be recorded on the enrolment log and be registered in the IRT as a screened patient.

Patients who fail screening following Visit 1 procedures should be registered as a screen failure in the IRT (refer to IRT user manual).

Run-in Period

From this visit on, patients should be fasting (no food or drinks, water only for at least 10 hours) prior to each visit.

Patients who fail the run-in period following Visit 2 procedures should be registered as a screen failure in the IRT (refer to IRT user manual).

The patients can take their background medication as they are used to, where it is suggested that basal insulin is always given in the evening. Morning dose of metformin/any permitted pre-mixed insulin and study medication should be taken after the visits blood sample collection, and the patients should have the same habits of dosing throughout the trial.

Monitor adverse events, document in the patients file (source data) and eCRF. For patients that fail on screening before or at this visit, only serious AE's that took place between screening and this Visit 2 must be recorded in the eCRF and the SAE form.
Instruct patients on the correct use of HBGM for glucose testing during the 2 week Run-In Period

- Patients should use the HBGM equipment/supplies to test glucose levels in a fasting state. During the Run-in period patients should test once a day before breakfast (i.e. after an overnight fast). Additionally, patients should test their glucose levels if they experience signs/symptoms of hypo- or hyperglycaemia. Test results should be documented on the HBGM testing log. More frequent HBGM testing is permitted at the Investigator's and/or patient's discretion.
- If the HBGM test reveals an overnight fasted blood glucose of >240 mg/dl (>13.3mol/l), the patient should contact the study site for a visit at the next day. The investigator will then draw a new blood sample (overnight fasted samples for FPG determination) to confirm the hyperglycaemia, document the AE if appropriate and decide about the possible exclusion from randomisation (screening failure).

Baseline Conditions
Chronic diseases, current observable conditions, any new clinically relevant findings discovered from the physical examination, ECG, safety labs, and any condition requiring therapy (excluding T2DM) will be reported on the Baseline Condition eCRF page.

Medical History
Medical history will be collected and reported in the Medical History eCRF page.

6.2.2 Treatment period

The treatment period is from Visit 3 to Visit 8. Patients will be dispensed medication at each of these visits (except for Visit 8). Medication number of each occasion will be allocated by IRT (refer to IRT user manual).

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

Randomisation visit (Visit 3)
Visits should be performed fasting and as indicated in the Flow Chart and the respective protocol sections.

Randomisation/treatment allocation and dispensing of study medication should be the last activity at this visit.

Visits 4-8
Visits should be performed as mentioned in the Flow Chart and the respective protocol sections.

If a patient prematurely discontinues from the 24-week treatment period, the patient must return to the trial site for both Visit 8 (within 7 days of stopping study treatment) and Visit 9 (7 days after Visit 8), which will be performed.

The investigator may initiate any additional antidiabetic therapy for the patient, based on his or her discretion, no sooner than one day after discontinuing study medication or after Visit 8.

6.2.3 Follow Up Period and Trial Completion

For all patients completing the study according to protocol a follow-up contact (Visit 9) with the patient (preferably by phone) should be done by the investigator at the end of the follow-up period of 7 days.

In case of premature discontinuation from the 24 week treatment period however, an End of Trial Visit (V9) should be performed and the patient should return to Visit 9 (7 days after Visit 8/end of treatment). The following examinations should be performed at Visit 9:

- Vital signs
- Collection of blood and urine samples for safety laboratory evaluation
- Documentation of any adverse events
- Documentation of concomitant therapies

7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

7.1 STATISTICAL DESIGN - MODEL

The objective of this randomised, double-blind, placebo-controlled study is to investigate the efficacy and safety of linagliptin compared to placebo given for 24 weeks as add-on therapy to insulin alone or in combination with metformin in Chinese patients with T2DM and insufficient glycemic control. The primary endpoint in this study is the change in HbA_{1c} from baseline after 24 weeks of treatment. HbA_{1c} will be measured in the unit of % at all clinical visits. It is planned to show superiority of linagliptin to placebo.

The primary analysis is a restricted maximum likelihood (REML) -based mixed model repeated measures (MMRM) approach. The statistical model will include fixed classification effects for treatment, type of insulin, week, the linear covariate baseline HbA_{1c}, treatment by week interaction, and baseline HbA_{1c} by week 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_{1c} change from baseline to week 24 at the level of α=0.05 (two-sided).

The primary hypothesis can be written as follows:

H0: Mean change from baseline in HbA_{1c} after 24 weeks of treatment with linagliptin = Mean change from baseline in HbA_{1c} after 24 weeks of treatment with placebo

H1: Mean change from baseline in HbA_{1c} after 24 weeks of treatment with linagliptin $\neq$ Mean change from baseline in HbA_{1c} after 24 weeks of treatment with placebo

7.3 PLANNED ANALYSES

The statistical analysis will be based on the following populations.

Treated Set

The treated set (TS) will consist of all patients who were randomised and treated with at least one dose of study drug.

Full Analysis Set

The full analysis set (FAS) will consist of all patients in the TS who had a baseline and at least one on-treatment HbA_{1c} measurement.

7.3.1 Primary endpoint analyses

The primary analysis will be performed on the FAS and patients will be assigned to the treatment they were randomised to. A REML-based MMRM approach is applied to compare the change in HbA_{1c} from baseline after 24 weeks of treatment (Section 7.2).

The statistical model will be

HbA_{1c} change from baseline = overall mean + baseline HbA_{1c} + treatment + type of insulin
+ week+ week by treatment interaction
+ baseline HbA_{1c} by week interaction
+ random error

This model includes effects accounting for the following sources of variation: 'baseline HbA_{1c}', 'treatment', 'type of insulin (basal insulin or any permitted pre-mixed insulin) ', 'week', 'week by treatment interaction' and 'baseline HbA_{1c} by week interaction'. 'Treatment', 'type of insulin', 'week' and 'week by treatment interaction' are fixed, categorical effects, and 'baseline HbA_{1c}' and 'baseline HbA_{1c} by week interaction' are continuous, linear covariates. For each patient, the error terms from the on-treatment visits represent the within-patient variability, and are assumed to follow a multivariate normal distribution with an unstructured covariance matrix.

If the model fails to converge, further covariance structures will be tested, details will be provided in the TSAP. The first model to converge will be used as the primary analysis. The Kenward-Roger approximation will be used to estimate the 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).

Only the available data which were observed whilst patients were on treatment will be included in the analysis. Missing data are handled implicitly by the above statistical model,

rather than by using any imputation. This approach, referred to as observed case (OC), will additionally set to missing all values measured after rescue medication use.

Superiority will be tested using the p-value of the treatment effect and a two-sided 95% confidence interval for the treatment difference.

7.3.2 Secondary endpoint analyses

The analyses for the secondary endpoints will be based on FAS and patients will be assigned to the treatment they were randomised. These analyses are exploratory in nature and the p-values provided by these analyses will only be nominal.

- In general, continuous endpoints will be analysed using a MMRM model similar to the primary endpoint analysis with the respective baseline parameter as an additional linear covariate. However for the endpoints with only one on-treatment measurement, an ANCOVA model similar to that used for the HbA_{1c} sensitivity analysis (refer to Section 7.3.1) will be applied with the respective baseline parameter as an additional linear covariate. In addition, descriptive statistics will be presented for each endpoint, and at each week if appropriate.
- Binary endpoints will be tabulated (with frequency and proportion in each treatment group, by week if appropriate). Logistic regression will be used to obtain odds ratios and their corresponding 95% confidence intervals and p-values.
- The analysis for safety endpoint is specified in Section 7.3.4.

7.3.4 Safety analyses

Safety analysis will be performed on TS, with patients assigned to the treatment they were randomised. In general, safety analyses will be descriptive in nature and will be based on BI standards. No hypothesis testing is planned.

Statistical analysis and reporting of AEs will concentrate on treatment-emergent AEs. To this end, all AEs occurring between start of treatment and end of REP will be considered 'treatment-emergent'. The REP is defined as a period of seven days after the last dose of trial medication. AEs that start before first drug intake and deteriorate under treatment will also be considered as 'treatment-emergent'. Frequency, severity, and causal relationship of AEs will be tabulated by system organ class and preferred term after coding according to the current version of the Medical Dictionary for Drug Regulatory Activities (MedDRA).

Laboratory data will be analysed both quantitatively as well as qualitatively. The latter will be done via comparison of laboratory data to their reference ranges. Values outside the reference range as well as values defined as clinically relevant will be highlighted in the listings. Treatment groups will be compared descriptively with regard to distribution parameters as well as with regard to frequency and percentage of patients with abnormal values or clinically relevant abnormal values.

Vital signs, physical examinations, or other safety-relevant data observed at screening, baseline, during the course of the trial and at the end-of-trial evaluation will be assessed with regard to possible changes compared to findings before start of treatment.

7.3.5 Pharmacokinetic and pharmacodynamic analyses

No pharmacokinetic and pharmacodynamic analyses are planned for this trial.

7.4 INTERIM ANALYSES

No interim analysis is planned for this trial.

7.5 HANDLING OF MISSING DATA

In the primary analysis, missing data will not be imputed (OC approach). The mixed effect model will handle missing data based on a likelihood method under the "missing at random" assumption.

If rescue therapy is initiated, HbA_{1c} and FPG values after rescue medication will be set to missing and the missing data will be handled as above (OC), according to the analysis strategy. For the analysis of secondary endpoints using ANCOVA, missing values will not be imputed (OC approach).

For binary endpoints including an HbA_{1c} response criterion, non-completers' considered failure (NCF) will be applied, i.e., patients who discontinued from the trial prematurely and have no HbA_{1c} measurement at Week 24 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.

With respect to safety evaluations, it is not planned to impute missing values. The handling of missing biomarkers will be specified in the TSAP.

7.6 RANDOMISATION

The sponsor will arrange for the randomisation as well as for packaging and labelling of trial medication. The trial will be performed as a double-blind design with respect to the two blinded treatment arms. Eligible patients will be randomly assigned to one of the two treatment groups, linagliptin and placebo, with an allocation of 1:1. 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 block size will be documented in the CTR. Access to the codes will be controlled and documented.

The randomisation will be stratified on the basis of patients belonging to any of the categories below at the beginning of the placebo run-in period:

1. HbA_{1c} value: $HbA_{1c} < 8.5\%$ or $\geq 8.5\%$.
2. Type of insulin: basal insulin or pre-mixed insulin (at least 90 randomised patients for each)

The allocation process will be performed on Visit 3 through IRT.

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 study will only be unblinded after all CRF / 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.

7.7 DETERMINATION OF SAMPLE SIZE

In order to be in line with local regulatory requirements, 100 patients per treatment group for primary analysis (i.e. FAS) are required. To compensate for the anticipated dropout rate (about 2.2% in global trial 1218.36 [P13-12370]), 206 patients (approximate 103 patients per treatment arm) will need to be randomised.

Assuming a standard deviation of 1.1% for HbA_{1c} change from baseline at 24 weeks, a sample of size 100 patients per treatment group is sufficient to detect a 0.55% difference between the treatment groups with a power of 94% and a two-sided type-I error of 5%. See Table 7.7: 1 for sample size calculation for different scenarios. The software ADDPLAN 6.0.4 is used to estimate the sample size.

Table 7.7:1 Sample size calculation based on two group t-test of equal means (equal N's)

Parameters	**Calculation of N for primary analysis**					
Test significance level, α	0.05	0.05	0.05	0.05	0.05	0.05
1 or 2 sided test?	2	2	2	2	2	2
Difference in means, $\mu_1 - \mu_2$	0.55	0.55	0.55	0.55	0.55	0.55
Common standard deviation, σ	1.2	1.2	1.1	1.1	1.1	1.1
Power (%)	80	90	80	90	94	95
N	76	101	64	86	100	103

8. INFORMED CONSENT, TRIAL RECORDS, DATA PROTECTION, PUBLICATION POLICY

The trial will be carried out in compliance with the protocol, the ethical principles laid down in the Declaration of Helsinki, in accordance with the ICH Harmonized Tripartite Guideline for Good Clinical Practice (GCP), relevant BI Standard Operating Procedures (SOPs), and other relevant regulations.

Standard medical care (prophylactic, diagnostic and therapeutic procedures) remains in the responsibility of the treating physician of the patient.

The Investigator will inform the sponsor immediately of any urgent safety measures taken to protect the trial subjects against any immediate hazard, and also of any serious breaches of the protocol or of ICH GCP.

The Boehringer Ingelheim transparency and publication policy can be found on the following web page: trials.boehringer-ingelheim.com. 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 rule, no trial results should be published prior to finalization of the Clinical Trial Report.

The certificate of insurance cover is made available to the Investigator and the patients, and is stored in the ISF.

8.1 TRIAL APPROVAL, PATIENT INFORMATION, INFORMED CONSENT

This trial will be initiated only after all required legal documentation has been reviewed and approved by the respective Institutional Review Board (IRB) / Independent Ethics Committee (IEC) and competent authority (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 Investigator must give a full explanation to trial patients based on the patient information form. A language understandable to the patient should be chosen, technical terms and expressions avoided, if possible. The patient must be 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.
Re-consenting may become necessary when new relevant information becomes available and should be conducted according to the sponsor's instructions.
The consent and re-consenting process should be properly documented in the source documentation.

8.2 DATA QUALITY ASSURANCE

A quality assurance audit/inspection of this trial may be conducted by the sponsor, sponsor's designees, or by IRB / IEC 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.

8.3 RECORDS

Case Report Forms (CRF) for individual patients will be provided by the sponsor. 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

In accordance with regulatory requirements the Investigator should prepare and maintain adequate and accurate source documents and trial records that include all observations and other data pertinent to the investigation on each trial subject. Source data as well as reported data should follow good documentation practices and be attributable, legible, contemporaneous, original and accurate. Changes to the data should be traceable (audit trail). Data reported on the CRF must be consistent with the source data or the discrepancies must be explained.
The current medical history of the subject may not be sufficient to confirm eligibility for the trial and the Investigator may need to request previous medical histories and evidence of any diagnostic tests. In this case the Investigator must make three documented attempts to retrieve previous medical records. If this fails a verbal history from the patient, documented in their medical records, would be acceptable.
Before providing any copy of patients' source documents to the sponsor the investigator must ensure that all patient identifiers (e.g. patient's name, initials, address, phone number, social security number) have properly been removed or redacted to ensure patient confidentiality.

If the patient is not compliant with the protocol, any corrective action e.g. re-training must be documented in the patient file.
For the CRF, data must be derived from source documents, for example:

- Patient identification: gender, date or year of birth (in accordance with local laws and regulations)
- Patient participation in the trial (substance, trial number, patient number, date patient was informed)

- Dates of Patient's visits, including dispensing of trial medication
- Medical history (including trial indication and concomitant diseases, if applicable)
- Medication history
- Adverse events and outcome events (onset date (mandatory), and end date (if available))
- Serious adverse events (onset date (mandatory), and end date (if available))
- Concomitant therapy (start date, changes)
- Originals or copies of laboratory results and other imaging or testing results, with proper documented medical evaluation (in validated electronic format, if available)
- Completion of Patient's Participation in the trial" (end date; in case of premature discontinuation document the reason for it).
- Prior to allocation of a patient to a treatment into a clinical trial, there must be documented evidence in the source data (e.g. medical records) that the trial participant meets all inclusion criteria and does not meet any exclusion criteria. The absence of records (either medical records, verbal documented feedback of the patient or testing conducted specific for a protocol) to support inclusion/exclusion criteria does not make the patient eligible for the clinical trial.

8.3.2 Direct access to source data and documents

The sponsor will monitor the conduct of the trial by regular on-site monitoring visits and in-house data quality review. The frequency of on-site monitoring will be determined by assessing all characteristics of the trial, including its nature, objective, methodology and the degree of any deviations of the intervention from normal clinical practice.
The Investigator /institution will allow on-site trial-related monitoring, audits, IRB / IEC review and regulatory inspections. Direct access must be provided to the CRF and all source documents/data, including progress notes, copies of laboratory and medical test results, which must be available at all times for review by the CRA, auditor and regulatory inspector (e.g. FDA). The CRA and auditor may review all CRFs and informed consents. The accuracy of the data will be verified by direct comparison with the source documents described in section 8.3.1. The sponsor will also monitor compliance with the protocol and ICH GCP.

8.3.3 Storage period of records

Trial sites:
The trial sites must retain the source and essential documents (including ISF) according to the national or local requirements (whatever is longer) valid at the time of the end of the trial.
Sponsor:
The sponsor must retain the essential documents according to the sponsor's SOPs.

8.4 EXPEDITED REPORTING OF ADVERSE EVENTS

BI is responsible to fulfil their legal regulatory reporting obligation and in accordance to the requirements defined in this CTP.

8.5 STATEMENT OF CONFIDENTIALITY AND PATIENT PRIVACY

Individual patient data obtained as a result of this trial is considered confidential and disclosure to third parties is prohibited with the exceptions noted below. Patient privacy will be ensured by using patient identification code numbers.
Data protection and data security measures are implemented for the collection, storage and processing of patient data in accordance with the principles 6 and 12 of the WHO GCP handbook.
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 / IEC and the regulatory authorities.

8.5.1 Collection, storage and future use of biological samples and corresponding data

Measures are in place to comply with the applicable rules for the collection, storage and future use of biological samples from clinical trial participants and the corresponding data, in particular

- A Quality Management System has been implemented to ensure the adherence with the Principles of Good Clinical Practice as outlined in 'Note For Guidance On Good Clinical Practice' (CPMP/ICH/13 5/95)
- The BI-internal facilities storing and analysing biological samples and data from clinical trial participants as well as the laboratories' activities for clinical trials sponsored by Boehringer Ingelheim are regularly audited. The analytical groups and the banking facility are therefore assessed to be qualified for the storage and use of biological samples and data collected in clinical trials.
- Samples and data are used only if an appropriate informed consent is available.

8.6 TRIAL MILESTONES

The **start of the trial** is defined as the date of the enrolment of the first patient in the whole trial.
The end of the trial is defined as the date of the last visit of the last patient in the whole trial ("Last Patient Out"). The "**Last Patient Drug Discontinuation"** (LPDD) date is defined as the date on which the last patient at an individual trial site ends trial medication (as scheduled per protocol or prematurely). Individual Investigators will be notified of SUSARs occurring with the trial medication until 30 days after LPDD at their site. **Early termination of the trial** is defined as the premature termination of the trial due to any reason before the end of the trial as specified in this protocol.
Temporary halt of the trial is defined as any unplanned interruption of the trial by the sponsor with the intention to resume it.
Suspension of the trial is defined as an interruption of the trial based on a Health Authority request.

9. REFERENCES

9.1 PUBLISHED REFERENCES

P10-14001 Taskinen MR, Rosenstock J, Tamminen I, Kubiak R, Patel S, Dugi KA, Woerle HJ. Safety and efficacy of linagliptin as add-on therapy to metformin in patients with type 2 diabetes: a randomised, double-blind, placebocontrolled study. Diabetes Obes Metab 2011. 13(1): 65-74.

P11-02847 Prato S del, Barnett AH, Huisman H, Neubacher D, Woerle HJ, Dugi KA. Effect of linagliptin monotherapy on glycaemic control and markers of betacell function in patients with inadequately controlled type 2 diabetes: a randomised controlled trial. Diabetes Obes Metab 2011. 13(3): 258-267.

P11-06845 Gomis R, Espadero RM, Jones R, Woerle HJ, Dugi KA Efficacy and safety of initial combination therapy with linagliptin and pioglitazone in patients with inadequately controlled type 2 diabetes: a randomised, double-blind, placebocontrolled study. Diabetes Obes Metab 2011. 13(7): 653-661.

P11-09378 Schlosser A, Owens D, Taskinen MR, Prato S del, Gomis R, Patel S, et al. Long-term safety and efficacy of the DPP-4 inhibitor linagliptin: data from a large 2-year study in subjects with type 2 diabetes mellitus. 47th Ann Mtg of the European Association for the Study of Diabetes (EASD), Lisbon, 12 – 16 Sep 2011 Diabetologia 2011. 54(1): S108 Abstr 242.

P11-12477 Gallwitz B, Taskinen MR, Rosenstock J, Tamminen I, Kubiak R, Patel S, et al. Efficacy and safety of linagliptin in with metformin monotherapy inadequately controlled type 2 diabetes. 46th Ann Mtg of the German Society of Diabetes, Leipzig, 1 - 4 Jun 2011 Diabetologie 2011. 6(Suppl 1): S19 Abstr FV44.

P11-14211 Budnitz DS, Lovegrove MC, Shehab N, Richards CL Emergency hospitalizations for adverse drug events in older Americans. N Engl J Med 2011. 365(21): 2002-2012.

P13-07824 Inzucchi SE, Nauck M, Eynatten M von, Hehnke U, Woerle HJ, Henry R Lower risk of hypoglycaemia in elderly type 2 diabetes patients when linagliptin is added to basal insulin: an exploratory analysis. 73rd Sci Sess of the American Diabetes Association (ADA), Chicago, 21 - 25 Jun 2013 (Poster) 2013.

P13-09565 Barnett AH, Huisman H, Jones R, Eynatten M von, Patel S, Woerle HJ Linagliptin for patients aged 70 years or older with type 2 diabetes inadequately controlled with common antidiabetes treatments: a randomised, double-blind, placebo-controlled trial. Lancet, Published Online August 13, 2013, doi: 10.1016/S0140-6736(13)61500-7 Lancet 2013. 382(9902): 1413-1423.

P13-12370 Yki-Jarvinen H, Rosenstock J, Duran-Garcia S, Pinnetti S, Bhattacharya S, Thiemann S, Patel S, Woerle HJ. Effects of adding linagliptin to basal insulin regimen for inadequately controlled type 2 diabetes: a >/= 52-week randomised, double-blind study. Diabetes Care, Publish Ahead of Print, published online September 23, 2013, doi: 10.2337/dc12-2718 Diabetes Care 2013. 36:3875-3881.

P13-14398 Websky K von, Reichetzeder C, Hocher B Linagliptin as add-on therapy to insulin for patients with type 2 diabetes. Vasc Health Risk Manage 2013. 9: 681-694.

P16-00852 Sarashina A. Comparable pharmacodynamics, efficacy and safety of linagliptin 5 mg among Japanese, Asian and White patients with type 2 diabetes. Journal of Diabetes Investigation, accepted article, Accepted manuscript online: 12 JAN 2016, doi: 10.1111/jdi.12482 J Diabetes Invest 2016

R07-1029 Wallace TM, Levy JC, Matthews DR. Use and abuse of HOMA modeling. Diabetes Care 2004. 27(6):1487-1495.

R08-2669 Guidance for industry: diabetes mellitus: developing drugs and therapeutic biologics for treatment and prevention (draft guidance, February 2008). Rockville: U.S.Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER) 2008.

R09-2151 FDA Guidance for Industry - Diabetes Mellitus - Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes

R10-5741 Nathan DM, Buse JB, Davidson MB, Ferrannini E, Holman RR, Sherwin R, Zinman B. Medical management of hyperglycaemia in type 2 diabetes mellitus: a consensus algorithm for the initiation and adjustment of therapy: a consensus statement from the American Diabetes Association and the European Association for the Study of Diabetes. Diabetologia 2009. 52:17-30.

R15-6052 Tradjenta (linagliptin) tablets (Boehringer Ingelheim) (China prescribing information, revised: 6/2014). 2015

R15-6053 Glucophage 500 mg (metformin hydrochloride) tablets, (Bristol-Myers Squibb) (China prescribing information, rev.Aug 2010). 2010

9.2 UNPUBLISHED REFERENCES

c01838725-16
Investigator's Brochure. Current version.

10. APPENDICES

Not applicable

11. DESCRIPTION OF GLOBAL AMENDMENT

Number of global amendment		1.0
Date of CTP revision		14 Oct 2016
BI Trial number		1218.102
BI Investigational Product		Linagliptin (Trajenta)
Title of protocol		A phase III, randomised, double-blind, placebo-controlled, parallel group, efficacy and safety study of linagliptin, administered orally once daily, in combination with insulin therapy for 24 weeks in Chinese type 2 diabetes mellitus patients with insufficient glycaemic control
To be implemented only after approval of the IRB / IEC / Competent Authorities		☒
To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval		☐
Can be implemented without IRB / IEC / Competent Authority approval as changes involve logistical or administrative aspects only		☐
Section to be changed		FLOW CHART note L
Description of change		Previous text: L At visit 3, AFTER blood sample of FPG drawing, patients will have a standardised breakfast, finished within 15 minutes, and PPG blood samples will be collected at time points 60 ±10 min and 120 ±10 min after the start of standardised breakfast. Study medication would be in-taken after PPG blood samples drawing. At visit 8, 30 min after blood sample of FPG drawing and administration of study medication, patients will have a standardised breakfast, finished within 15 min, and PPG blood samples would be collected at time points 60 ±10 minutes and 120 ±10 min after the start of

		standardised breakfast. (All patients at all sites should participate) Was changed to: L At visit 3, AFTER blood sample of FPG drawing, patients will have a standardised breakfast and intake metformin and/ or accepted pre-mixed insulin (if applicable), finished within 15 minutes, and PPG blood samples will be collected at time points 60 ±10 min and 120 ±10 min after the start of standardised breakfast. Study medication would be in-taken after PPG blood samples drawing. At visit 8, 30 min after blood sample of FPG drawing and administration of study medication, patients will have a standardised breakfast and intake metformin and/ or accepted pre-mixed insulin (if applicable), finished within 15 min, and PPG blood samples would be collected at time points 60 ±10 minutes and 120 ±10 min after the start of standardised breakfast. (All patients at all sites should participate)
Rationale for change		Clarification for the intake time of permitted pre-mixed insulin.
Section to be changed		ABBREVIATIONS
Description of change		Add “WOCBP women of childbearing potential”
Rationale for change		Add new abbreviation
Section to be changed		1.2 DRUG PROFILE
Description of change		Previous text: The favourable effects regarding the counteraction of hypoglycaemic make linagliptin especially interesting as an add-on to insulin. Was changed to: The limited intrinsic risk for hypoglycaemia makes linagliptin especially interesting as an add-on to insulin.
Rationale for change		For consistency of wording to the above paragraph.
Section to be changed		3.3.2 Inclusion criteria
Description of change		Previous text: 2. Chinese male or female patients who are pre-treated with insulin alone or in combination with metformin: - With maximum insulin dose of ≤ 1 unit/kg/day. Acceptable basal insulins could be insulin glargin, insulin detemir or NPH (neutral protamin hagedorn) insulin with duration of action up to 24 h; acceptable pre-mixed insulins (permitted for a pre-defined subset

		of patients) could be preparations with 25/75 or 30/70 ratio, with once or twice daily posology only. The total insulin dose should not be changed by more than 10% of the baseline value within the 12 weeks prior to randomisation (Visit 3). Was changed to: 2. Chinese male or female patients who are pre-treated with insulin alone or in combination with metformin: - With maximum insulin dose of ≤ 1 unit/kg/day. Acceptable basal insulins could be insulin glargin, insulin detemir or NPH (neutral protamin hagedorn) insulin with duration of action up to 24 h; acceptable pre-mixed insulins could be preparations with 25/75 or 30/70 ratio, with once or twice daily posology only. The total insulin dose should not be changed by more than 10% of the baseline value within the 12 weeks prior to randomisation (Visit 3). Both human insulin & insulin analogue are accepted.
Rationale for change		Pre-defined subset for pre-mixed insulin has been specified in protocol sections 3.3 and 7.6. Classification for the type of insulin.
Section to be changed		3.3.2 Inclusion criteria
Description of change		Previous text: 6. Women of childbearing potential must be ready and able to use highly effective methods of birth control per ICH M3 (R2) that result in a low failure rate of less than 1% per year when used consistently and correctly. A list of contraception methods meeting these criteria is provided in the patient information. Women of childbearing potential are defined as: - having experienced menarche and - not postmenopausal (12 months with no menses without an alternative medical cause) and - not permanently sterilised (e.g., tubal occlusion, hysterectomy, bilateral oophorectomy or bilateral salpingectomy). Was changed to: 6. Women of childbearing potential must be ready and able to use highly effective methods of birth control per ICH M3 (R2) that result in a low failure rate of less than 1% per year when used consistently and correctly. A list of contraception methods meeting these criteria is provided in the patient information.

<table>
<tr><td></td><td></td><td>- A woman is considered of childbearing potential (WOCBP), i.e. fertile, following menarche and until becoming post-menopausal unless permanently sterile.
- Permanent sterilisation methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy.</td></tr>
<tr><td>Rationale for change</td><td></td><td>Tubal occlusion is considered as a method of highly effective birth control, but NOT a method of permanent sterilisation according to BI updated Contraception Guidance.</td></tr>
<tr><td></td><td></td><td></td></tr>
<tr><td>Section to be changed</td><td></td><td>4.2.1 Other treatments and emergency procedures</td></tr>
<tr><td>Description of change</td><td></td><td>Previous text:
Morning dose of metformin and study medication should be taken after the visits blood sample collection, and the patients should have the same habits of dosing throughout the trial.

Was changed to:
Morning dose of metformin/any permitted pre-mixed insulin and study medication should be taken after the fasting visits blood sample collection, and the patients should have the same habits of dosing throughout the trial.</td></tr>
<tr><td>Rationale for change</td><td></td><td>Clarification for the intake time of permitted pre-mixed insulin.</td></tr>
<tr><td></td><td></td><td></td></tr>
<tr><td>Section to be changed</td><td></td><td>4.2.1 Other treatments and emergency procedures</td></tr>
<tr><td>Description of change</td><td></td><td>Previous text:
<u>Hyperglycaemic:</u>
<table>
<tr><th>Week</th><th>Visit</th><th>FPG level</th></tr>
<tr><td>Week 1-12</td><td>up to visit 6</td><td>>270 mg/dl (>15.0 mmol/l) after overnight fast</td></tr>
<tr><td>Week 12-24</td><td>after visit 6 until Visit 8</td><td>>240 mg/dl (>13.3 mmol/l) after overnight fast</td></tr>
</table>
Was changed to:
<u>Hyperglycaemia:</u>
<table>
<tr><th>Week</th><th>Visit</th><th>FPG level</th></tr>
<tr><td>Week 1-12</td><td>up to visit 6</td><td>>240 mg/dl (>13.3 mmol/l) after overnight fast</td></tr>
<tr><td>Week 12-24</td><td>after visit 6 until Visit 8</td><td>>200 mg/dl (>11.1 mmol/l) after overnight fast</td></tr>
</table></td></tr>
<tr><td>Rationale for change</td><td></td><td>Keep consistency with Chinese medical practice.</td></tr>
<tr><td></td><td></td><td></td></tr>
</table>

Section to be changed		5.2 ASSESSMENT OF EFFICACY
Description of change		Previous text: At Visit 3, after blood sample of FPG drawing, patients would have a standardised breakfast, finished within 15 min, and PPG blood samples would be collected at time points 60 ±10 min and 120 ±10 min after the start of standardised breakfast. Study medication would only be taken after last PPG blood samples drawing, i.e. following randomisation. At Visit 8, 30 min after blood sample of FPG drawing and administration of study medication, patients would have a standardised breakfast, finished within 15 min, and PPG blood samples would be collected at time points 60 ±10 min and 120 ±10 min after the start of standardised breakfast Was changed to: At Visit 3, after blood sample of FPG drawing, patients would have a standardised breakfast and intake metformin and/ or accepted pre-mixed insulin (if applicable), finished within 15 min, and PPG blood samples would be collected at time points 60 ±10 min and 120 ±10 min after the start of standardised breakfast. Study medication would only be taken after last PPG blood samples drawing, i.e. following randomisation. At Visit 8, 30 min after blood sample of FPG drawing and administration of study medication, patients would have a standardised breakfast and intake metformin and/ or accepted pre-mixed insulin (if applicable), finished within 15 min, and PPG blood samples would be collected at time points 60 ±10 min and 120 ±10 min after the start of standardised breakfast.
Rationale for change		Clarification for the intake time of permitted pre-mixed insulin.
Section to be changed		5.3.7 Criteria for hypoglycaemic events
Description of change		Previous text: Every episode of plasma glucose ⩽70 mg/dl (⩽3.9mmol/l) should be documented in the eCRF with the respective time and date of occurrence. Any hypoglycaemic with glucose values < 54 mg/dl (< 3.0 mmol/l) and all symptomatic and severe hypoglycaemics should be documented as an AE "hypoglycaemic event". - For the analysis, all hypoglycaemic events will be classified according to the criteria described in the Trial

		Statistical Analysis Plan. - All investigator defined hypoglycaemic events (i.e. those reported as AE) will be analysed in further detail depending on symptoms, severity and reported blood glucose measurements at time of occurrence of the reported hypoglycaemic event. This will include evaluation of confirmed hypoglycaemic events, i.e. those with a measured plasma glucose concentration ≤70 mg/dl (≤3.9 mmol/l) or being severe hypoglycaemic events (i.e. those requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions). Was changed to: Every episode of plasma glucose ⩽70 mg/dl (⩽3.9mmol/l) should be documented in the eCRF with the respective time and date of occurrence. Such hypoglycaemic events should be documented in the eCRF according to the following criteria: - Asymptomatic hypoglycaemia: event not accompanied by typical symptoms of hypoglycaemia but with a measured plasma glucose concentration ⩽ 70 mg/dl (3.9 mmol/l) - Documented symptomatic hypoglycaemia with glucose concentration ⩾ 54 mg/dl and ⩽70 mg/dl (⩾ 3.0 mmol/l and ⩽ 3.9 mmol/l): event accompanied by typical symptoms of hypoglycaemia - Documented symptomatic hypoglycaemia with glucose concentration < 54 mg/dl (< 3.0 mmol/l): event accompanied by typical symptoms of hypoglycaemia - Severe hypoglycaemic episode: Event requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions Note for severe hypoglycemia: 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. Any hypoglycaemia with glucose values < 54 mg/dl (< 3.0 mmol/l) and all symptomatic or severe hypoglycaemia events should be documented as an adverse event of hypoglycemia. Further details on documentation of hypoglycemia are provided on the respective eCRF pages.
Rationale for change		Clarification for hypoglycaemic events.

Section to be changed		6.2.1 Screening and run-in period 3rd paragraph of run-in period.
Description of change		Previous text: Morning dose of metformin and study medication should be taken after the visits blood sample collection, and the patients should have the same habits of dosing throughout the trial. Was changed to: Morning dose of metformin/any permitted pre-mixed insulin and study medication should be taken after the visits blood sample collection, and the patients should have the same habits of dosing throughout the trial.
Rationale for change		Clarification for the intake time of pre-mixed insulin.
Section to be changed		6.2.2 Treatment period Visits 4-8
Description of change		Previous text: If a patient prematurely discontinues from the 24-week treatment period, the patient must return to the trial site for both Visit 8 and Visit 9 (7 days after Visit 8), which will be performed. Was changed to: If a patient prematurely discontinues from the 24-week treatment period, the patient must return to the trial site for both Visit 8 (within 7 days of stopping study treatment) and Visit 9 (7 days after Visit 8), which will be performed.
Rationale for change		Clarification.
Section to be changed		8.3.2 Direct access to source data and documents
Description of change		Duplicated paragraphs were removed as below: ~~An adaptive approach to clinical trial monitoring will be utilised. The sponsor will perform a risk assessment of the trial to determine the extent and nature of monitoring required in order to ensure the reliability and robustness of the results. Regular review of risk reports will provide sponsor oversight during trial conduct and direct monitoring activities to the areas of greatest risk which have the most potential impact to subject safety and data quality.~~ ~~The Investigator /institution will allow on-site trial-related monitoring, audits, IRB / IEC review and regulatory inspections. Direct access should be granted to all source documents (paper and e-records) including progress notes, copies of laboratory and medical test results. The CRA and auditor may review all CRFs and informed consents. The accuracy of the data will be verified by direct comparison with~~

		~~the source documents described in section 8.3.1. The sponsor will also monitor compliance with the protocol and ICH GCP. An adaptive approach to clinical trial monitoring will be utilised. This is initiated by an assessment of the risk associated with the trial combined with identification of critical data and processes. An Integrated Quality and Risk Management Plan documents the strategies involved with the implementation of onsite, offsite and central monitoring activities in order to direct focus to the areas of greatest risk which have the most potential impact to subject safety and data quality. Trial oversight is achieved by regular review of a report of risk which then influences any monitoring adaptations.~~ ~~The Investigator /institution will allow on-site trial-related monitoring, audits, IRB/IEC review and regulatory inspections. Direct access should be granted to all source documents (paper and e-records) including progress notes, copies of laboratory and medical test results The CRA and auditor may review all CRFs and informed consents. The accuracy of the data will be verified by direct comparison with the source documents described in section 8.3.1. The sponsor will also monitor compliance with the protocol and ICH GCP.~~
Rationale for change		Delete duplicated content.
Section to be changed		Throughout protocol
Description of change		Typo correction for hypoglycaemia and hyperglycaemia.
Rationale for change		Typo correction.

Number of global amendment		2.0
Date of CTP revision		28 Nov 2017
BI Trial number		1218.102
BI Investigational Product		Linagliptin (Trajenta)
Title of protocol		A phase III, randomised, double-blind, placebo-controlled, parallel group, efficacy and safety study of linagliptin, administered orally once daily, in combination with insulin therapy for 24 weeks in Chinese type 2 diabetes mellitus patients with insufficient glycaemic control
To be implemented only after approval of the IRB / IEC / Competent Authorities		☒
To be implemented immediately in order to eliminate hazard –		☐

IRB / IEC / Competent Authority to be notified of change with request for approval		
Can be implemented without IRB / IEC / Competent Authority approval as changes involve logistical or administrative aspects only		☐
Section to be changed		3.3 SELECTION OF TRIAL POPULATION
Description of change		Previous text: It is planned to have not more than 25% of the overall randomised patients on background of pre-mixed insulin, which will be handled through IRT and refer to section 7.6. Was changed to: It is planned to have at least 90 randomised patients on both background of pre-mixed insulin and basal insulin, which will be handled through IRT and refer to section 7.6. If the patient's background type distribution is not balanced as expected, the impact on the study conduct should be carefully considered. The sponsor should further monitor the recruitment of the trial with regard to the type of patient's background treatment. The intent is to obtain a balanced mix of patients pre-treated with premixed insulin or basal insulin. As such the sponsor may cap specific patient populations.
Rationale for change		Keep consistency with Chinese medical practice.
Section to be changed		7.6 RANDOMISATION
Description of change		Previous text: The randomisation will be stratified on the basis of patients belonging to any of the categories below at the beginning of the placebo run-in period: 1. HbA1c value: HbA1c < 8.5% or 8.5%. 2. Type of insulin: basal insulin or pre-mixed insulin (no more than 25% of the overall randomised patients to be on background of pre-mixed insulin) The allocation process will be performed on Visit 3 through IRT. Was changed to:

		The randomisation will be stratified on the basis of patients belonging to any of the categories below at the beginning of the placebo run-in period: 1. HbA1c value: HbA1c < 8.5% or 8.5%. 2. Type of insulin: basal insulin or pre-mixed insulin (at least 90 randomised patients for each) The allocation process will be performed on Visit 3 through IRT.
Rationale for change		For consistency of wording to the above paragraph.

APPROVAL / SIGNATURE PAGE

Document Number: c11679959 **Technical Version Number:3.0**

Document Name: clinical-trial-protocol-revision-02

Title: A phase III, randomised, double-blind, placebo-controlled, parallel group, efficacy and safety study of linagliptin, administered orally once daily, in combination with insulin therapy for 24 weeks in Chinese type 2 diabetes mellitus patients with insufficient glycaemic control

Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Approval-Biostatistics		29 Nov 2017 08:35 CET
Approval-Trial Clinical Monitor		29 Nov 2017 09:08 CET
Approval-Team Member Medicine		29 Nov 2017 10:10 CET
Approval-Therapeutic Area		30 Nov 2017 10:28 CET

(Continued) Signatures (obtained electronically)

Meaning of Signature	**Signed by**	**Date Signed**