

## CLINICAL TRIAL PROTOCOL

<b>Document Number:</b>		<b>c03122586-03</b>
<b>BI Trial No.:</b>	1245.106	
<b>BI Investigational Product:</b>	Jardiance <sup>®</sup> , Empagliflozin	
<b>Title:</b>	A 52-week randomised, double-blind, parallel group, safety and efficacy study of empagliflozin once daily as add-on therapy to glucagon-like peptide-1 receptor agonist in Japanese type 2 diabetes mellitus patients with insufficient glycaemic control	
<b>Brief Title:</b>	Empa add-on to GLP-1 RA (Japan)	
<b>Clinical Phase:</b>	IV	
<b>Trial Clinical Monitor:</b>	<div style="background-color: black; width: 100%; height: 80px;"></div> Phone: <div style="background-color: black; width: 150px; height: 15px;"></div> Fax: <div style="background-color: black; width: 150px; height: 15px;"></div>	
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<b>Status:</b>	Final Protocol (Revised Protocol (based on global amendments 2))	
<b>Version and Date:</b>	<b>Version:</b>	<b>Date:</b>
	3.0	20 January 2017
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## CLINICAL TRIAL PROTOCOL SYNOPSIS

<b>Name of company:</b>		Boehringer Ingelheim	
<b>Name of finished product:</b>		Jardiance®	
<b>Name of active ingredient:</b>		Empagliflozin	
<b>Protocol date:</b> 31 AUG 2015	<b>Trial number:</b> 1245.106		<b>Revision date:</b> 20 JAN 2017
<b>Title of trial:</b>	A 52-week randomised, double-blind, parallel group, safety and efficacy study of empagliflozin once daily as add-on therapy to glucagon-like peptide-1 receptor agonist in Japanese type 2 diabetes mellitus patients with insufficient glycaemic control		
<b>Coordinating Investigator:</b>			
<b>Trial site(s):</b>	Multi-centre trial in Japan		
<b>Clinical phase:</b>	IV		
<b>Objective(s):</b>	The objective of the study is to investigate the safety and efficacy of empagliflozin (10 mg and 25 mg once daily) given for 52 weeks as add-on therapy to a glucagon-like peptide 1 (GLP-1) receptor agonist (RA) in Japanese patients with type 2 diabetes mellitus who have insufficient glycaemic control.		
<b>Methodology:</b>	Randomised, double-blind, parallel group		
<b>No. of patients:</b>			
<b>total entered:</b>	64 patients (128 patients enrolled)		
<b>each treatment:</b>	Empagliflozin 10 mg : 32 patients Empagliflozin 25 mg : 32 patients		
<b>Diagnosis :</b>	Type 2 diabetes mellitus		

<b>Name of company:</b>		<b>Boehringer Ingelheim</b>	
<b>Name of finished product:</b>		<b>Jardiance<sup>®</sup></b>	
<b>Name of active ingredient:</b>		<b>Empagliflozin</b>	
<b>Protocol date:</b> 31 AUG 2015	<b>Trial number:</b> 1245.106		<b>Revision date:</b> 20 JAN 2017
<b>Main criteria for inclusion:</b>	<ol style="list-style-type: none"> <li>1. Diagnosis of type 2 diabetes mellitus prior to informed consent</li> <li>2. Male and female patients on diet and exercise regimen who are pre-treated with any of the following: <ol style="list-style-type: none"> <li>A) Liraglutide at 0.9 mg/day alone for at least 10 weeks prior to Visit 1 (screening visit). <ul style="list-style-type: none"> <li>- HbA1c at Visit 1 : <math>\geq 7.0\%</math> and <math>\leq 10.0\%</math></li> </ul> </li> <li>B) Liraglutide at 0.9 mg/day in combination with one oral antidiabetic drug (OAD)<sup>i)</sup> for at least 10 weeks prior to Visit 1 (screening visit). <ul style="list-style-type: none"> <li>- HbA1c at Visit 1 : <math>\geq 7.0\%</math> and <math>\leq 9.0\%</math></li> <li>- HbA1c at Visit 6 : <math>\geq 7.0\%</math> and <math>\leq 10.0\%</math></li> </ul> </li> <li>C) One OAD<sup>i)</sup> for at least 10 weeks prior to Visit 1 (screening). The patients who are suitable for switching to liraglutide treatment<sup>ii)</sup> after Visit 1 at the investigator's discretion. <ul style="list-style-type: none"> <li>- HbA1c at Visit 1 and Visit 6: <math>\geq 7.0\%</math> and <math>\leq 10.0\%</math> <ol style="list-style-type: none"> <li>i) Sulfonylurea is permitted as pre-treatment drug only if the dose is equal or less than a half of daily maximum approval dose. Any other OADs except thiazolidine dione and SGLT-2 inhibitor are allowed at any dose.</li> <li>ii) Patients should stop their OAD and start switching to 0.3 mg/day of liraglutide at Visit 2 and the dose titration should complete within 2-4 weeks and also should be done in accordance with Japanese label (i.e., at least 1 week dosing period with 0.3 mg/day and 0.6 mg/day each is required.). Patients should be treated with liraglutide at 0.9 mg/day for at least 10 weeks (at least 14 weeks of switch period is required.) prior to placebo run-in period.</li> </ol> </li> </ul> </li> </ol> </li> <li>3. Age <math>\geq 20</math> years at informed consent</li> <li>4. Body mass index (BMI) <math>\leq 40.0</math> kg/m<sup>2</sup> at Visit 1 (screening)</li> <li>5. Signed and dated written informed consent by date of Visit 1 in accordance with GCP and Japanese legislation</li> </ol>		
<b>Test product:</b>	Empagliflozin		
<b>dose:</b>	10 mg 25 mg		
<b>mode of administration:</b>	Oral		
<b>Comparator products:</b>	Not Applicable		
<b>dose:</b>	Not Applicable		
<b>mode of administration:</b>	Not Applicable		

<b>Name of company:</b>		<b>Boehringer Ingelheim</b>	
<b>Name of finished product:</b>		Jardiance <sup>®</sup>	
<b>Name of active ingredient:</b>		Empagliflozin	
<b>Protocol date:</b> 31 AUG 2015	<b>Trial number:</b> 1245.106		<b>Revision date:</b> 20 JAN 2017
<b>Duration of treatment:</b>	<ul style="list-style-type: none"> <li>- Screening: 1 weeks</li> <li>- Switch period (including titration and washout periods) : 14 weeks<sup>i)</sup></li> <li>Or</li> <li>Washout period :10 weeks<sup>ii)</sup> <ul style="list-style-type: none"> <li>i) Patients on one OAD</li> <li>ii) Patients on liraglutide plus one OAD</li> </ul> </li> <li>- Placebo run-in period (open label): 2 weeks</li> <li>- Double-blind treatment period: 52 weeks</li> <li>- Follow up period: 1 week</li> </ul>		
<b>Endpoints</b>	<p>Primary endpoint:</p> <ul style="list-style-type: none"> <li>- Proportion of patients with drug-related adverse events (AE) during 52 weeks of treatment</li> </ul> <p>Secondary endpoint:</p> <ul style="list-style-type: none"> <li>- Change from baseline in HbA1c after 52 weeks of treatment</li> </ul>		
<b>Safety criteria:</b>	Adverse events, serious adverse events, adverse events of special interest, adverse events leading to discontinuation, hypoglycaemic adverse events, clinical laboratory assessments, vital signs		
<b>Statistical methods:</b>	Safety will be assessed by using frequency tabulations and descriptive statistics by treatment group. For efficacy, the change from baseline in HbA1c at Week 52 will be analysed by using MMRM including the fixed effects treatment, baseline renal function, prior use of antidiabetic agents, visit, treatment-by-visit interaction and the covariate baseline HbA1c, baseline HbA1c-by-visit interaction.		

## FLOW CHART

Trial Period	Screen- ing	Switch period <sup>6</sup>				Placebo run- in period	Double blind treatment period											Follow up
		Titration period		Washout period <sup>4</sup>														
<i>Visit</i>	1 <sup>1</sup>	2	3 <sup>7</sup>	4 <sup>7</sup>	5	6 <sup>25</sup>	7	7a <sup>24</sup>	8	9	10	11	12	13	14	15/EOT <sup>20</sup>	16(flow-up) <sup>21</sup>	
<i>Study week</i>	0	na <sup>26</sup>	na <sup>26</sup>	na <sup>26</sup>	na <sup>26</sup>	na <sup>26</sup>	0	1	4	8	12	20	28	36	44	52	7 days from EOT	
<i>Days from Visit 1 or Visit 7 (inclusion criterion 2-A)<sup>2</sup></i>	1	>	>	>	>	8	1	7	29	57	85	141	197	253	309	365	EOT+7	
<i>Days from Visit 1 or Visit 7 (inclusion criterion 2-B)<sup>3</sup></i>	1	>	>	8	43	78												
<i>Days from Visit 1 or Visit 7 (inclusion criterion 2-C)<sup>5</sup></i>	1	8	22	36	71	106												
<i>Visit window (days)</i>	na	na <sup>26</sup>	na <sup>26</sup>	na <sup>26</sup>	na <sup>26</sup>	na <sup>26</sup>	na	+/-3	+/-7	+/-7	+/-7	+/-7	+/-7	+/-7	+/-7	+/-7	+7	
Informed Consent	X																	
Medical History/Concomitant Diagnoses	X																	
Demographics	X																	
In-/Exclusion criteria	X						X <sup>8</sup>											
Physical examination <sup>9</sup>							X									X	X	
Vital signs <sup>10</sup>	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	
Height	X																	
Weight	X						X			X		X		X		X		
Waist circumference							X			X		X		X		X		
Diet and exercise counselling <sup>11</sup>	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X		

Trial Period	Screen- ing	Switch period <sup>6</sup>				Placebo run- in period	Double blind treatment period										Follow up
		Titration period		Washout period <sup>4</sup>													
<i>Visit</i>	1 <sup>1</sup>	2	3 <sup>7</sup>	4 <sup>7</sup>	5	6 <sup>25</sup>	7	7a <sup>24</sup>	8	9	10	11	12	13	14	15/EOT <sup>20</sup>	16(flow-up) <sup>21</sup>
<i>Study week</i>	0	na <sup>26</sup>	na <sup>26</sup>	na <sup>26</sup>	na <sup>26</sup>	na <sup>26</sup>	0	1	4	8	12	20	28	36	44	52	7 days from EOT
<i>Days from Visit 1 or Visit 7 (inclusion criterion 2-A)<sup>2</sup></i>	1	>	>	>	>	8	1	7	29	57	85	141	197	253	309	365	EOT+7
<i>Days from Visit 1 or Visit 7 (inclusion criterion 2-B)<sup>3</sup></i>	1	>	>	8	43	78											
<i>Days from Visit 1 or Visit 7 (inclusion criterion 2-C)<sup>5</sup></i>	1	8	22	36	71	106											
<i>Visit window (days)</i>	na	na <sup>26</sup>	na <sup>26</sup>	na <sup>26</sup>	na <sup>26</sup>	na <sup>26</sup>	na	+/-3	+/-7	+/-7	+/-7	+/-7	+/-7	+/-7	+/-7	+/-7	+7
Review Food log, completed for 3 days <sup>11</sup>		X	X	X	X	X	X		X	X	X	X	X	X	X	X	
12-lead-ECG <sup>10,12</sup>	X						X			X		X		X		X	
Pregnancy Test <sup>13</sup>	X						X			X		X		X		X	
Safety lab Tests (Urine and Blood) <sup>14</sup>	X <sup>18,23</sup>	X		X		X	X		X	X	X <sup>22</sup>	X	X <sup>22</sup>	X	X <sup>22</sup>	X	X
Fasting Plasma Glucose	X <sup>23</sup>	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X
HbA1c	X <sup>23</sup>					X <sup>19</sup>	X			X		X		X		X	
FFA and Ketone bodies						X	X		X	X	X	X	X	X	X	X	
Bone markers							X									X	
Insulin & glucagon							X									X	
SMBG measurement and check logs <sup>15,16</sup>		X	X	X	X	X	X		X	X	X	X	X	X	X	X	X
Adverse events		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Therapy	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Dispense placebo run-in medication <sup>17</sup>						X											

Trial Period	Screen -ing	Switch period <sup>6</sup>				Placebo run- in period	Double blind treatment period										Follow up
		Titration period		Washout period <sup>4</sup>													
<i>Visit</i>	1 <sup>1</sup>	2	3 <sup>7</sup>	4 <sup>7</sup>	5	6 <sup>25</sup>	7	7a <sup>24</sup>	8	9	10	11	12	13	14	15/EOT <sup>20</sup>	16(flow-up) <sup>21</sup>
<i>Study week</i>	0	na <sup>26</sup>	na <sup>26</sup>	na <sup>26</sup>	na <sup>26</sup>	na <sup>26</sup>	0	1	4	8	12	20	28	36	44	52	7 days from EOT
<i>Days from Visit 1 or Visit 7 (inclusion criterion 2-A)<sup>2</sup></i>	1	>	>	>	>	8	1	7	29	57	85	141	197	253	309	365	EOT+7
<i>Days from Visit 1 or Visit 7 (inclusion criterion 2-B)<sup>3</sup></i>	1	>	>	8	43	78											
<i>Days from Visit 1 or Visit 7 (inclusion criterion 2-C)<sup>5</sup></i>	1	8	22	36	71	106											
<i>Visit window (days)</i>	na	na <sup>26</sup>	na <sup>26</sup>	na <sup>26</sup>	na <sup>26</sup>	na <sup>26</sup>	na	+/-3	+/-7	+/-7	+/-7	+/-7	+/-7	+/-7	+/-7	+/-7	+7
Randomisation (via IRT)							X										
Dispense double-blind medication <sup>17</sup>							X		X	X	X	X	X	X	X		
Medication compliance check							X		X	X	X	X	X	X	X	X	

Abbreviations: > = skip, EOT=end of trial, na= not applicable, SMBG= Self Monitoring Blood Glucose

1. Patients on Visit 1 do not proceed to the next visit until laboratory results are ascertained by their investigator.
2. If patients on liraglutide alone, directly start placebo run in period (Visit 6) after screening.
3. If patients on liraglutide and one OAD, stop their OAD at Visit 4 and start washout after screening.
4. Day of randomisation for inclusion criterion is 84 days (12 weeks).
5. If patients on one OAD, stop their OAD and start switching to liraglutide treatment at Visit 2. The dose titration should be completed within 2-4 weeks and also should be done in accordance with Japanese label (i.e., at least 1 week dosing period with 0.3 mg and 0.6 mg each is required.) and liraglutide 0.9 mg/day should be maintained for at least 10 weeks prior to placebo run-in period.
6. 14 weeks of switch period should be completed.
7. At least 1 week interval is necessary between Visit 2 and Visit 3 and also between Visit 3 and Visit 4.
8. Check inclusion and exclusion criteria before making the IRT call/notification.
9. Complete physical examination (including cardiac, neurological, dermatological, and pulmological) should be performed by the investigator.
10. Vital signs and ECG must be done prior to blood sampling.
11. Diligent diet and exercise counselling by a diet specialist or trained staff member. Counselling is based on the diet and exercise recommendations of the Japanese Diabetes Society and should include a food log (recording of food intake for 3 consecutive days in the week before the actual visit). A food log does not need to be provided at Visit 15/EOT.
12. In addition to the visits indicated, ECG should be recorded in case of respective cardiac symptoms (indicating rhythm disorders or cardiac ischaemia)
13. For female patients (local urine pregnancy test in women of child bearing potential)
14. Fasting blood samples for central lab testing except for urine dipstick, which is to be done locally; upon positive result at site for leukocyte esterase (for white blood cells [WBC]) or nitrites, a midstream urine sample for urine culture (for central lab analysis) should be taken.
15. Self Monitoring Blood Glucose (SMBG) device to be provided at Visit 2 for one OAD, Visit 4 for liraglutide plus one OAD, and Visit 6 for liraglutide alone. Instruction on how the device should be used and the frequency of the measurements should be done when SMBG is provided. Additional instructions and training may be done on other visits as per investigator's discretion and considering patient compliance with protocol-defined measurement and clinical status of the patient.
16. Throughout the whole trial participation, SMBG testing is recommended to be done daily prior to breakfast but should be performed at least weekly prior to breakfast and at any time when the patient is symptomatic, i.e., experiences signs/symptoms of hyper- or hypoglycaemia.
17. At all the visits, the respective medication number has to be allocated to the patient via IRT.
18. For the screening Visit 1, laboratory only includes liver transaminases (AST and ALT), alkaline phosphatase (ALP), serum creatinine, TSH and urinalysis in addition to HbA1c and FPG.
19. HbA1c at Visit 6 is to be skipped if patients are on liraglutide alone.
20. In case of early discontinuation from double-blind treatment, Visit 15/EOT visit has to be performed within 7 days of the last dose of the study drugs.



21. For patients who completed the trial without any persisting adverse event at Visit 15/EOT, a Visit 16 (Follow-up visit) can be performed as a phone visit (only information on SMBG log, adverse events, and concomitant therapies are to be obtained). For patients who completed the trial with persisting adverse event(s) at Visit 15/EOT and patients who prematurely discontinued the 52-week treatment, a Visit 15/EOT and a Visit 16 (as the follow up-visit, physical examination, vital signs, and safety lab and FPG measurement should be performed additionally) should be performed after 7 days of the Visit15/EOT (with +7 days allowance) as clinic visits.
22. Only blood sampling for haematology and urine dipstick test will be performed.
23. Blood sample can be taken at any time in non-fasted state.
24. The investigator or a designated site staff member makes a call to patients to confirm patients' safety through checking their SMBG results, adverse events and concomitant therapies.
25. 14 days (+7 days) interval is necessary between Visit 6 and Visit 7
26. The visit window (day) prior to randomisation has been shown as follows.

*In case of inclusion criterion 2-A*

Patients on Visit 1 can proceed to the Visit 6 after laboratory results are ascertained by their investigator.

Trial Period	Screening period	Switch period				Placebo Run-in period <sup>1</sup>	Randomisation
		Titration period		Washout period <sup>1</sup>			
<i>Visit</i>	1	2	3	4	5	6	7
<i>Study week</i>	0	>	>	>	>	1	0
<i>Days from Visit 1 (inclusion criterion 2-A)</i>	1	>	>	>	>	8	1
<i>Visit window (day)</i>	na	>	>	>	>	+/-7	na

<sup>1</sup> 14 days (+7 days) interval is necessary between Visit 6 and Visit 7

*In case of inclusion criterion 2-B*

Patients on Visit 1 can proceed to the Visit 4 after laboratory results are ascertained by their investigator.

Trial Period	Screening period	Switch period				Placebo Run-in period <sup>2</sup>	Randomisation
		Titration period		Washout period <sup>1</sup>			
<i>Visit</i>	1	2	3	4	5	6	7
<i>Study week</i>	0	>	>	1	6	11	0
<i>Days from Visit 1 (inclusion criterion 2-B)</i>	1	>	>	8	43	78	1
<i>Visit window (day)</i>	na	>	>	+/-7	+/-7	+/-7	na

<sup>1</sup> At least 10 weeks of washout period should be completed.

<sup>2</sup> 14 days (+7 days) interval is necessary between Visit 6 and Visit 7

*In case of inclusion criterion 2-C*

Patients on Visit 1 can proceed to the Visit 2 after laboratory results are ascertained by their investigator.

Trial Period	Screening period	Switch period <sup>1,2</sup>				Placebo Run-in period <sup>4</sup>	Randomisation
		Titration period		Washout period			
<i>Visit</i>	1	2	3 <sup>3</sup>	4 <sup>3</sup>	5	6	7
<i>Study week</i>	0	1	3	5	10	15	0
<i>Days from Visit 1 (inclusion criterion 2-C)</i>	1	8	22	36	71	105	1
<i>Visit window (day)</i>	na	+/-7	+/-7	-14/+7	-14/+7	+/-7	na

- 1 At least 14 weeks of switch period should be completed.
- 2 Liraglutide 0.9 mg/day should be maintained for at least 10 weeks prior to placebo run-in period.
- 3 At least 1 week interval is necessary between Visit 2 and Visit 3 and also between Visit 3 and Visit 4.
- 4 14 days (+7 days) interval is necessary between Visit 6 and Visit 7

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## **ABBREVIATIONS**

AE	adverse event
AESI	adverse event of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
BI	Boehringer Ingelheim
BMI	body mass index
CEC	clinical event committee
CK	creatinine kinase
CML	local clinical monitor
CRA	clinical research associate
CRO	contract research organization
CTP	clinical trial protocol
DBP	diastolic blood pressure
DILI	drug induced liver injury
DMC	data monitoring committee
ECG	electrocardiogram
eCRF	electronic case report form
EOT	end of treatment
EudraCT	European Clinical Trials Database
FAS	full analysis set
FFA	free fatty acid
FPG	fasting plasma glucose
GCP	good clinical practice
GLP-1-RA	glucagon like peptide -1 receptor agonist
GTI	genital tract infection
Hb	haemoglobin
HbA1c	glycosylated haemoglobin A1c
IB	investigator's brochure
ICH	international conference on harmonization
IEC	independent ethics committee
IRB	institutional review board
IRT	interactive response technology
ISF	investigator site file
LDH	lactate dehydrogenase
MedDRA	medical dictionary for drug regulatory activities
MMRM	mixed model repeated measures
NBI	Nippon Boehringer Ingelheim
OAD	oral antidiabetic drug
OPU	operative unit
PMDA	Pharmaceuticals and Medical Devices Agency
PT	preferred term
RBC	red blood cells

RDC	remote data capture
REP	residual effect period
SAE	serious adverse event
SBP	systolic blood pressure
SGLT-2	sodium-glucose co-transporter 2
SMBG	self-monitoring blood glucose
SOC	system organ class
SOP	standard operation procedure
TCM	trial clinical monitor
TS	treated set
TSAP	trial statistical analysis plan
TSH	thyroid stimulation hormone
T2DM	type 2 diabetes mellitus
ULN	upper limit of normal
UTI	urinary tract infection
WBC	white blood cells



## 1. INTRODUCTION

Empagliflozin is an orally available inhibitor of the sodium-glucose co-transporter 2 (SGLT-2), which promotes enhanced glucose excretion in the urine, thereby lowering blood glucose concentrations in patients with type 2 diabetes mellitus (T2DM).

### 1.1 MEDICAL BACKGROUND

Type 2 diabetes mellitus accounts for 90 to 95% of all cases of diabetes and is an increasingly prevalent disease with an estimated 387 million affected people worldwide. Its prevalence is expected to increase to approximately 592 million people during the next 20 years.

Complications induced by hyperglycemia are a common and serious global health problem, which have evolved from adult-onset loss of vision, renal failure, and amputation in the industrialised world. Diabetes is also associated with macrovascular complications with a 2- to 4-fold increase in cardiovascular disease risk. The high frequency of complications leads to a significant reduction of life expectancy.

Commonly available oral antidiabetic drugs are efficacious for a time, but still fail to achieve an optimal blood glucose control in many patients. In Japan, approximately 9.5 million people are strongly suspected to be affected by T2DM and approximately 11.0 million people are undeniable to be affected by T2DM; total 20.5 million people are suffering from either T2DM or pre-diabetic, which is approximately 1 out of 6 of Japanese population (Ministry of Health, Labour and Welfare, National Health and Nutrition Examination Survey, 2012).

The Treatment Guide for Diabetes 2014-2015 in Japan recommends to achieve the glycaemic goal of HbA1c to <7.0% in preventing the onset of microangiopathy and inhibiting its progress, while it states that suitable current treatment aims should be established according to age and complications on a case-by-case basis [R14-4302]. If good control cannot be achieved with one type of oral antidiabetic agent, combination therapy with another drug having a different mode of action should be recommended.

SGLT-2 is a member of a larger group of sodium substrate co-transporters, the sodium-glucose co-transport 5 (SLC5) gene family. [R05-0939] Under normoglycaemia, glucose is almost completely reabsorbed by SGLTs in the kidney, whereas the reuptake capacity of the kidney is saturated at plasma glucose concentrations higher than approximately 10-11 mmol/L, resulting in increasing glucosuria typically seen in patients with diabetes mellitus. The capacity to reabsorb glucose can be decreased by inhibition of SGLT-2. In humans, empagliflozin very highly selectively blockades glucose transport via SGLT-2 (IC<sub>50</sub> 1.3 nmol/l), with a 5000-fold selectivity over SGLT-1 (IC<sub>50</sub> 6278 nM).

In 2014, the Japan Diabetes Society released a recommendation for a proper use of SGLT2 inhibitors. In the recommendation, it is told that when using SGLT2 inhibitors in combination with insulin or sulfonylureas, occurrence of hypoglycaemia should be carefully watched and the administration of SGLT2 inhibitor should be done carefully for elderly patients; and also

it is mentioned that the occurrence of dehydration should be paid attention. For further details see the recommendation [[R15-2908](#)].

## 1.2 DRUG PROFILE

Empagliflozin received its first worldwide marketing approval in Australia on 17 April 2014. As of May in 2015, marketing approval has been received in many countries including European countries and US. In Japan, empagliflozin received marketing approval on 26 Dec 2014. The efficacy of empagliflozin is expected to be similar to the current oral antidiabetic drugs (OADs) and empagliflozin can be administered in a combination with other OADs and may show additional efficacy in terms of glucose control when used in combination with insulin or glucagon-like peptide-1 (GLP-1) receptor agonist (RA) in diabetic patients.

### Non-clinical assessment of safety

A comprehensive package of safety pharmacology, genetic toxicology, reproductive toxicology and general toxicology studies were conducted in mice, rats, rabbits and dogs to support the chronic administration of the 2 doses of empagliflozin (10 mg/day and 25 mg/day) to humans. The compound is well tolerated in animals at clinically relevant plasma exposures, while adverse effects were observed at higher exposures. For further preclinical details see the current version of the empagliflozin Investigator's Brochure (IB) [[c01838761](#)].

### Clinical pharmacokinetics

Empagliflozin predominantly showed linear pharmacokinetics following single oral doses and at steady-state after multiple oral doses in Caucasian and Japanese subjects. Empagliflozin was rapidly absorbed reaching peak levels at approximately 1.5 hours in Caucasian and 1 to 2.5 hours in Japanese, and showed a biphasic decline with the terminal elimination half-life ranging from 10 to 19 hours in Caucasian and from 8 to 12 hours in Japanese. In Caucasian subjects, following oral administration of [<sup>14</sup>C]-empagliflozin, approximately 41.2% and 54.4% of drug-related radioactivity was excreted in faeces and urine, respectively. None of the detected metabolites were major. Empagliflozin tablets can be administered with or without food. Empagliflozin exposure increased with hepatic and/or renal impairment; however, no dose adjustment is recommended for patients with renal and hepatic impairment as the observed changes in empagliflozin exposure in those patients were not clinically meaningful. No clinically relevant pharmacokinetic interactions were observed with metformin, glimepiride, pioglitazone, sitagliptin, warfarin, linagliptin, verapamil, ramipril, simvastatin, digoxin, hydrochlorothiazide, torasemide, gemfibrozil, rifampicin, probenecid and oral contraceptives.

There is no clinical data investigating the interaction between empagliflozin and GLP-1 RA.

### Clinical efficacy and safety

The empagliflozin clinical trials are expected to include a total of approximately 21,000 patients by the end of 2015. Empagliflozin demonstrated good efficacy with approximately 70 to 90 g/day of urinary glucose excretion (UGE), without inducing any increased risk in overall frequency of hypoglycaemia. The 12-week global Phase II studies demonstrated an HbA1c reduction of up to 0.72 % (placebo subtracted), a fasting plasma glucose (FPG)

reduction of up to 33 mg/dL and a weight loss of approximately 1.5 kg, in both the monotherapy setting and as an add-on to metformin ( $\geq 1500$  mg/day).

In clinical studies, empagliflozin was well tolerated in both healthy subjects and patients with T2DM up to maximal treatment duration of 104 weeks in completed studies. Treatment with empagliflozin resulted in similar percentage of adverse events (AEs) to that of placebo and active comparators. Treatment with empagliflozin showed a higher frequency of genital tract infections and symptoms of increased micturition frequency and/or volume, yet was not associated with a higher incidence of urinary tract infections or hypoglycaemia. In Japan, phase II/III trials were conducted and approximately 2000 patients were participated in those trials. Treatment with once daily empagliflozin 10 mg and 25 mg showed continuous blood glucose control as shown in improvement/reduction in both HbA1c and FPG. In addition, reductions in body weight and blood pressure strongly suggest that empagliflozin can offer additional benefits.

Based on the Japanese guideline of “Clinical Evaluation Guidelines for Oral Antihyperglycemic Drugs [[R10-4692](#)]” which was released in July 2010, an add-on therapy to an oral antidiabetic drug (sulfonylurea, biguanide, thiazolidine dione, alpha glucosidase inhibitor, DPP-IV inhibitor, or glinide) was carried out in Japanese patients (study:1245.52 [[U13-1730-01](#)]) and the result showed that empagliflozin 10 mg and 25 mg were well tolerated, safe, and efficacious when used in combination with one other oral antidiabetic drug

In summary, given the safety profile in the preclinical studies, and the safety, tolerability and efficacy seen in the adequately designed and conducted clinical studies to date, the available clinical and non-clinical data support safe and efficacious use of empagliflozin in humans and further development in adults and adolescents with type 1 and type 2 diabetes mellitus.

More information about the known and expected benefits, risks, and anticipated AEs can be found in the current version of IB [[c01838761](#)].

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

### **2.1 RATIONALE FOR PERFORMING THE TRIAL**

Empagliflozin was approved as an antihyperglycaemic drug for indication of T2DM on 26 Dec 2014 in Japan. There is no limitation regarding combination with empagliflozin and any existing antihyperglycaemic drug. However, no clinical data has been obtained in Japanese patients, which demonstrate safety and efficacy results of empagliflozin as add-on therapy to glucagon-like peptide-1 (GLP-1) receptor agonist (RA). Therefore, it is planned to conduct a post marketing clinical trial to investigate the safety and efficacy of empagliflozin given for 52 weeks as add-on therapy to GLP-1 RA in Japanese patients with T2DM who have insufficient glycaemic control.

We will plan to implement this trial on the risk management plan of empagliflozin submitted to the Japanese authorities.

### **2.2 TRIAL OBJECTIVES**

The objective of the study is to investigate the safety and efficacy of empagliflozin (10 mg or 25 mg once daily) given for 52 weeks as add-on therapy to a GLP-1 RA (i.e. liraglutide) in Japanese patients with T2DM who have insufficient glycaemic control.

### **2.3 BENEFIT - RISK ASSESSMENT**

The overall safety profile of empagliflozin is outlined in the current IB [[c01838761](#)].

All patients with T2DM participating in this trial may derive a direct benefit from being treated with an active compound and not a placebo. In addition, beneficial effects like body weight reduction and a moderate blood pressure lowering are expected based on Phase III studies of empagliflozin and publications of other SGLT-2 inhibitors.

All patients taking part in the trial may derive general medical benefit from careful and close monitoring by medical personnel during the study. Safety will be ensured by monitoring the patients for AEs both clinically and by laboratory testing and by the Self Monitoring Blood Glucose (SMBG). If any investigator should have a clinical concern, the safety of the patients will be paramount.

Approximately 50% of the patients will receive empagliflozin 25 mg without starting lower dose of empagliflozin 10 mg although the Japanese label defines the starting dose as 10 mg. Empagliflozin 25 mg as well as 10 mg were used in the phase III trials as for the expected therapeutic doses and both empagliflozin doses were well tolerated as initial start dosage. Moreover, patient's safety will be ensured by monitoring the patients for AEs both clinically and by laboratory testing. Therefore, the risk of safety related to starting dose of

empagliflozin 25 mg is considered to be low. Because of the mechanism of action of empagliflozin, the risk of hypoglycaemic episodes is considered to be low. Symptoms attributed to not only hypoglycaemia but also hyperglycaemia, or hypo- and hypertension will be closely monitored in the trial. In addition, patients who are not adequately controlled, as evidenced by a confirmed high glucose value (see [Section 3.3.4.1](#)) will be excluded from further study participation.

Diabetic ketoacidosis (DKA) has not been observed in clinical trials of empagliflozin in T2DM patients so far in Japan, but special attention will be paid to prevent DKA in this trial in accordance with the recommendation from “Committee on the proper use of SGLT2 inhibitors” of the Japanese Diabetes Society that requests physicians to pay attention to DKA when using an SGLT2 inhibitor [[R15-2908](#)]. Rare cases of DKA have been reported in patients treated with SGLT2 inhibitors, including empagliflozin. In a number of reported cases, the presentation of the condition was atypical with only moderately increased blood glucose values, below 250 mg/dL (14 mmol/L).

The risk of DKA must be considered in the event of non-specific symptoms such as nausea, vomiting, anorexia, abdominal pain, excessive thirst, difficulty breathing, confusion, unusual fatigue or sleepiness. In addition it needs to be taken into account that, due to the insulin independent mode of action, there is a possibility that ketoacidosis in patients treated with SGLT2 inhibitors is not accompanied by typical hyperglycemia as usually expected for DKA.

Patients who may be at higher risk of DKA while taking SGLT2 inhibitors include patients on a very low carbohydrate diet (as the combination may further increase ketone body production), severely dehydrated patients, and patients with a history of ketoacidosis or who are known to have a low beta-cell function reserve. Special measurements are performed like follow-up on genito-urinary tract infections (urine culture) in order to evaluate if possible side effects observed for other SGLT-2 inhibitors are also present for empagliflozin.

The overall frequency of volume depletion is similar between empagliflozin and placebo [[c01838761](#)]. However, the frequency of volume depletion events was increased in patients 75 years and over of age treated with empagliflozin compared to placebo. Based on the mode of action of SGLT-2 inhibitors, osmotic diuresis may lead to a modest decrease in blood pressure and dehydration. Therefore, careful monitoring of volume status (e.g., physical examination, blood pressure measurements, and laboratory tests including haematocrit) and electrolytes is recommended for patients receiving empagliflozin. Also, patients as precautionary measure will be requested to drink plenty of fluids. Temporary interruption of treatment with empagliflozin should be considered until the fluid loss is corrected.

As with all drugs, the potential for hypersensitivity and allergic reactions has to be taken into consideration when empagliflozin is administered. Other risks to the patients are the risks inherent to any treatment such as unexpected adverse clinical or laboratory events.

Although rare, a potential for drug-induced liver injury (DILI) is under constant surveillance by sponsors and regulators. Therefore, this study requires timely detection, evaluation, and

follow-up of laboratory alterations of selected liver laboratory parameters to ensure patients' safety (see [Section 5.3.6.1](#)).

In the embryo-foetal and fertility studies in rats and rabbits, no effects on early embryonic development, mating, male and female fertility, and bearing live young were observed up to a dose of 300 mg/kg. Therefore, women who are of child-bearing potential may participate in this study provided that they are using adequate contraceptive methods.

Given the good safety profile in the toxicity studies of empagliflozin and the good tolerability seen in the human studies so far, the careful monitoring to be conducted during the study visits and the blood glucose monitoring to be performed by the patients at home during the study, the sponsor considers the risks to the participating patients will be minimised and justified when compared with the potential benefits.

Empagliflozin is market approved as an antihyperglycaemic drug for patients with T2DM in many countries including European countries, US and Japan.

### 3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

#### 3.1 OVERALL TRIAL DESIGN AND PLAN

This is a randomised, multi-centre, double-blind, and parallel groups study. The T2DM patients with insufficient glycaemic control despite treatment with liraglutide will receive either 10 mg or 25 mg of empagliflozin once daily as add-on therapy for 52 weeks.

In total, about 128 patients with T2DM are planned to be screened to ensure that 64 patients (32 patients for each treatment) are randomised in the double blind treatment period.

Patients who have signed the informed consent are enrolled in the study. Patients on liraglutide alone and suitable for the study after screening (Visit 1) undergo a 2-week open-label placebo run-in period before randomisation. Patients treated with liraglutide plus one OAD and suitable for the study after screening (Visit 1) undergo a 10-weeks OAD washout period followed by the placebo run-in period before randomisation. Patients treated with one OAD alone and suitable for the study after screening undergo 14-week switch period (from OAD to liraglutide, including 2 to 4-week dose titration period) followed by the placebo run-in period before randomisation.

Patients who successfully complete the placebo run-in period and who still meet the inclusion but not meet the exclusion criteria will enter the 52-week double-blind treatment period of the study in which they will receive 10 mg or 25 mg of empagliflozin once daily. Randomisation of the treatment arms will be double-blinded and assigned at a ratio of 1:1 to one of 2 treatment arms shown in [Figure 3.1: 1](#). The patient participation is completed when they have undergone the last planned visit.

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

The overall trial design is displayed in [Figure 3.1: 1](#).



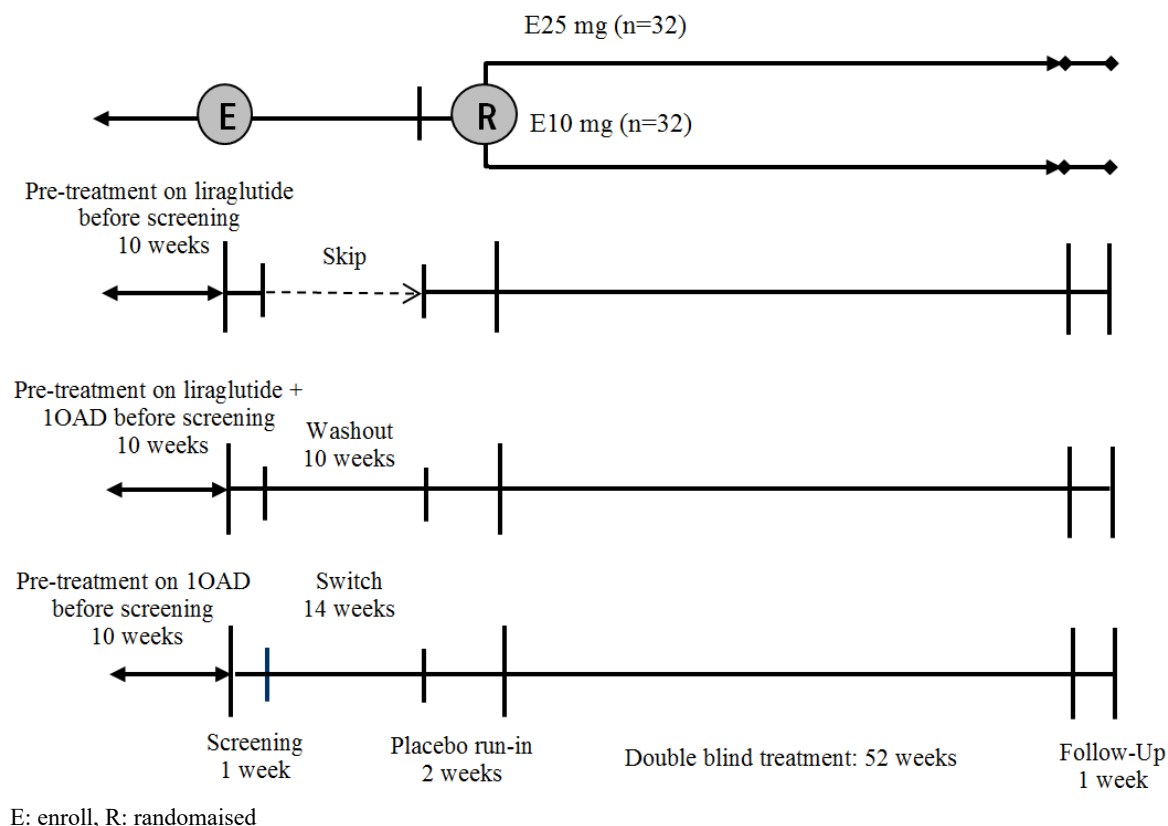


Figure 3.1: 1 Trial design

### 3.1.1 Administrative structure of the trial

Boehringer Ingelheim has appointed a trial clinical monitor (TCM), responsible for coordinating all required activities, in order to

- manage the trial in accordance with applicable regulations and internal SOPs,
- direct the clinical trial team in the preparation, conduct, and reporting of the trial,
- order the materials as needed for the trial,
- ensure appropriate training and information of local clinical monitors (CML), clinical research associates (CRAs), and Investigators of participating countries.

Data management and statistical evaluation will be done by the BI according to BI SOPs.

A list of responsible persons and relevant local information (as protocol reference, if applicable) can be found in the ISF.

A coordinating investigator will be nominated and will be responsible to coordinate investigators at different centres participating in this multicentre trial. Tasks and responsibilities will be defined in a contract. Relevant documentation on the participating



(Principal) investigators and other important participants, including their curricula vitae, will be filed in the ISF.

### 3.1.1.1 Hepatic external adjudication

Certain hepatic events will be adjudicated by external independent experts for severity and causal relationship with the trial medication in a blinded fashion. The events which will be reviewed are defined in a charter for hepatic events. Events may either be defined by abnormal laboratory values and/or relevant adverse events or both. For example, assessments will be made for hepatic injury events, including liver enzyme elevations.

For qualifying events, relevant source documents generated from any medical evaluations of these events will be requested including laboratory values, histological analysis, results of ultrasound, CT, MRI, scintigraphy, hospital discharge letters, and medical reports from other physicians. All evaluations will be performed in a blinded fashion. The assessments will be analysed based on empagliflozin data combined from multiple trials (i.e. on project level).

### 3.1.1.2 Clinical Event Committee for Diabetic ketoacidosis (DKA)

An independent external committee (CEC) will be established to adjudicate centrally and in a blinded fashion events suspected of DKA (for further details see [Section 5.3.3](#)). The CEC will evaluate whether pre-specified criteria for adjudication endpoints are met.

For any events that qualify for adjudication, study sites will be asked to provide clinical documentation such as laboratory values, discharge summaries etc. to support the external event adjudication.

The tasks and responsibilities of the CEC will be specified in a charter. The CEC will maintain the adjudication results in writing.

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

The aim of this trial is to evaluate the long-term safety and efficacy of empagliflozin 10 mg and 25 mg in Japanese patients with T2DM whose glycaemic control is insufficient despite diet/exercise and treatment with liraglutide, which is currently the only approved GLP-1 RA in Japan with the monotherapy indication in addition to the combination therapy.

The design of this study is decided according to the draft version of the revised Japanese guideline 'Clinical Evaluation Guidelines for Antihyperglycemic Drugs' [[R15-2907](#)] in which 1-year long term study is required for any antihyperglycaemic investigational products when used as concomitant therapy to existing antihyperglycaemic drugs.

The 14-week switch period, which consists of 2 to 4 weeks of dose titration period and 10 to 12 weeks of washout period, indicates that patients currently receiving one OAD at screening should stop their OAD treatment and start treatment with liraglutide at Visit 2. The duration of the switch period is considered to be appropriate since adequate treatment duration with liraglutide monotherapy is provided.

The 10-week OAD washout period indicates that patients currently receiving liraglutide and one OAD should stop their OAD for 10 weeks. The duration of the washout period is considered to be appropriate to minimise the effect of OAD on glycaemic control of the patients pre-treated with liraglutide and one OAD.

The open label 2-weeks placebo run-in period indicates that the patients check medical compliance by mimicking the dosing in the double-blind treatment period. The patients who have been pre-treated with liraglutide alone at screening (Visit 1) will directly enter into the placebo run-in period.

A double-blind and double-dummy design is adopted in order to minimise bias to evaluate the safety and efficacy of two doses (i.e. 10 mg and 25 mg) of empagliflozin.

The 52 weeks for treatment period is planned in order to investigate the long term safety of empagliflozin 10 mg and 25 mg in accordance with the revised guideline (draft version).

The 1-week follow-up period is considered to be sufficient, as previous studies with empagliflozin have shown that the pharmacodynamic effect of empagliflozin only extends to about 3 days after the last dose and half-life of empagliflozin in Japanese T2DM patients after 4 weeks of treatment ranged from 12 to 18 hours.

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

### **3.3 SELECTION OF TRIAL POPULATION**

A sufficient number of patients will be screened for the trial to ensure that 64 patients are randomised to the trial's double-blind treatment period (32 patients in treatment arm: empagliflozin 10 mg plus placebo, 32 patients in treatment arm: empagliflozin 25 mg plus placebo).

The screening failure rate for this trial is expected to be around 10 % for the screening visit and approximately 40 % of the patients are not expected to fulfil the criteria for randomisation. These rates would give an estimate of the number of patients needed to be screened to be 128.

Screening of patients may be stopped before reaching 128 enrolled or might continue beyond these numbers, if the screening failure rate differs from the rates anticipated above.

Enrolment of patients for this trial is competitive, i.e. enrolment for the trial will stop at all centres when it has been anticipated that a sufficient number of patients will be randomised to

double-blind treatment period. Investigators will be notified when the appropriate number of patients has been enrolled and the enrolment is completed, and will not be allowed to recruit additional patients for this trial.

Patients who have signed written informed consent before this notification may not participate in double-blind treatment period after 68 patients are randomised, and the patients who are in switch/washout/placebo run-in period should be discontinued quickly when the sponsor notify to stop the randomisation.

Investigators who fail to enrol at least one patient in the first 10 weeks of the trial may be excluded from further participation. If enrolment of the study is delayed, additional centres may be recruited.

Permission to enter more than 12 patients per site must be obtained from the TCM at NBI.

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.

Re-testing:

Re-testing for eligibility criteria is only to be performed for a laboratory result which is obviously received beyond stability at the central laboratory or thought to be a spurious result based on previously available laboratory results only for the corresponding laboratory test. The re-test should be carried out as soon as possible so the laboratory test results will be received within the next planned visit windows in order to avoid protocol visit violations.

### **3.3.1 Main diagnosis for trial entry**

The study will be performed in Japanese patients with T2DM who have insufficient glycaemic control despite diet, exercise and receiving liraglutide or one OAD or both. Please refer to [Section 8.3.1](#) (Source Documents) for the documentation requirements pertaining to the in- and exclusion criteria.

### **3.3.2 Inclusion criteria**

1. Diagnosis of type 2 diabetes mellitus prior to informed consent
2. Male and female patients on diet and exercise regimen who are pre-treated with:
  - A) liraglutide at 0.9 mg/day for at least 10 weeks prior to Visit 1 (screening visit).  
HbA1c at Visit 1 :  $\geq 7.0\%$  and  $\leq 10.0\%$

- B) liraglutide at 0.9 mg/day in combination with one OAD<sup>i)</sup> for at least 10 weeks prior to Visit 1 (screening visit).

HbA1c at Visit 1 :  $\geq 7.0\%$  and  $\leq 9.0\%$

HbA1c at Visit 6 :  $\geq 7.0\%$  and  $\leq 10.0\%$

- C) One OAD<sup>i)</sup> for at least 10 weeks prior to Visit 1 (screening visit). The patients who are suitable for switching to liraglutide treatment<sup>ii)</sup> after Visit 1 at the investigator's discretion .

HbA1c at Visit 1 and Visit 6:  $\geq 7.0\%$  and  $\leq 10.0\%$

- i) Sulfonylurea is permitted as pre-treatment drug only if the dose is equal or less than a half of daily maximum approval dose. Any other OADs excepting thiazolidine dione and SGLT-2 inhibitor are allowed at any dose.
- ii) Patients should stop their OAD and start switching to liraglutide treatment at Visit 2 and the dose titration completed within 2-4 weeks and also should be done in accordance with Japanese label (i.e., at least 1 week dosing period with 0.3 mg and 0.6 mg each is required.). Patients should be treated with liraglutide at 0.9 mg/day for at least 10 weeks (14 weeks of switch period is required.) prior to placebo run-in period.
3. Age  $\geq 20$  years at informed consent
4. Body mass index (BMI)  $\leq 40.0$  kg/m<sup>2</sup> at Visit 1 (screening visit)
5. Signed and dated written informed consent by date of Visit 1 in accordance with Good Clinical Practice (GCP) and Japanese legislation

### 3.3.3 Exclusion criteria

1. Uncontrolled hyperglycaemia with a glucose values  $>270$  mg/dL ( $>15.0$  mmol/L) after an overnight fast during switch/washout/placebo run-in period and confirmed by a second measurement (not on the same day and one of the measurement should be performed at the investigational site after overnight fast)
2. Patients who are drug-naïve at Visit 1 (screening visit) or treat with any of insulin, thiazolidine dione, SGLT-2 inhibitor within 10 weeks prior to informed consent.
3. Acute coronary syndrome (ST elevation myocardial infarction [STEMI], non-STEMI, and unstable angina pectoris), stroke or transient ischemic attack (TIA) within 12 weeks prior to informed consent
4. Indication of liver disease, defined by serum levels of either alanine aminotransferase (ALT [SGPT]), aspartate aminotransferase (AST [SGOT]), or alkaline phosphatase (ALP) above 3 x upper limit of normal (ULN) as determined during screening and/or switch/washout/placebo run-in period
5. Impaired renal function, defined as eGFR  $<45$  mL/min/1.73m<sup>2</sup> (Japanese equation) as determined during screening and/or switch/washout/placebo run-in period

6. Any previous (within 2 years prior to informed consent) bariatric surgery or other gastrointestinal surgery that induce chronic malabsorption
7. Medical history of cancer (except for basal cell carcinoma) and/or treatment for cancer within the last 5 years of informed consent
8. Blood dyscrasias or any disorders causing haemolysis or unstable red blood cells (RBC) (e.g., malaria, babesiosis, haemolytic anaemia)
9. Contraindications to liraglutide and empagliflozin according to the Japanese label
10. Known allergy or hypersensitivity to liraglutide or empagliflozin
11. The patients who are not able to receive liraglutide 0.9 mg/day for 10 weeks prior to placebo run-in period and who do not treat with the same dose during run-in period
12. Treatment with anti-obesity drugs (e.g. mazindol) within 12 weeks prior to informed consent or any other treatment at the time of screening and/or switch/washout/placebo run-in period (i.e. surgery, aggressive diet regimen, etc.) leading to unstable body weight
13. Current treatment with systemic steroids(exclude inhaled or local 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
14. Pre-menopausal women (last menstruation  $\leq 1$  year prior to informed consent) who:
  - a) are nursing or pregnant or plan to become pregnant while in the trial
  - b) are of child-bearing potential and are not practicing an acceptable method of birth control, or do not plan to continue using this method throughout the study and do not agree to submit to periodic pregnancy testing during participation in the trial. Acceptable methods of birth control include intra uterine devices/systems (IUDs/IUSs), oral contraceptives, barrier method\* and vasectomised partner.
- \* Barrier method: condom or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository
15. Alcohol or drug abuse within the 12 weeks 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 judgement of the investigator
16. Participation in another trial with an investigational drug within 30 days prior to informed consent
17. Any other clinical condition that would jeopardize patients' safety while participating in this clinical trial by investigator's judgement

### 3.3.4 Removal of patients from therapy or assessments

#### 3.3.4.1 Removal of individual patients

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

- The patient withdraws consent for study treatment or study participation, without the need to justify the decision.
- The patient needs to take concomitant drugs, including herbal/nutritional supplements/medication that interfere with the investigational product or other study trial medications (see [Section 4.2.2.1](#)).
- The patient can no longer be treated with trial medication for other medical reasons (such as surgery, adverse events, other diseases, or pregnancy).
- Occurrence of hyperglycaemia that meets the following criteria. In this case, the reason for study drug discontinuation will be classified as “lack of efficacy”.
  - Visit 7 to Visit 10: The patient has glucose values of >270 mg/dL (>15.0 mmol/L) after an overnight fast.
  - Next day after Visit 10 to Visit 15/EOT: The patient has glucose values of >240 mg/dL (>13.3 mmol/L) after an overnight fast.

The above result should be confirmed, 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 if possible, and on a different day to the initial measurement.

- Occurrence of hypoglycaemia (e.g. repeated hypoglycaemic episodes) or ·  
DKA that may put the patient at risk with continued participation. Patients should be assessed for ketoacidosis immediately if symptoms occur, regardless of blood glucose level. Discontinuation or temporary interruption of study medication should be considered, until the situation is clarified.
- 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.

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

Given the patient's agreement, the patient will undergo the procedures for early treatment discontinuation and follow-up as outlined in the [flow chart](#) and [Section 6.2.3](#).

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

Patients who drop out before placebo run-in period will be considered a screening failure. They have to be recorded as a screening failure in the eCRFs and no further follow-up is required (except for AEs, if needed).

Patients who drop out during the screening phase prior to placebo run-in period will be considered a screening failure. They have to be recorded as screening failure in eCRFs and no further follow-up is required (except for AEs, if needed).

Patients who discontinue or withdraw from the study during placebo run-in period and before being randomised in Visit 7 will be considered a run-in failure. They have to be recorded as run-in failure in eCRFs and no further follow-up is required (except for AEs, if needed).

Patients who discontinue or withdraw from the study after randomisation (Visit 7) and before completing Visit 15/EOT will be considered as early discontinuations and the reason for premature discontinuation must be recorded in the eCRFs. The reason will be included in the trial database and will be reported. If determined by the investigator as necessary for the patient's safety, a new antidiabetic medication regimen can be started immediately after discontinuation and must be recorded in eCRFs. In this case, end of treatment (Visit 15/EOT) must be performed before taking any new antidiabetic drug.

Patients who are withdrawn or discontinued from the trial after randomisation will not be replaced.

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

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

1. Failure to meet expected enrolment goals overall or at a particular trial site
2. Emergence of any efficacy/safety information invalidating the earlier positive benefit-risk-assessment that could significantly affect the continuation of the trial
3. Violation of GCP, the 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 TREATMENTS TO BE ADMINISTERED**

The trial medication will be provided from NBI.

#### **4.1.1 Identity of BI investigational product(s) and comparator product(s)**

The characteristics of test product 1 are below.

Substance:	Empagliflozin
Pharmaceutical form:	film-coated tablet
Source:	Boehringer Ingelheim
Unit Strength:	10 mg
Route of administration:	oral, once daily

The characteristics of test product 2 are below.

Substance:	Empagliflozin
Pharmaceutical form:	film-coated tablet
Source:	Boehringer Ingelheim
Unit Strength:	25 mg
Route of administration:	oral, once daily

The characteristics of the reference product placebo 1 are below.

Substance:	Placebo matching empagliflozin 10 mg
Pharmaceutical form:	film-coated tablet
Source:	Boehringer Ingelheim
Unit Strength:	-
Route of administration:	oral, once daily

The characteristics of the reference product placebo 2 are below.

Substance:	Placebo matching empagliflozin 25 mg
Pharmaceutical form:	film-coated tablet
Source:	Boehringer Ingelheim
Unit Strength:	-



Route of administration: oral, once daily

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

After the patient's eligibility has been confirmed, the patient will be assigned to placebo at Visit 6 and randomly assigned to either empagliflozin 10 mg plus placebo or empagliflozin 25 mg plus placebo (1:1 ratio) at Visit 7 via Interactive Response Technology (IRT) (see [Section 4.1.4](#)). To facilitate the use of the IRT, the investigator will receive all necessary instructions.

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 see [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.

#### 4.1.3 Selection of doses in the trial

The selected doses of empagliflozin are based on the approved and marketed doses in Japan. Approximately 50% of the patients will receive empagliflozin 25 mg without starting lower dose of empagliflozin 10 mg although the Japanese label defines the starting dose of empagliflozin 10 mg. Empagliflozin 25 mg as well as 10 mg were used in the phase III clinical trials as for the expected therapeutic doses and both empagliflozin doses were well tolerated as initial dosage.

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

The treatments to be evaluated are outlined in [Table 4.1.4: 1](#) below. Patients who are qualified will be randomised to one of the dosage and treatment schedules described below. Medication will be dispensed in a double-blind and double-dummy fashion.

All patients will be assigned to a placebo run-in kit at the beginning of the placebo run-in period (Visit 6), and dispensing will be done just once. Dispensing of kits for the double-blind treatment period will begin at Visit 7. Dispensing will be done on 8 occasions over a period of 52 weeks (i.e. every 4 weeks in Visit 7 to Visit 10; every 8 weeks in Visit 11 to Visit 14). Patients will receive empagliflozin as trial medication. However, background medication will not be dispensed as trial medication. Therefore, background medication (liraglutide) will be prescribed at each clinical site. For details regarding packaging (e.g. number of tablets per container), please see [Section 4.1.6](#).

Table 4.1.4: 1 Empagliflozin, oral administration per dose group and day

Dose group	Empagliflozin 10 mg	Empagliflozin 25 mg	Total units per dose	Timing
Placebo run-in period (open label)				
All patients	Matching placebo	Matching placebo	2 tablets	Once daily, Morning
Treatment period				
Empagliflozin 10 mg	Active drug	Matching placebo	2 tablets	Once daily, Morning
Empagliflozin 25 mg	Matching placebo	Active drug	2 tablets	Once daily, Morning

Placebo run-in period (open label):

From the start of the placebo run-in period, patients should be instructed to take their trial medication once daily with water. 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.

Double-blind period:

During the treatment period, 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 but the patient is aware of missing the trial medication within 12 hours from planned intake, the dose should be taken immediately, and if a dose is missed by more than 12 hours, that dose should be skipped and the next dose should be taken as scheduled. On days before the next visit, the dose should be taken 22-26 hours before the planned dose at the visit. No double doses should be taken. Empagliflozin can be taken with or without food.

The dosage and usage of background medication should remain unchanged during the double-blind treatment period (see [Section 4.2.1](#)).

Patients should be instructed not to take their trial medication in the morning of study visits as they will be dosed while in the study site. Patients who fail to do so should have the visit rescheduled as soon as possible, ideally on the following day. Patients are asked to bring their trial medication to the sites from. Visits should be routinely scheduled in the morning, at approximately the same time of day for each visit. The actual date and time of administration of the medication at the trial visit will be recorded in the eCRF.

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

##### **4.1.5.1 Blinding**

Trial medication during run-in period will be open-labelled.

After randomisation at Visit 7, patients, investigators and everyone involved in trial conduct or analysis or with any other interest in this double-blind study will remain blinded with regard to randomised treatment assignments until database lock. To achieve all dose combinations and to ensure blinding, empagliflozin and placebo tablets are combined in double-dummy fashion as shown in [Table 4.1.4: 1](#) and patients will have to take two tablets for each dose.

However, due to the requirements to report suspected serious unexpected adverse reactions (SUSARs), it may be necessary for a representative from BI's drug safety group to access the randomisation code for individual patients during study conduct. In such cases, access to the code will only be permitted by authorised drug safety representatives. Access to the code will be via the IRT.

The randomisation code will be kept secret by Clinical Trial Support up to database lock. Please see [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**

In this blinded trial, an emergency code break will be available to the investigator via IRT system. This code break may only be accessed in emergency situations when the identity of the trial drug must be known to the investigator in order to provide appropriate medical treatment or if required to assure the safety of trial participants. Each site receives a manual from the IRT provider that contains instructions on how to unblind the treatment of a patient via the IRT (via 24-hour Emergency helpline). If the code break for a patient is accessed, the sponsor must be informed immediately. The reason for accessing the code break, together with the date, must be documented on the appropriate eCRF page. In case third party needs to break the code, however, when the investigator cannot be reached, the code can be opened by calling emergency code manager (see Emergency Code Break Manual) in the ISF.

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

Study medication will be provided by BI.

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

The placebo run-in kit, assigned to all patients successfully completing Visit 6, will contain 42 tablets in a wallet (i.e., sufficient supply for 2-week administration, with supply for 1-week administration in reserve). One kit type (wallet) will be used for the double-blind treatment either 4 weeks or 8 weeks interval. Wallet will contain 84 tablets (i.e., sufficient supply for 4-week administration, with supply for 2-week administration in reserve). When patients are in the 4 weeks interval at Visits 7, 8, and 9, they will receive one wallet. When patients are in the 8 weeks interval at Visit 10, 11, 12, 13 and 14, they will receive 2 wallets. The total number of tablets dispensed to a patient during the double-blind treatment period will therefore be 1092 at a maximum.

Supply and re-supply will be managed by IRT.

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

#### **4.1.7 Storage conditions**

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.

If the storage conditions are found to be outside the specified range, the local clinical monitor (as provided in the list of contacts) must be contacted immediately.”

#### **4.1.8 Drug accountability**

The investigational drug storage manager will receive the investigational drugs delivered by the sponsor when the following requirements are fulfilled:

- Approval of the trial protocol by the 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

The 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 alternative disposal of unused products.

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 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 and/or appointed CRO, the 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.

Back ground medication:

One auxiliary Medicinal Products (AMPs) accountability form will be provided for liraglutide to the trial site. This record will include dates, quantities, batch / serial numbers, expiry ('use-by') dates and unique code numbers to the investigational product and trial patients.

## **4.2 CONCOMITANT THERAPY, RESTRICTIONS, AND RESCUE TREATMENT**

Details of all concomitant therapy during the clinical trial will be recorded on the appropriate pages of the eCRFs.

### **4.2.1 Rescue medication, emergency procedures, and additional treatment(s)**

Throughout the duration of the trial, patients should continue to take background therapy, the dose of which should remain unchanged if at all possible (for further details see below). This background medication will not be provided as part of the clinical trial supplies. Only the liraglutide is allowed to be used as GLP-1 RA background medication.

The use of antidiabetic agents other than liraglutide and the allocated medication after randomisation (Visit 7) will be prohibited during the course of the study.

In case of conditions that may lead to fluid loss (e.g. gastrointestinal illness), careful monitoring of volume status (e.g. physical examination, blood pressure measurements, laboratory tests including haematocrit) and electrolytes is recommended for patients receiving empagliflozin. Temporary interruption of treatment with empagliflozin should be considered until the fluid loss is corrected.

In the case of hypoglycaemia that may put the patient at risk (e.g. repeated symptomatic hypoglycaemia or severe hypoglycaemia), appropriate dose adjustment of liraglutide, such as a dose reduction/discontinuation, should be initiated.

If, in the investigator's clinical consideration, the patient's hyper- or hypoglycaemia cannot be controlled, the patient should be discontinued from the trial as specified in [Section 3.3.4](#).

Special attention must be paid to the prevention of DKA. All patients must be made aware of this risk and need to be instructed to contact the Investigator or other healthcare professional in case of symptoms of DKA. For further details see [Section 2.3](#).

In case of a suspected DKA the Investigator should ensure that appropriate tests are performed at the earliest opportunity according to guidelines in Japan, such as a blood gas test (i.e. pH, bicarbonate anion gap, potassium, blood glucose, etc; the results will be

collected on the relevant page of the eCRF) and that the patient is appropriately treated (i.e. hospitalized or referred to emergency treatment) according to treatment guidelines in Japan.

Any additional treatment which 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](#).

There are no special emergency procedures to be followed.

## **4.2.2 Restrictions**

### **4.2.2.1 Restrictions regarding concomitant treatment**

The use of antidiabetic agents other than liraglutide and the allocated study drugs after randomisation will be prohibited during the course of the study.

Short-term use of 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 such insulin treatment over more than 2 weeks vs. treatment discontinuation should be discussed on a case-by-case basis between the investigator and the TCM.

Additionally, treatment with anti-obesity drugs or systemic steroids will be prohibited due to their influence on glucose metabolism. However, one off or short-term use (i.e.  $\leq 2$  weeks 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 occur, they should be recorded in the source documents and in the eCRF.

The risk of volume depletion may be increased in a patient treated with diuretic in addition to SGLT-2 inhibitor. Therefore, the co-administration of diuretic had to be avoided if there are not sufficient reasons to use these drugs according to the investigators' clinical judgement.

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

Patients will receive diet and exercise counselling by a diet specialist or trained staff member throughout the duration of the study. The counselling should be based on the diet and exercise recommendation of the Japanese diabetes society. In principle, the contents of diet and exercise should not be changed through the study period. Patients keep record (food intake diary) of the actual food intake over a time of 3 consecutive days in the week before the actual clinic visit and bring the diary at each visit. The patients will be reminded to follow the agreed diet and exercise plan at every visit. An investigator will check compliance with the diet and exercise therapy based on the records of the food intake diary and also by interview with patients.

SGLT-2 inhibitor has a diuretic action and the patients may show signs or symptoms of dehydration. Therefore, the investigator should instruct the patients to drink appropriate volume of water or other drinks every day.

Patients also should not take any investigational drug in other trials within the last 30 days before the date of informed consent for this trial.

There are no other restrictions on diet and lifestyle.

#### 4.2.2.3 Restrictions regarding women of childbearing potential

Women of child-bearing potential must continue to practice an acceptable method of birth control (in accordance with the trial exclusion criteria [Section 3.3.3](#)) throughout the duration of the study.

### 4.3 TREATMENT COMPLIANCE

Patients are requested to bring all remaining trial medication including empty package material when attending visits.

Based on tablet counts, treatment compliance will be calculated as the number of tablet taken, divided by the number of tablet 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.

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

If the treatment compliance is not between 80-120%, site staff will explain the patient the importance of treatment compliance.

## **5. VARIABLES AND THEIR ASSESSMENT**

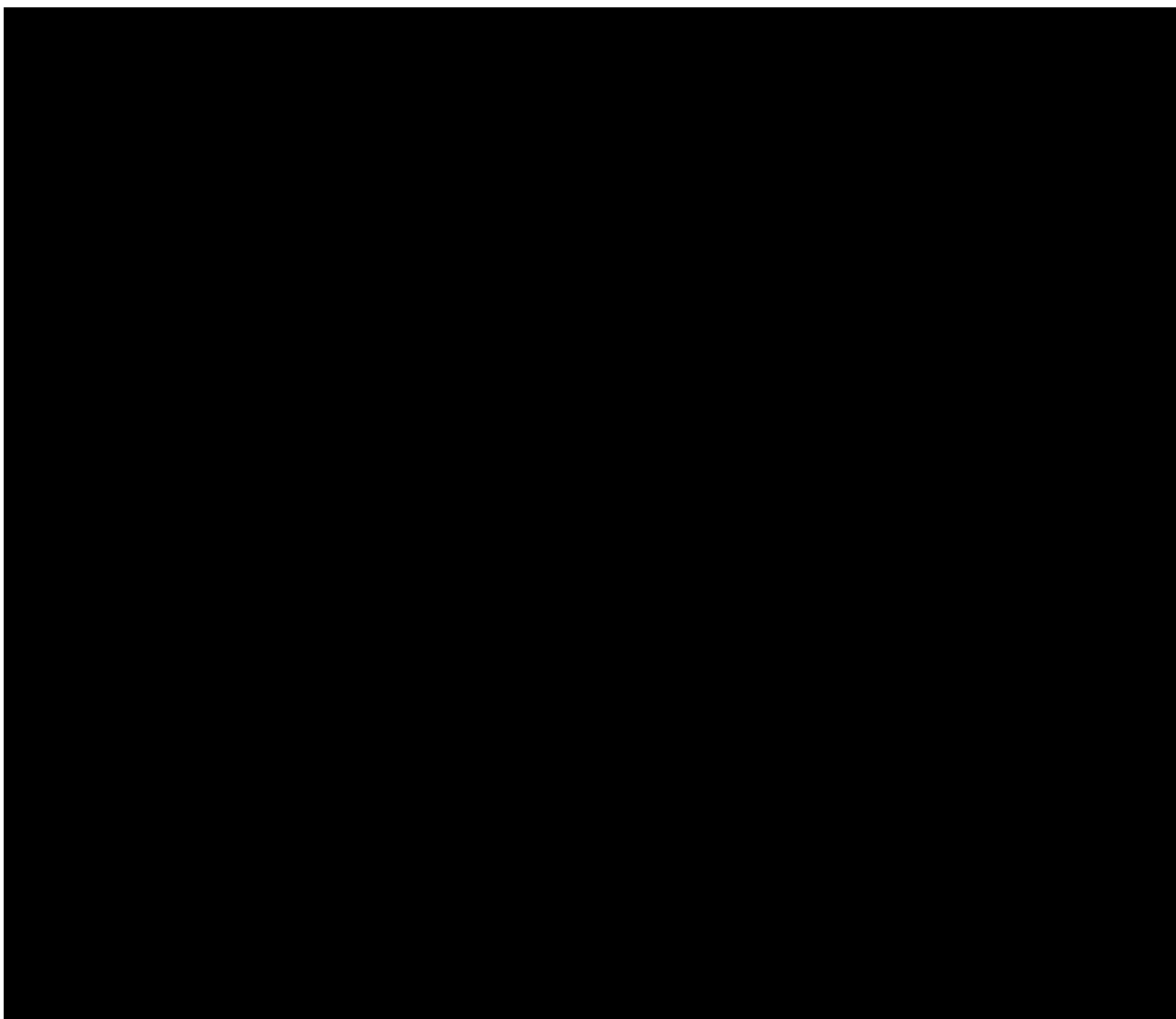
### **5.1 TRIAL ENDPOINTS**

#### **5.1.1 Primary Endpoint(s)**

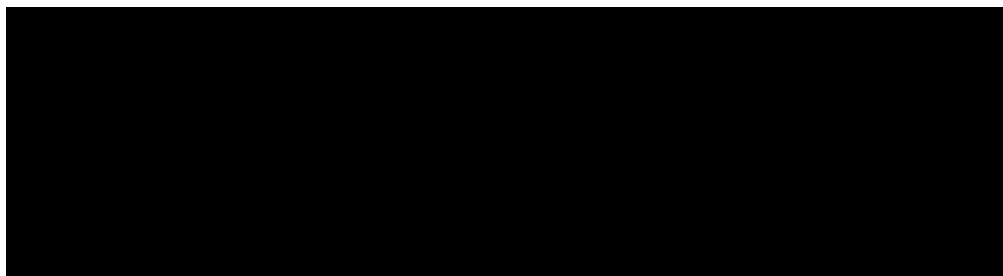
The primary endpoint of the trial is the proportion of patients with drug-related adverse events (AE) during 52 weeks of treatment with empagliflozin as add-on to GLP-1 RA (i.e. liraglutide).

#### **5.1.2 Secondary Endpoint(s)**

The secondary endpoint is a change in HbA1c from baseline after 52 weeks of treatment of empagliflozin as add-on to GLP-1 RA (i.e. liraglutide).



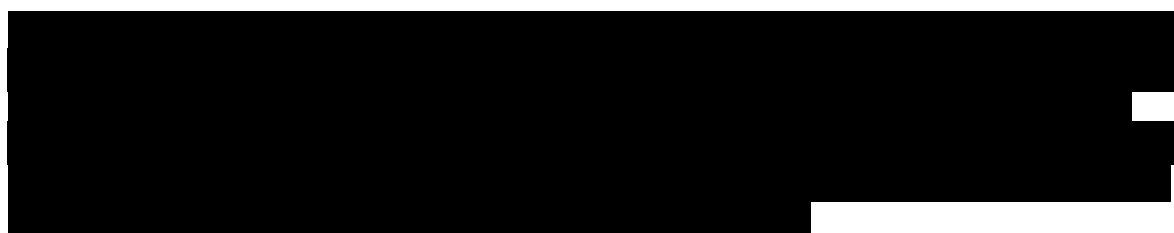




## 5.2 ASSESSMENT OF EFFICACY

### HbA1c:

Blood samples for the determination of HbA1c at the central laboratory will be taken. At the screening visit 1, the blood sample can be taken at any time in non-fasted state. At all other visits, the blood samples should be drawn before breakfast and before trial drug administration. The samples will be analysed at a central laboratory having a National Glycohaemoglobin Standardization Program (NGSP) Level I certificate. Further details about sample handling, shipment, and assay procedures can be found in the ISF (Lab manual).



## 5.3 ASSESSMENT OF SAFETY

### 5.3.1 Physical examination

A complete physical examination (including cardiac, neurological, dermatological, pulmonological) will be performed by the investigator as described in the [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

The seated pulse rate (electronically or by palpation, count for 1 minute) will be measured as described in the [Flow chart](#). Further details on the procedure for seated pulse rate measurements are given in [Appendix 10.1](#).

### 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 the investigational drug is taken 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 [Tables 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 are planned for the following visits:

- For the screening Visit 1, laboratory only includes HbA1c, FPG, liver transaminases (i.e. AST and ALT), ALP, serum creatinine, thyroid stimulation hormone (TSH) and urinalysis.
- FFA and Ketone bodies will be performed as described in the [Flow chart](#).
- Bone markers iPTH (intact parathyroid hormone), 25OH Vitamin D, NTx in urine: planned as described in the [Flow chart](#).
- Only blood sampling for haematology and urine dipstick test will be performed as described in the [Flow chart](#).

Table 5.3.3: 1                      Safety laboratory parameters – whole blood, serum or plasma

---

**Haematology**

- Haematocrit
- Haemoglobin
  - Reticulocyte count (reflex test if Hb outside normal range)
- RBC/Erythrocytes
- WBC/Leukocytes
- Platelet count/Thrombocytes
- Differential automatic (relative and absolute count):  
Neutrophils, eosinophils, basophils, monocytes, lymphocytes

---

**Clinical chemistry**

- Albumin
  - ALP
  - $\gamma$ -GT (gamma-glutamyl transferase)  
(reflex test triggered by elevated ALP on two sequential measures)
  - ALT (alanine aminotransaminase, SGPT)
  - AST (aspartate aminotransaminase, SGOT)
  - Bicarbonate
  - Bilirubin total, fractionated if increased
  - Calcium
  - Chloride
  - Creatinine
  - Creatine kinase (CK)
  - CK-MB, troponin (reflex tests if CK is elevated)
  - Lactate dehydrogenase (LDH)
  - Lipase
  - Magnesium
  - Phosphate
  - Potassium
  - Protein total
  - Sodium
  - TSH (only at Visit 1)
  - Urea (BUN)
  - Uric acid
  - Cholesterol (total)
  - HDL cholesterol
  - Calculated LDL cholesterol
  - Triglycerides (reflex test for direct measurement of LDL cholesterol triggered if triglycerides are >400 mg/dL or 4.52 mmol/L)
-

Table 5.3.3: 1 Safety laboratory parameters – whole blood, serum or plasma  
(continued)

**Bone Marker (only at selected visits)**

- iPTH
- 25OH Vitamin D
- NTx in Urine

**FFA and Ketone bodies (only at selected visits)**

- Total ketone body
- Acetoacetic acid
- 3-hydroxybutyric acid
- Free fatty acid (FFA)

Table 5.3.3: 2 Safety laboratory parameters – urine

**Urinalysis**

**Semi quantitative (dipstick)**

- Nitrite\*
- Protein
- Ketone
- Urine pH
- Leukocyte esterase (for WBC)\*

**Quantitative**

- Albumin
- Creatinine

**Microscopic analysis**

Will be performed as reflex test if any of the semi quantitative tests/dipsticks are abnormal:

- Urine RBC/Erythrocyte
- Urine WBC/Leukocytes
- Urine sediment microscopic examination
- Urine culture (including antibiogram test) :
  - reflex test triggered by positive leukocyte esterase (for WBC) and/or nitrite in the semi-quantitative test/dipstick

\* Nitrite and leukocyte esterase (for WBC) will be determined both locally on site (not recorded in eCRF) and via central lab. A positive result at site triggers the sampling of mid-stream urine for urine culture.

Albumin/creatinine ratio in spot urine will be calculated at the central lab.

Glomerular filtration rate

The eGFR will be derived from serum creatinine values for Japanese equation:

$$\text{eGFR (mL/min/1.73m}^2\text{)} = 194 \times [\text{Screatinine (mg/dL)}]^{-1.094} \times [\text{age}]^{-0.287} \times [0.739 \text{ if patient is female}]$$

Renal function impairment will be classified in the following way:

- No renal function impairment:  $\text{eGFR} \geq 90 \text{ mL/min/1.73m}^2$ ;
- Mild renal function impairment:  $\text{eGFR} 60 \text{ to } <90 \text{ mL/min/1.73m}^2$ ;
- Moderate renal function impairment:  $\text{eGFR} 30 \text{ to } <60 \text{ mL/min/1.73m}^2$ ;
- Severe renal function impairment:  $\text{eGFR} <30 \text{ mL/min/1.73m}^2$ .

These classes of renal impairment will be the basis for stratification of subgroup analysis.

#### Pregnancy testing

Pregnancy testing (urine) will be performed in female patients of child bearing potential only according to the time points indicated in the [flow chart](#).

#### Criteria for hypoglycaemic events

Every episode of glucose concentrations  $\leq 70$  mg/dL (3.9 mmol/L) should be documented in the eCRF with the respective time and date of occurrence. Any hypoglycaemia with glucose concentrations  $< 54$  mg/dL ( $< 3.0$  mmol/L) and all symptomatic and severe hypoglycaemias should be documented as an AE "hypoglycaemic event".

For the analysis, all hypoglycaemias will be classified according to the following criteria:

- Asymptomatic hypoglycaemia: event not accompanied by typical symptoms of hypoglycaemia but with a measured glucose concentrations  $\leq 70$  mg/dL (3.9 mmol/L)
- Documented symptomatic hypoglycaemia with glucose concentrations  $\geq 54$  mg/dL and  $\leq 70$  mg/dL ( $\geq 3.0$  mmol/L and  $\leq 3.9$  mmol/L): event accompanied by typical symptoms of hypoglycaemia
- Documented symptomatic hypoglycaemia with glucose concentrations  $< 54$  mg/dL ( $< 3.0$  mmol/L): event accompanied by typical symptoms of hypoglycaemia but no need for external assistance
- Severe hypoglycaemic episode: event requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions

#### Follow-up on suspicion for urinary tract infections

Patients having a history of chronic/recurrent urinary tract infections (UTIs) or genital tract infections (GTIs) or an acute episode of UTI or GTI at screening will be identified and this condition has to be documented as medical history or baseline condition in the eCRF, respectively.

For documentation of acute urinary tract infections during trial conduct, the following measures have to be taken:

- In any case of suspected UTI (symptomatic or asymptomatic) a urine culture sample has to be taken and sent to the central lab for confirmation of the diagnosis (including antibiogram).
- To be able to identify asymptomatic UTIs immediately, a dipstick-test (leukocyte esterase [for WBC] and Nitrite) will be performed at the site at each safety visit with urinalysis. In case of a positive result at site, a urine culture sample has to be taken and sent to the central lab for confirmation of the diagnosis (including antibiogram).

### **5.3.4 Electrocardiogram**

Printed paper traces from 12 lead ECGs (I, II, III, aVR, aVL, aVF, V1-V6) will be collected as described in flow chart for all patients. In the event of any cardiac symptoms (i.e. suspicion of heart rhythm disorders or cardiac ischaemia), an additional ECG will be

recorded. All ECGs will be evaluated, (signed, dated and commented upon) by the investigator and stored locally. Any clinically relevant changes in the ECG will be reported as AEs (see [Section 5.3.6](#)) and followed up and/or treated locally until normal or stable condition.

Any ECG abnormalities will be carefully monitored and if necessary the patient will be removed from the trial and medically treated.

Investigators will use the ECG machine available at the site. BI will not provide ECG machine centrally.

### 5.3.5 Other safety parameters

#### Self-Monitoring blood Glucose (SMBG)

Patients who are eligible for screening phase (Visit 1) will be provided at the following visit with SMBG equipment and supplies for use at home during the study periods. Instructions on the proper use of the SMBG equipment will be provided by the study staff. The patient will be asked to record the results of the SMBG test on a SMBG Testing Log that will be included in the patients source document file. Only in the case of linked AEs or of hypoglycaemia, the single SMBG value will be recorded in the eCRF.

Throughout the whole trial participation, SMBG testing is recommended to be done daily but should be performed at least weekly in the fasted state at morning and at any time the patient is symptomatic, i.e., experiences signs/symptoms of hyper- or hypoglycaemia. If the results of a SMBG test reveal glucose values of >270 mg/dL (15.0 mmol/L) after an overnight fast up to Visit 10, the patient should contact the site. The investigator should ask the patient to visit the site for FPG determination as soon as possible, preferably on the next day. The investigator will take two blood samples, one for local determination of FPG for acute patient management, and one for central laboratory determination for trial analysis. If two consecutive measurements at either the local or central laboratory, or SMBG on different days (at least one measurement has to be done at the local or central lab) reveal overnight fasted blood glucose of >270 mg/dL (15.0 mmol/L), then the patient should be withdrawn from the trial (see [Section 3.3.3](#)).

After Visit 10 if the results of a SMBG test reveal glucose values of >240 mg/dL (13.3 mmol/L) after an overnight fast, the patient should contact the site. The investigator should follow the instructions given in [Section 3.3.4.1](#).

### 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 pharmaceutical 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.

### **Serious adverse event**

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

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

Life-threatening in this context 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.

Every new occurrence of cancer must be reported as a serious event regardless of the duration between discontinuation of the drug and the occurrence of the cancer.

The following events will be handled as “deemed serious for any other reason”. An AE which possibly leads to disability will be reported as an SAE.

### **AEs considered “Always Serious”**

In accordance with the European Medicines Agency initiative on Important Medical Events, Boehringer Ingelheim has set up a list of 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 in [Section 5.3.7](#).

### **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, see [Section 5.3.7](#).

The following are considered as AESIs:

Metabolic acidosis, ketoacidosis and diabetic ketoacidosis (DKA)

In case of metabolic acidosis, ketoacidosis and DKA further investigations should be done according to the medical judgement and the clinical course until a diagnosis is made and/or the patient is recovered.

DKA is defined as a state in which a severe shortage of insulin and an increase in counter regulatory hormones combine to induce hyperglycemia ( $\geq 250$  mg/dL), hyperketonemia (increased  $\beta$ -hydroxybutyric acid), and acidosis ( $\text{pH} < 7.30$ ; bicarbonate concentration  $< 18$  mEq/L), and as defined by the Japanese guideline, Evidence-based Practice Guideline for the Treatment for Diabetes in Japan 2013 [[R13-3738](#)].

Investigators should note that not all criteria in the described above need to apply for the diagnosis of DKA, and clinical judgement should also be taken into consideration. Due to its mechanism of action, empagliflozin may potentially modify the clinical presentation of DKA which may occur at lower plasma glucose levels than stated above.

Hepatic injury

A hepatic injury is defined by the following alterations of hepatic laboratory parameters at randomisation at Visit 7:

- An elevation of AST and/or ALT  $\geq 3$  fold ULN combined with an elevation of total bilirubin  $\geq 2$  fold ULN measured in the same blood draw sample, and/or
- Marked peak aminotransferase (ALT, and/or AST) elevations  $\geq 5$  fold ULN

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 the RDC system.

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.

Decreased renal function

A decreased renal function is defined by the following alterations of renal laboratory parameters:

- Creatinine value shows a  $\geq 2$  fold increase from baseline and is above the upper limit of normal (ULN)

The patient with any of the events is mentioned above need to be followed up appropriately. The investigator should consider which, if any, concomitant therapies should not be taken during evaluation. Discontinued treatments can be reintroduced per investigator discretion.

For any of these AESI, the investigator should report the event to the local pharmacovigilance centre immediately (within 24 hours of being informed, and without



waiting for confirmation of the result via a second measurement) on the SAE form, even if they do not meet any of the seriousness criteria.

The investigator should collect the relevant unscheduled laboratory sample(s) as soon as possible (i.e. lipase, creatinine, or hepatic enzymes). Further follow-up laboratory tests should be done according to medical judgement depending on the clinical course.

#### Events involving lower limb amputation

This definition includes amputation (i.e. resection of a limb through a bone), disarticulation (i.e. resection of a limb through a joint) and auto-amputations (i.e. spontaneous separation of non-viable portion of the lower limb).

Not included in this definition are debridement (removal of callus or dead tissue), procedures on a stump (like stump revision, drainage of an abscess, wound revision etc.) and other procedures (e.g., nail resection or removal) without a concomitant resection of a limb (amputation or disarticulation).

Each lower limb amputation, disarticulation, or auto-amputation should be reported separately. The SAE report should include the date of the procedure, the level of amputation or disarticulation, the medical condition(s) leading to the procedure and if the patient had some of the known risk factor(s) for lower limb amputation.

#### Intensity of AEs

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

Mild:	Awareness of sign(s) or symptom(s) 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

Medical judgement should be used to determine the relationship, considering all relevant factors, including pattern of reaction, temporal relationship, de-challenge or re-challenge, confounding factors such as concomitant medication, concomitant diseases and relevant history. Assessment of causal relationship should be recorded in the eCRFs. The reason for the decision on causal relationship other than the related listed AEs in the respective IBs [[c01838761](#)]. In addition to that the Japanese package insert of empagliflozin is used to assess local expectedness in Japan.

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

### **5.3.7 Adverse event collection and reporting**

#### **AE Collection**

The following must be collected and documented on the appropriate eCRF 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.
- 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.

The REP is defined as a period of 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 (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 (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.

All SAEs and AESIs must be reported immediately to the head of the trial site. 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 eCRF pages and the BI SAE form, e.g. onset, end date, intensity, treatment required, outcome, seriousness, and action taken with the investigational drugs. The investigator should determine the causal relationship to the trial medication, the trial procedures outlined under [Section 6.2](#), and any possible interactions between the investigational drugs and the AMP.

The following should also be recorded as an (S)AE in the eCRF 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 characterized, or no further information can be obtained.

## **Pregnancy**

In rare cases that a female patient or a female partner to a male patient participating in this clinical trial becomes pregnant after having taken trial medication, the investigator must report immediately (within 24 hours) any drug exposure during pregnancy (DEDP) to the sponsor pharmacovigilance. Pregnancy Monitoring Form for Clinical Trial (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).

As pregnancy itself is not to be reported as an AE, in the absence of an accompanying SAE, only the Pregnancy Monitoring Form for Clinical Trials and not the SAE form is to be completed. If there is an SAE/AESI associated with the pregnancy, then the SAE/AESI has to be reported on the SAE form in addition.

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

## **5.4 DRUG CONCENTRATION MEASUREMENTS AND PHARMACOKINETICS**

Not Applicable

## **5.5 ASSESSMENT OF EXPLORATORY BIOMARKERS**

Not Applicable

## **5.6 OTHER ASSESSMENTS**

No other assessment such as pharmacogenomics samples will be performed in this study.

## **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 OAD, and they are widely used in this kind of study.

Therefore, all measurements applied in this trial are appropriate.

## 6. INVESTIGATIONAL PLAN

### 6.1 VISIT SCHEDULE

All trial visits, except for screening (Visit 1), should take place between 7:00 AM and 11:00 AM. If a patient mistakenly takes trial medication in the morning of a visit before attending the clinic (excluding visits starting before randomisation) or comes in fed condition 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 of 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

Trial procedures to be performed at each visit are listed in the [Flow chart](#) and the respective protocol sections. Explanations of procedures are provided in [Section 5](#). Additional details regarding visit procedures are provided below. Please also reference the RDC instructions provided in the ISF for clarification on eCRF issues.

All visits, except screening (Visit 1), must be performed in fasted state (at least 10 hours with no food but only water).

At the end of every visit from Visit 2 to 17 the patient must be reminded to bring SMBG log and the dispensed medication kit (from Visit 7) at the next scheduled visit. Preferably, a phone call to remind the patient must take place one or two days before the patient's next visit.

#### 6.2.1 Screening and run-in period

##### Screening Period (Visit 1)

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

Once they have consented, the patient is considered to be enrolled in the trial and should then be recorded in the enrolment log, and screening will be started. The patient should be registered in the IRT and record in the eCRF as a screened patient at Visit 1.

Blood Pressure (BP) and ECG should always be measured before any blood samples are taken. For details regarding the correct method for measuring BP, see [Appendix 10.1](#).

At the end of the screening visit, patients will be given a food intake log which is requested to be completed for three consecutive days in the week prior to the next visit.

Details of any patient who is screened for the study but is found to be ineligible must be entered in an enrolment log and documented in the eCRF.

Those patients who are treated with one OAD and qualify after Visit 1 procedures will enter a 14-week switch period (Visit 2).

Those patients who are treated with liraglutide plus one OAD and qualify after Visit 1 procedures will enter a 10-week washout period (Visit 4).

Those patients who are treated with liraglutide alone will directly enter the placebo run-in period for 2-week (Visit 6).

All patients on Visit 1 do not proceed to the next visit until laboratory results are ascertained by investigator.

#### Switch Period (Visit 2 to Visit 5)

During this period, the patients should stop their OAD and start 0.3 mg/day liraglutide at Visit 2.

Following Visit 2 procedures, the patient will return to the clinic at Visit 3 (at least 1 week interval is necessary between Visit 2 and Visit 3) and are treated with 0.6 mg/day liraglutide. Following Visit 3 procedures, the patients will return to the clinic at Visit 4 (at least 1 week interval is necessary between Visit 3 and Visit 4) and are treated with 0.9 mg/day liraglutide. Dose titration of liraglutide should complete within 2-4 weeks in accordance with Japanese label. Following Visit 4 procedures, the patients will return to the clinic for regularly scheduled follow up visit, Visit 5 and Visit 6 as specified in the [Flow chart](#).

Patients will also be given SMBG equipment and all the necessary supplies to use it at Visit 2. Instruction on the proper use of SMBG equipment will be provided by site staff. Please refer to [Section 5.3.5](#) (Self-Monitoring blood Glucose) for the details of measurement frequency and the record.

If the SMBG test reveals an overnight fasted blood glucose of >270 mg/dL (15.0 mmol/L), the patient should contact the study site for a visit as soon as possible, ideally the next day. For details of handling of SMBG test, see [Section 5.3.5](#).

Blood Pressure should always be measured before any blood samples are taken. For details regarding the correct method for measuring BP, see [Appendix 10.1](#).

At the end of the each visit, patients will be given a food intake log which is requested to be completed for three consecutive days in the week prior to the next visit.

#### Washout Period (Visit 4 to Visit 5)

During this period, the patients should stop currently receiving OAD. Following Visit 4 procedures, the patients will return to the clinic for regularly scheduled follow up visit, Visit 5 and Visit 6 as specified in the [Flow Chart](#).

Patients will also be given SMBG equipment and all the necessary supplies to use it at Visit 4. Instruction on the proper use of SMBG equipment will be provided by site staff. Please refer to [Section 5.3.5](#) (Self-Monitoring blood Glucose) for the details of measurement frequency and the record.

If SMBG test reveals an overnight fasted blood glucose of  $>270$  mg/dL (15.0 mmol/L), the patient should contact the study site for a visit as soon as possible, ideally the next day. For details of handling of SMBG test, see [Section 5.3.5](#).

Blood Pressure should always be measured before any blood samples are taken. For details regarding the correct method for measuring BP, see [Appendix 10.1](#).

At the end of the each visit, patients will be given a food intake log which is requested to be completed for 3 consecutive days in the week prior to the next visit.

#### Placebo Run-in Period (Visit 6)

At Visit 6, the patients should be fasting (no food or drinks but water only for at least 10 hours) prior to each visit.

Those patients who are treated with liraglutide alone will be provided SMBG equipment and supplies at Visit 6. Instruction on the proper use of the SMBG equipment will be provided by site staff. Please refer to [Section 5.3.5](#) (Self-Monitoring blood Glucose) for the details of measurement frequency and the record.

If SMBG test reveals an overnight fasted blood glucose of  $>270$  mg/dL (15.0 mmol/L), the patient should contact the study site for a visit as soon as possible, ideally the next day. For details of handling of SMBG test, see [Section 5.3.5](#).

Blood Pressure should always be measured before any blood samples are taken. For details regarding the correct method for measuring BP, see [Appendix 10.1](#).

At the end of Visit 6, patients will be given a food intake log which is requested to be completed for three consecutive days in the week prior to the next visit (Visit 7).

Following Visit 6 procedures, a run-in kit will be dispensed through the IRT. Trial medication for the day of the visit will be administered at the investigational site.

Patients with HbA1c  $\geq 7.0\%$  and  $\leq 10.0\%$  at Visit 6 will be contacted and asked to return to the clinic at Visit 7 to complete the eligibility assessments and baseline measurements.

Patients with HbA1c outside the previously mentioned range will also be contacted and will be asked to return to the clinic soon.

### 6.2.2 Treatment period

The treatment period is from Visit 7 to Visit 15/EOT. Patients will be dispensed medication at each of these visits (except Visit 7a and Visit 15/EOT) and will receive a new kit number through the IRT on each occasion.

Patients must satisfy all inclusion and exclusion criteria prior to randomisation (see [Section 3.3](#)). In addition, if the placebo run-in period, there is any indication that a patient's conditions of T2DM are not stable enough for the patient to complete the study or that the patient will not be compliant with the study medication or restrictions, the patient should not be randomised to the treatment.

The date of visit should be determined based on the date of Visit 7 and visits should occur within the allowed time frame shown in the [Flow chart](#).

At Visit 7a, the investigator or a designated site staff member makes a call to patients to confirm patient's safety through checking patient's SMBG results, adverse events and concomitant therapies. The investigator should ask the patient to visit the clinic, if determined by the investigator as concerning the patient's safety.

Assessments should be performed as mentioned in the [Flow chart](#) and the respective protocol sections. Randomisation/treatment allocation and dispensing of study medication should be the last activity at each visit. Trial medication for the day of the visit will be administered at the investigational site after all necessary procedures are completed. The time patients visit the investigational site should be arranged to allow patients to take the trial medication at the same time as usual.

At the end of each visit, patients will be given a food intake log which is requested to be completed for three consecutive days in the week prior to the next visit.

Visit 15/EOT will need to be performed for any patients who complete/discontinue the study, i.e. both for patients who complete the full 52-week double-blind treatment period and for patients who prematurely discontinue the study.

Patients who prematurely discontinue the study should be registered as withdrawn, and patients who complete the full 52-week double-blind treatment period should be registered as completed in the IRT.

### 6.2.3 Follow Up Period and Trial Completion

For all patients completing the study according to the protocol without persisting AE at Visit 15/EOT, a follow-up visit (Visit 16) can be performed as a phone visit by the investigator at the end of the follow-up period of 7 days. Visit 16 should occur 7 days after Visit 15/EOT within the timeframe (+7 days).



During the follow-up period, results of a SMBG test reveal blood glucose of >240 mg/dL (13.3 mmol/L) after an overnight fast the patient should contact the site, and the investigator should follow procedure described in the [Sections 4.2.1](#) and [3.3.4.1](#).

The following should be confirmed and recorded at Visit 16 via telephone:

- Concomitant therapies
- Any AEs
- SMBG result

Patients completing the study according to the protocol with persisting AE at Visit 15/EOT and patients who prematurely discontinue the study, the patient should return to follow up visit (Visit 16, 7 days after Visit 15/EOT). The following examinations should be performed at Visit 16 in addition to the above mentioned items:

- Physical examination
- Vital signs
- Collection of blood (include FPG sample) and urine samples for safety laboratory evaluation.

## **7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE**

### **7.1 STATISTICAL DESIGN - MODEL**

This is a 52-week, randomised, multi-centre, parallel group study to investigate the safety and efficacy of empagliflozin (10 mg or 25 mg administered orally once daily) as add-on therapy to GLP-1 RA (i.e., liraglutide) in patients with T2DM with insufficient glycaemic control.

Patients to be enrolled in this study are those with T2DM who have insufficient glycaemic control despite background monotherapy with liraglutide. Empagliflozin 10 mg or 25 mg is administered with liraglutide over 52 weeks. Patients will be randomly assigned to empagliflozin 10 mg or 25 mg.

The primary endpoint in this trial is frequency of patients with drug-related adverse events (AE) during 52 weeks of treatment. The secondary endpoint in this study is the change from baseline in HbA1c after 52 weeks of treatment.

Based upon these design considerations, the trial will be analysed using descriptive statistics for the primary endpoint. For the secondary endpoint, the HbA1c changes from baseline is considered as normally distributed based on experiences with similar endpoints in other trials and literature data. Therefore, the statistical model used for the secondary endpoint is a restricted maximum likelihood (REML)-based mixed model with repeated measures (MMRM) including the fixed effects treatment, baseline renal function, prior use of antidiabetic agents, visit, treatment-by-visit interaction and the covariate baseline HbA1c, baseline HbA1c-by-visit interaction.

### **7.2 NULL AND ALTERNATIVE HYPOTHESES**

There will be no confirmatory statistical testing in this study.

### **7.3 PLANNED ANALYSES**

No confirmatory statistical analysis is planned. The statistical analysis will be based on the following populations. With regard to each efficacy and safety endpoint during the randomised 52-week treatment period, the term "baseline" refers to the last observed measurement prior to the administration of any randomised trial medication.

#### Treated set

The treated set (TS) will consist of all patients who were randomised and treated with at least one dose of the study drug. The assignment of patients to treatment group will be based on the first study drug intake in the double-blind treatment period.

#### Full analysis set

The full analysis set (FAS) will consist of all patients in TS who were treated with at least one dose of the randomised study drug and had a baseline HbA1c assessment. The assignment of patients to treatment groups will be based on the randomised study drug at time of randomisation.

### 7.3.1 Primary endpoint analyses

The primary endpoint in this trial is frequency of patients with drug-related adverse events (AE) during 52 weeks of treatment, which will be analysed in the same way as other safety analysis. More details are given in [Section 7.3.4](#).

### 7.3.2 Secondary endpoint analyses

#### HbA1c

The change from baseline in HbA1c after 52 weeks of treatment will be calculated on FAS by treatment using MMRM. The statistical model is as follows:

HbA1c change from baseline = overall mean + treatment + baseline HbA1c + baseline renal function + prior use of antidiabetic agents + visit + treatment-by-visit + baseline HbA1c-by-visit + error

Analyses will include “treatment”, “baseline renal function”, “prior use of antidiabetic agents”, “visit” and “treatment-by-visit” interaction as fixed effects, “baseline HbA1c”, and “baseline HbA1c-by-visit” interaction as covariates. The term “baseline HbA1c” refers to the last HbA1c assessment prior to the administration of any randomised medication (HbA1c values at Visit 7) and not to the HbA1c measurement used for the stratification in the randomisation. “Baseline renal function” will be a classification effect derived from the categorisation of eGFR at baseline. Regarding “prior use of antidiabetic agents”, patients will be classified as liraglutide only, OAD only or liraglutide plus OAD. An unstructured covariance structure will be used to model the within-patient measurements. If the analysis fails to converge, the following covariance structure will be tested: compound symmetry, variance components and Toeplitz. The covariance structure converging to the best fit, as determined by Akaike’s information criterion, will be used. The Kenward-Roger approximation will be used to estimate the denominator degrees of freedom. This model will also be used to evaluate the change from baseline in HbA1c overtime during the 52-week treatment period.

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 will also additionally set to missing all values measured after the restricted antidiabetic medication during the trial (See [Section 4.2.2](#))

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

The last available on-treatment HbA1c value is defined as the last available HbA1c value measured up to a period of seven days after the last dose of the randomised study medication or the last available HbA1c value prior to the restricted antidiabetic medication during the trial (See [Section 4.2.2](#)).

[REDACTED]

#### 7.3.4 Safety analyses

All treated patients will be included in the safety analysis. 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 adverse events will concentrate on treatment-emergent adverse events. For this, all AEs occurring between start of study treatment and end of the residual effect period (REP) will be considered “treatment-emergent”. The REP is defined as a period of 7 days after the last dose of double-blind trial medication. Adverse events that start before first study drug intake and deteriorate under treatment will also be considered as ‘treatment-emergent’. AEs occurring one day before the first intake of the double-blind treatment will be assigned to the ‘screening period’. AEs occurring between the first intake of the double-blind treatment and 7 days after the last intake of double-blind treatment will be assigned to ‘double-blind treatment period’ for evaluation. AEs occurring thereafter will be assigned to ‘post-treatment period’.

Frequency, severity, and causal relationship of adverse events 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).

Number of patients with hypoglycaemia episodes, intensity, the presence of typical hypoglycaemia symptoms and the need for assistance due to hypoglycaemia will be displayed.

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 observed, during the course of the trial and at the end-of-trial evaluation will be compared to findings before the start of double-blind treatment.

### **7.3.5 Pharmacokinetic analyses**

Not applicable

## **7.4 INTERIM ANALYSES**

No interim analysis is planned for this study.

## **7.5 HANDLING OF MISSING DATA**

As defined for the MMRM, missing data are handled implicitly by the statistical model, rather than by using any imputation (see [Section 7.3.2](#)). In case of ANCOVA analyses, missing data will be imputed using the LOCF approach. If no value after first intake of trial medication is available, the baseline value will be used for HbA1c. Further details will be provided in the TSAP.

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

## **7.6 RANDOMISATION**

The trial will be performed as a double-blind design with respect to the two active dose groups of empagliflozin. Eligible patients assessed by investigator will be randomised in blocks to the two study treatments in a 1:1 ratio. The randomisation will be stratified by the following factors:

- Pre-randomisation HbA1c value ( $<8.0\%$ ,  $\geq 8.0\%$ ) using the Visit 1 HbA1c values for patients pre-treated with liraglutide alone and Visit 6 HbA1c values for other patients
- Pre-randomisation eGFR value ( $\geq 90$  mL/min/1.73m<sup>2</sup>, 60 to  $<90$  mL/min/1.73m<sup>2</sup>, 45 to  $<60$  mL/min/1.73m<sup>2</sup>) calculated based on Visit 6 creatinine values.

The randomisation of patients to the treatment groups will be performed via an IRT. BI will arrange for the randomisation as well as packaging and labelling of trial medication. The randomisation list will be generated using a validated system, which involves a pseudorandom number generator and a supplied seed number so that the resulting allocation of medication numbers to treatment is both reproducible and non-predictable. The access to the randomisation codes will be controlled and documented.

## 7.7 DETERMINATION OF SAMPLE SIZE

The draft version of Japanese guideline 'Clinical Evaluation Guidelines for Antihyperglycemic Drugs' [[R15-2907](#)] requires one year long-term study on background therapies with several approved antidiabetic drugs. The guideline requires observing 50 to 100 patients during one year for each background therapy. The sample size for this trial was determined according to the outcome of the PMDA consultation on December 2014. At least 50 patients as 52-week completers including two doses were necessary for the background therapy with GLP-1 RA for safety evaluation.

Based on the above, and allowing for a discontinuation/dropout rate of approximately 20% during the trial, the sample size for empagliflozin 10 mg and 25 mg were determined at 32 per arm in the GLP-1 RA background group.

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

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 Harmonised Tripartite Guideline for Good Clinical Practice (GCP), relevant BI Standard Operating Procedures (SOPs), and the Japanese GCP regulations (Ministry of Health and Welfare Ordinance No. 28, March 27, 1997) and the Japanese GPSP regulations (Ministry of Health, Labour and Welfare Ordinance No. 171, December 20, 2004). 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 patients against any immediate hazard, and also of any serious breaches of the protocol, or of ICH GCP and the Japanese GCP regulations (Ministry of Health and Welfare Ordinance No. 28, March 27, 1997).

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

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

### **8.1 TRIAL APPROVAL, PATIENT INFORMATION, AND INFORMED CONSENT**

This trial will be initiated only after all required legal documentation has been reviewed and approved by the respective Institutional Review Board (IRB) 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 by using the patient information form, which is prepared avoiding the use of technical terms and expressions. The patient is given sufficient time to consider participation in the trial. The investigator obtains written consent of the patient's own free will with the informed consent form after confirming that

the patient understands the contents. The investigator must sign and date the informed consent form. If a trial collaborator has given a supplementary explanation, the trial collaborator also signs 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.

## **8.2 DATA QUALITY ASSURANCE**

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

eCRFs for individual patients will be provided by the sponsor via remote data capture. See [Section 4.1.5.2](#) for rules about emergency code breaks. For drug accountability, refer to [Section 4.1.8](#).

### **8.3.1 Source documents**

Source documents provide evidence for the existence of the patient and substantiate the integrity of the data collected. Source documents are filed at the Investigator's site. Data reported on the eCRF must be consistent with the source data or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the trial; current medical records must also be available.

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

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

- ECG results (original or copies of printouts)
- Physical examinations (original documentation)

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

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



review all eCRFs, and written informed consents. The accuracy of the data will be verified by reviewing the documents described in [Section 8.3.1](#).

### **8.3.3 Storage period of records**

#### Trial sites:

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

#### Sponsor:

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

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

### **8.4.1 Listedness**

To fulfil the regulatory requirements for expedited safety reporting, the sponsor evaluates whether a particular adverse event is "listed", i.e. is a known side effect of the drug or not. Therefore a unique reference document for the evaluation of listedness needs to be provided. For empagliflozin, this is the current version of the IB [[c01838761](#)]. In addition to that the Japanese package insert of empagliflozin is used to assess local expectedness in Japan. For liraglutide, the reference document is the EPAR product information. The current versions of these reference documents are to be provided in the ISF. No AEs are classified as listed for matching placebo, study design, or invasive procedures.

### **8.4.2 Expedited reporting to health authorities and IEC / IRB**

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

## **8.5 STATEMENT OF CONFIDENTIALITY**

Individual patient medical information obtained as a result of this trial is considered confidential and disclosure to third parties is prohibited with the exceptions noted below. Patient confidentiality will be ensured by using patient identification code numbers. Treatment data may be given to the patient's personal physician or to other appropriate medical personnel responsible for the patient's welfare. Data generated as a result of the trial need to be available for inspection on request by the participating physicians, the sponsor's representatives, by the IRB and the regulatory authorities.

## **8.6 END OF TRIAL**

The end of the trial is defined as last patient out.

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

## **8.7 PROTOCOL VIOLATIONS**

The investigator should document any deviation from the protocol regardless of their reasons. Only when the protocol was not followed in order to avoid an immediate hazard to trial patients or for other medically compelling reason, the principal investigator should prepare and submit the records explaining the reasons thereof to the sponsor, and retain a copy of the records.

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

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

## 9. REFERENCES

### 9.1 PUBLISHED REFERENCES

- R05-0939 Wright EM, Turk E. The sodium/glucose cotransport family SLC5. Pfluegers Archiv - European Journal of Physiology 2004; 447 (5), 510 - 518.
- R10-4692 MHLW Guideline - Clinical Evaluation Guidelines for Oral Antihyperglycaemic Drugs
- R13-3738 Evidence-based Practice Guideline for the Treatment for Diabetes in Japan 2013
- R14-5435 American Diabetes Association Hyperglycemic crises in diabetes. Diabetes Care 27 (Suppl. 1), S94 - S102, 2004
- R14-4302 The Japan Diabetes Society. Treatment Guide for Diabetes 2014-2015. Tokyo, Bunkodo; 2014.
- R15-2907 MHLW draft revised guideline - Clinical Evaluation Guidelines for Antihyperglycemic Drugs
- R15-2908 The Japan Diabetes Society. Recommendation from “Committee on the proper use of SGLT2” inhibitors
- R13-3738 Evidence-based Practice Guideline for the Treatment for Diabetes in Japan 2013
- R14-5435 American Diabetes Association Hyperglycemic crises in diabetes. Diabetes Care 27 (Suppl. 1), S94 - S102, 2004

### 9.2 UNPUBLISHED REFERENCES

- c01838761 Investigator’s Brochure: empagliflozin and empagliflozin/linagliptin FDC, Indication: type 2 diabetes mellitus, Project No. 1275.P1, 1245.P1, Current Version
- U13-1730-01 [REDACTED] A 52-week, randomised, multi-centre, parallel group study to investigate the safety and efficacy of BI 10773 (10 mg or 25 mg administered orally once daily) as add-on therapy to an oral antidiabetic drug (sulfonylurea, biguanide, thiazolidinedione, alpha glucosidase inhibitor, DPP-IV inhibitor, or glinide) in patients with type 2 diabetes mellitus with insufficient glycaemic control. BI Trial No. 1245.52. 26 September 2013.

## **10. APPENDICES**

### **10.1 BLOOD PRESSURE MEASUREMENT PROCEDURE**

The preferred method for blood pressure measurement is electronic sphygmomanometer provided by NBI. If, for some reason, the electronic sphygmomanometer cannot be used for the measurement of blood pressure, a standard mercury sphygmomanometer may be used as an alternate method.

Initially, blood pressure should be taken 3 times in both arms. If the pressures differ by more than 10 mmHg (as in the presence of a subclavian steal syndrome), the arm with the higher pressure (systolic or – if needed to decide- diastolic) should be used for subsequent measurements.

Blood pressure measurements should be performed on the same arm and, if possible, by the same person. The same method must be used throughout the trial, for a given patient, i.e. if a patient receives the first blood pressure measurement for example with an electronic device, the same method and device should be used throughout the study for this patient (without switching to manual blood pressure measurement). On the other hand, inter-patients variability is acceptable, i.e. a study site is allowed to consistently use an electronic device to measure the blood pressure in a given patient throughout the study and a manual technique in another patient.

After patients have rested quietly, in the seated position for 5 minutes, 3 times of blood pressure measurements will be taken approximately 2 minutes apart. The seated pulse rate at the second measurement will be used as the study data when an electronic device is used for the blood pressure measurement. In case of the measurement by using standard mercury sphygmomanometer, the seated pulse rate will be taken during the 2-minute interval between the second and third blood pressure reading.

## 11. DESCRIPTION OF GLOBAL AMENDMENT(S)

<b>Number of global amendment</b>		1
<b>Date of CTP revision</b>		13 October 2016
<b>EudraCT number</b>		
<b>BI Trial number</b>		1245.106
<b>BI Investigational Product(s)</b>		Jardiance <sup>®</sup> , Empagliflozin
<b>Title of protocol</b>		A 52-week randomised, double-blind, parallel group, safety and efficacy study of empagliflozin once daily as add-on therapy to glucagon-like peptide-1 receptor agonist in Japanese type 2 diabetes mellitus patients with insufficient glycaemic control
<b>To be implemented only after approval of the IRB / IEC / Competent Authorities</b>		x
<b>To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval</b>		
<b>Can be implemented without IRB / IEC / Competent Authority approval as changes involve logistical or administrative aspects only</b>		
<b>Section to be changed</b>	1	Throughout the whole protocol
<b>Description of change</b>		Randomization  To be changed to:  Randomisation
<b>Rationale for change</b>		Typographical error
<b>Section to be changed</b>	2	Abbreviations
<b>Description of change</b>		european clinical trials database  To be changed to:  European Clinical Trials Database
<b>Rationale for change</b>		Typographical error
<b>Section to be changed</b>	3	Section 1.1
<b>Description of change</b>		normoglycemia

		To be changed to: normoglycaemia
<b>Rationale for change</b>		Typographical error
<b>Section to be changed</b>	4	Throughout the whole protocol
<b>Description of change</b>		antihyperglycemic  To be changed to: antihyperglycaemic
<b>Rationale for change</b>		Typographical error
<b>Section to be changed</b>	5	Throughout the whole protocol
<b>Description of change</b>		therapeutic  To be changed to: therapeautic
<b>Rationale for change</b>		Typographical error
<b>Section to be changed</b>	6	Section 2.3
<b>Description of change</b>		Labolatory  To be changed to: laboratory
<b>Rationale for change</b>		Typographical error
<b>Section to be changed</b>	7	Section 2.3
<b>Description of change</b>		250 mg/dl (14 mmol/l)  To be changed to: 250 mg/dL (14 mmol/L)
<b>Rationale for change</b>		Typographical error
<b>Section to be changed</b>	8	Section 3.1.1
<b>Description of change</b>		co-ordinating investigator  To be changed to: coordinating investigator
<b>Rationale for change</b>		Typographical error
<b>Section to be changed</b>	9	Section 3.2
<b>Description of change</b>		Liraglutide  To be changed to: liraglutide
<b>Rationale for change</b>		Typographical error

<b>Section to be changed</b>	10	Section 3.3
<b>Description of change</b>		<p>pateints</p> <p>To be changed to:</p> <p>patients</p>
<b>Rationale for change</b>		Typographical error
<b>Section to be changed</b>	11	Throughout the whole protocol
<b>Description of change</b>		<p>judgment</p> <p>To be changed to:</p> <p>judgement</p>
<b>Rationale for change</b>		Typographical error
<b>Section to be changed</b>	12	Section 5.3.6.1
<b>Description of change</b>		<p>The following description for “events involving lower limb amputation” is added,</p> <p><b><u>Events involving lower limb amputation</u></b>  <b>This definition includes amputation (i.e. resection of a limb through a bone), disarticulation (i.e. resection of a limb through a joint) and auto-amputations (i.e. spontaneous separation of non-viable portion of the lower limb).</b></p> <p><b>Not included in this definition are debridement (removal of callus or dead tissue), procedures on a stump (like stump revision, drainage of an abscess, wound revision etc.) and other procedures (e.g., nail resection or removal) without a concomitant resection of a limb (amputation or disarticulation).</b></p> <p><b>Each lower limb amputation, disarticulation, or auto-amputation should be reported separately. The SAE report should include the date of the procedure, the level of amputation or disarticulation, the medical condition(s) leading to the procedure and if the patient had some of the known risk factor(s) for lower limb amputation.</b></p>
<b>Rationale for change</b>		To align with the updated AESI definition of empagliflozin project.
<b>Section to be changed</b>	13	Section 7.3.2
<b>Description of change</b>		Categorization

		To be changed to:  categorisation
<b>Rationale for change</b>		Typographical error
<b>Section to be changed</b>	14	Section 7.4
<b>Description of change</b>		interm  To be changed to:  interim
<b>Rationale for change</b>		Typographical error
<b>Section to be changed</b>	15	Section 7.6
<b>Description of change</b>		labeling  To be changed to:  labelling
<b>Rationale for change</b>		Typographical error

<b>Number of global amendment</b>		2
<b>Date of CTP revision</b>		20 January 2017
<b>EudraCT number</b>		
<b>BI Trial number</b>		1245.106
<b>BI Investigational Product(s)</b>		Jardiance®, Empagliflozin
<b>Title of protocol</b>		A 52-week randomised, double-blind, parallel group, safety and efficacy study of empagliflozin once daily as add-on therapy to glucagon-like peptide-1 receptor agonist in Japanese type 2 diabetes mellitus patients with insufficient glycaemic control
<b>To be implemented only after approval of the IRB / IEC / Competent Authorities</b>		X
<b>To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval</b>		
<b>Can be implemented without IRB / IEC / Competent Authority approval as changes involve logistical or administrative aspects only</b>		
<b>Section to be changed</b>	1	Section 3.1.1.2



<b>Description of change</b>	<p>The following section for “Clinical Event Committee for Diabetic ketoacidosis (DKA)” is added,</p> <p><b>An independent external committee (CEC) will be established to adjudicate centrally and in a blinded fashion events suspected of DKA (for further details see <a href="#">Section 5.3.3</a>). The CEC will evaluate whether pre-specified criteria for adjudication endpoints are met.</b></p> <p><b>For any events that qualify for adjudication, study sites will be asked to provide clinical documentation such as laboratory values, discharge summaries etc. to support the external event adjudication.</b></p> <p><b>The tasks and responsibilities of the CEC will be specified in a charter. The CEC will maintain the adjudication results in writing.</b></p>
<b>Rationale for change</b>	<p>To newly align with the DKA adjudication of empagliflozin project.</p>



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**Signatures (obtained electronically)**

Meaning of Signature	Signed by	Date Signed
Author-Trial Clinical Monitor		23 Jan 2017 03:35 CET
Author-Trial Statistician		23 Jan 2017 04:20 CET
Approval-Team Member Medicine		23 Jan 2017 08:32 CET
Approval-Clinical 		26 Jan 2017 14:29 CET
Verification-Paper Signature Completion		02 Feb 2017 07:34 CET

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

Meaning of Signature	Signed by	Date Signed
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