

## Cover Page for Protocol

Sponsor name:	Novo Nordisk A/S
NCT number	NCT02762578
Sponsor trial ID:	NN5401-3598
Official title of study:	A Trial Comparing Efficacy and Safety of Insulin Degludec/Insulin Aspart and BIAsp 30 in Subjects with Type 2 Diabetes
Document date:	20 November 2017

## 16.1.1 Protocol and protocol amendments

### List of contents

<b>Protocol .....</b>	<a href="#">Link</a>
<b>Appendix A - Insulin Titration Guideline.....</b>	<a href="#">Link</a>
<b>Attachment I and II.....</b>	<a href="#">Link</a>
<b>Protocol amendment 1 .....</b>	<a href="#">Link</a>
<b>Protocol amendment 2 .....</b>	<a href="#">Link</a>
<b>Protocol amendment 3 .....</b>	<a href="#">Link</a>

Protocol  
Trial ID: NN5401-3598  
EudraCT No.: 2011-000085-36  
UTN: U1111-1118-8578

~~CONFIDENTIAL~~

Date:  
Version:  
Status:  
Page:

31 May 2017  
4.0  
Final  
1 of 102

**Novo Nordisk**

## Protocol

**Trial ID: NN5401-3598**

**BOOST<sup>®</sup>: INTENSIFY PREMIX/ALL 2**

### **Title:**

**A trial comparing efficacy and safety of  
insulin degludec/insulin aspart and BIAsp 30  
in subjects with type 2 diabetes**

*Redacted protocol  
Includes redaction of personal identifiable information only.*

**Trial phase: 3a**

### **Protocol originators:**



TrialOps 2, Insulin & Devices

This ~~confidential~~ document is the property of Novo Nordisk. ~~No unpublished information contained herein may be disclosed without prior written approval from Novo Nordisk. Access to this document must be restricted to relevant parties.~~

## Table of contents

	Page
<b>Table of contents</b> .....	<b>2</b>
<b>Table of figures</b> .....	<b>6</b>
<b>Table of tables</b> .....	<b>6</b>
<b>List of abbreviations</b> .....	<b>7</b>
<b>1 Summary</b> .....	<b>10</b>
<b>2 Flow chart</b> .....	<b>13</b>
<b>3 Background information and rationale for the trial</b> .....	<b>16</b>
3.1 Rationale for the trial.....	18
<b>4 Objectives and endpoints</b> .....	<b>20</b>
4.1 Objectives .....	20
4.1.1 Primary.....	20
4.1.2 Secondary.....	20
4.2 Endpoints.....	20
4.2.1 Primary.....	20
4.2.2 Confirmatory secondary efficacy endpoints.....	21
4.2.3 Supportive secondary endpoints .....	21
4.2.3.1 Efficacy .....	21
4.2.3.2 Safety.....	22
4.2.3.3 PRO.....	22
<b>5 Trial design</b> .....	<b>23</b>
5.1 Type of trial .....	23
5.2 Rationale for trial design .....	23
5.3 Treatment of subjects .....	24
5.3.1 Treatment after early discontinuation of trial product .....	26
5.4 Rationale for treatment.....	26
<b>6 Trial population</b> .....	<b>28</b>
6.1 Number of subjects .....	28
6.2 Inclusion criteria .....	28
6.3 Exclusion criteria .....	29
6.4 Withdrawal criteria .....	30
6.5 Subject replacement .....	31
6.6 Rationale for trial population.....	31
<b>7 Trial schedule</b> .....	<b>33</b>
<b>8 Methods and assessments</b> .....	<b>34</b>
8.1 Visit procedures .....	34
8.1.1 Screening visit (Visit 1) .....	34
8.1.2 Screening failures .....	35
8.1.2.1 Re-screening .....	35

8.1.3	Randomisation visit (Visit 2) – to follow-up visit (P 30).....	35
8.1.4	Phone contacts .....	36
8.1.5	Unscheduled visits .....	36
8.1.6	Re-scheduled visits .....	36
8.1.7	Withdrawn subjects.....	36
8.2	Concomitant illness and medical history.....	37
8.3	Concomitant medication.....	37
8.4	Diaries .....	37
8.5	Laboratory assessments.....	38
8.6	Other assessments .....	40
8.6.1	Insulin dose .....	40
8.6.2	Physical examination .....	41
8.6.3	Vital signs.....	41
8.6.4	Eye examination .....	41
8.6.5	Electrocardiogram – 12 lead.....	42
8.6.6	Height.....	43
8.6.7	Body weight .....	43
8.6.8	Patient reported outcome questionnaires.....	43
8.6.9	Self measured plasma glucose.....	44
8.6.9.1	2-point profile (SMPG) .....	44
8.6.9.2	9-point profile (SMPG) .....	44
8.7	Adverse events.....	45
8.7.1	Adverse events with additional data collection .....	45
8.7.1.1	Medication errors .....	45
8.7.1.2	Acute coronary syndrome.....	46
8.7.1.3	Cerebrovascular events.....	46
8.7.1.4	Neoplasm.....	47
8.8	Recording of Hypoglycaemia .....	47
8.8.1	Definitions of Hypoglycaemia.....	48
8.8.1.1	Confirmed hypoglycaemia.....	49
8.8.1.2	ADA classification of hypoglycaemia.....	49
8.9	Subject compliance .....	50
<b>9</b>	<b>Trial supplies.....</b>	<b>51</b>
9.1	Trial products.....	51
9.2	Non-investigational medicinal product .....	51
9.3	Labelling.....	51
9.4	Storage, accountability and destruction.....	51
9.4.1	Storage and handling of trial products .....	51
9.4.2	Drug accountability and destruction of trial products.....	53
9.5	Auxiliary supply.....	53
<b>10</b>	<b>Directions for use (DFU)Interactive voice/web response system.....</b>	<b>54</b>
<b>11</b>	<b>Randomisation procedure.....</b>	<b>55</b>
<b>12</b>	<b>Adverse events, technical complaints and pregnancies.....</b>	<b>56</b>
12.1	Definitions .....	56
12.2	Reporting of adverse events.....	60
12.3	Follow-up of adverse events.....	62

12.4	Technical complaints and technical complaint samples	63
12.4.1	Reporting of technical complaints	63
12.4.2	Collection, storage and shipment of technical complaint samples	63
12.5	Pregnancies	64
12.6	Precautions and/or overdose	64
12.7	Committees related to safety	65
12.7.1	Novo Nordisk safety committee	65
12.7.2	Event adjudication committee	65
12.7.2.1	Acute coronary syndrome	67
12.7.2.2	Stroke	68
12.7.2.3	Cardiovascular death	69
<b>13</b>	<b>Case report forms</b>	<b>70</b>
13.1	Corrections to case report forms	70
13.2	Case report form flow	71
<b>14</b>	<b>Monitoring procedures</b>	<b>72</b>
<b>15</b>	<b>Data management</b>	<b>73</b>
<b>16</b>	<b>Computerised systems</b>	<b>74</b>
<b>17</b>	<b>Statistical considerations</b>	<b>75</b>
17.1	Sample size calculation	76
17.2	Definition of analysis sets	78
17.3	Primary endpoint	79
17.4	Secondary endpoints	80
17.4.1	Confirmatory secondary endpoints	80
17.4.2	Supportive secondary endpoints	82
17.4.2.1	Efficacy	82
17.4.2.2	Safety	84
17.4.3	Other assessments	87
17.5	Interim analysis	87
17.6	Sequential safety analysis and safety monitoring	87
17.7	Explorative statistical analysis for pharmacogenetics and biomarkers	87
17.8	PK and/or PD modelling	87
17.9	Health economics and/or patient reported outcomes	87
<b>18</b>	<b>Ethics</b>	<b>89</b>
18.1	Informed consent	89
18.2	Data handling	90
18.3	Premature termination of the trial and/or trial site	90
<b>19</b>	<b>Protocol compliance</b>	<b>91</b>
<b>20</b>	<b>Audits and inspections</b>	<b>92</b>
<b>21</b>	<b>Critical documents</b>	<b>93</b>
<b>22</b>	<b>Responsibilities</b>	<b>94</b>
<b>23</b>	<b>Reports and publications</b>	<b>95</b>
23.1	Communication of results	95
23.1.1	Authorship	96

23.1.2	Site-specific publication(s) by investigator(s) .....	96
23.2	Investigator access to data and review of results .....	96
<b>24</b>	<b>Retention of clinical trial documentation .....</b>	<b>97</b>
<b>25</b>	<b>Institutional Review Boards/Independent Ethics Committees and regulatory authorities .....</b>	<b>98</b>
<b>26</b>	<b>Indemnity statement .....</b>	<b>99</b>
<b>27</b>	<b>References .....</b>	<b>100</b>

**Attachment I – Global List of key staff and relevant departments**

**Attachment II – Country List of key staff and relevant departments**

**Appendix A: Insulin Titration Guideline**

## Table of figures

	Page
Figure 5–1 Trial design .....	23
Figure 8–1 ADA classification of hypoglycaemia.....	50
Figure 12–1 Adverse event flow and timelines .....	61

## Table of tables

	Page
Table 2–1 Flow chart.....	13
Table 2–2 Flow chart, phone contacts .....	15
Table 8–1 Timepoints for 9-point profile (SMPG).....	45
Table 12–1 AEs that require the completion of specific eCRFs and/or subject to event adjudication.....	59
Table 12–2 Description of events to be adjudicated.....	66
Table 17–1 Specifications assumed for sample size calculation.....	77
Table 17–2 Sensitivity of sample size (integers) to variations in SD and power .....	77
Table 17–3 Anticipated number of subjects in FAS and PP analysis set.....	78



## List of abbreviations

ACS	acute coronary syndrome
ADA	American Diabetes Association
AE	adverse event
ALT	alanine aminotransferase
ANOVA	Analysis of Variance
a.m.	ante meridiem (Latin for before noon)
AP	alkaline phosphatase
AST	aspartat aminotransferase
BHI 30	biphasic human insulin 30
BIAsp 30	biphasic insulin aspart 30
BID	twice daily
BMI	body mass index
CD	compact disc
CNS	central nervous system
CPMP	Committee for Proprietary Medicinal Products
CRF	case report form
CRO	contract research organisation
CTA	Clinical Trial Application
CTR	clinical trial report
CV	cardiovascular
CV(stat sect.)	coefficient of variance
CVD	cardiovascular disease
DFU	directions for use
DPP-4	Dipeptyl peptidase-4
DUN	dispensing unit number
EAC	event adjudication committee
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
EMA	European Medicines Agency
FAS	Full Analysis Set
FDA	Food and Drug Administration (US)
FDAAA	Food and Drug Administration Amendments Act
FPG	fasting plasma glucose
FPFV	first patient first visit
FU	Follow up visit
GCP	Good Clinical Practice
GLP-1	glucagon like peptide 1
HbA <sub>1c</sub>	glycosylated haemoglobin
HDL	high density lipoprotein
hh:mm	hour hour:minute minute
HI	human insulin

IAsp	insulin aspart
IB	investigator's brochure
ICH	International Conference on Harmonisation
ICMJE	The International Committee of Medical Journal Editors
ID	identification
IDeg	insulin degludec
IDegAsp 30	insulin degludec/insulin aspart (70 vol% insulin degludec + 30 vol% insulin aspart) 100 U/mL also known as IDegAsp 30
IDF	International Diabetes Federation
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product
IRB	Institutional Review Board
ITT	intention to treat
IUD	Intrauterine device
iv	intravenous
IWRS	interactive web response system
LDL	low density lipoprotein
LOCF	Last Observation Carried Forward
LPFV	last patient first visit
LPLV	last patient last visit
LSMeans	estimated mean treatment effects
MAO	monoamine oxidase
MedDRA	Medical Dictionary for Regulatory Activities
MI	myocardial infarction
NCR	non carbon required
NIMP	non-investigational medicinal product
NYHA	New York Heart Association
OAD	oral antidiabetic drug
OC	oracle clinical
OD	once daily
PDF	portable document format
PG	plasma glucose
PP	per protocol
PRO	patient reported outcome
SAE	serious adverse event
SAS	statistical analysis system
sc	subcutaneous
SD	standard deviation
SF-36	short form with 36 questions (health related quality of life questionnaire)
SFDA	State Food and Drug Administration
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SMPG	self-measured plasma glucose
SPC	summary of product characteristics

Protocol  
Trial ID: NN5401-3598  
EudraCT No.: 2011-000085-36  
UTN: U1111-1118-8578

~~CONFIDENTIAL~~

Date:  
Version:  
Status:  
Page:

31 May 2017  
4.0  
Final  
9 of 102

**Novo Nordisk**

SU	sulphonylurea
SUSAR	suspected unexpected serious adverse reaction
TEAE	Treatment Emergent Adverse Event
TMM	Trial Materials Manual
TRIM-D	Treatment Related Impact Measure - Diabetes
T-T-T	treat-to-target
TZD	thiazolidinedione
U	Unit
US	United States

# 1 Summary

## Objectives and endpoints:

### Primary objective

To confirm the efficacy of IDegAsp 30 twice daily (BID) ± metformin in controlling glycaemia with respect to change from baseline in glycosylated haemoglobin (HbA<sub>1c</sub>) after 26 weeks of treatment. This is done by comparing the difference in change from baseline in HbA<sub>1c</sub> after 26 weeks of treatment between IDegAsp 30 and BIAsp 30 both BID ± metformin, to a non-inferiority limit of 0.4%, and if non-inferiority is confirmed, to a superiority limit of 0%.

### Secondary objectives

To confirm superiority of IDegAsp 30 BID ± metformin against BIAsp 30 BID ± metformin after 26 weeks of treatment in terms of:

- fasting plasma glucose (FPG) measured at central laboratory
- treatment emergent confirmed nocturnal hypoglycaemic episodes
- treatment emergent confirmed hypoglycaemic episodes
- body weight
- frequency of responders for HbA<sub>1c</sub> (<7.0 %) without confirmed hypoglycaemic episodes

To compare efficacy and safety of IDegAsp 30 BID ± metformin against BIAsp 30 BID ± metformin after 26 weeks of treatment in terms of:

- 9-point profile self-measured plasma glucose (SMPG)
- 2-point profile (SMPG) for dose adjustments
- frequency of responders for HbA<sub>1c</sub> targets
- adverse events (AEs)
- confirmed hypoglycaemic episodes
- clinical and laboratory assessments
- insulin dose
- insulin antibodies
- patient reported outcomes (PRO)

### Primary endpoint

Change from baseline in HbA<sub>1c</sub> (%) after 26 weeks of treatment (analysed by central laboratory).

### Key secondary endpoints

- Change from baseline in FPG after 26 weeks of treatment (analysed by central laboratory)

- Number of treatment emergent nocturnal confirmed hypoglycaemic episodes during 26 weeks of treatment
- Number of treatment emergent confirmed hypoglycaemic episodes during 26 weeks of treatment
- Change from baseline in body weight after 26 weeks of treatment
- Responder without hypoglycaemic episodes ( $HbA_{1c} < 7.0\%$  after 26 weeks of treatment and no confirmed hypoglycaemic episodes during the last 12 weeks of treatment or within 7 days after the last randomised treatment including only subjects exposed for at least 12 weeks)
- Incidence of treatment emergent adverse events (TEAEs) during 26 weeks of treatment

### **Trial design**

This is a 26 week, randomised, controlled, open label two-arm, parallel-group trial. The trial is conducted as a treat-to-target (T-T-T) trial.

Total trial duration for the individual subject will be approximately 31 weeks.

### **Trial population**

An expected number of 537 subjects with type 2 diabetes inadequately controlled on OD or BID premix/selfmix or basal insulin with or without metformin qualifying for intensification of therapy and who comply to the in- and exclusion criteria will be randomly allocated in a 2:1 manner into the two treatment groups.

### **Key inclusion criteria**

- Informed consent obtained before any trial-related activities. Trial-related activities are any procedures that are carried out as part of the trial, including activities to determine suitability for the trial
- Male or female  $\geq 18$  years of age
- Type 2 diabetes mellitus (diagnosed clinically) for  $\geq 6$  months
- Insulin treated subjects on current treatment: basal insulin, premixed insulin or a self-mixed insulin regimen, all administered once daily (OD) or BID with or without metformin. The treatment regimen should have remained unchanged for at least 8 weeks prior to randomisation
- $HbA_{1c}$  7.0-10.0 % (both inclusive) by central laboratory analysis
- Body mass index (BMI)  $\leq 40.0$  kg/m<sup>2</sup>

### **Key exclusion criteria**

- Treatment with sulphonylureas, meglitinides, DPP-4 inhibitors, alpha-glycosidase inhibitors within 8 weeks prior to screening (Visit 1) or thiazolidinediones (TZDs) or GLP-1 receptor agonists within 12 weeks prior to screening (Visit 1)
- Anticipated change in concomitant medication known to interfere significantly with glucose metabolism, such as systemic corticosteroids, beta-blockers and monoamine oxidase (MAO) inhibitors
- Anticipated significant lifestyle changes during the trial according to the discretion of the investigator, e.g. shift work (including permanent night/evening shift workers), as well as highly variable eating habits
- Cardiovascular disease, within the last 6 months prior to screening (Visit 1), defined as: stroke; decompensated heart failure NYHA<sup>1</sup> class III or IV; myocardial infarction; unstable angina pectoris; or coronary arterial bypass graft or angioplasty
- Any clinically significant disease or disorder, except for conditions associated with type 2 diabetes, which in the investigator's opinion could interfere with the results of the trial
- Previous participation in this trial. Participation is defined as screened.
- Known or suspected hypersensitivity to trial products or related products

### **Key assessments**

- HbA<sub>1c</sub>
- FPG
- SMPG profiles
- AEs
- Hypoglycaemic episodes
- Body weight
- Insulin antibodies
- PROs

### **Trial products**


- IDegAsp 30 100 U/ml, 3 ml pre-filled pen PDS290 (FlexTouch<sup>®</sup>)
- Biphasic insulin aspart 30 (BIAsp 30) (NovoMix<sup>®</sup> 30), 100 U/ml, 3 ml pre-filled pen (FlexPen<sup>®</sup>)
- Biphasic human insulin 30 (BHI 30, Novolin<sup>®</sup> 30), 100 U/ml prefilled pen (FlexPen<sup>®</sup>). For insulin coverage during the follow-up period.


All the insulin products are for subcutaneous (sc) injection

## 2 Flow chart

Trial procedures are outlined in [Table 2-1](#) and [2-2](#).

**Table 2–1 Flow chart**

Trial NN54-01-3598	Type 2	Screen	Rand	0-26 weeks														FU1	FU2
Visit Number (V)	V1	V2	V3	V4	V6	V8	V10	V12	V14	V16	V18	V22	V26	V28	V29				
 Phone Contact number (P) <sup>1</sup> (For details see separate flow chart)																P30			
<b>Time of visit (weeks)</b>	<b>-1<sup>2</sup></b>	<b>0<sup>2</sup></b>	<b>1</b>	<b>2</b>	<b>4</b>	<b>6</b>	<b>8</b>	<b>10</b>	<b>12</b>	<b>14</b>	<b>16</b>	<b>20</b>	<b>24</b>	<b>26</b>	<b>27<sup>5</sup></b>	<b>30<sup>5</sup></b>			
Visit window <sup>3</sup> (days)			±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	-3	+5	+3		
<b>SUBJECT RELATED INFO/ASSESSMENTS</b>																			
Informed consent	x																		
In/Exclusion criteria	x	x																	
Randomisation		x																	
Withdrawal criteria			x	x	x	x	x	x	x	x	x	x	x	x	x				
Demography	x																		
Diagnosis of diabetes	x																		
Concomitant ill/ medical history	x																		
Concomitant medication	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x			
Height	x																		
Body weight	x	x <sup>4</sup>							x <sup>4</sup>		x <sup>4</sup>				x <sup>4</sup>				
<b>EFFICACY</b>																			
Fasting plasma glucose <sup>4</sup>		x							x		x				x				
HbA <sub>1c</sub>	x	x					x		x		x	x	x		x				
2-point profile <sup>6</sup>			x	x	x	x	x	x	x	x	x	x	x	x	x				
9-point profile <sup>7</sup>		x							x		x				x				
<b>SAFETY</b>																			
Adverse events	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x <sup>16</sup>		
Insulin antibodies <sup>4</sup>		x							x						x	x			
Biochemistry	x														x				
Haematology	x														x				
Lipids <sup>4</sup>		x													x				
Urinalysis by stick	x														x				
Pregnancy test <sup>8</sup>	x														x				
Urine albumin/creatinine ratio (urinalysis)		x													x				
ECG – 12 lead <sup>9</sup>	x														x				
Eye examination <sup>10</sup> (fundoscopy/fundus photography)	x														x				
Hypoglycaemic episodes		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x			
Physical examination	x														x				
Vital signs	x														x				
<b>OTHER ASSESSMENTS</b>																			
PRO questionnaires <sup>11</sup>		x <sup>12</sup>							x <sup>12</sup>						x <sup>12</sup>				
End of trial <sup>15</sup>																	x		
<b>TRIAL MATERIAL</b>																			
IWRS session	x	x			x		x		x		x	x		x	x				
Drug accountability (IWRS)					x		x		x		x	x		x	x				

Trial NN54-01-3598	Type 2	Screen	Rand	0-26 weeks														FU1	FU2
Visit Number (V)	V1	V2	V3	V4	V6	V8	V10	V12	V14	V16	V18	V22	V26	V28	V29				
 Phone Contact number (P) <sup>1</sup> (For details see separate flow chart)			P5	P7	P9	P11	P13	P15	P17	P19	P23	P27			P30				
<b>Time of visit</b>	<b>(weeks)</b>	<b>-1<sup>2</sup></b>	<b>0<sup>2</sup></b>	<b>1</b>	<b>2</b>	<b>4</b>	<b>6</b>	<b>8</b>	<b>10</b>	<b>12</b>	<b>14</b>	<b>16</b>	<b>20</b>	<b>24</b>	<b>26</b>	<b>27<sup>5</sup></b>	<b>30<sup>5</sup></b>		
Visit window <sup>3</sup>	(days)			±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	-3	+5	+3		
Dispensing visit		x			x		x		x		x	x		x					
Dispense direction for use/package leaflet		x			x		x		x		x	x		x					
First date, doses and time points on trial insulin				x															
Dates and doses of trial insulin on three days prior to visit				x	x	x	x	x	x	x	x	x	x	x	x				
New dose of trial insulin				x	x	x	x	x	x	x	x	x	x	x					
Last date, dose and time point on trial insulin															x				
BHI 30, date and dose <sup>13</sup>																x			
<b>REMINDERS</b>																			
Attend visit fasting <sup>4</sup>		x								x		x			x	x			
Notes made if change in metformin dose or treatment				x	x	x	x	x	x	x	x	x	x	x	x				
Make appointment for eye examination													x						
Handling/training of product/device <sup>14</sup>		x	x												x				
Instruction/handout of glucose meter <sup>14</sup>		x																	
Hand-out/instruction/collect diary		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x			
Sign off casebook																	x		

1. A phone contact may be converted to a visit if for instance further titration attention is needed.
2. Randomisation will take place no later than 14 days after the screening visit (Visit 1). Randomisation can only take place if the results of the screening visit assessments (including blood sampling) are available and reviewed.
3. Time of visit is always calculated related to actual visit date of the randomisation visit.
4. Fasting visits: The subjects must attend Visits 2, 14, 18, 28 and 29 fasting, having consumed only water since midnight for measurement of lipids (Visits 2 and 28), weight and fasting plasma glucose (Visits 2, 14, 18, 28) and insulin antibodies (Visits 2, 14, 28, 29). No diabetes medication is allowed before these visits. If the subjects attend the site in a non-fasting condition the visit should be re-scheduled within the next two working days.
5. Two follow-up (FU) Visits are planned. FU1 (V29) must take place 7-12 days after the actual date Visit 28 is performed. FU 2 (P30) should take place 30 days after Visit 28.
6. 2-point profiles (SMPG): pre-breakfast and pre-dinner (main evening meal) SMPGs should be taken throughout the trial for titration/dose adjustments. Please see appendix A for details.
7. 9-point profiles (SMPG) must be started in the morning 2 days before Visits 2, 14, 18 and 28. Measurements are to be performed before and after (90 min after the start of the meal) breakfast, lunch, main evening meal, before bedtime, at 4 am and before breakfast on the following day. Please note that the 9-point profile (SMPG) is overlapping with the 2-point profile (SMPG).
8. Pregnancy test: At Visits 1 and 28 a blood pregnancy test will be performed in women of child bearing potential. During the trial a urine pregnancy test will be performed if a menstrual period is missed or pregnancy is suspected. If at phone contacts, subjects report missed menstrual period, the subject will have to attend the site for a urine pregnancy test.
9. The baseline ECG should be performed between the screening Visit 1 and the randomisation Visit 2, and results must be available before randomisation. The end of treatment ECG should be performed at Visit 28.
10. A funduscopy or fundus photography performed for any reason unrelated to this trial within 12 weeks prior to screening visit (Visit 1) is acceptable provided no clinical symptoms suggestive of eye disease have occurred in the meantime. It is allowed to perform the Visit 1 funduscopy or fundus photography between Visit 1 and Visit 2. The results must be available prior to randomisation. Funduscopy/fundus photography performed within a period of three weeks before Visit 28 is acceptable if results are available at the visit and provided no clinical symptoms suggestive of eye disease have occurred in the meantime.



11. PRO questionnaires; A battery of PRO questionnaires will evaluate health related quality of life, treatment satisfaction and preferences. The PRO questionnaires should be filled in by the subject at the visits preferably after conclusion of all fasting related activities, but before any other trial related procedures.
12. At baseline (Visit 2) only SF-36 & TRIM-D will be completed by subjects. At visit 14 & visit 28 all PROs (SF-36, TRIM-D, TRIM-D Device, and Device Specific Questionnaires (DSQ) I & II will be filled in.
13. .BHI 30 date, dose and time point (breakfast/ main evening meal) on first day (V28), 2 days and 4 days, after Visit 28 and on the the last day before FU1 (Visit 29). No BHI 30 is taken in the morning of Visit 29.
14. Instruction to be done in the start of the study and if required, and at visit 28.
15. If prematurely withdrawal, the procedures for the last treatment visit (Visit 28) and the follow-up visits (FU1 (Visit 29) & FU2 (P 30)) must be performed if possible
16. Only cardiovascular events and AEs will be collected.

**Table 2–2 Flow chart, phone contacts**

Phone contact number (P) <sup>1</sup>	P 5	P 7	P 9	P 11	P 13	P 15	P 17	P 19	P 20	P 21	P 23	P 24	P 25	P 27	P 30
Time of Phone contact (weeks)	3	5	7	9	11	13	15	17	18	19	21	22	23	25	
Visit window <sup>2</sup> (days)	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3
<b>SUBJECT RELATED INFO/ASSESSMENTS</b>															
Withdrawal criteria	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Concomitant medication	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
<b>EFFICACY</b>															
2-point profile <sup>3</sup>	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
<b>SAFETY</b>															
Adverse events	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Hypoglycaemic episodes	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
<b>TRIAL MATERIAL</b>															
Dates and doses of trial insulin onthree days prior to visit	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
New dose of trial insulin	x	x	x	x	x	x	x	x	x	x	x	x	x	x	

1. A phone contact may be converted to a visit if for instance further titration attention is needed.
2. Time of visit is always calculated related to actual visit date of the randomisation visit.
3. 2-point profiles (SMPG): pre-breakfast and pre-dinner SMPGs should be taken throughout the trial for titration/dose adjustments. Please see appendix A for details.

### 3 Background information and rationale for the trial

In this document, the term investigator refers to the individual responsible for the overall conduct of the clinical trial at a trial site.

Diabetes mellitus is characterised by chronic hyperglycaemia and encompasses various metabolic disorders. It is generally classified according to aetiological factors, where type 1 and type 2 constitute the vast majority of cases.

Type 2 diabetes mellitus (T2DM) is a progressive disorder characterised by a combination of insulin resistance at peripheral tissues and relative insulin secretion deficiency. The current treatment cascade follows a stepwise approach comprising lifestyle changes in combination with pharmacological intervention. The pharmacological intervention aims at decreasing insulin resistance or increasing insulin secretion. Treatment is usually initiated with metformin followed by combination therapy with other oral antidiabetic drugs (OADs), insulin and in countries where approved also glucagon-like peptide 1 (GLP-1) receptor agonists as the disease progresses.<sup>2</sup> In most Asian countries SU is still the most widely used OAD whereas in countries where insulin resistance is more prominent, metformin is recommended as initial therapy.<sup>2</sup>

A number of landmark studies have demonstrated the importance of maintaining tight glycaemic control to reduce the risk of long-term complications associated with diabetes.<sup>3</sup> In general, it is recommended to aim for a glycosylated haemoglobin (HbA<sub>1c</sub>) < 7.0%.<sup>2</sup> However, factors such as life expectancy, risk of hypoglycemia and the presence of cardiovascular disease (CVD) need to be considered for every patient before intensifying the therapeutic regimen.<sup>2</sup> Also, recent data suggest that very intensive glucose-lowering treatment (HbA<sub>1c</sub> < 6%) may be detrimental in subjects with type 2 diabetes with high risk of cardiovascular (CV) events.<sup>4,5</sup>

#### **Insulin degludec/insulin aspart**

Insulin analogues are now an established part of diabetes management. They have been developed to more closely mimic endogenous insulin secretion compared with human insulin preparations. Insulin degludec/insulin aspart (70 vol%/30 vol%) (IDegAsp 30) belongs to a new generation of insulin and represents the first soluble ultra-long acting basal insulin (insulin degludec (IDeg)) with a bolus boost (insulin aspart (IAsp)), with no need for resuspension prior to use.

IDeg is the approved international non-proprietary name for the formerly named insulin 454. Insulin degludec differs from human insulin (HI) in that the threonine in position B30 has been omitted, and a side-chain consisting of glutamic acid and a fatty acid has been attached. The protracted action of insulin degludec is related to its ability to self-assemble into soluble multi-hexamers at the injection site and, to a lesser degree, through the ability to bind to albumin via the fatty-acid side-chain.

IDegAsp 30 is the approved international non-proprietary name for the co-formulation of IDeg and IAsp. IAsp is homologous to human insulin (HI) with the exception of the substitution of proline with aspartic acid at position B28. The rapid action of IAsp is related to a weakened tendency of the insulin molecules to self-associate because of this modification, and thereby leads to faster absorption as compared with HI. IAsp is also the drug substance of the currently marketed NovoRapid<sup>®</sup> and NovoMix<sup>®</sup>. It is currently not recommended to self-mix rapid-acting and long-acting insulin analogues.<sup>6,7</sup> This has prompted the development of IDegAsp 30.

IDegAsp 30 is designed to result in similar or improved glycaemic control compared to treatment with currently available insulin products. IDeg appears to be even longer-acting than currently available basal insulin analogues such as insulin glargine and insulin detemir.

In insulin treated subjects with type 2 diabetes inadequately controlled on their current regimen (Trial NN5401-3592), 26 weeks of treatment with IDegAsp 30 twice daily with or without OADs, resulted in comparable glycaemic control as measured by HbA<sub>1c</sub> but significantly lower fasting plasma glucose (FPG) compared to that observed for biphasic insulin aspart 30 (BIAsp30) given twice daily with or without OADs. Furthermore, both the rate of 24-hour hypoglycaemia (-32%) and the rate of nocturnal hypoglycaemia (episodes occurring from midnight to 6AM) (-73%) was significantly lower for IDegAsp 30 compared to BIAsp30. In a similar study performed on an Asian T2DM population (participation from Hong Kong, Malaysia, Japan, South Korea and Taiwan), 26 weeks of treatment with IDegAsp 30 twice daily with or without metformin, resulted in comparable glycaemic control as measured by HbA<sub>1c</sub> but significantly lower FPG compared to that observed for BIAsp30 given twice daily with or without metformin. In this trial the rate of 24-hour hypoglycaemia was similar between the two arms while the rate of nocturnal hypoglycaemia was reduced by 33% (ns).

IDegAsp 30 received a positive opinion from the European regulatory authorities in October 2012 recommending marketing authorisation for the treatment of diabetes mellitus in adults. IDegAsp 30 has passed the review by the First Committee on Drugs of Japan's Pharmaceutical Affairs on Dec 2012 recommending marketing authorisation.

For more detailed information, please refer to the current version of the IDegAsp 30 investigator's brochure (IB).<sup>8</sup>

### **Novomix<sup>®</sup> 30**

IAsp is a rapid-acting analogue. BIAsp 30 (NovoMix<sup>®</sup> 30, NovoLog<sup>®</sup> Mix 70) is a mixture of 30% soluble (rapid-acting) and 70% protaminated (intermediate-acting) IAsp, indicated for the treatment of diabetes mellitus as monotherapy or in combination with OADs.

The faster absorption properties of the IAsp are reflected in BIAsp 30, as compared with biphasic human insulin (BHI) 30 (same ratio of fast and intermediate acting HI): lower glucose levels after meals at which the insulin is administered and decreased risk of nocturnal hypoglycaemia, but

higher fasting-blood-glucose levels. Similarly, BIAsp 30 can be administered just before (or even soon after) a meal, unlike with BHI products.<sup>9</sup>

For further details, please refer to the current version of the local package insert and any update hereof.

### 3.1 Rationale for the trial

Premixed/selfmixed and basal insulin treatment is widely used in type 2 diabetes as it provides a balance between efficacy, safety and convenience. In most Asian countries premixed/selfmixed insulin given twice daily (BID) is one of the most frequently used insulin treatment regimens and is used for initiating insulin treatment as well as for intensification of treatment. Patients with type 2 diabetes inadequately controlled on once daily (OD) or BID insulin regimen  $\pm$  metformin will benefit from treatment intensification to a BID insulin regimen and/or dose optimisation using a treat-to-target (T-T-T) approach.

IDegAsp 30 is the first fully soluble insulin analogue combination product, and no re-suspension prior to use is required. This is expected to improve patient's convenience and possibly adherence to treatment for the day-to-day use. In IDegAsp 30 the separation of the bolus and the basal component is sharper and the duration of action of the basal component is longer than in premixed insulin preparations.

This trial will assess the effect on glucose control, safety and tolerability of IDegAsp 30 BID versus BIAsp 30 BID, both with or without metformin in subjects with type 2 diabetes not optimally controlled on OD or BID premix/selfmix or basal insulin  $\pm$  metformin.

Regulatory agencies generally accept HbA<sub>1c</sub> as marker for overall, long-term glucose control in type 1 and type 2 diabetes and reduction of HbA<sub>1c</sub> is directly related to a reduced risk of development of CV complications.<sup>3</sup> Thus, HbA<sub>1c</sub> was included in the entire phase 3a development program for IDegAsp 30. Secondary endpoints evaluating glucose control include prandial plasma glucose, FPG and within-subject variability of self measured plasma glucose (SMPG).

This confirmatory trial will be used for the registration purposes in China to document the efficacy and safety of treatment with IDegAsp 30 in Chinese subjects with diabetes mellitus.

In addition, the safety of switching unit -to-unit from premix/selfmix or basal insulin (OD or BID) to IDegAsp 30 BID will be investigated in the trial.

Exposure to a new insulin product could trigger antibody development. As part of the assessment of the long-term safety of IDeg or IDegAsp 30, antibodies specific to IDeg as well as antibodies crossreacting to HI were measured in some phase 3 trials. From these trials there was no evidence of neutralising antibodies following treatment with IDeg or IDegAsp 30. There was no clinically

Protocol  
Trial ID: NN5401-3598  
EudraCT No.: 2011-000085-36  
UTN: U1111-1118-8578

~~CONFIDENTIAL~~

Date:	31 May 2017	<b>Novo Nordisk</b>
Version:	4.0	
Status:	Final	
Page:	19 of 102	

relevant influence of IDeg antibody formation on HbA<sub>1c</sub>, change in HbA<sub>1c</sub> at end of treatment or total daily dose at the end of the IDeg or IDegAsp 30 trials. Blood samples for detection of IDeg antibodies will be collected at baseline (Visit 2), Visit 14, at the end of the treatment (Visit 28) and at the 7 days follow-up visit FU1 (Visit 29). The immunological response to IDeg will be monitored following the European Medicines Agency (EMA) guideline on this subject.<sup>10</sup>

The trial will be conducted in accordance with global and local regulations.

## 4 Objectives and endpoints

### 4.1 Objectives

#### 4.1.1 Primary

To confirm the efficacy of IDegAsp 30 BID  $\pm$  metformin in controlling glycaemia with respect to change from baseline in HbA<sub>1c</sub> after 26 weeks of treatment. This is done by comparing the difference in change from baseline in HbA<sub>1c</sub> after 26 weeks of treatment between IDegAsp 30 and BIAsp 30 both BID  $\pm$  metformin, to a non-inferiority limit of 0.4%, and if non-inferiority is confirmed, to a superiority limit of 0%.

#### 4.1.2 Secondary

To confirm superiority of IDegAsp 30 BID  $\pm$  metformin against BIAsp 30 BID  $\pm$  metformin after 26 weeks of treatment in terms of:

- FPG measured at central laboratory
- treatment emergent confirmed nocturnal hypoglycaemic episodes
- treatment emergent confirmed hypoglycaemic episodes
- body weight
- frequency of responders for HbA<sub>1c</sub> (<7.0 %) without confirmed hypoglycaemic episodes

To compare efficacy and safety of IDegAsp 30 BID  $\pm$  metformin against BIAsp 30 BID  $\pm$  metformin after 26 weeks of treatment in terms of:

- 9-point profile (SMPG)
- 2-point profile (SMPG) for dose adjustments
- frequency of responders for HbA<sub>1c</sub> targets
- adverse events (AEs)
- confirmed hypoglycaemic episodes
- clinical and laboratory assessments
- insulin dose
- insulin antibodies
- patient reported outcomes (PRO)

### 4.2 Endpoints

For details on timing of assessments please refer to flow chart in section [2](#).

#### 4.2.1 Primary

Change from baseline in HbA<sub>1c</sub> (%) after 26 weeks of treatment (analysed by central laboratory).

#### 4.2.2 Confirmatory secondary efficacy endpoints

- Change from baseline in FPG after 26 weeks of treatment (analysed by central laboratory)
- Number of treatment emergent nocturnal confirmed hypoglycaemic episodes during 26 weeks of treatment
- Number of treatment emergent confirmed hypoglycaemic episodes during 26 weeks of treatment
- Change from baseline in body weight after 26 weeks of treatment
- Responder without hypoglycaemic episodes ( $HbA_{1c} < 7.0\%$  after 26 weeks of treatment and no confirmed hypoglycaemic episodes during the last 12 weeks of treatment or within 7 days after the last randomised treatment including only subjects exposed for at least 12 weeks)

#### 4.2.3 Supportive secondary endpoints

##### 4.2.3.1 Efficacy

Supportive secondary endpoints will be described in detail in section [17](#) of this protocol, and are therefore only listed below without detailed explanation. The timing of assessments is outlined in the trial flow chart.

- Responder for  $HbA_{1c}$  after 26 weeks of treatment
  - $HbA_{1c} < 7\%$
  - $HbA_{1c} \leq 6.5\%$
  - $HbA_{1c} < 7\%$  without severe hypoglycaemic episodes during the last 12 weeks of treatment or within 7 days after the last randomised treatment including only subjects exposed for at least 12 weeks
  - $HbA_{1c} \leq 6.5\%$  without confirmed hypoglycaemic episodes during the last 12 weeks of treatment or within 7 days after the last randomised treatment including only subjects exposed for at least 12 weeks
  - $HbA_{1c} \leq 6.5\%$  without severe hypoglycaemic episodes during the last 12 weeks of treatment or within 7 days after the last randomised treatment including only subjects exposed for at least 12 weeks
- 9-point profile (SMPG) after 26 weeks of treatment
  - 9-point profile (SMPG)
  - Mean of the 9-point profile (SMPG)
  - Fluctuation in the 9-point profile (SMPG)
  - Prandial plasma glucose (PG) increment
- 2-point profile (SMPG) measurements obtained throughout the trial for dose adjustment
  - Mean PG before meals after 26 weeks of treatment
  - Responder for PG titration targets
  - Time from randomisation (measured in weeks) to achieve titration targets

- Within-subject variability as measured by coefficient of variance (CV)% after 26 weeks of treatment

#### **4.2.3.2 Safety**

- Incidence of treatment emergent adverse events (TEAEs) during 26 weeks of treatment
- Number of treatment emergent hypoglycaemic episodes according to the American Diabetes Association (ADA) definition during 26 weeks of treatment
- Number of treatment emergent confirmed hypoglycaemic episodes in the maintenance period (from week 16 to end of treatment, including 1 week follow-up)
- Number of treatment emergent nocturnal (00:01-05:59) confirmed hypoglycaemic episodes in the maintenance period (from week 16 to end of treatment, including 1 week follow-up)
- Change from baseline in clinical evaluation during 26 weeks of treatment
  - Physical examination
  - Fundoscopy/fundus photography
  - 12-lead ECG
  - Vital signs
- Change from baseline in central laboratory assessments during 26 weeks of treatment
  - Haematology (haemoglobin, leucocytes, thrombocytes, haematocrit, differential counts and erythrocytes)
  - Biochemistry (creatinine, total protein, alanine aminotransferase (ALT), aspartat aminotransferase (AST), alkaline phosphatase (AP), sodium, potassium, albumin, and total bilirubin)
  - Lipid profile (low density lipoproteins (LDL), high density lipoproteins (HDL), triglyceride and total cholesterol)
  - Urinary albumin/creatinine ratio assessed in spot urine
  - Urine by sticks (tests for blood, protein and ketones)
  - Insulin antibodies
- Insulin dose after 26 weeks of treatment

#### **4.2.3.3 PRO**

The following questionnaires will be used to compare PROs and costs associated with hypoglycaemia between treatments:

- Health Related Quality of Life Questionnaire (SF-36)<sup>11,12</sup>
- Treatment Satisfaction Questionnaire (treatment related impact measure-diabetes (TRIM-D)<sup>13</sup> and treatment related impact measure-diabetes device (TRIM-D Device)<sup>13</sup>
- Device Specific Questionnaires I and II<sup>14</sup>



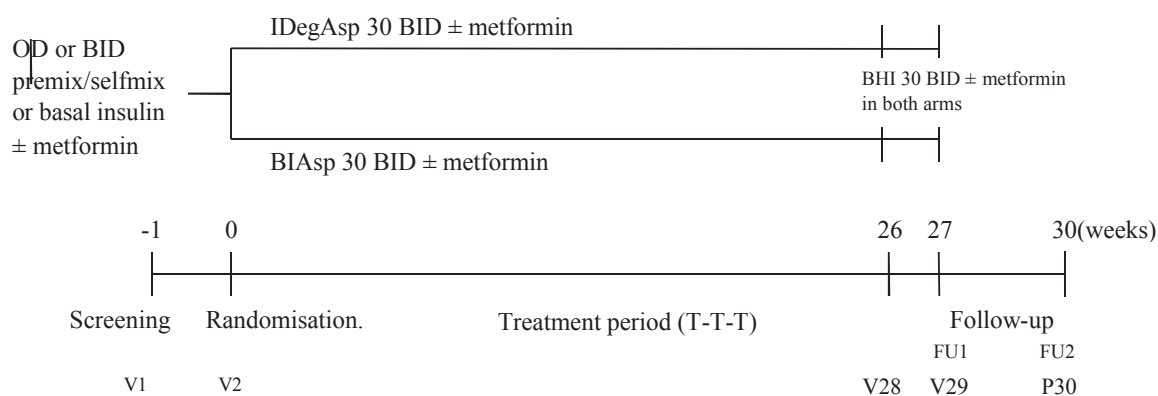
## 5 Trial design

### 5.1 Type of trial

This is a 26 week, 2:1 randomised, controlled, open label, two-arm, parallel-group, T-T-T trial comparing efficacy and safety of IDegAsp 30 and BIAsp 30 both  $\pm$  metformin, BID in subjects with type 2 diabetes inadequately controlled on OD or BID premix/selfmix or basal insulin  $\pm$  metformin.

Total trial duration for the individual subject will be approximately 31 weeks including screening and follow-up. Subjects will attend weekly visits/phone contacts throughout the trial as schematically described in the flow chart (section 2).

The trial design is summarised schematically in [Figure 5-1](#).



**Figure 5-1 Trial design**

### 5.2 Rationale for trial design

The parallel design has been chosen instead of a cross-over design as these are considered infeasible and time consuming due to the need for exposing the same subjects twice as well as leaving sufficient time for wash-out between treatment periods in order to avoid potential carry-over effect and further to evaluate the development of insulin antibodies.

The 26-week treatment period is expected to be sufficient to optimise the new treatment regimens and to evaluate the efficacy and safety of the new treatment.

An open label trial design has been chosen as the comparator product, BIAsp 30, cannot be blinded in an acceptable way. BIAsp 30 is not a clear solution and requires re-suspension prior to use. Blinding the trial using a double-dummy design would mean an unacceptable number of injections

and increase the trial design complexity and thereby introduce an increased risk of withdrawal or non-compliance. The use of double-dummy is therefore considered not applicable in this trial.

The T-T-T approach and thereby frequent visits, phone contacts and HbA<sub>1c</sub> monitoring during the 26 weeks has been chosen in order to ensure optimal titration of insulin based on SMPG values, in order to ensure improved HbA<sub>1c</sub> results. The weekly visit/phone contact has been chosen in order to optimise 1) titration of the insulin, based on SMPG values and 2) compliance.

Due to measurement of insulin antibodies, a 1-week interval between the end of treatment visit and the 7 days follow-up visit FU 1 (Visit 29) is necessary to allow for trial insulin washout. Subjects will be treated with BHI 30 for one week before the measurement of insulin antibodies. Due to the much shorter duration of BHI 30 insulin the levels of insulin will be lower at the sampling time point at the follow up FU1 (Visit 29). A 30 days follow up (FU2) after last trial insulin treatment (Visit 28) will be performed in order to collect information about potential major cardiovascular events and adverse events (AEs) occurring between FU1 and FU2.

Key visits are placed at week 0, 12, 16 and 26 (Visit 2, 14, 18 and 28 respectively). Results from week 12 and 16 (Visit 14 and 18) are expected to provide data on the time subjects reach steady state, with regards to the insulin given. The primary endpoint and all other assessments and safety parameters will be collected at week 26 (Visit 28).

### **5.3 Treatment of subjects**

Subjects will attend a screening visit (Visit 1) to assess their eligibility. If found eligible, subjects will return at Visit 2 within 14 days and have previous diabetes treatment discontinued except for metformin.

At Visit 2, subjects will be randomised in a 2:1 manner into one of the two treatment arms. Subjects will be instructed to discontinue current antidiabetic treatment except for metformin, which should be kept unchanged throughout the trial, and start treatment with IDegAsp 30 BID or BIAsp 30 BID both as sc injection and both ± metformin.

#### **Metformin therapy**

All subjects should continue treatment with metformin at unchanged, stable, pre-randomisation dose level and dosing frequency. The dose and dosing frequency should not be changed at any time during the treatment period, unless for safety reasons. Metformin should be taken according to labelling.

## Insulin therapy

For both IDegAsp 30 and BIAsp 30, the first dose should be administered with the breakfast (morning meal) or main evening meal, whichever comes first, following completion of the randomisation visit preferably on the day of randomisation. However, subjects on long acting basal insulin prior to inclusion in the trial should take the first trial insulin dose 24 hours after the last dose of long acting insulin. During the treatment period, the trial insulin should be administered BID with the breakfast meal and main evening meal. The treatment regimens should stay the same throughout the trial and no other insulin treatment is allowed.

Subjects on insulin OD are recommended to divide the total dose of their previous non trial insulin treatment into two equal doses of trial insulin to be administered with breakfast (morning meal) and dinner (main evening meal). Subjects on insulin BID will transfer to trial insulin treatment with doses unchanged administered at breakfast and dinner. Subjects on a self-mixed regimen will transfer to trial insulin treatment at doses corresponding to their total self-mixed pre-meal dose administered at breakfast and dinner.

For IDegAsp 30 the prioritised order of injection areas is the abdomen, upper arm (deltoid area) or thigh. BIAsp 30 should be administered subcutaneously preferably in the thigh or in the abdomen according to local labelling. If convenient, the gluteal or deltoid region may be used. For both IDegAsp 30 and BIAsp 30 the injection area should remain the same throughout the trial, but the location within the site should be changed for each injection. The investigator should ensure that the subject is instructed in how to inject the trial insulin.

At Visit 3 and throughout the 26 week treatment period, the subject's insulin dose will be titrated weekly primarily based on SMPG measurements according to a predefined titration algorithm (Appendix A).

The new recommended doses will be calculated in the electronic case report form (eCRF) when entering the SMPGs and the previous insulin doses. The insulin dose adjustments should aim to reach a pre-breakfast and pre-dinner FPG  $\leq 5.0$  mmol/l (90 mg/dl).

No maximum insulin dose is specified. Minimum insulin dose is specified to 4 Units daily (2U per injection). Subjects not tolerating the minimum dose must be withdrawn if occurring for more than 14 consecutive days.

Subjects will be allowed to adjust insulin doses in between visits according to individual requirements and in agreement with the investigator.

The treatment period is 26 weeks.

The last dose of IDegAsp 30 or BIAsp 30 should be administered the day before Visit 28. All subjects must attend Visit 28 fasting.

At week 26 (Visit 28), the subjects will discontinue all trial products and be switched to BHI 30 and continue the metformin treatment until the 7 days follow-up visit FU1 (Visit 29).

No earlier than one week after discontinuation of trial treatment (Visit 28) a follow-up visit FU1 (Visit 29) will be performed to ensure assessment of safety issues related to treatment discontinuation and for the measurement of insulin antibodies. All subjects must attend the 7 days follow-up visit FU1 (Visit 29) fasting without taking BHI 30 in the morning of the follow-up visit.

### **5.3.1 Treatment after early discontinuation of trial product**

If the treatment with trial insulin is discontinued earlier than expected the subject should be switched to BHI 30 until the 7 days follow-up visit (FU1) and withdrawal procedures should be followed as described in section 0 and 8.1.7. If the subject refuses to come in for the 7 days follow-up visit (FU1), the subject will be switched to a suitable marketed product as recommended by the investigator. Especially for the subjects on IDegAsp 30 careful titration of the subsequent antidiabetic treatment should be carried out based on PG measurements due to the stable effect and long half-life of IDegAsp 30. Please refer to the IB<sup>8</sup> and any updates hereof.

### **5.4 Rationale for treatment**

Premixed insulin treatment is widely used in type 2 diabetes as it provides a fair balance between efficacy, safety and convenience. Patients with type 2 diabetes inadequately controlled on OD or BID insulin regimen  $\pm$  metformin are expected to benefit from treatment intensification to a BID insulin regimen and/or dose optimisation using a treat-to-target (T-T-T) approach.

IDegAsp 30 is the first fully soluble insulin analogue combination product, and no re-suspension prior to use is required. This is expected to improve patient's convenience and possibly adherence to treatment for the day-to-day use. In IDegAsp 30 the separation of the bolus and the basal component is sharper and the duration of action of the basal component is longer than in other premixed insulin preparations.

Data from phase 3a have shown, that IDegAsp 30 administered BID effectively improves overall glycaemic control with a lower risk of hypoglycaemia compared to BIAsp 30.<sup>8</sup> For the comparator arm BIAsp 30 BID has been chosen since it contains the same rapid-acting component as IDegAsp 30. Furthermore, BIAsp 30 has a lower hypoglycaemia risk (nocturnal and major) than premixed human insulin.

In this trial patients already treated with insulin OD or BID will be included. Premixed insulin are commonly used BID for intensification of OD insulin treatment. In this trial, the transfer from

premixed insulin BID to IDegAsp 30 BID is seen as an intensification due to the improved insulin action profile.

Since this trial is investigating a BID regimen, subjects that cannot tolerate a dose of 2 units per injection (regarded as the minimum clinically significant dose) will be withdrawn.

Patients treated with metformin at randomisation will continue with an unchanged dose, since insulin sensitizers are known to improve glycaemic control with less hypoglycaemia at a lower insulin dose compared to insulin regimens without OADs.

The switch from trial insulin treatment to BHI 30 between end of treatment visit and the 7 days follow-up visit, is done in order to provide both bolus and basal insulin coverage while reducing the level of exogenous insulin present at antibody sampling and consequently to reduce the possibility for interference with antibody measurements.

## 6 Trial population

### 6.1 Number of subjects

Country planned to participate: China

Number of subjects planned to be screened (i.e. documented informed consent): 767

Number of subjects planned to be randomised/started on trial product(s): 537

Number of subjects expected to complete the trial: 450

A screening failure rate of 30 % and a withdrawal rate of 15% is anticipated for this trial.

### 6.2 Inclusion criteria

For an eligible subject, all inclusion criteria must be answered “yes”.

1. Informed consent obtained before any trial-related activities. Trial-related activities are any procedures that are carried out as part of the trial, including activities to determine suitability for the trial.
2. Male or female  $\geq 18$  years of age
3. Type 2 diabetes mellitus (diagnosed clinically) for  $\geq 6$  months
4. Insulin treated subjects on current treatment: basal insulin, premixed insulin or a self-mixed insulin regimen, all administered OD or BID with or without metformin. The treatment regimen should have remained unchanged for at least 8 weeks prior to randomisation (Visit 2).
5. HbA<sub>1c</sub> 7.0-10.0 % (both inclusive) by central laboratory analysis
6. Body mass index (BMI)  $\leq 40.0$  kg/m<sup>2</sup>
7. Ability and willingness to adhere to the protocol including performance of SMPG profiles according to the protocol
8. Subject is likely to comply with the investigators instruction

### 6.3 Exclusion criteria

For an eligible subject, all exclusion criteria must be answered “no”.

1. Treatment with other insulin regimens than those listed in inclusion criterion no. 4 within 8 weeks prior to Visit 2
2. Treatment with sulphonylureas, meglitinides, DPP-4 inhibitors, alpha-glycosidase inhibitors within 8 weeks prior to visit 1 or thiazolidinediones (TZDs) or GLP-1 receptor agonists within 12 weeks prior to Visit 1
3. Contraindications or restrictions to use of metformin (according to local labelling)
4. Anticipated change in concomitant medication known to interfere significantly with glucose metabolism, such as systemic corticosteroids, beta-blockers, monoamine oxidase (MAO) inhibitors
5. Use of non-herbal Chinese medicine or other non-herbal local medicine with unknown/unspecified content. Herbal traditional Chinese medicine or other local herbal medicines may, at the investigator's discretion, be continued throughout the trial unless the medicine is known to interfere with glucose metabolism.
6. Anticipated significant lifestyle changes during the trial according to the discretion of the investigator, e.g. shift work (including permanent night/evening shift workers), as well as highly variable eating habits
7. Cardiovascular disease, within the last 6 months prior to screening (Visit 1), defined as: stroke; decompensated heart failure New York Heart Association (NYHA)<sup>1</sup> class III or IV; myocardial infarction; unstable angina pectoris; or coronary arterial bypass graft or angioplasty
8. Uncontrolled treated/untreated severe hypertension (systolic blood pressure  $\geq$  180 millimetre (mm) mercury (Hg) and/or diastolic blood pressure  $\geq$  100 mmHg)
9. Impaired liver function, defined as ALT or AST  $\geq$  2.5 times upper limit of normal
10. Impaired renal function defined as serum-creatinine  $\geq$  125  $\mu$ mol/L ( $\geq$  1.4 mg/dL) for males and  $\geq$  110  $\mu$ mol/L ( $\geq$  1.3 mg/dL) for females
11. Recurrent severe hypoglycaemia (more than 1 severe hypoglycaemic event during the last 12 months), or hypoglycaemic unawareness as judged by the investigator or hospitalisation for diabetic ketoacidosis during the previous 6 months
12. Proliferative retinopathy or maculopathy (as verified by funduscopy/fundus photography performed within 12 weeks prior to Visit 2) requiring treatment according to the investigator

13. Females of childbearing potential who are pregnant, breast-feeding or intend to become pregnant or are not using adequate contraceptive methods (adequate contraceptive methods as required by local law or practice. For China: sterilisation, Intrauterine device (IUD), oral contraceptives or barrier methods)
14. Cancer and medical history of cancer (except basal cell skin cancer or squamous cell skin cancer)
15. Any clinically significant disease or disorder, except for conditions associated with type 2 diabetes, which in the investigator's opinion could interfere with the results of the trial
16. Mental incapacity, psychiatric disorder, unwillingness or language barriers precluding adequate understanding or co-operation, including subjects not able to read or write
17. Previous participation in this trial. Participation is defined as screened.
18. Known or suspected hypersensitivity to trial products or related products
19. Receipt of any investigational medicinal product (IMP) within one month prior screening (Visit 1)
20. Donation of blood or participation in other trials within one month prior to screening (Visit 1)
21. Known or suspected abuse of alcohol, narcotics or illicit drugs

#### **6.4 Withdrawal criteria**

The subject may withdraw at will at any time.

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

Subjects randomised in error (not fulfilling the inclusion and/or exclusion criteria) must be withdrawn from the trial.

A subject must be withdrawn if the following applies:

1. Hypoglycaemia during the treatment period posing a safety problem as judged by the investigator
2. Protocol deviation having influence on efficacy or safety data as judged by the investigator
3. Initiation or significant change of any systemic treatment which in the investigator's opinion could interfere with glucose metabolism (inhaled corticosteroids are allowed, pausing metformin treatment for a planned radiographic procedure including the use of iodine containing contrast material is allowed)



4. Pregnancy or intention of becoming pregnant
5. Use of a different antidiabetic treatment regimen during the treatment period than metformin including use of insulin secretagogues (sulfonylurea or glinide), dipeptidyl peptidase IV (DPP-IV) inhibitors,  $\alpha$ -glucosidase-inhibitors, thiazolidinediones (TZDs) or GLP-1 receptor agonists during the treatment period
6. Donation of blood or participation in other trials throughout the trial
7. Lack of effect: After week 12, if the subject has not had a reduction in HbA<sub>1c</sub> and has a pre-breakfast SMPG reading > 13.3 mmol/L (> 240 mg/dL) on three consecutive days despite appropriate dose adjustments. The subject should contact the investigator and come in for an unscheduled visit as soon as possible (within 2 weeks). The next scheduled visit should not be awaited. An FPG should be obtained and analysed by the central laboratory. If this FPG exceeds 13.3 mmol/L (>240 mg/dL) and no treatable intercurrent cause for the hyperglycaemia has been diagnosed, the subject must be withdrawn.
8. The subject does not tolerate the minimum dose of 4 Units daily (2U per injection) during 14 consecutive days

A withdrawn subject should be called in for Visit 28 and the follow-up FU 1 (Visit 29) procedures and an appointment for the 30 days follow-up Visit FU2 phone contact (P30) should be made as described in section 0 and 8.1.7.

## 6.5 Subject replacement

Subjects who are withdrawn after randomisation will not be replaced.

## 6.6 Rationale for trial population

Data generated from this trial will be used in the Chinese registration file to document the efficacy and safety of treatment with IDegAsp 30 in Chinese subjects with type 2 diabetes mellitus previously treated with insulin.

The trial population for this trial has been chosen to reflect a type 2 diabetes mellitus population with regards to demographic characteristics.

Enrolment of subjects inadequately controlled on OD or BID premix/selfmix or basal insulin with/without metformin has been chosen to investigate the effect of IDegAsp 30 BID used as an intensification regimen from a premixed/selfmixed or basal insulin regimen or the effect when dose optimisation (T-T-T) of a BID regimen is implemented.

Subjects on premixed/self-mixed or basal insulin (OD or BID) will be included to investigate 1:1 dose transfer from their previous insulin treatment to IDegAsp 30 and efficacy and safety of subsequent titration.

Using metformin under conditions not approved by labelling or not in accordance with local instructions for use is not allowed, since improper use of medication affecting the primary endpoint may impair the interpretation of data.

Patients with type 2 diabetes inadequately controlled on a OD or BID premixed/self-mixed or basal insulin regimen with or without metformin will benefit from treatment intensification to a BID insulin regimen and/or dose optimisation using a T-T-T approach.

Subjects on premixed or self-mixed HI BID will benefit from a transfer to BIAsp 30 BID which has demonstrated safer hypoglycaemia profile than premixed HI,<sup>9</sup> or to IDegAsp 30 BID which, in the phase 3 studies,<sup>8</sup> has indicated to have safer hypoglycaemia profile than BIAsp 30 BID. Therefore it is expected that the lower hypoglycaemia risk will allow for safer insulin titration of both IDegAsp 30 BID and BIAsp 30 BID resulting in improvement of glycaemic control.

Subjects already on premixed insulin analogue BID will benefit from treatment with BIAsp 30 and IDegAsp 30 as they will be offered frequent follow-up in a T-T-T setting, and therefore further improvement in glycaemic control is expected.

Eligible subjects are presenting an HbA<sub>1c</sub> 7.0 – 10.0% (both inclusive), even though they have already been treated with insulin and will benefit from treatment intensification. The upper HbA<sub>1c</sub> limit of 10% is set in order to avoid inclusion of subjects presenting compliance issues. Amongst the type 2 diabetic population, one likely cause of elevated HbA<sub>1c</sub> is poor compliance with lifestyle recommendations and/or treatment regimens. This T-T-T trial involves a rigorous protocol that requires strict adherence on the part of investigators and subjects. Thus, good subject compliance is critical for the conduct of this trial.

The trial will include subjects with a BMI of  $\leq 40.0$  kg/m<sup>2</sup>. A BMI limit of  $\leq 40.0$  kg/m<sup>2</sup> was chosen to include as broad a population as possible while excluding morbidly obese individuals who might be more insulin resistant and require a more individualised treatment.

Subjects with recurrent severe hypoglycaemia, proliferative retinopathy or uncontrolled severe hypertension and subjects who within the last 6 months prior to screening (Visit 1) have experienced a CV event as defined in the exclusion criteria are not eligible for inclusion due to the T-T-T approach in the trial with weekly optimisation of insulin therapy aiming for normoglycaemia.

Donation of blood is not allowed since blood donation can affect the primary endpoint, i.e. HbA<sub>1c</sub> results. Patients who donate blood  $\leq 1$  month prior to screening (Visit 1) are not eligible to participate in the trial and subjects who donate blood during the trial should be withdrawn from the trial.

Subjects with impaired renal or hepatic function are not eligible, as the use of IDeg in these populations will be investigated in separate trials.

## 7 Trial schedule

Planned duration of recruitment period (First patient first visit (FPFV) – last patient first visit (LPLV)):	28 weeks
Planned date for FPFV:	Q2 2016
Planned date for last patient last visit (LPLV):	Q2 2017
The end of the clinical trial is defined as last patient last visit (LPLV)	
Planned completion of clinical trial report (CTR):	Q4 2017

The screening rate and the screen failure rate will be followed closely on regular basis in order to estimate when to stop screening. All investigators will be notified immediately when the enrolment period comes to an end. Hereafter, no more subjects can be screened, and the interactive voice/web response system (IWRS) will be closed for screening. All subjects enrolled and eligible for randomisation will be randomised.

Information of the trial will be disclosed at [clinicaltrials.gov](http://clinicaltrials.gov) and [novonordisk-trials.com](http://novonordisk-trials.com). According to the Novo Nordisk Code of Conduct for Clinical Trial Disclosure, it will also be disclosed according to other requirements such as those of the International Committee of Medical Journal Editors (ICMJE)<sup>15</sup>, the Food and Drug Administration Amendment Act (FDAAA)<sup>16</sup>, European Commission Regulation for EudraCT<sup>17</sup> and other relevant recommendations or regulations. If a patient requests to be included in the trial via the Novo Nordisk e-mail contact at these web sites, Novo Nordisk may disclose the investigator's contact details to the patient.

## 8 Methods and assessments

Timing of assessments and procedures for the scheduled visits and phone contacts are described in the section below and in the flowchart (please refer to section [2](#)).

### 8.1 Visit procedures

#### 8.1.1 Screening visit (Visit 1)

Screening will take place approximately one week and no more than 14 days prior to the randomisation (Visit 2). Before screening takes place, subjects will be provided with written information about the trial and the procedures involved, in accordance with local requirements. Subjects will be fully informed, orally and in writing about their responsibilities and rights while participating in the trial, as well as about possible advantages/disadvantages when being treated with the trial medication (IDegAsp 30, BIAsp 30 and BHI 30). Subjects will have the opportunity to ask questions and have ample time to consider participation. The informed consent process may take place before the screening visit (Visit 1).

Subjects who wish to participate in the trial will sign and date the informed consent form for the trial before any trial-related procedures.

All subjects must be provided with a copy of their own signed and dated Informed Consent form(s).

Subjects enrolled in the trial will be provided with a card stating that he/she is in a trial, site contact address(es) and telephone number(s). The subjects must keep the card with them at all times. The subjects should be instructed to return the card to the investigator at the subjects' last visit or destroy the card after the last visit.

At screening (Visit 1), the subjects will be assigned a unique subject identification (ID) which will remain the same throughout the trial. The subject ID will consist of 6 digits (the first 3 digits indicating site number and the last 3 digits indicating subject number).

The investigator must keep a subject screening log, a subject identification code list and a subject enrolment log. The subject screening log and subject enrolment log may be combined in one list and may be generated from IWRS.

Subjects will continue on their current diabetes treatment until the day before the randomisation visit (Visit 2). Subjects will not be supplied with any trial product until the randomisation visit.

At screening (Visit 1), information on type and daily dose of current antidiabetic treatment should be recorded in the eCRF. Dose and frequency of metformin should not be changed during the trial unless for safety reasons. In case of change in metformin dose during the trial this should be registered on the antidiabetic treatment form in the eCRF.

The following will be performed and/or recorded in the eCRF in addition to what is already described in the flow chart and in the assessment sections (sections [8.5-8.6](#)):

- Signed informed consent(s)
- Demography:
  - date of birth
  - sex
  - race
  - ethnicity
- Diagnosis of diabetes:
  - date of diagnosis of diabetes
- Diabetes treatment history:
  - current diabetes treatment (prior to the screening visit and until randomisation)
  - dose of current diabetes treatment
  - start date of current diabetes treatment

### **8.1.2 Screening failures**

If the subject is ineligible to participate in the trial the subject will be considered a screening failure.

For screening failures the screening failure form must be completed with the reason for not continuing in the trial. Serious and non-serious adverse events from screening failures must be transcribed by the investigator into the eCRF. Follow-up of serious adverse events (SAEs) should be carried out according to section [12](#). A screening failure session must be made in the IWRS.

#### **8.1.2.1 Re-screening**

Re-screening is NOT allowed if the subject has failed one of the inclusion or exclusion criteria, this includes no re-sampling if the subject has failed one of the inclusion or exclusion criteria related to laboratory parameters. Randomisation visit (Visit 2) – to follow-up (P 30)

### **8.1.3 Randomisation visit (Visit 2) – to follow-up visit (P 30)**

For randomisation visit (Visit 2) to follow-up contact (P 30), please see flow chart and assessment sections (sections [8.5– 8.6](#)).

At Visit 3, information on first date, dose and time point on trial product must be recorded.

At last treatment visit (Visit 28) information on last date, dose and time point on trial product (IDegAsp 30 or BIAsp30) must be recorded.

At Visit 28 subjects will be instructed to switch IDegAsp 30 or BIAsp 30 treatment to BHI 30 until the 7 days follow-up visit FU1 (Visit 29). The first dose of insulin BHI 30 should be given at the earliest 24 hours after last dose of IDegAsp 30 or BIAsp 30.

At the follow-up visit FU1 (Visit 29), no earlier than 7 days after Visit 28, information on date, dose and time point (breakfast/ main evening meal) of the BHI 30 injection on the first day (Visit 28), 2 days and 4 days after Visit 28 and on the last day before the FU1 (Visit 29) must be recorded.

All subjects must attend the follow-up visit FU 1 (Visit 29) fasting without taking BHI 30 in the morning of the follow-up visit.

FU 2 (P 30) will be performed as a phone contact. At this contact focus will be on cardiovascular events and AEs reported by the subject.

#### **8.1.4 Phone contacts**

A phone contact may be converted to a site visit if preferred. Scheduled phone contacts and their time points are included in the flow chart (section [2](#)).

Before any phone contacts, the delegated site staff and the subject should agree on the timing and direction of the call. The investigator remains responsible for ensuring the contacts occur, even if it is agreed that subject should be calling the site.

If a planned phone contact for some reason is not performed, the investigator must ensure that the phone contact is performed within the visit window for the originally planned phone contact.

#### **8.1.5 Unscheduled visits**

If the subject attends the clinic for an unscheduled visit, the Unscheduled Visit form must be completed unless the subject attends the clinic to obtain additional trial products or auxiliary supplies. If the subject wants to obtain additional trial products an additional dispensing session should be made in the IWRS and the subject records should be updated accordingly.

#### **8.1.6 Re-scheduled visits**

If the subject attends a fasting visit in a non-fasting condition, blood sampling must be re-scheduled within the next two working days.

#### **8.1.7 Withdrawn subjects**

Subjects randomised in error must be withdrawn from the trial.

If a subject is withdrawn from the trial, the investigator must aim to undertake procedures similar to those for the last treatment visit (Visit 28), as soon as possible. This should be followed by the 7 days FU1 (Visit 29) and the 30 days FU2 phone contact (P 30). The end-of-trial form must be completed, and final drug accountability must be performed even if the subject is not able to come to the site. A withdrawal session must be made in IWRS. The case book must be signed.

Although a subject is not obliged to give his/her reason(s) for withdrawing from a trial, the investigator should make a reasonable effort to ascertain the reason(s), while fully respecting the subject's rights. Where the reasons are obtained, the primary reason(s) (adverse event, non-compliance with protocol or other) for discontinuation must be specified in the eCRF.

Subjects on insulin should be switched to BHI 30 at the last treatment visit (Visit 28) until the follow-up visit FU1 (Visit 29) and an appointment for the 30 days FU2 phone contact (P30) should be made.

## 8.2 Concomitant illness and medical history

A **concomitant illness** is any illness that is present at the start of the trial (i.e. at the first visit) or found as a result of the screening procedures performed at screening (Visit 1) or for lipids and urine albumin/creatinine ratio performed at randomisation (Visit 2).

**Medical history:** is an account of medical events that the subject has experienced in the past. Relevant medical history as judged by the investigator should be reported.

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

Any change to a concomitant illness should be recorded during the trial. A clinically significant worsening of a concomitant illness must be reported as an AE.

## 8.3 Concomitant medication

A **concomitant medication** is any medication (including herbal or traditional Chinese medication allowed by the investigator), other than the trial products, which is taken during the trial.

Details of any concomitant medication must be recorded at trial entry (i.e. at the first visit) and until Visit 29 on the concomitant medication form in the eCRF. Information on pre-trial antidiabetic treatment must be recorded on the antidiabetic treatment form in the eCRF. Any changes in concomitant medication must be recorded at each visit as they occur.

The information collected for each concomitant medication includes (at a minimum) trade name or generic name, indication, start date and stop date or continuation.

If a change is due to an AE, then this must be recorded and reported according to section [12](#). If the change influences the subject's eligibility to continue in the trial, the monitor must be informed.

## 8.4 Diaries

All subjects will be provided with diaries. The subject's diaries will be collected after each site visit and will be kept at the trial site as source documents.



The subjects will be instructed in recording the following in the diary:

- date and value of all 2-point profile (SMPG) measurements (V3-V28)
- date, actual clock time (hh:mm) and value of all 9-point profile (SMPG) measurements (V2, V14, V18 and V28)
- dates and doses of IDegAsp 30 or BIAsp 30, on three days before Visit (V3-V28)
- date, time point and dose of first doses of trial product (IDegAsp 30 or BIAsp 30) (V3)
- date, time point and dose of last dose of trial product (IDegAsp 30 or BIAsp 30) (V28)
- date, dose and time point (breakfast/ main evening meal) of the BHI 30 injection on the first day (V28), 2 days and 4 days after Visit 28 and on the last day before FU1 (V29) hypoglycaemic episodes V2-V29
- medical problems (V2-P30)
- changes in concomitant medication (including changes in doses of metformin if any) (V3-V29)

The above data will be transcribed into the eCRF by the investigator.

The investigator is allowed to record the following in the diary:

- prescribed doses of trial insulin
- time and date of next visit and/or phone contact
- subject ID and site contact details

Diaries must be reviewed by the investigator to ensure that AEs, including any overall change in health and concomitant medication, are reported. The review must be documented on the front page of the diary and data must be transcribed into the eCRF.

If clarification of entries or discrepancies in the diary is needed, the subject should be questioned and a conclusion made in the medical record. Care should be taken not to bias the subject.

## **8.5 Laboratory assessments**

For laboratory analysis of efficacy and safety parameters a total of approximately 75 ml blood will be drawn during the 28 weeks of the trial.

The laboratory analyses will be performed by a central laboratory unless otherwise specified. Descriptions of assay methods, laboratory supplies and procedures for obtaining samples, handling and storage of samples and information on who will perform the assessments, will be described in a trial-specific laboratory manual provided by a central laboratory.

Samples will be coded in order to keep subject identity anonymous.



Laboratory results, except for antibody results, will be sent by the central laboratory to the investigator on an ongoing basis. Data from the analysis will be included in the clinical trial report and in the trial database. The data (including the antibody results) will also be included in an analytical report. All laboratory printouts must be dated and signed by the investigator on the day of evaluation. If a result is outside the normal range, the investigator must judge whether the abnormality is clinically significant. If considered clinically significant the result must be reported as an AE according to section [12](#).

Antibody results will be available after the end of trial and will be reported to the investigator for notification only.

If a clinical laboratory abnormality, which is clinically significant at screening (Visit 1) or for lipids and urine albumin/creatinine ratio is clinical significant at randomisation (Visit 2), this must be recorded on the medical history/concomitant illness form. In the case of any clinical significant worsening since screening (Visit 1) the investigator must comment in the subject records and the change must be reported as an AE according to section [12](#).

All samples will be destroyed on an ongoing basis after analysis except for antibody samples which will be destroyed after receiving final feedback from the authorities.

Blood samples will be drawn to determine levels of the following:

- **HbA<sub>1c</sub>**
- **FPG** – (subjects must be fasting)
- **lipids** – (subjects must be fasting)
  - cholesterol (total)
  - HDL cholesterol
  - LDL cholesterol
  - triglycerides
- **haematology**
  - erythrocytes
  - haematocrit
  - haemoglobin
  - leucocytes
  - thrombocytes
  - differential count (eosinophils, neutrophils, lymphocytes, basophils and monocytes)

- **biochemistry**
  - creatinine
  - total protein
  - ALT/ serum glutamic pyruvic transaminase (SGPT)
  - AST/serum glutamic oxaloacetic transferase (SGOT)
  - AP
  - sodium
  - potassium
  - albumin
  - bilirubin (total)
- **Pregnancy test** performed as a blood sample for females of childbearing potential
- **Insulin antibodies** (subjects must be fasting)
  - insulin degludec specific antibodies (IDegAsp 30 arm)
  - insulin aspart specific antibodies (both arms)
  - cross-reacting antibodies to human insulin (both arms)

Urine samples will be taken for the following parameters:

- **albumin/creatinine ratio by urine spot** must be sent for analysis at the central laboratory
- **urinalysis by stick** – urine samples must be analysed centrally for:
  - blood
  - protein
  - ketones

Pregnancy test using urine-dipsticks will be performed locally during the trial if a menstrual period is missed or if pregnancy is suspected.

Laboratory equipment may provide standard analyses not requested in the protocol but produced automatically in connection with the requested analyses. Such data will not be transferred to the CRF or the trial database, but abnormal values will be reported to the investigator. The investigator must review all laboratory results for concomitant illnesses and adverse events and report these according to this protocol.

## **8.6 Other assessments**

### **8.6.1 Insulin dose**

During the trial, starting at the randomisation visit (Visit 2), the subjects will be instructed to report the date and the insulin dose in the diary three consecutive days before each visit.

The recommended insulin doses will be calculated in the eCRF based on recommendations from the insulin titration guideline (Appendix A).

### **8.6.2 Physical examination**

Physical examination should include:

- head, ears, eyes, nose, throat, neck
- respiratory system
- cardiovascular system
- gastrointestinal system incl. mouth
- musculoskeletal system
- central and peripheral nervous system
- skin

In case of an “abnormal, clinically significant” finding, the investigator must comment in the subject records and, if it occurs at screening (Visit 1), record this on the medical history/concomitant illness form.

Any new abnormal, clinically significant finding during the trial and any clinical significant worsening from baseline must be reported as an AE.

### **8.6.3 Vital signs**

Diastolic blood pressure, systolic blood pressure and pulse will be assessed while the subject is sitting. Measurements should be performed after resting for 5 minutes. At the screening visit (Visit 1) and the last treatment visit (Visit 28) only one blood pressure measurement is required.

In case of an “abnormal, clinically significant” finding at screening, the investigator must record the finding on the medical history/concomitant illness form.

Any new abnormal, clinically significant finding during the trial and any clinical significant worsening from baseline must be reported as an AE.

### **8.6.4 Eye examination**

A baseline funduscopy/fundus photography will be performed by the investigator, a local Ophthalmologist or an Optometrist according to local practice. The funduscopy/fundus photography performed for any reason unrelated to this trial within 12 weeks prior to screening visit (Visit 1) is acceptable provided results are available before randomisation and no clinical symptoms suggestive of eye disease have occurred in the meantime. If the funduscopy/fundus photography is performed before the subject has signed the informed consent form, it must be documented in the subject records that the reason for performing the procedure was not related to this trial.

Fundoscopy/fundus photography performed within the three weeks before last treatment visit (Visit 28) is acceptable as Visit 28 data. To ensure a funduscopy/fundus photography in time before Visit 28 the investigator will assist the subject in making an appointment for the final eye examination at Visit 22 (roughly six weeks before Visit 28).

Result of the funduscopy/fundus photography will be interpreted locally by the investigator in relation to the trial. To document this, the investigator must sign and date the result page. The interpretation must follow the categories:

- normal
- abnormal, not clinically significant
- abnormal, clinically significant

In case of an “abnormal, clinically significant” funduscopy/fundus photography at baseline, the investigator must record this on the medical history/concomitant illness form.

A new abnormal, clinically significant finding during the trial and any clinical significant worsening from baseline must be reported as an AE.

The dates of funduscopy/fundus photography must be recorded in the eCRF and be source data verifiable.

### **8.6.5 Electrocardiogram – 12 lead**

At baseline, a 12-lead ECG must be performed and interpreted locally by the investigator in relation to the trial. To document this, the investigator must sign and date the ECG print out.

The baseline ECG should be performed between the screening (Visit 1) and the randomisation (Visit 2), and results must be available before randomisation. The end of treatment ECG should be performed at Visit 28.

The interpretation must follow the categories:

- normal
- abnormal, not clinically significant
- abnormal, clinically significant

In case of “abnormal, clinically significant”, the investigator must record the finding on the concomitant illness form if it is present at baseline. A new abnormal, clinically significant finding during the trial and any clinical significant worsening from baseline must be reported as an AE.

The dates of the ECG must be recorded in the eCRF and be source data verifiable.

### **8.6.6 Height**

At screening visit (Visit 1) height (without shoes) will be measured. Height is measured in meters and recorded to two decimal places.

### **8.6.7 Body weight**

Body weight will be measured in kilograms (kg) without coat and shoes and wearing only light clothing. Body weight will be recorded to one decimal place. The subjects must attend these visits fasting (i.e. only intake of water since midnight is allowed) except for screening visit (Visit 1).

### **8.6.8 Patient reported outcome questionnaires**

A self-completed PRO battery containing four questionnaires will be used to investigate the subject's treatment satisfaction, productivity and quality of life in relation to IDegAsp 30 and BIAsp 30 during the course of the trial.

The self-completed PRO battery consists of the following:

- Health Related Quality of Life questionnaire (SF-36 version 2)<sup>11,12</sup>
- TRIM-D<sup>13</sup> and TRIM-D Device<sup>13</sup>
- Device Specific Questionnaires I and II<sup>14</sup>

Please refer to section [17](#) for statistical considerations on PRO data.

The self-completed PROs will be administered at selected scheduled visits. For an overview of the applicable visits, please refer to the flow chart in section [2](#). The self-completed questionnaires must be completed by the subject him/herself and should preferably be completed after conclusion of all fasting related activities but before any other visit related activities. All questionnaires will be supplied in linguistically validated versions in languages relevant for this trial.

The PRO questionnaires must be reviewed for completeness and for potential AEs and if any overall change in health are reported. Review must be documented, on the front page of the questionnaires and potential AEs must be reported according to section [12.2](#). Site staff is only allowed to write in the headers and on the front page of the questionnaire. If clarification of entries is needed, the subject should be questioned and a conclusion made in the subject's medical record. Care should be taken not to bias the subject.

All questionnaires will be supplied in 3-layer NCR paper CRFs. The original of the completed CRF will be shipped to Novo Nordisk for data-entry. The first copy (2<sup>nd</sup> page) is monitor's copy for filing. The second copy (3<sup>rd</sup> page) must be filed at site as source documents.

### 8.6.9 Self measured plasma glucose

At screening (Visit 1) subjects will be supplied with a glucose meter and instructions on use of the device including regular calibration according to the manufacturer's instructions. Subjects will also be provided with written instructions. Sites will, as necessary, repeat the instructions of use at visits to the clinic.

The glucose meters use test strips calibrated to plasma values. Therefore, all glucose measurements performed with drawn capillary blood are automatically calibrated to plasma equivalent glucose values, which will be shown on the display and are the values to be used.

Subjects will be instructed in how to record the results of the SMPG values in the provided diaries and should only record the PG values based on glucose meter measurements. The record of each PG measurement must include date and PG value.

All SMPG data from the diary will be transcribed into the eCRF during the following visit throughout the trial. The SMPG values will be recorded for insulin titration purposes.

All SMPG data obtained at a phone contact will be entered into the eCRF during or following the phone contact. When the subject comes in for the following site visit and if there is a discrepancy between the diary and the SMPG data obtained at the phone contact the diary will be considered source data and values should be changed accordingly, by the subject, and a comment should be entered into the eCRF.

The targets for the titration of the insulin treatment are provided in the insulin titration guideline (Appendix A). The target for insulin treatment is given as PG values.

#### 8.6.9.1 2-point profile (SMPG)

Subjects will be asked to perform SMPG measurements before breakfast and before main evening meal. Pre-breakfast measurements should preferably be performed on the day of the dose adjustment and the two consecutive days just before Visit 3-28. Pre-main evening meal measurements should preferably be performed three consecutive days just before Visit 3-28. The measurements should be performed using the glucose meter provided. SMPG measurements before breakfast should preferably be performed after having consumed only water since midnight. These measurements are required for optimal insulin dose adjustment and maintenance as described in the titration guideline (Appendix A).

#### 8.6.9.2 9-point profile (SMPG)

Subjects will be instructed to perform a 9-point profile (SMPG) before Visits 2, 14, 18 and 28. The 9-point profiles should be started in the morning 2 days before the visits. Note that the 9-point (SMPG) profile is overlapping with the 2-point (SMPG) profile as illustrated in [Table 8-1](#) below

The PG levels should be measured and recorded in the diary at the time points listed in [Table 8–1](#), always starting with the measurement before breakfast on 2 days before the visit.

**Table 8–1 Timepoints for 9-point profile (SMPG)**

Timepoint	2 Days before visit	1 Day before visit
Before breakfast	✓	✓
90 min after the start of breakfast	✓	
Before lunch	✓	
90 min after the start of lunch	✓	
Before main evening meal	✓	
90 min after the start of main evening meal	✓	
Before bedtime	✓	
At 4 am	✓	

## 8.7 Adverse events

Adverse Events (AEs) must be reported at each visit in accordance with the procedures outlined in section [12](#). During each contact with the trial site staff, the subject must be asked about AEs and technical complaints. This must be documented in the subject’s medical record.

### 8.7.1 Adverse events with additional data collection

For some AEs additional data collection is required and specific event forms must be completed in the eCRF in addition to the adverse event (AE). Furthermore some of these events are subject to adjudication as described in section [12.7.2](#).

[Table 12–1](#) provides an overview of events requiring additional data collection on specific forms and/ or are subject to event adjudication.

Below a list of events requiring additional data collection:

- Medication errors
- Acute coronary syndrome
- Cerebrovascular events
- Neoplasms

In case any of these events fulfil the criteria for a serious adverse event, please report accordingly. Refer section [12.2](#) and [Figure 12–1](#) for further details.

#### 8.7.1.1 Medication errors

If a medication error is observed during the trial, the following additional information should be obtained:

- Trial product(s) involved
- Classification of medication error
  - Wrong drug(s) administered
  - Wrong route of administration
  - Wrong dose administered
- Whether the subject experienced any hypoglycaemic episode and/or adverse event(s) as a result of the medication error
- Suspected primary reason for the medication error

#### **8.7.1.2 Acute coronary syndrome**

If an event of Acute Coronary Syndrome (ranging from unstable angina pectoris to myocardial infarction) is observed during the trial the following additional information must be reported if available

- Duration of symptoms
- Changes in ECG
- Collection of cardiac biomarkers
- Cardiac imaging
- Cardiac stress testing
- Angiography
- Use of thrombolytic drugs
- Revascularisation procedures

#### **8.7.1.3 Cerebrovascular events**

If a cerebrovascular event (e.g. transient ischaemic attack, stroke, haemorrhage) is observed during the trial the following additional information must be reported if available:

- Type of event (e.g. TIA, Stroke)
- Contributing condition
- Neurologic signs and symptoms
- History of neurologic disease
- Imaging supporting the event
- Treatment given for the event



#### **8.7.1.4 Neoplasm**

All events of benign, pre-malignant/carcinoma in-situ and malignant neoplasms must be reported during the trial and the following additional information should be obtained if available as part of standard of care:

- Type of neoplasm
- Symptoms leading to identification of event
- Diagnostic imaging
- Pathological examination results
- Treatment given for the event
- Participation in screening programs
- Relevant Risk factors associated to the event

#### **8.8 Recording of Hypoglycaemia**

Plasma glucose should always be measured and recorded when a hypoglycaemic episode is suspected.

All plasma glucose values:

- equal or below 3.9 mmol/L (70 mg/dL) or
- higher than 3.9 mmol/L (70 mg/dL) when they occur in conjunction with hypoglycaemic symptoms

should be recorded by the subject in the diary.

These must be transcribed into the eCRF (hypoglycaemic episode form) throughout the trial from Visit 2 to Visit 29.

The record should include the following information:

- The plasma/blood glucose level before treating the episode (if available)
- Date and time of hypoglycaemic episode
- Whether the episode was symptomatic (Yes/No)
- Whether the subject was able to treat him/herself
- Date and time and dose of last trial insulin administration prior to episode
- Date and time of last main meal prior to episode
- Whether the episode occurred in relation to physical activity
- Change in any concomitant illness
- Any sign of fever or other acute disease Whether the subject was asleep when the episode occurred
  - If yes, whether the symptoms of the episode woke up the subject

The answer to the question: “Was the subject able to treat him/herself?” must be answered “No” for an episode requiring assistance of another person to actively administer carbohydrates, glucagon or IV glucose or other corrective actions. Plasma glucose concentrations may not be available during an event, but neurological recovery following the return of plasma glucose to normal is considered sufficient evidence that the event was induced by a low plasma glucose concentration.

Oral carbohydrates should not be given if the subject is unconscious.

If the question “Was the subject able to treat him/herself?” is answered “No”, the following information should be recorded by the subject:

- Who assisted in the treatment of the hypoglycaemic episode (i.e. medical person or non-medical person)
- Where the treatment was administered (in clinic/ emergency room/ hospital or other. If the subject was treated in clinic/emergency room/hospital, whether they were transported in an ambulance or not.)
- Type of treatment provided by other person (ie oral carbohydrates, glucagon, IV glucose or other)
- Were symptoms alleviated by the administration of treatment?
- Factors contributing to the episode (ie physical activity, missed meal, diet changed, medication error (ie overdose, mix-up between products), miscalculation of insulin dose, other factors not listed or unknown)
- Did the subject experience seizure?
- Was the subject unconscious/comatose?
- Did the subject experience any of the following symptoms?
  - Autonomic: sweating, trembling, hunger or palpitations (rapid or irregular heart beat)
  - Neuroglycopenic: confusion, drowsiness, speech difficulty, visual disturbances, odd behaviour, impaired balance or incoordination (reduced ability to coordinate movement)
  - General malaise: headache or malaise (feeling discomfort/unease)
  - Other symptoms? Please specify

The subject must be re-trained in how to report hypoglycaemic episodes if the investigator identifies low SMPG values not reported as hypoglycaemic episodes.

If a hypoglycaemic episode fulfils the criteria for an SAE then an AE form and a safety information form must also be filled in, see Section 12

### **8.8.1 Definitions of Hypoglycaemia**

A hypoglycaemic episode will be defined as treatment emergent if the onset of the episode occurs on or after the first day of randomised treatment administration, and no later than seven days after the last dose of randomised treatment.

Hypoglycaemic episodes will be defined as nocturnal if the time of onset is between 00:01 and 05.59 inclusive.

### 8.8.1.1 Confirmed hypoglycaemia

Confirmed hypoglycaemic episodes are defined as episodes that are either:

- severe (i.e., an episode requiring assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions) or
- an episode biochemically confirmed by a plasma glucose value of  $<3.1$  mmol/L (56 mg/dL), with or without symptoms consistent with hypoglycaemia

In normal physiology, symptoms of hypoglycaemia occur below a plasma glucose level 3.1 mmol/L (56 mg/dL).<sup>18,19</sup> Therefore, Novo Nordisk has included hypoglycaemia with plasma glucose levels below this cut-off point in the definition of confirmed hypoglycaemia.

### 8.8.1.2 ADA classification of hypoglycaemia

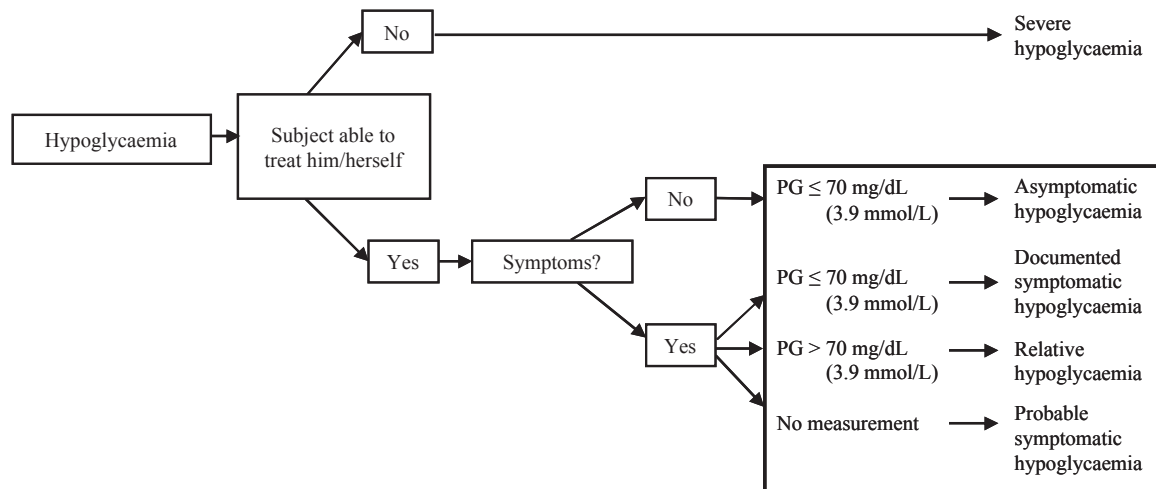
**Severe hypoglycaemia:** An episode requiring assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions.

**Asymptomatic hypoglycaemia:** An episode not accompanied by typical symptoms of hypoglycaemia, but with a measured plasma glucose concentration  $\leq 3.9$  mmol/L (70 mg/dL).

**Documented symptomatic hypoglycaemia:** An episode during which typical symptoms of hypoglycaemia are accompanied by a measured plasma glucose concentration  $\leq 3.9$  mmol/L (70 mg/dL).

**Relative hypoglycaemia:** An episode during which the person with diabetes reports any of the typical symptoms of hypoglycaemia, and interprets those as indicative of hypoglycaemia, but with a measured plasma glucose concentration  $> 3.9$  mmol/L (70 mg/dL).

**Probable symptomatic hypoglycaemia:** An episode during which symptoms of hypoglycaemia are not accompanied by a plasma glucose determination (but that was presumably caused by a plasma glucose concentration  $\leq 3.9$  mmol/L (70 mg/dL)).



**Figure 8–1 ADA classification of hypoglycaemia**

## 8.9 Subject compliance

At each visit the investigator will emphasise the necessity for the subject to adhere to trial procedures in order to encourage subject compliance.

Substantial failure to comply with the prescribed insulin dosage regimen can lead to withdrawal. In addition, the investigator should assess the compliance of the subject at each visit based on a review of glycaemic control, adherence of the visit schedule, completion of the subject's diary including the SMPG profiles. If a subject is discovered to be non-compliant, the investigator must inform the subject of the importance of taking trial products as directed.

For specification of subject evaluability, please refer to section [17](#).

## 9 Trial supplies

Trial supplies comprise trial products and auxiliary supplies.

Trial products comprise of the investigational medicinal products (IMPs).

Auxiliary supplies comprise supplies other than trial products, e.g. needles and BG meter.

No trial products should be dispensed to any person not enrolled in the trial.

### 9.1 Trial products

The IMPs during the treatment will be as follows:

- IDegAsp 30 100 U/ml, 3 ml pre-filled pen PDS290 (FlexTouch<sup>®</sup>)
- Biphasic insulin aspart 30 (BIAsp 30) (NovoMix<sup>®</sup> 30), 100 U/ml, 3 ml pre-filled pen (FlexPen<sup>®</sup>)
- Biphasic human insulin 30 (BHI 30) (Novolin<sup>®</sup> 30), 100 U/ml prefilled pen (FlexPen<sup>®</sup>)

Please refer to the Trial Materials Manual (TMM) provided by Novo Nordisk for details regarding the IMPs. The TMM will be distributed to investigational sites.

Novo Nordisk, Denmark, will provide the IMPs.

Trial products must not be dispensed to any person not included in the trial.

### 9.2 Non-investigational medicinal product

Metformin that is been taken by subjects when randomised (Visit 2) is a non-investigational medicinal product (NIMP) and will not be supplied by Novo Nordisk. Metformin must be purchased or otherwise supplied to subjects according to local labelling.

### 9.3 Labelling

Labelling of the IMP will be in accordance with Annex 13,<sup>20</sup> local law and trial requirements.

Please refer to the TMM provided by Novo Nordisk for details regarding trials products standard packages.

The subjects will be provided with a direction for use for IDegAsp 30, BIAsp 30 and for BHI 30.

### 9.4 Storage, accountability and destruction

#### 9.4.1 Storage and handling of trial products

Insulin preparations (both not in-use and in-use) must not be exposed to excessive heat or direct sunlight.

Insulin preparations which have been frozen must not be used.

Storage conditions for IDegAsp 30:

- Store in a refrigerator (2°C to 8°C)
- Do not freeze
- Keep the cap on in order to protect from light. Pen cap must be put back on after injection.
- In-use: do not refrigerate. Store below 30°C. Use within 4 weeks.
- IDegAsp 30 should not be used if it does not appear clear and colourless

Storage conditions for BIAsp 30:

- Store in a refrigerator (2°C to 8°C)
- Do not freeze
- Keep the cap on in order to protect from light. Pen cap must be put back on after injection.
- In-use: do not refrigerate. Store below 30°C. Use within 4 weeks. It is recommended to let BIAsp 30 reach room temperature before re-suspending as instructed for the first time use.
- BIAsp 30 must not be used if the suspension does not appear uniformly white and cloudy after resuspension

Storage conditions for BHI 30:

- Store in a refrigerator (2°C to 8°C)
- Do not freeze
- Keep the cap on in order to protect from light. Pen cap must be put back on after injection.
- In-use: do not refrigerate. Store below 30°C. Use within 6 weeks. It is recommended to let BHI 30 reach room temperature before re-suspending as instructed for the first time use.
- BHI 30 must not be used if the suspension does not appear uniformly white and cloudy after resuspension

Please refer to the TMM provided by Novo Nordisk for details regarding handling of trial products at sites.

The investigator must ensure the availability of proper storage conditions, and record and evaluate the temperature. The investigator must inform Novo Nordisk immediately if any trial product has been stored outside defined conditions (e.g. outside temperature range). The temperature during storage must either be recorded continuously with an acoustic alarm or recorded and evaluated every working day using as a minimum a calibrated minimum/maximum thermometer. If recorded continuously each site needs to log weekly checks of the device. If using a minimum/maximum thermometer, the temperature reading must be transferred to the temperature log every working day. Storage facilities should be checked frequently (at least once every working day). In case of storage outside the temperature range the investigator must contact the monitor immediately. Trial products stored outside the temperature range are not to be used and must be stored separately within allowed

temperature ranges until after evaluation of condition performed by Novo Nordisk. Fifteen minutes outside the indicated range is negligible and allowed, and should not be recorded as a deviation.

Returned trial products (used/partly used or unused including empty packaging material) must be stored separately from non-allocated trial products.

#### **9.4.2 Drug accountability and destruction of trial products**

The trial products will be dispensed to each subject as required according to treatment group. The IWRS will allocate trial product to the subject at each dispensing or randomisation visit. The correct dispensing unit numbers (DUNs) must be dispensed to the subject.

The investigator or delegated person, e.g. trial nurse, will perform drug accountability using the IWRS drug accountability module. All tasks concerning storage and drug accountability can be delegated to a pharmacist.

Subjects are instructed to return all used, partly used and unused trial product at each dispensing visit, at last treatment visit (Visit 28) and at the end of follow-up FU1 (Visit 29), please refer to the flow chart (section [2](#)).

The investigator must keep all returned trial products (used, partly used or unused including empty packaging material) until they are returned to the monitor.

The monitor will reconcile the drug accountability using the IWRS drug accountability module.

The monitor is responsible for arranging the destruction of used and unused trial products after drug accountability. The destruction of trial products will be recorded on a destruction form, which will be performed according to local procedures and must be documented.

#### **9.5 Auxiliary supply**

The following will be supplied by Novo Nordisk in accordance with the TMM:

- NovoFine® needles
- Blood glucose meters, incl. lancets, plasma-calibrated test strips and control solutions

## **10 Directions for use (DFU) Interactive voice/web response system**

A trial specific IWRS will be set-up, and can be accessed at any time by the internet. Some sessions may be available through a toll-free telephone number. Accessibility to the IWRS must be restricted to and controlled by authorised persons.

IWRS is used for:

- Screening
- Screening failure
- Randomisation
- Withdrawals
- Medication arrival
- Dispensing
- Treatment completion
- Drug accountability
- Data change
- Completion of the trial

This information will be integrated into the eCRF or clinical database.

An IWRS manual and user guide describing the details about using the IWRS will be provided to each trial site.



## 11 Randomisation procedure

Randomisation will be carried out in a (2:1) manner using an IWRS to randomise subjects into the treatment groups: IDegAsp 30 BID or BIAsp 30 BID both in combination with or without metformin.

The treatment is open labelled.

Treatment will be allocated using centralised IWRS. It is important to dispense the exact allocated DUNs to a subject.

It is important for the sites only to dispense medication allocated by the IWRS in order to:

- Secure available stock at site to cover the drug supply needed for the enrolled subjects
- Ensure that no subjects are provided with trial drugs that will expire in between dispensing visits
- Ensure that it will be possible to perform drug accountability by using the IWRS

## 12 Adverse events, technical complaints and pregnancies

### 12.1 Definitions

#### Adverse event

An **adverse event** (AE) is any untoward medical occurrence in a subject administered a product, and which does not necessarily 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 product, whether or not considered related to the product.

**Note:** This includes events from the first trial related activity after the subject has signed the informed consent and until post treatment follow-up period as defined in the protocol (see section [2](#)).

AEs include:

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

The following should **not** be reported as AEs:

- Pre-existing conditions, including those found as a result of screening procedures (pre-existing conditions should be reported as medical history or concomitant illness)
- Pre-planned procedures unless the condition for which the procedure was planned has worsened from the first trial related activity after the subject has signed the informed consent
- Non-serious hypoglycaemia are AEs, but are reported on hypoglycaemic forms instead of on AE forms

#### **Severity assessment definitions:**

- **Mild** – no or transient symptoms; no interference with the subject's daily activities
- **Moderate** – marked symptoms; moderate interference with the subject's daily activities
- **Severe** – considerable interference with the subject's daily activities; unacceptable

### **Causality:**

The following terms and definitions are used when assessing the relationship between each AE and the relevant trial product(s):

- **Probable** - good reason and sufficient documentation to assume a causal relationship
- **Possible** - a causal relationship is conceivable and cannot be dismissed
- **Unlikely** - the event is most likely related to aetiology other than the trial product

### **Final outcome:**

The following terms and definitions are used in assessing the **final outcome** of an AE:

- **Recovered** - the subject has fully recovered, or by medical or surgical treatment the condition has returned to the level observed at the first trial-related activity after the subject signed the informed consent
- **Recovering** - this term is only applicable if the subject has completed the trial or has died from another AE. The condition is improving and the subject is expected to recover from the event.
- **Recovered with sequelae** - the subject has recovered from the condition, but with lasting effect due to a disease, injury, treatment or procedure. If a sequela meets an SAE criterion, the AE must be reported as an SAE.
- **Not recovered** - the condition of the subject has not improved and the symptoms are unchanged, or the outcome is not known at the time of reporting
- **Fatal** - this term is only applicable if the subject died from a condition related to the reported AE. Outcomes of other reported AEs in a subject before he/she died should be assessed as “recovered”, “recovering”, “recovered with sequelae” or “not recovered”. An AE with fatal outcome must be reported as an SAE.
- **Unknown** - this term is only applicable if the subject is lost to follow-up

An AE is either a serious AE (SAE) or a non-serious AE.

### **Serious adverse event**

An **SAE** is an experience that at any dose results in any of the following:

- Death
- A life-threatening<sup>a</sup> experience
- In-patient hospitalisation<sup>b</sup> or prolongation of existing hospitalisation
- A persistent or significant disability or incapacity<sup>c</sup>
- A congenital anomaly or birth defect
- Important medical events that may not result in death, be life threatening<sup>a</sup> or require hospitalisation<sup>b</sup> may be considered an SAE - when based on appropriate medical judgement - they may jeopardise the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.<sup>d</sup> Suspicion of transmission of infectious agents must always be considered an SAE.

- a The term “life threatening” in the definition of SAE refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it was more severe.
- b The term “hospitalisation” is used when a subject:
- Is admitted to a hospital or in-patient, irrespective of the duration of physical stay, or
  - Stays at the hospital for treatment or observation for more than 24 hours
- Medical judgement must always be exercised, and when in doubt, the hospital contact should be regarded as a hospitalisation. Hospitalisations for administrative, trial related and social purposes do not constitute AEs and should therefore not be reported as AEs or SAEs. Hospital admissions for surgical procedures, planned before trial inclusion, are not considered AEs.
- c A substantial disruption of a subject’s ability to conduct normal life functions (e.g. following the event or clinical investigation the subject has significant, persistent or permanent change, impairment, damage or disruption in his/her body function or structure, physical activity and/or quality of life).
- d For example intensive treatment in an emergency room or at home of allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation, or development of drug dependency or drug abuse.

### **Non-serious AE**

A **non-serious AE** is any AE which does not fulfil the definition of an SAE.

### **Adverse Events with additional data collection**

Adverse events with additional data collection are AEs where the additional data will benefit the evaluation of the product safety. In this trial the following AEs require the completion of specific eCRFs :

- Medication errors concerning trial products:
- Acute coronary syndrome (*myocardial infarction or hospitalisation for unstable angina*)
- Cerebrovascular-event (*stroke or transient ischaemic attack*)
- Neoplasms

Some events in this trial will be adjudicated by an independent external committee as described in section 12.7.2.

See [Table 12–1](#) for AEs that require the completion of specific eCRFs and/or are subject to event adjudication.

When reporting adverse events with additional data collection, the following forms must be completed: the AE form and the event specific form. In case any of these events fulfil the criteria for a serious adverse event, please report accordingly (see section 12.2).

**Table 12–1 AEs that require the completion of specific eCRFs and/or subject to event adjudication**

<b>Event</b>	<b>Event adjudication</b>	<b>Specific event form</b>
Fatal event	Yes	No*
Acute coronary syndrome (myocardial infarction or hospitalisation for unstable angina)	Yes	Yes
Cerebrovascular event (stroke or transient ischaemic attack)	Yes	Yes
Neoplasm	No	Yes
Medication errors	No	Yes

\*) A Safety Information Form (SIF) must be completed for all SAEs, refer to section 12.2

### **Medication errors**

A medication error concerning trial products is defined as:

- Administration of wrong drug. Use of wrong DUN is not considered a medication error unless it results in administration of wrong drug.
- Wrong route of administration, such as intramuscular instead of subcutaneous.
- Administration of an overdose with the intention to cause harm (e.g. suicide attempt).
- Accidental administration of a lower or higher dose than intended (-/+ 20%), however the administered dose must deviate from the intended dose to an extent where clinical consequences for the trial subject were likely to happen as judged by the investigator, although they did not necessarily occur

## **Technical complaint**

A **technical complaint** is any communication that alleges defects on trial supplies. The technical complaint may be associated with an AE, but does not concern the AE itself.

Examples of technical complaints:

- The physical or chemical appearance of trial products (e.g. discoloration, particles or contamination)
- The packaging material (e.g. leakage, cracks, rubber membrane issues or errors in labelling text)
- Problems related to devices (e.g. to the injection mechanism, dose setting mechanism, glucose measurement, push button or interface between the pen and the needle)

### **12.2 Reporting of adverse events**

All events meeting the definition of an AE must be collected and reported. This includes events from the first trial-related activity after the subject has signed the informed consent until the end of the post-treatment follow-up period (including FU1 (Visit 29) and FU2 phone contact (P 30)). The events must be recorded in the applicable forms in a timely manner, see timelines described below.

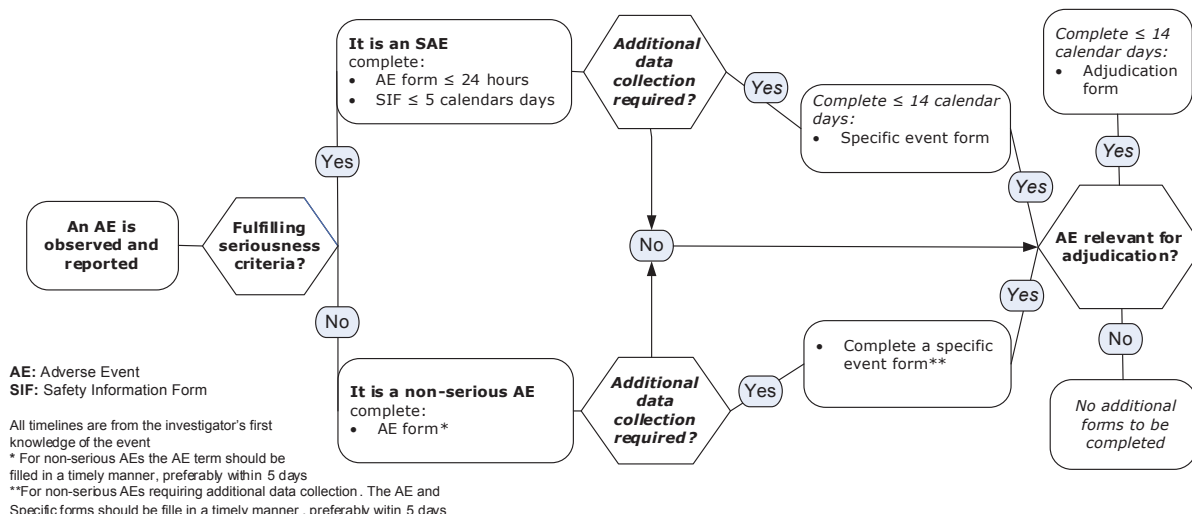
During each contact with the trial site staff (site visits and telephone contacts), the subject must be asked about AEs and technical complaints. For example: “Have you experienced any problems since the last contact?”

All AEs, either observed by the investigator or reported by the subject, must be reported by the investigator and evaluated. Novo Nordisk’s assessment of expectedness is performed according to the current edition of the IDegAsp 30 IB.<sup>8</sup> For BIAsp 30 please refer to the current version of the SPC or locally approved product information.<sup>9</sup>

The investigator should report the diagnosis, if available. If no diagnosis is available, the investigator should record each sign and symptom as an individual AE.

All AEs must be recorded by the investigator on the AE form in the eCRF. A separate AE form should be used for each diagnosis or sign and symptom. For each SAE a safety information form should be completed in addition to the standard AE form, see [Figure 12–1](#).

If several symptoms or diagnoses occur as part of the same clinical picture, one safety information form may be used to describe all the SAEs.



**Figure 12–1 Adverse event flow and timelines**

The investigator must ensure that the worst case severity and seriousness of an event is kept throughout the trial.

- If the AE fulfils the seriousness criteria the investigator must:
  - Enter the AE in the eCRF and tick the seriousness box **within 24 hours** of obtaining knowledge of the SAE
  - Complete and forward the safety information form to Novo Nordisk **within 5 calendar days** of obtaining knowledge of the SAE

Non-serious AEs requiring additional data collection must be reported using both the AE form and the specific event form in a timely manner. The specific event form is a form tailored to collect specific information related to the individual event.

- SAEs with additional data collection, in addition to AE within 24 hours and SIF forms within 5 calendar days, the specific event form must be reported within 14 calendar days of investigator's first knowledge of the event
- For events requiring adjudication, complete the adjudication form within 14 calendar days

The AE form for all non-serious AE should be signed in the eCRF when the event is resolved or at the end of the trial.

For serious adverse events, the AE form must be signed within 7 calendar days from the date the information was entered in the eCRF

If for some reason the eCRF is unavailable, the AE information should be reported to Novo Nordisk by fax, telephone, e-mail or courier within the same timelines.

Contact details (fax, telephone, e-mail and address) are provided to each investigator to be kept in the investigator file.

Novo Nordisk will notify the investigator of trial product-related suspected unexpected serious adverse reactions (SUSARs) in accordance with local requirements and International Conference on Harmonisation for Good Clinical Practice (ICH GCP).<sup>21</sup> In addition, the investigator will be informed of any trial-related SAEs that may warrant a change to any trial procedure.

Novo Nordisk must inform the Institutional Review Board/Independent Ethics Committee (IRBs/IECs) in accordance with local requirements and GCP, unless locally this is an obligation of the investigator. Novo Nordisk must always inform the regulatory authorities in accordance with local requirements and GCP.

### 12.3 Follow-up of adverse events

All SAEs must be followed up until the outcome of the event is “recovered”, “recovered with sequelae” or “fatal”, and until all queries have been resolved. Cases of chronic conditions, cancer or AEs ongoing at time of death (where death is due to another AE) may be closed with the outcome “recovering” or “not recovered”, when the subject has completed the follow up period.

The follow-up information should only include new (corrections or new or additional) information and should be reported **within 24 hours** of obtaining knowledge of the information. This is also the case for previously non-serious AEs which subsequently become SAEs.

Non-serious AEs must be followed until the outcome of the event is “recovering”, “recovered” or “recovered with sequelae” or until the end of the follow-up period stated in the protocol, whichever comes first, and until all queries related to these AEs have been resolved. Cases of chronic conditions or cancer or AEs ongoing at time of death (where death is due to another AE) may be closed with the outcome “recovering” or “not recovered”.

Queries or follow-up requests from Novo Nordisk should be responded to within 14 calendar days.

The investigator must forward follow-up information on SAEs within 24 hours of obtaining the follow-up information by updating the AE form in the eCRF and/or completing a new safety information form marked follow-up, and forward this to Novo Nordisk. If for any reason the eCRF is unavailable or, after access to edit the eCRF is revoked, the investigator must record any SAE follow-up information on the provided paper CRFs and send the information by fax, telephone, e-mail or courier to Novo Nordisk.



The investigator must record follow-up information on non-serious AEs by updating the AE form in the eCRF. If the eCRF is revoked after access to edit, the investigator must record any follow-up information on the provided paper CRFs.

## **12.4 Technical complaints and technical complaint samples**

### **12.4.1 Reporting of technical complaints**

All technical complaints on any of the following products : IDegAsp 30, BIAsp30 and BHI 30, which occur from the time of first usage of trial supplies until the time of the last usage of trial supplies must be collected and reported to Novo Nordisk.

The investigator must assess whether the technical complaint is related to any AE(s) or SAE(s) .

Technical complaints must be reported on a separate technical complaint form and must be completed for each IMP and for auxiliary supplies listed on the technical complaint form. If the technical complaint involves more than one batch number, a technical complaint form for each batch number must be completed.

The investigator must complete the technical complaint form in the eCRF within 24 hours of the trial site obtaining knowledge of a technical complaint related to an SAE. All other technical complaints within 5 calendar days.

If the eCRF is unavailable, the information should be provided by fax, e-mail or courier to Novo Nordisk, within the same timelines.

### **12.4.2 Collection, storage and shipment of technical complaint samples**

The investigator must collect the technical complaint sample and notify the monitor within 5 calendar days. The monitor must initiate the shipment to Novo Nordisk and ensure the sample is sent in accordance with local regulations as soon as possible to Novo Nordisk complaint centre. A copy or a print of the technical complaint form should be sent with the sample.

The investigator should ensure that the technical complaint sample contains the batch number and, if available, the DUN.

If the technical complaint sample is unobtainable, the investigator must specify on the technical complaint form why it is unobtainable.

Storage and shipment of the technical complaint sample must be done in accordance with the conditions prescribed for the product (see section [9](#) and the TMM). The shipment of the technical complaint sample should be done in accordance with the same conditions as for storage.

## 12.5 Pregnancies

When an abnormality is reported in the foetus or newborn infant, information is needed from the male partner. Informed consent must be obtained prior to this.

Female subjects must be instructed to notify the investigator immediately if they become pregnant during the trial. The investigator must report any pregnancy in subjects who received Novo Nordisk provided trial product.

The investigator must report all information on pregnancies, including AEs in the subject, the foetus, and newborn infant on the trial related pregnancy forms. The pregnancy forms must be forwarded to Novo Nordisk preferably electronically in PDF format or by fax.

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

The following must be collected:

- Initial information within 14 calendar days of the investigator's first knowledge of the pregnancy
- Information on the outcome of her pregnancy - including the health status of the newborn infant at the age of one month **within 14 calendar days of the investigator's knowledge of the pregnancy outcome**
- All non-serious AEs in connection with the pregnancy and pregnancy outcome must be reported on the pregnancy forms within 14 calendar days of the investigator's knowledge. It must be clear in the description if the event occurs in the subject, the foetus or the newborn infant.
- All SAEs in connection with the pregnancy and pregnancy outcome must be reported on the pregnancy forms following the **same timelines as required for other SAEs** (see section 12.2). It must be clear in the description if the event occurs in the subject foetus or the newborn infant.
  - The SAEs that must be reported include abnormal outcome - such as congenital anomalies, foetal death and termination of pregnancy (spontaneous or elective abortion), including any anomalies of the foetus observed at gross examination or during autopsy - as well as other pregnancy complications fulfilling the criteria of an SAE

## 12.6 Precautions and/or overdose

During treatment with insulin, there is a risk of hypoglycaemia (please refer to section [8.8](#)). Symptoms of hypoglycaemia usually occur suddenly and may include cold sweat, nervousness or tremor, anxious feelings, unusual tiredness, confusion, difficulty in concentrating, excessive hunger, temporary vision changes, headache, nausea and palpitation. Severe hypoglycaemia may lead to unconsciousness.

Hypoglycaemic episodes should be treated after best practise at the discretion of the investigator. In case of treatment with IDegAsp 30 attention should be given to the fact that the action profile of the basal component (IDeg) is flat and of somewhat longer duration than currently marketed long-acting insulin preparations. It may therefore take several hours more before stable normal blood glucose is achieved after a hypoglycaemic episode when compared to existing long-acting basal insulin analogues.

Symptoms of minor hypoglycaemia should be treated by ingestion of carbohydrate. Major hypoglycaemia resulting in loss of consciousness must be treated according to best medical practice (e.g. 25 ml of 50% dextrose solution given intravenously, or 0.5 - 1 mg of glucagon given subcutaneously or intramuscularly).

Please refer to the current edition of the IDegAsp 30 investigator's Brochure (IB).<sup>8</sup> For BIAsp 30 please refer to the current version of the SPC or locally approved product information.<sup>9</sup>

## **12.7 Committees related to safety**

### **12.7.1 Novo Nordisk safety committee**

Novo Nordisk will constitute an internal safety committee to perform ongoing safety surveillance. The safety committee may recommend unblinding of any data for further analysis, as the members of the safety committee are blinded to the treatment though this is an open-label trial. If so, an independent ad hoc group will be established to maintain the blinding.

### **12.7.2 Event adjudication committee**

An independent external clinical safety event adjudication committee (EAC) is constituted for this trial to perform ongoing adjudication of cardiovascular events.

The EAC is composed of permanent members covering required medical specialities. The EAC members must disclose any potential conflicts of interest and must be independent of Novo Nordisk. The EAC will have no authorisations to impact on trial conduct, trial protocol or amendments. The events are reviewed by the EAC in an independent and blinded manner. Adjudication will be completed based on a review of data collected from the sites. The provided data will be anonymised by identifiers.

An adjudication vendor will ensure that the EAC has access to the relevant medical source documentation required (for example X-ray, ECGs, ultrasound images, discharge summaries, pathology reports, and death certificates). The EAC will initiate the review and may ask for additional information that the investigator needs to provide if available.

Table 12–2 provides an overview of events subject for adjudication.

For AEs requiring adjudication, an adjudication form should also be completed in addition to the AE form.

**Table 12–2 Description of events to be adjudicated**

Type of event	Event description
Acute coronary syndrome	All types of myocardial infarction (MI): <ul style="list-style-type: none"><li>• Spontaneous MI (including re-infarction)</li><li>• MI secondary to ischemia due to imbalance between oxygen demand and supplies</li><li>• Percutaneous coronary intervention (PCI) related MI (including MI associated with stent thrombosis)</li><li>• Coronary artery bypass graft surgery related MI</li><li>• Silent MI</li></ul> Hospitalisation for unstable angina pectoris.  All events with symptoms of myocardial ischemia requiring hospitalisation
Cerebrovascular event	Any acute episode of focal or global neurological dysfunction caused by brain, spinal cord, or retinal vascular injury as a result of haemorrhage or infarction
Fatal event	All-cause death

Event adjudication will be performed for AEs in randomised subjects including AEs with an onset date during the screening period and including the 30 days follow-up period. Event adjudication will not be performed for AEs in screening failures

Events for adjudication can be captured by:

**1. Direct reporting by investigator**

For each AE reported in the eCRF, the investigator should tick the appropriate AE category on the AE form field to capture the relevant event for adjudication. The relevant forms will appear in the eCRF. For fatal events the death adjudication form is triggered from the outcome field on the AE form and will appear in the eCRF for the investigator to complete.

The investigator should complete the event specific form and the adjudication form within 14 days and upload source data preferably within 4 weeks.

## 2. Screening of AEs

All AEs will be screened to detect potential missed events for adjudication. If needed, the investigator will be asked to provide additional information such as an alternative aetiology.

Based on the information provided, the adjudication vendor or EAC will decide if the event is relevant for adjudication, although not initially reported as an event for adjudication by the investigator.

If so, an adjudication form will be triggered by Novo Nordisk in the eCRF and the investigator must provide source documentation preferably within 4 weeks of request.

## 3. EAC identified events

Potentially unreported events may be detected by the EAC in the provided source data. Site will be informed and asked to consider reporting. Regardless of reporting, the event will be adjudicated based on the source documents already provided.

For all events for adjudication, the investigator should provide the source documentation as soon as possible and on an ongoing basis. For further details regarding reporting please refer to the Event Adjudication Site manual.

Cardiovascular diseases are the leading cause of illness and death in subjects with diabetes. Concerns have been raised that some antidiabetic agents may impart greater cardiovascular risk than previously anticipated. DegAsp is not suspected to cause any greater risk of cardiovascular events than other insulin products and is not expected to create a higher risk compared to the risk in general for the diabetes population.

A list of International Statistical Classification of Diseases and Related Health Problems, 10<sup>th</sup> revision (ICD-10) codes representing examples of diagnoses that may be linked to ACS, stroke or cardiovascular death is provided below. The list is not complete, and additional diagnosis, signs and symptoms (e.g. cardiac enzyme changes and ECG findings) may be related to ACS, stroke or cardiovascular death, as evaluated by the investigator, and should thus also be reported.

### 12.7.2.1 Acute coronary syndrome

ACS covers the spectrum of clinical conditions ranging from unstable angina pectoris (UAP) to non ST elevation myocardial infarction (NSTEMI, in ICD -10 termed subendocardial or nontransmural) and ST elevation myocardial infarction (STEMI, in ICD -10 termed transmural).

#### **I20 Angina pectoris**

- I20.0 Unstable angina

#### **I21 Acute myocardial infarction**

- I21.0 Acute transmural myocardial infarction of anterior wall
- I21.1 Acute transmural myocardial infarction of inferior wall

- I21.2 Acute transmural myocardial infarction of other sites
- I21.3 Acute transmural myocardial infarction of unspecified site
- I21.4 Acute subendocardial myocardial infarction (nontransmural myocardial infarction (NOS))
- I21.9 Acute myocardial infarction, unspecified (myocardial infarction (acute) NOS)

**I22 Subsequent myocardial infarction** (Includes: recurrent myocardial infarction)

- I22.0 Subsequent myocardial infarction of anterior wall
- I22.1 Subsequent myocardial infarction of inferior wall
- I22.8 Subsequent myocardial infarction of other sites
- I22.9 Subsequent myocardial infarction of unspecified site

**I24 Other acute ischaemic heart diseases**

- I24.0 Coronary thrombosis not resulting in myocardial infarction
- I24.8 Other forms of acute ischaemic heart disease
  - Coronary failure
  - Coronary insufficiency
- I24.9 Acute ischaemic heart disease, unspecified

**12.7.2.2 Stroke**

Stroke is suspected if a new focal neurological deficit develops that is transient (but present more than 24 hr) or permanent.

**G46 Vascular syndromes of brain in cerebrovascular diseases**

- G46.3 Brain stem stroke syndrome
- G46.4 Cerebellar stroke syndrome
- G46.5 Pure motor lacunar syndrome
- G46.6 Pure sensory lacunar syndrome
- G46.7 Other lacunar syndromes
- G46.8 Other vascular syndromes of brain in cerebrovascular diseases

**I61 Intracerebral haemorrhage**

- I61.0 Intracerebral haemorrhage in hemisphere, subcortical
- I61.1 Intracerebral haemorrhage in hemisphere, cortical
- I61.2 Intracerebral haemorrhage in hemisphere, unspecified
- I61.3 Intracerebral haemorrhage in brain stem
- I61.4 Intracerebral haemorrhage in cerebellum
- I61.5 Intracerebral haemorrhage, intraventricular
- I61.6 Intracerebral haemorrhage, multiple localised
- I61.8 Other intracerebral haemorrhage
- I61.9 Intracerebral haemorrhage, unspecified

**I63 Cerebral infarction** (occlusion and stenosis of cerebral and precerebral arteries, resulting in cerebral infarction)

- I63.0 Cerebral infarction due to thrombosis of precerebral arteries
- I63.1 Cerebral infarction due to embolism of precerebral arteries
- I63.2 Cerebral infarction due to unspecified occlusion or stenosis of precerebral arteries
- I63.3 Cerebral infarction due to thrombosis of cerebral arteries
- I63.4 Cerebral infarction due to embolism of cerebral arteries
- I63.5 Cerebral infarction due to unspecified occlusion or stenosis of cerebral arteries
- I63.6 Cerebral infarction due to cerebral venous thrombosis, nonpyogenic
- I63.8 Other cerebral infarction
- I63.9 Cerebral infarction, unspecified

**I64 Stroke, not specified as haemorrhage or infarction** (Cerebrovascular accident NOS)

#### **12.7.2.3 Cardiovascular death**

Sudden, unexpected cardiac death involving cardiac arrest or sudden unexpected vascular death.

#### **I 46 Cardiac arrest**

- I46.1 Sudden cardiac death
- I46.9 Cardiac arrest, unspecified

#### **R96 Other sudden death, cause unknown**

- R96.0 Instantaneous death
- R96.1 Death occurring less than 24 hours from onset of symptoms, not otherwise explained

#### **R98 Unattended death**

- R99 Other ill-defined and unspecified causes

## 13 Case report forms

For this trial a combination of eCRF and paper CRF will be used.

Novo Nordisk will provide a system for the eCRFs. This system and support services to the system will be supplied by a vendor.

The investigator must ensure that all relevant questions are answered, and that no empty data fields exist. If a test or an assessment has not been done and will not be available, or if the question is irrelevant (e.g. is not applicable), indicate this according to the data entry instructions.

The investigator must ensure that all information is consistent with the source documentation. By electronically signing the case book, the investigator confirms that the information in the eCRF and included related forms are complete and correct.

The following will be provided as paper CRFs only:

- Pregnancy forms
- PRO questionnaires

In addition, paper safety information forms, AE forms and technical complaint forms will be provided. These must be used when technical issues prevent access to the eCRF or access to the eCRF is revoked.

On the paper forms, print legibly, using a ballpoint pen. Ensure that all questions are answered, and that no empty data blocks exist. Ensure that no information is recorded outside the data blocks. If a test/assessment has not been done and will not be available, indicate this by writing “ND” (not done) in the appropriate answer field in the CRF. If the question is irrelevant (e.g. is not applicable) indicate this by writing “NA” (not applicable) in the appropriate answer field. Further guidance can be obtained from the instructions in the CRF.

### 13.1 Corrections to case report forms

Corrections to the eCRF data may be made by the investigator or the investigator’s authorised staff. An audit trail will be maintained in the CRF application containing as a minimum: the old and the new data, identification of the person entering the data, date and time of the entry and reason for the correction. If corrections are made by the investigator’s authorised staff after the date the investigator has signed the case book, the case book must be signed and dated again by the investigator.

Corrections to the data in the paper CRFs may only be made by drawing a straight line through the incorrect data and then writing the correct entry next to the data that were crossed out. Each correction must be initialled, dated and explained (if necessary) by the investigator or the



investigator's authorised staff. If corrections are made by the investigator's authorised staff after the date of the investigator's signature on the electronic signed case book, the case book must be signed again, electronically, by the investigator. Corrections necessary after the CRFs have been removed from the investigator's site must be documented on a data clarification form (DCF) or a monitor-initiated discrepancy form (MIDF). If the case book for the subject has not yet been electronically signed, any corrections must be approved by the investigator or her/his authorised staff. If the case book for the subject has already been signed, the investigator must approve any correction.

### **13.2 Case report form flow**

The investigator must ensure that data are recorded in the eCRF as soon as possible after the visit/phone contact, preferable within 5 calendar days. During the trial, SMPG measurements and corresponding insulin doses for titration purpose should be recorded within 24 hours after the visit/phone contact. At the end of the trial the investigator must ensure that all remaining data have been recorded in the eCRF no later than 24 hours after last subject's last visit at the site. Once data have been entered, they will be available to Novo Nordisk for data verification and validation purposes.

Site specific eCRF data (in an electronic readable format) will be provided to the site before access to the eCRF is revoked. These data must be retained at the site.

## 14 Monitoring procedures

During the course of the trial, the monitor will visit the trial site to ensure that the protocol is adhered to, that all issues have been recorded, to perform source data verification and to monitor drug accountability. The first monitoring visit will be performed as soon as possible after FPFV and no later than 4 weeks after. The monitoring visit intervals will depend on the outcome of the remote monitoring of the eCRFs, the trial site's recruitment rate and the compliance of the trial site to the protocol and GCP, but will not exceed 12 weeks.

The monitor must be given direct access to source documents (original documents, data and records). Direct access includes permission to examine, analyse, verify and reproduce any record(s) and report(s) that are important to the evaluation of the trial. If the electronic medical record does not have a visible audit trail, the investigator must provide the monitor with signed and dated printouts. In addition the relevant trial site staff should be available for discussions at monitoring visits and between monitoring visits (e.g. by telephone).

The monitor will collect CRF pages and other trial related forms containing data from screening failures. Data on the safety information form needs to be source data verified.

All data must be verifiable in source documentation other than the CRF.

There must be a source document agreement at each site. There should only be one source defined at any time for any data element.

Monitors must review the medical records and other source data (e.g. the diaries and PROs) to ensure consistency and/or identify omissions compared to the eCRF. If discrepancies are found, the investigator must be questioned about these. Diaries and 2<sup>nd</sup> copy (third page) of the PROs must not be removed from site.

## 15 Data management

Data management is always the responsibility of Novo Nordisk.

Appropriate measures, including encryption of data files containing person identifiable data, will be used to ensure confidentiality of subject data, when they are transmitted over open networks.

Laboratory data from central laboratories will be transferred electronically from the laboratory performing the analyses. In cases where laboratory data are transferred via non-secure electronic networks, data will be encrypted during transfer.

The subject and any biological material obtained from the subject will be identified by subject ID and trial identification number. Appropriate measures such as encryption or leaving out certain identifiers will be enforced to protect the identity of subjects in all presentations and publications as required by local, regional and national requirements.

## 16 Computerised systems

Novo Nordisk will capture and process clinical data using computerised systems that are described in Novo Nordisk Standard Operating Procedures (SOPs) and IT architecture documentation. The use and control of these systems are documented.

Investigators working on the trial may use their own electronic systems to capture source data. Novo Nordisk will collect information on the practical use of these systems within the conduct of this clinical trial.

## 17 Statistical considerations

Novo Nordisk will analyse and report data from all sites together.

Analyses of all endpoints will be based on the Full Analysis Set (FAS). The primary efficacy analysis will be repeated on the Per Protocol (PP) analysis set in accordance with the Committee for Proprietary Medicinal Products (CPMP) Points to Consider.<sup>22</sup>

Secondary confirmatory and supportive efficacy endpoints and patient reported outcome endpoints will be summarised using the FAS. Safety endpoints will be summarised using the Safety Analysis Set (SAS).

The impact of protocol deviations and outliers may be investigated further in sensitivity analyses if deemed relevant.

The primary objective of this trial is to confirm efficacy of the investigational product in terms of glycaemic control as assessed by HbA<sub>1c</sub>. If efficacy of the investigational product can be confirmed as assessed by comparing the mean HbA<sub>1c</sub> treatment difference to a non-inferiority limit of 0.4%, the trial also aims to show superiority of the investigational product over the comparator for a number of confirmatory secondary endpoints. The family-wise type I error rate will be controlled in the strong sense using a hierarchical (fixed sequence) testing procedure. This is based on a priori ordering of the null-hypotheses and testing them in this order using the two-sided 95% confidence interval approach until an insignificant result appears. The effect is that superiority only will be confirmed for endpoints where all previous null-hypotheses have been rejected.

In addition, if non-inferiority can be confirmed and the 95% confidence interval for the mean HbA<sub>1c</sub> treatment difference not only lies entirely below 0.4% but also below zero this will be considered as evidence of superiority of the investigational product over the comparator in terms of change from baseline in HbA<sub>1c</sub> after 26 weeks of treatment.

Only endpoints derived after 26 weeks of treatment will be analysed statistically. Missing values will be imputed using the Last Observation Carried Forward (LOCF) method. LOCF has been a standard approach in diabetes trials for many years, and was used as the primary analysis in all degludec phase 3a trials. LOCF is considered to be an appropriate method in the context of treat-to-target trials, where subjects after withdrawal typically continue their therapy using commercially available insulin. In previous treat-to-target trials with degludec LOCF has generally provided similar results to alternative methods to handle missing data, such as repeated measures models and completer analyses. In this trial, similar sensitivity analyses will be made to examine the robustness of the LOCF method. All endpoints will be summarised descriptively at each visit by treatment and in total using observed data. After 26 weeks of treatment, descriptive statistics will be presented based both on observed and LOCF imputed data. Endpoints that are analysed untransformed and

endpoints that are not formally analysed are summarised by the arithmetic mean, standard deviation (SD), median, and minimum and maximum value. Endpoints that are analysed log-transformed are summarised by the geometric mean, CV, median, minimum and maximum value.

LOCF imputed data will be used as the basis for plotting data if not otherwise specified.

Presentation of results from a statistical analysis will include the estimated mean treatment effects (least-squares means [LSMeans]) for absolute values and change from baseline if applicable. Estimated mean treatment differences (or ratios) will be presented together with two-sided 95% confidence intervals for all endpoints analysed statistically. p-values will only be presented for the primary and the confirmatory secondary endpoints for which formal statistical testing will be performed. The other endpoints are considered supportive and explorative in nature and no p-values will be presented.

For endpoints measured over time mean values will be plotted to explore the trajectory over time. For survival endpoints, Kaplan-Meier plots are presented for each treatment. Data collected before randomisation will only be summarised descriptively.

### 17.1 Sample size calculation

The primary objective of this trial is to confirm efficacy of IDegAsp 30 BID ± metformin in terms of glycaemic control.

This is done by showing that:

IDegAsp 30 BID ± metformin is non-inferior to BIAsp 30 BID ± metformin in terms of glucose lowering effect as assessed by change from baseline in HbA<sub>1c</sub> after 26 weeks of treatment using a non-inferiority margin of 0.4% (absolute). Sample size is determined based on this primary objective.

Throughout this section of the protocol the term “investigational product” will be used as a synonym for IDegAsp 30 and the term “comparator” will be used as a synonym for BIAsp 30 BID.

The non-inferiority margin of 0.4% (absolute) was chosen in accordance with the FDA guidance<sup>23</sup>. Let D be the mean treatment difference for change in HbA<sub>1c</sub> (investigational product minus comparator). The null-hypothesis will be tested against the alternative hypothesis of non-inferiority as given by

$H_0: D > 0.4\%$  against  $H_A: D \leq 0.4\%$

Operationally the null-hypothesis will be rejected and non-inferiority considered confirmed if the upper bound of the two-sided 95% confidence interval for the mean HbA<sub>1c</sub> treatment difference is below or equal to 0.4%. This is equivalent to using a one-sided test of size 2.5%.

Sample size is determined using a t-statistic under the assumption of a one-sided test of size 2.5% and a zero mean treatment difference (i.e. D=0%). Based on experience from previous phase 3 trials in subjects with type 2 diabetes treated with insulin an estimate for the standard deviation (SD) of 1.3% for HbA<sub>1c</sub> will be used in the sample size calculation ([Table 17-1](#)). The sample size calculation is done using SAS 9.3.

**Table 17-1 Specifications assumed for sample size calculation**

Statistical test	One sided Significance Level	Non-inferiority Margin	SD	Mean Difference	Randomisation Scheme	Required Power
two-group t test	2.5%	0.4% (absolute)	1.3%	0.0%	2:1	87%

**Table 17-2 Sensitivity of sample size (integers) to variations in SD and power**

#subjects in total	SD=1.1	SD=1.2	SD=1.3	SD=1.4
Power = 80%	270	321	375	435
Power = 85%	309	366	429	498
Power = 87%	327	390	456	528
Power = 90%	360	429	504	582

From [Table 17-2](#) it is seen that the primary objective will be met with at least 87% power with 456 subjects assuming a SD of 1.3%.

As this is a non-inferiority trial sample size will be determined such that the anticipated power is at least 87% in the evaluation of the PP analysis set. In previous phase 3 trials in type 2 diabetes treated with insulin 5-25% of the randomised subjects were excluded from the PP analysis set. The number of excluded subjects was dependent on the trial design. In this trial an estimate of 15% will be used and sample size is ceiled in the FAS to have integer sample size for each group that adheres exactly to the group allocation weights (2:1). Hence the total number of subject to be randomised must be 537 subjects in order to have at least 87% power in the evaluation of the PP analysis set ([Table 17-3](#)).

**Table 17–3 Anticipated number of subjects in FAS and PP analysis set**

	<b>IDegAsp 30 BID</b>	<b>BIAsp 30 BID</b>	<b>Total</b>
<b>Number of subjects in the FAS</b>	358	179	537
<b>Number of subjects in the PP analysis set</b>	304	152	456

## 17.2 Definition of analysis sets

- Full Analysis Set (FAS): includes all randomised subjects. In exceptional cases subjects from the FAS may be eliminated. In such cases the elimination will be justified and documented. The statistical evaluation of the FAS will follow the intention -to-treat (ITT) principle and subjects will contribute to the evaluation “as randomised”.
- The Per-Protocol analysis set will consist of all subjects in the Full Analysis Set who fulfils the following criteria:
  - Have not violated any inclusion criteria
  - Have not fulfilled any exclusion criteria
  - Have a non-missing HbA<sub>1c</sub> at screening or randomisation
  - Have at least one non-missing HbA<sub>1c</sub> after 12 weeks of exposure
  - Have at least 12 weeks of exposureSubjects will contribute to the evaluation “as treated”.
- Safety Analysis Set: includes all subjects receiving at least one dose of the investigational product or its comparator. Subjects in the safety set will contribute to the evaluation “as treated”.

Randomised subjects who are lost to follow up and where no exposure information of the investigational product or its comparator is available after randomisation will be handled as unexposed. The OADs that the subjects are included on and will stay on throughout the trial are concomitant medications and regarded as non-investigational products.

Before data are released for statistical analysis, a review of all data will take place to ensure a sufficient data quality and to ensure the planned statistical analyses are applicable. Any data decisions e.g. classification of anti-diabetic treatment not foreseen in the protocol, will be documented before database lock.



### 17.3 Primary endpoint

The primary endpoint is change from baseline in HbA<sub>1c</sub> (%) after 26 weeks of treatment

#### Statistical analysis

Change from baseline in HbA<sub>1c</sub> after 26 weeks of treatments will be analysed using an Analysis of Variance (ANOVA) method with treatment, anti-diabetic therapy at screening and sex as fixed factors, and age and baseline HbA<sub>1c</sub> as covariates. The anti-diabetic therapy at screening is a factor with the following four levels:

1. Basal insulin regimen without metformin
2. Basal insulin regimen with metformin
3. Premix/self-mix regimen without metformin
4. Premix/self-mix regimen with metformin

The model will be fitted to all the data simultaneously (all treatment groups) and from this model the relevant treatment differences will be estimated.

Non-inferiority will be considered confirmed if the upper bound of the two-sided 95% confidence interval is below or equal to 0.4% or equivalent if the p-value for the one-sided test of

$H_0: D > 0.4\%$  against  $H_A: D \leq 0.4\%$ ,

is less than or equal to 2.5%, where D is the mean treatment difference (investigational product minus comparator)

If non-inferiority is confirmed the superiority of the investigational product over comparator will be investigated. Superiority will be considered confirmed if the upper bound of the two-sided 95% confidence interval, which is calculated using the FAS, is below 0%. The PP analysis is considered supportive here.

#### Sensitivity analysis

The primary efficacy analysis will be repeated on the PP analysis set and the set of all completed subjects as sensitivity analyses.

The following sensitivity analyses will be performed using the FAS only.

All observed HbA<sub>1c</sub> measurements available post randomisation at scheduled measurement times will also be analysed in a linear mixed model using an unstructured residual covariance matrix (if possible), and with treatment, time, interaction between treatment and time, anti-diabetic treatment at screening and sex as fixed effects and age and baseline HbA<sub>1c</sub> as covariates.

This approach relies on the assumption that data are missing at random (MAR) according to the taxonomy defined by Rubin.<sup>24</sup> The results will be compared to the results of the LOCF method for dealing with missing data. Any marked difference concerning treatment differences between the MAR and LOCF approach will be commented upon in the CTR.

Change in HbA<sub>1c</sub> from baseline will also be analysed using a model with only treatment as fixed factor and baseline HbA<sub>1c</sub> as covariate to assess the sensitivity of the results to inclusion/exclusion of fixed factors and covariates.

## **17.4 Secondary endpoints**

### **17.4.1 Confirmatory secondary endpoints**

Provided that non-inferiority is confirmed for the primary endpoint, a number of confirmatory secondary endpoints will be tested to confirm superiority of the investigational product over the comparator.

The confirmatory secondary endpoints are given below together with the direction of the test for superiority. The order of the endpoints defines the testing sequence.

1. Change from baseline in FPG after 26 weeks of treatment (analysed at central laboratory)
  - Superiority is considered confirmed if the 95% confidence interval for the treatment difference (investigational product minus comparator) is entirely below zero
2. Number of treatment emergent nocturnal confirmed hypoglycaemic episodes
  - Superiority is considered confirmed if the 95% confidence interval for the relative risk (investigational product / comparator) is entirely below one
3. Number of treatment emergent confirmed hypoglycaemic episodes
  - Superiority is considered confirmed if the 95% confidence interval for the relative risk (investigational product / comparator) is entirely below one
4. Change from baseline in body weight after 26 weeks of treatment
  - Superiority is considered confirmed if the 95% confidence interval for the treatment difference (investigational product minus comparator) is entirely below zero
5. Responder without hypoglycaemic episodes (HbA<sub>1c</sub> <7.0% after 26 weeks of treatment and no confirmed episodes during the last 12 weeks of treatment or within 7 days after the last randomised treatment including only subjects exposed for at least 12 weeks)
  - Superiority is considered confirmed if the 95% confidence interval for the odds ratio (investigational product / comparator) is entirely above one

### **Change from baseline in FPG**

Change from baseline in FPG after 26 weeks of treatment will be analysed using an ANOVA method with treatment, anti-diabetic therapy at screening and sex as fixed factors, and age and baseline FPG as covariates.

### **Number of treatment emergent confirmed hypoglycaemic episodes**

A hypoglycaemic episode is defined as treatment emergent if the onset of the episode is on or after the first day of exposure to randomised treatment and no later than 7 days after the last day of randomised treatment.

The number of confirmed hypoglycaemic episodes will be analysed using a negative binomial regression model with a log-link function and the logarithm of the time period in which a hypoglycaemic episode is considered treatment emergent as offset. The model will include treatment, anti-diabetic therapy at screening and sex as fixed factors, and age as covariate.

### **Number of treatment emergent nocturnal confirmed hypoglycaemic episodes**

A hypoglycaemic episode that has time of onset between 00:01 and 05:59 a.m. (both included) will be considered nocturnal.

The number of treatment emergent nocturnal confirmed hypoglycaemic episodes will be analysed using a negative binomial regression model with a log-link function and the logarithm of the time period in which a hypoglycaemic episode is considered treatment emergent as offset. The model will include treatment, anti-diabetic therapy at screening and sex as fixed factors and age as covariate.

### **Change from baseline in body weight**

Body weight is assessed at trial site. Change from baseline in body weight after 26 weeks of treatment will be analysed using an ANOVA method with treatment, anti-diabetic therapy at screening and sex as fixed factors, and age and baseline body weight as covariates.

### **Responder without hypoglycaemic episodes**

Responder without hypoglycaemic episodes is a dichotomous endpoint (responder/non-responder) that is defined based on whether a subject has met the ADA HbA<sub>1c</sub> target (< 7%) after 26 weeks of treatment without treatment emergent confirmed hypoglycaemic episodes during the last 12 weeks of treatment or within 7 days after last randomised treatment. The endpoint will only be defined for subjects that have been exposed to the investigational product or its comparator for at least 12 weeks.

Responder analysis will be based on a logistic regression model using treatment, anti-diabetic therapy at screening and sex as fixed factors, and age and baseline HbA<sub>1c</sub> as covariates.

## **17.4.2 Supportive secondary endpoints**

### **17.4.2.1 Efficacy**

The timing of assessments is outlined in the trial flow chart.

#### **HbA<sub>1c</sub> responder endpoints**

Two dichotomous endpoints (responder/non-responder) will be defined based on whether a subject has met the ADA HbA<sub>1c</sub> target (HbA<sub>1c</sub> < 7.0%) and the International Diabetes Federation (IDF) HbA<sub>1c</sub> target (HbA<sub>1c</sub> ≤ 6.5%) after 26 weeks of treatment.

Additional dichotomous endpoints will be defined based on whether those treatment targets after 26 weeks of treatment are achieved without hypoglycaemic episodes in the last 12 weeks of treatment or within 7 days after last randomised treatment considering confirmed episodes and severe episodes only. These endpoints will only be defined for subjects that have been exposed for at least 12 weeks.

The responder endpoints will be analysed separately based on a logistic regression model using treatment, anti-diabetic therapy at screening and sex as fixed factors, and age and baseline HbA<sub>1c</sub> as covariates.

#### **Self measured plasma glucose**

Self-measured plasma glucose will be measured in terms of the 9-point profiles (SMPG) and glucose measurements used for insulin dose adjustments.

#### ***9-point profile (SMPG) after 26 weeks of treatment***

A 9-point profile (SMPG) will include measurements before and 90 minutes after start of breakfast, lunch and main evening meal, measurements prior to bedtime and at 4 a.m., and one before breakfast the following day.

The endpoints from the 9-point profiles (SMPG) will be:

- 9-point profile (SMPG)
- Mean of the 9-point profile (SMPG)
- Fluctuation in the 9-point profile (SMPG)
- Prandial plasma glucose (PG) increments

The mean of 9-point profile (SMPG) is defined as the area under the profile divided by the measurement time and is calculated using the trapezoidal method. The fluctuation in the 9-point profile (SMPG) is defined as

$$\frac{1}{T} \int_0^T |PG(t) - \overline{PG}| dt$$

where  $T$ ,  $PG(t)$  and  $\overline{PG}$  denotes the length of the profile, the PG value at time  $t$  and the mean of the profile, respectively.

Prandial PG increment for each meal will be derived from the 9-point profile (SMPG) as the difference between PG values available 90 minutes after meal and before meal. Mean prandial PG increment over all meals will be derived as the mean of all available meal increments.

A mixed effect model will be fitted to the 9-point profile (SMPG) data. The model will include treatment, time, interaction between treatment and time, anti-diabetic therapy at screening and sex as fixed factors, age and the values from the profile at baseline as covariates and subject as random effect. From the model, mean profile by treatment and relevant treatment differences will be estimated and explored.

Mean and fluctuation in the 9-point profile (SMPG) and prandial PG increment endpoints will be analysed separately using an ANOVA method with treatment, anti-diabetic therapy at screening and sex as fixed factors, and age and the relevant baseline value as covariates. Fluctuation in the 9-point profile (SMPG) will be logarithm transformed before analysed.

### ***2-point profile (SMPG) values used for dose adjustment***

The endpoints from the SMPG measurements obtained throughout the trial for dose adjustment will be:

- Mean PG before meals (breakfast and main evening meal) after 26 weeks of treatment
- Responder for PG titration targets
- Time from randomisation (measured in weeks) to achieve titration targets
- Within-subject variability as measured by CV% after 26 weeks of treatment

The mean PG value before a meal will be calculated at each visit using the available data and separately for breakfast and main evening meal.

The mean before meal PG values after 26 weeks of treatment will be analysed separately, using an ANOVA method with treatment, anti-diabetic therapy at screening and sex as fixed factors, and age and the corresponding mean PG value at baseline as covariates.

From the mean before meal PG value, a dichotomous endpoint (responder/non-responder) will be derived for each meal that shows if a subject has achieved the titration target at each visit.

For each target a survival endpoint will be derived as the time from randomisation to the date a subject achieves the titration target for the first time.

The two survival endpoints will be analysed separately in a Cox proportional hazards model including treatment, anti-diabetic therapy at screening and sex as fixed factors and age as covariate. An analysis will also be performed for the time to all titration targets are met. Subjects that are lost for follow up without meeting the target and subjects that never meet the target during treatment will be censored at the last day of treatment.

The logarithm transformed SMPG values available before breakfast and main evening meal, will be analysed separately as repeated measures in a linear mixed model with treatment, anti-diabetic therapy at screening and sex as fixed factors, age as covariate and subject as random factor. The model will assume independent within- and between-subject errors with variances depending on treatment. Within-subject variability as measured by CV% for a treatment can be calculated from the corresponding residual variance  $\sigma^2$  as  $CV\% = 100\sqrt{(\exp(\sigma^2)-1)}$ . The confidence interval for the CV ratio between treatments will be calculated using the delta method.

#### **17.4.2.2 Safety**

##### **Adverse Events**

Adverse Events will be coded using the most recent version of Medical Dictionary for Regulatory Activities (MedDRA) coding. All AEs will be presented based on system organ class and preferred terms.

When reporting the trial results the EAC evaluation will be employed. All discrepancies between EAC and the investigators' classification of the CV events will be listed by event.

A Treatment Emergent Adverse Event (TEAE) is defined as an event that has onset date on or after the first day of exposure to randomised treatment and no later than 7 days after the last day of randomised treatment.

TEAEs are summarised descriptively whereas AEs not defined as treatment emergent are presented in listings. The summaries of TEAEs are made displaying the number of subjects with at least one event, the percentage of subjects with at least one event, the number of events and the event rate per 100 years. These summaries are done by seriousness, severity, relation to insulin treatment, relation to device, withdrawal due to AEs and outcome.

Furthermore summary tables based on system organ class and preferred terms are made for:

- all TEAEs
- serious TEAEs
- possibly or probably related TEAEs
- severe TEAEs
- TEAEs with preferred term that are experienced by at least 5% of the subjects in any treatment arm or by at least 5% of all subjects

### **Hypoglycaemic episodes**

Hypoglycaemic episodes are recorded by subjects in their trial diaries throughout the trial. The information collected includes PG before treating the episode and whether the subject was able to treat him/herself. This information is used by Novo Nordisk A/S to classify an episode according to the confirmed hypoglycaemia definition and the ADA definition (severe, documented symptomatic, asymptomatic, probable symptomatic and relative) as further detailed in section [8.8](#).

A hypoglycaemic episode is defined as treatment emergent if the onset of the episode is on or after the first day of exposure to randomised treatment and no later than 7 days after the last day of randomised treatment. A hypoglycaemic episode that has time of onset between 00:01 and 05:59 a.m. (both included) is considered to be nocturnal.

Data on treatment emergent hypoglycaemic episodes are presented in terms of the number of subjects with at least one event (N), the percentage of subjects with at least one event (%), the number of events (E) and the event rate per 100 years (R). Separate summaries are made by severity considering all confirmed hypoglycaemic episodes, confirmed hypoglycaemic episodes in the maintenance period, nocturnal confirmed hypoglycaemic episodes, nocturnal confirmed hypoglycaemic episodes in the maintenance period and the ADA classification of hypoglycaemia.

The number of treatment emergent severe, confirmed, confirmed in the maintenance period, nocturnal confirmed hypoglycaemic episodes and nocturnal confirmed in the maintenance period will be analysed using a negative binomial regression model with a log-link function and the logarithm of the time period for which a hypoglycaemic episode is considered treatment emergent as offset. The model will include treatment, anti-diabetic therapy at screening and sex as fixed factors, and age as covariate. If the number of severe or nocturnal confirmed hypoglycaemic episodes is too small for statistical analysis, then these analyses may not be performed.

### **Fundoscopy/fundus photography**

Fundoscopy and fundus photography findings will be summarised descriptively including summaries of the change from baseline.

## **ECG**

ECG 12-lead findings will be summarised descriptively including summaries of the change from baseline.

## **Physical examination**

Physical examination should include:

- head, ears, eyes, nose, throat, neck
- respiratory system
- CV system
- gastrointestinal system incl. mouth
- musculoskeletal system
- central and peripheral nervous system
- skin

The physical examination measurements and their change from baseline will be summarised descriptively.

## **Vital signs**

Vital signs include diastolic blood pressure, systolic blood pressure and pulse findings will be summarised descriptively including summaries of the change from baseline.

## **Laboratory safety parameters**

The following laboratory assessments are performed:

- haematology (haemoglobin, leucocytes, thrombocytes, haematocrit, differential counts and erythrocytes)
- biochemistry (creatinine, total protein, ALT, AST, AP, sodium, potassium, albumin, total bilirubin)
- lipid profile (LDL, HDL, triglycerides and total cholesterol)
- urinary albumin-to-creatinine ratio assess in spot urine
- urine by sticks (tests for blood, protein and ketones)
- insulin antibodies

Individual laboratory values will be compared to their relevant reference range (when existing) and flagged as being below or above the range. Change from baseline will be summarised descriptively.

Change from baseline in lipid endpoints after 26 weeks of treatment will be analysed separately using an ANOVA method with treatment, anti-diabetic therapy at screening and sex as fixed factors, and age and baseline value as covariates.



Insulin degludec specific antibodies, insulin aspart specific antibodies, and cross-reacting antibodies will be illustrated using descriptive statistics and graphs.

### **Insulin dose**

Prescribed and actual insulin dose per day and separately for morning and evening dose will be recorded. The respective insulin doses will be summarised descriptively according to regimen as dose in units and units/kg per week.

### **Body weight**

In addition to the confirmatory statistical analysis after 26 weeks of treatment, body weight will summarised descriptively including summaries of the change from baseline.

#### **17.4.3 Other assessments**

The results from the blood pregnancy test will be presented in listings using the Safety Analysis Set.

#### **17.5 Interim analysis**

Not applicable

#### **17.6 Sequential safety analysis and safety monitoring**

Not applicable

#### **17.7 Explorative statistical analysis for pharmacogenetics and biomarkers**

Not applicable

#### **17.8 PK and/or PD modelling**

Not applicable

#### **17.9 Health economics and/or patient reported outcomes**

The following questionnaires will be used to compare PROs and costs associated with hypoglycaemia between treatments:

- SF-36<sup>11,12</sup>
- TRIM-D<sup>13</sup> and TRIM-D Device<sup>13</sup>
- Device Specific Questionnaires I and II<sup>14</sup>

For the questionnaires , SF-36 and TRIM-D the change in score (total score if appropriate) from baseline will be analysed separately using an ANOVA method with treatment, anti-diabetic therapy at screening and sex as fixed factors, and age and the relevant baseline value as covariates.

Protocol  
Trial ID: NN5401-3598  
EudraCT No.: 2011-000085-36  
UTN: U1111-1118-8578

~~CONFIDENTIAL~~

Date:	31 May 2017	<b>Novo Nordisk</b>
Version:	4.0	
Status:	Final	
Page:	88 of 102	

For the device questionnaire TRIM-D Device , which is not assessed at baseline, the score (total score if appropriate) will be analysed using an ANOVA method with treatment, anti-diabetic therapy at screening and sex as fixed factors, and age as covariate.

For Device Specific Questionnaires I and II, since there are no validated scoring algorithms, formal statistical analysis will not be conducted and only descriptive statistics will be presented.

## 18 Ethics

All subjects included in the trial will be treated with IDegAsp 30 or BIAsp 30 in order to improve their glycaemic control.

Subjects randomised to the trial will be transferred to a treatment regimen anticipated to be better than or equal to the treatment they receive at the time they enter the trial. However, they will have to spend some extra time, as additional visits to the clinic are required and some of these tests performed during the trial are outside normal practice.

The trial will be conducted in compliance with ICH GCP<sup>21</sup> applicable regulatory requirements, and in accordance with the Declaration of Helsinki.<sup>25</sup>

When treatment with trial products ends, the subject and investigator will decide on the best available treatment.

### 18.1 Informed consent

In seeking and documenting informed consent, the investigator must comply with the applicable regulatory requirement(s), and adhere to the ICH GCP<sup>21</sup> and the requirements in the Declaration of Helsinki.<sup>25</sup>

Before any trial-related activity, the investigator must give the subject oral and written information about the trial in a form that the subject can read and understand. This includes the use of impartial witness where required.

The investigator must ensure the subject has ample time to come to a decision whether or not to participate in the trial.

A voluntary, signed and personally dated informed consent form will be obtained from the subject before any trial-related activity. The subject must be provided with a copy of his/her signed informed consent.

The responsibility for seeking informed consent must remain with the investigator but the task may be delegated by the investigator to a medically qualified person, in accordance with local requirements. The written informed consent must be signed and personally dated, by the person who seeks the informed consent.

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

## 18.2 Data handling

If the subject is withdrawn from the trial or lost to follow up, then the subject's data will be handled as follows:

- Data already collected will be retained by Novo Nordisk, entered into the database and used for the trial report
- Safety events will be reported to the Novo Nordisk and regulatory authorities according to local/national requirements

If data are used, it will always be in accordance with local law and IRBs/IECs.

## 18.3 Premature termination of the trial and/or trial site

Novo Nordisk, the investigator, the IRBs/IECs or a regulatory authority may decide to stop the trial, part of the trial or a trial site at any time, but agreement on procedures to be followed must be obtained.

If a trial is suspended or prematurely terminated, the investigator must inform the subjects promptly and ensure appropriate therapy and follow-up. The investigator and/or Novo Nordisk should also promptly inform the IRBs/IECs and provide a detailed written explanation. The relevant regulatory authorities should be informed.

If, after the termination of the trial, the risk/benefit analysis changes, the new evaluation should be provided to the IRBs/IECs in case it has an impact on the planned follow-up of subjects who have participated in the trial. If it does have an impact, the actions needed to inform and protect the subjects should be described.

## 19 Protocol compliance

Deviations from the protocol should be avoided.

If deviations do occur, the investigator must inform the monitor and the implications of the deviation must be reviewed and discussed.

Investigator must document and explain protocol deviations by stating the reason, date, and the action(s) taken. Some deviations, for which corrections are not possible, can be acknowledged and confirmed via edit checks in the eCRF or via listings from the clinical database.

Documentation on all protocol deviations must be kept in the investigator's trial file and Novo Nordisk trial master file.

## 20 Audits and inspections

Any aspect of the clinical trial may be subject to audits conducted by Novo Nordisk or inspections from domestic or foreign regulatory authorities or from IRBs/IECs. Audits and inspections may take place during and after the trial. The investigator and the site staff as well as Novo Nordisk staff have an obligation to cooperate and assist in such audits and inspections. This includes giving auditors and inspectors direct access to all source documents and other documents at the site relevant to the clinical trial. This includes permission to examine, analyse, verify and reproduce any record(s) and report(s) that are relevant to the evaluation of the trial.

## 21 Critical documents

Before a site is allowed to start screening subjects, the following documents must be available to Novo Nordisk:

- Regulatory approval and/or acknowledgement of notification as required
- Curricula vitae of investigator and sub-investigator(s) (current, dated and signed and/or supported by an official regulatory document. Must include documented GCP training or a certificate)
- Signed receipt of IB, and any current updates hereof
- Signed and dated agreement on the final protocol
- Signed and dated agreement on any substantial protocol amendment(s), if applicable
- Approval/favourable opinion from IRBs/IECs clearly identifying the documents reviewed as follows: protocol, any substantial protocol amendments, subject information/informed consent form, any other written information to be provided to the subject and subject recruitment materials
- List of IRB/IEC members and/or constitution
- Financial agreement(s)
- Source document agreement
- Central laboratory certification and normal ranges
- Insurance statement, if applicable
- Signed and dated Investigator Agreement
- Financial disclosure form for all investigators

Novo Nordisk will analyse and report data from all sites together.

As documented in writing by protocol signature, each investigator agrees to comply fully with ICH standards of current Good Clinical Practice (GCP), applicable regulatory requirements and the declaration of Helsinki.

## 22 Responsibilities

All staff (Novo Nordisk, site, laboratory, CRO etc) will conduct the trial in compliance with ICH GCP<sup>21</sup>, applicable regulatory requirements and the Declaration of Helsinki<sup>25</sup>.

The investigator is accountable for the conduct of the trial at his/her site. If any tasks are delegated, the investigator should maintain a list of appropriately qualified persons to whom he/she has delegated specified significant trial-related duties. The investigator should ensure that there is adequate training for all staff participating in the conduct of the trial. It is the investigator's responsibility to supervise the conduct of the trial and to protect the rights, safety, and well-being of the subjects.

A qualified physician, who is an investigator or a sub-investigator for the trial, must be responsible for all trial-related medical decisions.

The investigator must ensure adequate supervision of the conduct of the trial at the trial site.

The investigator will follow instructions from Novo Nordisk when processing data.

The investigator is responsible for filing essential documents (ie those documents which individually and collectively permit evaluation of the conduct of a trial and the quality of the data produced) in the investigator's trial file. The documents should be kept in a secure locked facility, so no unauthorized persons can get access to the data. The subject ID list should be kept securely and separate from the personal data.

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

The investigator must be able to provide the necessary information or otherwise demonstrate to Novo Nordisk that such technical and organisational safety measures have been taken.

During any period of unavailability, the investigator should delegate responsibility for medical care of subjects to a specific qualified physician who will be readily available to subjects during that time.

If the investigator is no longer able to fulfil the role of investigator (eg if he/she retires), a new investigator will be appointed in consultation with Novo Nordisk.

The investigator and site personnel must have sufficient English skills according to their assigned task(s).



## 23 Reports and publications

The information obtained during the conduct of this trial is considered confidential, and may be used by Novo Nordisk for regulatory purposes and for the general development of the trial product. All information supplied by Novo Nordisk in connection with this trial shall remain the sole property of Novo Nordisk and is to be considered confidential information. No confidential information shall be disclosed to others without prior written consent from Novo Nordisk. Such information shall not be used except in the performance of this trial. The information obtained during this trial may be made available to other physicians who are conducting other clinical trials with the trial product, if deemed necessary by Novo Nordisk.

One principal investigator will be appointed to review and sign the Clinical Trial Report (CTR) (signatory investigator) on behalf of all participating investigators. The signatory investigator will be appointed based upon the criteria defined by the International Committee of Medical Journal Editors for research publications.<sup>15</sup>

### 23.1 Communication of results

Novo Nordisk commits to communicating, and otherwise making available for public disclosure, results of trials regardless of outcome. Public disclosure includes publication of a paper in a scientific journal, abstract submission with a poster or oral presentation at a scientific meeting, or disclosure by other means.

Novo Nordisk reserves the right to defer the release of data until specified milestones are reached, for example when the clinical trial report is available. This includes the right not to release the results of interim analyses, because the release of such information may invalidate the results of the entire trial.

At the end of the trial, one or more public disclosures may be prepared collaboratively by the investigator(s) and Novo Nordisk. Novo Nordisk reserves the right to postpone publication and/or communication for up to 60 days to protect intellectual property.

The results of this trial will be subject to public disclosure on external web sites according to international regulations, as reflected in the Novo Nordisk Code of Conduct for Clinical Trial Disclosure.

In all cases the trial results will be reported in an objective, accurate, balanced and complete manner, with a discussion of the strengths and limitations. All authors will be given the relevant statistical tables, figures, and reports needed to support the planned publication. In the event of any disagreement on the content of any publication, both the investigators' and Novo Nordisk opinions will be fairly and sufficiently represented in the publication.

Any publication of results in a journal article must acknowledge all trial sites. Where required by the journal, the principle investigator from each site will be named in the acknowledgment.

Novo Nordisk maintains the right to be informed of plans by any investigator to publish and to review any scientific paper, presentation, communication or other information concerning the investigation described in this protocol. Any such communication must be submitted in writing to the Novo Nordisk trial manager before submission for comments. Comments will be given within four weeks from receipt of the planned communication.

### **23.1.1 Authorship**

Authorship of publications should be in accordance with the Uniform Requirements of the International Committee of Medical Journal Editors (sometimes referred to as the Vancouver Criteria<sup>26</sup>).

The investigator(s) offered authorship will be asked to comment and approve the publication. No permission to publish will be granted to any clinical research organisation involved in the trial described in this protocol.

### **23.1.2 Site-specific publication(s) by investigator(s)**

For a multi-centre clinical trial, analyses based on single-site data usually have significant statistical limitations and frequently do not provide meaningful information for healthcare professionals or subjects, and therefore may not be supported by Novo Nordisk. It is a Novo Nordisk policy that such individual reports do not precede the primary manuscript and should always reference the primary manuscript of the trial.

Novo Nordisk reserves the right to prior review of such publications and to ask for deferment of publication of individual site results until after the primary manuscript is accepted for publication.

## **23.2 Investigator access to data and review of results**

As owners of the trial database, Novo Nordisk has discretion to determine who will have access to the database. Generally, trial databases are only made available to regulatory authorities.

Individual investigators will have their own research participants' data. The clinical data submitted in the eCRF by the investigator will be available on a compact disc (CD) containing documents in PDF format of the subject's eCRF data. The CD is for archiving and the investigator will receive it no earlier than one week after the key results meeting. The investigator will be required to confirm the receipt by signature.

## 24 Retention of clinical trial documentation

Subject records must be kept for the maximum period permitted by the hospital, institution or private practice.

The investigator must agree to archive the documentation (this includes both electronic and paper-based records) pertaining to the trial in an archive after completion or discontinuation of the trial if not otherwise notified. The investigator should not destroy any documents without prior permission from Novo Nordisk. If the investigator cannot archive the documents at the trial site, Novo Nordisk can refer the investigator to an independent archive provider that has a system in place to allow only the investigator to access the files.

The investigator must be able to access his/her trial documents without involving Novo Nordisk in any way. Site-specific CRFs and other subject data (in an electronic readable format or as paper copies or prints) will be provided to the investigator before access is revoked to the systems and/or electronic devices supplied by Novo Nordisk. These data must be retained by the site. If the Novo Nordisk provided data (eg the CD-ROM) is not readable during the entire storage period, the investigator can request a new copy, as a copy of all data will be stored by Novo Nordisk.

Novo Nordisk will maintain Novo Nordisk documentation pertaining to the trial for at least 20 years after discontinuation of the marketing authorisation, termination of the trial or cancellation of the research project whichever is longest.

The files from the investigator site/institution must be retained for 25 years after the completion of the trial, or longer if required by national regulations. The deletion process must ensure confidentiality of data and must be done in accordance with local requirements.

## **25 Institutional Review Boards/Independent Ethics Committees and regulatory authorities**

Written approval or favourable opinion must be obtained from IRB/IEC prior to commencement of the trial.

During the trial, the investigator or sponsor, as applicable, must promptly report the following to the IRB/IEC, in accordance with local requirements: updates to IB, unexpected SAEs where a causal relationship cannot be ruled out, substantial protocol amendments, non-substantial protocol amendments according to local requirements, deviations to the protocol implemented to eliminate immediate hazards to the subjects, new information that may affect adversely the safety of the subjects or the conduct of the trial (including new risk/benefit analysis in case it will have an impact on the planned follow-up of the subjects), annually written summaries of the trial status, and other documents as required by the local IRB/IEC.

Substantial protocol amendments must not be implemented before approval or favourable opinion, unless necessary to eliminate immediate hazards to the subjects.

The investigator must maintain an accurate and complete record of all submissions made to the IRB/IEC. The records should be filed in the investigator's trial file and copies must be sent to Novo Nordisk.

### **Regulatory Authorities**

Regulatory authorities will receive the clinical trial application (CTA), substantial/non-substantial protocol amendments, reports on SAEs, and the CTR according to national requirements. This trial will not be initiated prior to having obtained approval from the State Food and Drug Administration (SFDA) (where applicable).

Protocol  
Trial ID: NN5401-3598  
EudraCT No.: 2011-000085-36  
UTN: U1111-1118-8578

~~CONFIDENTIAL~~

Date:	31 May 2017	<b>Novo Nordisk</b>
Version:	4.0	
Status:	Final	
Page:	99 of 102	

## 26 Indemnity statement

Novo Nordisk carries product liability for its products, and liability is assumed under the special laws, acts and/or guidelines for conducting clinical trials in China, unless others have shown negligence.

Novo Nordisk assumes no liability in the event of negligence, or any other liability by the clinics or doctors conducting experiments, or by persons for whom the said clinic or doctors are responsible.

## 27 References

- 1 The Criteria Committee of the New York Heart Association. Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels. 9th ed., 253-256. 1994. Boston, Mass: Little, Brown & Co.
- 2 Inzucchi SE, Bergenstal RM, Buse JB, Diamant M, Ferrannini E, Nauck M et al. Management of hyperglycaemia in type 2 diabetes: a patient-centered approach. Position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetologia* 2012; 55(6):1577-1596.
- 3 Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HA. 10-year follow-up of intensive glucose control in type 2 diabetes. *N Engl J Med* 2008; 359(15):1577-1589.
- 4 Abaira C, Duckworth WC, Moritz T. Glycaemic separation and risk factor control in the Veterans Affairs Diabetes Trial: an interim report. *Diabetes Obes Metab* 2009; 11(2):150-156.
- 5 Gerstein HC, Miller ME, Byington RP, Goff DC, Jr., Bigger JT, Buse JB et al. Effects of intensive glucose lowering in type 2 diabetes. *N Engl J Med* 2008; 358(24):2545-2559.
- 6 Lantus - Summary of Product Characteristics. 2010.
- 7 Levemir - Summary of Product Characteristics.  
[http://www.ema.europa.eu/docs/en\\_GB/document\\_library/EPAR\\_-\\_Product\\_Information/human/000528/WC500036662.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000528/WC500036662.pdf). 2010.
- 8 Novo Nordisk A/S. Investigator's Brochure, Insulin degludec/insulin aspart (8th Edition). 1-11-2012.
- 9 NovoMix30 - Summary of Product Characteristics.  
<http://www.emea.europa.eu/humandocs/Humans/EPAR/novomix/novomix.htm>. 29-Nov-2010.
- 10 EMEA-Committee for Proprietary Medicinal Products. EMEA/CHMP/BMWP/14327/2006 - Guideline on Immunogenicity Assessment of Biotechnology-Derived Therapeutic Proteins. 2006.
- 11 Ware JE, Jr., Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Med Care* 1992; 30(6):473-483.
- 12 Ware JE, Kosinski M, Dewey JE. How to Score Version Two of the SF-36 Health Survey. Lincoln, RI: QualityMetric Incorporated, 2002.
- 13 Brod M, Skovlund SE, Wittrup-Jensen KU. Measuring the impact of diabetes through patient report of treatment satisfaction, productivity and symptom experience. *Qual Life Res* 2006; 15(3):481-491.

- 14 Niskanen L, Jensen LE, Rastam J, Nygaard-Pedersen L, Erichsen K, Vora JP. Randomized, multinational, open-label, 2-period, crossover comparison of biphasic insulin aspart 30 and biphasic insulin lispro 25 and pen devices in adult patients with type 2 diabetes mellitus. *Clin Ther* 2004; 26(4):531-540.
- 15 De Angelius C, Drazen JM, Frizelle FA, Haug C, Hoey J, Horton R et al. Clinical trial registration: a statement from the International Committee of Medical Journal Editors. *New England Journal of Medicine* 2004; 351(12):1250-1251.
- 16 Food and Drug Administration Amendments Act of 2007.  
<http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCAAct/SignificantAmendmentstotheFDCAAct/FoodandDrugAdministrationAmendmentsActof2007/default.htm>. 2007.
- 17 European Commission Regulation for EudraCT. 2011.
- 18 Mitrakou A, Ryan C, Veneman T, Moka M, Jenssen T, Kiss I et al. Hierarchy of glycemic thresholds for counterregulatory hormone secretion, symptoms, and cerebral dysfunction. *Am J Physiol* 1991; 260(1 Pt 1):E67-E74.
- 19 Schwartz NS, Clutter WE, Shah SD, Cryer PE. Glycemic thresholds for activation of glucose counterregulatory systems are higher than the threshold for symptoms. *J Clin Invest* 1987; 79(3):777-781.
- 20 The rules governing medicinal products in the European Union, volume 4, Annex 13, Manufacture of Investigational Products - Brussels.  
[http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol4\\_en.htm](http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol4_en.htm). 2003.
- 21 International Conference on Harmonisation. ICH Harmonised Tripartite Guideline: Guideline for Good Clinical Practice E6 (R1), Step 4. 10-6-1996.
- 22 EMEA-Committee for Proprietary Medicinal Products. CPMP/EWP/482/99 - Points to consider on switching between superiority and non-inferiority. 27-2-2000.
- 23 Food and Drug Administration. Food and Drug Administration, Code of Federal Regulations, Guidance for Industry, Diabetes Mellitus: Developing Drugs and Therapeutic Biologics for Treatment and Prevention. Draft Guidance. 2008.
- 24 Rubin DB. Inference and missing data. *Biometrika* 1976; 63(3):581-592.
- 25 World Medical Association. World Medical Association Declaration of Helsinki: Ethical principles for medical research involving human subjects - Last amended by the 59th WMA General Assembly, Seoul. 2008.

Protocol  
Trial ID: NN5401-3598  
EudraCT No.: 2011-000085-36  
UTN: U1111-1118-8578

~~CONFIDENTIAL~~

Date: 31 May 2017  
Version: 4.0  
Status: Final  
Page: 102 of 102

**Novo Nordisk**

- 26 Clever L, Colaianni LA, Davidoff F, Horton R, Kassirer JP, Angell M et al. Uniform requirements for manuscripts submitted to biomedical journals. *New Engl J Med* 1997; 336(4):309-315.



Protocol - Appendix A  
Trial ID: NN5401-3598  
EudraCT No.: 2011-000085-36  
UTN No: U1111-1118-8578

~~CONFIDENTIAL~~

Date:  
Version:  
Status:  
Page:

31 May 2017  
4.0  
Final  
1 of 9

**Novo Nordisk**

## **Appendix A: Titration Guideline**

### **Trial ID: NN5401-3598**

## **BOOST<sup>®</sup>: INTENSIFY PREMIX/ALL 2**

**A trial comparing efficacy and safety of insulin degludec/insulin aspart and BIAsp 30 in subjects with type 2 diabetes**

**Trial phase: 3a**

~~This confidential document is the property of Novo Nordisk. No unpublished information contained herein may be disclosed without prior written approval from Novo Nordisk. Access to this document must be restricted to relevant parties.~~

## Table of Contents

	<b>Page</b>
<b>Table of Contents</b> .....	<b>2</b>
<b>1 Introduction</b> .....	<b>3</b>
<b>2 Treatment regimens</b> .....	<b>4</b>
2.1 Injection areas .....	4
2.2 Insulin schedule .....	4
<b>3 Initiation and Titration</b> .....	<b>5</b>
3.1 Switch to IDegAsp or BIAsp 30 .....	5
3.2 Titration .....	5
3.3 Deviations from the algorithm .....	6
<b>4 Data collection</b> .....	<b>7</b>
<b>5 Review procedure</b> .....	<b>8</b>
<b>6 References</b> .....	<b>9</b>

## List of in-text tables

	<b>Page</b>
Table 3-1 Increase of insulin doses .....	5
Table 3-2 Reduction of insulin dose .....	6

## 1 Introduction

The goal of insulin therapy is to achieve near normoglycaemia, i.e. to reach a pre-defined HbA<sub>1c</sub> level with a low rate of hypoglycaemic episodes and as little weight gain as possible. Several trials have shown that this is difficult to achieve, unless plasma glucose (PG) values are intensively monitored and the insulin dose(s) frequently adjusted.<sup>1-6</sup>

To ensure treatment uniformity between the sites, as well as to ensure that subjects receive an optimal treatment, titration algorithms have been developed specifying recommended dose adjustments at different PG levels.

It is recognised that treatments differ between different regions and countries. Likewise, specific titration guidelines may not be applicable in certain clinical situations. It is important that other information, such as symptoms of hypo/hyperglycaemia, previous response to dose adjustments, other glucose measurements and other indicators of the subject's level of glycaemic control, is taken into consideration when decisions on dosing are made. The investigator should always use his clinical judgement to avoid safety hazards. The investigator is responsible for the treatment of the subjects and can therefore overrule the guideline.

To optimise and maintain glycaemic control, the investigator should throughout the trial at least be in weekly contact with the subjects to assist the subjects in adjusting insulin doses and to ensure the subject's welfare.

## 2 Treatment regimens

All subjects will receive twice daily treatment with insulin throughout the trial with or without metformin as the only OAD, dependent on previous diabetes therapy prior to trial participation. Prior insulin treatment should be changed to trial insulin according to section [3.1](#).

Minimum dose of insulin is 4U daily (2U per injection). No maximum insulin dose is specified.

### 2.1 Injection areas

IDegAsp should be injected subcutaneously preferably in the abdomen, upper arm (deltoid region) or thigh. BIAsp 30 should be administered subcutaneously preferably in the thigh or in the abdomen according to local labelling. If convenient, the gluteal or deltoid region may be used.

For both IDegAsp and BIAsp 30 the injection site should preferably remain the same throughout the trial, but the location within the site should be changed for each injection.

### 2.2 Insulin schedule

All subjects should be on a *twice daily* insulin treatment regimen, which should be administered pre-breakfast and pre-main evening meal.

### 3 Initiation and Titration

#### 3.1 Switch to IDegAsp or BIAsp 30

At randomisation (Visit 2), the switch from prior insulin will take place.

Subjects previously receiving basal insulin, premixed or self-mixed insulin **twice daily** will be transferred unit-to-unit to IDegAsp or BIAsp 30 pre-breakfast and pre-main evening meal.

Subjects previously receiving basal insulin, premixed or self-mixed insulin **once daily** are recommended to have their dose divided into two equal doses of IDegAsp or BIAsp 30 pre-breakfast and pre-main evening meal.

#### 3.2 Titration

The doses should be adjusted weekly in connection with visits or telephone contacts.

The dose taken with the main evening meal should be adjusted according to the mean pre-breakfast plasma glucose measured on the day of adjustment and the two preceding days.

The dose taken at breakfast should be adjusted according to the mean pre-main evening meal plasma glucose measured on the three days preceding the adjustment day.

Increase in doses will be in accordance with [Table 3-1](#).

**Table 3-1 Increase of insulin doses**

Mean of three pre-breakfast SMPG or pre-main evening meal SMPG		Increase of insulin doses
mmol/L	mg/dL	U
4.0 – 5.0	71 – 90	No adjustment
5.1 – 7.0	91 – 126	+ 2
7.1 – 8.0	127 – 144	+ 4
8.1 – 9.0	145 – 162	+ 6
> 9.0	> 162	+ 8

If one of the PG values is below target (< 4.0 mmol/L or < 71 mg/dL) corresponding dose should be reduced in accordance with [Table 3-2](#).

**Table 3-2 Reduction of insulin dose**

Lowest pre-breakfast SMPG or pre-main evening meal SMPG		Reduction of insulin dose
mmol/L	mg/dL	U
3.1 – 3.9	56 – 70	- 2 (or 5% if the dose >45U)
< 3.1	< 56	- 4 (or 10% if the dose > 45U)

If one or more SMPG values are missing, the adjustment should be performed on the remaining SMPG value(s).

### 3.3 Deviations from the algorithm

It is recommended that the algorithm is followed. However, the decision to adjust insulin doses should be based on all relevant information as described in Chapter 1. A reason for deviating from the algorithm should always be entered into the eCRF.

## 4 Data collection

The following data should be entered into the eCRF within 24 hours (on weekdays) after a subject's site visit/phone contact:

- Per protocol plasma glucose values measured since last visit/telephone contact
- Last insulin doses taken prior to the visit/telephone contact
- New insulin doses to be taken after titration
- Reasons for deviation from the titration algorithms, if applicable
- Hypoglycaemic events (date and PG value)

## 5 Review procedure

Surveillance of insulin titration will be performed centrally by Novo Nordisk in an unbiased manner. It is important that data regarding dose titration is entered into the eCRF within 24 hours (on weekdays). If delays occur, action cannot be taken in due time before the subject's next site visit/telephone contact. The aim is to reduce the time periods in which a subject may receive suboptimal treatment.

The data listed in section 4 regarding titration deviations will be reviewed by Novo Nordisk within 24 hours (on weekdays). The reviewer may contact the investigator to get clarification regarding the reason for deviation or to request entry of missing data.

When the investigator receives an inquiry, a response should be received at Novo Nordisk within 24 hours (on weekdays).

During the trial HbA<sub>1c</sub> will be monitored by Novo Nordisk for additional surveillance of the glycaemic control. Novo Nordisk may be in contact with sites (visit or telephone contact) to discuss progress in glycaemic control and titration of individual subjects based on SMPGs and HbA<sub>1c</sub>. This will be done in an unbiased and whenever possible in a blinded manner.



## 6 References

- 1 Garber AJ, King AB, Del PS, Sreenan S, Balci MK, Munoz-Torres M et al. Insulin degludec, an ultra-longacting basal insulin, versus insulin glargine in basal-bolus treatment with mealtime insulin aspart in type 2 diabetes (BEGIN Basal-Bolus Type 2): a phase 3, randomised, open-label, treat-to-target non-inferiority trial. *Lancet* 2012; 379(9825):1498-1507.
- 2 Heller S, Buse J, Fisher M, Garg S, Marre M, Merker L et al. Insulin degludec, an ultra-longacting basal insulin, versus insulin glargine in basal-bolus treatment with mealtime insulin aspart in type 1 diabetes (BEGIN Basal-Bolus Type 1): a phase 3, randomised, open-label, treat-to-target non-inferiority trial. *Lancet* 2012; 379(9825):1489-1497.
- 3 Hermansen K, Davies M, Derezinski T, Martinez RG, Clauson P, Home P. A 26-week, randomized, parallel, treat-to-target trial comparing insulin detemir with NPH insulin as add-on therapy to oral glucose-lowering drugs in insulin-naive people with type 2 diabetes. *Diabetes Care* 2006; 29(6):1269-1274.
- 4 Philis-Tsimikas A, Charpentier G, Clauson P, Ravn GM, Roberts VL, Thorsteinsson B. Comparison of once-daily insulin detemir with NPH insulin added to a regimen of oral antidiabetic drugs in poorly controlled type 2 diabetes. *Clin Ther* 2006; 28(10):1569-1581.
- 5 Riddle MC, Rosenstock J, Gerich J. The treat-to-target trial: randomized addition of glargine or human NPH insulin to oral therapy of type 2 diabetic patients. *Diabetes Care* 2003; 26(11):3080-3086.
- 6 Rosenstock J, Davies M, Home PD, Larsen J, Koenen C, Scherthaner G. A randomised, 52-week, treat-to-target trial comparing insulin detemir with insulin glargine when administered as add-on to glucose-lowering drugs in insulin-naive people with type 2 diabetes. *Diabetologia* 2008; 51(3):408-416.

IDegAsp  
Trial ID: NN5401-3598  
Clinical Trial Report  
Appendix 16.1.1

~~CONFIDENTIAL~~

Date:  
Version:  
Status:

20 November 2017  
1.0  
Final

**Novo Nordisk**

## **Global and country key Novo Nordisk staff**

Attachments I and II (if applicable) to the protocol are located in the Trial Master File.

Content: Global key staff and Country key staff

Protocol Amendment  
Trial ID: NN5401-3598  
EudraCT No.:2011-000085-36  
UTN: U1111-118-8578

~~CONFIDENTIAL~~

Date:  
Version:  
Status:  
Page:

27 August 2015  
1.0  
Final  
1 of 11

**Novo Nordisk**

**Protocol Amendment**  
no 1  
to Protocol, final version 2.0  
dated 21 December 2012

**Trial ID: NN5401-3598**  
**BOOST<sup>®</sup>: INTENSIFY PREMIX/ALL2**

**A trial comparing efficacy and safety of insulin degludec/insulin aspart  
and BIAsp 30 in subjects with type 2 diabetes**

**Trial phase: 3a**

**Applicable to China**

Amendment originator:



Clinical Operations 2, Insulin & Diabetes Outcomes

This ~~confidential~~ document is the property of Novo Nordisk. ~~No unpublished information contained herein may be disclosed without prior written approval from Novo Nordisk. Access to this document must be restricted to relevant parties.~~

## Table of Contents

	Page
Table of Contents .....	2
1 Introduction including rationale for the protocol amendment.....	3
2 Changes.....	4
2.1 Changes to Protocol .....	4
2.1.1 Optimisation and standardisation of safety reporting.....	4
2.1.1.1 Introducing: ‘Adverse Events with additional data collection’.....	4
2.1.1.2 Deletion of MESI definition and term .....	4
2.1.2 Events in scope for adjudication added.....	4
2.1.3 Extra follow-up visit added at the end of trial .....	4
2.1.4 Collection of data describing ‘severe hypoglycaemic episodes’ .....	5
2.1.5 Timing of ECG evaluation changed and clearly specified.....	5
2.1.6 Start of 9-point Self measured plasma glucose (SMPG) profile prior to visit changed.....	5
2.1.7 PRO questionnaires.....	5
2.1.7.1 Number of PROs reduced .....	5
2.1.7.2 DSQ1 and DSQ2 statistical section changed.....	6
2.1.8 Collection of dose information of trial insulin and BHI 30 .....	6
2.1.8.1 Trial insulin (IDegAsp/ BiAsp 30) .....	6
2.1.8.2 BHI 30.....	6
2.1.9 Flow Chart updates .....	6
2.1.11 Trade name of Biphasic Human Insulin (BHI) 30 changed.....	7
2.1.12 List of abbreviations .....	7
2.1.13 Rescreening not allowed.....	7
2.1.14 Trial Schedule (Page 30).....	8
2.1.15 Data collected in subject diaries specified in more detail .....	8
2.1.16 The term ‘end-of-trial’ corrected and EOT deleted .....	8
2.1.17 UTN number added.....	8
2.2 Changes to the SI/IC .....	8
2.2.1 UTN and EudraCT numbers added.....	8
2.2.2 Adhering to local regulations and legal requirement .....	9
2.2.3 Text describing cardiovascular safety and DEVOTE.....	10
2.2.4 Paternal information and Paternal SI/IC added.....	10
2.2.4.1 Update of section 2.4 If you become pregnant .....	10
2.2.4.2 New SI/IC for Male Partner has been added.....	10
2.2.5 Other SI/IC updates .....	11
2.2.5.1 30 days follow up visit (FU 2), phone contact 30, added .....	11
2.2.5.2 Record retention changed to 25 years.....	11

## 1 Introduction including rationale for the protocol amendment

The CFDA approval of the final protocol version 2.0, dated 21 December 2012 were approved on 23. July 2015. Since the preparation of the trial protocol in 2012, some of the Novo Nordisk standards and processes have evolved and updated, which is the primary reason for preparing the amendment and updating the protocol. Secondly, this is in accordance with the feed-back received from CFDA, refer to below text copied from the IDegAsp IDL approval letter, optimization of the protocol is allowed:

“Before the clinical trial, clinical research organization should further refine and optimize the protocol, pay attention to the exposed and potential safety risk of the product, and make a risk management plan.”

While amending the protocol, special attention has been on patient safety and reporting, data quality and GCP compliance. This means, that minor refinements have been made throughout the protocol with the purpose of improving data quality and clarifying issues, where applicable.

## 2 Changes

### 2.1 Changes to Protocol

#### 2.1.1 Optimisation and standardisation of safety reporting.

**Rationale:** This in order to standardise and align with the current and future internal safety reporting processes within Novo Nordisk ‘SHARP’, which will result in a more systematic way of collecting safety data and improve the quality of data collected. Further by updating the protocol, the safety processes and reporting will be simplified refer to the PNC 3004829, Reporting of medication error as AE requiring additional data rather than MESI.

**Impact:** The impact of the above is mentioned in sections below:

##### 2.1.1.1 Introducing: ‘Adverse Events with additional data collection’

**Impact:** Section 12 updated with relevant sections and a new section 8.7 introduced

##### 2.1.1.2 Deletion of MESI definition and term

**Impact:** Throughout the protocol MESI has been deleted and medication error are changed to AE requiring additional data collection

#### 2.1.2 Events in scope for adjudication added

**Rationale:** Since the preparation of the NN5401-3598 protocol back in 2012, Novo Nordisk has in line with global guideline implemented adjudication of all-cause death (not only cardiovascular death) Further, a sub-category has been specified for Silent Myocardial Infarction (Silent MI).

**Impact:** Protocol section 12.7.2 updated with new table 12.2 to reflect this.

#### 2.1.3 Extra follow-up visit added at the end of trial

**Rationale:** In line with current FDA guidance, an additional follow-up visit (30 days after last dose on trial product) will be added at the end of trial in order to collect further safety information on potential major cardiovascular events and subject reported AEs.

**Impact:** This will increase the trial duration with approximately 3 weeks – which has been updated in protocol where applicable (e.g. also figure 5.1 updated). Further the terms 7-days follow up visit (FU1) and 30-days follow-up visit FU2 (Phone contact 30) has been introduced throughout the protocol – especially Chapters 2, 5 and 8.

#### **2.1.4 Collection of data describing ‘severe hypoglycaemic episodes’**

**Rationale:** The protocol was written in 2012 based on SOP 110079 ed. 6.0. Since then the hypoglycaemia episode form has been updated to capture additional structured information on severe hypoglycaemia symptoms and resource use. Therefore a number of additional questions will be added to the subject diaries.

**Impact:** The severe hypo data being collected in the diaries has been added to protocol Chapter 8.8 and other text corrections made to comply with current standards and improve narrative quality.

#### **2.1.5 Timing of ECG evaluation changed and clearly specified**

**Rationale:** In order to collect more recent baseline data – relevant for potential identification of Silent MI at screening and prior to randomisation the ECG for subjects should be performed between screening Visit 1 and randomisation Visit 2. Also, it has specifically stated that ECG at end of trial needs to be performed at the day of the last treatment visit (Visit 28).

**Impact:** Chapter 8.6.5 and 2 (notes to the flow chart) updated

#### **2.1.6 Start of 9-point Self measured plasma glucose (SMPG) profile prior to visit changed**

**Rationale:** In the protocol the start for performing the 9-point SMPG measurements has mistakenly been written to start on the day before the visit. This is not in accordance with how this has been done in previous similar trials. The SMPG measurements should in fact start in the morning 2 days prior to the planned visit to the site. Reason is that the Before breakfast measurements (first and last measurements in profile) cannot directly be compared if measurements start day before and ends at the day of visit, since the breakfast at the day of visit might vary depending on the timing of the appointment at site and the fasting blood sampling performed at site at the day of the visit.

**Impact:** Chapter 8.6.9.2 ‘9-point profile (SMPG)’ (page 44) and Flowchart updated

#### **2.1.7 PRO questionnaires.**

##### **2.1.7.1 Number of PROs reduced**

**Rationale:** In the protocol a total of seven PRO questionnaires were included. In order to reduce the risk of ‘questionnaire fatigue’, and due to the fact that there is overlap between TRIM-D, DPM and DiabMedSat, it has been chosen to omit DPM and DiabMedSat questionnaires.

**Impact:** Chapter The DPM and DiabMedSat questionnaires have been deleted from sections: 4.2.3, 6.8.6 and 17.9 and 'list of abbreviations.

#### **2.1.7.2 DSQ1 and DSQ2 statistical section changed.**

**Rationale:** Since for the Device Specific Questionnaires DSQI and DSQII there are no validated scoring algorithms, formal statistical analysis will not be conducted and only descriptive statistics will be presented.

**Impact:** Section 17.9 has been updated to reflect this change.

#### **2.1.8 Collection of dose information of trial insulin and BHI 30**

##### **2.1.8.1 Trial insulin (IDegAsp/ BiAsp 30)**

**Rationale:** In previous similar trials both doses and corresponding SMPG values from 3 days prior to next visit/ phone contact have usually been collected. In version 2.0 of the protocol it was stated that dose information was only to be collected on day prior to visit. Mistake has now been corrected

**Impact:** Chapters 8.4, 8.6.1 and 2 (Flow Chart) have been updated.

##### **2.1.8.2 BHI 30**

**Rationale:** In protocol it was described that BHI 30 first dose and last dose, plus doses day 1, 3, 5 and day just prior to Visit 29 were to be collected. In previous trials it has been realised that this has been very confusing to trial subjects since first dose in some instances was identical to dose on day 1 and last dose in many instances was identical to last day prior to Visit 29 (since BHI were not to be given at day of Visit 29). Based on this the need for correction was evident. Days for dose collection changed to: First day (Visit 28), 2 days and 4 days after Visit 28, and on the last day before FU1 (Visit 29).

**Impact:** Chapter 8.4 has and Flow Chart has been updated accordingly.

#### **2.1.9 Flow Chart updates**

**Rationale:** Based on above mentioned changes related to additional Follow-up visit (2.3) Timing on ECG (2.5), 9-point profile (2.6) and PRO questionnaires (2.7), Insulin doses (2.8), and IWRS term (2.11). Further two additional dispense visits have been added in order to improve drug accountability.



**Impact:** Flow chart and footnotes updated accordingly. Further the following small modifications have been made.

#### **2.1.10 Monitoring procedures more clearly specified.**

**Rationale:** In order to comply with current edition of SOP 110079 and to ensure subject safety and GCP compliance as early as possible at trial sites, the protocol will be updated to define the maximum allowed time (4 weeks) from FPFV until the first monitoring at site.

Further, since PROs will be provided as 3-layer NCR paper forms, it has been specified which page of the NCR form that must be retained at site as source documentation.

**Impact:** Updated Chapter 14 Monitoring Procedures (page 67)

#### **2.1.11 Trade name of Biphasic Human Insulin (BHI) 30 changed**

**Rationale:** Since the name of the marketed product in China is Novolin<sup>®</sup> 30 and not Mixtard<sup>®</sup> 30 this has been corrected.

**Impact:** Updated Chapter 9.1 Trial products (page 48)

#### **2.1.12 List of abbreviations**

**Rationale:** Since protocol preparation back in 2012, new standard abbreviations have been implemented and the following terms will be modified throughout the protocol. Also a few new terms have been added, refer to below.

**Impact:** ASAT, ALAT, IV/WRS replaced by AST, ALT, IWRS throughout the protocol. Further FU (follow up) and MI (Myocardial Infarction) have been added.

#### **2.1.13 Rescreening not allowed**

**Rationale:** To comply with current standards, it has been specified that re-screening of subjects is NOT allowed.

**Impact:** A new section 8.1.2.1 has been added

#### **2.1.14 Trial Schedule (Page 30)**

**Rationale:** Since timelines stated in protocol are outdated these have been changed according to current plans.

**Impact:** Chapter 7 updated

#### **2.1.15 Data collected in subject diaries specified in more detail**

**Rationale:** In order to more clearly state at which visits information will be collected in the diaries, visit numbers have been added in parentheses.

**Impact:** Section 8.4 ‘Diaries’ has been updated.

#### **2.1.16 The term ‘end-of-trial’ corrected and EOT deleted**

**Rationale:** In order to clarify and being able to distinguish between ‘end-of-trial’ and ‘end-of-treatment’, especially since the 30 days FU visit has been introduced. Further the EOT abbreviation has been deleted and replaced by text.

**Impact:** Chapter 4.2.3.2, and Flow chart section 2 have been updated.

#### **2.1.17 UTN number added**

**Rationale:** When preparing the Protocol back in 2012, the UTN and EudraCT numbers were not originally part of the Protocol template used.

**Impact:** Header updated

### **2.2 Changes to the SI/IC**

#### **2.2.1 UTN and EudraCT numbers added**

**Rationale:** When preparing the SI/IC back in 2012, the UTN and EudraCT numbers were not originally part of the SI/IC template used.

**Impact:** Header updated

## **2.2.2 Adhering to local regulations and legal requirement**

**Rationale:** Below sections have been added based on experience with EC requested information.

- Blood sample handling & exportation (refer to 2.2.2.1)
- Liability information (refer to 2.2.2.2)
- Subject re-imburement (refer to 2.2.2.3)

### **2.2.2.1 1.11 Information about antibody sampling and exportation -added**

*According to the protocol, the serum antibody samples must never be taken before you have signed the informed consent. The serum antibody samples will not be identified by your name, but by a subject number and a trial identification number instead. In order to standardise the sample analysis used in this trial, all serum antibody samples including yours, will be shipped to a special laboratory, [REDACTED], located in [REDACTED]. By involving only one special laboratory, this will ensure comparability of results from subjects at all investigational sites involved in the trial. The procedures of serum antibody sampling, handling and shipment are done in accordance with applicable Chinese laws and regulations and the quality control standards confirmed by the Sponsor and [REDACTED]. According to local law, Chinese Human Genetic Resource Administration must always approve sample shipment, before any samples are shipped. Further, the serum antibody samples must only be used in relation to this trial, and all samples will be destroyed as biological/medical waste at [REDACTED], upon finalisation of study report and never shipped back to China.*

### **2.2.2.2 4.2 What if something goes wrong? - updated**

Novo Nordisk A/S carries product liability for its products and liability assumed under the special laws, acts and/or guidelines for conducting clinical research trials in any country, unless others have shown negligence. *Novo Nordisk A/S is insured for Clinical Trials in China, so the reasonable compensation and treatment will be available to the subject in the event of injury directly related caused by administration of the study drug or by the study procedures to which you would not have been exposed if you had not participated in the trial, unless others have shown negligence in accordance with local laws in China.* If you feel something has gone wrong, please contact the trial site staff in the first instance.

### **2.2.2.3 4.3 Will you receive any payment for your participation in the trial? - added**

*Your travel expenses in connection with your visit to the site will be reimbursed, it will be [REDACTED] per site visit(including screening visit),but the phone contact will not be covered. You will not be reimbursed for your time spent at the site nor will you receive any payment for taking part in the*

*trial. If you withdraw or are withdrawn before the end of the trial, or if the trial terminates early you will be paid only for visits you do complete. The trial will be performed under strictly defined inclusion and exclusion criteria. If these criteria are not met and consequently you do not enter the active trial period (following dosing on Day1), you will be compensated for [REDACTED] for the travel expense of screening visit, and you will have access to all results of examination performed on you.*

### **2.2.3 Text describing cardiovascular safety and DEVOTE**

**Rationale:** In order to include safety text requested by FDA in previous trials, and to present the most recent status on the CV outcome trial initiated based on FDA request the below section has been added.

**Impact:** The previous text section 1.3 has been deleted and below section added instead.

#### **2.1.1 Signal of increased cardiovascular risk**

*The U.S. Food and Drug Administration (FDA) concluded that a signal of increased cardiovascular risk associated with insulin degludec and insulin degludec/insulin aspart relative to comparators has been observed in the clinical development programme. In 2013 Novo Nordisk has upon FDA request initiated a multinational trial 'DEVOTE' in order to evaluate the cardiovascular safety. In this trial 7638 patients in 20 countries have been enrolled. Based on the interim data collected in DEVOTE, FDA has accepted to re-review the Novo Nordisk application for marketing approval of **insulin degludec and insulin degludec/insulin aspart**. Both insulin degludec and insulin degludec/insulin aspart have been approved for use in EU and Japan.*

### **2.2.4 Paternal information and Paternal SI/IC added**

**Rationale:** In order to comply with protocol, the below sentence have been added in the following section, which is also in accordance with current SOP:

Impact: Refer to below 2.2.4.1 and 2.2.4.2

#### **2.2.4.1 Update of section 2.4 If you become pregnant**

*In the case of anything out of the ordinary experienced by the unborn child during the pregnancy or by the new-born child, the child's father will be asked to sign and date a separate informed consent for collection of paternal information*

#### **2.2.4.2 New SI/IC for Male Partner has been added**

Refer to attached document.

Protocol Amendment  
Trial ID: NN5401-3598  
EudraCT No.:2011-000085-36  
UTN: U1111-118-8578

~~CONFIDENTIAL~~

Date:  
Version:  
Status:  
Page:

27 August 2015  
1.0  
Final  
11 of 11

**Novo Nordisk**

## **2.2.5 Other SI/IC updates**

**Rationale:** Based on updates made to the trial protocol

### **2.2.5.1 30 days follow up visit (FU 2), phone contact 30, added**

**Impact:** Section 1.6, 3.1, 3.2 and 3.3 updated.

### **2.2.5.2 Record retention changed to 25 years**

**Impact:** Section 3.4 updated.

**Novo Nordisk A/S**  
3598-protocol-amendment-1.0

**Electronic Signature Page**

**27 Aug 2015 11:13:54**

Documentum ObjectID : [REDACTED]

---

*This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.*

---

**Document signed by:**

<i>Initials</i>	<i>Full Name</i>	<i>Date and Time of Signature (Server Time)</i>
<i>Meaning</i>		
[REDACTED]	[REDACTED]	
Author Approval		27-Aug-2015 09:27 GMT+0000
[REDACTED]	[REDACTED]	
Author Approval		27-Aug-2015 09:40 GMT+0000
[REDACTED]	[REDACTED]	
Clinical Approval		27-Aug-2015 11:13 GMT+0000

Amendment to SI/IC  
Trial ID: NN5401-3598  
EudraCT No.:2011-000085-36  
UTN: U1111-118-8578

~~CONFIDENTIAL~~

Date: 28 August 2015  
Version: 1.0  
Status: Final  
Page: 1 of 4

**Novo Nordisk**

## **Amendment**

no 2

to Master subject information, final version 4.0,  
dated 27 August 2015

### **Trial ID: NN5401-3598** **BOOST<sup>®</sup>: INTENSIFY PREMIX/ALL2**

**A trial comparing efficacy and safety of insulin degludec/insulin aspart  
and BIAsp 30 in subjects with type 2 diabetes**

**Trial phase: 3a**

**Applicable to China**

Amendment originator:



Clinical Operations 2, Insulin & Diabetes Outcomes

This ~~confidential~~ document is the property of Novo Nordisk. ~~No unpublished information contained herein may be disclosed without prior written approval from Novo Nordisk. Access to this document must be restricted to relevant parties.~~

## Table of Contents

	Page
<b>Table of Contents.....</b>	<b>2</b>
<b>1 Introduction including rationale for the protocol amendment.....</b>	<b>3</b>
<b>2 Changes.....</b>	<b>4</b>
<b>2.1 Table of content updated.....</b>	<b>4</b>
<b>2.2 4.2 What if something goes wrong? – updated.....</b>	<b>4</b>



Amendment to SI/IC  
Trial ID: NN5401-3598  
EudraCT No.:2011-000085-36  
UTN: U1111-118-8578

~~CONFIDENTIAL~~

Date:	28 August 2015	<b>Novo Nordisk</b>
Version:	1.0	
Status:	Final	
Page:	3 of 4	

## 1 Introduction including rationale for the protocol amendment

Unfortunately, minor mistakes were identified in master subject information was identified after approval and finalisation.

## 2 Changes

### 2.1 Table of content updated

**Rationale:** In the SI/IC section 1.11 described the anti body sampling and transportation, however by mistake this section was not present in the table of content

**Impact:** The table of content updated to correct this mistake.

### 2.2 4.2 What if something goes wrong? – updated

**Rationale:** In order to correct text to the one originally intended based on legal input.

**Impact:** The word ‘related’ deleted - see below

Novo Nordisk A/S carries product liability for its products and liability assumed under the special laws, acts and/or guidelines for conducting clinical research trials in any country, unless others have shown negligence. Novo Nordisk A/S is insured for Clinical Trials in China, so the reasonable compensation and treatment will be available to the subject in the event of injury directly ~~related~~ caused by administration of the study drug or by the study procedures to which you would not have been exposed if you had not participated in the trial, unless others have shown negligence in accordance with local laws in China. If you feel something has gone wrong, please contact the trial site staff in the first instance.

Protocol Amendment  
Trial ID: NN5401-3598  
UTN: U1111-1118-8578  
EudraCT No.: 2011-000085-36

~~CONFIDENTIAL~~

Date:  
Version:  
Status:  
Page:

31 May 2017  
1.0  
Final  
1 of 5

**Novo Nordisk**

**Protocol Amendment**  
**no 3**  
**to Protocol, final version 2.0**  
**dated 21 December 2012**

**Trial ID: NN5401-3598**  
**BOOST<sup>®</sup>: INTENSIFY PREMIX/ALL 2**

**A trial comparing efficacy and safety of insulin degludec/insulin aspart  
and BIAsp 30 in subjects with type 2 diabetes**

**Trial phase: 3a**

**Applicable to China**

Amendment originator:

[REDACTED], [REDACTED]

Trial Operations, Insulin & Devices

This ~~confidential~~ document is the property of Novo Nordisk. ~~No unpublished information contained herein may be disclosed without prior written approval from Novo Nordisk. Access to this document must be restricted to relevant parties.~~

## Table of Contents

	<b>Page</b>
<b>Table of Contents</b> .....	<b>2</b>
<b>Table of Tables</b> .....	<b>2</b>
<b>1 Introduction including rationale for the protocol amendment</b> .....	<b>3</b>
<b>2 Changes</b> .....	<b>3</b>
2.1 UTN on page 1 and throughout the document:.....	3
2.2 Section 1 Summary, Primary objectives page 10, first line:.....	4
2.3 Section 2, Flow chart, page 14:.....	4
2.4 Section 7, Trial schedule, page 33, Trial schedule.....	5
2.5 Section 8.2 Concomitant illness and medical history, page 37, first line:.....	5
2.6 Section 8.3 Concomitant medication, third line, page 37:.....	5
2.7 Section 8.4 Diaries, page 38, second paragraph, last bullet point:.....	5
2.8 Section 8.5 Laboratory assessments, page 39, paragraph six:.....	5
2.9 Section 17.1 Sample size calculation, page 78, table 17-3:.....	5

## Table of Tables

	<b>Page</b>
<b>Table 17-3 Anticipated number of subjects in FAS and PP analysis set</b> .....	<b>5</b>

## 1 Introduction including rationale for the protocol amendment

In this protocol amendment:

- Any new text is written *in italics*.
- Any text deleted from the protocol is written using ~~strike through~~.

The following changes will be applied to the protocol. The rationale for the changes is:

1. Universal Trial Number (UTN) in the header of the protocol will be corrected from U1111-118-8578 to U1111-**1118**-8578
2. Section 1 (summary) and the following pages 8, 16-20, 23-26, 31-32, 35, 38, 40, 43, 52, 55, 60, 63, 65, 76 and 89 will be updated to be consistent in the use of IDegAsp 30 and not IDegAsp
3. Section 2 (Flow chart) will be updated as the sign off casebook is to take place after phone visit 30 and not at visit 29
4. Section 7 (trial schedule) will be updated to clarify that the recruitment period will be extended to in total 28 weeks, date for LPLV will be changed to Q2 2017 and date for CTR will be changed to Q4 2017
5. Section 8.2 (concomitant illness and medical history) will be updated to clarify that concomitant illness for lipids and urinalysis of albumin/creatinine ratio will be assessed at visit 2 (randomisation)
6. Section 8.3 (concomitant medication) will be updated to clarify that concomitant medication should be recorded until visit 29 as mentioned in section 2 (the flow chart)
7. Section 8.4 (diaries) will be updated to clarify that changes in concomitant medication should be recorded by the subjects until visit 29 as mentioned in section 2 (the flow chart)
8. Section 8.5 (laboratory assessment) will be updated to clarify that any clinically significant abnormalities seen for lipids and urine/creatinine ratio at visit 2 (randomisation) should be recorded in the medical history/concomitant illness form as these parameters are assessed for the first time at visit 2
9. Section 17.1 (sample size calculation) table 17-3 will be updated to clarify that comparator for the trial is BIAsp 30 and that IDegAsp and BIAsp 30 will be administered BID

## 2 Changes

### 2.1 UTN on page 1 and throughout the document:

UTN will be corrected from U1111-118-8578 to *U1111-1118-8578*



## 2.4 Section 7, Trial schedule, page 33, Trial schedule

Planned duration of recruitment period	
(First patient first visit (FPFV) – last patient first visit (LPLV)):	<del>16</del> 28 weeks
Planned date for FPFV:	Q2 2016
Planned date for last patient last visit (LPLV):	<del>Q1</del> Q2 2017
The end of the clinical trial is defined as last patient last visit (LPLV)	
Planned completion of clinical trial report (CTR):	<del>Q3</del> Q4 2017

## 2.5 Section 8.2 Concomitant illness and medical history, page 37, first line:

A concomitant illness is any illness that is present at the start of the trial (i.e. at the first visit) or found as a result of the screening procedures *performed at screening (Visit 1) or for lipids and the urine albumin/creatinine ratio at randomisation (Visit 2)*.

## 2.6 Section 8.3 Concomitant medication, third line, page 37:

Details of any concomitant medication must be recorded at trial entry (i.e. at the first visit) and until ~~the end of treatment (Visit 28)~~ Visit 29 on the concomitant medication form in the eCRF.

## 2.7 Section 8.4 Diaries, page 38, second paragraph, last bullet point:

- changes in concomitant medication (including changes in doses of metformin if any) (~~V3-V28~~ V29)

## 2.8 Section 8.5 Laboratory assessments, page 39, paragraph six:

If ~~any clinically significant abnormalities~~ a clinical laboratory abnormality, which is clinically significant ~~occurs~~ at screening (Visit 1) or for lipids and urine albumin/creatinine ratio is clinically significant at randomisation (Visit 2), this must be recorded on the medical history/concomitant illness form.

## 2.9 Section 17.1 Sample size calculation, page 78, table 17-3:

Anticipated number of subjects in FAS and PP analysis set

	<del>Insulin degludec OD</del> IDegAsp 30 BID	<del>Insulin glargine OD</del> BIAsp 30 BID	Total
Number of subjects in the FAS	358	179	537
Number of subjects in the PP analysis set	304	152	456