Cover Page for Protocol

Sponsor name:	Novo Nordisk A/S
NCT number	NCT02582242
Sponsor trial ID:	BIAsp-4200
Official title of study:	A 24-week, Multinational, Multicentre, Randomised, Open Label, Parallel-group Treat-to-target Trial to Compare Efficacy and Safety of Thrice Daily Versus Twice Daily NovoMix® 30 (Biphasic Insulin Aspart 30) in Subjects With Type 2 Diabetes Inadequately Controlled With Basal Insulin
Document date:	13 September 2017

16.1.1 Protocol and protocol amendments

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Protocol

Trial ID: BIAsp-4200

A 24-week, multinational, multicentre, randomised, open label, parallel-group treat-to-target trial to compare efficacy and safety of thrice daily versus twice daily NovoMix® 30 (Biphasic insulin aspart 30) in subjects with type 2 diabetes inadequately controlled with basal insulin

Redacted protocol
Includes redaction of personal identifiable information only.

Trial phase: 4

Protocol originator
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CMR Dept., Novo Nordisk (China) Pharmaceutical Co., Ltd

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List of abbreviations

ADA	American Diabetes Association
AE	adverse event
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
BG	blood glucose
BIAsp	Biphasic insulin aspart
BID	twice daily
BMI	body mass index
CCDS	Company Core Data Sheet
CLAE	clinical laboratory adverse event
CRA	clinical research assistant
CRF	case report form
CSII	continuous subcutaneous insulin infusion
DCF	data clarification form
DTSQ	Diabetes Treatment Satisfaction Questionnaire
DFU	direction for use
DUN	dispensing unit number
EASD	European Association for the Study of Diabetes
eCRF	electronic case report form
eGFR	estimated glomerular filtration rate
EMA	European Medicines Agency
EOT	end-of-treatment
EU	European Union
FAS	full analysis set
FDA	U.S. Food and Drug Administration
FDAAA	U.S. Food and Drug Administration Amendment Act
FPFV	first patient first visit

FPG	fasting plasma glucose
FU	follow-up
GCP	Good Clinical Practice
HbA_{1c}	glycosylated haemoglobin
HDL	high density lipoprotein
HI	human insulin
IAsp	insulin aspart
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
IEC	independent ethics committee
IMP	investigational medicinal product
IRB	institutional review board
ITT	intention-to-treat
IUD	intrauterine device
IV/WRS	interactive voice/web response system
LDL	low density lipoprotein
LOCF	last observation carried forward
LPFV	last patient first visit
LPLV	last patient last visit
MESI	medical event of special interest
MIDF	monitor-initiated discrepancy form
MMRM	mixed model for repeated measurements
NPH	Neutral Protamine Hagedorn
NYHA	New York Heart Association
OAD	oral antidiabetic drug
OD	once daily
PPG	postprandial glucose
PRO	patient reported outcome
SAE	serious adverse event

SAP	statistical analysis plan
s.c.	subcutaneous(ly)
SD	standard deviation
SGLT2	sodium glucose co-transporter 2
SI/IC	subject information/informed consent form
SmPC	summary of product characteristics
SMPG	self-measured plasma glucose
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment emergent adverse events
TID	thrice daily
TMM	Trial Materials Manual
UTN	Universal Trial Number

1 Summary

Objectives and endpoints:

Primary objective

To compare the efficacy of thrice daily biphasic insulin aspart (BIAsp) 30 versus twice daily BIAsp 30, both in combination with metformin, in subjects with type 2 diabetes inadequately controlled on basal insulin combined with oral anti-diabetic drugs (OADs).

Key secondary objectives

To compare safety of thrice daily BIAsp 30 versus twice daily BIAsp 30, both in combination with metformin, in subjects with type 2 diabetes inadequately controlled on basal insulin combined with oral anti-diabetic drugs (OADs)

Primary endpoint

Change from baseline in glycosylated haemoglobin (HbA_{1c}) after 24 weeks of treatment

Key secondary endpoints

- Proportion of subjects achieving $HbA_{1c} < 7.0\%$ without severe hypoglycaemic episodes after 24 weeks of treatment
- Number of treatment emergent hypoglycaemic episodes classified according to the American Diabetes Association (ADA) and Novo Nordisk definition during 24 weeks of treatment

Trial design:

This is an open-labelled, randomised, two-armed, parallel group, multinational, multicentre, treat-to-target trial. It consists of a screening period (of up to 2 weeks), a 24-week treatment period and 30-day follow-up period.

Randomisation will be stratified according to HbA_{1c} value and pre-trial OAD treatment. The strata correspond to the HbA_{1c} intervals of 7.5%−8.5% (both inclusive) and 8.6%−10.0% (both inclusive). The strata regarding OADs are: metformin monotherapy and metformin + one additional OAD.

The eligible subjects will be randomised in a 1:1 manner into one of the two arms with the following treatment:

- BIAsp 30 thrice daily (TID) + metformin
- BIAsp 30 twice daily (BID) + metformin

Within each participating country it will be aimed at including a maximum of 20% of randomised subjects on treatment with neutral protamine hagedorn (NPH) prior to screening.

Subjects must continue metformin all throughout the trial and any other OAD should be discontinued at randomisation. The insulin dose will be titrated on a weekly basis for all subjects throughout the trial. Titration will be performed according to a titration algorithm for BIAsp 30 in order to achieve the pre-meal self-measured plasma glucose (SMPG) target of 4.4−6.1 mmol/L (80−110 mg/dl).

Trial population:

Number of subjects planned to be randomised: 426

Key inclusion criteria:

- Male or female, age ≥ 18 years at the time of signing informed consent
  For Algeria only: age ≥19 years at the time of signing informed consent
- Type 2 diabetes subjects clinically diagnosed ≥ 12 months prior to the day of screening (Visit 1)
- Treated with basal insulin ≥ 90 days prior to the day of screening (Visit 1).
  - The following basal insulin are allowed :
  - insulin analogue once daily (OD)
  - Neutral Protamine Hagedorn (NPH) OD or BID
- Treatment with metformin with or without one additional OAD for at least 90 days prior to the day of screening (Visit 1)
  - Metformin must be at a stable dose of at least 1500 mg daily or maximum tolerated dose for at least 60 days prior to screening (Visit 1)
  - One additional OAD:
    - Sulphonylurea
    - Glinides
    - α-glucosidase inhibitors
    - Dipeptidyl-peptidase-4 inhibitors
    - Sodium glucose co-transporter 2 (SGLT2) inhibitors (if applicable)
- HbA_{1c} 7.5%−10.0% (both inclusive) by central laboratory analysis at screening (Visit 1)
- Able and willing to intake three main meals daily (breakfast, lunch and main evening meal) throughout the trial. Definition of main meal as judged by the investigator

Key exclusion criteria

- Previous insulin intensification regimen for more than 14 days: premixed insulin thrice daily, basal-bolus regimen or continuous subcutaneous insulin infusion (CSII). Treatment during hospitalisation or during gestational diabetes is allowed for periods longer than 14 days
- Anticipated initiation or change in concomitant medications for more than 14 consecutive days or on a frequent basis known to affect weight or glucose metabolism (e.g. orlistat, thyroid hormones, systemic corticosteroids)
- Impaired liver function, defined as alanine aminotransferase (ALT) ≥ 2.5 times upper normal limit at screening (Visit 1)

Assessments:

The key assessments in the trial are:

- HbA_{1c}
- Fasting plasma glucose (FPG)
- SMPG measurements
- Hypoglycaemic episodes
- Dose of trial insulin
- Body weight

Trial product:

- BIAsp 30, 100 U/ml, 3 ml FlexPen®, suspension for injection, administered subcutaneously (s.c.)

2 Flow chart

Trial periods[1]	S	R	Treatment period																							E	FU
Visit type[2]	C	C	P	C	P	C	P	P	P	C	P	P	P	C	P	P	P	C	P	P	P	C	P	P	P	C	P
Visit number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27
Timing of visit Weeks	-2	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	+30 days
Visit window Days	±3	0	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	+5
SUBJECT RELATED INFO/ASSESSMENTS																											
Informed consent	X																										
In/exclusion criteria	X	X																									
Randomisation[3]		X																									
Withdrawal criteria			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Concomitant illness	X																										
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Demography	X																										
Diagnosis of diabetes	X																										
Diabetes complications	X																										
Diabetes treatment history																											
Current diabetes treatment	X																										
Dose of current diabetes treatment	X	X																									

Trial periods[1]	S	R	Treatment period																							E	FU
Visit type[2]	C	C	P	C	P	C	P	P	P	C	P	P	P	C	P	P	P	C	P	P	P	C	P	P	P	C	P
Visit number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27
Timing of visit Weeks	-2	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	+30 days
Start date of current diabetes treatment	X																										
Stop date of current diabetes treatment		X																									
Medical history	X																										
Pregnancy test																											
Blood sample	X																									X	
Urine-sticks[4]		[X]	[X]	[X]	[X]	[X]	[X]	[X]	[X]	[X]	[X]	[X]	[X]	[X]	[X]	[X]	[X]	[X]	[X]	[X]	[X]	[X]	[X]	[X]	[X]		
Tobacco use	X																										
EFFICACY																											
Glucose metabolism																											
HbA_{1c}	X	X				X				X				X				X				X				X	
Fasting plasma glucose		X												X												X	
Self-measured plasma glucose																											
7-point profile[5]		X												X												X	
Three times daily[6]			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
SAFETY																											
Body measurements																											
Height	X																										
Body weight	X	X												X												X	
BMI	X																										
Physical examination	X																									X	
Eye examination	X																									X	

Trial periods[1]	S	R	Treatment period																							E	FU
Visit type[2]	C	C	P	C	P	C	P	P	P	C	P	P	P	C	P	P	P	C	P	P	P	C	P	P	P	C	P
Visit number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27
Timing of visit Weeks	-2	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	+30 days
Vital signs	X																									X	
Haematology	X																									X	
Lipids		X																								X	
Biochemistry	X																									X	
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hypoglycaemic episodes[7]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Technical complaints		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
OTHER ASSESSMENTS																											
PRO questionnaires		X																								X	
TRIAL MATERIAL																											
Administration of trial product																											
Dispensing visit		X				X				X				X				X				X					
Dose of trial insulin[8]		X	X	X	X	X	X	X	X	X	X	X	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	X	X	X	X	X	X	X	X	X	X		
Drug		X				X				X				X				X				X				X	
IV/WRS call	X	X				X				X				X				X				X				X	
REMINDERS																											
End of trial																											X
Trial Conduct																											
End of treatment																										X	

Trial periods[1]	S	R	Treatment period																							E	FU
Visit type[2]	C	C	P	C	P	C	P	P	P	C	P	P	P	C	P	P	P	C	P	P	P	C	P	P	P	C	P
Visit number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27
Timing of visit Weeks	-2	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	+30 days
Attend visit fasting		X												X												X	
Training in trial products and pen handling[9]		X				X				X				X				X				X					
Hand out and instruct in diary	X	X		X		X				X				X				X				X				X	
Hand out and instruct in BG meter	X																										
Hand out ID card	X																										
Sign off Casebook																											X
Confirmation of unchanged metformin		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Dispensing DFU[11]		X				[X]				[X]				[X]				[X]				[X]					

1. S: screening; R: randomisation; E: end-of-treatment; FU: follow-up
2. C: clinic; P: phone contact. A phone contact can be converted to a clinic visit at the investigator's discretion.
3. Randomisation should take place no later than 14 days after screening visit (Visit 1). Randomisation cannot take place until all results are available, reviewed and the subject is confirmed eligible, evaluating all inclusion and exclusion criteria.

4. If at a phone contact, the subject reports a missed menstrual period, the subject would have to go to the trial site for an unscheduled visit as soon as possible. During the unscheduled visit, a urine-stick pregnancy test will be performed. If the result is positive, a confirmatory blood pregnancy test will be performed and analysed by the central laboratory.
5. The 7-point SMPG profile should be performed on the day prior to Visit 2, Visit 14 and Visit 26.
6. The three times daily SMPG will be performed on 3 random days in the week prior to the clinic visit/phone contact.
7. The hypoglycaemic episode will be collected from visit 1 to 7 days after Visit 26.
8. The insulin doses should be recorded in the diary on the days when three times daily SMPG are performed.
9. Once during the trial after initial training of the subject, site staff must ensure that the subject is using the trial product and the pen correctly. The follow-up on correct use of the trial product and the pen must be documented in the subject's medical record.
10. Once during the trial after initial training of the subject, site staff must ensure that the subject is using the BG meter correctly. The follow-up on correct use of the BG meter must be documented in the subject's medical record.
11. Document that the direction for use (DFU) is provided at Visit 2. DFUs may be given at other visits if deemed appropriate by the investigator.

3 Background information and rationale for the trial

The trial will be conducted in compliance with this protocol, ICH GCP[1] and applicable regulatory requirements, and in accordance with the Declaration of Helsinki[2].

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

3.1 Background information

3.1.1 Type 2 diabetes

Type 2 diabetes is a progressive disorder characterised by a combination of insulin resistance and relative insulin secretion deficiency due to a declining beta-cell function[3]. The overall treatment goal is to achieve optimal glycaemic control and to reduce the risk of development and progression of microvascular and macrovascular complications. Initially, the treatment of subjects with type 2 diabetes aims at reducing insulin resistance and enhancing beta-cell secretion through lifestyle adjustments and use of metformin, followed by combination therapy with other OADs[4,3]. However due to the progressive nature of type 2 diabetes, many subjects need further intensification with insulin therapy. Generally, insulin will be initiated for subjects with type 2 diabetes and unsatisfactory glycaemic control on OADs[3,4]. Basal insulin, including NPH and basal insulin analogues, is the most convenient strategy to start with, and is recommended by the Position Statement of the ADA and the European Association for the Study of Diabetes (EASD)[5]. Basal-bolus therapy or premixed insulin could be considered as the insulin intensification regimen for subjects who fail to attain optimal glycaemic control when significant postprandial plasma glucose (PPG) excursions occur[5].

3.1.2 Biphasic insulin aspart 30

Biphasic insulin aspart (BIAsp) 30 is a mixture of soluble insulin aspart (IAsp) 30% and protaminated IAsp 70%. BIAsp 30 is marketed under the brand name NovoMix® 30 in the planned countries participating in this trial.

The rationale for having developed BIAsp 30 is to provide a premixed insulin product with faster absorption of the bolus component, as compared with human insulin (HI), allowing subjects to inject immediately before meals resulting in improved PPG regulation. BIAsp 30 also offers adequate basal insulin coverage without increasing the risk for hypoglycaemic episodes. BIAsp 30 can be injected OD, BID or TID[6].

Previous data indicate that administration of BIAsp 30 BID could effectively improve glycaemic control in subjects with type 2 diabetes inadequately controlled on OADs with or without basal insulin[7,8]. A non-interventional international, multicenter, prospective, open-label study suggested

that both BIAsp 30 BID and BIAsp 30 TID may benefit subjects with poor glycaemic control on basal insulin regimens[9].

For further information on BIAsp 30, please see the latest local product information and the latest European Union (EU) Summary of Product Characteristics (SmPC)[6] as applicable.

3.2 Rationale for the trial

Premixed insulin regimens such as BIAsp 30 can provide coverage of both fasting and postprandial blood glucose and could be beneficial to subjects inadequately controlled on basal insulin. Moreover, the epidemic increase in the numbers of subjects with type 2 diabetes will continue to put pressure on health care resources. Health care providers will be looking for products that are not only safe and effective, but also less resource demanding in terms of cost and time (i.e. products should be simple to use).

In subjects with type 2 diabetes inadequately controlled on basal insulin, switching to either BIAsp 30 BID or BIAsp 30 TID has been indicated as an effective intensifying treatment[7,9]. However, there is few data to investigate the difference of treatment effect between BIAsp 30 TID and BIAsp 30 BID on type 2 diabetes inadequately controlled with basal insulin.

The purpose of this 24-week, randomised clinical trial is to generate data comparing the efficacy and safety of BIAsp 30 TID versus BIAsp 30 BID in subjects with type 2 diabetes inadequately controlled with basal insulin and OADs.

4 Objectives and endpoints

4.1 Objectives

Primary objective

To compare the efficacy of thrice daily BIAsp 30 versus twice daily BIAsp 30, both in combination with metformin, in subjects with type 2 diabetes inadequately controlled on basal insulin combined with OADs.

Secondary objectives

- To compare safety of thrice daily BIAsp 30 versus twice daily BIAsp 30, both in combination with metformin, in subjects with type 2 diabetes inadequately controlled on basal insulin combined with oral anti-diabetic drugs (OADs)
- To compare patient reported treatment satisfaction of thrice daily BIAsp 30 versus twice daily BIAsp 30

4.2 Endpoints

4.2.1 Primary endpoint

Change from baseline in HbA_{1c} after 24 weeks of treatment

4.2.2 Secondary endpoints

4.2.2.1 Supportive secondary endpoints

Supportive secondary efficacy endpoints

- Proportion of subjects achieving $HbA_{1c} < 7.0\%$ after 24 weeks of treatment
- Proportion of subjects achieving $HbA_{1c} < 7.0\%$ without severe hypoglycaemic episodes after 24 weeks of treatment*
- Proportion of subjects achieving $HbA_{1c} < 7.0\%$ without severe or blood glucose (BG) confirmed hypoglycaemic episodes (according to the Novo Nordisk classification) after 24 weeks of treatment
- Change from baseline in FPG by central laboratory analysis after 24 weeks of treatment
- 7-point SMPG profiles after 24 weeks of treatment
  - 7-point SMPG profile
  - Change from baseline in 2-hour PPG and PPG increment at individual meal (breakfast, lunch and main evening meal)
  - Change from baseline in mean of 2-hour PPG and PPG increment over 3 main meals (breakfast, lunch and main evening meal)

- Change from baseline in mean of the 7-point profile
- Fluctuation in the 7-point profile

Supportive secondary safety endpoints

- Number of treatment emergent hypoglycaemic episodes classified according to the American Diabetes Association (ADA) and Novo Nordisk definition during 24 weeks of treatment*
- Incidence of treatment emergent adverse events (TEAEs) during 24 weeks of treatment
- Change from baseline in clinical evaluations after 24 weeks of treatment
  - Vital signs
  - Physical examination
  - Eye examination
- Change from baseline in laboratory assessments after 24 weeks of treatment
  - Haematology
  - Biochemistry
  - Lipids
- Total daily insulin dose
- Change from baseline in body weight after 24 weeks of treatment

Supportive secondary health economics endpoint:

- Change from baseline in patient-reported treatment satisfaction as assessed by the Diabetes Treatment Satisfaction Questionnaire (status) (DTSQs) after 24 weeks of treatment

*Key supportive secondary endpoint prospectively selected for posting on clinicaltrials.gov.

5 Trial design

5.1 Type of trial

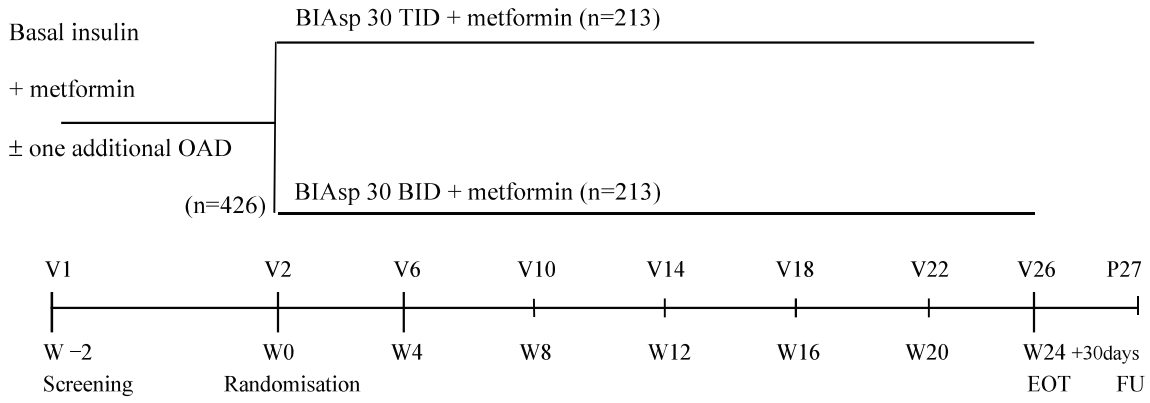
This is an open-labelled, randomised, two-armed, parallel group, multinational, multicentre, treat-to-target trial. It consists of a screening period (of up to 2 weeks) a 24-week treatment period and 30-day follow-up period (Figure 5–1).

Randomisation will be stratified according to HbA_{1c} value and pre-trial OAD treatment. The strata correspond to the HbA_{1c} intervals of 7.5%–8.5% (both inclusive) and 8.6%–10.0% (both inclusive). The strata regarding OADs are: metformin monotherapy and metformin + one additional OAD.

The eligible subjects will be randomised in a 1:1 manner into one of the two arms with the following treatment:

- BIAsp 30 TID + metformin
- BIAsp 30 BID + metformin

Within each participating country it will be aimed at including a maximum of 20% of randomised subjects on treatment with NPH prior to screening (Visit 1).



n: number of subjects to be randomised; V: Visit; W: Week; EOT: end-of-treatment; FU: follow-up

Figure 5–1 Trial design

Subjects must continue metformin throughout the trial and any other OAD should be discontinued at randomisation (Visit 2).

The insulin dose will be titrated on a weekly basis for all subjects throughout the trial. Titration will be performed according to a titration algorithm for BIAsp 30 in order to achieve the pre-meal SMPG target of 4.4−6.1 mmol/L (80−110 mg/dl) (refer to Appendix A).

5.2 Rationale for trial design

The trial has been designed to compare the efficacy and safety of BIAsp 30 TID versus BIAsp 30 BID, both in combination with a stable dose of metformin, in subjects with type 2 diabetes inadequately controlled on basal insulin combined with OADs.

The 24-week treatment duration is chosen to allow sufficient time for reaching a stable HbA_{1c} level and to obtain sufficient data for efficacy and safety evaluation for BIAsp 30 TID and BID treatment.

A 30-day follow-up visit is introduced in order to collect information on adverse events occurring in the follow-up period.

The trial is open-labelled since blinding the insulin regimens in the present trial is considered inappropriate and unethical due to the fact that this would introduce placebo injections in subjects who are randomized to BIAsp 30 BID. In addition, the present trial is a treat-to-target trial with different titration algorithms for BIAsp 30 BID and BIAsp 30 TID, and blinding the insulin regimens would make titration surveillance somewhat complicated.

5.3 Treatment of subjects

In this trial, BIAsp 30 is classified as Investigational Medicinal Products (IMP).

At randomisation the subjects' pre-trial basal insulin and OAD treatments (except for metformin) will be discontinued. The eligible subjects will be randomised in a 1:1 ratio to receive trial treatment of BIAsp 30 TID or BID, both in combination with metformin.

5.3.1 BIAsp 30

Subjects randomised to the BIAsp 30 TID arm will receive BIAsp 30 before breakfast, lunch and main evening meal. Subjects randomised to the BIAsp 30 BID arm will receive BIAsp 30 before breakfast and main evening meal.

The total daily dose of pre-trial basal insulin should be transferred to the total daily starting dose of BIAsp 30 by unit-to-unit, which will be distributed along meals at the investigator's discretion.

During the 24-week treatment period, the insulin dose will be individually titrated on a weekly basis for all subjects in accordance with the titration guideline described in Appendix A in order to achieve the pre-meal SMPG target of 4.4−6.1 mmol/L (80−110 mg/dL)[6].

An independent Novo Nordisk Titration Group will centrally perform insulin titration surveillance as described in Section 14.2.

BIAsp 30 should be administered as s.c. injections according to the locally approved label and as described in the Direction For Use (DFU). The chosen region of the body where the injection is to be administered should remain the same throughout the trial. However, the injection site within the chosen body region should rotate or change for each administration.

For further details, please refer to the titration guideline in Appendix A.

5.3.2 Metformin

In this trial metformin is classified as Non-Investigational Medicinal Product (NIMP).

Metformin should be administered orally according to the locally approved label. At randomisation, eligible subjects must continue with their stable, pre-trial dose of metformin (a total daily dose of at least 1500 mg metformin or maximum tolerated dose).

During the treatment period, the metformin dose and dosing frequency should not be changed at any time, unless due to safety concerns.

Metformin will not be supplied by Novo Nordisk. However, metformin will be reimbursed if required by the country's regulatory authority or institutional review boards (IRBs)/independent ethics committees (IECs).

5.4 Treatment after discontinuation of trial product

When discontinuing trial products the subject should be switched to a suitable marketed product at the discretion of the investigator.

5.5 Rationale for treatment

BIAsp 30 is a marketed product in all planned participating countries as NovoMix® 30 and will be administered s.c. during the trial[6]. The treatment is designed in order to investigate the efficacy and safety of BIAsp 30 TID versus BIAsp 30 BID in subjects with type 2 diabetes inadequately controlled on basal insulin. Plasma glucose will be monitored intensively throughout the insulin dose adjustments to achieve optimal glycaemic control without additional safety concern.

Subjects should continue metformin throughout the trial since insulin sensitizers are known to improve glycaemic control with less hypoglycaemia at a lower insulin dose compared to insulin regimens without OADs.[10]

6 Trial population

6.1 Number of subjects

Number of subjects planned to be screened (i.e. documented informed consent): 610

Number of subjects planned to be randomised: 426

Number of subjects expected to complete the trial: 340

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, age ≥ 18 years at the time of signing informed consent

   For Algeria only: age ≥19 years at the time of signing informed consent
3. Type 2 diabetes subjects clinically diagnosed ≥ 12 months prior to the day of screening (Visit 1)
4. Treated with basal insulin ≥ 90 days prior to the day of screening (Visit 1). The following basal insulin are allowed :
   - insulin analogue once daily (OD)
   - Neutral Protamine Hagedorn (NPH) OD or BID
5. Treatment with metformin with or without one additional OAD for at least 90 days prior to the day of screening (Visit 1)
   - Metformin must be at a stable dose of at least 1500 mg daily or maximum tolerated dose for at least 60 days prior to screening (Visit 1)
   - One additional OAD:
     - Sulphonylurea
     - Glinides
     - α-glucosidase inhibitors
     - Dipeptidyl-peptidase-4 inhibitors
     - Sodium glucose co-transporter 2 (SGLT2) inhibitors (if applicable)
6. HbA_{1c} 7.5%–10.0% (both inclusive) by central laboratory analysis at screening (Visit 1)
7. Body Mass Index (BMI) ≤ 35.0 kg/m^2
8. Able and willing to intake three main meals daily (breakfast, lunch and main evening meal) throughout the trial. Definition of main meal as judged by the investigator

9. Able and willing to adhere to the protocol including compliance with injection regimen and titration
10. Able and willing to perform mandatory SMPG measurements

6.3 Exclusion criteria

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

1. Previous participation in this trial. Participation is defined as signed informed consent
2. Known or suspected hypersensitivity to trial product or related products
3. Receipt of any investigational medicinal product (IMP) within 30 days prior to the day of screening (Visit 1)
4. Previous insulin intensification regimen for more than 14 days: premixed insulin thrice daily, basal-bolus regimen or continuous subcutaneous insulin infusion (CSII). Treatment during hospitalisation or during gestational diabetes is allowed for periods longer than 14 days
5. Treatment with any medication for the indication of diabetes or obesity other than stated in the inclusion criteria in a period of 90 days before the day of screening (Visit 1)
6. Anticipated initiation or change in concomitant medications for more than 14 consecutive days or on a frequent basis known to affect weight or glucose metabolism (e.g. orlistat, thyroid hormones, systemic corticosteroids)
7. Use of non-herbal Chinese medicine or other non-herbal local medicine with unknown/unspecified content within 90 days prior to the day of screening (Visit 1). Herbal traditional Chinese medicine or other local herbal medicines may, at the investigator's discretion, be continued throughout the trial
8. Subjects presently classified as being in New York Heart Association (NYHA)[11] Class IV
9. Planned coronary, carotid or peripheral artery revascularisation on the day of screening
10. Impaired liver function, defined as ALT $\geq$ 2.5 times upper normal limit at screening
11. Proliferative retinopathy or maculopathy requiring acute treatment. Verified by fundus photography or dilated fundoscopy performed within 90 days prior to randomisation (Visit 2)
12. Female who is pregnant, breast-feeding or intends to become pregnant or is of childbearing potential not using an adequate contraceptive method (adequate contraceptive measure as required by local regulation or practice)

China: sterilisation, intrauterine device (IUD), oral contraceptives or barrier methods.

13. History or presence of malignant neoplasms within the last 5 years (except basal and squamous cell skin cancer and in-situ carcinomas)

14. Any contraindications to BIAsp 30 or metformin according to local label

15. Mental incapacity, unwillingness or language barrier precluding adequate understanding or co-operation, as judged by the investigator

16. Any disorder which, in the opinion of the investigator might jeopardise subject's safety or compliance with the protocol

6.4 Withdrawal criteria

The subject may withdraw at will at any time. The subject's request to discontinue must always be respected.

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.

The subject must be withdrawn from the trial if the following applies:

1. Included in the trial in violation of the inclusion and/or exclusion criteria
2. Pregnancy
3. Intention of becoming pregnant
4. Participation in another clinical trial throughout the trial

6.5 Subject replacement

Subjects who are withdrawn will not be replaced.

6.6 Rationale for trial population

The trial population consists of subjects with type 2 diabetes on basal insulin and OAD treatment who have failed to achieve appropriate glycaemic control. These subjects, often presenting with HbA_{1c} between 7.5 and 10.0% (both inclusive), are expected to benefit from insulin intensification and optimisation. One of the choices for insulin intensification will be premixed insulin such as BIAsp 30.

It is expected that some subjects in the target population will be on one other OAD in addition to metformin. At randomisation, subjects will be stratified according to whether or not they have received treatment with metformin, with or without one other OAD.

Both insulin NPH OD/BID and basal insulin analogue OD are commonly used basal insulin regimen in many countries. In order to mimic the practice in clinical setting, the majority (approximately 80%) of subjects included into this trial will be those on basal insulin analogue prior to the trial.

Based on that, subjects with type 2 diabetes who are inadequately controlled on basal insulin combined with metformin with or without one additional OAD will be included in the trial, as they are expected to benefit from premixed insulin either TID or BID regimen.

7 Milestones

Planned duration of recruitment period (i.e. FPFV–LPFV): 48 weeks

End of trial (P27) is defined as LPLV.

Recruitment:
The screening and randomisation rate will be followed closely via the interactive voice/web response system (IV/WRS) in order to estimate when to stop screening. Within each participating country it will be aimed at including a maximum of 20% of randomised subjects on treatment with NPH prior to screening. All investigators will be notified immediately when the recruitment period ends, after which no further subjects may be screened and the IV/WRS will be closed for further screening. All subjects included in the screening period and eligible for randomisation can be randomised.

Trial registration:
Information of the trial will be disclosed at clinicaltrials.gov and novonordisk-trials.com. According to the Novo Nordisk Code of Conduct for Clinical Trial Disclosure[12], it will also be disclosed according to other applicable requirements such as those of the International Committee of Medical Journal Editors (ICMJE)[13], the Food and Drug Administration Amendment Act (FDAAA)[14], European Commission Requirements[15,16] and other relevant recommendations or regulations. If a subject 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 subject. As a result of increasing requirements for transparency, some countries require public disclosure of investigator names and their affiliations.

8 Methods and assessments

8.1 Visit procedures

Throughout the trial the investigator must ensure working in accordance with International Conference on Harmonisation Good Clinical Practice (ICH GCP)[1] and local regulations. The investigator must ensure that trial procedures are performed as described in the protocol. Any discrepancies will result in protocol and/or GCP deviations and the investigator must take appropriate action to avoid recurrence of the detected discrepancies.

The investigator must keep a log of staff and delegation of task(s) at the site. The investigator must sign the log of staff and delegation of task(s) at site at the time of delegation.

The subjects will be asked to attend a screening visit, a randomisation visit, 6 clinic visits and 17 phone contacts during the treatment period, an end-of-treatment visit and a follow-up phone contact

Review of laboratory reports, patient reported outcomes (PROs), diaries etc. must be documented either on the documents and/or in the subject's medical record.

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

The following sections describe the assessments and procedures. These are also included in the flow chart (Section 2).

8.1.1 Informed consent

Before screening takes place, potential subjects must be provided with written and oral information about the trial and the procedures involved, in accordance with local requirements. Subjects will be fully informed, orally and in writing, of their responsibilities and rights while participating in the trial, as well as of possible advantages/disadvantages when being treated with the trial medication. Subjects will have the opportunity to ask questions, and have ample time to consider participation.

Subjects who wish to participate in the trial must sign and date the subject information/informed consent form (SI/IC) before any trial-related procedures (Section 18.3). All subjects must be provided with a copy of their signed and dated informed consent form(s).

The informed consent process may take place before the screening visit (Visit 1).

8.1.2 Screening visit (Visit 1)

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 IV/WRS.

At screening, subjects will be provided with a card stating that they are participating in a trial and giving contact address(es) and telephone number(s) of relevant trial site staff. Subjects should be instructed to return the card to the investigator at the last trial visit or to destroy the card after the last visit.

Each subject will be assigned a unique 6-digit subject number which will remain the same throughout the trial. The screening session must be made in the IV/WRS.

The investigator must document the review and evaluation of all screening data, especially how subjects fulfil the eligibility criteria. The assessments and blood samplings listed in the flow chart (see Section 2) for the screening visit should be performed according to Section 8 and relevant data recorded in the electronic case report form (eCRF).

8.1.3 Screening failures

If any inclusion criterion is answered “no” or any exclusion criterion is answered “yes”, the subject is a screening failure.

For screening failures the screening failure form in the eCRF must be completed with the reason for not continuing in the trial. Serious and non-serious adverse events (AEs) from screening failures must be transcribed by the investigator into the eCRF. Follow-up of serious adverse events (SAEs) must be carried out according to Section 12.

A screening failure session must be made in the IV/WRS. The case book must be signed.

8.1.4 Re-screening

Re-sampling or re-screening is NOT allowed if the subject has failed one of the inclusion or exclusion criteria related to laboratory parameters. Re-screening is NOT allowed in any case.

8.1.5 Randomisation visit (Visit 2) and treatment period

Eligible subjects will attend the randomisation visit no later than 14 days following the screening visit. The procedures and assessments listed in the flow chart (Section 2) for the randomisation visit must be performed. All inclusion and exclusion criteria must be checked again to confirm the subject’s eligibility and relevant data will be recorded in the eCRF.

A randomisation session in the IV/WRS will be performed whereby eligible subjects will be randomised either to the BIAsp 30 TID or BIAsp 30 BID arm, both in combination with metformin.

Relevant training of the subject in the use of the trial product will be conducted by the investigator or designated staff.

Following randomisation, subjects will undergo 24 weeks of treatment. The treatment period consists of 6 clinic visits and 17 phone contacts. The investigator should use the IV/WRS drug accountability module and confirm dispensing of allocated trial products at each dispensing visit (Section 9.4). The IV/WRS will allocate trial product to the subjects. All procedures and assessments listed in the flow chart in Section 2 for treatment period should be performed and relevant data will be recorded in the eCRF. Insulin dose will be titrated in accordance with the titration guideline in Appendix A.

Subjects must attend the randomisation visit (Visit 2) and Visit 14 in a fasting state. Fasting is defined as no food or drink intake, except water, after midnight prior to the visit. Trial product, metformin and any medication which should be taken with or after a meal must be withheld on the day of the visit until blood sampling and body weight measurements have been performed. Any other concomitant medication should be taken as usual.

If the subject is not fasting as required, all other assessments can be performed except for blood sampling and body weight measurement which must be rescheduled within the visit window. The date of the fasting assessment must be documented in the medical record and entered accordingly in the eCRF. Rescheduling of fasting visits/assessments is not considered an unscheduled visit.

The investigator must document review and evaluation of all data which has been reported during the phone contacts. If discrepancies are found i.e. in the diary once the subject attends a clinic visit, the subject must be questioned and a conclusion made in the subject's medical record.

8.1.6 End-of-treatment visit (Visit 26)

All procedures and assessments listed in the flow chart in Section 2 for end-of-treatment should be performed and relevant data will be recorded in the eCRF.

Subjects must attend the end-of-treatment visit fasting according to the definition in Section 8.1.5.

The end-of-treatment form must be completed, final drug accountability performed and a completion session made in the IV/WRS. The case book must be signed.

8.1.7 Withdrawn subjects

If a subject is withdrawn from the trial, the investigator must aim to undertake procedures similar to those for Visit 26 as soon as possible. The subject should also have the follow-up contact performed, if possible. The subjects should be requested to return all used, partly used and unused trial product.

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 trial site. A withdrawal session must be made in the IV/WRS. 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 must make a reasonable effort to ascertain the reason(s), while fully respecting the subject's rights. Where the reasons are obtained, the primary reason for not completing the trial must be specified on the end-of-trial form in the eCRF.

8.1.8 Follow-up period (Phone contact 27)

The investigator or delegated staff should call the subjects 30 days after Visit 26 has been conducted. Phone contact 27 (P27) will not be registered in IV/WRS.

The following information since Visit 26 will be reported by the subjects to the investigator via phone contact:

- Any AEs
- Any hypoglycaemia episode which occurs within 7 days after Visit 26
- Any changes in concomitant medications

8.2 Subject related information

8.2.1 Concomitant illness and medical history

A **concomitant illness** is any illness that is present at the start of the trial (i.e. at the screening visit) or found as a result of screening procedures. The disease under investigation (type 2 diabetes) is not considered as a concomitant illness and it is captured under diagnosis of diabetes.

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.

Medical history is a medical event that the subject has experienced in the past. Only medical history considered relevant by the investigator should be reported.

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

8.2.2 Concomitant medication

A **concomitant medication** is any medication, other than the trial products, which is taken during the trial, including the screening and follow-up period.

Details of any concomitant medication must be recorded at the screening visit. Changes in concomitant medication must be recorded at each visit as they occur.

The information collected for each concomitant medication includes 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 reported according to Section 12. If the change influences the subject's eligibility to continue in the trial, the monitor must be informed.

8.2.3 Smoking status

Details of smoking status must be recorded at the screening visit. Smoking is defined as smoking at least one cigarette, cigar or pipe daily. The collected information should include whether or not the subject smokes or has smoked.

8.2.4 Demography

The following information has to be recorded, unless not permitted by local regulations:

- Date of birth
- Age
- Sex
- Race
- Ethnicity

8.2.5 Diagnosis of diabetes

The date of diagnosis of type 2 diabetes has to be recorded.

8.2.6 Diabetes complications

The following information has to be recorded:

- Diabetic retinopathy
- Diabetic neuropathy
- Diabetic nephropathy
- Macroangiopathy including peripheral vascular disease

8.2.7 Concomitant diabetes treatment

The following information has to be recorded:

- Current diabetes treatment (specify OD or BID basal insulin treatment)
- Total daily dose of current diabetes treatment
- Start date of current diabetes treatment
- Stop date of current diabetes treatment if applicable

8.3 Assessments for efficacy

The timing of the assessments and procedures are specified in the flow chart in Section 2.

8.3.1 Self-measured plasma glucose (SMPG)

At Visit 1, subjects will be provided with a blood glucose meter including lancets, plasma-calibrated test strips and control solutions as well as instructions for use. The subject will be instructed in how to use the device, and the instruction will be repeated as necessary during the trial.

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

Subjects should be instructed in how to record the results of the SMPGs in the diaries. The record of each SMPG should include date and value at each time point (before breakfast, 120 minutes after the start of breakfast, before lunch, 120 minutes after the start of lunch, before main evening meal, 120 minutes after the start of main evening meal, at bedtime) . All data from the diary must be transcribed into the eCRF during or following the contact. If obtained via phone and a discrepancy is later detected, the values in the eCRF should be corrected. If clarification of entries of discrepancies in the diary is needed, the subject must be questioned and a conclusion made in the subject's medical record. Care must be taken not to bias the subject.

8.3.1.1 Three times daily self-measured plasma glucose

Subjects will be instructed to perform the following SMPG measurements:

- Before breakfast
- Before lunch
- Before main evening meal

The three times daily SMPG will be performed on 3 random days in the week prior to a clinic visit/phone contact (Visit 3−Visit 26), according to the flow chart in Section 2. The plasma glucose value at each time point should be recorded in the diary.

8.3.1.2 7-point self-measured plasma glucose profiles

Subjects will be instructed to perform the following SMPG measurements:

- Before breakfast
- 120 minutes after the start of breakfast
- Before lunch
- 120 minutes after the start of lunch
- Before main evening meal
- 120 minutes after the start of main evening meal
- At bedtime

The 7-point SMPG profile should be performed on the day just prior to Visit 2, Visit 14 and Visit 26, according to the flow chart in Section 2. The plasma glucose value at each time point should be recorded in the diary.

Note that for Visit 14 and Visit 26, both three times daily SMPG and 7-point SMPG profiles are required. In the week prior to these visits, the measurements for both SMPGs may overlap. Since the 7-point SMPG profile includes the following:

- Before breakfast
- Before lunch
- Before main evening meal

these measurements can be used to replace one of the three times daily SMPG values required.

8.4 Assessments for safety

8.4.1 Hypoglycaemic episodes

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

All plasma glucose values:

- ≤ 3.9 mmol/L (70 mg/dL) or
- > 3.9 mmol/L (70 mg/dL) when they occur in conjunction with hypoglycaemic symptoms

- should be recorded by the subject. These must be transcribed into the eCRF (hypoglycaemic episode form) throughout the trial from Visit 2 to the follow-up phone contact 27.

The record should include the following information:

- Date and time of hypoglycaemic episode
- The plasma glucose level before treating the episode (if available)
- Whether the episode was symptomatic
- Whether the subject was able to treat him/herself

- Date and time of last trial insulin and metformin administration prior to episode
- Dose of last trial insulin and metformin administration prior to episode
- Date and time of last main meal prior to episode. The definition for 'main meal' will be according to the investigator's discretion.
  - Whether the episode occurred in relation to physical activity
  - Any sign of fever or other 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 subject able to treat him/herself?" must be answered "No" for an episode requiring assistance of another person to actively administer carbohydrate, glucagon, or take 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 subject able to treat him/herself?" is answered "No", the following information should be recorded:

- Who assisted in the treatment of the hypoglycaemic episode (i.e. family/friend/co-worker or similar, paramedic, doctor or other, please specify)
- Where the treatment was administered (i.e. at home/at friends/at work or similar, in an ambulance, emergency room/hospital or other, please specify)
- Type of treatment provided by other person (i.e. oral carbohydrates, glucagon, IV glucose or other, please specify)
- Were symptoms alleviated after administration of treatment?
- Factors contributing to the episode (i.e. physical activity, missed meal, diet changed, medication error (i.e. overdose, mix-up between products), miscalculation of insulin dose, other factors not listed, please specify or none)
- Did the subject experience seizure?
- Was the subject unconscious/comatose?
- Did the subject experience any of the following symptoms[17]?

– Autonomic: sweating, trembling, hunger or palpitations
– Neuroglycopenic: confusion, drowsiness, speech difficulty, visual disturbances, odd behaviour, impaired balance or incoordination

– General malaise: headache or malaise
  - Did the subject experience other symptoms? Please specify
  - Description of the episode, if applicable

A hypoglycaemic episode form must be filled in for each hypoglycaemic episode. If the 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.

8.4.2 Adverse events

AEs must be recorded in accordance with the procedures outlined in Section 12.

Any clinically significant worsening from baseline of a previous finding must be reported as an AE.

8.4.3 Technical complaints

Technical complaints must be recorded from Visit 2 to Visit 26 in accordance with the procedures outlined in Section 12.

8.4.4 Physical examination

Physical examination will be carried out at Visit 1 and Visit 26, and will include examination of:

- Head, ears, eyes, nose, throat, neck
- Respiratory system
- Cardiovascular system
- Gastrointestinal system incl. mouth
- Musculoskeletal system
- Central and peripheral nervous system
- Skin

Any abnormal, clinically significant findings at Visit 1 must be reported as concomitant illness. Any clinically significant worsening from Visit 1 must be reported as an AE (Section 12).

8.4.5 Eye examination

At Visits 1 and Visit 26, an eye examination will be performed by the investigator, a local ophthalmologist or an optometrist according to local practice. Result of the fundus photography or dilated fundoscopy 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" or "abnormal, clinically significant" fundus photography or dilated fundoscopy the investigator must add a comment in the eCRF and in the subject notes. Any abnormal, clinically significant findings at Visit 1 must be recorded as concomitant illness. Any clinically significant worsening from Visit 1 onwards must be recorded as an AE (Section 12).

An eye examination performed within 90 days prior to randomisation (Visit 2) is acceptable if the results and relevant documentation are available at the scheduled visit specified in the flow chart (Section 2). The investigator must still interpret, sign and date the fundus photography or dilated fundoscopy. If the fundus photography or dilated fundoscopy is performed before the subject has signed the informed consent form, it must be documented in the subject notes that the reason for performing the procedure was not related to this trial. However, if clinically warranted, an eye examination (i.e. fundus photography or dilated fundoscopy) should be repeated.

Fundus photography or dilated fundoscopy performed within the three weeks before Visit 26 is acceptable as Visit 26 data.

The dates of fundus photography or dilated fundoscopy must be recorded in the eCRF and should be source data verifiable.

8.4.6 Vital signs

Vital signs will be measured at Visit 1 and Visit 26 and include:

- Diastolic blood pressure
- Systolic blood pressure
- Pulse

The measurements should be performed after resting in a sitting position for 5 minutes and will be assessed while the subject is sitting.

Any abnormal, clinically significant findings at Visit 1 must be reported as concomitant illness. Any clinically significant worsening from Visit 1 onwards must be reported as an AE (Section 12).

8.4.7 Insulin dose

Subjects will be instructed in how to record their insulin treatment in the diaries. Each record should include date, time point (i.e. before breakfast, before lunch, before main evening meal) and dose of insulin.

Insulin doses will be recorded and collected on the days when three times daily SMPG are performed. The new insulin dose prescribed by the investigator at each visit/contact should be recorded in the diary.

Details regarding insulin treatment and intensification are found in Section 5.3 and in the titration guideline in Appendix A.

8.4.8 Body measurements

8.4.8.1 Height

The subject's height will be measured at Visit 1. When measuring the height, the subject should be without shoes. Height is measured in meters (m) or inches (in) and recorded with two decimal places.

8.4.8.2 Body weight

The subject's body weight will be measured at Visit1, Visit 2 (fasting), Visit 14 (fasting) and Visit 26 (fasting). When measuring the body weight, the subject should only be wearing light clothing, without any coat and shoes. The body weight will be recorded in kilogram (kg) or pounds (lb) with one decimal place.

A calibrated scale must be used. It is preferred that the same weighing scale equipment is used all throughout the trial.

8.4.8.3 Body mass index (BMI)

BMI will be calculated at Visit 1 by the eCRF using the equation:

BMI kg/m^2 = Body weight (kg)/ (Height (m) × Height (m)) or (kg/m^2 = (lb/in^2 × 703))

8.5 Laboratory assessments

Blood samples will be drawn for laboratory analysis of efficacy and safety parameters, as specified in the flow chart (Section 2). Except for the urine pregnancy test, all laboratory analyses will be performed by a central laboratory.

Descriptions of assay methods, laboratory supplies and procedures for obtaining samples, handling conditions including coding in order to keep subject identity confidential, storage and shipment of samples, disposition and destruction will be described in a trial specific laboratory manual provided by the central laboratory.

The laboratory equipment may provide analyses not requested in the protocol but produced automatically in connection with the requested analyses according to specifications in the laboratory standard operating procedures. Such data will not be transferred to the trial database, but abnormal

values will be reported to the investigator. The investigator must review all laboratory results for concomitant illnesses and AEs and report these according to this protocol.

Laboratory results will be made available by the central laboratory to the investigator on an ongoing basis.

Review of laboratory reports must be documented either on the document and/or in the subject's medical record. 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.

Any abnormal, clinically significant findings at baseline must be reported as concomitant illness. Any clinically significant worsening from baseline must be recorded as an AE (see Section 12).

8.5.1 Laboratory assessment for efficacy

The timing of the blood samples are outlined in the flow chart in Section 2.

8.5.1.1 HbA_{1c}

HbA_{1c} will be handled and measured according to a trial specific laboratory manual as mentioned in Section 8.5 and as scheduled in the flow chart in Section 2.

8.5.1.2 Fasting plasma glucose (FPG)

For the measurement of FPG, the subjects must attend the randomisation visit (Visit 2), clinic Visit 14 and end-of-treatment (Visit 26) fasting according to the definition in Section 8.1.5.

8.5.2 Laboratory assessment for safety

The timing of the blood samples are outlined in the flow chart in Section 2.

8.5.2.1 Haematology

Blood samples for haematology will be taken at Visit 1 and Visit 26, and the analysis consists of:

- Erythrocytes
- Haematocrit
- Haemoglobin
- Leucocytes
- Thrombocytes

8.5.2.2 Lipids

Blood samples for lipids will be taken at Visit 2 and Visit 26, and the analysis consists of:

- Cholesterol
- High density lipoprotein (HDL) cholesterol
- Low density lipoprotein (LDL) cholesterol
- Triglycerides

Any abnormal, clinically significant findings that occur as part of the baseline assessments prior to any trial product provided (Visit 2) must be reported as concomitant illness. Any clinically significant worsening from Visit 2 onwards must be recorded as an AE (Section 12).

8.5.2.3 Biochemistry

Blood samples for biochemistry will be taken at Visit 1 and Visit 26, and the analysis consists of:

- ALT
- Albumin
- Alkaline phosphatase
- Aspartate aminotransferase (AST)
- Bilirubin, total
- Creatinine
- eGFR
- Potassium
- Sodium

8.5.2.4 Pregnancy test

At Visit 1 and Visit 26, females of childbearing potential will have a human chorionic gonadotropin serum pregnancy test analysed by the central laboratory.

At any time during the trial, a urine pregnancy test will be performed for females of childbearing potential if a menstrual period is missed or as required by local law. If a subject, during a phone contact, reports a (or more) missing menstrual period, the subject should be called in to the trial site for an unscheduled visit as soon as possible for a urine pregnancy test. Urine pregnancy kits will be supplied by the central laboratory and the test will be performed at the trial site. If the urine pregnancy test is positive, a blood sample will be taken and sent to the central lab for a serum pregnancy test.

Pregnancy tests will not be required for females who have undergone a hysterectomy or bilateral tubal ligation, or for women who have been menopausal for at least one year.

8.6 Other assessments

8.6.1 Patient-reported outcome questionnaire

The PRO questionnaire of DTSQs will be collected at Visit 2 and Visit 26. The questionnaire is self-administered and must be completed by the subject without any assistance from the site staff or anyone else, prior to any other trial related activities during the designated visits. The estimated average subject completion time is 5 minutes.

Review of PRO questionnaires by investigator or delegated staff must be documented either on the documents and/or in the subject's medical record. This includes ensuring that any potential adverse events (AEs), any overall changes in health and concomitant medication, are reported.

If clarification of entries or discrepancies in the PRO questionnaires is needed, the subject must be questioned and a conclusion made in the subject's medical record. Care must be taken not to bias the subject.

Data from the PRO questionnaires will be transferred into the eCRF by the investigator or delegated staff.

8.6.2 Subject diary

At all clinic visits, the subject should be provided with diaries, including instructions. However, the last diary collecting data from after end-of-treatment V26 will not be returned to the clinic by the subject since the follow-up contact is a phone call. Consequently source will be the notes written in subject's medical records for follow-up visit (P27).

The following information should be recorded in the diary:

- Date, time point and value of three times daily SMPG according to the flow chart in Section 2
- Date, time point and value of 7-point SMPG profiles according to the flow chart in Section 2
- Dose, date and time point when BIAsp 30 is administered on the first day
- Dose, date and time point when BIAsp 30 is administered on the day of the three times daily SMPG
- Dose, date and time point when BIAsp 30 is administered on the last day
- New dose to be taken after titration
- Hypoglycaemic episodes
- Confirmation of unchanged metformin

Review of diaries by investigator or delegated staff must be documented either on the document and/or in the subject's medical record.

All data from the diary must be transcribed into the eCRF during or following the contact. If clarification of entries of discrepancies in the diary is needed, the subject must be questioned and a conclusion made in the subject's medical record. Care must be taken not to bias the subject.

8.7 Subject compliance

Throughout the trial the investigator will remind the subjects to follow the trial procedures and requirements to ensure subject compliance. If a subject is found to be non-compliant, the investigator will remind the subject of the importance of following the instructions given including taking the trial products as prescribed. Substantial failure to comply with the prescribed dose regimen can lead to withdrawal at the discretion of the investigator. Withdrawal of subjects due to non-compliance should be discussed with monitor and or clinical research assistant (CRA) of Novo Nordisk in advance. In case of withdrawal contact the IV/WRS and perform a withdrawal session.

Treatment compliance:

The investigator must assess the treatment compliance of the subject at each visit/phone contact by evaluating the glycaemic control, the SMPG profiles and all relevant data in the subject's diary.

8.8 Unscheduled visits

In case further titration is needed or an adverse event (AE) occurs that requires further attention, extra visits can be arranged. If laboratory samples need to be re-taken due to missing result(s) (e.g. haemolysed, sample leaked during transit, sample not being conclusive, lost in transit etc.), the subject should be called in for an unscheduled visit. The repeated blood sampling must be marked with the related visit number. The last sample will be conclusive. It should be specified which visit number the unscheduled visits is related to in the eCRF.
An unscheduled visit form must be completed in the eCRF indicating the reason for the visit e.g.;

- Adverse event (AE)
- Laboratory re-sampling
- Other

If the subject attends the clinic to obtain additional product or auxiliary supplies then this should **NOT** be recorded as an unscheduled visit. In this case an additional dispensing session should be made in the IV/WRS and the Subject's medical record should be updated accordingly.

8.9 Re-scheduled visits

If the Subject attends the fasting visits in a non-fasting condition all blood samples, body weight must be re-scheduled within the visit window. The date of the laboratory sampling and body weight measurement in the eCRF should reflect the actual date of the re-sampling/body weight measurement, i.e. the actual visit date will differ from the assessment date under the same visit.

9 Trial supplies

Trial supplies comprise trial products and auxiliary supplies. Additional details regarding trial supplies can be found in the Trial Materials Manual (TMM).

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

BIAsp 30 must not be used, if it does not appear white and cloudy after resuspension.

9.1 Trial products

The following trial products will be provided by Novo Nordisk:

Trial product	Strength	Dosage form	Route of administration
Biphasic insulin aspart 30, FlexPen® (IMP)	100 U/ml	Suspension for injection	Subcutaneous (s.c.)

In this trial metformin is classed as NIMP and will not be supplied by Novo Nordisk.

9.2 Labelling

The trial products will be labelled in accordance with Annex 13[18], local regulations and trial requirements.

Each trial site will be supplied with sufficient trial products for the trial on an on-going basis controlled by the IV/WRS. Trial supplies will be distributed to the trial sites according to enrolment and randomisation.

Subjects will be instructed in trial product administration. The investigator must document that direction for use (DFU) is given to the subject orally and in writing at the first dispensing visit (Visit 2). Subsequent DFUs will be given at succeeding dispensing visits if deemed appropriate by the investigator.

It is the investigator's or delegated staff's responsibility to assess if the subject is capable of following instructions during training and those in the DFU.

9.3 Storage

Trial product	Storage conditions (not-in-use)	In-use conditions	In-use time*
BIAsp 30	Store in a refrigerator (2°C–8°C) Do not freeze Protect from light	Store below 30°C Do not refrigerate Do not freeze Protect from light	4 weeks

* In-use time starts when first dose is taken or when used as a spare

The investigator must ensure the availability of proper storage conditions, and also record and evaluate the temperature. The investigator must inform Novo Nordisk **immediately** if any trial product has been stored outside specified conditions (e.g. outside temperature range).

Trial product that has been stored improperly must not be dispensed to any subject before it has been evaluated and approved for further use by Novo Nordisk. The investigator must take appropriate action to ensure correct storage.

9.4 Drug accountability and destruction

The trial products will be dispensed to each subject as required according to allocated treatment arm. The IV/WRS will allocate trial product to the subject at Visit 2, Visit 6, Visit 10, Visit 14, Visit 18 and Visit 22. The correct dispensing unit number(s) (DUN(s)) must be dispensed to the subject.

The investigator or delegated person is responsible for ensuring that:

- Trial products are not dispensed to any person not included in the trial.
- Drug accountability is performed using the IV/WRS drug accountability module and will be at pen level for BIAsp 30.
- Subjects are instructed to return all used, partly used and unused trial products, including empty packaging material, at each dispensing visit and at end-of-trial visit.

Drug accountability is the responsibility of the investigator.

Returned trial product (used/partly used or unused including empty packaging material) can be stored at room temperature and must be stored separately from non-allocated trial product.

Destruction will be done according to local procedures after drug accountability is finalised and verified by the monitor. Destruction of products must be documented.

The destruction of trial products will be recorded on a Destruction Form, which will be signed by the person responsible for the destruction.

9.5 Auxiliary supplies

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

- Needles for prefilled pens (the maximum needle length to be used is 8 mm)
- Blood glucose meters and supplies
- DFU for the trial products

10 Interactive voice/web response system

A trial-specific IV/WRS will be set up which can be accessed at any time via the internet or telephone. Access to the IV/WRS must be restricted to and controlled by authorised persons.

IV/WRS is used for:

- Screening
- Screening failure
- Randomisation
- Medication arrival
- Dispensing
- Withdrawal
- Treatment completion
- Drug accountability
- Data change

It is important that at all times during the trial only DUNs allocated by the IV/WRS are dispensed to the Subject.

If a Subject requires additional trial product between dispensing visits, the site must perform an additional dispensing session in IV/WRS.

An IV/WRS user manual will be provided to each trial site.

11 Randomisation procedure and breaking of blinded codes

A randomisation session will be carried out in a 1:1 manner to the two treatment groups using the IV/WRS. At the randomisation visit (Visit 2), subjects meeting all inclusion criteria and none of the exclusion criteria will be randomised in a 1:1 manner into one of the two arms with the following initial treatment:

- BIAsp 30 TID + metformin
- BIAsp 30 BID + metformin

The randomisation will be stratified according to baseline HbA_{1c} value (7.5%–8.5% or 8.6%–10%) and previous OADs treatment (metformin monotherapy or metformin + one additional OAD therapy).

11.1 Breaking of blinded codes

This is an open-label trial. Breaking of blinded codes is not applicable for this trial.

12 Adverse events, and technical complaints and pregnancies

12.1 Definitions

Adverse event

An 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.

An AE includes:

- 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 is an AE, but is reported on a hypoglycaemic episode form instead of on an AE form, see Section 8.4.1.

The following three definitions are used when assessing an AE:

- **Severity**

– **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**

Relationship between an 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**

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

Serious adverse event

A serious adverse event (SAE) is an experience that at any dose results in any of the following:

- Death.
- A life-threatening[a] experience.
- In-patient hospitalisation[b] or prolongation of existing hospitalisation.
- A persistent or significant disability or incapacity[c].
- A congenital anomaly or birth defect.
- Important medical events that may not result in death, be life threatening[a] or require hospitalisation[b] 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 the definition of SAE[d].
  Suspicion of transmission of infectious agents via the trial product 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 or SAEs.

[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 dyscrasiasis or convulsions that do not result in hospitalisation, or development of drug dependency or drug abuse.

Note: The seriousness criterion "important medical event" is not the same as the term "Medical event of special interest" (MESI).

Non-serious adverse event

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

Medical event of special interest

A medical event of special interest (MESI) is an event which, in the evaluation of safety, has a special focus. A MESI is an AE (SAE or non-serious AE) which fulfils one or more of the below defined MESI criteria.

Medication errors concerning trial products:
- Administration of wrong drug.
  Note: Use of wrong DUN(s) 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. That is a dose lower or higher than the intended dose; 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 written, electronic, or oral communication that alleges product (medicine or device) defects. 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, 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 (i.e. Visit 1 to P 27). The events must be recorded in the applicable eCRF forms in a timely manner, see timelines below and Figure 12–1.

During each contact with the trial site staff, the subject must be asked about AEs and technical complaints, for example by asking: “Have you experienced any problems since the last contact?”

All AEs, either observed by the investigator or subject, must be reported by the investigator and evaluated. Novo Nordisk assessment of expectedness is performed according to the following reference documents:

- Company core data sheet (CCDS) for NovoMix® 30, current version and any updates thereto

All AEs must be recorded by the investigator on an AE form. The investigator should report the diagnosis, if available. If no diagnosis is available, the investigator should record each sign and symptom as individual AEs using separate AE forms.

For SAEs, a safety information form must be completed in addition to the AE form. If several symptoms or diagnoses occur as part of the same clinical picture, one safety information form can be used to describe all the SAEs.

MESIs, regardless of seriousness, must be reported using both the AE form and the safety information form.

The AE form for a non-serious AE not fulfilling the MESI criteria should be signed when the event is resolved or at the end of the trial.

Timelines for initial reporting of AEs:

The investigator must complete the following forms in the eCRF within the specified timelines:

- **SAEs:** The AE form **within 24 hours** and the safety information form **within 5 calendar** days of the investigator's first knowledge of the SAE.

  Both forms must be signed within 7 calendar days from the date the information was entered in the eCRF.

- **Non-serious AE fulfilling the MESI criteria:** The AE form, and safety information form **within 14 calendar days** of the investigator's first knowledge of the event.

If the eCRF is unavailable, the concerned AE information must be reported on paper forms and sent to Novo Nordisk by fax, e-mail or courier within the same timelines as stated above. When the eCRF becomes available again, the investigator must enter the information on the appropriate forms in the eCRF.

Contact details (fax, telephone, e-mail and address) are provided in the investigator trial master file.

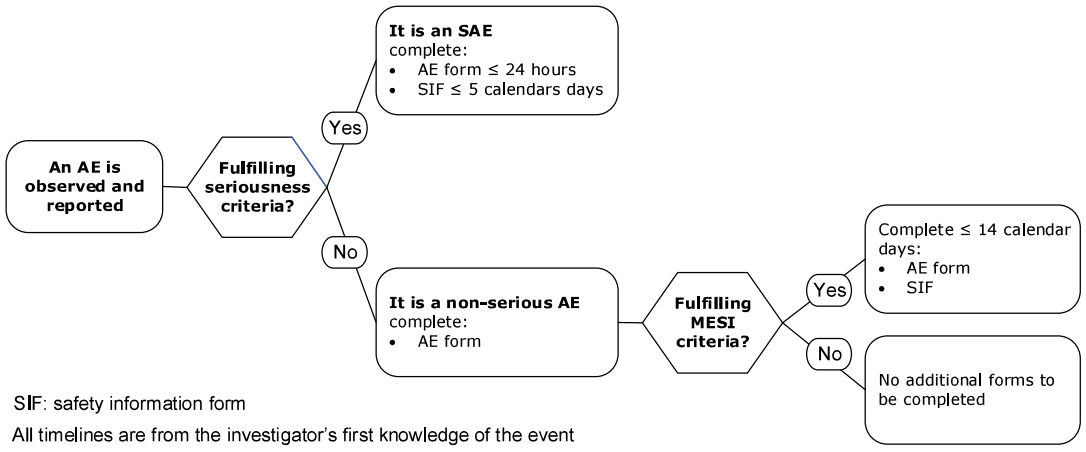


Figure 12–1 Initial reporting of AEs

Reporting of trial product-related SUSARs by Novo Nordisk:

Novo Nordisk will notify the investigator of trial product-related suspected unexpected serious adverse reactions (SUSARs) in accordance with local requirements and GCP. In addition, the investigator will be informed of any trial-related SAEs that may warrant a change in any trial procedure.

In accordance with regulatory requirements, Novo Nordisk will inform the regulatory authorities, including European Medicines Agency (EMA), of trial product-related SUSARs. In addition, Novo Nordisk will inform the institutional review boards (IRBs)/independent ethics committees (IECs) of trial product-related SUSARs in accordance with local requirement and GCP, unless locally this is an obligation of the investigator.

Novo Nordisk products used as concomitant medication:

If a SAE and/or MESI is considered to have a causal relationship with a Novo Nordisk marketed product used as concomitant medication in the trial, it is important that the suspected relationship is reported to Novo Nordisk, e.g. in the alternative aetiology section on the safety information form. Novo Nordisk may need to report this adverse event to relevant regulatory authorities.

12.3 Follow-up of adverse events

The investigator must record follow-up information by updating the forms in the eCRF.

Follow-up information must be reported to Novo Nordisk according to the following:

- **SAEs**: All SAEs must be followed until the outcome of the event is "recovered/resolved", "recovered/resolved 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/resolving" or "not recovered/not resolved". Cases can be closed with the outcome of "recovering/resolving" when the subject has completed the follow-up period and is expected by the investigator to recover.

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

- **Non-serious AEs:** Non-serious AEs must be followed until the outcome of the event is "recovering/resolving", "recovered/resolved" or "recovered/resolved 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, cancer or AEs

ongoing at time of death (where death is due to another AE) may be closed with the outcome "recovering/resolving" or "not recovered/not resolved". Cases can be closed with the outcome of "recovering/resolving" when the subject has completed the follow-up period and is expected by the investigator to recover.

- **Non-serious AE fulfilling the MESI criteria:** Non-serious AE fulfilling the MESI criteria must be followed as specified for non-serious AEs. Follow-up information on MESIs should only include new (e.g. corrections or additional) information and must be reported **within 14 calendar days** of the investigator's first knowledge of the information. This is also the case for previously reported non-serious AEs which subsequently fulfil the MESI criteria.

The investigator must ensure that the worst case severity and seriousness of an event is kept throughout the trial. A worsening of an unresolved AE must be reported as follow-up with re-assessment of severity and/or seriousness of the event.

Queries or follow-up requests from Novo Nordisk must be responded to **within 14 calendar days** from the date of receipt of the request, unless otherwise specified in the follow-up request.

12.4 Technical complaints and technical complaint samples

12.4.1 Reporting of technical complaints

All technical complaints on any of the following products:

- BIAsp 30 (NovoMix® 30), 100 U/ml, 3 ml FlexPen®
- Needles for prefilled FlexPen®

which occur from the time of first usage of the product until the time of the last usage of the product, must be collected and reported to Customer Complaint Center, Novo Nordisk.

Contact details (fax, e-mail and address) are provided in Attachment I to the protocol.

The investigator must assess whether the technical complaint is related to any AEs, SAEs, and/or MESI.

Technical complaints must be reported on a separate technical complaint form for each product listed. If the technical complaint involves more than one batch or lot number or more than one DUN, a technical complaint form for each batch or lot number or for each DUN must be completed.

The investigator must complete the technical complaint form in the eCRF within the following timelines of the trial site obtaining knowledge of the technical complaint:

- Technical complaint assessed as related to an SAE **within 24 hours**
- All other technical complaints within **5 calendar days**

If the eCRF is unavailable or when reporting a technical complaint that is not subject related, the information must be provided on a paper form by fax, e-mail or courier to Customer Complaint Center, Novo Nordisk, within the same timelines as stated above. When the eCRF becomes available again, the investigator must enter the information on the technical complaint form in the eCRF.

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** of obtaining the sample at trial site. The monitor must coordinate the shipment to Customer Complaint Center, Novo Nordisk (the address is provided in Attachment I) and ensure that the sample is sent as soon as possible. A print or copy of the technical complaint form must be sent with the sample.

The investigator must ensure that the technical complaint sample contains the batch or lot 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 of the technical complaint sample must be done in accordance with the conditions prescribed for the product. The shipment of the technical complaint sample should be done in accordance with the same conditions as for storage (Section 9.3).

12.5 Pregnancies

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 have received trial product(s).

The investigator must follow the pregnancy until the pregnancy outcome and the newborn infant is one month of age.

The investigator must report information about the pregnancy, pregnancy outcome, and health of the newborn infant(s), as well as AEs in connection with the pregnancy, and AEs in the foetus and newborn infant.

The following must be collected and reported by the investigator to Novo Nordisk - electronically (e.g. in PDF format), or by fax or courier:

1. **Reporting of pregnancy information**
   Information about the pregnancy and pregnancy outcome/health of the newborn infant(s) has to be reported on Maternal Form 1A and 1B, respectively.

   When the pregnancy outcome is abnormal (i.e. congenital anomalies, foetal death including spontaneous abortion and/or any anomalies of the foetus observed at gross examination or during autopsy), and/or when a congenital anomaly is diagnosed within the first month, further information has to be reported for the female subject on Maternal Form 2. In addition, information from the male partner has to be reported on the Paternal Form, after an informed consent has been obtained from the male partner.

   Initial reporting and follow-up information must be reported **within 14 calendar days** of the investigator's first knowledge of initial or follow-up information.

2. **Reporting of AE information**
   The investigator has to report AEs in connection with the pregnancy as well as in the foetus and newborn infant(s). The SAEs that must be reported include abnormal outcome, such as foetal death (including spontaneous abortion), and congenital anomalies (including those observed at gross examination or during autopsy of the foetus), as well as other pregnancy complications fulfilling the criteria of an SAE.

   <u>Forms and timelines for reporting AEs:</u>

   Non-serious AEs:
   - Paper AE form* **within 14 calendar days** of the investigator's first knowledge of the initial or follow-up information to the non-serious AE.

   SAEs:
   - Paper AE form* **within 24 hours** of the investigator's first knowledge of the SAE.
   - Paper safety information form **within 5 calendar days** of the investigator's first knowledge of the SAE.
   - **SAE follow-up information** to the AE form and/or safety information form **within 24 hours** of the investigator's first knowledge of the follow-up information.

   * It must be clearly stated in the AE diagnosis field on the AE form if the event occurred in the subject, foetus or newborn infant.

Any queries or follow-up requests from Novo Nordisk to non-serious AEs, SAEs and pregnancy forms must be responded to by the investigator **within 14 calendar days** from the date of receipt of the request, unless otherwise specified in the follow-up request.

12.6 Precautions and/or overdose

Treatment with insulin may result in hypoglycaemia. A specific overdose for insulin cannot be defined. However, hypoglycaemia may develop over sequential stages if too high doses relative to the patient's requirement are administered. Symptoms may occur suddenly and 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 and even death.

Hypoglycaemia should be treated according to best available medical practice at the discretion of the investigator. Mild hypoglycaemic episodes can be treated by oral administration of glucose or sugary products. It is therefore recommended that the diabetic patient always carries sugar containing products. Severe hypoglycaemic episodes, where the patient has become unconscious, can be treated with glucagon (0.5 to 1 mg) given intramuscularly or subcutaneously, by a trained person, or with glucose given intravenously by a healthcare professional. Glucose must be given intravenously, if the patient does not respond to glucagon within 10 to 15 minutes. Upon regaining consciousness, administration of oral carbohydrates is recommended for the patient in order to prevent a relapse.

If hypoglycaemia is caused by an overdose, the event should be reported as a MESI.

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.

13 Case report forms

Novo Nordisk will provide a system for the eCRF. This system and support services to the system will be provided by an external supplier.

Ensure that all relevant questions are answered, and that no empty data field exists. 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.

Data entry instructions will be available in the eCRF system.

The following will be provided as paper CRFs:

- Pregnancy forms
- PRO questionnaire

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

On the paper CRF 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.

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

13.1 Corrections to case report forms

13.1.1 eCRF

Corrections to the eCRF data may be made by the investigator or the investigator's delegated staff. An audit trail will be maintained in the eCRF 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 delegated staff after the date the investigator has signed the case book, the case book must be signed and dated again by the investigator.

13.1.2 Paper CRF

Corrections to the data in 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 was crossed out. Each correction must be initialled, dated and explained (if necessary). If corrections are made by the investigator's delegated staff after the date of the investigator's signature on the form, the form must be signed and dated again by the investigator.

Corrections necessary after the CRFs have been removed from the trial site must be documented on a data clarification form (DCF) or a monitor-initiated discrepancy form (MIDF). If the form for the subject has not been signed, any corrections must be approved by the investigator or her/his delegated staff. If the form for the subject has already been signed, the investigator must approve any correction.

The site staff should not perform any entries on or corrections to the data recorded by the subjects on the PRO questionnaires.

13.2 Case report form flow

The investigator must ensure that data is recorded in the eCRF as soon as possible, preferably within 5 days after the visit/phone contact. Once data has been entered, it will be available to Novo Nordisk for data verification and validation purposes.

There are certain data that have to be entered in the eCRF, with defined timelines, in reference to the insulin titration surveillance. Please refer to Section 14.2 for details.

Queries will be generated in the eCRF on an ongoing basis, and the investigator should resolve these queries preferably **within 3 business days**. AE, technical complaints and pregnancy related queries or follow-up requests from Novo Nordisk must be responded to within the timelines specified in Section 12.

At the end of the trial the investigator must ensure that all remaining data have been entered into the eCRF no later than 3 business days after the last subject's last visit. In addition, queries must be resolved immediately. This is done in order to ensure the planned database lock is achieved.

Site specific eCRF data (in an electronic readable format) will be provided to the trial site before access to the eCRF is revoked. This data must be retained at the trial 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 at the trial site and no later than 4 weeks after. The monitoring visit intervals will depend on the outcome of the remote monitoring of the CRFs, the trial site's recruitment rate and the compliance of the trial site to the protocol and GCP, but will not exceed 12 weeks.

14.1 Source data verification

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).

All data must be verifiable in source documentation other than the eCRF, except for the following data that may be recorded directly in the paper CRFs, and will be considered source data:

- Pregnancy forms
- PRO questionnaire

If source data is entered directly in a paper CRF, each data entry or clear series of data entry must be signed and dated separately by the trial staff making the entry.

For all data recorded the source document must be defined in a source document agreement at each trial site, which is signed by the investigator. There must only be one source defined at any time for any data element.

Considering the electronic source data environment, it is accepted that the earliest practically retainable record should be considered as the location of the source data and therefore transcription to the diary from the glucometer is considered the source for recordings of SMPG values.

Data recorded in subject diary is considered source data with respect to:

- SMPG values (three times daily and 7-point profiles)
- Insulin doses recorded
- Hypoglycaemic episodes

The data for medical problems and concomitant medication (start and stop date) from the diary will only be considered as a reminder for both the subject and the investigator to discuss any medical

problems or new medications during the clinic visit. The investigator will assess whether the medical problem is to be considered an adverse event. If the medical problem is considered as an adverse event, data should be transcribed to the subject's medical notes and to the applicable form in eCRF and reported according to Section 12. Likewise, the investigator will transfer information regarding concomitant medication to the subject's medical record and complete and/or update the appropriate form in eCRF.

Source data generated by the trial site can be corrected by another person than the person entering the source data if accepted by local regulations; any correction must be explained, signed and dated by the person making the correction.

The diaries and PROs must not be removed from the trial site.

The monitor will ensure that the CRFs are completed and that paper CRFs (pregnancy forms and PRO questionnaire) are collected.

The following data will be source data verified for screening failures:

- Date for obtaining informed consent.
- Screen failure reason

For screening failed subjects the screening failure form and any adverse event forms must be completed in the eCRF. The case book should be signed electronically by the investigator.

Monitors must review the subject's medical records and other source data (e.g. the diaries and PRO questionnaires) to ensure consistency and/or identify omissions compared to the eCRF. If discrepancies are found, the investigator must be questioned about these.

A follow-up letter (paper or electronic) will be sent to the investigator following each monitoring visit. This should address any action to be taken.

14.2 Titration Surveillance

An independent Novo Nordisk Titration Group will centrally perform insulin titration surveillance. This is also described in Section 5 of the Titration Guideline found in Appendix A.

Surveillance will be performed on an on-going basis throughout the trial. The Novo Nordisk Titration Group reviews the information provided by the investigator in the eCRF after each visit/phone contact and follows-up on significant deviations from the titration guideline.

It is important that information regarding BIAsp 30, dose titration and hypoglycaemic episodes is entered within **24 hours** after the visit/phone contact. Data to be entered are described in Section 8.6.2.

15 Data management

Data management is 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.

Data from central laboratories will be transferred electronically. In cases where data is transferred via non-secure electronic networks, data will be encrypted during transfer. The laboratory will also provide all laboratory reports to the investigator for storage at the trial site.

The subject and any biological material obtained from the subject will be identified by subject number and trial ID. 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 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.

17 Statistical considerations

Novo Nordisk will be responsible for the statistical analysis and reporting. Analysis and reporting will be done with data from all sites pooled together.

The statistical analyses will be performed with a significance level of 5% (two-sided tests).

If necessary, a statistical analysis plan (SAP) may be written in addition to the protocol, including a more technical and detailed elaboration of the statistical analyses. The SAP will be finalised before database lock.

Presentation of results from a statistical analysis of a continuous endpoint analysed by a mixed model for repeated measurements (MMRM) analysis will include the estimated mean (= Least Square Mean) change from baseline for each treatment as well as the estimated mean treatment difference including a two-sided 95% confidence interval and a p-value for test of no difference between treatments.

If an assessment has been made both at screening and randomisation, and if not otherwise specified, the value from the randomisation visit will be used as the baseline value. If the value measured at the randomisation visit is missing and the assessment also has been made at screening, then the screening value will be used as the baseline value. If an assessment is only made at randomisation or at screening the relevant value will be the baseline value.

For efficacy variables missing values will not be replaced by imputed values unless otherwise specified. In the primary analysis missing values are handled by a MMRM.

17.1 Sample size calculation

The primary objective of this trial is to compare the efficacy of thrice daily BIAsp 30 versus twice daily BIAsp 30, both in combination with metformin, in subjects with type 2 diabetes inadequately controlled on basal insulin combined with OADs. The primary endpoint is change from baseline in HbA_{1c} after 24 weeks of treatment and the sample size is determined based on this endpoint.

Let D be the mean treatment difference for change in HbA_{1c} (BIAsp 30 TID minus BIAsp 30 BID). The null-hypothesis will be tested against the alternative hypothesis as given by

H_0: D = 0 % against H_A: D ≠ 0 %

Sample size is determined using a t-statistic under the assumption of a two-sided test and a significance level of 5%. Based on experience from previous trials[19,20], an estimated treatment difference of 0.3% and a standard deviation (SD) of 1.1% for HbA_{1c} will be used in the sample size calculation (see Table 17–1). The randomisation scheme will be 1:1. The sample size calculation is done using Statistical Analysis System (SAS) 9.3.

Table 17–1 Number of subjects required totally under different SD and different power requirement

Subjects in total	Estimated SD in HbA_{1c} (%)			
Power	**1.0**	**1.1**	**1.2**	**1.3**
80%	352	**426**	506	592
85%	402	486	578	678
90%	470	568	676	792
95%	580	702	834	978

Assuming a SD of 1.1%, a total of 426 subjects (213 subjects per group) in the FAS analysis set will give 80% power in detecting the treatment difference between BIAsp 30 TID and BIAsp 30 BID based on the primary endpoint.

17.2 Definition of analysis sets

The following analysis sets are defined:

- Full Analysis Set (FAS): includes all randomised subjects who have been dosed and have any post randomisation data. The subjects and observations excluded from analysis sets, and the reason for this, will be described in the clinical trial report. The statistical evaluation of the FAS will follow the intention-to-treat (ITT) principle and subjects will contribute to the evaluation "as randomised".
- Safety Analysis Set: includes all subjects receiving at least one dose of investigational product. Subjects in the safety set will contribute to the evaluation "as treated".

17.3 Primary endpoint

The primary objective of this trial is to compare the efficacy of thrice daily BIAsp 30 versus twice daily BIAsp 30, both in combination with metformin, in subjects with type 2 diabetes inadequately controlled on basal insulin combined with OADs.

The primary efficacy endpoint is the change from baseline in HbA_{1c} after 24 weeks of treatment. Change in HbA_{1c} from baseline to the 4, 8, 12, 16, 20 and 24 week's measurements will be analysed using a Mixed Model for Repeated Measurements (MMRM), with treatment, combination of the two stratification factors (HbA_{1c} value and previous OAD treatment) and region (China/non-China)

as fixed factors and baseline HbA_{1c} as a covariate, all variables nested within visit as a factor. Region China includes China, Hong Kong and Taiwan and non-China includes all the other participating countries. An unstructured covariance matrix will be used to describe the variability for the repeated measurements for a subject. From the MMRM model the treatment difference at week 24 will be estimated and the corresponding 95% confidence interval and p-value will be calculated. All subjects in the FAS will be included in this analysis.

If p-value <0.05, or equivalently, if the upper bound of the 95% confidence interval is below 0% or the lower bound of the 95% confidence interval is above 0%, the treatment difference will be regarded as statistically significant.

An important assumption for using MMRM is that the missing data are missing at random (MAR).

For this trial, missing data are mainly expected to occur due to withdrawal/discontinuation from the trial. Intermittent missing data (visits with missing data in between visits with data) is expected to be less common.

The main reasons for withdrawal/discontinuation are expected to be ineffective therapy and adverse events. Discontinuation due to ineffective therapy is expected be MAR to some extent. For missing data due to adverse events, the MAR assumption may be questionable.

Sensitivity analyses will be performed for the primary efficacy endpoint. They will include:

- An analysis of covariance (ANCOVA) model with last observation carried forward (LOCF) imputation. Effects in the model are treatment, combination of the two stratification factors and region as factors, and baseline HbA_{1c} as a covariate.

- A pattern mixture model approach mimicking an ITT scenario where withdrawn subjects are assumed to be switched to the control treatment (i.e., BIAsp 30 BID) after withdrawal. Multiple copies (100 copies) of the full dataset will be generated by imputing missing values based on estimated parameters for the control group. This will be done as follows:
  - In the first step intermittent missing values are imputed using a Markov Chain Monte Carlo method, in order to obtain a monotone missing data pattern. This imputation is done for each treatment group separately and 100 copies of the dataset will be generated.
  - In the second step, for each of the 100 copies of the dataset, an ANCOVA model with combination of the two stratification factors and region as factors and baseline HbA_{1c} and HbA_{1c} at 4 weeks as covariates is fitted to the change in HbA_{1c} from baseline to 8 weeks for the control group only. The estimated parameters, and their variances, from this model are used to impute missing values at 8 weeks for subjects

in both treatment groups, based on their combination of the two stratification factors and region and HbA_{1c} at baseline and 4 weeks.

- In the next steps, for each of the 100 copies of the dataset, missing HbA1c values at 12, 16, 20 and 24 weeks are imputed sequentially in the same way as for 8 weeks. The imputations are based on an ANCOVA model with combination of the two stratification factors and region as factors and the HbA_{1c} values at baseline and previous post-baseline visits as covariates, fitted to the control group.
- After imputation, for each of the complete data sets, the change from baseline to Week 24 is analysed using an ANCOVA model with treatment, combination of the two stratification factors and region as factors, and the baseline HbA_{1c} value as a covariate.
- The estimates and standard deviations for the 100 data sets are pooled to one estimate and associated standard deviation using Rubin's formula:

$$m_{MI} = \frac{1}{100}\sum_{i=1}^{100} m_i \quad , \quad SD_{MI} = \sqrt{\frac{1}{100}\sum_{i=1}^{100} SD_i^2 + \left(1+\frac{1}{100}\right)\left(\frac{1}{100-1}\right)\sum_{i=1}^{100}\left(m_i - m_{MI}\right)^2}$$

where m_i and SD_i are the estimated means and standard deviations for the 100 copies of the dataset, and m_{MI}, SD_{MI} are the pooled estimates.

- From m_{MI} and SD_{MI}, the 95% confidence interval for the treatment difference and the associated p-value are calculated.

17.4 Secondary endpoint

17.4.1 Supportive secondary endpoints

17.4.1.1 Efficacy endpoints

The following continuous endpoints are defined:

- Change from baseline in FPG after 24 weeks of treatment (analysed by central laboratory)
- 7-point SMPG profiles after 24 weeks of treatment
  - 7-point SMPG profile
  - Change from baseline in 2-hour PPG and PPG increment at individual meal (breakfast, lunch and main evening meal)

- Change from baseline in mean of 2-hour PPG and PPG increment over 3 main meals (breakfast, lunch and main evening meal)
- Change from baseline in mean of the 7-point profile
- Fluctuation in the 7-point profile

To compare the 7-point SMPG profiles of the two treatments after 24 weeks, a mixed effect model will be fitted to the data. The model will include treatment, time, interaction between treatment and time, combination of the two stratification factors and region as fixed effects. The within-subject residual variance structure will be modelled as 'unstructured'. The time corresponds to planned measurement times during the 24h period. The treatment group by time interaction express whether the profiles of the two treatment groups are parallel over the 7-points. Mean differences between the two treatments and corresponding 95% confidence intervals will be estimated for each time point.

All the other continuous endpoints described above, including change from baseline in FPG and the endpoints derived from 7-point SMPG profile, will be analysed with a similar method as the primary endpoint, where the relevant baseline value will replace baseline HbA1c in the model. The mean of 7-point SMPG profile is defined as the area under the profile divided by the measurement time and is calculated using the trapezoidal method. The fluctuation in the 7-point SMPG profile is defined as

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

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. Fluctuation in the 7-point SMPG profile and the relevant baseline value will be log transformed before analysed.

The following dichotomous endpoints are defined:

Subjects who after 24 weeks of treatment achieve (yes/no):

- HbA_{1c} <7.0%
- HbA_{1c} <7.0 % without severe hypoglycaemic episodes
- HbA_{1c} <7.0 % without severe or blood glucose (BG) confirmed hypoglycaemic episodes

The dichotomous endpoints will be analysed by a logistic regression model. Effects in the model are treatment, combination of the two stratification factors and region as factors, and baseline HbA_{1c} as a covariate. The results will include the 95% confidence interval for the odds ratio (BIAsp 30 TID

over BIAsp 30 BID) and the p-value for test of no difference between the groups as part of the presentation.

For the dichotomous endpoint of HbA_{1c}<7% at week 24 (yes/no), missing HbA_{1c} values at week 24 will be imputed using the predicted value from an MMRM analysis. For the other two dichotomous endpoints, as a conservative approach, subjects withdrawn before 24 weeks will be handled as non-responders.

17.4.1.2 Safety endpoints

All safety endpoints will be summarised and analysed using the safety analysis set. Unless otherwise specified safety endpoints will be analysed by descriptive statistics only.

Adverse events

All AEs will be coded using the most recent version of the MedDRA coding. A TEAE is defined as an event that has onset date (or increase in severity) on or after the first day of exposure to trial product and no later than 7 days after the last day on trial product.

TEAEs are summarised descriptively and displayed 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 1000 years of exposure (R)

Summaries of TEAEs and of serious TEAEs will be presented as an overview including all AEs, serious AEs, number of deaths, AEs by severity, AEs by relation to treatment and AEs leading to withdrawal.

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

- All TEAEs
- Serious TEAEs
- Possibly or probably related TEAEs
- Severe, moderate and mild 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
- TEAEs leading to withdrawal

Definition of Hypoglycaemia

Treatment emergent: hypoglycaemic episodes will be defined as treatment emergent if the onset of the episode occurs on or after the first day of trial product administration, and no later than 7 days after the last day on trial product.

Nocturnal hypoglycaemic episodes: are episodes with time of onset between 00:01 and 05.59 both inclusive.

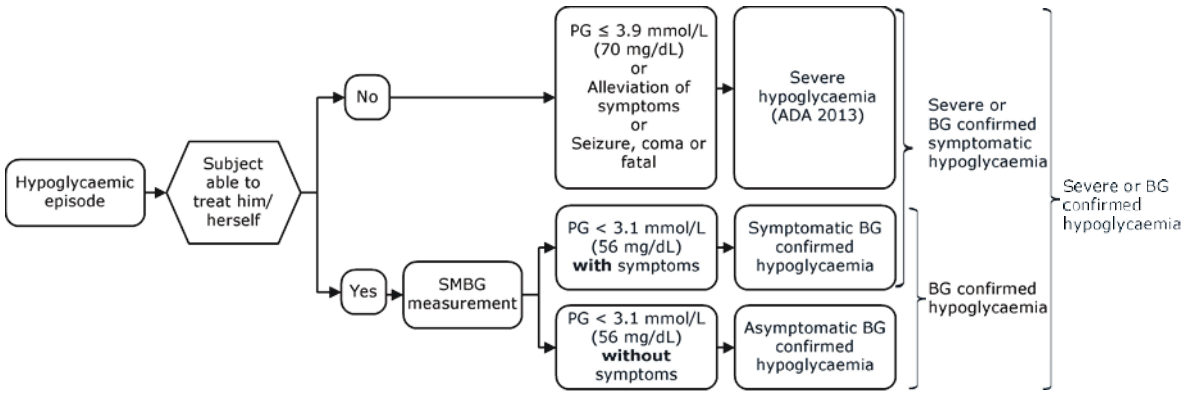
Hypoglycaemic episodes are classified according to the Novo Nordisk classification of hypoglycaemia (see Figure 17–1) and the ADA classification of hypoglycaemia (see Figure 17–2).

Novo Nordisk classification of hypoglycaemia

In normal physiology, symptoms of hypoglycaemia occur below a plasma glucose level of 3.1 mmol/L (56 mg/dL)[21]. Therefore, Novo Nordisk has included hypoglycaemia with plasma glucose levels below this cut-off point in the definition of blood glucose (BG) confirmed hypoglycaemia.

Novo Nordisk uses the following classification in addition to the ADA classification:

- Severe hypoglycaemia according to the ADA classification[22].
- BG confirmed hypoglycaemia: An episode that is BG confirmed by a plasma glucose value <3.1 mmol/L (56 mg/dL) with or without symptoms consistent with hypoglycaemia.
- Severe or BG confirmed hypoglycaemia: An episode that is severe according to the ADA classification[22] or BG confirmed by a plasma glucose value <3.1 mmol/L (56 mg/dL) **with** or **without** symptoms consistent with hypoglycaemia.



Note: Glucose measurements are performed with capillary blood calibrated to plasma equivalent glucose values

Figure 17–1 Novo Nordisk classification of hypoglycaemia

ADA classification[22] of hypoglycaemia

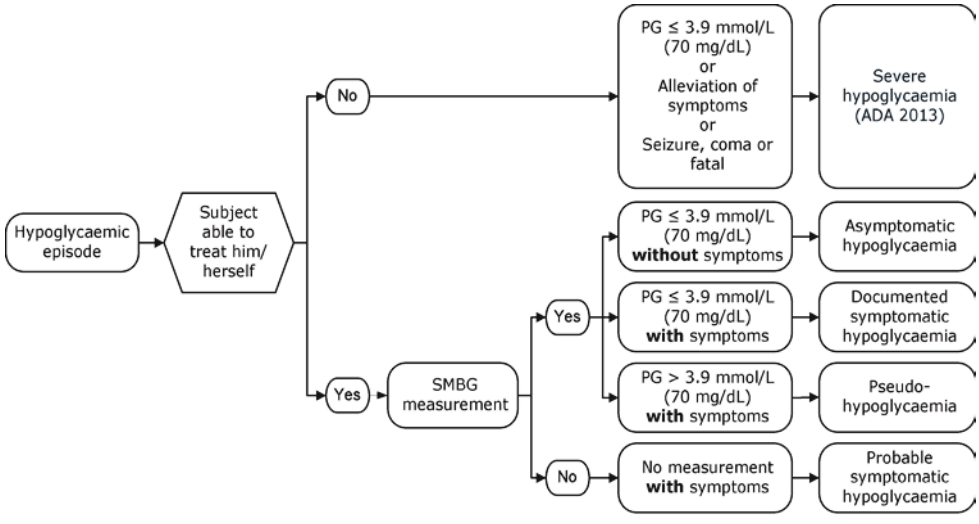
1. Severe hypoglycaemia: An episode requiring assistance of another person to actively administer carbohydrate, glucagon, or take other corrective actions. Plasma glucose concentrations may not be available during an event, but neurological recovery following the return of plasma glucose to normal is considered sufficient evidence that the event was induced by a low plasma glucose concentration.

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

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

4. Pseudo-hypoglycaemia: An episode during which the person with diabetes reports any of the typical symptoms of hypoglycaemia with a measured plasma glucose concentration > 3.9 mmol/L (70 mg/dL) but approaching that level.

5. 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 ≤ 3.9 mmol/L (70 mg/dL).



Note: Glucose measurements are performed with capillary blood calibrated to plasma equivalent glucose values

Figure 17–2 ADA classification of hypoglycaemia

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 of exposure (R). Separate summaries are made for all hypoglycaemic episodes, nocturnal hypoglycaemic episodes, severe or BG confirmed hypoglycaemic episodes, nocturnal severe or BG confirmed hypoglycaemic episodes and the ADA classification of hypoglycaemia.

The number of treatment emergent severe or BG confirmed hypoglycaemic episodes will be analysed by a negative binomial regression model with a log-link function and the logarithm of the time period in which the hypoglycaemic episodes are considered treatment emergent as offset. The model will include treatment, combination of the two stratification factors and region as factors. The results will include the 95% confidence interval for the event rate ratio (BIAsp TID over BIAsp BID) and p-value as part of the presentation. To the extent where data allow, analyses will be performed on all severe or BG confirmed episodes and nocturnal severe or BG confirmed episodes separately.

Vital signs

Vital signs (systolic blood pressure, diastolic blood pressure and pulse) will be summarised and tabulated by treatment and visit together with the change from the baseline to end-of-treatment.

Laboratory assessments

All continuous laboratory parameters will be evaluated by descriptive statistics and tabulated by visit together with change from baseline to end-of-treatment. Shift tables showing changes from baseline to end-of-treatment (normal and abnormal) will be constructed for each laboratory safety variable. No formal statistical analyses of laboratory parameters will be performed and abnormal values will be listed.

Eye examination and physical examination

For eye examination and physical examination, a shift table for change from baseline to end-of-treatment will be generated. Subjects with any change in examination result will be listed.

Change in body weight after 24 weeks of treatment

Change from baseline in body weight after 24 weeks of treatment will be analysed with a similar method as the primary endpoint, where baseline body weight will replace baseline HbA_{1c} in the model.

Total daily insulin dose

The actual daily insulin dose is recorded on the three random days when 3-point SMPG are performed prior to each visit for visits 3-26. The calculated/prescribed insulin dose is recorded for visits 2-25. The actual insulin dose from the last of the three days and calculated/prescribed insulin dose will be summarized descriptively according to regimen as dose in units and units/kg per visit. Total daily dose, which is the sum of doses given before breakfast and before main evening meal for the BID treatment group, and the sum of doses given before breakfast, before lunch and before main evening meal for the TID treatment group, will also be summarized descriptively as dose in units and units/kg per visit.

17.5 Patient reported outcomes

Diabetes Treatment Satisfaction Questionnaire (status): DTSQs

The DTSQs is a self-completion questionnaire used to investigate the subject's treatment satisfaction and will be completed at Visit 2 and Visit 26. The eight items in the DTSQs are scored on a scale from 0 to 6. Overall treatment satisfaction is defined as the sum of items 1, 4, 5, 6, 7, and 8. The DTSQs scores at baseline and at end-of-treatment will be summarized descriptively. Change from baseline to end-of-treatment will be calculated and summarized.

18 Ethics

The trial will be conducted in compliance with ICH GCP[1], applicable regulatory requirements, and in accordance with the Declaration of Helsinki[2].

At the termination of the trial, the subject will consult their investigator to decide on the best available marketed treatment.

18.1 Benefit-risk assessment of the trial

BIAsp 30 has been on the market for more than 10 years and has been exposed to several million subjects. BIAsp 30 has well-known safety profiles and offers a treatment regimen presumed to be better than or equal to the treatment subjects received at the time of entering the trial.

All subjects included in the trial will be treated with BIAsp 30 TID or BIAsp 30 BID in addition to metformin in order to improve glycaemic control. The trial insulin will be titrated by the investigator. Titration will be performed according to titration algorithms for BIAsp 30 in order to achieve the pre-meal SMPG target 4.4−6.1 mmol/L (80−110 mg/dL).

The most frequently reported adverse reaction during treatment with BIAsp 30 is hypoglycaemia. The frequencies of hypoglycaemia vary with patient population, dose regimens and level of glycaemic control. However, the investigator will explain to the subject how to check their blood sugar with the blood glucose meter provided by Novo Nordisk and to take precautions.

The subjects will have to spend some extra time, as additional visits to the clinic are required and some of the tests performed during the trial are outside normal practice. However, the anticipated benefit of participating in this trial, i.e. improved glycaemic control due to the closer and more frequent assessments of the subject's diabetes and intensified diabetes treatment and the close contact with the trial site (including physical examinations) is expected to outweigh the risk for these subjects who have already failed their previous diabetes treatment.

Subjects participating in the proposed trial must have an HbA_{1c} value between 7.5% and 10.0%, since it is expected that this population will most likely benefit from intensification of premixed insulin treatment with BIAsp 30. All subjects in the proposed trial will have their blood glucose monitored regularly, and will receive BIAsp 30 TID or BID. Thus, their diabetes treatment and glycaemic control will most likely be optimised during the trial period.

Participation in this trial can lead to an increase in subjects' understanding regarding the importance of glucose control.

An internal Novo Nordisk safety committee for BIAsp 30 will perform ongoing safety surveillance during the trial.

18.2 Non-clinical Benefit and Risk Assessment

No new non-clinical information on BIAsp 30 is available.

18.3 Informed consent

In seeking and documenting informed consent, the investigator must comply with applicable regulatory requirement(s) and adhere to ICH GCP[1] and the requirements in the Declaration of Helsinki[2].

Before any trial-related activity, the investigator must give the subject verbal and written information about the trial and the procedures involved in a form that the subject can read and understand.

The subjects must be fully informed of their rights and responsibilities while participating in the trial as well as possible disadvantages of being treated with the trial products.

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

A voluntary, signed and personally dated informed consent must be obtained from the subject before any trial-related activity.

The responsibility for seeking informed consent must remain with the investigator, but the investigator may delegate the task 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 before any trial-related activity.

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 subject information must be provided and a new informed consent must be obtained.

18.4 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 and data collected at the end-of-trial visit will be retained by Novo Nordisk, entered into the database and used for the trial report.
- Safety events will be reported to Novo Nordisk and regulatory authorities according to local/national requirements.

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

18.5 Information to subject during trial

The site will be offered a communication package to the subject during the conduct of the trial. The package content is issued by Novo Nordisk. The communication package will contain the letters intended for distribution to the subjects. The letters will be translated and adjusted to local requirements and distributed to the subject by discretion of the investigator. The subject may receive a "welcome to the trial letter" before enrolled in the trial and a "thank you for your participation letter" after completion of the trial. Further the subject may receive letters during the trial.

All written information to subjects must be sent to IRB/IEC for approval/favourable opinion and to regulatory authorities for approval or notification according to local regulations.

18.6 Premature termination of the trial and/or trial site

Novo Nordisk, 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 must also promptly inform the regulatory authorities and IRBs/IECs and provide a detailed written explanation.

If, after the termination of the trial, the benefit-risk analysis changes, the new evaluation must 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 has 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.

Deviations must be documented and explained in a protocol deviation 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 protocol deviations must be kept in the investigator's trial master file and sponsor 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 or after the trial. The investigator and the site staff as well as Novo Nordisk staff have an obligation to cooperate and assist in audits and inspections. This includes giving auditors and inspectors direct access to all source documents and other documents at the trial 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 trial 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
- Approval/favourable opinion from IRBs/IECs clearly identifying the documents reviewed as follows: protocol, any 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 (or a general assurance number/statement of compliance)
- Curricula vitae of investigator and sub-investigator(s) (current, dated and signed - must include documented GCP training* or a certificate)
- Signed receipt of SmPC or similar labelling
- Signed and dated Agreement on Protocol
- Signed and dated agreement on protocol Amendment, if applicable
- Contract, signed by the investigator and/or appropriate parties on behalf of the investigator's site and Novo Nordisk
- Source document agreement
- Central laboratory certification and normal ranges
- Insurance statement, if applicable
- Financial disclosure form from investigator and sub-investigator(s)

* Documented GCP training not more than 2 years prior to FPFV is allowed

Novo Nordisk will analyse and report data from all sites together if more than one site is involved in the trial.

By signing the protocol, each investigator agrees to comply fully with ICH GCP[1], applicable regulatory requirements and the Declaration of Helsinki[2].

By signing the protocol, each investigator also agrees to allow Novo Nordisk to make investigator's name and information about site name and address publically available if this is required by national or international regulations.

22 Responsibilities

The investigator is accountable for the conduct of the trial at his/her site. If any tasks are delegated, the investigator must maintain a log of appropriately qualified persons to whom he/she has delegated specified trial-related duties. The investigator must 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 (i.e. those documents which individually and collectively permit evaluation of the conduct of a trial and the quality of the data produced) in the investigator trial master file. The documents including the subject identification code list should be kept in a secure locked facility, so no unauthorized persons can get access to the 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 must 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 as investigator (e.g. if he/she moves or retires), a new investigator will be appointed in consultation with Novo Nordisk.

The investigator and other 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 or on behalf of Novo Nordisk for regulatory purposes as well as 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. Provided that certain conditions are fulfilled, Novo Nordisk may grant access to information obtained during this trial to researchers who require access for research projects studying the same disease and/or trial product studied in this trial.

Novo Nordisk may publish on its clinical trials website a redacted clinical trial report for this trial.

One investigator will be appointed by Novo Nordisk to review and sign the clinical trial report (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[23].

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.

The results of this trial will be subject to public disclosure on external web sites according to international and national regulations, as reflected in the Novo Nordisk Code of Conduct for Clinical Trial Disclosure[12].

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.

At the end of the trial, one or more scientific publications 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.

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 evaluate 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.

Where required by the journal, the investigator from each trial site will be named in an acknowledgement or in the supplementary material, as specified by the journal.

23.1.1 Authorship

Authorship of publications should be in accordance with the Uniform Requirements of the International Committee of Medical Journal Editors[23] (sometimes referred to as the Vancouver Criteria).

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. Further to allow for the primary manuscript to be published as the first, Novo Nordisk asks for deferment of publication of individual site results until the primary manuscript is accepted for publication. As Novo Nordisk wants to live up to the industry publication policy, submission of a primary publication will take place no later than 18 months after trial completion.

23.2 Investigator access to data and review of results

As owner of the trial database, Novo Nordisk has the discretion to determine who will have access to the database.

Individual investigators will have their own research subjects' data.

24 Retention of clinical trial documentation

Subject's medical 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 trial site. If the provided data (e.g. the CD-ROM) is not readable during the entire storage period, the investigator can request a new copy. A copy of all data will be stored by Novo Nordisk.

Novo Nordisk will maintain Novo Nordisk documentation pertaining to the trial for as long as the product is on the market plus 20 years.

The files from the trial site/institution must be retained for 15 years after the completion of the trial, or longer if required by local regulations or Novo Nordisk. In any case trial files cannot be destroyed until the trial site/institution is notified by Novo Nordisk. The deletion process must ensure confidentiality of data and must be done in accordance with local regulatory requirements.

25 Institutional Review Boards/Independent Ethics Committees and regulatory authorities

IRB/IEC:

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

During the trial, the investigator or Novo Nordisk, as applicable, must promptly report the following to the IRB/IEC, in accordance with local requirements: unexpected SAEs where a causal relationship cannot be ruled out, 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 benefit-risk 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.

The investigator must ensure submission of the clinical trial report synopsis to the IRB/IEC.

Protocol amendments must not be implemented before approval or favourable opinion according to local regulations, 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 must be filed in the investigator trial master file and copies must be sent to Novo Nordisk.

Regulatory Authorities:

Regulatory authorities will receive the clinical trial application, protocol amendments, reports on SAEs, and the clinical trial report according to national requirements.

26 Indemnity statement

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

Novo Nordisk assumes no liability in the event of negligence, or any other liability of the sites or investigators conducting the trial, or by persons for whom the said site or investigator are responsible.

27 References

1 International Conference on Harmonisation. ICH Harmonised Tripartite Guideline. Guideline for Good Clinical Practice. E6 (R1), Step 4. 10 Jun 1996.

2 World Medical Association. Declaration of Helsinki. Ethical Principles for Medical Research Involving Human subjects. Last amended by the 64th WMA General Assembly, Fortaleza, Brazil.

3 Standards of medical care in diabetes--2014. Diabetes Care 2014; 37 Suppl 1:S14-S80.

4 Chinese Diabetes Society. Chinese Diabetes Society, Chinese Guideline for Type 2 Diabetes Mellitus 2013.Chin J Diabetes Mellitus, 2014, 6(7): 447-498. 2015.

5 Inzucchi S E, Bergenstal R M, Buse J B, et al. Management of hyperglycemia in type 2 diabetes, 2015: a patient-centered approach: update to a position statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes care, 2015, 38(1): 140-149.

6 EU SmPC for Insulin NovoMix® 30, current version or any updates hereafter.

7 Gao Y, Luquez C, Lynggaard H, Andersen H, Saboo B. The SimpleMix study with biphasic insulin aspart 30: a randomized controlled trial investigating patient-driven titration versus investigator-driven titration. Curr Med Res Opin 2014; 30(12):2483-2492.

8 Liebl A, Prager R, Binz K, Kaiser M, Bergenstal R, Gallwitz B. Comparison of insulin analogue regimens in people with type 2 diabetes mellitus in the PREFER Study: a randomized controlled trial. Diabetes Obes Metab 2009; 11(1):45-52.

9 Haddad J, Khoshniatnikoo M, Benabbas Y, Guler S, Prusty V, Soewondo P. Safety and Effectiveness of Switching from a Basal-only to Biphasic Insulin Aspart 30 Insulin Regimen. Diabetes Ther 2013; 4(2):309-319.

10 Hemmingsen B, Christensen LL, Wetterslev J, Vaag A, Gluud C, Lund SS et al. Comparison of metformin and insulin versus insulin alone for type 2 diabetes: systematic review of randomised clinical trials with meta-analyses and trial sequential analyses. BMJ 2012; 344:e1771

11 Criteria Committee of the New York Heart Association. Nomenclature and criteria for diagnosis of diseases of the heart and great vessels. Boston, MA: Little, Brown & Co, 1994.

12 Novo Nordisk A/S. http://novonordisk-trials.com/website/content/how-we-disclose-trial-information.aspx (Update link if changed). 2015.

13 De Angelis C, Drazen J, Frizelle F, Haug C, Hoey J, Horten R et al. Clinical Trial Registration: A Statement from the International Committee of Medical Journal Editors. New Engl J Med 2004; 351(12):1250-1251.

14 U.S. Food and Drug Administration. Food and Drug Administration Amendments Act (FDAAA) of 2007. 2007.

15 The European Parliament and the Council of the European Council: Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use, article 11. Official Journal of the European Communities . May 2001.

16 The European Parliament and the Council of the European Council: Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency, article 57. Official Journal of the European Communities . Apr 2001.

17 McAulay V, Deary IJ, Frier BM. Symptoms of hypoglycaemia in people with diabetes. Diabetic Medicine 2001; 18(9):690-705.

18 European Commission; The Rules Governing Medicinal Products in the European Union, Volume 4, Annex 13, Investigational Medicinal Products. Brussels. Feb 2010.

19 Clinical Trial Report: Trial ID: BIAsp-1707, A Multicentre, Randomised, Open-label, Parallel-group Trial to Study the Efficacy and Safety of Twice Daily or Thrice Daily NovoMix30 (Biphasic Insulin Aspart 30) in Type 2 Diabetic Patients Inadequately Controlled with OADs: P93

20 Clinical Trial Report: Trial ID: BIAsp-2191, NovoLog Mix 70/30 (biphasic insulin aspart 70/30) bid vs. Once Daily Lantus (insulin glargine) in Subjects withType 2 Diabetes and Inadequate Glycaemic Control on Basal Insulin Plus Oral Antidiabetic Therapy: A Multicenter, Randomized, Open-Label, Parallel Group Study

21 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. 2015.

22 Seaquist ER, Anderson J, Childs B, Cryer P, Dagogo-Jack S, Fish L et al: Hypoglycemia and Diabetes: A Report of a Workgroup of the American Diabetes Association and The Endocrine Society. Diabetes Care 2013; 36:1384-1395. 2015.

23 International Committee of Medical Journal Editors. Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals; current version available at www.icmje.org.

Appendix A: Biphasic insulin aspart Titration Guideline

Trial ID: BIAsp-4200

A 24-week, multinational, multicentre, randomised, open label, parallel-group treat-to-target trial to compare efficacy and safety of thrice daily versus twice daily NovoMix® 30 (Biphasic insulin aspart 30) in subjects with type 2 diabetes inadequately controlled with basal insulin

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1 Introduction

The goal of insulin therapy is to achieve near normoglycaemia, i.e. to reach a pre-defined HbA_{1c} 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 [1-7].

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 be at least in weekly contact with the subjects to assist the subjects in adjusting insulin doses and to ensure the subject's welfare.

2 Treatment regimens

At randomisation (Visit 2) eligible subjects will be transferred from their previous basal insulin dose to Biphasic insulin aspart 30 (BIAsp 30) BID or TID regimen according to Section 3.1.

2.1 Injection area

According to the local approved label, BIAsp 30 should be administered by subcutaneous injection in the abdominal region, buttocks, thigh, or upper arm.

The chosen region should be the same throughout the trial. Rotation of injection sites within a given region is recommended.

2.2 Time of injection

For those subjects who are randomised to BID regimen, BIAsp 30 should be injected before breakfast and main evening meal respectively.

For those subjects who are randomised to TID, BIAsp 30 should be injected before breakfast, lunch and main evening meal respectively.

BIAsp 30 should be injected accordingly to local approved label.

3 Initiation and titration of BIAsp 30

3.1 Initiation of BIAsp 30

At randomisation (Visit 2), the subject's total daily dose of basal insulin prior to the trial (NPH once or twice daily or basal insulin analogue once daily) should be transferred to the total daily dose of BIAsp 30 unit-to-unit [7,8], which will be distributed along meals by the Investigator's discretion.

3.2 Titration of BIAsp 30

All subjects will be requested to measure SMPG three times daily (pre-breakfast, pre-lunch, and before main evening meal) on three random days before each scheduled site visit or phone contact.

The titration of BIAsp 30 will be done according to the lowest values of three pre-meal SMPG measurements by the Investigator's discretion.

For those subjects who are randomised to BIAsp 30 BID (Table 1),

- the lowest of three pre-breakfast SMPG values measured on previous days will be used to adjust the BIAsp 30 before main evening meal dose
- the lowest of three before main evening meal SMPG values measured on previous days will be used to adjust the BIAsp 30 pre-breakfast dose

Table 1 Time-point of SMPG measurement and BIAsp 30 BID dose adjustment

Insulin BIAsp30 dosing	Before main evening meal dosing	Pre-breakfast dosing
SMPG values on previous days used for titration	Pre-breakfast	Before main evening meal

For those subjects who are randomised to BIAsp 30 TID (Table 2),

- the lowest of three pre-breakfast SMPG values measured on previous days will be used to adjust the BIAsp 30 before main evening meal dose
- the lowest of three pre-lunch SMPG values measured on previous days will be used to adjust the BIAsp 30 pre-breakfast dose
- the lowest of three before main evening meal SMPG values measured on previous days will be used to adjust the BIAsp 30 pre-lunch dose

Table 2 Time-point of SMPG measurement and BIAsp 30 TID dose adjustment

Insulin BIAsp30 dosing	before main evening meal dosing	Pre-breakfast dosing	Pre-lunch dosing
SMPG values on previous days used for titration	Pre-breakfast	Pre-lunch	Before main evening meal

The BIAsp 30 dose titration will be done according to the following algorithm (Table 3).

Table 3 Increase of pre-meal dose of BIAsp 30

Lowest of three pre-meal SMPGs values at pre-breakfast, pre-lunch, or before main evening meal		**Dose adjustment**
mmol/L	**mg/dL**	**U**
4.4 – 6.1	**80 – 110**	**No adjustment**
6.2 – 7.8	111 – 140	+ 2
7.9 – 10.0	141 – 180	+ 4
> 10.0	> 180	+ 6

If one or more pre-meal SMPG value(s) are < 4.4 mmol/L (< 80 mg/dL) subjects should reduce BIAsp 30 according to (Table 4).

Table 4 Decrease of pre-meal dose of BIAsp 30

Pre-meal SMPGs values at pre-breakfast, pre-lunch, or before main evening meal		**Dose adjustment**
mmol/L	**mg/dL**	**U**
< 4.4	< 80	-2

3.3 Deviations from the algorithm

It is recommended that the algorithm is followed. However, it is also important that the decision to adjust the BIAsp 30 doses is based on all relevant information as described in Section 1. A reason for deviating from the algorithm should be entered into the eCRF.

4 Data collection

The following titration data from the diary should be entered into the eCRF for all subjects within 24 hours on work days after each scheduled visit/phone contact:

- Per protocol SMPG values
- Date, dose and time point of BIAsp 30 administration
- Hypoglycaemic episodes (Protocol Section 8.4.1)
- Prescribed doses of BIAsp 30
- Reasons for deviations from the titration guideline, if applicable

A reduction of data to be transcribed into the eCRF can be agreed on an individual basis for each subject. This decision will be taken in mutual agreement by the Investigator and Novo Nordisk when only reduced data is used for titration surveillance.

If titration data on a subject is missing then the Investigator will be asked for the reason and will be asked to provide the data, if available.

5 Review procedure

Surveillance of titration data 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/phone contact. The aim is to reduce the time periods in which a subject may receive suboptimal treatment.

The data listed in Section 4 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_{1c} will be monitored by Novo Nordisk for additional surveillance of the glycaemic control. Novo Nordisk may be in contact with sites (visit or phone contact) to discuss progress in glycaemic control and titration of individual subjects based on SMPGs and HbA_{1c}.

6 References

1. Rosenstock J, Davies M, Home PD, Larsen J, Koenen C, Schernthaner 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.

2. 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.

3. 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.

4. Riddle et al. 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.

5. Garber AJ, King AB, Del Prato S, Sreenan S, Balci MK, Muñoz-Torres M, Rosenstock J, Endahl LA, Francisco AM, Hollander P: Insulin degludec, an ultra-long acting 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 Apr 21;379(9825):1498-507.

6. Heller S, Buse J, Fisher M, Garg S, Marre M, Merker L, Renard E, Russell-Jones D, Philotheou A, Francisco AM, Pei H, Bode B: Insulin degludec, an ultra-long acting 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 Apr 21;379(9825):1489-97.

7. Christiansen JS, Vaz JA, Metelko Z, Bogoev M, Dedov I: Twice daily biphasic insulin aspart improves postprandial glycaemic control more effectively than twice daily NPH insulin, with low risk of hypoglycaemia, in patients with type 2 diabetes. *Diabetes Obes Metab* 5:446-454, 2003

8. NovoMix : EPAR - Product Information 2008: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000308/WC500029441.pdf

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 no 1-IN

to Protocol, final version 1.0 dated 17 April 2015

Trial ID:BIAsp-4200

A 24-week, multinational, multicentre, randomised, open label, parallel-group treat-to-target trial to compare efficacy and safety of thrice daily versus twice daily NovoMix® 30 (Biphasic insulin aspart 30) in subjects with type 2 diabetes inadequately controlled with basal insulin

Trial phase: 4

Applicable to India

Amendment originator:

[redacted], [redacted]

Clinical Operations Management Unit 1, India

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1 Introduction including rationale for the protocol amendment

Rationale for Changes

New exclusion criteria has been added based on the below condition of Central Drug Standard Control Organisation (CDSCO), Office of Drugs Controller General (India).

"Subject with impaired Kidney function should be excluded from the study as subjects should be receiving OADs ".

In this protocol amendment:

- Any new text is written *in italics.*
- Any text deleted from the protocol is written using ~~strike through~~.

2 Changes

2.1 Section 6.3 – Exclusion Criteria

14. Any contraindications to BIAsp 30 or metformin according to local label

For India Only

Renal disease or renal dysfunction with serum creatinine levels ≥1.5 mg/dL in males & ≥1.4 mg/dL in females measured at the screening visit will be excluded.