# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

**21-810**

# MEDICAL REVIEW

**MEDICAL TEAM LEADER MEMO**
Completed 21-August-2008

Hylton V. Joffe, M.D., M.M.Sc.

**NDA:** 21-810
**Sponsor:** Novo Nordisk
**Drug:** NovoLog 50/50 Mix
**Indications:** To improve glycemic control in patients with diabetes mellitus
**Primary Medical Reviewers:** Joanna Zawadzki, M.D. and Somya Verma, M.D.

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## I. INTRODUCTION AND BACKGROUND

NovoLog 50/50 mix has been approved in 37 countries and has been launched in 4 countries (France, Italy, Croatia, and the Netherlands). On April 28, 2008, we issued an Approvable letter for marketing in the United States. The only deficiency identified during the last review cycle was potential confusion with other NovoLog products because of an inadequate carton and container coloring scheme for the FlexPen and PenFill presentations. In the letter, we also communicated minor editorial revisions for the Patient Package Insert (PPI) and Instructions for Use Leaflets. The letter also requested that the resubmission contain a safety update from all non-clinical and clinical studies of NovoLog 50/50 in accordance with regulations.

The sponsor submitted a complete response on June 26, 2006. The sponsor submitted revised labels, changing the color from blue to grey and increasing the prominence of the differentiating color bar on the PenFill container labels. The Division of Medication Error Prevention and Analysis (DMEPA) has reviewed these changes and has determined that the sponsor has adequately addressed the deficiency cited in the approvable letter. Please see Ms. Melina Griffis' review for details.

The sponsor accepted all the minor editorial revisions to the PPI and Instructions for Use Leaflets described in our Approvable letter. During the current review cycle, the Office of Surveillance and Epidemiology and our Division requested additional minor edits to these documents (e.g., changed to a better font for the visually impaired, revised some text to be more patient-friendly), all of which were accepted by the sponsor. Please see Dr. Somya Verma's review for a description of these edits.

During this review cycle, there was internal discussion with the Safety Requirements Team (SRT) as to whether the PPI triggers a Medication Guide under Risk Evaluation and Mitigation Strategies (REMS) because of hypoglycemia associated with the use of the product. The SRT determined that a

PPI would be sufficient for this expected risk that is shared with all insulin products and many other anti-diabetic agents. The SRT stated that a Medication Guide under REMS would have been triggered had there been a unique concern related to the product (e.g., excessive hypoglycemia relative to other insulin products), but this is not the case.

The remainder of the submission pertains to the safety update, which is discussed in more detail in the next section and in Dr. Verma's review.

## II. SAFETY UPDATE

The safety update focuses on two clinical trials (Study 1440 and Study 1746) that have been completed since the cut-off date for the previously submitted Summary of Clinical Safety (1-April-2005). Adverse event data from these trials are summarized below. The complete study reports have not yet been submitted.

### STUDY 1440

**1. Study Design:** This was a multi-national, open-label, 3-arm, treat-to-target trial that randomized 599 patients (1:1:1) with type 2 diabetes to 36 weeks of treatment with NovoLog 70/30 twice daily, NovoLog 50/50 three times daily, and NovoLog 30/70 three times daily (which is not FDA approved). If the fasting plasma glucose exceeded 126 mg/dL after 12 weeks of treatment with either NovoLog 50/50 or NovoLog 30/70, the evening injection was switched to NovoLog 70/30. The sponsor did not report in the current submission the number of patients in these 2 treatment groups who required evening NovoLog 70/30.

Inclusion criteria included:
- Type 2 diabetes with HbA1c 7.5-12%
- Treatment with insulin once or twice daily for ≥3 months
- Treatment with metformin 1,000-2,550 mg daily (stable for ≥2 months)

Exclusion criteria included:
- Treatment with thiazolidinediones within the preceding 6 months

**2. Results:**

Deaths: There were a total of 4 deaths. Two deaths occurred during treatment with NovoLog 50/50 (esophageal cancer; intracranial hemorrhage from probable aneurysm in a patient on anticoagulation without another precipitating factor). The other 2 deaths occurred during treatment with 70/30 (myocardial infarction; traffic accident as a passenger). None of these deaths appear to be treatment-related.

Other serious adverse events: There were 8 cases of hypoglycemia (2 cases of hypoglycemia coma and 6 cases of hypoglycemia) reported as serious adverse

events in the NovoLog 30/70 treatment group. There were no reports of hypoglycemia as a serious adverse event in the 2 other treatment groups. Please see Dr. Verma's review of these hypoglycemic events. Dr. Verma notes that there were contributing precipitants for approximately one-half of these events (e.g., small meals or skipping of meals) and notes that many of the episodes occurred within hours of the insulin injection, probably attributable to the larger amount of short-acting insulin received with NovoLog 30/70.

Myocardial ischemic serious adverse events were reported in three NovoLog 70/30 treated patients (1.5%), two NovoLog 50/50 treated patients (1.0%), and three NovoLog 30/70 treated patients (1.5%).

All other reported serious adverse events occurred in 1-2 patients.

Withdrawals due to adverse events: There were 5 withdrawals due to adverse events in the NovoLog 70/30 group (2.5%), 6 in the NovoLog 50/50 group (3.0%), and 6 in the NovoLog 30/70 group (3.0%). Three of the withdrawals were due to hypoglycemia (all occurred in the NovoLog 30/70 group). The other withdrawals are not expected to be due to study medication (e.g., cholecystitis, which occurred in 2 patients, diabetic foot infection, lumbar spinal stenosis).

Other adverse events: Hypoglycemia was a commonly reported adverse event in all 3 treatment groups, as would be expected for any insulin product. The incidence of hypoglycemia (major, minor, diagnosed based only on symptoms, or unclassified) was 76% in the NovoLog 70/30 group, 85% in the NovoLog 50/50 group and 84% in the NovoLog 30/70 group. When adjusted for patient-year exposure, the incidence of hypoglycemia was 13.7 in the NovoLog 70/30 group, 15.8 in the NovoLog 50/50 group, and 21.6 in the NovoLog 30/70 group. The incidence of major hypoglycemia was comparable in the NovoLog 70/30 (n=2 or 1.0%) and 50/50 groups (n=1 or 0.5%) but higher in the NovoLog 30/70 group (n=11 or 5.6%).

The most commonly reported adverse events were nasopharyngitis (12% with NovoLog 50/50 vs. 11-13% in the other 2 treatment groups), headache (9% with NovoLog 50/50 vs. 5-6% in the other 2 treatment groups), diarrhea (6% with NovoLog 50/50 vs. 3-4% in the other 2 treatment groups), and hypertension (6% with NovoLog 50/50 vs. 2% in the other treatment groups). Reports of hypertension are not as reliable as the objective blood pressure data – these data will be reviewed when the complete study report is submitted.

**STUDY 1746**

**1. Study design:** This was a double-blind, randomized, 4-period crossover pharmacokinetic and pharmacodynamic study comparing single, subcutaneous 0.4 U/kg doses of NovoLog 70/30, NovoLog 50/50, NovoLog 30/70, and NovoLog in 32 patients with type 1 diabetes during a euglycemic insulin clamp.

**2. Results:** There were no deaths, serious adverse events, or withdrawals due to adverse events in this trial. There were no hypoglycemic events reported with NovoLog 50/50. The most commonly reported adverse event was headache (reported in 6 subjects during treatment with NovoLog 70/30 and 2 subjects in each of the other treatment periods). All other reported adverse events occurred in no more than 1 subject in any given treatment group.

## III. OTHER REGULATORY REQUIREMENTS

**1. Financial Disclosure:** The sponsor did not include financial disclosure information in this submission.

**2. Pediatrics:** I recommend a full waiver for the requirement for pediatric studies with NovoLog 50/50, which is consistent with our approach used for other insulin mixes.

NovoLog 50/50 does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients and is unlikely to be used in a substantial number of all pediatric age groups. Excellent glycemic control reduces some of the complications of type 1 and type 2 diabetes. However, the fixed ratio of short-acting insulin to long-acting insulin in NovoLog 50/50 limits the ability to achieve tight glycemic control because the short-acting insulin component and long-acting insulin component cannot be titrated individually. Most pediatric patients with diabetes, especially those who are prepubescent, have type 1 diabetes. These patients are typically treated with a long-acting basal insulin and a premeal, rapid-acting insulin analog. In post-pubertal patients with type 2 diabetes primarily linked to childhood obesity, metformin is the preferred anti-diabetic therapy because, unlike insulin, metformin carries a low risk of hypoglycemia and does not cause weight gain.

We have submitted this rationale to the Pediatric Review Committee (PeRC). As of the writing of this memorandum, we are awaiting their recommendations and may be discussing our rationale with PeRC on August 27, 2008.

## IV. CONCLUSIONS AND RECOMMENDATIONS

**1. Conclusions:** The Sponsor has adequately addressed the carton and container labeling deficiency cited in our April approvable letter. A review of the safety update included in the complete response has not identified new safety signals with NovoLog 50/50 mix. The PI, PPI, and Instructions for Use Leaflets are all acceptable. Therefore, the NovoLog 50/50 mix NDA can be approved.

**2. Recommendation:** APPROVAL

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/s/
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Hylton Joffe
8/22/2008 10:40:28 AM
MEDICAL OFFICER

Mary Parks
8/23/2008 09:42:39 AM
MEDICAL OFFICER

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On Original

**DIVISION OF METABOLISM AND ENDOCRINOLOGY PRODUCTS**
**SAFETY TEAM**
**MEMO TO THE FILE**

**NDA/Submission #/Submission type:** 21-810/000/AZ

**Product Name:** NovoLog® Mix 50/50 (50% insulin aspart protamine suspension and 50% insulin aspart injection, [rDNA origin])

**Application submission date:** 26 June 2008

**Safety team reviewer:** Amy G. Egan, M.D., M.P.H.

**Safety review completion date:** 05 August 2008

**PDUFA date:** 26 August 2008

**Reason for Review:** New PPI

**Items Reviewed:** NovoLog® PPI

**Synopsis of Findings:** The PPI contains language that is standard to other insulin PPIs, including allergic reactions, conditions altering insulin requirements, and extensive language regarding hypoglycemia and hyperglycemia.

**Determination:**

**REMS triggered: Y N I**

**If yes (Y) or indeterminate (I), was submission referred to the SRT?: Y N**

**Date submitted:** 05 August 2008
**Date response received:** 20 August 2008
**SRT response:** Concurrence – no need for MedGuide or REMS

**If no (N), why not?:** N.A.

**If no (N), please check one (or more) of the following reasons below:**

**_____ No new safety issue identified**

**_____Only editorial changes made**

**_____Changes pertain only to proper use of a device**

__X__ **Other:** Clearly one of the most serious risks associated with the use of insulin products is the risk of hypoglycemia. PIs and PPIs for other approved insulin products carry extensive language regarding this potential adverse reaction. Undoubtedly this information is to ensure that the benefit of taking insulin products outweighs the risk. This risk is well-known to patients and clinicians alike.

If we are to take the stance that this product's PPI triggers a REMS, then are we not obligated to mandate that all of the PPIs for insulin products constitute REMS, or more importantly, given the serious nature of this risk and its inclusion in both the Warnings (bolded) and Precautions sections of the PI, shouldn't all PPIs for insulin products be converted to MedGuides?

Realistically, this is an issue that requires further review and discussion, by both DMEP and OSE. It is the opinion of this Safety Reviewer that until it can be ascertained that it is necessary to ensure the safe use of insulin products that they all employ a MedGuide as part of a REMS that the current PPIs under review not be held to such a standard.

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/s/
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Amy Egan
8/21/2008 09:00:32 AM
MEDICAL OFFICER

Mary Parks
8/21/2008 09:46:18 PM
MEDICAL OFFICER

# CLINICAL REVIEW

| | |
|---|---|
| Application Type | NDA |
| Submission Number | 21-810 |
| Submission Code | N0006 |
| Letter Date | June 26, 2008 |
| Stamp Date | June 26, 2008 |
| PDUFA Goal Date | August 26, 2008 |
| Reviewer Name | Somya Verma, M.D. |
| Review Completion Date | August 19, 2008 |
| Established Name | Biphasic Insulin Aspart 50 |
| (Proposed) Trade Name | NovoLog 50/50 Mix® |
| Therapeutic Class | Insulin |
| Applicant | Novo Nordisk |
| Priority Designation | S |
| Formulation | 50% soluble insulin aspart and 50% protamine co-crystallized insulin aspart |
| Dosing Regimen | Subcutaneous; titrated based on clinical response |
| Indication | To improve glycemic control |
| Intended Population | Patients with diabetes mellitus |

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# 1 EXECUTIVE SUMMARY

## 1.1 Recommendation on Regulatory Action

I recommend approval of NovoLog Mix 50/50. My review of the safety update that was submitted did not uncover any new or unusual risks that would indicate that this drug poses heightened risk for its drug category. The conditions placed on the Applicant for carton labeling changes prior to approval were met according to documentation from the Office of Surveillance and Epidemiology (OSE).

## 1.2 Recommendation on Postmarketing Actions

None

1.2.1 Risk Management Activity

None

1.2.2 Required Phase 4 Commitments

None

1.2.3 Other Phase 4 Requests

We are waiving requirements under Pediatric Research and Equity Act (PREA) for pediatric studies for NovoLog Mix 50/50 because the product fails to represent a meaningful therapeutic benefit over existing therapies for pediatric patients **and** is unlikely to be used in a substantial number of all pediatric age groups or the pediatric age group(s) for which a waiver is being requested. We have previously waived pediatric requirements for the other insulin mixes; therefore, the current decision is consistent with our prior approach to insulin mixes.

## 1.3 Summary of Clinical Findings

The only new clinical information was submitted in the Safety Information Update. There was a 36-week randomized controlled trial and a small pharmacokinetic (PK)/pharmacodynamic (PD) study.

1.3.1 Brief Overview of Clinical Program

Summary results from two studies are reported, Trial BIAsp-1440 and Trial BIAsp-1746. 1440 was a randomized, open-label parallel group treat-to-target trial in 599 subjects with type 2 diabetes mellitus (DM). There were three treatment arms, one group receiving NovoLog 30/70 mix (known as BIAsp 70 in Europe) three times a day, another group receiving NovoLog 50/50 mix (BIAsp 50) three times a day, and the third group receiving NovoLog 70/30 mix (BIAsp 30) twice a day. 1746 was a double-blind, randomized, four period cross over trial comparing the PK and PD after a single dose of BIAsp 30, BIAsp 50, BIAsp 70 and insulin aspart (IAsp) in patients with Type 1 DM.

1.3.2 Efficacy

Only safety data were presented in the safety update.

1.3.3 Safety

In Trial 1440, there were a total of 4 deaths. The 2 deaths that occurred in the NovoLog 50/50 group (esophageal cancer and intracranial hemorrhage) do not appear to be treatment-related. Each of the reported serious adverse events typically occurred in only 1-2 patients, except for 6 cases of serious hypoglycemia among the NovoLog 30/70 treated patients (there were no cases of serious hypoglycemia among the NovoLog 50/50 or 70/30 treated patients). Hypoglycemia was a commonly reported adverse event in all 3 treatment groups, as would be expected for any insulin product. The incidence of minor hypoglycemia was 64% in the NovoLog 70/30 group, 79% in the NovoLog 50/50 group and 75% in the NovoLog 30/70 group. When adjusted for patient-year exposure, the incidence of minor hypoglycemia was 7.9 in the 70/30 group, 9.3 in the 50/50 group, and 13.3 in the 30/70 group.

In Trial 1746, there were no reported deaths, serious adverse events, or withdrawals due to adverse events. None of the NovoLog 50/50 treated patients in Trial 1746 reported hypoglycemia. Headache was the only adverse event reported by more than 1 patient in any given treatment group.

The safety update did not include analyses of laboratory data or vital sign data.

In summary, pertinent safety findings from the review of adverse events in Trials 1440 and 1746 do not change the risk-benefit profile of NovoLog 50/50 as determined prior to issuance of the Approvable Letter.

1.3.4 Dosing Regimen and Administration

As with all insulins, patients should be titrated based on blood glucose measurements and HbA1c to achieved glucose control as close to the ideal range as possible.

1.3.5 Drug-Drug Interactions

This submission does include new data on drug-drug interactions.

1.3.6 Special Populations

As with all insulin products, lower doses of this product may be needed in patients with liver or renal impairment.

## 2 INTRODUCTION AND BACKGROUND

NDA 21-810 for BIAsp 50 or NovoLog Mix 50/50 received an Approvable action on April 28, because of deficiencies related to the carton labels. The specific request was that the color scheme of NovoLog Mix 50/50 be changed to be more distinct from the already U.S. marketed NovoLog 70/30 to reduce the likelihood of medication errors. The Applicant resubmitted carton and container labeling changes on June 26, 2008 along with accepted minor changes to the Patient Package Insert, Flex Pen Instructions for Use and PenFill Instructions. In addition, they had completed two trials since the original NDA submission and submitted a safety update containing data from these two studies, Trial BIAsp-1440 and Trial BIAsp-1746. As mentioned above, Study 1440 had three treatment arms, one group receiving BIAsp 70 (NovoLog 30/70 mix or biphasic insulin aspart 70—70% soluble insulin aspart, 30% protamine cocrystallized insulin aspart) three times a day, another group receiving BIAsp 50 (NovoLog 50/50 mix or biphasic insulin aspart—50% soluble insulin aspart, and 50% protamine cocrystallized insulin aspart) three times a day, and the third group receiving BIAsp 30 (NovoLog 70/30 mix or biphasic insulin aspart—30% soluble insulin aspart and 70% protamine cocrystallized insulin aspart) twice a day. 1746 was a double-blind, randomized, four period cross over trial comparing PK and PD after a single dose of BIAsp 30, BIAsp 50, BIAsp 70 and insulin aspart (IAsp) in patients with Type 1 DM.
The purpose of this review was to evaluate the submitted safety update and data in detail and ensure BIAsp 50 did not present with any new safety issues.

## 3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

### 3.1 CMC (and Product Microbiology, if Applicable)

The safety update did not include new CMC data.

### 3.2 Animal Pharmacology/Toxicology

The safety update did not include new pharmacology/toxicology data.

## 4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

### 4.1 Sources of Clinical Data

All clinical data reviewed came from Trial BIAsp-1440 and Trial BIAsp-1746. 1440 predominantly was a study for safety in patients with Type 2 DM using the new insulin mix, BIAsp 50. The other trial medication, BIAsp 30 had already been not approved by FDA. 1746 focused on PK and PD data of these drugs.

### 4.2 Tables of Clinical Studies

**Table 1 Table of Trial population and design for both 1440 and 1746**

| | Trial 1440 | Trial 1746 |
|---|---|---|
| **Patient Population** | Type 2 DM, 599 subjects—male and female | Type 1 DM, 32 subjects—male and female |
| **Study Design** | Randomized, stratified, open label, parallel group | Double-Blind, randomized, four period crossover |
| **Main Objectives** | Glycemic Control (HbA1c) | PK and PD after single dosing |
| **Treatment Duration** | 36 weeks | Single doses administered at four different occasions at intervals of 7-14 days |

### 4.3 Review Strategy

The safety report, tables and patient narratives were all read and evaluated in detail.

### 4.4 Data Quality and Integrity

Most relevant data appears to have been submitted for both studies in terms of safety.

### 4.5 Compliance with Good Clinical Practices

These studies appear to have been conducted in compliance with Good Clinical Practices (e.g., informed consent, oversight by investigational review boards or equivalent organizations)

### 4.6 Financial Disclosures

These disclosures were not included in the safety update, but are expected to be included in the complete study reports, which will be submitted at a later date.

## 6 INTEGRATED REVIEW OF EFFICACY

### 6.1 Indication

6.1.1 Methods

1440

The stated objective of Study 1440 was to compare 36 weeks of treatment of twice daily biphasic insulin aspart 30 (BIAsp 30) to three times a day BIAsp 50 and three times a day BIAsp 70. The submitted document defines BIAsp 30 as 30% soluble insulin aspart and 70% protamine co-crystallized insulin aspart (known as NovoLog 70/30 mix in the United States)—in other words,

short acting form followed by long acting form. This vernacular is also true for the BIAsp 70 (70% short acting and 30% long acting). This review will refer to the experimental group (taking BIAsp 50 three times a day) as the 50-50-50 group. The "control" group was given the already approved and marketed BIAsp 30 twice a day; this treatment is referred to as 30-30. The group given BIAsp 70, another experimental formulation, three times a day will be referred to as 70-70-70. This formulation was not approved by FDA ——— However, some of this data will still be covered in this review. All regimens were combined with metformin therapy. For further details of the treatment arms, please see section 6.1.3.

b(4)

**1746**

The stated objective of Study 1746 was to compare the pharmacokinetics and pharmacodynamics of 0.4 U/kg BIAsp 30, 0.4 U/kg BIAsp 50, 0.4 U/kg BIAsp 70 and 0.4 U/kg IAsp (aspart) in patients with Type I DM.

6.1.2. General Discussion of Endpoint

**1140**

The main objective is stated as "glycemic control" indicated by HBA1c, which is the usual endpoint for trials of anti-diabetic therapies. Safety is also listed as a secondary objective.

**1746**

The main objective is stated as pharmacokinetics (PK) and pharmacodynamics (PD) along with safety.

6.1.3 Study Design

**1440**

Trial BIAsp-1440 was a randomized, open-label parallel group treat-to-target trial in 599 subjects with type 2 DM.
Patients were stratified according to whether they were treated with once or twice daily insulin prior to randomization. The document also states patients were stratified on whether or not they were on oral treatments—this contradicts the inclusion criteria which stated patients must be on an oral agent—metformin.
A predefined algorithm was used to titrate insulin doses to achieve premeal glucose levels of 79-110 mg/dL.
There were three treatment arms, one group receiving BIAsp 70 three times a day, another group receiving BIAsp 50 three times a day, and the third group receiving BIAsp 30 twice a day. After 12 weeks, if patients did not have pre breakfast glucoses of less than or equal to 127 mg/dL, dinner injection was changed to BIAsp 30 (in the tid groups). However, the number of patients

that were switched to BIAsp 30 in the evening was not given. Number of patients achieving desired goals in each group was also not given.
Main inclusion criteria included a diagnosis of type 2 DM, current treatment with human or insulin analog once or twice daily for at least 3 months, current treatment with metformin, HbA1c $\geq$ 7.5% and $\leq$ 12 %, and total daily insulin less than 1/8 U/kg of body weight. Patients that had been treated with thiazolidinediones within 6 months prior to randomization were excluded from the study.
Design of the trial is summarized in Table 2:

**Table 2**
**Design of Trial BIAsp 1440**

| Trial | Treatment[a] Duration | Dose | Trial Design | Main Objectives | Subjects Planned | Subjects Exposed |
|---|---|---|---|---|---|---|
| **Long-term Trial** | | | | | | |
| BIAsp -1440 | BIAsp 70+70+70 (30)[b] or BIAsp 50+50+50 (30)[b] BIAsp 30 b.i.d. Metformin in all regimens<br><br>36 weeks | Individual dosing | Randomised, stratified, open-label, parallel group trial | Glycemic control ($HbA_{1c}$) Safety | Type 2 600 male or female | Type 2 599 |

a. BIAsp xx+xx+xx: biphasic insulin aspart (BIAsp) in which xx denotes the BIAsp dosing form injected for breakfast, lunch and dinner.
b. Subjects on t.i.d. BIAsp 70 and t.i.d. BIAsp 50 were to switch to BIAsp 30 at dinner if pre-breakfast plasma glucose > 7.0 mmol/L after 12 weeks of treatment.

**Taken from Applicant's Table 1**

**1746**

This was a double-blind, randomized, four period cross over trial comparing PK and PD after a single dose of BIAsp 30, BIAsp 50, BIAsp 70 and insulin aspart (IAsp) in patients with Type 1 DM. Patients were randomized to one of eight treatment sequences at four different dosing visits There was a 7-14 day washout period between visits. Prior to each visit, patients received an IV infusion of glucose and human soluble insulin for 4-6 hours (glucose clamp) prior to trial drug to keep the blood glucose level stable at 90 mg/dL. This was terminated 12 hours post dose for IAsp, and 28 hours post dose for trial medications. It was terminated earlier if blood glucose levels were greater than 160 mg/dL.
Design of this trial is summarized in Table 3.

**Table 3**
**Design of PK/PD Trial BIAsp 1746**

| Trial | Treatment Duration | Dose | Trial Design | Main Objectives | Subjects Planned | Subjects Exposed |
|---|---|---|---|---|---|---|
| BIAsp -1746 | Four single doses of BIAsp 30, BIAsp 50, BIAsp 70 and IAsp, respectively, administered at four different occasions at intervals of 7-14 days. | PK and PD after single dosing | Double-Blind, Randomised, Four-Period Crossover Trial | PK and PD, Safety | Type 1 32 male or female | Type 1 32 |

**Taken from Applicant's Table 2**

6.1.4 Efficacy Findings

Not submitted for either 1440 or 1746.

6.1.5 Clinical Microbiology

None submitted for either study; not applicable.

6.1.6 Efficacy Conclusions

Not able to comment on due to lack of information.

## 7 INTEGRATED REVIEW OF SAFETY

### 7.1 Methods and Findings

**1440**

Table 4 below summarizes patient disposition for Study 1440. Most patients (~97%) completed the trial. Seven patients discontinued prematurely, but the Sponsor did not provide reasons for their discontinuation (except if the withdrawal was due to adverse events – see Section 7.1.3.1).

**Table 4 Subject Enrollment 1440**

| | 30 bid | 50-50-50 | 70-70-70 |
|---|---|---|---|
| **Total # Enrolled** | 200 | 201 | 198 |
| **Total # Completed** | 195 (97.5%) | 195 (97.0%) | 192 (97.0%) |
| **Total # Discontinued** | 5 | 6 | 6 |

b(4)

**1746**

Subject Enrollment in 1746 consisted of 32 patients per each of the four arms of the study. All patients appeared to have completed the study.

7.1.1 Deaths

**1440**

There were a total of four deaths during this trial. Two occurred in the 50-50-50 group and were due to esophageal cancer and intracranial hemorrhage.
The patient that was reported to have the intracranial hemorrhage (3453) was an 83 year old man with a history of hypertension and hypercholesterolemia. The hemorrhage is described as due to a "probable aneurysm rupture favoured by anticoagulant therapy." There is no indication of preceding fall, loss of balance or other accident that could indicate the event could be related to hypoglycemia. The other two events occurred during treatment in the 30-30 group and causes were myocardial infarction and motor vehicle accident. In the case of myocardial infarction, the patient had several risk factors, including hypertension, hypercholesterolemia and hypertrophic cardiomyopathy. In the case of the vehicle accident, the patient was a passenger. No deaths occurred in the 70-70-70 group. b(4)

**Reviewers Comments**
There were no reported deaths that appear related to hypoglycemia. All deaths reported appear unrelated to trial medication.

**1746**

No deaths occurred during the course of this trial.

7.1.2 Other Serious Adverse Events

**1440**

There were a total of 60 serious adverse events. Cardiac, nervous system and metabolism and nutrition disorders were the most frequently reported. Further breakdown of these events is reviewed in Table 5

## Table 5
## Serious TEAEs In Order of Descending Frequency of System Organ Class and MedDRA Preferred Term—Trial 1440

| | BIAsp 30-30 N | (%) | E | BIAsp 50-50-50(30) N | (%) | E | BIAsp 70-70-70(30) N | (%) | E |
|---|---|---|---|---|---|---|---|---|---|
| Number of Subjects in ITT | 200 | | | 201 | | | 198 | | |
| Adverse Events | 18 | (9.0) | 19 | 14 | (7.0) | 17 | 22 | (11.1) | 24 |
| Cardiac disorders | 4 | (2.0) | 4 | 2 | (1.0) | 2 | 3 | (1.5) | 3 |
| Myocardial infarction | 2 | (1.0) | 2 | 1 | (0.5) | 1 | 1 | (0.5) | 1 |
| Angina pectoris | | | | | | | 1 | (0.5) | 1 |
| Angina unstable | | | | 1 | (0.5) | 1 | | | |
| Brugada syndrome | 1 | (0.5) | 1 | | | | | | |
| Coronary artery disease | | | | | | | 1 | (0.5) | 1 |
| Myocardial ischaemia | 1 | (0.5) | 1 | | | | | | |
| Nervous system disorders | 1 | (0.5) | 1 | 4 | (2.0) | 5 | 3 | (1.5) | 3 |
| Hypoglycaemic coma | | | | | | | 2 | (1.0) | 2 |
| Carpal tunnel syndrome | 1 | (0.5) | 1 | | | | | | |
| Cerebrovascular accident | | | | 1 | (0.5) | 1 | | | |
| Dizziness | | | | 1 | (0.5) | 1 | | | |
| Intraventricular haemorrhage | | | | 1 | (0.5) | 1 | | | |
| Syncope | | | | 1 | (0.5) | 1 | | | |
| Transient ischaemic attack | | | | | | | 1 | (0.5) | 1 |
| Vertebrobasilar insufficiency | | | | 1 | (0.5) | 1 | | | |
| Metabolism and nutrition disorders | | | | | | | 6 | (3.0) | 7 |
| Hypoglycaemia | | | | | | | 6 | (3.0) | 7 |
| Gastrointestinal disorders | 1 | (0.5) | 1 | 3 | (1.5) | 3 | | | |
| Constipation | | | | 1 | (0.5) | 1 | | | |
| Gastritis | | | | 1 | (0.5) | 1 | | | |
| Pancreatitis acute | 1 | (0.5) | 1 | | | | | | |
| Volvulus | | | | 1 | (0.5) | 1 | | | |
| Infections and infestations | 2 | (1.0) | 2 | | | | 2 | (1.0) | 2 |
| Diabetic foot infection | 1 | (0.5) | 1 | | | | | | |
| Gastroenteritis | 1 | (0.5) | 1 | | | | | | |
| Otitis media | | | | | | | 1 | (0.5) | 1 |
| Respiratory tract infection viral | | | | | | | 1 | (0.5) | 1 |
| Injury, poisoning and procedural complications | 1 | (0.5) | 1 | 1 | (0.5) | 1 | 2 | (1.0) | 2 |
| Complication of device insertion | | | | | | | 1 | (0.5) | 1 |
| Meniscus lesion | | | | | | | 1 | (0.5) | 1 |
| Road traffic accident | 1 | (0.5) | 1 | | | | | | |
| Spinal fracture | | | | 1 | (0.5) | 1 | | | |
| Musculoskeletal and connective tissue disorders | 1 | (0.5) | 1 | | | | 3 | (1.5) | 3 |
| Ostecarthritis | | | | | | | 2 | (1.0) | 2 |
| Lumbar spinal stenosis | | | | | | | 1 | (0.5) | 1 |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Tendonitis | 1 | (0.5) | 1 | | | | | | |
| Respiratory, thoracic and mediastinal disorders | 1 | (0.5) | 1 | 2 | (1.0) | 2 | 1 | (0.5) | 1 |
| Chronic obstructive pulmonary disease | 1 | (0.5) | 1 | | | | | | |
| Dyspnoea | | | | | | | 1 | (0.5) | 1 |
| Hyperventilation | | | | 1 | (0.5) | 1 | | | |
| Pulmonary embolism | | | | 1 | (0.5) | 1 | | | |
| Vascular disorders | 3 | (1.5) | 3 | | | | | | |
| Arterial thrombosis limb | 1 | (0.5) | 1 | | | | | | |
| Hypertension | 1 | (0.5) | 1 | | | | | | |
| Macroangiopathy | 1 | (0.5) | 1 | | | | | | |
| Eye disorders | 2 | (1.0) | 2 | | | | | | |
| Diabetic retinopathy | 1 | (0.5) | 1 | | | | | | |
| Retinal vascular thrombosis | 1 | (0.5) | 1 | | | | | | |
| Hepatobiliary disorders | | | | 2 | (1.0) | 2 | | | |
| Cholecystitis | | | | 1 | (0.5) | 1 | | | |
| Cholecystitis acute | | | | 1 | (0.5) | 1 | | | |
| Investigations | 1 | (0.5) | 1 | | | | 1 | (0.5) | 1 |
| International normalised ratio fluctuation | | | | | | | 1 | (0.5) | 1 |
| Weight increased | 1 | (0.5) | 1 | | | | | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | | 1 | (0.5) | 1 | 1 | (0.5) | 1 |
| Oesophageal carcinoma | | | | 1 | (0.5) | 1 | | | |
| Rectal cancer | | | | | | | 1 | (0.5) | 1 |
| Ear and labyrinth disorders | | | | 1 | (0.5) | 1 | | | |
| Vertigo | | | | 1 | (0.5) | 1 | | | |
| Renal and urinary disorders | 1 | (0.5) | 1 | | | | | | |
| Renal impairment | 1 | (0.5) | 1 | | | | | | |
| Reproductive system and breast disorders | | | | | | | 1 | (0.5) | 1 |
| Metrorrhagia | | | | | | | 1 | (0.5) | 1 |
| Skin and subcutaneous tissue disorders | 1 | (0.5) | 1 | | | | | | |
| Eczema | 1 | (0.5) | 1 | | | | | | |

N: Number of subjects with adverse event
%: Proportion of subjects in analysis set having adverse event
E: Number of adverse events

**Taken from Applicant's Table 13**

**Cardiac disorders:**

The incidence of cardiac disorders in the 50-50-50 group was 1% compared to 2% in the 30-30 group. The other treatment arm, 70-70-70, had an incidence of 1.5%. In the 50-50-50 group, the actual number of subjects and events was 2 compared to 4 in the 30-30 group. In the breakdown of these events, myocardial infarction is the most common event occurring in 1 subject in the 50-50-50 group and 2 events/subjects in the 30-30 group. All patients with cardiac disorders were age 50 or older, had a history of coronary artery disease, ischemic heart disease, or at high risk for cardiac events (hypertension and/or hypercholesterolemia).

**Reviewer's comments**

The rate of cardiac events is low across all arms of the study. BIAsp 50 does not appear to pose an increased risk for cardiac events when compared to the other groups.

**Nervous system disorders:**

Nervous system disorders of special interest include cerebrovascular accident and transient ischemic attack in terms of relation to cardiovascular health. One episode of each event was

reported - CVA in the 70-70-70 group and TIA occurred in the 50-50-50 group. The incidence for each was 0.5% for each respectively. Each subject was over 50 years of age.

Two other nervous system events that are of interest are the intraventricular hemorrhage (IVH) and vertebrobasilar insufficiency. The IVH event is described in section 7.1.1. The patient was an 83 year old man in the 50-50-50 group with no apparent preceding injury due to hypoglycemia. The patient that had vertebrobasilar insufficiency was also in the 50-50-50 group. This was a 66 year old female (1068) with a history of vertigo and hypertension that was described as having instability of gait and bilious vomiting. She reportedly did not have abdominal pain. Head CT and ECG were both normal. No blood glucose level or preceding insulin dose is reported. The patient was hospitalized for 5 days and remained on her usual doses of trial medications throughout.

Also of special interest are the hypoglycemia related nervous system events. Two hypoglycemic comas occurred in the 70-70-70 group with an incidence of 1%. None were reported in the other two groups. Each is reviewed in detail below.

One of the patients was a 62 year old woman. The hypoglycemia occurred at 21:15 with glucose level of 27 mg/dL. The patient became unconscious and paramedics were called and administered IV dextrose. The patient's last dose of insulin was at 18:30 and was followed by a meal. No details on the dose was given although the patient was noted to have no new diet or physical activity changes. Trial drugs were discontinued the next day. Recovery was documented for the same day but subsequent blood sugar level or need for hospitalization were not documented.

The other patient that suffered a hypoglycemic coma was a 56 year old male. This patient is recorded as having administered 70 units and 74 units as a pre dinner dose—this is not clear. He had dinner and then fell asleep but could not be awakened. Blood sugar at admission to the hospital was 48 mg/dL. The patient was given a glucose infusion. The patient was considered recovered the next day. He has an extensive history of hypoglycemic events. Three days later he withdrew himself from this study.
Other hypoglycemic events will be discussed in the next section.

Another episode that could be related to hypoglycemia was a syncope episode that occurred in a 78 year old woman in the morning. Neither her evening nor morning dosing are reported. The subject was riding the bus at the time and the incident resolved itself. A pre lunch glucose was reported elevated at 232 mg/dL; however, no glucose from the time around the event itself is reported.

A patient with dizziness was also reported in the nervous system group. The subject was an 83 year old man. He was hospitalized twice for dizziness episodes about 2 weeks apart—although this was recorded as only one event. No glucose levels were reported for either hospitalization. This subject, 3453, was discontinued from the trial two months later due to intraventricular hemorrhage.

**Reviewer's Comments**
Adverse Event Report narratives were used to obtain more detailed information about the SAEs. Overall, the trial medication, BIAsp 50 does not appear to increase risk for cardiovascular related nervous system events.
Both reported episodes of hypoglycemic coma do not have clear etiology. However, hypoglycemia is a known, common side effect of insulin therapy. There are no such episodes in the trial medication group (50-50-50).
The other nervous system disorders that could be related to hypoglycemia are also unclear in terms of etiology. Due to lack of data reported, hypoglycemia cannot be ruled out as a cause; however it does seem unlikely in the woman who had glucose level of 232 mg/dL pre lunch. Both of these patients received 50-50-50.
Other adverse events reported in the table are not summarized or commented on due to lack of suspected relation to study or trial drug and very low event rates.

**Injury, poisoning and procedural complications**
This category is also of special interest as these complications could be due hypoglycemic events.

Patient 1095 was a 66 year old man in the 70-70-70 group who was reported to have a complication of device insertion. The narrative describes a wire defect in the patient's defibrillator that was changed during the course of the study. This defect was found on routine device check.

Patient 3144 was a 70 year old woman with a medical history of rheumatism that was seen for right knee pain while on the 70-70-70 arm of the study. There is no preceding accident of any sort reported. The patient was diagnosed with chronic meniscus damage of the right knee and subsequently underwent knee surgery approximately two months later.

A description of patient 3346 who died as a passenger from a motor vehicle accident was given in the prior section.

Patient 3224 was a 59 year old woman in the 50-50-50 treatment group who experienced a spinal fracture. The patient experienced back pain following a car accident in which she was a passenger. Several months later, she underwent MRI and was found to have a vertebral corpus fracture. No other preceding accident, such as a fall, was reported.

**Reviewer's Comments**
In reviewing the narratives of all patients from this category under SAEs, none appear to be due to hypoglycemia and/or due to trial medication.

**Metabolism and Nutrition Disorders**
The only SAE listed here is hypoglycemia of which all seven episodes in six patients occurred in the 70-70-70 group.
A brief summary of each event follows:

Patient 95803, a 62 year old female, reportedly had blood glucose of 18 mg/dL at 1645. Paramedics were called and administered glucagon. The patient had last dose of insulin (dose not given) at 1630 followed by a meal at 1635. No dietary or physical activity changes were noted.

Patient 40304 a 64 year old male, injected 48 units of BIAsp 70 at 1100 hours and then did not have breakfast. He felt weak at 1200 and called an ambulance. The patient was hospitalized for three hours, given glucose infusions and recovered.

Patient 3427 was a 65 year old female who injected 57 units of BIAsp 70 at 1500 and had a glucose level of 28 mg/dL. She reportedly had a small lunch. She did experience a short loss of consciousness and was treated with glucose infusion.

Patient 1440 was a 79 year old female who took an insulin dose at 1400 (not reported) and had limited physical activity that day due to vertigo. At 1600 the patient was hospitalized due to blurred vision, vertigo, weakness, and clouded consciousness. Her blood glucose at the time was 36 mg/dL. She was discharged 11 days later. The patient had a hypoglycemic episode a few months later at a level of 49 mg/dL. She was discontinued from the trial a few months later due to noncompliance.

Patient 3140 was a 67 year old man. He reportedly took insulin (dose not given) and fell asleep without eating. Three hours later, he was unarousable by a friend and blood glucose was 28 mg/dL. He was treated with IV glucose that day and recovered. Three days later in a similar episode, the same patient administered insulin and then ate less than a normal amount of food. He was hospitalized with a blood glucose of 36 mg/dL, although symptoms are not described.

Patient 3287 was a 69 year old female. She took insulin at 1905 and experienced blood glucose of 24 mg/dL at 2330. There were no changes to diet or physical activity. Paramedics were called and gave a glucose infusion.

**Reviewer's comments**
Data recording is inconsistent in terms of dosing, insulin formulation (there is no record or submission of which patients were taking BIAsp 30 at night although we know this was an option from the design study), symptoms, and need for hospitalization. In addition, the distinction between the comas reported in the nervous system section and the events in this section that led to loss of consciousness is not entirely clear.
However, in reviewing all serious events of hypoglycemia, four of the seven events are reported with some suspected patient contribution to the event with either small meals or skipping of meals after administration of insulin. All events took place within the 70-70-70 group indicating that perhaps this form of insulin with larger amount of short acting insulin poses more of a risk to patients within the first few hours following the dose. However, in the case of nighttime or evening events (Pts 3140 and 3287), it is not stated if they took the BIAsp 30 mix in the evening, which we know is an option in the protocol.

The BIAsp 50 mix overall appears to be acceptable with no serious adverse events of hypoglycemia reported in patients on this formulation.

**1746**

No SAEs reportedly took place during this study.

7.1.3 Dropouts and Other Significant Adverse Events

7.1.3.1 Overall profile of dropouts

**1440**

Only withdrawals related to AEs are documented. In the 50-50-50 treatment group, six subjects were withdrawn due to AEs. None were reported as due to hypoglycemia. As mentioned in the SAE section, there was as syncope episode that does not report the glucose level—this patient was recorded as a withdrawal. Three withdrawals that are listed are likely related to study drug and were in the 70-70-70 group. These were all hypoglycemia related and two were listed as hypoglycemic comas. The control group, 30-30, had five withdrawals. More details on drop out patients are to follow.
No patients were reported as treatment failure or lost to follow up.

**1746**

There were no withdrawals due to AEs in this study. No other types of withdrawals are noted in the submission.

7.1.3.2 Adverse events associated with dropouts

**1440**

In treatment group 50-50-50, two subjects that were withdrawn suffered from cholecystitis, the other four had esophageal carcinoma, intraventricular hemorrhage, syncope, and myocardial infarction. The syncope episode does not report blood glucose level around the time of the event as mentioned in section 7.1.2 under Nervous System Disorders. In addition, the intraventricular hemorrhage was not due to a fall or other type of accident. Overall, the drop out rate was 3%.
The 70-70-70 group reports six drop outs. In this group, at least four appear related to medication as they are resulting from hypoglycemic events. The overall drop out rate was 3% with likely study related withdrawals being 2%.
There were five withdrawals in the 30-30 group, none appear related to the study. There were two fatalities and three SAEs. The patient that died in a road traffic accident was a passenger in the car. The SAEs (renal impairment, foot infection and leg thrombosis) occurred only once during the study. None have apparent relation to study drug, although they could result as diabetic complications. The rate of withdrawal was 2.5%.
Details of all withdrawals are summarized in Table 6.

## Table 6
## Subjects with Adverse Events that Leading to Withdrawal—Trial 1440

| Subject ID | Days Since Start of Treatment | System Organ Class/ MedDRA Preferred Term/ MedDRA Lowest Level Term | Onset Date | Serious Severity | Outcome | Relation to Trial Drug | Changes to Trial Drug |
|---|---|---|---|---|---|---|---|
| Treatment: BIAsp 30-30 | | | | | | | |
| 15005 | 132 | Renal and urinary disorders/ Renal impairment/ Renal function aggravated | 06SEP2005 | yes Moderate | Not recovered | Unlikely | Product withdrawn |
| 30101 | 199 | Infections and infestations/ Diabetic foot infection | 25NOV2005 | yes Severe | Recovered | Unlikely with sequelae | Product withdrawn |
| 35104 | 26 | Vascular disorders/ Arterial thrombosis limb/ Thrombosis arterial leg | 25JUN2005 | yes Severe | Recovered | Unlikely | Product withdrawn |
| 55305 | 250 | Cardiac disorders/ Myocardial infarction | 04FEB2006 | yes Severe | Fatal | Unlikely | Dose not changed |
| 55611 | 131 | Injury, poisoning and procedural complications/ Road traffic accident | 08OCT2005 | yes Severe | Fatal | Unlikely | Dose not changed |
| Treatment: 50-50-50(30) | | | | | | | |
| 10109 | 129 | Hepatobiliary disorders/ Cholecystitis | 05SEP2005 | yes Severe | Recovered | Unlikely | Product withdrawn |
| 15302 | 30 | Neoplasms benign, malignant and unspecified (incl cysts ps) Oesophageal carcinoma | 26MAY2005 | yes Severe | Fatal | Unlikely | Product withdrawn |
| 35117 | 165 | Nervous system disorders/ Intraventricular haemorrhage | 28NOV2005 | yes Severe | Fatal | Unlikely | Product withdrawn |
| 50209 | 28 | Nervous system disorders/ Syncope | 07JUL2005 | yes Severe | Recovered | Unlikely | Product withdrawn |
| 55511 | 230 | Cardiac disorders/ Myocardial infarction/ | 24JAN2006 | yes Severe | Recovered | Unlikely | Product withdrawn |
| 55601 | 167 | Hepatobiliary disorders/ Cholecystitis acute/ Acute cholecystitis | 06NOV2005 | yes Severe | Recovered | Unlikely | Product withdrawn |
| Treatment: 70-70-70(30) | | | | | | | |
| 10201 | 170 | Investigations/ Alanine aminotransferase increased/ GPT increased | 13OCT2005 | no Moderate | Recovered | Unlikely | Product withdrawn |
| 41301 | 97 | Musculoskeletal and connective connective Lumbar spinal stenosis | 01AUG2005 | yes Moderate | Recovering | Unlikely | Dose not changed |
| 50403 | 13 | Nervous system disorders/ Transient ischaemic attack | 23MAY2005 | yes Mild | Recovered | Unlikely | Product withdrawn |
| 95701 | 86 | Eye disorders/ Abnormal sensation in eye/ Sensation of pressure in eye | 28JUL2005 | no Moderate | Recovered | Unlikely | Product withdrawn |
| 95803 | 29 | Metabolism and nutrition disorders/ Hypoglycaemia/ Hypoglycaemic episode | 01JUN2005 | yes Severe | Recovered | Probable | Dose reduced |
| 95803 | 48 | Nervous system disorders/ Hypoglycaemic coma/ Hypoglycaemic coma | 20JUN2005 | yes Severe | Recovered | Probable | Product withdrawn |
| 90010 | 218 | Nervous system disorders/ Hypoglycaemic coma/ | 26JAN2006 | yes Severe | Recovered | Probable | Product withdrawn |

**Taken from Applicant's Table 11**

### Reviewer's comments

In the case of non-approved BIAsp 70, there does appear to be a relation between drug and withdrawals. However, rates are very small. Overall, most withdrawals from the study appear unrelated to study medications. The syncope episode is not described in enough detail to rule out

a relationship (hypoglycemia). Regardless, this is only one event. None of the withdrawals in the 50-50-50 group appear related to study medication.

**1746**

There were no withdrawals due to AEs in this study. No other types of withdrawals are noted.

7.1.3.3. Other significant adverse events

**1440**

There are no submitted data that isolates adverse events that led to dosage changes in patients. If dose adjustments were made in the SAEs, at least some of these were reported in the narratives, although the completeness of this is unknown.

Hypoglycemic events are summarized in Table 7. Only 2 patients in the 30-30 group and 1 patient in the 50-50-50 group reported major hypoglycemia compared to 11 (5.6%) patients in the 70-70-70 group. The proportion of patients who developed minor hypoglycemia was lowest in the 30-30 group (64%), intermediate in the 70-70-70 group (75%), and highest in the 50-50-50 group (79%). However, the 70-70-70 group had the highest rate of minor hypoglycemia when adjusted for patient year-exposure (13.3 vs. 7.9 for 30-30 and 9.3 for 50-50-50). Although the safety summaries do not define how the rates of hypoglycemia were calculated, it appears that these rates were obtained by dividing the number of hypoglycemic episodes by the patient-year exposures.

**Table 7**
**Treatment Emergent Hypoglycemic Episodes by Treatment and Classification—Trial 1440**

| | BIAsp 30-30 | | | | BIAsp 50-50-50(30) | | | | BIAsp 70-70-70(30) | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | N | (%) | E | Rate | N | (%) | E | Rate | N | (%) | E | Rate |
| Number of Subjects In ITT | 200 | | | | 201 | | | | 198 | | | |
| Major | 2 | (1.0) | 4 | 0.0 | 1 | (0.5) | 1 | 0.0 | 11 | (5.6) | 14 | 0.1 |
| Minor | 128 | (64.0) | 987 | 7.9 | 159 | (79.1) | 1213 | 9.3 | 148 | (74.7) | 1619 | 13.3 |
| Symptoms only | 120 | (60.0) | 705 | 5.7 | 125 | (62.2) | 851 | 6.5 | 140 | (70.7) | 984 | 8.1 |
| Unclassifiable | 2 | (1.0) | 7 | 0.1 | 1 | (0.5) | 1 | 0.0 | 1 | (0.5) | 2 | 0.0 |
| All | 151 | (75.5) | 1703 | 13.7 | 170 | (84.6) | 2066 | 15.8 | 167 | (84.3) | 2619 | 21.6 |

N = Number of Subjects with episodes
% = Proportion of exposed subjects having episode
E = Number of hypoglycemic episodes

**Taken from Applicant's Table 18**

Weight gain is a known side effect of insulin therapy. Weight increase was reported as an adverse event in only one patient in the 30-30 group and 2 patients in the 70-70-70 group. Also

of note, disorders associated with site of medication administration were very few with one person in the 30-30 group experiencing injection site swelling, one person in the 70-70-70 group experiencing injection site pruritis and one subject also having swelling. No patients in the 50-50-50 group experienced events at the injection site.

**1746**

Hypoglycemic events are summarized in Table 8. There are two subjects/events in the BIAsp 70 trial group and one subject/event in the IAsp group. None are reported for BIAsp 50.
In terms of hypoglycemic symptoms, there is one patient/event reported for BIAsp 30, BIAsp 70 and IAsp, but none for BIAsp 50.

Other significant adverse events, as shown in Table 9, that could be related to trial medications would include hyperglycemia and headache. No syncope or accidents that could be related to hypoglycemia are reported. One case of circulatory collapse is noted in the BIAsp 30 group but details are not available and it is not noted as an SAE.

There is one report of hyperglycemia in the BIAsp 30 group. There were six subjects that had headache in that group as well. There are two that report headache in each of the other groups.

**Table 8**
**Summary of Hypoglycemic Events by Severity—Trial 1746**

| | BIAsp 30 N (%) E | BIAsp 50 N (%) E | BIAsp 70 N (%) E | IAsp N (%) E |
|---|---|---|---|---|
| Number of Subjects Exposed | 32 | 32 | 32 | 32 |
| Major | 0 ( 0) 0 | 0 ( 0) 0 | 0 ( 0) 0 | 0 ( 0) 0 |
| Minor | 0 ( 0) 0 | 0 ( 0) 0 | 2 ( 6) 2 | 1 ( 3) 1 |
| Symptoms Only | 1 ( 3) 1 | 0 ( 0) 0 | 1 ( 3) 1 | 1 ( 3) 1 |

BIAsp 30 is BIAsp 30-30; BIAsp 50 is BIAsp 50-50-50(30); and BIAsp 70 is BIAsp 70-70-70(30)
N = Number of Subjects with episodes
% = Proportion of exposed subjects having episode
E = Number of hypoglycemic episodes

**Taken from Applicant's Table 26**

**Table 9**
**Summary of Treatment Emergent Adverse Events—Trial 1746**

| System organ class | BIAsp 30 N (%) E | BIAsp 50 N (%) E | BIAsp 70 N (%) E | IAsp N (%) E |
|---|---|---|---|---|
| Number of Subjects Exposed | 32 | 32 | 32 | 32 |
| All Adverse Events | 9 ( 28) 12 | 2 ( 6) 2 | 2 ( 6) 2 | 3 ( 9) 4 |
| Gastrointestinal Disorders | 3 ( 9) 3 | 0 ( 0) 0 | 0 ( 0) 0 | 1 ( 3) 2 |
| Abdominal Pain Upper | 1 ( 3) 1 | 0 ( 0) 0 | 0 ( 0) 0 | 0 ( 0) 0 |
| Diarrhoea | 1 ( 3) 1 | 0 ( 0) 0 | 0 ( 0) 0 | 0 ( 0) 0 |
| Nausea | 0 ( 0) 0 | 0 ( 0) 0 | 0 ( 0) 0 | 1 ( 3) 1 |
| Vomiting | 1 ( 3) 1 | 0 ( 0) 0 | 0 ( 0) 0 | 1 ( 3) 1 |
| Infections and Infestations | 1 ( 3) 1 | 0 ( 0) 0 | 0 ( 0) 0 | 0 ( 0) 0 |
| Nasopharyngitis | 1 ( 3) 1 | 0 ( 0) 0 | 0 ( 0) 0 | 0 ( 0) 0 |
| Metabolism and Nutrition Disorders | 1 ( 3) 1 | 0 ( 0) 0 | 0 ( 0) 0 | 0 ( 0) 0 |
| Hyperglycaemia | 1 ( 3) 1 | 0 ( 0) 0 | 0 ( 0) 0 | 0 ( 0) 0 |
| Nervous System Disorders | 6 ( 19) 6 | 2 ( 6) 2 | 2 ( 6) 2 | 2 ( 6) 2 |
| Headache | 6 ( 19) 6 | 2 ( 6) 2 | 2 ( 6) 2 | 2 ( 6) 2 |
| Vascular Disorders | 1 ( 3) 1 | 0 ( 0) 0 | 0 ( 0) 0 | 0 ( 0) 0 |
| Circulatory Collapse | 1 ( 3) 1 | 0 ( 0) 0 | 0 ( 0) 0 | 0 ( 0) 0 |

N = Number of Subjects with adverse event
% = Proportion of subjects in Analysis Set having adverse event
E = Number of adverse events

**Taken from Applicant's Table 10**

**Reviewer's Comments**
Hypoglycemic events are very few and none are reported in the group taking the medication being reviewed, BIAsp 50.
The rate of headache in the "control" group, BIAsp 30 is quite high at 19%. However, the trial medications, BIAsp 50 and BIAsp 30 have lower rates of 6% each. There is also one subject/event of hyperglycemia in the BAIsp 30 group.
Overall, the numbers reported are very small and definitive conclusions are difficult to draw from these data. However, the trial medication BIAsp 50 does not appear to pose any particular increased risk of hypoglycemia, headache or hyperglycemia based on given data.

7.1.4 Other Search Strategies

None performed for either 1440 or 1746.

7.1.5 Common Adverse Events

**1440**

The most common adverse events (incidence ≥5% in at least one of the treatment groups) reported in Study 1440 include nasopharyngitis, headache, diarrhea, and hypertension (Table 10). The 50-50-50 treatment group had a slightly higher incidence of headache, diarrhea, and hypertension compared to the other treatment groups, but a lack of a placebo arm limits the ability to determine the background rate of these events.

**Table 10**
**Most Frequently Reported AEs by System Organ Class and Frequency of Treatment Emergent AEs (>5%)**

| | BIAsp 30-30 | | | BIAsp 50-50-50(30) | | | BIAsp 70-70-70(30) | | |
|---|---|---|---|---|---|---|---|---|---|
| | N | (%) | E | N | (%) | E | N | (%) | E |
| Most Reported System Organ classes | | | | | | | | | |
| Number of Subjects in ITT | 200 | | | 201 | | | 198 | | |
| Adverse Events | 102 | (51.0) | 258 | 110 | (54.7) | 289 | 105 | (53.0) | 260 |
| Infections and infestations | | | | | | | | | |
| Nasopharyngitis | 21 | (10.5) | 28 | 25 | (12.4) | 29 | 26 | (13.1) | 30 |
| Nervous system disorders | | | | | | | | | |
| Headache | 10 | (5.0) | 11 | 17 | (8.5) | 23 | 12 | (6.1) | 22 |
| Gastrointestinal disorders | | | | | | | | | |
| Diarrhoea | 7 | (3.5) | 8 | 11 | (5.5) | 20 | 5 | (2.5) | 6 |
| Vascular disorders | | | | | | | | | |
| Hypertension | 3 | (1.5) | 3 | 12 | (6.0) | 12 | 3 | (1.5) | 3 |

N = Number of subjects with adverse event
% = Proportion of subjects in analysis set having adverse event
E = Number of adverse events

**Taken from Applicant's Table 5**

**Reviewer's Comments**
Rates for all common adverse events were similar across treatment groups. Hypertension stands out slightly with a 6% rate in the treatment group 50-50-50 as compared to the 30-30 group (1.5%) and the 70-70-70 group (1.5%). However, numbers are very few and it is difficult to form any association. In addition, review of the objective blood pressure data will better evaluate the effect of the NovoLog products on blood pressure. Cardiac events—which could result from hypertension, are described under SAEs, and the rate was low (less than 2%) and similar across all treatment arms.

1746

The most common AE in all three treatment arms was headache. There were no other AEs experienced by more than one patient and/or at more than one episode/event. See Table 9 in previous section, 7.1.3.3 for details on these events.

7.1.5.1 Eliciting adverse events data in the development program

This methodology was not submitted in the safety update.

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

The applicant used MedDRA (version unspecified) for categorizing all AEs.

7.1.5.5 Identifying common and drug-related adverse events

Hypoglycemia and weight gain can be reasonably related to the study drugs. Rates of hypoglycemia were low and SAEs related to hypoglycemia are discussed in Section 7.1.2. Weight gain was only reported in one patient in trial 1440, this is described in Section 7.1.3.3. A better assessment of weight changes could be obtained by reviewing the objective weight measurements. Headaches could also be related to either hypoglycemia and/or study drug. Again, rates were low with details discussed in Section 7.1.3.3.

7.1.5.6 Additional analyses and explorations

Not applicable, no dose dependency or demographic data submitted.

7.1.6 Less Common Adverse Events

Study numbers are quite small, these data are not reported.

7.1.7 Laboratory Findings

Laboratory data were not submitted for review.

7.1.8 Vital Signs

Vital sign data were not submitted for review.

7.1.9 Electrocardiograms (ECGs)

ECG data were not submitted for review.

7.1.10 Immunogenicity

All insulin products elicit the formation of anti-insulin antibodies in a subset of patients. To date, there has been no association between anti-insulin antibody production and the effect of the insulin product on efficacy or safety parameters. Immunogenicity data from Trial 1440 were not included in the safety update.

## 7.2 Adequacy of Patient Exposure and Safety Assessments

It has previously been determined that there are adequate data to support the approval of BIAsp 50-50. The current study was submitted as a safety update in response to an "Approvable" action (due to carton and container labeling deficiencies). This safety update did not contradict previous conclusions on patient exposure and safety. Additional details from these studies will be available when the applicant submits complete study reports.

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

Tables and narratives provided by the Applicant were used to review safety. Other data such as patient demographics were not submitted. Individual doses were also not submitted. Trial 1440 exposed patients to trial medication for 36 weeks.

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

Not applicable—not submitted.

## 8 ADDITIONAL CLINICAL ISSUES

### 8.4 Pediatrics

The Division is recommending a waiver for requiring pediatric studies with NovoLog Mix 50/50. Our recommendation has been submitted to the Pediatric Research Committee (PeRC) and we are awaiting PeRC's response. This formulation of insulin is unlikely to be used in large numbers of pediatric patients that frequently need very fine tuned insulin regimens (which cannot be achieved with the relatively inflexible dosing regimen of insulin mixes). On the form, the reason was stated as, "The product fails to represent a meaningful therapeutic benefit over existing therapies for pediatric patients **and** is unlikely to be used in a substantial number of all pediatric age groups or the pediatric age group(s) for which a waiver is being requested."

### 8.7 Postmarketing Risk Management Plan

None needed.

## 9 OVERALL ASSESSMENT

### 9.1 Conclusions

After thoroughly reviewing the safety update, the trial medication, BIAsp 50, or NovoLog Mix 50/50, does not present with any new safety concerns.

### 9.2 Recommendation on Regulatory Action

None.

### 9.3 Recommendation on Postmarketing Actions

None.

9.3.1 Risk Management Activity

None.

9.3.2 Required Phase 4 Commitments

None.

9.3.3 Other Phase 4 Requests

None.

**9.4 Labeling Review**

Label changes were requested in the Approvable letter as previously mentioned. These changes have been made and reviewed by OSE and found to be adequate.
In addition, OSE and our Division has requested that the Sponsor make the following changes to the Patient Package Insert (PPI):

FDA Comments:

- Please use one of the following fonts, Arial, Verdana, or APH font to make medical information more accessible for patients with low vision as recommended in the "Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss" published by the American Society of Consultant Pharmacists Foundation for the Blind.
- In the future, please provide the Patient Package Insert separately from the Patient Instructions for Use when submitting to FDA. This will avoid the need for line by line review to determine that the Patient Package Inserts are identical. For distribution purposes, you may attach the Patient Package Insert to each Patient Instruction for Use.

**Also under these sections we have requested that the Sponsor make the following changes. The final version of these labels may differ, pending future labeling discussions between the Sponsor and FDA that take place after this review is finalized:**

**Patient Package Insert (PPI)**

b(4)

# 2 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

✓ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

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

/s/
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Somya Verma
8/20/2008 02:46:18 PM
MEDICAL OFFICER

Hylton Joffe
8/20/2008 03:47:01 PM
MEDICAL OFFICER
Please see clinical team leader memo.

# 92 Page(s) Withheld

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_____ Draft Labeling (b5)

_____ Deliberative Process (b5)