CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER
21-172

Clinical Pharmacology and Biopharmaceutics Review

Clinical Pharmacology and Biopharmaceutics Review

NDA Number	21-172
Date of Submission	2/21/2001
Compound:	70% insulin aspart [rDNA origin] protamine suspension and 30% insulin aspart [rDNA origin] (*BIAsp 30*)
Brand Name:	*NovoLog Mix 70/30*
Dosage form and Strength:	Injection s.c., *100 u/ml, 3 ml Penfill.*
Indication:	Diabetes, ——— , *Bid dose. To be titrated.*
Sponsor:	Novo Nordisk Pharmaceuticals, Inc.
Type of Submission:	NDA Amendment (information update)
Reviewer:	He Sun, Pharmacometrics, DPE II
Team Leader:	Hae-Young Ahn, DPE II
ORM division:	HFD-510, Metabolism and Endocrine Product

I. EXECUTIVE SUMMARY

The main focal points of the clinical pharmacology and biopharmaceutics review for this NDA were:

1. To examine if the new formulation of *NovoLog Mix 70/30* (*Biphasic Insulin Aspart 70/30*, also known as *BIAsp 30*) provides the desired faster onset of action compared with a market comparator, Novolin 70/30 (*Biphasic Human Insulin 70/30*, also known as *BHI 30*) formulation.

2. To examine if the new 70/30 combination is kinetically and dynamically distinctive from other combinations in its formulation family, such as the 50/50 combination (*BIAsp 50*), and 100% Insulin Aspart (*IAsp*).

The answers to these two questions will impact the approvability of this NDA, since there were no formal clinical efficacy and safety trials for this formulation. A multi-year study to assess long-term efficacy and toxicity was requested in prior agreements.

In a previous review completed on Sept. 20, 2000, the first question has been answered. *BIAsp 30* provides a faster absorption profile and faster onset of action when compared with *BHI 30*. In this NDA amendment, the second question was adequately addressed per an OCPB point of view. The new *BIAsp 30* formulation demonstrated a clinically significant (i.e. more than 20%) different pharmacokinetic profile (as measured by insulin concentration versus time profile) and pharmacodynamic effect (as measured by glucose infusion rate change) when compared with *IAsp* formulation. Compared to BIAsp 50 (a formulation that is not on the market), BIAsp 30 showed more than 20% different pharmacokinetic profile in terms of AUC and Cmax but less than 20% different pharmacodynamic effect.

No specific comments need to be conveyed to the sponsor. No additional clinical pharmacology studies are requested at this time from OCPB. Labeling comments are included in this review.

II. RECOMMENDATION:

The Division of Pharmaceutical Evaluation II (DPE II) of the Office of Clinical Pharmacology and Biopharmaceutics has reviewed Section 6 of NDA 21-172. For meeting the Agency's bio-regulations, when taking into consideration of the formulation difference, performance of other approved similar products, and Agency's draft guidance entitled "Insulin and Insulin Analogs," from the clinical pharmacology point-of-view, the submitted information is sufficient to support that *NovoLog 70/30* is kinetically and dynamically different from the insulin comparator *Novolin Mix 70/30* and from *NovoLog*. The product is also kinetically distinctive from the nearest biphasic comperator, *NovoLog Mix 50/50*, but is not dynamically different than the *NovoLog Mix 50/50*. However, *NovoLog Mix 50/50* is not an approved product. Therefore, it is recommended the product to be approved.

S

He Sun, Ph.D.
Pharmacometrics, DPE 2

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FT initialed by Hae-Young Ahn, Ph.D. TL

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ON ORIGINAL

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Note:

NovoLog = 100% insulin aspart = IAsp

NovoLog Mix 70/30 = 70% insulin aspart protamine + 30% insulin aspart = BIAsp 30

NovoLog Mix 50/50 = 50% insulin aspart protamine + 50% insulin aspart = BIAsp 50

Novolin 70/30 = Biphasic Human Insulin 70/30 = BHI 30

III. SUMMARY OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FINDINGS FROM THIS AMENDMENT.

From the results of study #1086, the following conclusions are drawn:

Pharmacokinetics

- The differences between formulations were more apparent in pharmacokinetic profiles than in pharmacodynamic profiles.
- *BIAsp 30* showed more than 20% differences in insulin AUC values as compared with *BIAsp50* and 100% *IAsp* at each measurement time point.
- Insulin aspart C_{max} of *BIAsp 30* was less than 50% of *IAsp* C_{max}, and was about 70% of the C_{max} value of *BIAsp50*.

Pharmacodynamics:

- The primary onset measures for *BIAsp 30*, the $AUC_{GIR\ 0\text{-}2h}$ value, was 17% smaller compared with *BIAsp 50*, and was 34% smaller compared with 100% *IAsp*; This smaller first two hour AUC_{GIR} value indicates a delayed onset of GIR effect of *BIAsp 30*.
- $Tmax_{GIR}$ did not differ significantly between all three formulations, being approx. 2 hours.
- The protamine protracted component of *BIAsp* preparations resulted in slightly prolonged activity as demonstrated by larger $AUC_{GIR\ 0\text{-}24h}$ compared with those of *IAsp*.
- AUC_{GIR} data tended to be equivalence between the *BIAsp 50* and *BIAsp 30*.

Additional PK-PD analysis comment:

- It seems the 0.3 U/Kg dose is an over dose in the studies included. The pharmacodynamic effect has approached the plateau of concentration-effect curve, which may explain why the pharmacodynamic distinction is less apparent than pharmacokinetic differences. Therefore, a study using a lower dose can have provided better information on pharmacodynamic differences among formulations.

IV. QUESTION-BASED REVIEW

General Attributes

NovoLog Mix 70/30 is indicated for use in diabetes mellitus, and is a premixed insulin which consists of a rapid-acting component displaying the features of the human insulin analogue insulin Aspart (*IAsp*) and an intermediate-acting component with properties similar to those of human NPH-insulin. *NovoLog Mix 70/30* (*BIAsp 30*) is a sterile biphasic suspension with 30% soluble rapid-acting *IAsp* and 70% protamine-

bound *IAsp* intended for s.c. use. It is contained in —— 3.0 ml PenFill® cartridges for use with Novo Nordisk delivery devices, and will also be available in vials.

The rationale for developing *BIAsp 30* is to provide a combination of intermediate-acting insulin and a true meal-time s.c. insulin with a time-action profile that mimics the food-induced insulin secretion in non-diabetic subjects more closely than its comparator, *Novolin 70/30* (*BHI 30*) does.

From HFD-510's draft guidance the following is stated under the section entitled "Insulin and Insulin Analogs":

> *"...approval of a new fixed dose combination (NPH/regular 90/10 for example)*
>
> *would require pharmacokinetic and/or pharmacodynamic data to show that the combination product is different from each of its components (NPH insulin and regular insulin) and is different from other combinations (such as 70/30) which are already available. A 20 % difference in peak insulin concentration, area under the curve, glucose infusion rate, or time to maximal effect would be the minimal level of difference we are likely to accept. A Sponsor wishing to market a new insulin analog or combination products will need to provide PK/PD data which show that the products are different from each other in ways which are clinically relevant."*
>
> *[Note: In discussions with the NDA's current reviewing Medical Officer, it was learned that in addition to the PK and PD parameters that were analyzed in the UK study and outlined in HFD-510's guidance, we would ask the sponsor to determine the times to achieve AUC25%, AUC50%, AUC75%, and AUC100% per product for insulin and glucose infusion rate. It was felt that these analyses would be of clinical importance.]*

In the original NDA, the sponsor submitted two single dose PK trials in healthy volunteers (031/UK and 033/D) and one PK study in type 2 diabetic subjects (046/NL, UK) that compared the new formulation *BIAsp 30* versus *BHI 30*. Results indicate that, while the total kinetic and dynamic AUC values are equivalent between *BIAsp 30* and *BHI 30*, the rate of absorption and GIR measure is faster for *BIAsp 30* compared to *BHI 30*. The differences in $AUC_{0\text{-}6\ hours}$, GIR $AUC_{0\text{-}6\ hours}$, C_{max}, and GIR_{max} are near or greater than 20%.

$AUC_{ins,\ 0\text{-}1.5h}$ with *BIAsp 30* was approximately double that observed with *BHI 30*. t_{max} was statistically significantly shorter with *BIAsp 30* (shorten by 60 min); C_{max} was estimated to be approximately 50% higher following treatment with *BIAsp 30* than with *BHI 30*. Serum insulin levels returned towards baseline between 15 and 18 hours following s.c. administration of *BIAsp 30* and *BIH 30*. The estimated relative bioavailability of *BIAsp 30* compared to *BHI 30* following s.c administration in healthy subjects was 1.048 (90% CI 0.968 - 1.135) (Assuming that clearance of *IAsp* is similar to *HI*, as has been previously with *IAsp*).

The OCPB reviewer accepted these studies. An approvable letter for the original NDA was sent to the sponsor pending resolve several issues include the completion of study 1086 in which *BIAsp 30* was compared to 100% rapid-acting *IAsp* and *NovoLog Mix 50/50* (*BIAsp 50*, which includes 50% soluble rapid-acting *IAsp* and 50% protamine-bound *IAsp*). This amendment NDA is to provide the final study results for study 1086.

The Key question: How *NovoLog Mix 70/30* performs as compared with other *NovoLog Mix* formulations in study 1086 ?

The study is a single center, randomized, four-way crossover trial in healthy subject using the euglycaemic clamp technique. Three premixed biphasic insulin aspart (B*IAsp*) products were administered in a double-blind fashion (*BIAsp 30*, *BIAsp 50*, and B*IAsp* 70), where soluble insulin aspart (*IAsp*) was administered open label. Thirty-five healthy male and female subjects participated in the study.

Trial Product	Number of subjects exposed
IAsp	33
BIAsp 30	34
BIAsp 50	32
BIAsp 70	33
ALL trial products	32

The product, dose and batch number were:
Insulin aspart 100 u/ml, 3 ml Penfill; 0.3 U/kg injected s.c.; batch no. C98006
Biphasic insulin aspart 30, 3 ml Penfill; 0.3 U/kg injected s.c.; batch no. C97009
Biphasic insulin aspart 50, 3 ml Penfill; 0.3 U/kg injected s.c.; batch no. C99001
Biphasic insulin aspart 70, 3 ml Penfill; 0.3 U/kg injected s.c.; batch no. C99002

1. The ratio of geometric means (with 90% CI) of PK and PD parameters

The mean *IAsp* concentration-time profiles and mean GIR profiles are shown in Figure 2 and 1. The logarithmically transformed kinetic and dynamic data were analyzed in an analysis of variance (ANOVA) model with treatment as fixed effect and subject as random effect. The mean ratios and 90% CI were calculated and present in tables 1 and 2.

Figure 2. Mean Profiles
Insulin Aspart

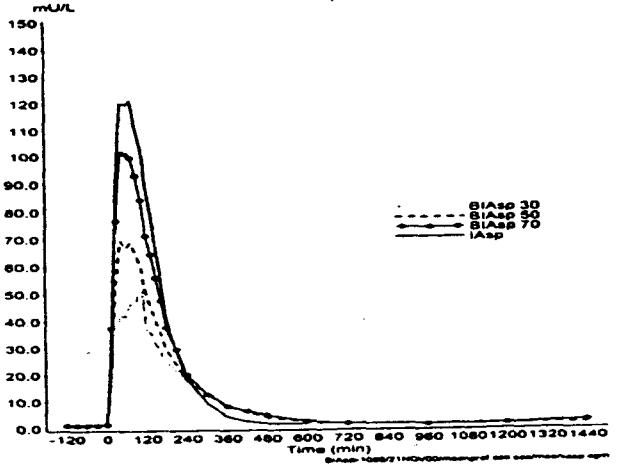


Table 1 **Results of pharmacokinetic comparison among BIAsp 30, BIAsp 50, and IAsp.**

PK parameters	Comparison	Value	Mean Ratio	90 % C.I
AUC (0-2 hrs)	IAsp/BIAsp 30	10957/4489	2.58	2.34 – 2.85
AUC (0-4 hrs)	IAsp/BIAsp 30		2.28	2.10 – 2.48
AUC (0-24 hrs)	IAsp/BIAsp 30	18407/11486	1.69	1.57 - 1.82
Cmax	IAsp/BIAsp 30	139/63.17	2.58	2.28 – 2.92
Tmax	IAsp/BIAsp 30	72.7/79.4	0.92	0.82 – 1.05
AUC (0-2 hrs)	BIAsp 50/BIAsp 30	6381/4489	1.50	1.36 - 1.66
AUC (0-4 hrs)	BIAsp 50/BIAsp 30		1.36	1.25 - 1.49
AUC (0-24 hrs)	BIAsp 50/BIAsp 30	13612/11486	1.24	1.15 - 1.34
Cmax	BIAsp 50/BIAsp 30	74.18/63.17	1.37	1.21 - 1.55
Tmax	BIAsp 50/BIAsp 30	68.9/79.4	0.86	0.76 - 0.98

The above pharmacokinetic comparison results indicated that *BIAsp 30* shows far more than 20% kinetic difference compared to *IAsp* (69-158%) and *BIAsp 50* (24-50%) in terms of AUC and Cmax. Tmax is unchanged.

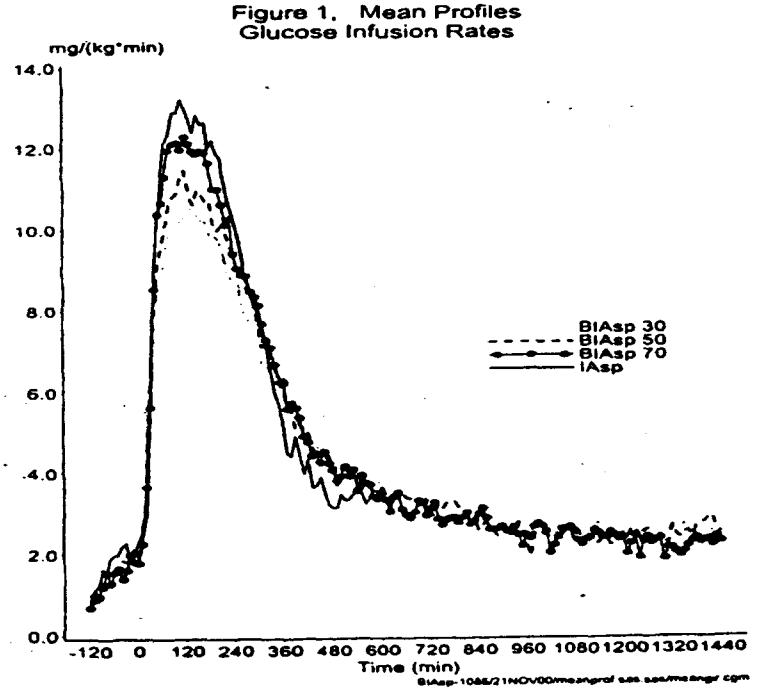


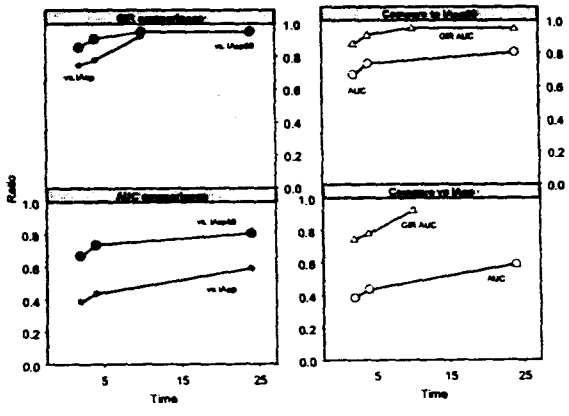
Table 2 **Results of pharmacodynamic equivalence test among BIAsp 30, BIAsp 50, and IAsp.**

PD parameters	Comparison	Value	Mean Ratio	90 % C.I.
GIR AUC (0-2 hrs)	IAsp/BIAsp 30	913.9/702.0	1.34	1.25 - 1.45
GIR AUC (0-4 hrs)	IAsp/BIAsp 30	2149/1724	1.28	1.21 – 1.35
GIR AUC (0-10 hrs)	IAsp/BIAsp 30	3345/3168	1.08	1.02 – 1.16
GIR AUC (0-24hrs)	IAsp/BIAsp 30	3345/4194	0.84	0.70 – 0.95
GIR max	IAsp/BIAsp 30	13.76/10.24	1.33	1.25 – 1.42
GIR Tmax	IAsp/BIAsp 30	132/140	0.89	0.78 – 1.02
GIR AUC (0-2 hrs)	BIAsp 50/BIAsp 30	803.2/702.0	1.17	1.08 - 1.26
GIR AUC (0-4 hrs)	BIAsp 50/BIAsp 30	1867/1724	1.10	1.04 - 1.17
GIR AUC (0-10 hrs)	BIAsp 50/BIAsp 30	3280/3168	1.05	0.98 - 1.12
GIR AUC (0-24hrs)	BIAsp 50/BIAsp 30	4266/4194	1.05	0.79 - 1.11
GIR max	BIAsp 50/BIAsp 30	10.87/10.24	1.07	1.00 - 1.14
GIR Tmax	BIAsp 50/BIAsp 30	135/140	0.95	0.82 - 1.09

The above pharmacodynamic comparison results indicate that, (1) *BIAsp 30* shows greater than 20% dynamic difference compared to *IAsp* in GIR $AUC_{0\text{-}2\ hrs}$ (34%), GIR $AUC_{0\text{-}4\ hrs}$ (28%) and GIRmax (33%), and (2) *BIAsp 30* shows less than 20% dynamic difference compared to *BIAsp 50* in terms of GIR AUCs and GIR max.

Additional comparisons of the pharmacokinetic and pharmacodynamic differences are displayed in Figure 3 below:

Figure 3. **Comparison of pharmacokinetic and pharmacodynamic AUC of *BIAsp 30* versus *IAsp* and *IAsp* 50 at various time points post dose. Data were re-calculated by the reviewer.**



The above analysis indicate that:

1. Kinetic differences are more apparent than dynamic differences when the new B*IAsp*30 is compared to *IAsp* or B*IAsp*50 formulations.
2. *BIAsp 30* demonstrated more than 20% kinetic differences compared to *IAsp* and *BIAsp 50.*
3. The dynamic difference between BIAsp 30 and *IAsp* is more apparent than that between *BIAsp 30* and *BIAsp 50. BIAsp 30* **does not** show more than 20% dynamic difference compared to *BIAsp 50.*
4. For both kinetic (AUC) and dynamic (GIR AUC) comparisons, the *BIAsp 30* formulation shows smaller initial value at 2 and 4 hours post-dose and approaches equivalent value to *IAsp* and *IAsp*50 at 24 hours. Therefore, a slower onset and sustained effect from *BIAsp 30* are suggested.

2. Comparisons between the time to reach per product AUC25%, AUC50%, AUC75%, and AUC100% (Type 1 comparison) and the time to reach a predetermined AUC25%, AUC50%, AUC75%, and AUC100% (Type 2 comparison) for insulin and glucose infusion rate.

To compare the clinical performance of the new mixture product versus the approved products *BHI 30* and *IAsp*, and a neighbor formulation *BIAsp 50* which is not approved, times to achieve AUC25%, AUC50%, AUC75%, and AUC100% (TAUCs) per product for insulin and glucose infusion rate were also determined and compared (Type 1 comparison). In this type of comparison, the **Larger** the TAUC25% and TAUC50%, indicates the **Slower** the absorption per product.

However, using this parameter to assess between product differences is felt to be somewhat limited or potentially misleading because the determined time is based on a percentage of total AUC of the product, which is a function of the extent of drug absorbed from the product, rather than a general standard. If different products have different extents of absorption the findings might be misleading.

In an attempt to circumvent the problems above, type 2 analyses were conducted. For these analyses, times for *IAsp, IAsp 50* and *BHI 30* to reach the AUC values for *BIAsp 30* were calculated. In this comparison, the **Larger** the TAUC value indicates the **Slower** overall absorption or GIR onset of action relative the comparetors.

These two types of comparisons were applied to the original review. In this amendment, since the total AUC of all formulations are similar, type 1 comparison will provide the key comparison information.

The results of type 1 and type 2 comparisons are given in table 3 to 6 below:

Table 3. Type 1 Pharmacokinetic comparisons

	Values			Ratios	
Parameter	BIAsp30	BIAsp50	IAsp	BIAsp30/BIasp50	BIAsp30/BIAsp
TAUC25%	1.43	1.23	1.07	1.17	1.34
TAUC50%	2.62	2.18	1.73	1.20	1.51
TAUC75%	4.95	4.13	2.62	1.20	1.89
TAUC100%	16.67	8.97	5.95	1.86	2.80

Table 4. Type 2 Pharmacokinetic comparisons

	Values			Ratios	
Parameter	BIAsp30	BIAsp50	IAsp	BIAsp30/BIAsp50	BIAsp30/IAsp
TAUC25%	1.43	1.10	0.84	1.31	1.71
TAUC50%	2.62	1.89	1.27	1.39	2.07
TAUC75%	4.95	3.65	1.66	1.36	2.98
TAUC100%	24.00	9.90	2.27	2.42	10.58

Table 5. Type 1 Pharmacodynamic comparisons

	Values			Ratios	
Parameter	BIAsp30	BIAsp50	IAsp	BIAsp30/BIAsp50	BIAsp30/IAsp
TAUC25%	2.63	2.47	1.90	1.07	1.39
TAUC50%	5.02	4.68	3.17	1.07	1.58
TAUC75%	10.10	9.18	4.77	1.10	2.12
TAUC100%	24.00	19.17	9.00	1.25	2.67

Table 6. Type 2 Pharmacodynamic comparisons

	Values			Ratios	
Parameter	BIAsp30	BIAsp50	IAsp	BIAsp30/Biasp50	BIAsp30/IAsp
TAUC25%	2.63	2.35	2.12	1.12	1.24
TAUC50%	5.02	4.50	3.60	1.12	1.39
TAUC75%	10.10	9.12	8.10	1.11	1.25
TAUC100%	24.00	23.0	-	1.04	-

Figure 4. Type 1 comparison of pharmacokinetic and pharmacodynamic AUC of *BIAsp 30* versus *IAsp* and *IAsp* 50 at various time points post dose.

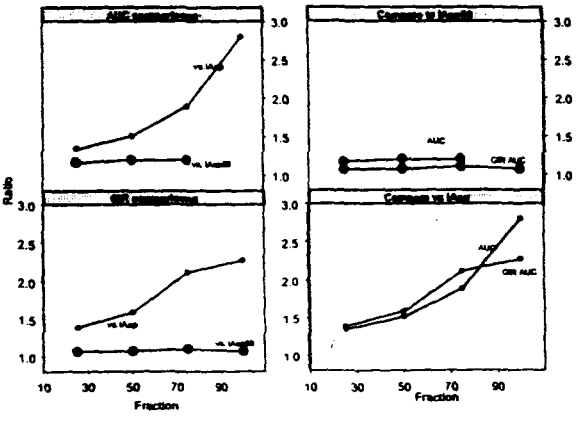


Figure 5. **Pharmacodynamic GIR AUC of *BIAsp 30*, *IAsp* and *BIAsp 50* at various time points post dose. It is clear that to reach a given GIR AUC, the time required for *IAsp* 30 is longer than for *IAsp* and *BIAsp 50*. However, the total GIR AUC value is larger for B*IAsp*30 and B*IAsp*70 than that of *IAsp*.**

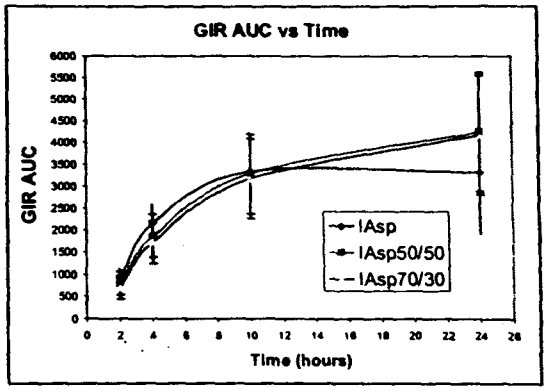
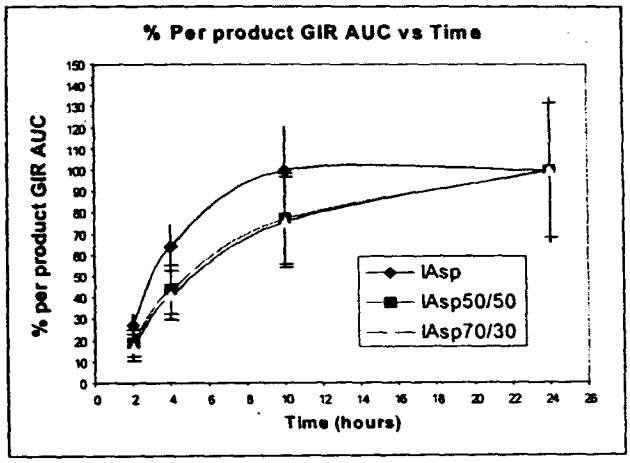


Figure 6. **Pharmacodynamic % Per Product GIR AUC of *BIAsp 30*, *IAsp* and *BIAsp 50* at various time points post dose. It is clear that the time required to reach a given % of GIR AUC per product is much longer for B*IAsp* products than for *IAsp*.**



The comparison analyses show that, *BIAsp 30* has slower absorption and slower onset of action compared to 100% *IAsp*, and *BIAsp 50* from both type 1 and type 2 comparisons.

Compared to *BIAsp 50*, the time required to reach a given fraction of kinetic AUC for *BIAsp 30* is significantly (i.e. more than 20%) increased, however, the dynamic differences were less than the FDA required 20% (as stated in the Agency's draft guidance entitled "Insulin and Insulin Analogs").

3. Overall conclusions:

a. *Pharmacokinetics*

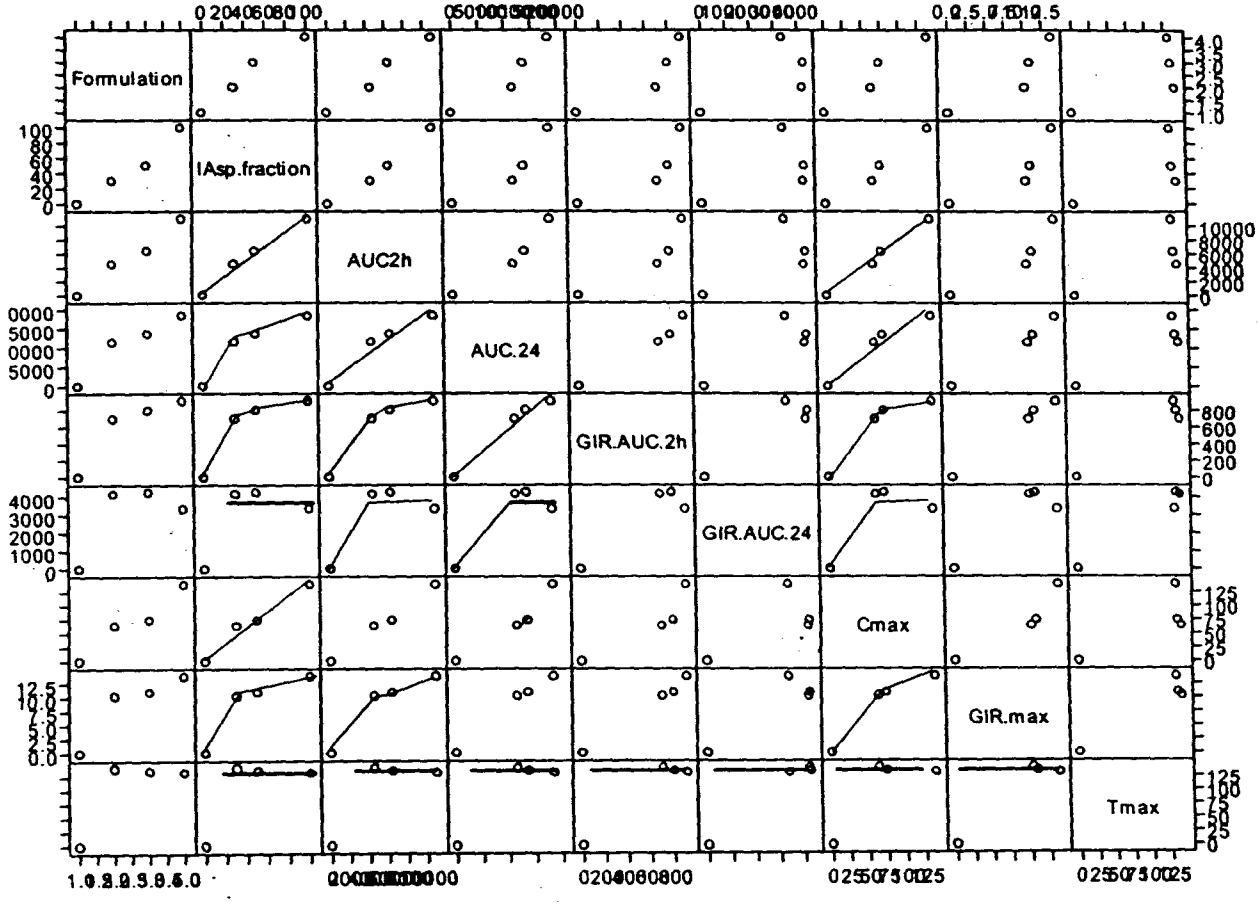
- The differences between formulations were more apparent in pharmacokinetics profiles than in pharmacodynamics profiles.
- *BIAsp 30* showed more than 20% differences in AUC values as compared to B*IAsp*50 or 100% *IAsp* at all times.
- Insulin aspart Cmax of *BIAsp 30* is less than 50% of *IAsp* Cmax, and is about 70% of Cmax of B*IAsp*50.
- Cumulative total AUC data tend to be inequivalence between *BIAsp* preparations.

Pharmacodynamics:

- *BIAsp 30* shows greater than 20% dynamic difference compared to *IAsp* in GIR $AUC_{0\text{-}2\ hrs}$ (34%), GIR $AUC_{0\text{-}4\ hrs}$ (28%) and GIRmax (33%),
- *BIAsp 30* shows less than 20% dynamic difference compared to *BIAsp 50* in terms of GIR AUCs and GIR max.
- $Tmax_{GIR}$ does not differ significantly between all three formulations, being approx. 2 hours.
- The protamine protracted component of B*IAsp* preparations resulted in slightly prolonged activity as demonstrated by $AUC_{GIR\ 0\text{-}24h}$.
- AUC_{GIR} data tend to be equivalence between two B*IAsp* preparations.

c. *Additional analysis on parameter relationships*

Figure below may explain why kinetic distinction is more apparent than dynamic distinction. It seems the effect approach PK-PD plateau with 0.3 U/Kg dose.



LABELING RECOMMENDATION:

General comments:

- Acceptable final wording for the product label is pending. The name for the new formulation should be in the same format as the other Novolin products.

Recommended changes:

In standard biological assays in mice and rabbits, one unit of NovoLog has the same glucose-lowering effect as one unit of regular human insulin. However, the effect of NovoLog Mix 70/30 is more rapid in onset compared to Novolin 70/30 due to its faster absorption after subcutaneous injection.

Pharmacokinetics

Absorption: The single substitution of the amino acid proline with aspartic acid at position B28 in insulin aspart reduces the molecule's tendency to form hexamers as observed with regular human insulin.

Comment: Figure 2 should be a pharmacokinetic data. The figure below with format modifications is recommended

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Labeling

Distribution and elimination- ~~NovoLog~~ NovoLog has low binding to plasma proteins, 0-9%, similar to regular human insulin. After subcutaneous administration in normal male volunteers (n=24), ~~NovoLog~~ NovoLog was more rapidly eliminated than regular human insulin with an average apparent half-life of 81 minutes compared to 141 minutes for regular human insulin.

Pharmacodynamics

The duration of action may last as long as 24 hours

Figure 3: Activity profile of NovoLog Mix 70/30 and ~~Novolin~~ Novolin 70/30 in ~ healthy subjects.

Reviewer's additional comment: the sponsor should carefully reformat the figure above to include standard deviations and to properly label the figure.

Special populations

Children and adolescents-

-The pharmacokinetics and pharmacodynamic properties of NovoLog Mix 70/30

Geriatrics-The effect of age on the pharmacokinetics and pharmacodynamics of NovoLog Mix 70/30 has not been studied.

Gender-

The effect of gender on the pharmacokinetics and pharmacodynamics of NovoLog Mix 70/30 has not been studied

Obesity-The effect of obesity and/or subcutaneous fat thickness on the pharmacokinetics and of NovoLog Mix 70/30 has not been studied.

Ethnic origin-The effect of ethnic origin on the pharmacokinetics of NovoLog Mix 70/ 30 has not been studied.

Renal impairment- The effect of renal function on the pharmacokinetics and pharmacodynamics of NovoLog Mix 70/30 has not been studied. Some studies with human insulin have shown increased circulating levels of insulin in patients with renal failure[6].

-Careful glucose monitoring and dose adjustments of insulin, including NovoLog Mix 70/30, may be necessary in patients with renal dysfunction (see PRECAUTIONS, Renal Impairment).

Hepatic impairment- The effect of hepatic impairment on the pharmacokinetics of NovoLog Mix 70/30 has not been studied. Some studies with human insulin have shown increased circulating levels of insulin in patients with liver failure. Careful glucose monitoring and dose adjustments of insulin, including NovoLog Mix 70/30, may be necessary in patients with hepatic dysfunction (see PRECAUTIONS, Hepatic Impairment).

Pregnancy-The effect of pregnancy on the pharmacokinetics and of NovoLog Mix 70/30 has not been studied (see PRECAUTIONS, Pregnancy).

Smoking-The effect of smoking on the pharmacokinetics/pharmacodynamics of NovoLog Mix 70/30 has not been studied.

PRECAUTIONS SECTION:

Reviewer's comment: Language in PRECAUTIONS section is in agreement with the Medical Officer.

APPEARS THIS WAY ON ORIGINAL

V. HUMALOG 75/25 REFERENCE

To cpmpare the NovoLog Mix product versus HumaLog Mix, two plots are extracted from NDA 21-017 and 21-018, Humalog 75/25 and Humalog 50/50:

The ratio $AUC_{0\text{-}5}$ hours for Humalog 50/50 vs. Humalog 75/25 is 1.41 (90% CI: 1.31 – 1.51).

The Cmax ratio for Humalog 50/50 vs. Humalog 75/25 is 1.64 (90% CI: 1.49 – 1.81)

Figure 4: Mean insulin concentration vs. time curves for Study IODJ

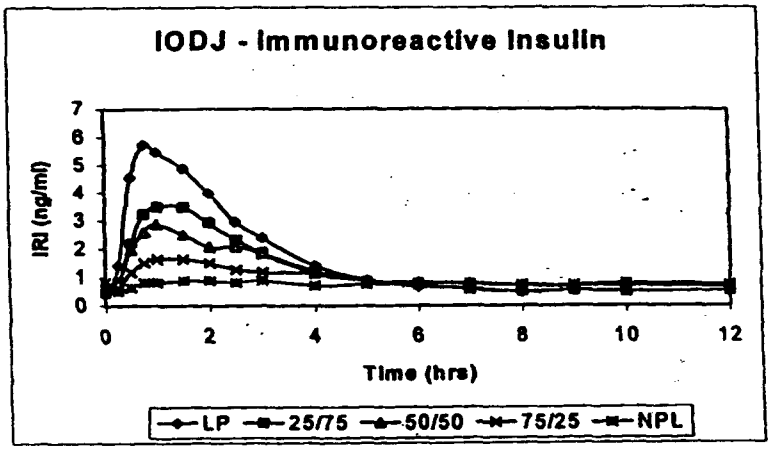
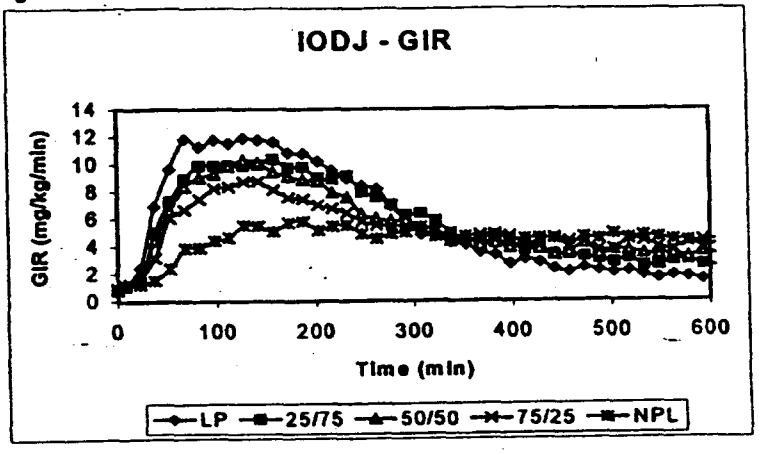


Figure 5: Mean GIR vs. times curves for Study IODJ.



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BIOPHARMACEUTICS

Comments faxed to Novo 9/28/00

Clinical Pharmacology and Biopharmaceutics Review

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Compound:	Biphasic Insulin Aspart 30
Type of Submission:	Original NDA submission
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I. RATIONAL FOR BIPHASIC INSULIN ASPART 30

Biphasic insulin aspart (BIAsp) is indicated for use in diabetes mellitus, and is a premixed insulin with a rapid-acting component displaying the features of the human insulin analogue insulin Aspart (IAsp) and an intermediate-acting component with properties similar to those of human NPH-insulin. BIAsp 30 is a sterile biphasic suspension with 30% soluble rapid-acting IAsp and 70% protamine-bound IAsp intended for s.c. use. BIAsp is contained in —— 3.0 ml PenFill® cartridges for use with Novo Nordisk delivery devices, and will also be available in vials.

The rationale for developing BIAsp 30 is to try to provide a combination of an intermediate-acting insulin and a true meal-time s.c. insulin with a time-action profile that mimics the food-induced insulin secretion in non-diabetic subjects more closely than biphasic human insulin (BHI 30) does. It is stated that the BIAsp 30 preparation provides the possibility for immediate pre-meal injection as well as a potential to improve postprandial glycemic control. Thus, the objective is to provide a meal-time insulin that can be administered immediately before morning and evening meals in a twice daily regimen.

II. REVIEW QUESTIONS AND FINDING

1. What are the key parameters to evaluate for a new mixture insulin product per the review Division's current requirement?

From HFD-510's draft guidance the following is stated under the section entitled "Insulin and Insulin Analogs":

> *"...approval of a new fixed dose combination (NPH/regular 90/10 for example) would require pharmacokinetic and/or pharmacodynamic data to show that the combination product is different from each of its components (NPH insulin and regular insulin) and is different from other combinations (such as 70/30) which are already available. A 20 % difference in peak insulin concentration, area under the curve, glucose infusion rate, or time to maximal effect would be the minimal level of difference we are*

likely to accept. A Sponsor wishing to market a new insulin analog or combination products will need to provide PK/PD data which show that the products are different from each other in ways which are clinically relevant."

[Note: In discussions with the NDA's current reviewing Medical Officer, it was learned that in addition to the PK and PD parameters that were analyzed in the UK study and outlined in HFD-510's guidance, we would ask the sponsor to determine the times to achieve AUC25%, AUC50%, AUC75%, and AUC100% per product for insulin and glucose infusion rate. It was felt that these analyses would be of clinical importance.]

The studies submitted include two single dose PK trials in healthy volunteers (031/UK and 033/D) and one PK study in type 2 diabetic subjects (046/NL, UK) that compared the new formulation BIAsp30 versus BHI 30. A more than 20% difference in Cmax and AUC of insulin were observed when products were administered under either fast conditions (031/UK and 033/D,) or immediately following a meal (046/NL, UK) (see review attachment).

In study 1086, BIAsp 30 was compared to 100% rapid-acting IAsp. Results indicated that the BIAsp 30 has slower absorption kinetics and delayed pharmacodynamic (as determined by glucose infusion rate (GIRmax) action.

However, the sponsor didn't conduct a study to demonstrate that the new combination formulation, BIAsp 30, produces faster absorption kinetics and faster pharmacodynamic action than

Trial	Subjects	Design
031	Healthy.	Single dose, fasting, BIAsp 30 vs. BHI 30, PK
033	Healthy	Single dose, clamp study, fasting, BIAsp 30 vs. BHI 30, PK and PD
046	Type 2 diabetic patients	Multiple doses, non fasting, PK and PD measures.
1086	Healthy	Single dose, clamp study, fasting, BIAsp 30 vs. IAsp. PK and PD.

Please note that the formulations used in study 031 and 033 are slightly different than the clinical formulation which is the to be marketed formulation. See section V.2 Formulations. Formulation used in study 033 is more close to the clinical formulation and the total change (in weight) is less than 5%. Borrowing regulations for oral dosage forms, such change may be allowed without a BE trial.

2. ***Does the submitted PK/PD data demonstrated that BIAsp 30 performs differently from each of its components*** ?

For study 031, 033 and 1086, logarithmically transformed kinetic and dynamic data were analyzed in an analysis of variance (ANOVA) model with treatment as fixed effect and subject as random effect. The mean ratios and 90% CI were calculated and present in tables below. For study 046, similar comparison was not conducted since the quality of the data is in question.

Table 1 **Results of pharmacokinetic equivalence test of BIAsp 30 versus BHI 30 and IAsp.**

PK parameters	Study	Comparison	Mean Ratio	90 % C.I
AUC (0-24 hrs)	031	BIAsp 30/BHI 30	1.048	0.968 - 1.135
	033	BIAsp 30/BHI 30	1.158	1.080 - 1.241
	1086	BIAsp 30/IAsp	0.58	0.546 - 0.63
	NA[a]	BIAsp 30/ —	NA	NA
AUC (0-6 hrs)	031	BIAsp 30/BHI 30	1.231	1.144 - 1.325
	033	BIAsp 30/BHI 30	1.608	1.468 - 1.760
	1086	BIAsp 30/IAsp	0.485	0.446 – 0.526
	NA	BIAsp 30/ —	NA	NA
Cmax	031	BIAsp 30/BHI 30	1.512	1.375 - 1.662
	033	BIAsp 30/BHI 30	2.020	1.798 - 2.270
	1086	BIAsp 30/IAsp	0.38	0.336 – 0.433
	NA	BIAsp 30/ —	NA	NA

a. Study should be submitted but not included in the submission.

Table 2 **Results of pharmacodynamic equivalence test of BIAsp 30 versus BHI 30 and IAsp.**

PD parameters	Study	Comparison	Mean Ratio	90 % C.I.
GIR AUC (0-24 hrs)	033	BIAsp 30/BHI 30	0.975	0.902 - 1.055
	1086	BIAsp 30/IAsp	0.93	0.87 – 0.99
	NA	BIAsp 30/ —	NA	NA
GIR AUC (0-6 hrs)	033	BIAsp 30/BHI 30	1.219	1.140 - 1.305
	1086	BIAsp 30/IAsp	0.83	0.78 – 0.877
	NA	BIAsp 30/ —	NA	NA
GIR MAX	033	BIAsp 30/BH130	1.197	1.125 - 1.274
	1086	BIAsp 30/IAsp	0.76	0.72 – 0.81
	NA	BIAsp 30/ —	NA	NA

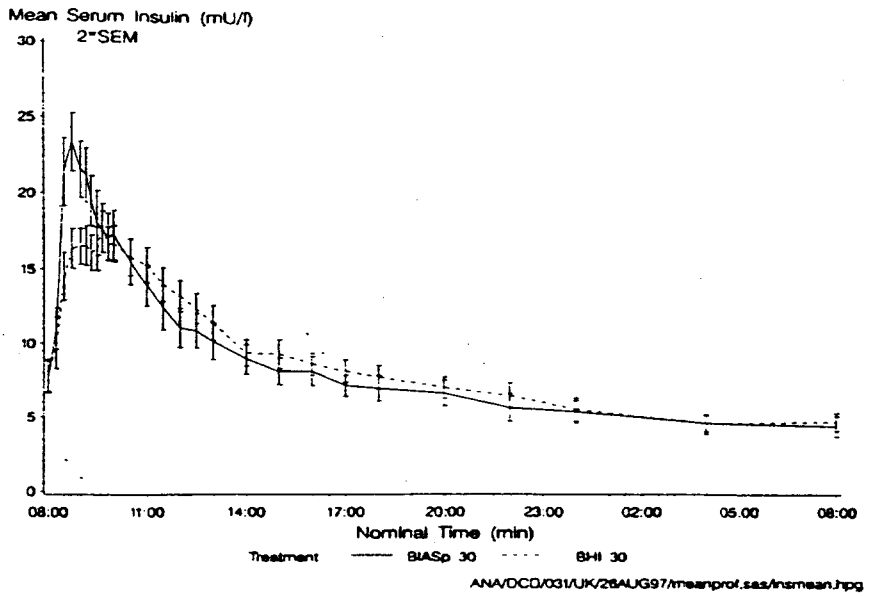

FIGURE 1 **Mean 24-hour Total Insulin Profiles for BIAsp 30 and BHI 30 - Healthy Subjects (031/UK)**

Results indicate that, although the total kinetic and dynamic AUC values are equivalent between BIAsp 30 vs. BHI 30, the rate of absorption and GIR action is faster for BIAsp 30 compared to BHI 30. The differences in AUC 0-6 hours, GIR AUC 0-6, Cmax, and GIR max are near or greater than 20%.

$AUC_{ins,\ 0\text{-}90\ min}$ with BIAsp 30 was approximately double that observed with BHI 30. t_{max} was statistically significantly shorter with BIAsp 30 (shorten by 60 min); C_{max} was estimated to be approximately 50% higher following treatment with BIAsp 30 than with BHI 30. Serum insulin levels returned towards baseline between 15 and 18 hours following s.c. administration of BIAsp 30 and BIH 30; see Figure 1.

The estimated relative bioavailability, F (AUC), of BIAsp 30 compared to BHI 30 following s.c administration in healthy subjects was 1.048 (90% CI 0.968 - 1.135) (Assuming that clearance of IAsp is similar to HI, as has been previously with IAsp). Metabolism and excretion of BIAsp 30 is identical to that described for IAsp, since it is IAsp that is absorbed into the blood.

The apparent terminal half-life ($t_{½}$) of BIAsp 30 was determined from 10-24 hours in order to ensure that the results were not influenced by the fast acting soluble fraction. The reviewer considers that calculation of terminal t1/2 has no implementations. There was no indication that the pharmacokinetic properties of BIAsp 30 differed in healthy males and females (see attachment).

3. Are study results from study 031 similar to study 033?

The overall results were consistent with 031/UK and 033/D. BIAsp 30 was absorbed statistically significantly more rapidly than BHI 30. However, the estimates of all three pharmacokinetic endpoints were higher for both insulins in the euglycemic clamp trial. The higher estimates for $AUC_{ins,\ 0\text{-}90min}$ and

C_{max} in 033/D are related to the higher dose (0.3 U/kg) and, more importantly, a continuous infusion of basal insulin used in the euglycemic clamp procedure performed. The total serum insulin profiles in 033/D were not corrected for either of these factors. Therefore, parameters to be reported in labeling should be based on 031/UK.

Table 3 Area Under Curve during the first 90 minutes after injection (AUCins,0-90min) - Healthy Subjects

Trial	Dose[a] (U/kg)	$AUC_{ins,0-90min}$ (mU/l x hr) BIAsp 30 N	Mean	SD	BHI 30 N	Mean	SD
Single Dose							
031/UK	0.20	23	23.38	6.20	23	12.53	3.18
Clamp							
033/D[d]	0.30	24	60.21	22.48	24	26.30	7.64

a. All doses were administered s.c. into the abdominal wall
b. Long and thin crystal version of BIAsp 30 formulation
c. Short and broad crystal version of BIAsp 30 formulation
d. Sum of endogenous, exogenous and infused insulin

Table 4 Time to Maximum Concentration (t_{max}) - Healthy Subjects

Trial	Dose[a] (U/kg)	t_{max} (min) BIAsp 30 N	Median	1st to 3rd Quartile	BHI 30 N	Median	1st to 3rd Quartile
Single dose							
031/UK	0.20	23	60.0	[illegible]	23	110.0	[illegible]
Clamp							
033/D[d]	0.30	24	80.0	[illegible]	24	165.0	[illegible]

a. All doses were administered s.c. into the abdominal wall
b. Long and thin crystal version of BIAsp 30 formulation
c. Short and broad crystal version of BIAsp 30 formulation
d. Sum of endogenous, exogenous and infused insulin

Table 5 Maximum Concentration (C_{max}) - Healthy Subjects

Trial	Dose[a] (U/kg)	C_{max} (mU/l) BIAsp 30 N	Mean	SD	BHI 30 N	Mean	SD
Single dose							
031/UK	0.20	23	23.4	5.3	23	15.5	3.7
Clamp							
033/D[d]	0.30	24	61.25	20.10	24	29.90	8.13

a. All doses were administered s.c. into the abdominal wall
b. Long and thin crystal version of BIAsp 30 formulation
c. Short and broad version of BIAsp 30 formulation
d. Sum of endogenous, exogenous and infused insulin

Table 6 **Results of Analyses of BIAsp 30 versus BHI 30 - AUC_{0-90}, t_{max} and C_{max} - Healthy Subjects**

Insulin Endpoint	Diff/ Ratio[a]	95% C.I.	P-value
Single dose			
031/UK			
$AUC_{ins,\ 0-90\ min}$	1.86	[1.66 ; 2.07]	<0.001*
t_{max} (min)	-60.0	[-77.5 ; -42.5]	<0.001*
C_{max}	1.51	[1.35 ; 1.70]	<0.001*
Clamp			
033/D			
$AUC_{ins,\ 0-90\ min}$	2.24	[1.94;2.59]	<0.001*
t_{max} (min)	-95.0	[-135.0 ; -60.0]	<0.001*
C_{max}	2.02	[1.76;2.33]	<0.001*

a Ratios are presented for C_{max} and $AUC_{ins,\ 0-90\ min}$
Differences are presented for t_{max}
* Statistically significant

Although the corresponding estimates for $AUC_{ins,6-24hr}$ in 033/D were much higher than in 031/UK due to the euglycemic clamp procedure, the total serum insulin profile with BIAsp 30 remained similar to the BHI 30 profile from 6 to 24 hours.

Table 7 **Area Under Curve from 6 to 24 hours after injection ($AUC_{ins,6-24hr}$) - Healthy Subjects**

Trial[a]	Dose (U/kg)	$AUC_{ins,6-24hr}$ (mU/l x hr) BIAsp 30			BHI 30		
		N	Mean	SD	N	Mean	SD
Single dose							
031/UK	0.20	23	65.5	21.4	23	71.3	12.1
Clamp							
033/D[d]	0.30	24	243.2	36.1	24	261.4	41.5

a. All doses were administered s.c. into the abdominal wall
b. Long and thin crystal version of BIAsp 30 formulation
c. Short and broad crystal version of BIAsp 30 formulation
d. Sum of endogenous, exogenous and infused insulin

Table 8 **Analysis of AUC_{6-24hr} - BIAsp 30 versus BHI 30 - Healthy Subjects**

Trial Insulin Endpoint	Ratio BIAsp 30/BHI 30	95% C.I.	P-value
Single dose			
031/UK			
AUC_{6-24hr}	0.89	[0.76 ; 1.03]	0.110
Clamp			
033/D			
AUC_{6-24hr}	0.93	[0.85 ; 1.02]	0.120

Again, the sponsor didn't conduct study to compare the new combination formulation, BIAsp 30 versus

4. What are the comparisons between the time to reach per product AUC25%, AUC50%, AUC75%, and AUC100% and relative AUC25%, AUC50%, AUC75%, and AUC100% for insulin and glucose infusion rate?

To compare the performance of the new mixture product, times to achieve AUC25%, AUC50%, AUC75%, and AUC100% per product for insulin and glucose infusion rate were determined and compared (Type 1 comparison). In this type of comparison, the smaller the TAUC25% and TAUC50%, indicates the faster the absorption per product. We also expect the ratio of TAUC25% and TAUC50% of BIAsp 30 versus BHI to be less than 1.

In addition, the time for the new mixture product BIAsp 30 to reach the same AUC values of comparetors were calculated and compared. The smaller the TAUC values indicates the faster overall absorption and GIR action relative the comparetor.

Data from study 046 were not included in this analysis as food was given and insulin concentration was not corrected.

Table 9. Type 1 Pharmacokinetic comparisons

	Study 031		
Parameter	BIAsp 30	BHI 30	Ratio
TAUC25%	2.41(22)	3.32(14)	0.73
TAUC50%	5.45 (21)	6.80 (14)	0.81
TAUC70%	11.02 (16)	12.38 (15)	0.91
TAUC100%	23.83 (4)	24.00 (0)	0.99

	Study 033		
Parameter	BIAsp 30	BHI 30	Ratio
TAUC25%	2.78 (21)	4.58 (16)	0.61
TAUC50%	7.16 (22)	9.85 (15)	0.73
TAUC70%	14.70 (11)	15.92 (9)	0.93
TAUC100%	24.00 (0)	24.00 (0)	1.00

	Study 1086		
Parameter	IAsp	BIAsp 30	Ratio
TAUC25%	1.08 (24)	1.44 (20)	0.76
TAUC50%	1.74 (22)	2.61 (21)	0.68
TAUC70%	2.62 (24)	4.95 (20)	0.54
TAUC100%	10.00 (0)	24.00 (0)	0.42

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Table 10. Type 2 Pharmacokinetic comparisons

	Study 031		
Parameter	BIAsp 30	BHI 30	Ratio
TAUC25%	2.34 (23)	4.32 (14)	0.70
TAUC50%	5.39 (34)	6.80 (14)	0.79
TAUC70%	11.15 (40)	12.33 (15)	0.92
TAUC100%	15.81 (32)	24.00 (0)	0.66

	Study 033		
Parameter	BIAsp 30	BHI 30	Ratio
TAUC25%	2.48 (30)	4.58 (16)	0.55
TAUC50%	6.08 (38)	9.8S (13)	0.62
TAUC70%	11.85 (36)	15.92 (9)	0.74
TAUC100%	15.66 (24)	24.00 (0)	0.65

	Study 1086		
Parameter	IAsp	BIAsp 30	Ratio
TAUC25%	0.84 (27)	1.44 (20)	0.59
TAUC50%	1.27 (30)	2.61 (21)	0.49
TAUC70%	1.66 (35)	4.95 (20)	0.34
TAUC100%	2.27 (48)	24.00 (0)	0.09

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Table 11. Type 1 Pharmacodynamic comparisons

	Study 033		
Parameter	BIAsp 30	BHI 30	Ratio
TAUC25%	3.18 (15)	4.13 (17)	0.79
TAUC50%	6.48 (16)	8.33 (14)	0.79
TAUC70%	12.90 (14)	14.30 (12)	0.91
TAUC100%	23.98 (0)	24.00 (0)	1.00

	Study 1086		
Parameter	IAsp	BIAsp 30	Ratio
TAUC25%	1.91 (15)	2.17 (17)	0.89
TAUC50%	3.18 (16)	3.66 (14)	0.87
TAUC70%	4.78 (17)	5.70 (14)	0.85
TAUC100%	10.00 (0)	10.00 (0)	1.00

Table 12. Type 2 Pharmacodynamic comparisons

	Study 033		
Parameter	BIAsp 30	BHI 30	Ratio
TAUC25%	3.31 (21)	4.13 (17)	0.81
TAUC50%	7.30 (36)	8.33 (14)	0.87
TAUC70%	12.70 (34)	13.90 (11)	0.91
TAUC100%	17.02 (25)	24.00 (0)	0.71

	Study 1086		
Parameter	IAsp	BIAsp 30	Ratio
TAUC25%	1.84 (24)	2.17	0.85
TAUC50%	3.07 (26)	3.66	0.84
TAUC70%	4.52 (29)	5.65	0.80
TAUC100%	5.52 (29)	10.00	0.55

Both type 1 and type 2 comparisons indicate that BIAsp 30 has faster absorption and faster on set of action compared to BHI 30, and slower absorption and slower on set of action compared 100% IAsp.

5. What about the formulation consistency ?

The to be marketed formulation is slightly different than the testing formulations (see attachment). The pharmacokinetic and pharmacodynamic observations were neither confirmed for the to be marketed final formulation and nor a bioequivalence study was submitted to compare the testing formulation and the to be marketed formulation. Considering that this drug product is for s.c. injection, with the small changes in formulation it seems unlikely that the above PK and PD study conclusions would different.

III. RECOMMENDATION

The Division of Pharmaceutical Evaluation II of the Office of Clinical Pharmacology and Biopharmaceutics has reviewed Section 6 of NDA 21-172. To fulfill/meet the Agency's Bioavailability and Bioequivalence Requirements (21 CFR 320), the sponsor has submitted:

i) Pivotal studies to characterize and compare the bioavailability (i.e., systemic exposure) (031 and 033) and pharmacodynamic characteristics (033 and 1086) of the new insulin mixture product, IAsp 30 ([redacted] 70/30) to a appropriate US marketed reference product, BHI 30;

ii) A bioequivalence study to compare long, thin, very fragile crystals versus the short and broad crystals of protamine protracted fraction of BIAsp 30;

iii) A biopharmaceutics study in type 2 patients (046).

iv) And a study (1086) to compare the kinetics profile of BIAsp 30 versus 100% IAsp.

The formulations used in the above-mentioned studies 031, 033, however, are not the same as the to be marketed (clinical formulation) formulation (see formulation section). Data from study 046 has reference value but cannot be used as key data for product evaluation since food was given.

For meeting the Agency's bio-regulations, taking consideration of the formulation difference, the information submitted is insufficient to support the approval of the new insulin mixture product

It is recommended that a new study be requested to meet the combined requirements of the Medical Officer (i.e. the sponsor should compare the new 70/30 formulation versus ——— and the Clinical Pharmacology Reviewer (i.e. the sponser should conduct a PK and PD study with the to be marketed formulation for proper labeling support).

IV. SPECIFIC COMMENTS (TO BE CONVEYED TO THE SPONSOR)

1. An additional pharmacokinetic and pharmacodynamic study to compare the in vivo performance of BIAsp 30 versus ——— using the to be marketed BIAsp 30 formulation should be conduced and submitted for review and support labeling.

2. In future submissions, when compare the in vivo performance of two insulin products, the sponsor should calculate the geometric mean ratios and 90% CI of PK and PD parameters.

3. In future submissions, when compare the in vivo performance of two insulin products, the sponsor should also calculate the time to reach 25, 50, 75 and 100% AUC per product and their ratios (see table 9 of this review, for example), and the time to reach a pre-determined AUC value per product and their ratios (see table 10 of this review).

V. LABELING COMMENTS

Labeling rewording recommendations will be provided when the above requested PK and PD study using clinical formulation is submitted.

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Hf Sun, Ph.D.
Senior Pharmacokinetic reviewer / Pharmacometrics

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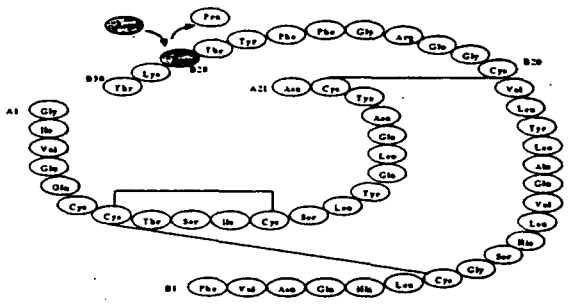
FI' initialed by John Hunt, Deputy
Division Director

cc: NDA 21-172 (orig., 1 copy), HFD-510 (Koller, Rhee), HFD-870 (Huang, Ahn, Hunt), HFD340 (Vish), Central Document Room (Barbara Murphy)

VI. APPENDIX

1. Chemistry of Aspart 30

IAsp is homologous to human insulin, with the exception of the substitution of the amino acid proline with aspartic acid at position 28 on the B-chain (see Figure 1). This substitution produces intermolecular charge repulsion and thereby reduces the tendency of the insulin molecules to self-associate. This causes s.c. IAsp to be absorbed more rapidly than regular human insulin (HI).



Molecular formula: $C_{256}H_{381}N_{65}O_{79}S_6$ Molecular weight: 5825.8

Figure 2 Structure of Insulin Aspart

2. Drug Formulation

Overview

Three formulations of BIAsp 30 were used in the clinical development program. The composition of each BIAsp 30 formulation is presented in Table 1. The formulation used for Phase II and Phase III clinical trials is identical to the final formulation. However, two earlier formulations were used in Phase I clinical trials. The differences between the three formulations involved

[ ]

There was no bioequivalence study to compare the phase I formulation vs. to be marketed formulation.

The protamine bound fraction of BIAsp 30 forms long, thin crystals, which are evident when viewed under a microscope. It was found that under certain conditions of physical stress, these crystals may be broken down to short and broad crystals. The bioequivalence of the two versions of BIAsp 30 (long and thin versus short and broad crystals) was demonstrated in healthy male and female subjects in 032/UK (see section VIII).

All batches of BIAsp 30 used in the clinical trials were produced by Novo Nordisk A/S. When marketed, BIAsp 30 will continue to be produced by Novo Nordisk A/S.

Table 13 Formulations for Clinical Trials of Biphasic Insulin Aspart 30.

Ingredients	Formulation Candidate C(0)	Optimized Formulation Candidate C(I)	Final Product Formulation C(II)
Trial	031/UK, 032/UK	033/D	046/NL,UK, 038/UK,D, 067/UK,D, [redacted] 1086
Insulin aspart	[redacted] nmol/ml	[redacted] nmol/ml	[redacted] nmol/ml
[redacted]	[redacted]	[redacted]	[redacted]
Mannitol	[redacted]	[redacted]	36.4 mg/ml [redacted]
Sodium chloride	[redacted]	0.58 mg/ml [redacted]	0.58 mg/ml [redacted]
Phenol	1.50 mg/ml [redacted]	1.50 mg/ml [redacted]	1.50 mg/ml [redacted]
m-Cresol	1.72 mg/ml [redacted]	1.72 mg/ml [redacted]	1.72 mg/ml [redacted]
Zinc	32.7 µg/ml [redacted]	32.7 µg/ml [redacted]	32.7 µg/ml [redacted]
[redacted]	[redacted]	[redacted]	[redacted]
Protamine sulphate	Approx. 0.33 mg/ml	Approx. 0.33 mg/ml	Approx. 0.33 mg/ml
Sodium Hydroxide	q.s. for pH-adjustment	q.s. for pH-adjustment	q.s. for pH-adjustment
Hydrochloric Acid	q.s. for pH-adjustment	q.s. for pH-adjustment	q.s. for pH-adjustment
[redacted]	[redacted]	[redacted]	[redacted]

q.s., quantum satis (sufficient quantity)

a) Drug Substance

The active ingredient in BIAsp 30 is IAsp. IAsp is the product of the [redacted] of genetically modified yeast cells.

[redacted] In IAsp, the amino acid proline has been replaced by the amino acid aspartic acid at the B28 position in the insulin molecule. Protamine forms crystals with IAsp. This results in delayed absorption of IAsp.

[redacted]

b) Drug Product

BIAsp 30 is a neutral biphasic suspension of IAsp monocomponent insulin; consisting of 30% soluble IAsp and 70% protamine-bound IAsp crystals. After re-suspension, the suspension appears uniformly white and cloudy.

c) Stability

Like other insulin preparations, BIAsp 30 should not be exposed to heat or sunlight, and must never be frozen. It has been shown that the drug product is adequately protected from light when packed as intended for marketing or when assembled in the injection devices. Once in use, the BIAsp 30 cartridge can be kept at ambient temperature (not above 30°C) for up to 4 weeks. On the basis of current stability studies, BIAsp 30 is estimated to have a shelf-life of [redacted] when stored between 2°C to 8°C and protected from light.

VII. ANALYTICAL METHODS

VIII. PHARMACOKINETICS IN TYPE 2 DIABETIC SUBJECTS

The pharmacokinetic profile of BIAsp 30 has been investigated in Type 2 diabetic subjects in one phase II trial (046/NL,UK). Due to problems in analytical method and study design, The study was not fully reviewed rather than listed for reference.

The trial designs and results for the clinical pharmacology trials with Type 2 diabetic subjects are summarized in Trial Tabulation A.2. The corresponding pharmacokinetic parameters are summarized in Trial Tabulation B.2.

The pharmacokinetic profile of BIAsp 30 observed in Type 2 diabetic subjects corresponded with that observed in healthy subjects. Total serum insulin concentrations increased more rapidly and reached higher peak concentrations with BIAsp 30 compared to BHI 30 following both dinner and breakfast; see

Figure 3 and Table 8. Serum insulin concentrations were lower both before and after lunch while subjects were treated with BIAsp 30.

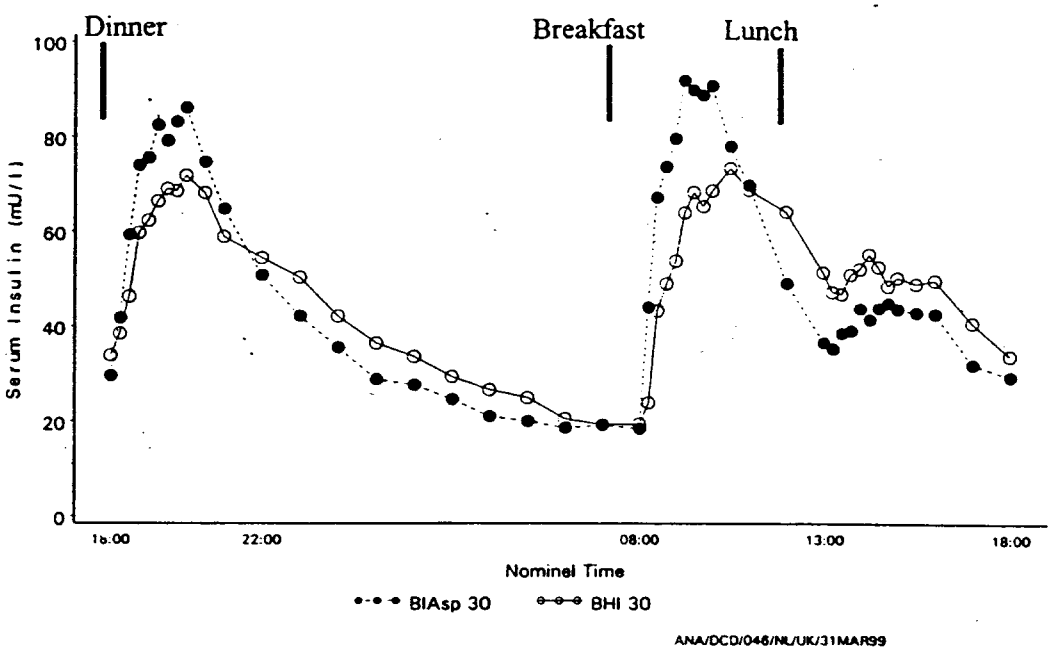


Figure 3 **Estimated Mean 24-hour Total Serum Insulin Profiles - Type 2 Diabetic Subjects (046/NL,UK)**

BIAsp 30 was absorbed more rapidly than BHI 30 when both insulins were administered s.c. immediately before the meal. The estimated AUC during the 2-hour interval following treatment with BIAsp 30 was 17% greater after dinner, and 44% greater after breakfast than when subjects were treated with BHI 30.

The median t_{max} for BIAsp 30 after dinner and breakfast was 95 minutes. t_{max} occurred approximately 48 minutes earlier following dinner and 62 minutes earlier following breakfast with BIAsp 30 than with BHI 30; only the difference following breakfast was statistically significant. t_{max} for BIAsp 30 occurred after 95 minutes (median) in Type 2 diabetic subjects compared to 60 minutes (median) in healthy subjects.

Table 14 **Pharmacokinetics of BIAsp 30 and BHI 30 Based on Estimates of Total Serum Insulin - Type 2 Diabetic Subjects (046/NL,UK)**

Insulin		BIAsp 30		BHI 30		Treatment Comparison	
Endpoint	N	mean (median)	SD (Q1-Q3)[c]	mean (median)	SD (Q1-Q3)[c]	Ratio/ Diff[b]	95% C.I
AUC (mU/l×hr)[a]							
$AUC_{ins,\ 0\text{-}2h\ (dinner)}$	13	136	72	114	66	1.17	[1.01 ; 1.36]*

$AUC_{ins,\ 0\text{-}2h\ (breakfast)}$	13	144	68	102	55	1.44	[1.16 ; 1.78]*
t_{max} (min)[b]							
$t_{max\ (ins.\ dinner)}$	13	89	32	137	83	-47.9[c]	[-97.6 ; 1.7]
		(95)	[redacted]	(124)	[redacted]		
$t_{max\ (ins.\ breakfast)}$	13	94	35	155	42	-61.5[c]	[-94.9 ; -28.2] *
		(95)	[redacted]	(155)	[redacted]		
C_{max} (mU/l)[a]							
$C_{max\ (ins.\ dinner)}$	13	96	54	79	43	1.18[d]	[1.03 ; 1.36] *
$C_{max\ (ins.\ breakfast)}$	13	108	55	81	45	1.35[d]	[1.10 ; 1.66] *

*Statistically significant

Ratios are presented for C_{max} and AUC

Differences are presented for t_{max}

The estimated mean difference and confidence interval (C.I.) are based on an ANOVA with adjustment for sex and centre

The estimated ratio and confidence interval (C.I.) are based on an ANOVA with Log-transformed response and adjustment for sex and centre

e.Q1 and Q3 are the 1st and 3rd quartiles, respectively

C_{max} was 18% and 35% higher following dinner and breakfast with BIAsp 30 than with BHI 30; both differences were statistically significant. Note that it is not possible to compare the estimates for C_{max} in Type 2 diabetic subjects with those for healthy subjects, as insulin dose in Type 2 diabetic subjects varied according to individual needs.

When serum IAsp was measured with the IAsp-specific [redacted] assay, the pharmacokinetics of the resulting 24-hour serum IAsp profiles correspond closely with the mean 24-hour total serum IAsp profile. AUC and C_{max} following dinner and breakfast were approximately 25% lower with the IAsp-specific profile than the total insulin profile, however, median t_{max} was the same.

IX. BIOEQUIVALENCE TRIAL - LONG AND THIN VERSUS SHORT AND BROAD CRYSTALS

The protamine bound fraction of BIAsp 30 forms long, thin, very fragile crystals, which are evident when viewed under a microscope. It was found that the crystals may be broken down to short and broad crystals under certain conditions of physical stress.

A crossover trial comparing the pharmacokinetics of the two versions indicated that crystal form and size have no influence on the kinetics of the protamine protracted fraction of BIAsp 30. The 90% C.I. for $AUC_{ins,\ 0\text{-}24\ h}$ and $C_{max(ins,\ 0\text{-}24\ h)}$ satisfied the bioequivalence criteria. t_{max} was unaffected by crystal form and size. Thus, BIAsp 30 composed of either long and thin crystals is bioequivalent with BIAsp 30 composed of short and broad crystals. This was further supported by the comparisons of $AUC_{(ins,\ 6\text{-}24\ h)}$ which predominantly reflects the concentration-time profiles for protamine protracted portion of BIAsp 30, was within the [redacted] range (Table 11).

Table 15 Bioequivalence Analyses of Long and Thin versus Short and Broad BIAsp 30 Crystals - Healthy Subjects (032/UK)

Insulin Endpoint	N	Long Thin Crystals mean (median)	SD (Q1-Q3)[a]	Short Broad Crystals mean	SD	Treatment Comparison Ratio/ Diff[b]	90% C.I
AUC (mU/l×hour)							
$AUC_{ins,6-24hr}$	22	57.3	19.0	54.7	14.8	1.04	[0.93 ; 1.15]
$AUC_{ins,\ 0-24hr}$	22	140.1	25.9	130.4	27.4	1.08	[1.02 ; 1.15]
t_{max} (min)[b]	22	68.2	68.9	68.9	42.6	0.00	[-7.5 ; 15.0]
		(60.0)		(60.0)			
C_{max} (mU/l)	22	26.0	9.5	23.7	8.6	1.10	[0.96 ; 1.25]

Pooled data for men and women

a. Q1 and Q3 are the 1st and 3rd quartiles, respectively

b. Difference is presented for t_{max}

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New Drug Application Filing Memorandum

Office of Clinical Pharmacology and Biopharmaceutics

NDA:	21-172	**Priority Classification:**	
IND:		**Indication:**	Diabetes
Brand Name:	[redacted] 70/30 injection	**Submission Date:**	12/17/99
Generic Name:	Biphasic Insulin Aspart 30	**Route of Administration:**	SC
Chemical Type:		**UFGD:**	
Sponsor:	Novo Nordisk	**Review Division:**	HFD-870
Reviewer:	Xiaoxiong (Jim) Wei, Ph.D.	**Medical Division:**	HFD-510
Team Leader:	Hae-Young Ahn, Ph.D.		

Items included in NDA (CTD)	*Yes*	*No*	*Request*
Table of Contents present and sufficient to locate reports, tables, data, etc.	X		
Tabular Listing of All Human Studies	X		
HPK Summary	X		DISK
Study Synopses	X		DISK
Labeling	X		DISK
Bioavailability and Bioequivalence Studies:			
ADME Study –	X		
BA Studies – **Absolute BA** **Relative BA**		X	
BE Studies – **Average BE** **Population BE** **Individual BE**	X		
Food-Drug Interaction Study		X	
In Vitro-In Vivo Comparison (IVIVc) Studies		X	
Reference Bioanalytical and Analytical Methods	X		
Dissolution Profiles		X	
Studies Using Human Biomaterials		X	
Plasma Protein Binding Studies		X	
Metabolism Studies Using Hepatocytes, Microsomes, etc.		X	
Blood / Plasma Ratio		X	
Human Pharmacokinetics (PK) Studies:			
PK and Initial Safety and Tolerability in Healthy Volunteers – **Single Dose** **Multiple Dose**	X		
PK and Initial Safety and Tolerability in Patient Volunteers – **Single Dose** **Multiple Dose**	X		
Dose Proportionality – **Single Dose** **Multiple Dose**		X	
PK in Population Subsets to Evaluate Intrinsic Factor Effects – **Ethnicity** **Gender** **Pediatrics**		X	

/S/

Xiaoxiong (Jim) Wei, Ph.D.; FDA / CDER / OPS / OCPB / DPE-II

/S/ 1/24/00

Hae-Young Ahn, Ph.D., Team Leader; FDA / CDER / OPS / OCPB / DPE-II

CC: NDA 21-172, HFD-510 (Rheej, Koller), HFD-850 (Lee), HFD-870 (Huang, Ahn, Wei), CDR (MurphyB)