# CLINICAL REVIEW

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| Application Type | NDA 21629 |
| Submission Number | 015 |
| Submission Code | SE-05 |
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| Reviewer Name | K. Eddie Gabry, M.D.<br>Hylton V. Joffe, M.D., M.M.Sc. |
| Review Completion Date | October 2, 2008 |
| Established Name | Insulin glulisine |
| Trade Name | Apidra |
| Therapeutic Class | Rapid Acting Insulin Analog |
| Applicant | Sanofi-Aventis |
| Priority Designation | S |
| Formulation | Solution for injection |
| Dosing Regimen | Variable |
| Indication | Diabetes mellitus |
| Intended Population | Pediatric subjects age 4-17 years |

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# 1 EXECUTIVE SUMMARY

## 1.1 Recommendation on Regulatory Action

Approval. This supplement satisfies the Sponsor's pediatric postmarketing requirement for subcutaneously administered Apidra.

## 1.2 Recommendation on Postmarketing Actions

### 1.2.1 Risk Management Activity

There is no need for a postmarketing risk management plan for the pediatric use of Apidra beyond the package insert and patient package insert. The American Diabetes Association Clinical Practice Guidelines recommends higher HbA1c targets for children compared to adults, because of vulnerability to hypoglycemia. Based on the results of Study 3001, there are no other unique safety concerns with Apidra in children that warrant Risk Evaluation and Mitigation Strategies (REMS).

### 1.2.2 Required Phase 4 Commitments

In the approval letter for Apidra, the Division waived the required pediatric study requirement for Apidra under the Pediatric Research Equity Act (PREA) for ages newborn up to four years and deferred pediatric studies for ages five to seventeen years. The current supplement satisfies this deferred pediatric postmarketing requirement. In addition, the current supplement does not trigger a new requirement for pediatric studies with Apidra. This submission was presented to the Pediatric Review Committee (PeRC), which agreed with the above conclusions.

### 1.2.3 Other Phase 4 Requests

None.

## 1.3 Summary of Clinical Findings

### 1.3.1 Brief Overview of Clinical Program

Study 3001 was the only newly completed clinical trial included in the current submission. Study 3001 was a multicenter, multinational, open-label, randomized, non-inferiority study. Patients 4-17 years old with type 1 diabetes entered a 4-week run-in period on lispro + NPH or lispro + glargine. At the end of the run-in period, 572 patients were randomized 1:1 to 26 weeks of treatment with Apidra or lispro administered at least twice daily by subcutaneous injection

within 15 minutes prior to meals. Randomization was stratified by type of long-acting insulin (NPH or glargine). During the study, NPH was administered twice daily, and glargine was administered once daily in the evening. Investigators were to titrate study medication to achieve pre-specified, age-specific glycemic targets. The titration procedure was left to the discretion of the investigators.

The primary efficacy endpoint was the change in glycated hemoglobin (GHb) from baseline to endpoint. The sponsor pre-specified that Apidra would be declared non-inferior to lispro if the upper limit of the 95% confidence interval for the difference of the two treatments (Apidra minus lispro) was less than 0.4%.

### 1.3.2 Efficacy

The mean baseline GHb was 8.2% in both treatment groups. In the primary efficacy analysis, the adjusted mean change in GHb from baseline to endpoint was very small: +0.1% with Apidra and +0.2% with lispro. The 95% confidence interval for the change in GHb with Apidra relative to lispro was -0.2% to 0.1%. Because the upper limit of this confidence interval (0.1%) was less than the pre-specified margin (0.4%), Apidra was declared non-inferior to lispro. Subgroup analyses of GHb based on age, duration of diabetes, baseline GHb, and type of long-acting insulin yielded results consistent with the overall primary efficacy findings.

The rapid-acting insulin, basal insulin, and total daily insulin doses were comparable between the 2 treatment groups at baseline with very small changes from baseline to endpoint, consistent with the minimal changes in HbA1c over the course of the trial.

Less than one-half of patients in the 6-12 year-old age group and less than one-third of patients in the 13-17 year-old age group met the age-specific GHb targets at baseline and study end.

### 1.3.3 Safety

In Study 3001, there were no clinically relevant differences between the Apidra-treated patients and insulin lispro-treated patients with respect to the frequency and type of adverse events, serious adverse events and adverse events of special interest (e.g., hypoglycemia, hypersensitivity reactions, injection site abnormalities, diabetic ketoacidosis, body weight changes). There were no unexpected findings among Apidra-treated patients and the safety profile in the study is consistent with what is expected in a pediatric population with type 1 diabetes.

Of note, over the 26-week treatment period, 16% of the Apidra-treated patients and 19% of the insulin lispro-treated patients reported at least 1 episode of severe, symptomatic hypoglycemia (requiring the assistance of another person to treat and either having a blood glucose <36 mg/dL or showing prompt recovery after oral carbohydrate, intravenous glucose, or glucagon administration). The incidence rate of this event was similar in the 2 treatment groups (125 events with Apidra corresponding to 0.1 episode per patient per month vs. 132 events with insulin lispro corresponding to 0.1 episode per patient per month). This incidence rate is higher

than the rate of severe hypoglycemia seen in the Apidra trials of adults with type 1 diabetes but is not unexpected. The American Diabetes Association Clinical Practice Guidelines recommends higher HbA1c targets for children compared to adults, because of vulnerability to hypoglycemia. Nonetheless, the higher incidence of severe hypoglycemia in the pediatric study will be included in the package insert.

The analyses of antibody data indicate that Apidra does not elicit a significant anti-insulin antibody response and that there were no clinically relevant effects associated with anti-insulin antibody formation, except, perhaps, more favorable changes in GHb for patients who had the greatest increases in cross-reactive insulin antibodies.

Global, postmarketing pediatric data are limited but have not identified unique safety signals in children compared to adults treated with Apidra. There have been reports in adults of medication error mix-ups involving Apidra and insulin glargine (Lantus). **(b) (4)** .

## 1.3.4 Dosing Regimen and Administration

Apidra is a rapidly-acting insulin that is typically administered subcutaneously within 15 minutes prior to a meal in patients with diabetes or used continuously in an insulin pump. The current submission did not evaluate a new dosing regimen or route of administration. Instead, the current submission tested the safety and efficacy of premeal, subcutaneous Apidra in a new patient population - children with type 1 diabetes.

## 1.3.5 Drug-Drug Interactions

The current submission does not contain new data on drug interactions with Apidra.

## 1.3.6 Special Populations

The current submission tested the safety and efficacy of subcutaneous, premeal insulin in children with type 1 diabetes and does not contain information on other patient populations. Please see the currently approved Apidra label for information about the use of Apidra in other patient populations.

# 2 INTRODUCTION AND BACKGROUND

## 2.1 Product Information

Apidra (insulin glulisine) is a recombinant human insulin analog with a faster onset of action than regular human insulin. Insulin glulisine differs from human insulin in that the amino acid asparagine at position B3 is replaced by lysine and the lysine in position B29 is replaced by glutamic acid. Apidra was approved on April 16, 2004 for subcutaneous administration to control hyperglycemia in adults with diabetes mellitus. In the approval letter for Apidra, we waived the required pediatric study requirement under PREA for ages newborn up to four years and deferred pediatric studies for ages five to seventeen years. The current efficacy supplement contains the final study report for the deferred pediatric postmarketing study commitment, which was submitted several months before the December 21, 2007 due date. Obtaining efficacy and safety information for the insulin products in the pediatric population is important because type 1 diabetes has its peak onset in the pediatric age group.

## 2.2 Currently Available Treatment for Indications

The following recombinant mealtime insulins are currently available for the treatment of type 1 and type 2 diabetes.

- Apidra (insulin glulisine)
- NovoLog (aspart)
- Humalog (lispro)
- Humulin (recombinant regular human insulin)
- Novolin (recombinant regular human insulin)

Animal-derived (beef and pork) insulins are no longer marketed.

Apidra, Humalog, and NovoLog have a more rapid onset of action than regular human insulin. As a result, these insulin analogs can be administered within 15 minutes of a meal (compared to 30-45 minutes before a meal for regular human insulin).

Novo Nordisk recently submitted the results from a pediatric insulin pump study that triggered a change of their NovoLog label to the PLR format. Based on results from a previously reviewed subcutaneous injection (ages 6-18) study and the newly submitted insulin pump study (ages 4-18) in children with type 1 diabetes, we granted NovoLog an indication for the treatment of adults and children with diabetes.

The Humalog label contains results from 2 cross-over studies evaluating subcutaneous injection in children (3-19 years old) with type 1 diabetes. Humalog is indicated for treating patients with diabetes. We are permitting Lilly, the manufacturer of HumaLog, to market Humalog for

subcutaneous injection to children. (b) (4)

The current Apidra label contains results from a small pharmacokinetic and pharmacodynamic study of Apidra vs. regular human insulin in children and adolescents 7-16 years of age with type 1 diabetes. As a result, the current Apidra label states that Apidra is only indicated for the treatment of adults with diabetes.

### 2.3 Availability of Proposed Active Ingredient in the United States

Apidra is marketed and widely available in the United States.

### 2.4 Important Issues With Pharmacologically Related Products

Hypoglycemia is the major safety concern with all insulin therapy, particularly in patients with type 1 diabetes. The incidence of hypoglycemia increases as glycemic control is tightened.

Anti-insulin antibodies develop in a subset of patients treated with insulin analogs, including Apidra. The clinical significance of these antibodies is unknown. However, these antibodies do not appear to alter the efficacy or safety profile of the insulin products.

Severe, life-threatening, generalized allergy, including anaphylaxis can occur with any insulin product.

### 2.5 Presubmission Regulatory Activity

The protocol for Study 3001 was reviewed as a Special Protocol Assessment (SPA). In a letter dated July 21, 2004, FDA informed the Sponsor that "The Agency concurs that study HMR1964D/3001 qualifies as a valid assessment of the efficacy and safety of the use of Apidra™ in a pediatric population to support the claim of pediatric use."

At the time of the SPA review, the biometrics reviewer noted that the protocol was not clear on the imputation method proposed for the missing data for the intent-to-treat analysis. Dr. Lee Pian (Biostatistics) has reviewed the study results and notes that the sponsor used the last observation carried forward, which is a standard imputation method for diabetes trials.

## 3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

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

This supplement does not contain new chemistry data.

### 3.2 Animal Pharmacology/Toxicology

This supplement does not contain new non-clinical pharmacology or toxicology data.

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

### 4.1 Sources of Clinical Data

The current submission includes:

- One clinical pharmacology study (Study HMR1964A/1017, hereafter referred to as Study 1017), which was submitted with the original NDA and is included for reference in the current efficacy supplement. Study 1017 was a single center, double-blind, randomized, two-way crossover study that investigated the pharmacokinetics and pharmacodynamics of a single subcutaneous injection of insulin glulisine (0.15 U/kg) and regular human insulin (0.15 IU/kg) in 10 children (7-11 years old) and 10 adolescents (12-16 years old) with type 1 diabetes. Information from this study is included in the currently approved Apidra label.

- One completed phase 3 study (Study HMR1964D/3001, hereafter referred to as Study 3001). The current efficacy supplement contains the complete study report for this 26-week, multicenter, open-label, parallel-group clinical trial, which compared the efficacy and safety of Apidra to insulin lispro in children and adolescents with type 1 diabetes also treated with NPH insulin or glargine.

The efficacy supplement was submitted electronically to the Electronic Document Room (EDR) and was accessed at \\CDSESUB1\N21629\S_015\2007-06-27.

## 4.2 Tables of Clinical Studies

**Table 1. Pediatric development program**

| Type of study | Study identifier Patient population | Study objectives and design | Treatments | Number of subjects |
|---|---|---|---|---|
| PK/PD Safety | HMR1964A/1017<br><br>Pediatric subjects with type 1 diabetes | PK, PD and safety<br><br>Single-center, double-blind, randomized, 2-way crossover study<br><br>Single dose | Insulin glulisine 0.15 IU/kg SC x 1<br>vs.<br>Regular human insulin 0.15 IU/kg SC x 1 | 20 randomized<br>20 completed<br><br>10 adolescents and 10 children |
| Efficacy Safety | EFC6096 (HMR1964D/3001)<br><br>Pediatric subjects with type 1 diabetes | Efficacy and safety<br><br>Multicenter, open-label, parallel-group, randomized<br><br>26-weeks | Insulin glulisine SC<br>vs.<br>Insulin lispro SC<br><br>at least twice daily with basal insulin therapy (NPH or insulin glargine) | 572 randomized<br>552 completed<br><br>277 Apidra<br>295 Lispro |

## 4.3 Review Strategy

This review focuses on the newly completed phase 3 study (3001) because the other study, the single dose pharmacokinetic/pharmacodynamic study (1017) was submitted with the original NDA and reviewed at that time.

Dr. Gabry performed the initial efficacy and safety review of Study 3001. Dr. Joffe performed a secondary review of this study. The current document integrates the findings from both Dr. Gabry's and Dr. Joffe's reviews and serves as both the primary medical officer review and clinical team leader memorandum.

This submission triggered conversion of the Apidra label to PLR format. The review disciplines, as well as members of the SEALD team and the Division of Risk Management revised the proposed PLR label and patient labeling, accordingly.

## 4.4 Data Quality and Integrity

The Sponsor submitted a debarment certification statement confirming that no debarred persons were used in connection with this application. No FDA site inspections were conducted for this

efficacy supplement. The Sponsor took several important steps to ensure the accuracy of the study data, including study initiation meetings at each site prior to subject enrollment, site monitoring, and an independent double data entry method to ensure accurate transfer of data from case report forms to the database.

### 4.5 Compliance with Good Clinical Practices

Study 3001 appears to have been conducted according to Good Clinical Practices. The protocol was approved by Independent Ethics Committees and Institutional Review Boards. Because the study participants were children and adolescents, the protocol required a signature from a representative who was legally authorized to consent on behalf of the child. Children who were able to understand the nature, scope, and possible consequences of the study also gave informed consent or assent.

### 4.6 Financial Disclosures

The Sponsor submitted FDA Form 3454 stating that none of the investigators involved in Study 3001 had any known financial conflicts of interest.

## 5 CLINICAL PHARMACOLOGY

This efficacy supplement also contained a written report for Study 1017, which was a single-dose, double-blind, randomized, cross-over pharmacokinetic (primary objective) and pharmacodynamic (secondary objective) study in 20 children and adolescents with type 1 diabetes. This study compared single subcutaneous doses of Apidra (0.15 units/kg) and recombinant human insulin (0.15 units/kg). Ten subjects were between 7 and 11 years of age and the remaining 10 subjects were between 12 and 16 years of age. This study was previously reviewed aspart of the Apidra original NDA; therefore, the findings are not re-reviewed here. Please see Dr. Manoj Khurana's clinical review (DFS July 17, 2008) for a summary of the pertinent findings. Dr. Khurana noted that some of the pharmacokinetic parameters in the clinical pharmacology section of the currently approved label were based on model predicted values instead of observed data. Dr. Khurana requested the electronic raw datasets for the pertinent clinical pharmacology studies and has revised the values in the label accordingly. Of note, Drs. Khurana and Choe have maintained the following language in the label "The relative differences in pharmacokinetics and pharmacodynamics between APIDRA and regular human insulin in these patients with type 1 diabetes were similar to those in healthy adult subjects and adults with type 1 diabetes."

# 6 INTEGRATED REVIEW OF EFFICACY

## 6.1 Indication: Glycemic control in patients with diabetes mellitus

The Sponsor proposes using the results from the current phase 3 pediatric study to broaden the indication for Apidra from "APIDRA is indicated for the treatment of adult patients with diabetes mellitus for the control of hyperglycemia" to (b) (4)

### 6.1.1 Methods

The only new information to support the pediatric indication is the 26-week phase 3 study (3001), which is summarized in Sections 4.1 and 6.1.3.

### 6.1.2 General Discussion of Endpoints

The primary efficacy measure in Study 3001 was the change from baseline to endpoint in glycated hemoglobin (GHb), which was measured using affinity chromatography at a centralized laboratory that is standardized to the data from the Diabetes Control and Complications Trial (DCCT). The Sponsor chose GHb (which measures all glycated hemoglobin) instead of HbA1c as the primary efficacy measure because of lower susceptibility of GHb to degrade over the time required to ship specimens to the single central laboratory from multinational study sites. The Sponsor reports that the correlation between GHb and HbA1c is >0.97 and references the original NDA for Apidra, which also used GHb as the primary efficacy measure.

The primary efficacy analysis was to demonstrate non-inferiority of Apidra to insulin lispro for the change in GHb from baseline to endpoint. The prespecified non-inferiority margin was 0.4%, which has been accepted by FDA for other active-controlled trials testing insulin therapies, including the adult Apidra clinical development program. Therefore, non-inferiority would be concluded if the upper bound of the 95% confidence interval for the difference of the two treatments (Apidra minus lispro) was less than 0.4%.

### 6.1.3 Study Design (Study 3001)

Study 3001 was a multicenter (65 sites), multinational (16 countries including the United States), open-label, randomized, active controlled, parallel group non-inferiority study. Patients 4-17 years old with type 1 diabetes entered a 4-week run-in period on lispro + NPH or glargine. At the end of the run-in period, patients were randomized 1:1 to 26 weeks of Apidra or lispro administered at least twice daily by subcutaneous injection within 15 minutes prior to a meal. Randomization was stratified by type of long-acting insulin (NPH or glargine). During the study, NPH was administered twice daily, and glargine was administered once daily in the evening.

**Reviewer's comments: The open-label design is not ideal for a non-inferiority trial, because differential management of glycemia could bias results towards non-inferiority. That said, active-controlled insulin trials have traditionally had open-label designs because of difficulty blinding insulin therapies.**

After the baseline visit, clinic visits occurred at Week 4, 12, 18 and 26. There was a mandatory telephone visit (or optional clinic visit) at Week 2.

Study assessments included:

- Vital signs and body weight at Week -5, Day 1, Week 12 and 26
- Pregnancy test for postmenarchal girls at Week -5 and Week 26.
- Clinical chemistry and hematology at Week -5, Day 1, and Week 26
- GHb and insulin antibodies (both at centralized labs) at Day 1, Week 12 and 26
- Self-monitored blood glucose (SMBG) profiles at 3 timepoints (fasting before breakfast, before the main meal of the day, and 2 hours after the start of the main meal of the day) on 3 different days in the week before the Day 1 and Week 4, 12, 18, and 26 visits.
- Review of hypoglycemic events and adjustments in insulin dose at all visits

**3. Treatments:** Patients randomized to Apidra started the treatment phase with the same dose they would have used if they remained on lispro. The number of daily injections of Apidra or lispro was decided during the run-in period and was not altered from the time of randomization until the end of the study, unless deemed necessary for safety reasons. NPH and Apidra or lispro could be mixed (this was decided at the start of the run-in phase and remained the same throughout the study). Investigators were to titrate study medication to achieve pre-specified, age-specific glycemic targets (Table 2). The titration procedure was left to the discretion of the investigators. Investigators assessed compliance by inspecting cartridges/vials and roughly comparing the number of units of insulin preparations used with the estimated number of insulin units that should have been used since last drug dispensing.

**Table 2. Titration goals for blood glucose**

| Fasting or pre-meal value | Plasma-referenced blood glucose meters | Whole blood-referenced blood glucose meters |
|---|---|---|
| <8 years old | 106-150 mg/dL | 100-140 mg/dL |
| ≥8 years old | 95-150 mg/dL | 90-140 mg/dL |
| **2-hour post-prandial value** | | |
| <8 years old | 128-194 mg/dL | 120-180 mg/dL |
| ≥8 years old | 106-172 mg/dL | 100-160 mg/dL |

**4. Study population:**

Major inclusion criteria included:

- Age 4-17 years with type 1 diabetes for at least 1 year prior to screening
- Uninterrupted insulin therapy for at least 1 year prior to screening and on a stable regimen consisting of either NPH or glargine as the basal insulin
- HbA1c 6-11%
- Signed informed consent by parent/legal guardian and child assent (if applicable)

Major exclusion criteria included:
- Systemic corticosteroids in the month before screening
- Active, proliferative retinopathy
- Pancreatectomized subjects or prior pancreas/islet cell transplantation
- Seizure disorder
- Severe hypoglycemia in the 3 months prior to screening or hypoglycemia unawareness
- Laboratory abnormalities exceeding pre-defined criteria (e.g., serum creatinine >1.5x ULN, ALT >2x ULN)

**5: Efficacy endpoints:** Please see Section 6.1.2. The primary efficacy endpoint was the change in GHb from baseline to endpoint.

Secondary efficacy endpoints included:
- GHB change from baseline at Week 12 and 26
- Responder analyses (e.g., GHb <8.5% at Week 12 and 26)
- SMBG profiles (e.g., means, postprandial excursions)
- Symptomatic hypoglycemia (discussed in the safety section of the review)
- Insulin doses (collected with the SMBG profiles)

**6. Statistics:** The primary analysis population was the modified intent-to-treat (ITT) population (all randomized patients who received at least one dose of study medication having a baseline and at least one post-baseline efficacy evaluation). To assess robustness of the results, the Sponsor also analyzed the efficacy endpoints using the per-protocol population (randomized patients with no pre-defined major protocol violations and treatment duration of at least 20 weeks). Hypoglycemia was listed as an efficacy parameter, but was analyzed using the safety population (all patients who received at least 1 dose of study medication).

The primary endpoint was analyzed using an ANCOVA model with treatment, type of basal insulin at randomization, and center as fixed effects and baseline GHb as a covariate. The pre-specified non-inferiority margin was 0.4%, which has been accepted by FDA for other active-controlled trials testing insulin therapies. Therefore, non-inferiority would be concluded if the upper limit of the 95% confidence interval for the difference of the two treatments (Apidra minus lispro) was less than 0.4%. If non-inferiority is established, the Sponsor would test for superiority.

The Sponsor estimated that enrollment of 560 patients would have 90% power to show non-inferiority with a margin of 0.4% assuming a drop-out rate of 20%, a standard deviation for GHb of 1.3%, a one-sided alpha of 0.025, and a true difference between treatment groups of zero.

Please see Dr. Pian's biometrics review for further details.

### 6.1.4 Efficacy Findings

A total of 277 patients were treated with insulin glulisine and 295 with insulin lispro. The median treatment duration was 26 weeks in both treatment groups.

A. Primary Efficacy Analysis:

In the modified ITT, the mean baseline GHb was 8.2% in both treatment groups. The adjusted mean change in GHb from baseline to study end was very small: +0.1% with Apidra and +0.2% with lispro. The 95% confidence interval for the change in GHb with Apidra relative to lispro was -0.2% to 0.1% (Table 3). Therefore, Apidra is non-inferior to lispro with regard to change in GHb because the upper limit of this 95% confidence interval is less than the pre-specified non-inferiority margin of 0.4%. Dr. Pian confirmed these results (please see her biometrics review for additional details). The per-protocol population (12 fewer Apidra-treated patients and 18 fewer lispro-treated patients) yielded virtually identical results.

**Table 3: Change from baseline at endpoint for GHb (modified intent-to-treat and per-protocol populations)**

| Timepoint | Apidra | | Lispro | | Apidra – Lispro |
|---|---|---|---|---|---|
| | N | Mean (SD)* | N | Mean (SD)* | Difference in adjusted mean (95% CI) |
| **Modified intent-to-treat population** | | | | | |
| Baseline | 271 | 8.2 (1.1) | 291 | 8.2 (1.0) | |
| Endpoint | 271 | 8.3 (1.4) | 291 | 8.4 (1.3) | |
| Adjusted mean change | 271 | 0.1 (0.1) | 291 | 0.2 (0.1) | - 0.1 (-0.2 ; 0.1) |
| **Per protocol population** | | | | | |
| Baseline | 259 | 8.2 (1.1) | 273 | 8.1 (1.0) | |
| Endpoint | 259 | 8.3 (1.4) | 273 | 8.3 (1.3) | |
| Adjusted mean change | 259 | 0.1 (0.1) | 273 | 0.1 (0.1) | - 0.1 (-0.2 ; 0.1) |

*Standard deviation (SD) for mean and standard error (SE) for adjusted mean

B. Select Secondary Analyses:

**Responder analyses:** Approximately 60% of patients in both treatment arms had a baseline GHb <8.5%. As expected (based on the small adjusted mean reduction in GHb from baseline to endpoint), the proportion of patients with GHb <8.5% remained essentially unchanged in both treatment groups throughout the study (Table 4). Approximately one-fifth of the patients in both treatment groups had a decrease in GHb >0.7% at Weeks 12 and 26, but these patients had

unusually large responses given that the adjusted mean change in HbA1c was 0.1% in the Apidra group and +0.2% with lispro.

**Table 4. Number of subjects reaching GHb categories (modified intent-to-treat population)**

| | Apidra N (%) | Lispro N (%) |
|---|---|---|
| **Subjects with GHb <8.5%** | | |
| Baseline | 161 (59) | 181 (62) |
| Week 12 | 167 (65) | 174 (63) |
| Week 26 | 156 (61) | 152 (57) |
| Endpoint | 168 (62) | 167 (57) |
| **Subjects with a decrease of GHb of >0.7%** | | |
| Week 12 | 49 (19) | 54 (20) |
| Week 26 | 46 (18) | 49 (18) |
| Endpoint | 48 (18) | 53 (18) |

**Age-Specific Responder Analyses:** The American Diabetes Association (ADA) 2008 Clinical Practice Guidelines recommends less stringent HbA1c targets for children and adolescents (>7.5% to <8.5% for children 0-6 years of age; <8% for children 6-12 years of age; <7.5% for adolescents and young adults 13-19 years of age) compared to adults (<7%) because of vulnerability to severe hypoglycemia.

The Sponsor added these age-specific responder analyses after the protocol was finalized but prior to database lock.

Data from the <6 year-old age group are limited by small sample sizes (3 patients in the Apidra group and 5 patients in the lispro group). In the 6-12 year-old age group, a similar proportion of patients in both treatment groups achieved the age-specific GHb target of <8% at baseline and endpoint (44-48%). In the 13-17 year-old age group, the proportion of Apidra-treated patients with GHb <7.5% increased from 24% at baseline to 31% at endpoint, whereas the lispro-treated group had a similar proportion of patients with GHb <7.5% at baseline (24%) and endpoint (21%).

**Insulin dosage:** Throughout the trial, approximately two-thirds of patients in both treatment groups injected Apidra or lispro in the abdomen, and one-fourth injected the rapid-acting insulin in the thigh. The basal insulin was injected in the thigh in approximately one-half of patients and in the abdomen in one-fourth of patients.

The rapid-acting insulin, basal insulin, and total daily insulin doses were comparable between the 2 treatment groups at baseline with very small changes from baseline at endpoint (Table 5), consistent with the minimal changes in HbA1c over the course of the trial.

| Table 5. Mean daily insulin dose (modified intent-to-treat population) | | | | |
|---|---|---|---|---|
| **Daily insulin doses** | **Glulisine** | | **Lispro** | |
| | **N** | **Dose (units)** | **N** | **Dose (units)** |
| **Baseline** | | | | |
| Total daily insulin dose, mean±SD | 275 | 51±24 | 294 | 51±22 |
| Rapid-acting insulin, mean±SD | 274 | 24±15 | 294 | 24±15 |
| Basal insulin, mean±SD | 275 | 27±14 | 294 | 27±14 |
| **Change from baseline at endpoint** | | | | |
| Total daily insulin dose, mean±SE | 275 | 3±1 | 294 | 5±1 |
| Rapid-acting insulin, mean±SE | 274 | 1±1 | 294 | 3±0.5 |
| Basal insulin, mean±SE | 275 | 1±0.3 | 294 | 2±0.3 |

**Subgroup analyses of GHb:** Subgroup analyses of GHb based on age (<8 years, ≥8-<12 years, ≥12 years), duration of diabetes (<5 years, ≥5 years), baseline GHb (<8.5% or ≥8.5%), and type of long-acting insulin (glargine vs. NPH) yielded results consistent with the overall primary efficacy findings (Table 6). The upper bound of the 95% confidence interval for the treatment difference in GHb between Apidra and lispro was <0.4% for all subgroups analyzed except for the <8 year-old age group (which consisted of only 19 patients per treatment group).

| Table 6. Subgroup analyses of GHb (modified intent-to-treat population) | | | | |
|---|---|---|---|---|
| **Subgroup** | **Sample size** | | **Mean treatment differences in change from baseline (Apidra – lispro)** | |
| | **Apidra** | **Lispro** | **Adjusted Mean (SE)** | **95% CI** |
| **Age** | | | | |
| < 8 years | 19 | 19 | 0.2 (0.3) | (-0.4 ; 0.9) |
| ≥ 8 - < 12 years | 77 | 70 | -0.1 (0.2) | (-0.5 ; 0.3) |
| ≥ 12 years | 175 | 202 | -0.1 (0.1) | (-0.4 ; 0.1) |
| **Duration of diabetes** | | | | |
| < 5 years | 148 | 160 | -0.1 (0.1) | (-0.4 ; 0.1) |
| ≥ 5 years | 123 | 131 | -0.03 (0.1) | (-0.3 ; 0.2) |
| **Baseline GHb** | | | | |
| < 8.5% | 161 | 181 | -0.1 (0.1) | (-0.3 ; 0.1) |
| ≥ 8.5% | 110 | 110 | -0.1 (0.2) | (-0.4 ; 0.3) |
| **Basal insulin** | | | | |
| Glargine | 189 | 211 | -0.1 (0.1) | (-0.3 ; 0.1) |
| NPH | 82 | 80 | -0.1 (0.2) | (-0.5 ; 0.2) |

### 6.1.6 Efficacy Conclusions

- The mean baseline GHb was 8.2% in both treatment groups. In the primary efficacy analysis, the adjusted mean change in GHb from baseline to endpoint was very small: +0.1% with Apidra and +0.2% with lispro. Apidra was non-inferior to lispro based on the non-inferiority margin of 0.4%. Subgroup analyses of GHb based on age, duration of diabetes, baseline GHb, and type of long-acting insulin yielded results consistent with the overall primary efficacy findings.

- The rapid-acting insulin, basal insulin, and total daily insulin doses were comparable between the 2 treatment groups at baseline with very small changes from baseline at endpoint, consistent with the minimal changes in HbA1c over the course of the trial.

- Less than one-half of patients in the 6-12 year-old age group and less than one-third of patients in the 13-17 year-old age group met the age-specific GHb targets at baseline and study end.

# 7 INTEGRATED REVIEW OF SAFETY

This section focuses on safety data from Study 3001. For the PK/PD study (1017), only deaths, serious adverse events, and discontinuations due to adverse events are summarized (this study was reviewed as part of the original NDA and involved only single-dose administration of study drug).

## 7.1 Methods and Findings

### 7.1.1 Deaths

No deaths were reported in Study 3001 and Study 1017.

### 7.1.2 Other Serious Adverse Events

No serious adverse events were reported in Study 1017.

In Study 3001, 30 (11%) Apidra-treated patients and 37 (13%) lispro-treated patients reported a serious adverse event. None of the serious adverse events led to discontinuation from the trial. Most of the serious adverse events were related to hypoglycemia or diabetic ketoacidosis (see Section 7.1.3.3). The remaining serious adverse events included appendicitis, gastroenteritis, tonsillitis, upper respiratory tract infection, and injury from accident (not hypoglycemia associated) – i.e., experiences not unexpected for a pediatric age group. One lispro-treated

patient was reported to have developed an acute abdomen. This event was attributed to a right ovarian cyst, was associated with ketonuria, and resolved within 3 days without the need for surgery. A 12-year old Apidra-treated patient was reported on Day 57 to have developed interstitial lung disease that resolved 11 days later. The verbatim term for this patient was "interstitial acute pneumopathy", and the investigator attributed this event to a respiratory tract infection.

### 7.1.3 Dropouts and Other Significant Adverse Events

#### 7.1.3.1 Overall profile of dropouts

In Study 3001, 12 Apidra-treated patients (4.3%) and 8 lispro-treated patients (2.7%) were discontinued from the trial (Table 7).

**Table 7. Patient disposition**

| Reason for discontinuation | Number of subjects (%) | |
|---|---|---|
| | Apidra | Lispro |
| Total randomized and treated | 277 | 295 |
| Total completed | 265 (95.7) | 287 (97.3) |
| Total discontinued | 12 (4.3) | 8 (2.7) |
| Adverse event | 1 (0.4) | 0 |
| Lack of efficacy | 1 (0.4) | 0 |
| Protocol violation | 1 (0.4) | 1 (0.3) |
| Subject did not wish to continue | 3 (1.1) | 4 (1.4) |
| Legal representative withdrew consent | 3 (1.1) | 0 |
| Other reason | 3 (1.1) | 3 (1.0) |

The most common reason for withdrawal was "subject did not wish to continue" (3 glulisine-treated patients; 4 lispro-treated patients). None of these patients reported an adverse event in the month leading up to discontinuation, except for 1 case of sore throat.

Withdrawals coded as "legal representative withdrew consent" or "other reason" were not related to adverse events except for 2 Apidra-treated patients who had hypoglycemia (one patient had recurrent asymptomatic hypoglycemia and another patient had an episode of severe hypoglycemia 2 days prior to withdrawal).

7.1.3.2 Adverse events associated with dropouts

No discontinuations due to adverse events were reported in Study 1017.

In Study 3001, one patient discontinued due to an adverse event – this 8-year old girl was treated with Apidra and developed injection site swelling on Day 16. The glulisine was temporarily discontinued on Day 19 and was restarted on Day 24. However, on Day 26, a second episode of injection site swelling occurred. The patient recovered on Day 28 and was permanently discontinued from the study on Day 30. There were no reports of systemic hypersensitivity.

7.1.3.3 Other significant adverse events

**Hypoglycemia**

The Sponsor used the following definitions for hypoglycemia:

Symptomatic: event with symptoms that were considered to result from hypoglycemia

Nocturnal: occurring between midnight and 6 am

Severe symptomatic hypoglycemia: clinical symptoms that were considered to result from hypoglycemia requiring the assistance of another person to treat because the subject could not self-treat due to acute neurological impairment AND meeting one of the following criteria

- Blood glucose <36 mg/dL
- Prompt recovery after oral carbohydrate, intravenous glucose, or glucagon administration

Serious hypoglycemia: hypoglycemia meeting one of the following criteria

- Loss of consciousness requiring a parenteral countermeasure by a third party
- Seizure
- Emergency room visit or hospital admission
- Investigator assessment of seriousness

Patients were instructed to measure blood glucose prior to the administration of glucose whenever symptomatic hypoglycemia was suspected, assuming it was safe to do so. Patients were asked to record symptomatic hypoglycemic episodes in sponsor-provided diaries.

Table 8 summarizes the hypoglycemia data. For each hypoglycemia category, the incidence rate of events per patient per month was similar during the 4-week run-in period on lispro and during the 26-week treatment period on randomized study medication. Approximately 80% of patients in both groups reported at least 1 episode of symptomatic hypoglycemia during the treatment period, and 15-20% reported at least 1 episode of severe, symptomatic hypoglycemia corresponding to 0.1 episode per patient per month. Hypoglycemia reported as a serious adverse event occurred in 7-8% of patients, mostly due to hypoglycemic seizure (6% of Apidra-treated patients and 5% of lispro-treated patients experienced a hypoglycemic seizure). None of the

hypoglycemic events reported as a serious adverse event led to permanent study medication discontinuation.

Two episodes of serious hypoglycemia resulted from incorrect insulin administration – one Apidra-treated patient accidentally injected Apidra instead of glargine, and one lispro-treated patient accidentally injected lispro instead of glargine.

Among patients reporting a serious hypoglycemic episode, only 1 patient reported associated trauma (head injury in a 10-year old Apidra-treated patient who fell in the bathroom then seized – the patient reportedly recovered the same day).

**Table 8. Hypoglycemia (Safety Population)**

| | Apidra (n=277) | | Lispro (n=295) | |
|---|---|---|---|---|
| | N (%) | **No. of episodes** | n (%) | **No. of episodes** |
| **Symptomatic hypoglycemia** | | | | |
| Screening/Run-in phase | 198 (71.5) | 1269<br>3.8/pt/month | 213 (72.2) | 1144<br>3.2/pt/month |
| Treatment phase | 230 (83.0) | 5543<br>3.5/pt/month | 238 (80.7) | 5346<br>3.0/pt/month |
| **Severe symptomatic hypoglycemia** | | | | |
| Screening/Run-in phase | 22 (7.9) | 29<br>0.1/pt/month | 27 (9.2) | 46<br>0.1/pt/month |
| Treatment phase | 45 (16.2) | 125<br>0.1/pt/month | 57 (19.3) | 132<br>0.1/pt/month |
| **Nocturnal symptomatic hypoglycemia** | | | | |
| Screening/Run-in phase | 51 (18.4) | 90<br>0.3/pt/month | 51 (17.3) | 82<br>0.2/pt/month |
| Treatment phase | 110 (39.7) | 398<br>0.3/pt/month | 90 (30.5) | 336<br>0.2/pt/month |
| **Severe nocturnal symptomatic hypoglycemia** | | | | |
| Screening/Run-in phase | 3 (1.1) | 3<br>0.01/pt/month | 7 (2.4) | 7<br>0.02/pt/month |
| Treatment phase | 10 (3.6) | 13<br>0.01/pt/month | 13 (4.4) | 17<br>0.01/pt/month |
| **Hypoglycemia reported as a serious adverse event** | 20 (7.2) | | 24 (8.1) | |
| Hypoglycemic seizure | 17 (6.1) | | 14 (4.7) | |
| Hypoglycemia NOS | 6 (2.2) | | 7 (2.4) | |
| Hypoglycemic coma/unconsciousness | 1 (0.4) | | 3 (1.0) | |

**Systemic hypersensitivity**

Many of the reports of hypersensitivity reactions (e.g., allergic conjunctivitis, allergic rhinitis, and seasonal allergies) are more likely related to environmental factors rather than drug reaction. There were 2 reports of asthma and 1 report of bronchospasm in the Apidra group, but these patients had a history of asthma; therefore, these events are not likely related to study medication. The only remaining event possibly consistent with drug reaction was "drug hypersensitivity" reported in 1 Apidra-treated patient, although this reaction was attributed to an antibiotic, not Apidra.

**Injection site reactions**

A total of 10 (3.6%) Apidra-treated patients and 6 (2.0%) lispro-treated patients reported an injection site reaction. Nine of these patients (7 in the Apidra group and 2 in the lispro group) reported injection site hypertrophy. Other reported reactions (which each occurred in 1-2 patients in the study) included injection site hemorrhage, swelling, bruising, atrophy, hematoma, and pain.

**Diabetic ketoacidosis**

Ten patients reported diabetic ketoacidosis – 6 (2.2%) Apidra-treated patients reported 9 episodes and 4 (1.4%) lispro-treated patients reported 4 episodes. Contributing factors (e.g., infection, stress, non-compliance) were identified in 7 of the 9 Apidra cases and in 3 of the 4 lispro cases.

### 7.1.5 Common Adverse Events

All patients received lispro during the run-in phase. For those patients who were subsequently randomized to insulin glulisine, adverse events beginning during the run-in phase and worsening after randomization were attributed to insulin glulisine, even though these patients were receiving insulin lispro when the event began.

Adverse events were collected from informed consent signature until 24 hours after study end. All events were coded using MedDRA version 9.1.

Table 9 summarizes adverse events occurring in >3% of Apidra- or lispro-treated patients. Besides hypoglycemic seizure (which is clearly related to a mismatch in insulin dose relative to need), the other common adverse events are typical among children (e.g., gastroenteritis, nasopharyngitis). Some of these events were more common with Apidra (e.g., influenza, cough) and others were more common with lispro (e.g., headache, pharyngolaryngeal pain).

| Table 9. Adverse events occurring in >3% of Apidra- or lispro-treated patients | | |
|---|---|---|
| **Preferred term** | **Number (%) of patients** | |
| | **Apidra (N=277)** | **Lispro (N=295)** |
| N with adverse events | 148 (53.4%) | 173 (58.6%) |
| Nasopharyngitis | 25 (9.0%) | 28 (9.5%) |
| Upper respiratory tract infection | 23 (8.3%) | 32 (10.8%) |
| Headache | 19 (6.9%) | 33 (11.2%) |
| Hypoglycemic seizure | 17 (6.1%) | 14 (4.7%) |
| Influenza | 13 (4.7%) | 5 (1.7%) |
| Vomiting | 12 (4.3%) | 11 (3.7%) |
| Gastroenteritis | 11 (4.0%) | 8 (2.7%) |
| Cough | 11 (4.0%) | 3 (1.0%) |
| Ear infection | 9 (3.2%) | 4 (1.4%) |
| Abdominal pain upper | 8 (2.9%) | 12 (4.1%) |
| Pharyngitis | 8 (2.9%) | 10 (3.4%) |
| Pharyngolaryngeal pain | 7 (2.5%) | 14 (4.7%) |
| Abdominal pain | 7 (2.5%) | 9 (3.1%) |
| Diarrhea | 3 (1.1%) | 10 (3.4%) |

### 7.1.7 Laboratory Findings

In Study 3001, clinical laboratory evaluations were performed according to standard laboratory procedures at a central laboratory, where the normal reference ranges were defined. There were no noteworthy findings or relevant differences between treatment groups for any clinical laboratory analyte.

#### 7.1.7.1 Overview of laboratory testing in the development program

The following safety laboratories were obtained during Study 3001:

- Pregnancy testing for postmenarchal girls at Week -5 and Week 26
- Clinical chemistry and hematology at Week -5, Day 1, and Week 26
- Insulin antibodies were measured on Day 1, Week 12, and Week 26

#### 7.1.7.3 Standard analyses and explorations of laboratory data

##### *7.1.7.3.1 Analyses focused on measures of central tendency*

There were no clinically significant changes from baseline in mean and median values for hematology and chemistry parameters. Mean serum creatinine increased from 0.68 mg/dL to

0.74 mg/dL in the Apidra group and from 0.68 mg/dL to 0.71 mg/dL in the lispro group. However, the precision of serum creatinine is typically to 1 decimal place. Using this approach, results were stable (0.7 mg/dL) in both treatment groups at baseline and endpoint. Mean serum alkaline phosphatase decreased from 238 U/L to 228 U/L with Apidra and from 241 U/L to 231 U/L with lispro. Although alkaline phosphatase often improves with a reduction in glycemia, the minimal changes in glycemia in the current study are not likely to account for these reductions. Mean platelet counts decreased from 299 x $10^9$/L to 292 x $10^9$/L with Apidra and increased from 293 x $10^9$/L to 295 x $10^9$/L with lispro. These minor changes in alkaline phosphatase and platelet count are not expected to have clinical significance.

*7.1.3.3.3 Marked outliers and dropouts for laboratory abnormalities*

Only 1 patient (see below) developed a "clinically significant" abnormal laboratory value. To qualify as a clinically significant abnormal laboratory value, the laboratory parameter needed to increase or decrease by a prespecified amount (if the baseline value was known) and then exceed a cutoff value. The cutpoints for selected parameters are shown below:

Leukocytes <3 x $10^3$/L or >15 x $10^3$/L
Platelets < 100 x $10^9$/L
ALT, AST, alkaline phosphatase, or total bilirubin >2x ULN

Based on these definitions, only one patient had a clinically significant abnormal laboratory value. This 17 year-old patient was treated with Apidra and had a normal white blood cell count at baseline (5.7 x $10^3$/L) but a low white blood cell count at endpoint (3.0 x $10^3$/L; with a lower limit of normal of 3.8 x $10^3$/L). All her other laboratory values were within the normal reference range. The clinical significance of this change is unknown but likely inconsequential and of uncertain relation to Apidra.

7.1.7.5 Special assessments

**Insulin antibodies**

Insulin antibodies were measured using a radioactive tracer and radioimmunoprecipitation. Anti-insulin antibodies in the serum were incubated with insulin tracers ($^{125}$I-glulisine, $^{125}$I-lispro, and $^{125}$I-human insulin). Then, the unbound tracer was washed away. The remaining immunoglobulins were precipitated and the amount of radioactivity was measured.

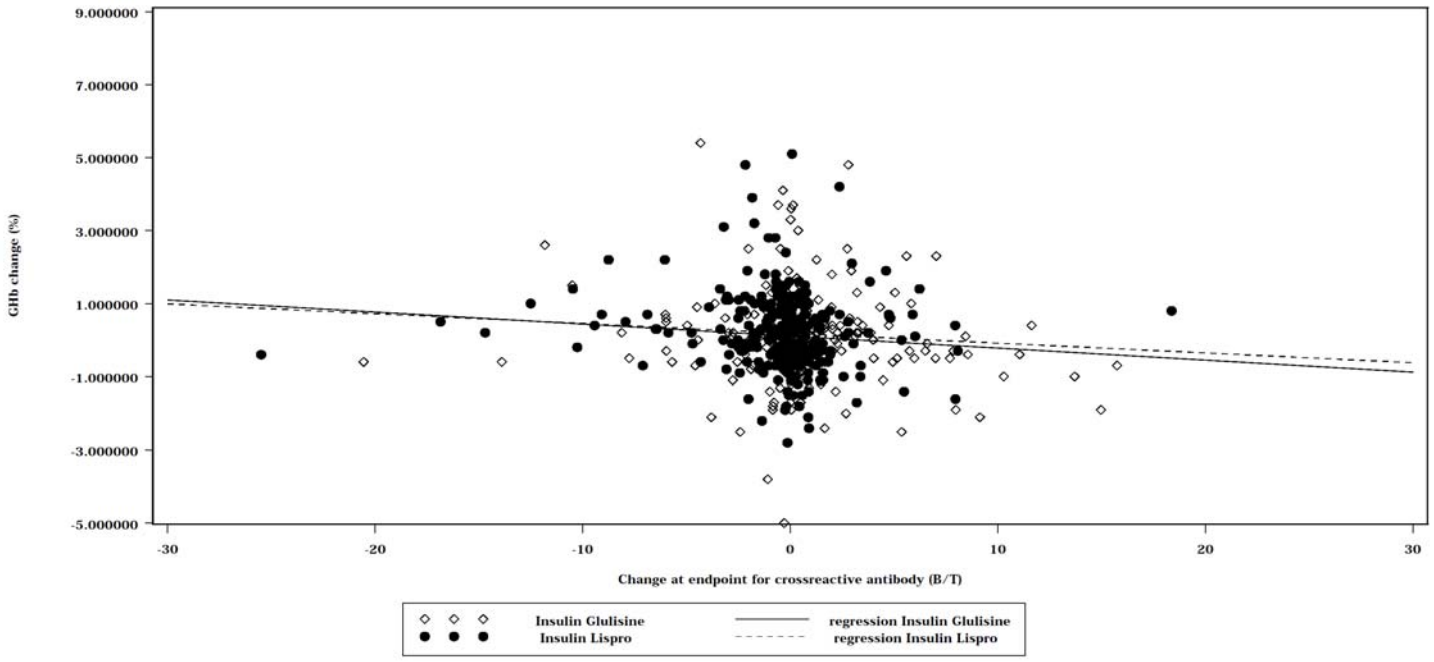
Values for insulin binding were expressed as bound radioactivity/total radioactivity, expressed as a percentage. The change of binding of radioactive insulin tracers was evaluated after adding the different insulins to the incubations.

Approximately 40% of the patients were receiving insulin lispro at study entry, whereas Apidra was only introduced at the time of randomization. Nonetheless, both treatment groups had very small changes in the median values representing antibody binding (Table 10).

| Table 10. Anti-insulin antibodies | | | | | | |
|---|---|---|---|---|---|---|
| **Timepoint** | **Glulisine** | | | **Lispro** | | |
| | **N** | **Median** | **Min, Max** | **N** | **Median** | **Min, Max** |
| **Cross-reactive insulin antibodies levels (% bound/total)** | | | | | | |
| Baseline | 271 | 2.8 | -0.2, 36.5 | 293 | 2.8 | -0.6, 46.1 |
| Change from baseline at | | | | | | |
| Week 12 | 265 | 0.5 | -15.8, 15.8 | 286 | -0.04 | -19.9, 21.9 |
| Endpoint | 271 | 0.3 | -20.6, 15.8 | 293 | -0.2 | -25.5, 18.4 |
| **Specific antibodies against insulin glulisine and insulin lispro (% bound/total)** | | | | | | |
| Baseline | 270 | 0.04 | -0.4, 0.7 | 293 | 0.3 | -0.4, 1.3 |
| Change from baseline at | | | | | | |
| Week 12 | 264 | 0.1 | -0.8, 13.1 | 286 | 0.0 | -1.1, 0.7 |
| Endpoint | 270 | 0.1 | -0.7, 8.0 | 293 | 0.0 | -0.8, 1.2 |
| **Specific antibodies against human insulin (% bound/total)** | | | | | | |
| Baseline | 271 | 0.4 | -0.2, 23.5 | 293 | 0.2 | -0.8, 7.0 |
| Change from baseline at | | | | | | |
| Week 12 | 265 | -0.04 | -5.3, 1.1 | 286 | 0.0 | -1.3, 1.9 |
| Endpoint | 271 | -0.1 | -7.5, 2.5 | 293 | 0.0 | -1.6, 3.8 |

In the Apidra group, there was no statistically significant correlations between changes in cross-reactive antibody levels and changes in GHb (Figure 1; p=0.10), total daily insulin dose (p=0.55), total daily rapid-acting insulin dose (p=0.30), or total daily long-acting insulin dose (p=0.93)

Figure 1. Change at endpoint (%) in GHb vs. change for cross-reactive antibodies




Insulin Glulisine: Correlation coefficient = 0.1016, Regression coefficient = -0.0329, P-value = 0.0970
Insulin Lispro : Correlation coefficient = 0.0863, Regression coefficient = -0.0269, P-value = 0.1432

The Sponsor also performed an analysis of the most extreme cases of increases from baseline to endpoint in cross-reactive insulin antibodies (i.e., increases above the 95% population quantile). The maximum change was observed in the insulin lispro group (21.9% bound/total); however, the Apidra group had a significantly higher (p=0.01) proportion of patients above the 95% quantile at endpoint (20/271 or 7%) compared to insulin lispro (8/293 or 3%). In both treatment groups, there were minor clinical differences among those who had the smallest change (i.e., below the 10% quantile) in cross-reactive insulin antibodies (n=24 for Apidra and n=32 for insulin lispro) compared to those with increases above the 95% population quantile (Table 11), although, in both treatment groups those in the 90% and 95% quantiles appeared to have more favorable changes in GHb than those below the 10% quantile.

| Table 11. GHb, insulin doses, and hypoglycemia according to cross-reactive insulin antibodies at endpoint | | | | | | |
|---|---|---|---|---|---|---|
| | Apidra | | | Insulin lispro | | |
| | <10% quantile | >90% quantile | >95% quantile | <10% quantile | >90% quantile | >95% quantile |
| **Change in GHb** | | | | | | |
| n | 24 | 37 | 20 | 32 | 17 | 8 |
| Mean | 0.3 | -0.1 | -0.3 | 0.5 | 0.1 | 0.0 |
| **Change in basal insulin dose** | | | | | | |
| n | 24 | 38 | 20 | 32 | 18 | 8 |
| Median | 1 | 2 | 1 | 1 | 4 | 3 |
| **Change in rapid-acting insulin dose** | | | | | | |
| n | 24 | 38 | 20 | 32 | 18 | 8 |
| Median | 2 | 3 | 4 | 1 | 5 | 5 |
| **Hypoglycemia, n (%)** | | | | | | |
| Symptomatic | 23 (96%) | 32 (84%) | 16 (80%) | 25 (78%) | 16 (89%) | 8 (100%) |
| Severe, symptomatic | 4 (17%) | 7 (18%) | 3 (15%) | 6 (19%) | 4 (22%) | 2 (25%) |

None of the patients who had an increase in cross-reactive antibodies exceeding the 95% quantile reported a systemic hypersensitivity reaction, and only 1 patient (who was in the insulin lispro group) reported an injection site abnormality.

### 7.1.8 Vital Signs

Vital signs, including blood pressure, heart rate, and body weight were obtained at baseline, Week 12, and Week 26. Neither treatment group in Study 3001 had clinically relevant changes in blood pressure or heart rate.

Baseline body weight was 51.5 kg in the Apidra group and 50.8 kg in the lispro group. The mean change in body weight from baseline to endpoint was 2.2 kg in both treatment groups.

### 7.1.9 Electrocardiograms (ECGs)

Electrocardiograms were not obtained in Study 3001. Insulin products are not known to affect electrocardiogram parameters.

### 7.1.10 Immunogenicity

Please see Sections 7.1.3.3. and 7.1.7.5.

### 7.1.11 Human Carcinogenicity

The current submission does not contain new data regarding human carcinogenicity. Please see the current Apidra label for additional information.

### 7.1.12 Special Safety Studies

None.

### 7.1.13 Withdrawal Phenomena and/or Abuse Potential

None of the marketed insulin products, including Apidra, are known to have withdrawal effects or abuse potential.

### 7.1.14 Human Reproduction and Pregnancy Data

The current submission does not contain new data regarding pregnancy. Please see the current Apidra label for additional information.

### 7.1.15 Assessment of Effect on Growth

In Study 3001, the mean baseline height was 155.5 cm in the Apidra group and 157.9 cm in the lispro group. The mean change in height from baseline to endpoint was 2.5 cm in the Apidra group (n=270) and 2.8 cm in the lispro group (n=290). Therefore, on average, patients had an increase in height of over 2 cm over the course of the 6 month trial. Poorly controlled hyperglycemia may affect linear growth, but insulin itself is not known to affect growth.

### 7.1.16 Overdose Experience

Overdosing with subsequent hypoglycemia may occur as a result of an excess of insulin relative to food intake, energy expenditure, or both.

In Study 3001, the definition of a "significant overdose" of insulin was based on clinical judgment and was at the discretion of the investigators. There were 2 cases of serious hypoglycemia resulting from accidental overdose due to injection of the incorrect insulin (see Section 7.1.3.3 for further details).

### 7.1.17 Postmarketing Experience

The safety data consists of cases from spontaneous notifications, as well as cases from regulatory authorities, and published literature. All cases were entered into ClinTrace™, the sanofi-aventis Global Pharmacovigilance and Epidemiology database. The Sponsor performed a cumulative search of this database on April 16, 2007 to identify all spontaneous reports of adverse drug reactions associated with Apidra and involving patients 17-years old and younger. This database

search identified a total of 14 individual case safety reports. Seven of these 14 cases were medically confirmed and 7 cases were reported by consumers.

Among the medically confirmed cases, 1 was serious: it was a case of diabetic ketoacidosis and decreased blood glucose. The remaining 6 cases were non serious and consisted of 2 reports of hyperglycemia, 1 hypoglycemia, 1 nausea with dyspepsia, 1 face edema and 1 injection site irritation.

The 7 cases reported by consumers consisted of 1 serious event (hyperglycemia, weight decreased, asthenia, vomiting, muscle spasms and malaise) and 6 non-serious events (5 hyperglycemic events and 1 injection site irritation).

These 14 cases do not represent unexpected events, but the small number of reported cases limits conclusions.

Annual Report (letter date June 12, 2008; covering April 16, 2007 through April 15, 2008):

During this time period, there have been no safety changes to the package insert. This submission does not contain data from clinical trials (there are data from clinical pharmacology studies).

Under "Status of Postmarketing Study Commitments", the Sponsor notes that there is a deferred pediatric study under PREA for the intravenous administration of Apidra for the treatment of pediatric patients ages 8-16 years. The study is planned, and the final study report is due to FDA by April 2011.

PADER (letter date August 8, 2008; covering April 16, 2008 through July 15, 2008):

There were no labeling changes or initiation of safety studies during this reporting period.

There were 6 new serious, unexpected events during this reporting period:

1. Death of unknown etiology in a 72-year old woman with type 2 diabetes, heart failure, and oxygen-dependent pulmonary disease
2. Suicide attempt with massive insulin overdose
3. Medication mix-up between Apidra and Lantus. The patient used 2 gray OptiClik pens to deliver the insulins (the OptiClik device manual advises patients to use different color pens for different insulins)
4. Ketoacidosis in an insulin pump user
5. Difficulty managing glycemia during pregnancy and fetal loss because of a "doctor's mistake"
6. A 30 kg weight gain over an 18 month period in a 50-year old woman with obesity and a history of hypothyroidism

The PADER contained follow-up information for 5 serious unexpected cases. None of the follow-up information alters the initial conclusions of these cases.

During this reporting period, there were 28 worldwide, initial reports of medication error mix-ups involving Apidra. In all cases, the other involved insulin was glargine (Lantus). Eight of these cases involved the OptiClik pens, 9 cases involved the SoloStar pens, 1 case involved Apidra via OptiClik and Lantus via SoloStar, 1 case involved pens that were not specified, 3 cases involved vials, 1 case involved an insulin pump, and the remaining 5 cases did not specify the method of delivery. There were 5 serious adverse events associated with these mix-ups – 3 cases of hypoglycemia and 2 cases of hypoglycemic unconsciousness.

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## 7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1.2 Demographics

The 2 treatment groups in Study 3001 had similar baseline characteristics (Table 12). Approximately one-half of the patients were female and 90% were Caucasian. The mean age at baseline was 12-13 years with <10% of patients under 8 years of age. The mean duration of diabetes was 5 years and, as expected, a minority of participants had a diabetes-related complication. At baseline, a slightly higher proportion of patients were using glargine compared to NPH for their basal insulin. For premeal insulin, two-thirds of patients were using rapid-acting insulin analogs and one-fourth were using regular insulin.

| Table 12. Study 3001 demographics (randomized and treated population) | | |
|---|---|---|
| **Characteristic** | **Apidra (N=277)** | **Lispro (N=295)** |
| Female, n (%) | 131 (47.3) | 156 (52.9) |
| **Age (years), mean (SD)** | 12.5 (3.1) | 12.6 (2.9) |
| <8 years, n (%) | 22 (7.9) | 19 (6.4) |
| ≥12 years, n (%) | 177 (63.9) | 205 (69.5) |
| **Race** | | |
| White, n (%) | 246 (88.8) | 275 (93.2) |
| Multiracial, n (%) | 17 (6.1) | 10 (3.4) |
| Asian, n (%) | 8 (2.9) | 7 (2.4) |
| Other, n (%) | 6 (2.2) | 3 (1.0) |
| Body mass index ($kg/m^2$), mean (SD) | 20.8 (3.4) | 20.5 (3.3) |
| Years since diagnosis of diabetes, mean (SD) | 5.3 (3.6) | 5.2 (3.2) |
| **Number of patients with ≥1 complication** | 10 (3.6) | 12 (4.1) |
| Diabetic retinopathy | 1 (0.4) | 0 |
| Diabetic neuropathy | 5 (1.8) | 6 (2.0) |
| Autonomic neuropathy | 0 | 0 |
| Diabetic nephropathy | 1 (0.4) | 0 |
| Micro- or macro-albuminuria | 4 (1.4) | 6 (2.0) |
| **Patients taking basal insulin** | 272 (98.2) | 292 (99.0) |
| NPH | 116 (41.9) | 107 (36.3) |
| Insulin glargine | 153 (55.2) | 181 (61.4) |
| Other | 3 (1.1) | 4 (1.4) |
| **Patients taking short-acting insulin** | 271 (97.8) | 291 (98.6) |
| Regular insulin | 65 (23.5) | 67 (22.7) |
| Rapid-acting insulin analog | 186 (67.1) | 195 (66.1) |
| Regular insulin + rapid-acting insulin analog | 20 (7.2) | 29 (9.8) |
| **Patients taking a fixed combination insulin** | 11 (4.0) | 7 (2.4) |

### 7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

None.

### 7.2.3 Adequacy of Overall Clinical Experience

### 7.2.4 Adequacy of Special Animal and/or In Vitro Testing

Not applicable. The current submission does not contain new non-clinical data.

### 7.2.5 Adequacy of Routine Clinical Testing

Efficacy and safety parameters were obtained at reasonable timepoints (see Sections 6.1.3. and 7.1). In addition, appropriate parameters were monitored (e.g., HbA1c, body weight, hypoglycemia, injection site reactions, insulin antibodies).

### 7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

Not applicable. The current submission does not contain new data with regard to metabolic, clearance, or interaction testing.

### 7.2.9 Additional Submissions, Including Safety Update

In a submission dated 29-August-2008, the sponsor requested a waiver for the requirements of a safety update. The sponsor has submitted 17 quarterly periodic adverse drug experience reports (PADERs) from August 2004 through August 2008 and states that the pattern of serious listed and non-serious reports is consistent with the known profile of insulin glulisine. I agree with the sponsor's request for a waiver of the safety update. Please see Section 7.1.17 (Postmarketing Experience) for my review of the most recent annual report (submitted June 12, 2008) and most recent PADER covering April 16, 2008 through July 15, 2008.

## 7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

In Study 3001, there were no noteworthy differences between the Apidra-treated patients and insulin lispro-treated patients with respect to the frequency and type of adverse events, serious adverse events and adverse events of special interest (e.g., hypoglycemia, hypersensitivity reactions, injection site abnormalities, diabetic ketoacidosis, body weight changes). There were no unexpected findings for Apidra and the safety profile in the study was consistent with what is

expected in a pediatric population with type 1 diabetes.

Of note, over the 26-week treatment period, 16% of the Apidra-treated patients and 19% of the insulin lispro-treated patients reported at least 1 episode of severe, symptomatic hypoglycemia (requiring the assistance of another person to treat and either having a blood glucose <36 mg/dL or showing prompt recovery after oral carbohydrate, intravenous glucose, or glucagon administration). The incidence rate of this event was similar in the 2 treatment groups (125 events with Apidra corresponding to 0.1 episode per patient per month vs. 132 events with insulin lispro corresponding to 0.1 episode per patient per month). This incidence rate is higher than that seen in the trials of adults with type 1 diabetes but is not unexpected (Ryan CM and Becker DJ. Hypoglycemia in children with type 1 diabetes mellitus: risk factors, cognitive function and management. *Endocrinol Metab Clin North Am.* 1999; 28: 883-900). The American Diabetes Association Clinical Practice Guidelines recommends higher HbA1c targets for children compared to adults, because of vulnerability to hypoglycemia.

The analyses of antibody data indicate that Apidra does not elicit a significant anti-insulin antibody response and that there were no clinically notable effects associated with anti-insulin antibody formation, except, perhaps, more favorable changes in GHb for patients who had the greatest increases in cross-reactive insulin antibodies.

Global, postmarketing pediatric data are limited but have not identified unique safety signals in children compared to adults treated with Apidra. There have been reports in adults of medication error mix-ups involving Apidra and, typically, insulin glargine.

## 7.4 General Methodology

### 7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

Not applicable. The 2 clinical studies in the current submission differed substantially (e.g., single-dose vs. 26-week treatment duration); therefore, data from these studies were not pooled.

# 8 ADDITIONAL CLINICAL ISSUES

## 8.1 Dosing Regimen and Administration

Apidra is a rapidly-acting insulin that is typically administered subcutaneously within 15 minutes prior to a meal in patients with diabetes or used continuously in an insulin pump. The current submission did not evaluate a new dosing regimen or route of administration. Instead,

the current clinical studies tested the safety and efficacy of premeal, subcutaneous Apidra in a new patient population - children with type 1 diabetes.

### 8.2 Drug-Drug Interactions

The current submission does not contain new data on drug interactions with Apidra.

### 8.3 Special Populations

The current submission tested the safety and efficacy of subcutaneous, premeal insulin in healthy children and does not contain information on other populations – please see the currently approved Apidra label for additional information.

### 8.4 Pediatrics

The current supplement fulfills the deferred pediatric postmarketing study commitment for subcutaneously administered Apidra.

### 8.5 Advisory Committee Meeting

No advisory committee meeting was held in relation to this submission.

### 8.7 Postmarketing Risk Management Plan

There is no need for a postmarketing risk management plan for the pediatric use of Apidra beyond the package insert and patient package insert. The American Diabetes Association Clinical Practice Guidelines recommends higher HbA1c targets for children compared to adults, because of vulnerability to hypoglycemia. Based on the results of Study 3001, there are no unique safety concerns with Apidra in children that warrant a Risk Evaluation and Mitigation Strategy (REMS).

### 8.8 Other Relevant Materials

None.

## 9 OVERALL ASSESSMENT

### 9.1 Conclusions

In this 26-week, open-label, randomized trial, Apidra was shown to be non-inferior (with respect to change from baseline to endpoint in GHb) to insulin lispro in children and adolescents (4-17

years old) with type 1 diabetes also treated with NPH insulin or glargine. There were no clinically significant differences between the Apidra-treated patients and insulin lispro-treated patients with respect to the frequency and type of adverse events, serious adverse events and adverse events of special interest (e.g., hypoglycemia, hypersensitivity reactions, injection site abnormalities, diabetic ketoacidosis, body weight changes). There were no unexpected findings among Apidra-treated patients and the safety profile in the study is consistent with what is expected in a pediatric population with type 1 diabetes.

Over the 26-week treatment period, 15-20% of patients reported at least 1 episode of severe, symptomatic hypoglycemia (requiring the assistance of another person to treat and either having a blood glucose <36 mg/dL or showing prompt recovery after oral carbohydrate, intravenous glucose, or glucagon administration) corresponding to 0.1 episode per patient per month. This incidence rate is higher than the rate of severe hypoglycemia seen in the Apidra trials of adults with type 1 diabetes, but is not unexpected. The American Diabetes Association Clinical Practice Guidelines recommends higher HbA1c targets for children compared to adults, because of vulnerability to hypoglycemia.

Global, postmarketing pediatric data are limited but have not identified unique safety signals in children compared to adults treated with Apidra. There have been reports in adults of medication error mix-ups involving Apidra and, typically, insulin glargine (Lantus).

## 9.2 Recommendation on Regulatory Action

Approval and fulfillment of the sponsor's required pediatric postmarketing commitment.

## 9.3 Recommendation on Postmarketing Actions

No postmarketing actions related to the current submission are needed.

### 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

This application is triggering a conversion of the package insert into the Physician Labeling Rule (PLR) format. Please see the approved label for the revisions that were agreed to by FDA and the sponsor.

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/s/
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Hylton Joffe
10/2/2008 04:02:00 PM
MEDICAL OFFICER

Mary Parks
10/2/2008 05:05:05 PM
MEDICAL OFFICER
I concur with Drs. Joffe and Gabry