

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**Approval Package for:**

***APPLICATION NUMBER:***

**NDA 021081/S-034**

***Trade Name:*** LANTUS

***Generic Name:*** insulin glargine [rDNA origin] injection)

***Sponsor:*** SANOFI AVENTIS US

***Approval Date:*** 09/09/2009

***Indications:***

- LANTUS is a long- acting human insulin analog indicated to improve glycemic control in adults and children with type 1 diabetes mellitus and in adults with type 2 diabetes mellitus.

# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*  
**NDA 021081/S-034**

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**CENTER FOR DRUG EVALUATION AND  
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*APPLICATION NUMBER:*  
**NDA 021081/S-034**

**APPROVAL LETTER**



NDA 21-081/S-034

**SUPPLEMENT APPROVAL**

sanofi-aventis Inc.  
Attention: Rima Nassar, Ph.D.  
Global Director of Diabetes  
200 Crossing Boulevard  
P.O. Box 6890, Mailstop: BX2-700B  
Bridgewater, NJ 08807

Dear Dr. Nassar:

Please refer to your supplemental new drug application dated and received December 21, 2007, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Lantus, insulin glargine [rDNA origin] injection.

We acknowledge receipt of your submissions dated August 8, October 3 and 31, and December 22, 2008, and January 14, 28, and 30, and June 9, 2009.

This "Prior Approval" supplemental new drug application provides information from clinical study HOE901/4016, titled "*Evaluation of Diabetic Retinopathy Progression in Subjects with Type 2 Diabetes Mellitus Treated with Oral Agents Plus Insulin*" and converts the Package Insert to the Physician's Labeling Rule format.

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text and with the minor editorial revision changing the revision date from June to September.

**CONTENT OF LABELING**

As soon as possible, but no later than 14 days from the date of this letter, please submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/oc/datacouncil/spl.html> that is identical to, except for including the revision listed, the enclosed labeling text for the package insert submitted June 9, 2009. Upon receipt, we will transmit that version to the National Library of Medicine for public dissemination. For administrative purposes, please designate this submission, "**SPL for approved NDA 21-081/S-034.**"

**PROMOTIONAL MATERIALS**

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert(s) to:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Drug Marketing, Advertising, and Communications  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. For instructions on completing the Form FDA 2253, see page 2 of the form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications, see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>.

### **LETTERS TO HEALTH CARE PROFESSIONALS**

If you issue a letter communicating important safety-related information about this drug product (i.e., a “Dear Health Care Professional” letter), we request that you submit an electronic copy of the letter to both this NDA and to the following address:

MedWatch  
Food and Drug Administration  
5600 Fishers Lane, Room 12B-05  
Rockville, MD 20857

### **REPORTING REQUIREMENTS**

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Rachel Hartford, Regulatory Project Manager, at (301) 796-0331.

Sincerely,

*{See appended electronic signature page}*

Mary H. Parks, M.D.  
Director  
Division of Metabolism and Endocrinology Products  
Office of Drug Evaluation II  
Center for Drug Evaluation

Enclosure:  
Package Insert

Application  
Type/Number

Submission  
Type/Number

Submitter Name

Product Name

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NDA-21081

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SUPPL-34

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SANOFI AVENTIS  
US LLC

-----  
LANTUS

-----  
**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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MARY H PARKS

09/09/2009

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**NDA 021081/S-034**

**LABELING**

## HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use LANTUS safely and effectively. See full prescribing information for LANTUS.

**LANTUS (insulin glargine [rDNA origin] injection) solution for subcutaneous injection**  
Initial U.S. Approval: 2000

### INDICATIONS AND USAGE

LANTUS is a long-acting human insulin analog indicated to improve glycemic control in adults and children with type 1 diabetes mellitus and in adults with type 2 diabetes mellitus. (1)

Important Limitations of Use:

- Not recommended for treating diabetic ketoacidosis. Use intravenous, short-acting insulin instead.

### DOSAGE AND ADMINISTRATION

- The starting dose should be individualized based on the type of diabetes and whether the patient is insulin-naïve (2.1, 2.2, 2.3)
- Administer subcutaneously once daily at any time of day, but at the same time every day. (2.1)
- Rotate injection sites within an injection area (abdomen, thigh, or deltoid) to reduce the risk of lipodystrophy. (2.1)
- Converting from other insulin therapies may require adjustment of timing and dose of LANTUS. Closely monitor glucoses especially upon converting to LANTUS and during the initial weeks thereafter. (2.3)

### DOSAGE FORMS AND STRENGTHS

Solution for injection 100 units/mL (U-100) in

- 10 mL vials
- 3 mL cartridge system for use in OptiClik (Insulin Delivery Device)
- 3 mL SoloStar disposable insulin device (3)

### CONTRAINDICATIONS

Do not use in patients with hypersensitivity to LANTUS or one of its excipients (4)

### WARNINGS AND PRECAUTIONS

- Dose adjustment and monitoring: Monitor blood glucose in all patients treated with insulin. Insulin regimens should be modified cautiously and only under medical supervision (5.1)
- Administration: Do not dilute or mix with any other insulin or solution. Do not administer subcutaneously via an insulin pump or intravenously because severe hypoglycemia can occur (5.2)
- Do not share reusable or disposable insulin devices or needles between patients (5.2)
- Hypoglycemia: Most common adverse reaction of insulin therapy and may be life-threatening (5.3, 6.1)
- Allergic reactions: Severe, life-threatening, generalized allergy, including anaphylaxis, can occur (5.4, 6.1)
- Renal or hepatic impairment: May require a reduction in the LANTUS dose (5.5, 5.6)

### ADVERSE REACTIONS

Adverse reactions commonly associated with Lantus are:

- Hypoglycemia, allergic reactions, injection site reaction, lipodystrophy, pruritus, and rash. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact sanofi-aventis at 1-800-633-1610 or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).

### DRUG INTERACTIONS

- Certain drugs may affect glucose metabolism, requiring insulin dose adjustment and close monitoring of blood glucose. (7)
- The signs of hypoglycemia may be reduced or absent in patients taking anti-adrenergic drugs (e.g., beta-blockers, clonidine, guanethidine, and reserpine). (7)

### USE IN SPECIFIC POPULATIONS

- Pregnancy category C: Use during pregnancy only if the potential benefit justifies the potential risk to the fetus (8.1)
- Pediatric: Has not been studied in children with type 2 diabetes. Has not been studied in children with type 1 diabetes <6 years of age (8.4)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: June 2009

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## FULL PRESCRIBING INFORMATION

### 1. INDICATIONS AND USAGE

LANTUS is indicated to improve glycemic control in adults and children with type 1 diabetes mellitus and in adults with type 2 diabetes mellitus.

Important Limitations of Use:

- LANTUS is not recommended for the treatment of diabetic ketoacidosis. Intravenous short-acting insulin is the preferred treatment for this condition.

### 2. DOSAGE AND ADMINISTRATION

#### 2.1 Dosing

LANTUS is a recombinant human insulin analog for once daily subcutaneous administration with potency that is approximately the same as the potency of human insulin. LANTUS exhibits a relatively constant glucose-lowering profile over 24 hours that permits once-daily dosing.

LANTUS may be administered at any time during the day. LANTUS should be administered subcutaneously once a day at the same time every day. The dose of LANTUS must be individualized based on clinical response. Blood glucose monitoring is essential in all patients receiving insulin therapy.

Patients adjusting the amount or timing of dosing with LANTUS, should only do so under medical supervision with appropriate glucose monitoring [*see Warnings and Precautions (5.1)*].

In patients with type 1 diabetes, LANTUS must be used in regimens with short-acting insulin.

The intended duration of activity of LANTUS is dependent on injection into subcutaneous tissue [*see Clinical pharmacology (12.2)*]. LANTUS should not be administered intravenously or via an insulin pump. Intravenous administration of the usual subcutaneous dose could result in severe hypoglycemia [*see Warnings and Precautions (5.3)*].

As with all insulins, injection sites should be rotated within the same region (abdomen, thigh, or deltoid) from one injection to the next to reduce the risk of lipodystrophy [*See Adverse Reactions (6.1)*].

In clinical studies, there was no clinically relevant difference in insulin glargine absorption after abdominal, deltoid, or thigh subcutaneous administration. As for all insulins, the rate of absorption, and consequently the onset and duration of action, may be affected by exercise and other variables, such as stress, intercurrent illness, or changes in co-administered drugs or meal patterns.

## **2.2 Initiation of LANTUS therapy**

The recommended starting dose of LANTUS in patients with type 1 diabetes should be approximately one-third of the total daily insulin requirements. Short-acting, premeal insulin should be used to satisfy the remainder of the daily insulin requirements.

The recommended starting dose of LANTUS in patients with type 2 diabetes who are not currently treated with insulin is 10 units (or 0.2 Units/kg) once daily, which should subsequently be adjusted to the patient's needs.

The dose of LANTUS should be adjusted according to blood glucose measurements. The dosage of LANTUS should be individualized under the supervision of a healthcare provider in accordance with the needs of the patient.

## **2.3 Converting to LANTUS from other insulin therapies**

If changing from a treatment regimen with an intermediate- or long-acting insulin to a regimen with LANTUS, the amount and timing of shorter-acting insulins and doses of any oral anti-diabetic drugs may need to be adjusted.

- If transferring patients from once-daily NPH insulin to once-daily LANTUS, the recommended initial LANTUS dose is the same as the dose of NPH that is being discontinued.
- If transferring patients from twice-daily NPH insulin to once-daily LANTUS, the recommended initial LANTUS dose is 80% of the total NPH dose that is being discontinued. This dose reduction will lower the likelihood of hypoglycemia [*see Warnings and Precautions (5.3)*].

## **3. DOSAGE FORMS AND STRENGTHS**

LANTUS solution for injection 100 Units per mL is available as:

- 10 mL Vial (1000 Units/10 mL)
- 3 mL Cartridge systems for use only in OptiClik® (300 Units/3 mL)
- 3 mL SoloStar® disposable insulin device (300 Units/3 mL)

## **4. CONTRAINDICATIONS**

LANTUS is contraindicated in patients with hypersensitivity to LANTUS or one of its excipients.

## **5. WARNINGS AND PRECAUTIONS**

### **5.1 Dosage adjustment and monitoring**

Glucose monitoring is essential for all patients receiving insulin therapy. Changes to an insulin regimen should be made cautiously and only under medical supervision.

Changes in insulin strength, manufacturer, type, or method of administration may result in the need for a change in insulin dose or an adjustment in concomitant oral anti-diabetic treatment.

As with all insulin preparations, the time course of action for LANTUS may vary in different individuals or at different times in the same individual and is dependent on many conditions, including the local blood supply, local temperature, and physical activity.

## **5.2 Administration**

Do not administer LANTUS intravenously or via an insulin pump. The intended duration of activity of LANTUS is dependent on injection into subcutaneous tissue

Intravenous administration of the usual subcutaneous dose could result in severe hypoglycemia [*see Warnings and Precautions (5.3)*].

Do not dilute or mix LANTUS with any other insulin or solution. If LANTUS is diluted or mixed, the solution may become cloudy, and the pharmacokinetic or pharmacodynamic profile (e.g., onset of action, time to peak effect) of LANTUS and the mixed insulin may be altered in an unpredictable manner. When LANTUS and regular human insulin were mixed immediately before injection in dogs, a delayed onset of action and a delayed time to maximum effect for regular human insulin was observed. The total bioavailability of the mixture was also slightly decreased compared to separate injections of LANTUS and regular human insulin. The relevance of these observations in dogs to humans is unknown.

Do not share disposable or reusable insulin devices or needles between patients, because doing so carries a risk for transmission of blood-borne pathogens.

## **5.3 Hypoglycemia**

Hypoglycemia is the most common adverse reaction of insulin, including LANTUS. The risk of hypoglycemia increases with intensive glycemic control. Patients must be educated to recognize and manage hypoglycemia. Severe hypoglycemia can lead to unconsciousness or convulsions and may result in temporary or permanent impairment of brain function or death. Severe hypoglycemia requiring the assistance of another person or parenteral glucose infusion or glucagon administration has been observed in clinical trials with insulin, including trials with LANTUS.

The timing of hypoglycemia usually reflects the time-action profile of the administered insulin formulations. Other factors such as changes in food intake (e.g., amount of food or timing of meals), exercise, and concomitant medications may also alter the risk of hypoglycemia [*See Drug Interactions (7)*].

The prolonged effect of subcutaneous LANTUS may delay recovery from hypoglycemia. Patients being switched from twice daily NPH insulin to once-daily LANTUS should have their initial LANTUS dose reduced by 20% from the previous total daily NPH dose to reduce the risk of hypoglycemia [*see Dosage and Administration (2.3)*].

As with all insulins, use caution in patients with hypoglycemia unawareness and in patients who may be predisposed to hypoglycemia (e.g., the pediatric population and patients who fast or have erratic food intake). The patient's ability to concentrate and react may be impaired as a result of

hypoglycemia. This may present a risk in situations where these abilities are especially important, such as driving or operating other machinery.

Early warning symptoms of hypoglycemia may be different or less pronounced under certain conditions, such as longstanding diabetes, diabetic neuropathy, use of medications such as beta-blockers, or intensified glycemic control. These situations may result in severe hypoglycemia (and, possibly, loss of consciousness) prior to the patient's awareness of hypoglycemia.

#### **5.4 Hypersensitivity and allergic reactions**

Severe, life-threatening, generalized allergy, including anaphylaxis, can occur with insulin products, including LANTUS.

#### **5.5 Renal impairment**

Due to its long duration of action, Lantus is not recommended during periods of rapidly declining renal function because of the risk for prolonged hypoglycemia.

Although studies have not been performed in patients with diabetes and renal impairment, a reduction in the LANTUS dose may be required in patients with renal impairment because of reduced insulin metabolism, similar to observations found with other insulins. [*See Clinical Pharmacology (12.3)*].

#### **5.6 Hepatic impairment**

Due to its long duration of action, Lantus is not recommended during periods of rapidly declining hepatic function because of the risk for prolonged hypoglycemia.

Although studies have not been performed in patients with diabetes and hepatic impairment, a reduction in the LANTUS dose may be required in patients with hepatic impairment because of reduced capacity for gluconeogenesis and reduced insulin metabolism, similar to observations found with other insulins. [*See Clinical Pharmacology (12.3)*].

#### **5.7 Drug interactions**

Some medications may alter insulin requirements and subsequently increase the risk for hypoglycemia or hyperglycemia [*See Drug Interactions (7)*].

### **6. ADVERSE REACTIONS**

The following adverse reactions are discussed elsewhere:

- Hypoglycemia [*See Warnings and Precautions (5.3)*]
- Hypersensitivity and allergic reactions [*See Warnings and Precautions (5.4)*]

#### **6.1 Clinical trial experience**

Because clinical trials are conducted under widely varying designs, the adverse reaction rates reported in one clinical trial may not be easily compared to those rates reported in another clinical trial, and may not reflect the rates actually observed in clinical practice.

The frequencies of treatment-emergent adverse events during LANTUS clinical trials in patients with type 1 diabetes mellitus and type 2 diabetes mellitus are listed in the tables below.

**Table 1: Treatment –emergent adverse events in pooled clinical trials up to 28 weeks duration in adults with type 1 diabetes (adverse events with frequency  $\geq 5\%$ )**

	<b>LANTUS, % (n=1257)</b>	<b>NPH, % (n=1070)</b>
Upper respiratory tract infection	22.4	23.1
Infection *	9.4	10.3
Accidental injury	5.7	6.4
Headache	5.5	4.7

**\*Body System not Specified**

**Table 2: Treatment –emergent adverse events in pooled clinical trials up to 1 year duration in adults with type 2 diabetes (adverse events with frequency  $\geq 5\%$ )**

	<b>LANTUS, % (n=849)</b>	<b>NPH, % (n=714)</b>
Upper respiratory tract infection	11.4	13.3
Infection*	10.4	11.6
Retinal vascular disorder	5.8	7.4

**\*Body System not Specified**

**Table 3: Treatment –emergent adverse events in a 5-year trial of adults with type 2 diabetes (adverse events with frequency  $\geq 10\%$ )**

	<b>LANTUS, % (n=514)</b>	<b>NPH, % (n=503)</b>
Upper respiratory tract infection	29.0	33.6
Edema peripheral	20.0	22.7
Hypertension	19.6	18.9
Influenza	18.7	19.5
Sinusitis	18.5	17.9
Cataract	18.1	15.9
Bronchitis	15.2	14.1
Arthralgia	14.2	16.1

Pain in extremity	13.0	13.1
Back pain	12.8	12.3
Cough	12.1	7.4
Urinary tract infection	10.7	10.1
Diarrhea	10.7	10.3
Depression	10.5	9.7
Headache	10.3	9.3

**Table 4: Treatment –emergent adverse events in a 28-week clinical trial of children and adolescents with type 1 diabetes (adverse events with frequency  $\geq 5\%$ )**

	LANTUS, % (n=174)	NPH, % (n=175)
Infection*	13.8	17.7
Upper respiratory tract infection	13.8	16.0
Pharyngitis	7.5	8.6
Rhinitis	5.2	5.1

\*Body System not Specified

- *Severe Hypoglycemia*

Hypoglycemia is the most commonly observed adverse reaction in patients using insulin, including LANTUS [See *Warnings and Precautions (5.3)*]. Tables 5 and 6 summarize the incidence of severe hypoglycemia in the LANTUS individual clinical trials. Severe symptomatic hypoglycemia was defined as an event with symptoms consistent with hypoglycemia requiring the assistance of another person and associated with either a blood glucose below 50 mg/dL ( $\leq 56$  mg/dL in the 5-year trial) or prompt recovery after oral carbohydrate, intravenous glucose or glucagon administration.

The rates of severe symptomatic hypoglycemia in the LANTUS clinical trials (see Section 14 for a description of the study designs) were comparable for all treatment regimens (see Tables 5 and 6). In the pediatric phase 3 clinical trial, children and adolescents with type 1 diabetes had a higher incidence of severe symptomatic hypoglycemia in the two treatment groups compared to the adult trials with type 1 diabetes. (see Table 5) [See *Clinical Studies (14)*].

**Table 5: Severe Symptomatic Hypoglycemia in Patients with Type 1 Diabetes**

	Study A Type 1 Diabetes Adults 28 weeks In combination with regular insulin		Study B Type 1 Diabetes Adults 28 weeks In combination with regular insulin		Study C Type 1 Diabetes Adults 16 weeks In combination with insulin lispro		Study D Type 1 Diabetes Pediatrics 26 weeks In combination with regular insulin	
	LANTUS	NPH	LANTUS	NPH	LANTUS	NPH	LANTUS	NPH
Percent of patients (n/total N)	10.6 (31/292)	15.0 (44/293)	8.7 (23/264)	10.4 (28/270)	6.5 (20/310)	5.2 (16/309)	23.0 (40/174)	28.6 (50/175)

**Table 6: Severe Symptomatic Hypoglycemia in Patients with Type 2 Diabetes**

	Study E Type 2 Diabetes Adults 52 weeks In combination with oral agents		Study F Type 2 Diabetes Adults 28 weeks In combination with regular insulin		Study G Type 2 Diabetes Adults 5 years In combination with regular insulin	
	LANTUS	NPH	LANTUS	NPH	LANTUS	NPH
Percent of patients (n/total N)	1.7 (5/289)	1.1 (3/281)	0.4 (1/259)	2.3 (6/259)	7.8 (40/513)	11.9 (60/504)

- Retinopathy

Retinopathy was evaluated in the LANTUS clinical studies by analysis of reported retinal adverse events and fundus photography. The numbers of retinal adverse events reported for LANTUS and NPH insulin treatment groups were similar for patients with type 1 and type 2 diabetes.

LANTUS was compared to NPH insulin in a 5-year randomized clinical trial that evaluated the progression of retinopathy as assessed with fundus photography using a grading protocol derived from the Early Treatment Diabetic Retinopathy Scale (ETDRS). Patients had type 2 diabetes (mean age 55 yrs) with no (86%) or mild (14%) retinopathy at baseline. Mean baseline HbA1c was 8.4%. The primary outcome was progression by 3 or more steps on the ETDRS scale at study endpoint. Patients with pre-specified post-baseline eye procedures (pan-retinal photocoagulation for proliferative or severe nonproliferative diabetic retinopathy, local photocoagulation for new vessels, and vitrectomy for diabetic retinopathy) were also considered as 3-step progressors regardless of actual change in ETDRS score from baseline. Retinopathy graders were blinded to treatment group assignment. The results for the primary endpoint are

shown in Table 7 for both the per-protocol and Intent-to-Treat populations, and indicate similarity of Lantus to NPH in the progression of diabetic retinopathy as assessed by this outcome.

**Table 7. Number (%) of patients with 3 or more step progression on ETDRS scale at endpoint**

	Lantus (%)	NPH (%)	Difference <sup>a,b</sup> (SE)	95% CI for difference
<b>Per-protocol</b>	53/374 (14.2%)	57/363 (15.7%)	-2.0% (2.6%)	-7.0% to +3.1%
<b>Intent-to-Treat</b>	63/502 (12.5%)	71/487 (14.6%)	-2.1% (2.1%)	-6.3% to +2.1%

a: Difference = Lantus – NPH

b: using a generalized linear model (SAS GENMOD) with treatment and baseline HbA1c strata (cutoff 9.0%) as the classified independent variables, and with binomial distribution and identity link function

- *Insulin initiation and intensification of glucose control*

Intensification or rapid improvement in glucose control has been associated with a transitory, reversible ophthalmologic refraction disorder, worsening of diabetic retinopathy, and acute painful peripheral neuropathy. However, long-term glycemic control decreases the risk of diabetic retinopathy and neuropathy.

- *Lipodystrophy*

Long-term use of insulin, including LANTUS, can cause lipodystrophy at the site of repeated insulin injections. Lipodystrophy includes lipohypertrophy (thickening of adipose tissue) and lipoatrophy (thinning of adipose tissue), and may affect insulin absorption. Rotate insulin injection or infusion sites within the same region to reduce the risk of lipodystrophy. [See *Dosage and Administration (2.1)*].

- *Weight gain*

Weight gain can occur with insulin therapy, including LANTUS, and has been attributed to the anabolic effects of insulin and the decrease in glucosuria.

- *Peripheral Edema*

Insulin, including LANTUS, may cause sodium retention and edema, particularly if previously poor metabolic control is improved by intensified insulin therapy.

- *Allergic Reactions*

*Local Allergy*

As with any insulin therapy, patients taking LANTUS may experience injection site reactions, including redness, pain, itching, urticaria, edema, and inflammation. In clinical studies in adult patients, there was a higher incidence of treatment-emergent injection site pain in LANTUS-treated patients (2.7%) compared to NPH insulin-treated patients (0.7%). The reports of pain at the injection site did not result in discontinuation of therapy.

Rotation of the injection site within a given area from one injection to the next may help to reduce or prevent these reactions. In some instances, these reactions may be related to factors other than insulin, such as irritants in a skin cleansing agent or poor injection technique. Most minor reactions to insulin usually resolve in a few days to a few weeks.

### *Systemic Allergy*

Severe, life-threatening, generalized allergy, including anaphylaxis, generalized skin reactions, angioedema, bronchospasm, hypotension, and shock may occur with any insulin, including LANTUS and may be life threatening.

- *Antibody production*

All insulin products can elicit the formation of insulin antibodies. The presence of such insulin antibodies may increase or decrease the efficacy of insulin and may require adjustment of the insulin dose. In phase 3 clinical trials of LANTUS, increases in titers of antibodies to insulin were observed in NPH insulin and insulin glargine treatment groups with similar incidences.

### **6.2 Postmarketing experience**

The following adverse reactions have been identified during post-approval use of LANTUS. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to estimate reliably their frequency or establish a causal relationship to drug exposure.

Medication errors have been reported in which other insulins, particularly short-acting insulins, have been accidentally administered instead of LANTUS [*See Patient Counseling Information (17)*]. To avoid medication errors between LANTUS and other insulins, patients should be instructed to always verify the insulin label before each injection.

## **7. DRUG INTERACTIONS**

A number of drugs affect glucose metabolism and may require insulin dose adjustment and particularly close monitoring.

The following are examples of drugs that may increase the blood-glucose-lowering effect of insulins including LANTUS and, therefore, increase the susceptibility to hypoglycemia: oral anti-diabetic products, pramlintide, angiotensin converting enzyme (ACE) inhibitors, disopyramide, fibrates, fluoxetine, monoamine oxidase inhibitors, propoxyphene, pentoxifylline, salicylates, somatostatin analogs, and sulfonamide antibiotics.

The following are examples of drugs that may reduce the blood-glucose-lowering effect of insulins including LANTUS: corticosteroids, niacin, danazol, diuretics, sympathomimetic agents (e.g., epinephrine, albuterol, terbutaline), glucagon, isoniazid, phenothiazine derivatives, somatropin, thyroid hormones, estrogens, progestogens (e.g., in oral contraceptives), protease inhibitors and atypical antipsychotic medications (e.g. olanzapine and clozapine).

Beta-blockers, clonidine, lithium salts, and alcohol may either potentiate or weaken the blood-glucose-lowering effect of insulin. Pentamidine may cause hypoglycemia, which may sometimes be followed by hyperglycemia.

The signs of hypoglycemia may be reduced or absent in patients taking sympatholytic drugs such as beta-blockers, clonidine, guanethidine, and reserpine.

## 8. USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

Pregnancy Category C: Subcutaneous reproduction and teratology studies have been performed with insulin glargine and regular human insulin in rats and Himalayan rabbits. Insulin glargine was given to female rats before mating, during mating, and throughout pregnancy at doses up to 0.36 mg/kg/day, which is approximately 7 times the recommended human subcutaneous starting dose of 10 Units/day (0.008 mg/kg/day), based on mg/m<sup>2</sup>. In rabbits, doses of 0.072 mg/kg/day, which is approximately 2 times the recommended human subcutaneous starting dose of 10 Units/day (0.008 mg/kg/day), based on mg/m<sup>2</sup>, were administered during organogenesis. The effects of insulin glargine did not generally differ from those observed with regular human insulin in rats or rabbits. However, in rabbits, five fetuses from two litters of the high-dose group exhibited dilation of the cerebral ventricles. Fertility and early embryonic development appeared normal.

There are no well-controlled clinical studies of the use of LANTUS in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. It is essential for patients with diabetes or a history of gestational diabetes to maintain good metabolic control before conception and throughout pregnancy. Insulin requirements may decrease during the first trimester, generally increase during the second and third trimesters, and rapidly decline after delivery. Careful monitoring of glucose control is essential in these patients.

### 8.3 Nursing Mothers

It is unknown whether insulin glargine is excreted in human milk. Because many drugs, including human insulin, are excreted in human milk, caution should be exercised when LANTUS is administered to a nursing woman. Use of LANTUS is compatible with breastfeeding, but women with diabetes who are lactating may require adjustments of their insulin doses.

### 8.4 Pediatric Use

The safety and effectiveness of subcutaneous injections of LANTUS have been established in pediatric patients (age 6 to 15 years) with type 1 diabetes [*see Clinical Studies (14)*]. LANTUS has not been studied in pediatric patients younger than 6 years of age with type 1 diabetes. LANTUS has not been studied in pediatric patients with type 2 diabetes.

Based on the results of a study in pediatric patients, the dose recommendation when switching to LANTUS is the same as that described for adults [*see Dosage and Administration (2.3)* and *Clinical Studies (14)*]. As in adults, the dosage of LANTUS must be individualized in pediatric patients based on metabolic needs and frequent monitoring of blood glucose.

### 8.5 Geriatric Use

In controlled clinical studies comparing LANTUS to NPH insulin, 593 of 3890 patients (15%) with type 1 and type 2 diabetes were ≥65 years of age and 80 (2%) patients were ≥75 years of age. The only difference in safety or effectiveness in the subpopulation of patients ≥65 years of

age compared to the entire study population was a higher incidence of cardiovascular events typically seen in an older population in both LANTUS and NPH insulin-treated patients. Nevertheless, caution should be exercised when LANTUS is administered to geriatric patients. In elderly patients with diabetes, the initial dosing, dose increments, and maintenance dosage should be conservative to avoid hypoglycemic reactions. Hypoglycemia may be difficult to recognize in the elderly [*See Warnings and Precautions (5.3)*].

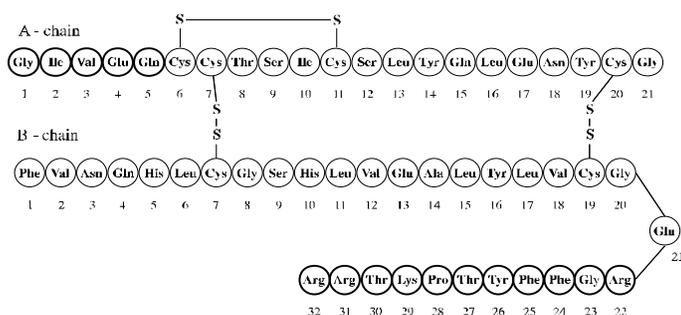
## 10. OVERDOSAGE

An excess of insulin relative to food intake, energy expenditure, or both may lead to severe and sometimes prolonged and life-threatening hypoglycemia. Mild episodes of hypoglycemia can usually be treated with oral carbohydrates. Adjustments in drug dosage, meal patterns, or exercise may be needed.

More severe episodes of hypoglycemia with coma, seizure, or neurologic impairment may be treated with intramuscular/subcutaneous glucagon or concentrated intravenous glucose. After apparent clinical recovery from hypoglycemia, continued observation and additional carbohydrate intake may be necessary to avoid recurrence of hypoglycemia.

## 11. DESCRIPTION

LANTUS (insulin glargine [rDNA origin] injection) is a sterile solution of insulin glargine for use as a subcutaneous injection. Insulin glargine is a recombinant human insulin analog that is a long-acting (up to 24-hour duration of action), parenteral blood-glucose-lowering agent [*See Clinical Pharmacology (12)*]. LANTUS is produced by recombinant DNA technology utilizing a non-pathogenic laboratory strain of *Escherichia coli* (K12) as the production organism. Insulin glargine differs from human insulin in that the amino acid asparagine at position A21 is replaced by glycine and two arginines are added to the C-terminus of the B-chain. Chemically, insulin glargine is 21<sup>A</sup>-Gly-30<sup>B</sup>a-L-Arg-30<sup>B</sup>b-L-Arg-human insulin and has the empirical formula C<sub>267</sub>H<sub>404</sub>N<sub>72</sub>O<sub>78</sub>S<sub>6</sub> and a molecular weight of 6063. Insulin glargine has the following structural formula:



LANTUS consists of insulin glargine dissolved in a clear aqueous fluid. Each milliliter of LANTUS (insulin glargine injection) contains 100 Units (3.6378 mg) insulin glargine.

The 10 mL vial presentation contains the following inactive ingredients per mL: 30 mcg zinc, 2.7 mg m-cresol, 20 mg glycerol 85%, 20 mcg polysorbate 20, and water for injection.

The 3 mL cartridge presentation contains the following inactive ingredients per mL: 30 mcg zinc, 2.7 mg m-cresol, 20 mg glycerol 85%, and water for injection.

The pH is adjusted by addition of aqueous solutions of hydrochloric acid and sodium hydroxide. LANTUS has a pH of approximately 4.

## **12. CLINICAL PHARMACOLOGY**

### **12.1 Mechanism of Action**

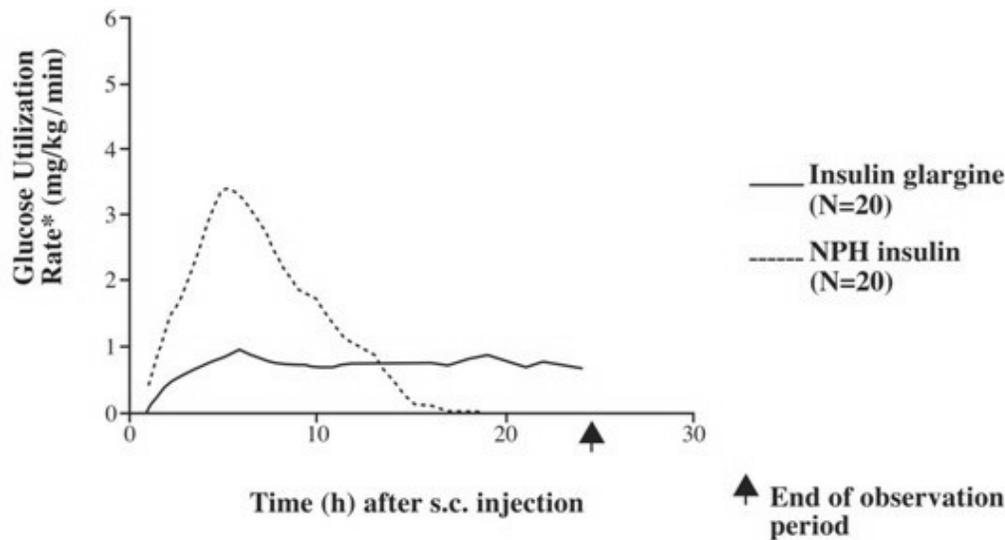
The primary activity of insulin, including insulin glargine, is regulation of glucose metabolism. Insulin and its analogs lower blood glucose by stimulating peripheral glucose uptake, especially by skeletal muscle and fat, and by inhibiting hepatic glucose production. Insulin inhibits lipolysis and proteolysis, and enhances protein synthesis.

### **12.2 Pharmacodynamics**

Insulin glargine is a human insulin analog that has been designed to have low aqueous solubility at neutral pH. At pH 4, as in the LANTUS injection solution, insulin glargine is completely soluble. After injection into the subcutaneous tissue, the acidic solution is neutralized, leading to formation of microprecipitates from which small amounts of insulin glargine are slowly released, resulting in a relatively constant concentration/time profile over 24 hours with no pronounced peak. This profile allows once-daily dosing as a basal insulin.

In clinical studies, the glucose-lowering effect on a molar basis (i.e., when given at the same doses) of intravenous insulin glargine is approximately the same as that for human insulin. In euglycemic clamp studies in healthy subjects or in patients with type 1 diabetes, the onset of action of subcutaneous insulin glargine was slower than NPH insulin. The effect profile of insulin glargine was relatively constant with no pronounced peak and the duration of its effect was prolonged compared to NPH insulin. *Figure 1* shows results from a study in patients with type 1 diabetes conducted for a maximum of 24 hours after the injection. The median time between injection and the end of pharmacological effect was 14.5 hours (range: 9.5 to 19.3 hours) for NPH insulin, and 24 hours (range: 10.8 to >24.0 hours) (24 hours was the end of the observation period) for insulin glargine.

### **Figure 1. Activity Profile in Patients with Type 1 Diabetes**



\* Determined as amount of glucose infused to maintain constant plasma glucose levels (hourly mean values); indicative of insulin activity.

The longer duration of action (up to 24 hours) of LANTUS is directly related to its slower rate of absorption and supports once-daily subcutaneous administration. The time course of action of insulins, including LANTUS, may vary between individuals and within the same individual.

### 12.3 Pharmacokinetics

**Absorption and Bioavailability.** After subcutaneous injection of insulin glargine in healthy subjects and in patients with diabetes, the insulin serum concentrations indicated a slower, more prolonged absorption and a relatively constant concentration/time profile over 24 hours with no pronounced peak in comparison to NPH insulin. Serum insulin concentrations were thus consistent with the time profile of the pharmacodynamic activity of insulin glargine.

After subcutaneous injection of 0.3 Units/kg insulin glargine in patients with type 1 diabetes, a relatively constant concentration/time profile has been demonstrated. The duration of action after abdominal, deltoid, or thigh subcutaneous administration was similar.

**Metabolism.** A metabolism study in humans indicates that insulin glargine is partly metabolized at the carboxyl terminus of the B chain in the subcutaneous depot to form two active metabolites with in vitro activity similar to that of insulin, M1 (21<sup>A</sup>-Gly-insulin) and M2 (21<sup>A</sup>-Gly-des-30<sup>B</sup>-Thr-insulin). Unchanged drug and these degradation products are also present in the circulation.

#### Special Populations

**Age, Race, and Gender.** Information on the effect of age, race, and gender on the pharmacokinetics of LANTUS is not available. However, in controlled clinical trials in adults (n=3890) and a controlled clinical trial in pediatric patients (n=349), subgroup analyses based on age, race, and gender did not show differences in safety and efficacy between insulin glargine and NPH insulin [see *Clinical Studies (14)*].

**Smoking.** The effect of smoking on the pharmacokinetics/pharmacodynamics of LANTUS has not been studied.

**Pregnancy.** The effect of pregnancy on the pharmacokinetics and pharmacodynamics of LANTUS has not been studied [*see Use in Specific Populations (8.1)*].

**Obesity.** In controlled clinical trials, which included patients with Body Mass Index (BMI) up to and including 49.6 kg/m<sup>2</sup>, subgroup analyses based on BMI did not show differences in safety and efficacy between insulin glargine and NPH insulin [*see Clinical Studies (14)*].

**Renal Impairment.** The effect of renal impairment on the pharmacokinetics of LANTUS has not been studied. However, some studies with human insulin have shown increased circulating levels of insulin in patients with renal failure. Careful glucose monitoring and dose adjustments of insulin, including LANTUS, may be necessary in patients with renal impairment [*See Warnings and Precautions (5.5)*].

**Hepatic Impairment.** The effect of hepatic impairment on the pharmacokinetics of LANTUS has not been studied. However, 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 LANTUS, may be necessary in patients with hepatic impairment [*See Warnings and Precautions (5.6)*].

## **13. NONCLINICAL TOXICOLOGY**

### **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

In mice and rats, standard two-year carcinogenicity studies with insulin glargine were performed at doses up to 0.455 mg/kg, which was for the rat approximately 10 times and for the mouse approximately 5 times the recommended human subcutaneous starting dose of 10 Units/day (0.008 mg/kg/day), based on mg/m<sup>2</sup>. The findings in female mice were not conclusive due to excessive mortality in all dose groups during the study. Histiocytomas were found at injection sites in male rats (statistically significant) and male mice (not statistically significant) in acid vehicle containing groups. These tumors were not found in female animals, in saline control, or insulin comparator groups using a different vehicle. The relevance of these findings to humans is unknown.

Insulin glargine was not mutagenic in tests for detection of gene mutations in bacteria and mammalian cells (Ames- and HGPRT-test) and in tests for detection of chromosomal aberrations (cytogenetics in vitro in V79 cells and in vivo in Chinese hamsters).

In a combined fertility and prenatal and postnatal study in male and female rats at subcutaneous doses up to 0.36 mg/kg/day, which was approximately 7 times the recommended human subcutaneous starting dose of 10 Units/day (0.008 mg/kg/day), based on mg/m<sup>2</sup>, maternal toxicity due to dose-dependent hypoglycemia, including some deaths, was observed. Consequently, a reduction of the rearing rate occurred in the high-dose group only. Similar effects were observed with NPH insulin.

## 14. CLINICAL STUDIES

The safety and effectiveness of LANTUS given once-daily at bedtime was compared to that of once-daily and twice-daily NPH insulin in open-label, randomized, active-controlled, parallel studies of 2,327 adult patients and 349 pediatric patients with type 1 diabetes mellitus and 1,563 adult patients with type 2 diabetes mellitus (see Tables 8-11). In general, the reduction in glycated hemoglobin (HbA1c) with LANTUS was similar to that with NPH insulin. The overall rates of hypoglycemia did not differ between patients with diabetes treated with LANTUS compared to NPH insulin [*See Adverse Reactions (6.1)*].

### Type 1 Diabetes—Adult (see Table 8).

In two clinical studies (Studies A and B), patients with type 1 diabetes (Study A; n=585, Study B; n=534) were randomized to 28 weeks of basal-bolus treatment with LANTUS or NPH insulin. Regular human insulin was administered before each meal. LANTUS was administered at bedtime. NPH insulin was administered once daily at bedtime or in the morning and at bedtime when used twice daily.

In another clinical study (Study C), patients with type 1 diabetes (n=619) were randomized to 16 weeks of basal-bolus treatment with LANTUS or NPH insulin. Insulin lispro was used before each meal. LANTUS was administered once daily at bedtime and NPH insulin was administered once or twice daily.

In these 3 studies, LANTUS and NPH insulin had similar effects on HbA1c (Table 8) with a similar overall rate of hypoglycemia [*See Adverse Reactions (6.1)*].

**Table 8: Type 1 Diabetes Mellitus–Adult**

	<u>Study A</u>		<u>Study B</u>		<u>Study C</u>	
	28 weeks Regular insulin		28 weeks Regular insulin		16 weeks Insulin lispro	
Treatment duration Treatment in combination with	<u>LANTUS</u>	<u>NPH</u>	<u>LANTUS</u>	<u>NPH</u>	<u>LANTUS</u>	<u>NPH</u>
Number of subjects treated	292	293	264	270	310	309
HbA1c						
Baseline HbA1c	8.0	8.0	7.7	7.7	7.6	7.7
Adj. mean change from baseline	+0.2	+0.1	-0.2	-0.2	-0.1	-0.1
LANTUS – NPH	+0.1		+0.1		0.0	
95% CI for Treatment difference	(0.0; +0.2)		(-0.1; +0.2)		(-0.1; +0.1)	
Basal insulin dose						
Baseline mean	21	23	29	29	28	28
Mean change from baseline	-2	0	-4	+2	-5	+1
Total insulin dose						
Baseline mean	48	52	50	51	50	50
Mean change from baseline	-1	0	0	+4	-3	0
Fasting blood glucose (mg/dL)						
Baseline mean	167	166	166	175	175	173
Adj. mean change from baseline	-21	-16	-20	-17	-29	-12
Body weight (kg)						
Baseline mean	73.2	74.8	75.5	75.0	74.8	75.6
Mean change from baseline	0.1	-0.0	0.7	1.0	0.1	0.5

**Type 1 Diabetes–Pediatric (see Table 9).**

In a randomized, controlled clinical study (Study D), pediatric patients (age range 6 to 15 years) with type 1 diabetes (n=349) were treated for 28 weeks with a basal-bolus insulin regimen where regular human insulin was used before each meal. LANTUS was administered once daily at bedtime and NPH insulin was administered once or twice daily. Similar effects on HbA1c (Table 9) and the incidence of hypoglycemia were observed in both treatment groups [See *Adverse Reactions (6.1)*].

**Table 9: Type 1 Diabetes Mellitus–Pediatric**

Treatment duration Treatment in combination with	Study D 28 weeks Regular insulin	
	<u>LANTUS</u>	<u>NPH</u>
Number of subjects treated	174	175
HbA1c		
Baseline mean	8.5	8.8
Adj. mean change from baseline	+0.3	+0.3
LANTUS – NPH	0.0	
95% CI for Treatment difference	(-0.2; +0.3)	
Basal insulin dose		
Baseline mean	19	19
Mean change from baseline	-1	+2
Total insulin dose		
Baseline mean	43	43
Mean change from baseline	+2	+3
Fasting blood glucose (mg/dL)		
Baseline mean	194	191
Adj. mean change from baseline	-23	-12
Body weight (kg)		
Baseline mean	45.5	44.6
Mean change from baseline	2.2	2.5

**Type 2 Diabetes–Adult (see Table 10).**

In a randomized, controlled clinical study (Study E) (n=570), LANTUS was evaluated for 52 weeks in combination with oral anti-diabetic medications (a sulfonylurea, metformin, acarbose, or combinations of these drugs). LANTUS administered once daily at bedtime was as effective as NPH insulin administered once daily at bedtime in reducing HbA1c and fasting glucose (Table 10). The rate of hypoglycemia was similar in LANTUS and NPH insulin treated patients [See *Adverse Reactions (6.1)*].

In a randomized, controlled clinical study (Study F), in patients with type 2 diabetes not using oral anti-diabetic medications (n=518), a basal-bolus regimen of LANTUS once daily at bedtime or NPH insulin administered once or twice daily was evaluated for 28 weeks. Regular human insulin was used before meals, as needed. LANTUS had similar effectiveness as either once- or twice-daily NPH insulin in reducing HbA1c and fasting glucose (Table 10) with a similar incidence of hypoglycemia [See *Adverse Reactions (6.1)*].

In a randomized, controlled clinical study (Study G), patients with type 2 diabetes were randomized to 5 years of treatment with once-daily LANTUS or twice-daily NPH insulin. For patients not previously treated with insulin, the starting dose of LANTUS or NPH insulin was 10 units daily. Patients who were already treated with NPH insulin either continued on the same total daily NPH insulin dose or started LANTUS at a dose that was 80% of the total previous NPH insulin dose. The primary endpoint for this study was a comparison of the progression of diabetic retinopathy by 3 or more steps on the Early Treatment Diabetic Retinopathy Study (ETDRS) scale. HbA1c change from baseline was a secondary endpoint. Similar glycemic control in the 2 treatment groups was desired in order to not confound the interpretation of the retinal data. Patients or study personnel used an algorithm to adjust the LANTUS and NPH insulin doses to a target fasting plasma glucose  $\leq 100$  mg/dL. After the LANTUS or NPH insulin dose was adjusted, other anti-diabetic agents, including pre-meal insulin were to be adjusted or added. The LANTUS group had a smaller mean reduction from baseline in HbA1c compared to

the NPH insulin group, which may be explained by the lower daily basal insulin doses in the LANTUS group (Table 10). Both treatment groups had a similar incidence of reported symptomatic hypoglycemia. The incidences of severe symptomatic hypoglycemia are given in Table 6 [See Adverse Reactions (6.1)].

**Table 10: Type 2 Diabetes Mellitus–Adult**

Treatment duration Treatment in combination with	<u>Study E</u> 52 weeks Oral agents		<u>Study F</u> 28 weeks Regular insulin		<u>Study G</u> 5 years Regular insulin	
	<u>LANTUS</u>	<u>NPH</u>	<u>LANTUS</u>	<u>NPH</u>	<u>LANTUS</u>	<u>NPH</u>
Number of subjects treated	289	281	259	259	513	504
HbA1c						
Baseline mean	9.0	8.9	8.6	8.5	8.4	8.3
Adj. mean change from baseline	-0.5	-0.4	-0.4	-0.6	-0.6	-0.8
LANTUS – NPH	-0.1		+0.2		+0.2	
95% CI for Treatment difference	(-0.3; +0.1)		(0.0; +0.4)		(+0.1, +0.4)	
Basal insulin dose*						
Baseline mean	14	15	44.1	45.5	39	44
Mean change from baseline	+12	+9	-1	+7	+23	+30
Total insulin dose*						
Baseline mean	14	15	64	67	48	53
Mean change from baseline	+12	+9	+10	+13	+41	+40
Fasting blood glucose (mg/dL)						
Baseline mean	179	180	164	166	190	180
Adj. mean change from baseline	-49	-46	-24	-22	-45	-44
Body weight (kg)						
Baseline mean	83.5	82.1	89.6	90.7	100	99
Adj. mean change from baseline	2.0	1.9	0.4	1.4	3.7	4.8

\*In Study G, the baseline dose of basal or total insulin was the first available on-treatment dose prescribed during the study (on visit month 1.5).

### LANTUS Timing of Daily Dosing (see Table 11).

The safety and efficacy of LANTUS administered pre-breakfast, pre-dinner, or at bedtime were evaluated in a randomized, controlled clinical study in patients with type 1 diabetes (study H, n=378). Patients were also treated with insulin lispro at mealtime. LANTUS administered at different times of the day resulted in similar reductions in HbA1c compared to that with bedtime administration (see Table 11). In these patients, data are available from 8-point home glucose monitoring. The maximum mean blood glucose was observed just prior to injection of LANTUS regardless of time of administration.

In this study, 5% of patients in the LANTUS-breakfast arm discontinued treatment because of lack of efficacy. No patients in the other two arms discontinued for this reason. The safety and efficacy of LANTUS administered pre-breakfast or at bedtime were also evaluated in a randomized, active-controlled clinical study (Study I, n=697) in patients with type 2 diabetes not adequately controlled on oral anti-diabetic therapy. All patients in this study also received glimepiride 3 mg daily. LANTUS given before breakfast was at least as effective in lowering HbA1c as LANTUS given at bedtime or NPH insulin given at bedtime (see Table 11).

**Table 11: LANTUS Timing of Daily Dosing in Type 1 (Study H) and Type 2 (Study I) Diabetes Mellitus**

Treatment duration Treatment in combination with:	Study H 24 weeks			Study I 24 weeks		
	Insulin lispro			Glimepiride		
	LANTUS Breakfast	LANTUS Dinner	LANTUS Bedtime	LANTUS Breakfast	LANTUS Bedtime	NPH Bedtime
Number of subjects treated*	112	124	128	234	226	227
HbA1c						
Baseline mean	7.6	7.5	7.6	9.1	9.1	9.1
Mean change from baseline	-0.2	-0.1	0.0	-1.3	-1.0	-0.8
Basal insulin dose (U)						
Baseline mean	22	23	21	19	20	19
Mean change from baseline	5	2	2	11	18	18
Total insulin dose (U)						
Baseline mean	52	52	49	NA***	NA	NA
Mean change from baseline	2	3	2			
Body weight (kg)						
Baseline mean	77.1	77.8	74.5	80.7	82	81
Mean change from baseline	0.7	0.1	0.4	3.9	3.7	2.9

\*Intent to treat \*\*total number of patients evaluable for safety \*\*\*Not applicable

## 16. HOW SUPPLIED/STORAGE AND HANDLING

### 16.1 How supplied

LANTUS solution for injection 100 units per mL (U-100) is available as:

Dosage Unit/Strength	Package size	NDC # 00886
<b>10 mL vials</b> 100 Units/mL	Pack of 1	2220-33
<b>3 mL cartridge system*</b> 100 Units/mL	package of 5	2220-52
<b>3 mL SoloStar® disposable insulin device</b> 100 Units/mL	package of 5	2220-60

\*Cartridge systems are for use only in OptiClik® (Insulin Delivery Device)

Needles are not included in the packs.

BD Ultra-Fine™ needles<sup>†</sup> to be used in conjunction with SoloStar and OptiClik are sold separately and are manufactured by BD.

### 16.2 Storage:

LANTUS should not be stored in the freezer and should not be allowed to freeze. Discard LANTUS if it has been frozen.

Unopened Vial/Cartridge system/SoloStar disposable insulin device:

Unopened LANTUS vials, cartridge systems and SoloStar device should be stored in a refrigerator, 36°F - 46°F (2°C - 8°C). Discard after the expiration date.

Open (In-Use) Vial:

Vials must be discarded 28 days after being opened. If refrigeration is not possible, the open vial can be kept unrefrigerated for up to 28 days away from direct heat and light, as long as the temperature is not greater than 86°F (30°C).

Open (In-Use) Cartridge system:

The opened (in-use) cartridge system in OptiClik should NOT be refrigerated but should be kept at room temperature (below 86°F [30°C]) away from direct heat and light. The opened (in-use) cartridge system in OptiClik must be discarded 28 days after being opened. Do not store OptiClik , with or without cartridge system, in a refrigerator at any time.

Open (In-Use) SoloStar disposable insulin device:

The opened (in-use) SoloStar should NOT be refrigerated but should be kept at room temperature (below 86°F [30°C]) away from direct heat and light. The opened (in-use) SoloStar device must be discarded 28 days after being opened.

These storage conditions are summarized in the following table:

	<b>Not in-use (unopened)</b> <b>Refrigerated</b>	<b>Not in-use (unopened)</b> <b>Room Temperature</b>	<b>In-use (opened)</b> <b>(See Temperature Below)</b>
10 mL Vial	Until expiration date	28 days	28 days Refrigerated or room temperature
3 mL Cartridge system	Until expiration date	28 days	28 days Refrigerated or room temperature
3 mL Cartridge system inserted into OptiClik®			28 days Room temperature only (Do not refrigerate)
3 mL SoloStar® disposable insulin device	Until expiration date	28 days	28 days Room temperature only (Do not refrigerate)

### 16.3 Preparation and handling

Parenteral drug products should be inspected visually prior to administration whenever the solution and the container permit. LANTUS must only be used if the solution is clear and colorless with no particles visible.

Mixing and diluting: LANTUS must NOT be diluted or mixed with any other insulin or solution [See *Warnings and Precautions (5.2)*].

Vial: The syringes must not contain any other medicinal product or residue.

Cartridge system/SoloStar: If OptiClik, the Insulin Delivery Device used with the LANTUS cartridge system, or SoloStar disposable insulin device, malfunctions, LANTUS may be drawn from the cartridge system or from SoloStar into a U-100 syringe and injected.

## **17. PATIENT COUNSELING INFORMATION**

### **17.1 Instructions for patients**

Patients should be informed that changes to insulin regimens must be made cautiously and only under medical supervision.

Patients should be informed about the potential side effects of insulin therapy, including lipodystrophy (and the need to rotate injection sites within the same body region), weight gain, allergic reactions, and hypoglycemia. Patients should be informed that the ability to concentrate and react may be impaired as a result of hypoglycemia. This may present a risk in situations where these abilities are especially important, such as driving or operating other machinery. Patients who have frequent hypoglycemia or reduced or absent warning signs of hypoglycemia should be advised to use caution when driving or operating machinery.

Accidental mix-ups between LANTUS and other insulins, particularly short-acting insulins, have been reported. To avoid medication errors between LANTUS and other insulins, patients should be instructed to always check the insulin label before each injection.

LANTUS must only be used if the solution is clear and colorless with no particles visible. Patients must be advised that LANTUS must NOT be diluted or mixed with any other insulin or solution.

Patients should be advised not to share disposable or reusable insulin devices or needles with other patients, because doing so carries a risk for transmission of blood-borne pathogens.

Patients should be instructed on self-management procedures including glucose monitoring, proper injection technique, and management of hypoglycemia and hyperglycemia. Patients must be instructed on handling of special situations such as intercurrent conditions (illness, stress, or emotional disturbances), an inadequate or skipped insulin dose, inadvertent administration of an increased insulin dose, inadequate food intake, and skipped meals.

Patients with diabetes should be advised to inform their health care professional if they are pregnant or are contemplating pregnancy.

Refer patients to the LANTUS “Patient Information” for additional information.

### **17.2 FDA approved patient labeling**

See attached document at end of Full Prescribing Information.

Rx only

Rev. June 2009

sanofi-aventis U.S. LLC  
Bridgewater, NJ 08807

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Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21081	SUPPL-34	SANOFI AVENTIS US LLC	LANTUS

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/s/

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MARY H PARKS  
09/09/2009

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**NDA 021081/S-034**

**SUMMARY REVIEW**



**DIVISION DIRECTOR'S MEMO TO THE FILE**

**NDA** 21-081/S-034  
**Sponsor** sanofi-aventis  
**Drug Product** Lantus (insulin glargine)  
**Date of Submission** December 21, 2007  
**Subject** Phase 4 commitment to address imbalance of retinopathy in original NDA

Drs. Misbin and Joffe have completed their reviews of this supplement which was submitted in response to a Phase 4 commitment to evaluate the effect of Lantus on the development of retinopathy in T2DM compared to NPH insulin. Both their reviews have concluded that the applicant has adequately addressed the agency's concern and that based on this study, the postmarketing commitment has been fulfilled. I concur with their conclusions and have signed off on Dr. Joffe's memo noting that his review will serve as the decisional memo for the approval action of this supplement.

During labeling negotiations for this supplement, 4 epidemiologic studies were published in *Diabetologia* which merit a brief memo to the administrative record for this supplement. All four studies had some findings suggesting an increased risk for cancer associated with insulin use, in particular glargine; however, there were inconsistencies within an individual study and across the different studies which has led to an overall conclusion by FDA, EMEA and leading medical organizations that additional studies will be necessary before a definitive conclusion of cancer risk can be made. (b) (4)

[Redacted]

DMEP has been in discussion with OSE and the assigned epidemiologist, Dr. Talia Zhang, on the issue of insulin glargine and cancer risk. The overall assessment at this juncture is that the data from the epidemiologic studies have limitations because of duration of follow-up, imbalances in demographics and baseline characteristics of the different treatment cohorts, and conflicting results across the studies with respect to cancer risk. Consequently, it was agreed that labeling should not be modified on the basis of these 4 studies. However, FDA is evaluating what additional studies can be conducted to better evaluate this potential signal.

A summary of the 4 epidemiologic studies is appended to this memo.

## APPENDIX – SUMMARY OF COHORT STUDIES

### Hemkens LG et al. Risk of malignancies in patients with diabetes treated with human insulin or insulin analogues: a cohort study.

The primary objective of this study was to investigate the risk of malignant neoplasms in patients with diabetes treated with either human insulin or an insulin analogue. This cohort study evaluated data from a German statutory health insurance fund on adult patients who had received first-time insulin therapy for diabetes exclusively with human insulin or with only one type of insulin analogue (lispro, aspart, or glargine). The period of data collection was from January 1, 2001 until June 30, 2005. The mean follow-up time was approximately 1.6 yrs with the maximum time of approximately 4.4 years. Patients with a known history of malignant disease were excluded from the study (i.e., no corresponding diagnosis within 3 yrs prior to study inclusion). The primary outcome was the diagnosis of a malignant neoplasm defined by ICD codes. All-cause mortality was a secondary outcome.

Data for potential confounders were available for age, sex, start date of treatment, # of hospital stays, duration of hospitalization and concomitant meds. Insulin dose was calculated as cumulative dose over time. These variables were assessed for interaction with the overall finding; however, no adjustments for multiplicity were done as the authors stated the study was intended to generate hypotheses (*Comments: no data on BMI, duration of diabetes, type of diabetes reported*)

Data from a total of 127,031 patients were evaluated from the following treatment cohorts:

1. Human insulin (n=95,804)
2. Aspart (n=4,103)
3. Lispro (n=3,269)
4. Glargine (n=23,855)

The crude incidence rate for malignant neoplasm (per 100 pt-yrs) was as follows (secondary endpoint of total mortality in parentheses) The overall unadjusted analyses showed a lower incidence of malignant neoplasms and all-cause mortality for the analogues versus human insulin:

- Human insulin = 2.50 (9.24)
- Aspart = 2.16 (5.75)
- Lispro = 2.13 (6.91)
- Glargine = 2.14 (6.30)

Authors noted lower mean dose of insulin use in analogues versus human insulin, particularly in glargine group and that models evaluating effect of covariates on the overall results showed a significant effect of insulin dose. Adjusting for dose, there was a dose-dependent increase in risk for glargine compared to human insulin for the development of malignant neoplasms.

Excerpted from Table 2 in the article:

HRs (95% CI) for insulin analogues compared to human insulin for malignant neoplasms based on covariate analyses factoring in insulin dose

Dose	Aspart	Lispro	Glargine
10 IU	1.00 (0.82-1.21)	0.99 (0.82-1.19)	1.09 (1.00-1.19)
30 IU	1.02 (0.85-1.22)	0.98 (0.83-1.16)	1.19 (1.10-1.30)
50 IU	1.04 (0.87-1.24)	0.98 (0.83-1.16)	1.31 (1.20-1.42)

*Comments:*

- *Extreme caution in interpreting these HRs 95% CI given the limitations and confounders of the cohort study. The HR in this type of study, which the authors acknowledge is hypothesis-generating, is very modest and may likely shift with slight changes in event rates contributing to*

*its calculation. In fact, the authors failed to provide the # of events and sample sizes of each of the subgroups analyzed in the table above.*

- *The study observation period was only between January 1, 2001 and June 30, 2005. The mean duration of f/u of 1.63 yrs (max 4.4 yrs) appears short for detecting cancers, especially with the majority of patients starting therapy with insulin occurring in 2003/2004. An argument that insulin therapy accelerated pre-existing cancer can not be made here since the authors excluded patients with any diagnosis of cancer within 3 years prior to study inclusion.*
- *This study did not provide information on specific cancer types.*
- *A finding of an increased risk based on dose doesn't take into consideration how dose was calculated. The article describes dose calculations based on cumulative dose/time at risk but it is not clear where this information is derived. Patients routinely adjust their insulin dose, if not on a daily basis, a weekly basis. Adjustments are particularly common with the short-acting insulins (aspart and lispro) because their effect is very dependent upon meal time and meal consumed. The accuracy and reliability of dose information must be considered.*
- *The absence of BMI data and duration of diabetes is a real limitation with respect to analyzing for important covariates. BMI is not only a risk for certain solid tumors but also correlates with degree of insulin resistance (purported risk factor for cancer) and insulin dose. Duration of diabetes often correlates with many complications of the disease and its treatments.*
- *The authors note that the study could not distinguish between type 1 and type 2 diabetes. It is highly probable that more type 1 patients were present in the aspart and lispro group because a patient with type 1 diabetes would unlikely be treated with glargine alone. The authors commented that the patient would likely have T2DM if there is concomitant use of an oral agent. This is true; however, Table 1 reveals that the highest percentage of patients using an oral agent was in the glargine group (92.1%) whereas aspart and lispro groups had 80.1% and 66% oral agent use, respectively. Because information on pump use was not obtained, it is possible that some of the type 1 patients were prescribed aspart and lispro through continuous pump infusion. Not only is the underlying pathology different for these two forms of diabetes, but certain baseline characteristics including insulin resistance, obesity, and BMI may be different and contribute to cancer risk.*

Jonasson JM et al. Insulin glargine use and short-term incidence of malignancies – a population based follow-up study in Sweden.

This study was undertaken at the request of the EASD in light of the results from the study by Hemkens et al. This cohort study linked the personal identity number, unique to each Swedish resident, to 7 population registers to obtain selected variables in determining whether there was an increased risk of certain solid tumors associated with insulin use.

114,841 adults who had at least one prescription dispensed for insulin between July 1 and December 31, 2005 and who were alive at the start of the observation period (January 1, 2006) were studied. The follow-up period was two years between January 1, 2006 to December 31, 2007. The following three insulin groups were studied:

- Glargine monotherapy (n=5970)
- Glargine plus other insulins (n=20,316)
- Other insulins/non-glargine group (n=88,555)

Unlike the Hemkens et al. study, this study had information on type of diabetes, age at onset, BMI, and smoking status. Not surprisingly, the glargine plus other insulin group had a higher percentage of patients with T1DM (38.9%) than the glargine monotherapy group (9.4%) since it is unusual for a patient with T1DM to take basal insulin alone.

The outcomes of interest were all malignancies, breast cancer, prostate cancer, GI cancers, all-cause mortality, and MI. Analyses for the malignancies excluded patients with prior diagnoses of cancer (either all or the specific cancer of interest depending upon the analysis).

This study found no difference in the incidence rates of GI cancers, prostate cancer and “all malignancies” among the different cohorts of insulin use. There was a statistically significant increase rate of breast cancer in the insulin glargine monotherapy group compared to other insulin groups (unadjusted RR 1.91; 95%CI: 1.25-2.89). Similar results were observed when adjustments were made for age, BMI, smoking, age at onset of DM, CVD, and age at birth of first child. However, this increased risk was not observed in the glargine plus other insulin cohort for both adjusted and unadjusted analyses. Authors stated that an analysis was performed by type of diabetes (T1 vs T2DM) and a significant difference was still observed; however, data were not presented. Interestingly, women in the glargine monotherapy group had a lower rate of MI, which when adjusted for age and a variety of variables, almost made statistical significance (RR 0.77; 95% CI 0.59-1.00).

The authors could not rule out the possibility that the finding of an increased rate of breast cancer in just the glargine monotherapy group reflected random fluctuation and pointed to the contradictory findings of no increased rate of other malignancies as supportive of this explanation. Overall conclusions were that more data were needed.

*Comments:*

- *A strength of this study with respect to cancer diagnosis is the mandatory reporting of all new cases of cancer to the Cancer Register which reduces the chances of under-ascertainment in this event of interest.*
- *This study was undertaken as a result of the Hemken’s study which found a significant increase in cancer with glargine but only after adjusting for dose use. These authors reported no statistically significant increase in the incidence rate of breast cancer with increasing number of daily defined doses of glargine (data were not presented).*

SDRN Epidemiology Group. Use of insulin glargine and cancer incidence in Scotland: A study from the Scottish Diabetes Research Network Epidemiology Group.

This study analyzed data from a diabetes database (SCI-DC) covering the majority of the Scottish population with diabetes. From January 1, 2002 until December 31, 2005, patients with diabetes in this database who received an insulin prescription were linked to a cancer registry data. The objective of the study was to compare the incidence of all cancers and cancers of the breast, colon, prostate, pancreas, and lung between those who received glargine versus those who did not.

Three different treatment groups were evaluated: glargine only, glargine plus non-glargine insulin, and non-glargine insulin. These 3 treatment groups were analyzed in three different cohort analyses:

- Fixed cohort analysis – selected patients who received any insulin prescription during the 4-month period of July 1, 2003 through October 31, 2003. These patients were then divided into the above 3 treatment groups. Follow-up beyond this 4-month treatment period for outcomes of interest did not take into consideration whether the patients remained on the same therapy as observed during the 4-month period. Considered to be similar to an ITT analysis, authors argued that this analysis minimized possible reverse causation bias (where the outcome of interest influences the selection of cases).
- Incident insulin cohort – restricted patient selection to those who *initiated* insulin therapy during the time period of January 1, 2002 until December 31, 2005. This analysis was considered to address concerns that prior treatments might influence the outcome.
- Analysis with exposure classification across the follow-up period – patients were analyzed based on their exposure to the treatments of interest over the entire follow-up period.

Data were also analyzed by type of diabetes. This is particularly relevant as the Baseline characteristics of the 3 treatment groups were significantly different on several variables which might influence the development of cancer.

Overall, there were no differences in incidence rate of all cancers between the glargine users and non-glargine users (HR 1.02; 95% CI: 0.77-1.36) in the fixed-cohort analysis. This was also observed in the other types of analyses. Incident cohort analysis yielded HR 0.93 (95% CI: 0.70-1.25) and Exposure Across Entire F/U analysis yielded HR 0.66 (95% CI: 0.57-0.76).

The only signal for cancer was detected in subgroup analyses by cancer-specific type and in the glargine-only treatment group. This yielded HRs above one, many with 95% CIs including 1.0 and some reaching marginal statistical significance. Similar to the Swedish study, these authors noted that glargine-only users were found to have a higher rate of breast cancer compared with non-glargine users or glargine plus other insulins. In the fixed cohort analysis the increased risk was not statistically significant but this trend was observed across all 3 different analyses (HR 1.49; 95% CI: 0.79-2.83). The authors pointed out that this finding may be due to allocation bias, particularly as the use of glargine only may be preferentially prescribed to less healthy individuals since there is a once-daily regimen with a lower risk of nocturnal hypoglycemia.

*Comments:*

- *The SCI-DC database from which data were extracted covers approximately 99% of the total adult diabetic population in Scotland. Patient records from a variety of sources (e.g., hospital clinics, primary healthcare systems, prescription data) appear extensive. However, dose and directions for use are not available.*
- *It is not clear if all cases of newly diagnosed cancers are required to be reported to the Cancer Registry, as in Sweden. However, authors report that the breast cancer ascertainment exceeds 98% and that accuracy and sensitivity for breast cancer are 95.7% and 97.8%.*

- *Data on drug dose are not available.*

Currie CJ et al. The influence of glucose-lowering therapies on cancer risk in type 2 diabetes.

This retrospective cohort study utilized data from The Health Information Network (THIN) of the United Kingdom. Data from patients diagnosed with diabetes after the age of 40 were analyzed according to the following 4 cohorts.

1. Metformin (Met) only (n=31,421)
2. Sulfonylurea (SU) only (n=7,439)
3. Met plus SU (n=13,882)
4. Insulin use with interest in the following subclasses (n=10,067)
  - glargine only (n=2286)
  - long-acting human insulin (n=1262)
  - human biphasic insulin (n=2003)
  - biphasic analogue insulin (n=2483)

Authors also evaluated a subgroup of diabetic patients who had no record of any anti-diabetic drug use (diet-only group).

The primary outcome was time to first record of any solid tumor. Secondary outcome measure evaluated the specific cancer types: breast, pancreas, colorectal, and prostate.

There were notable differences in the Baseline characteristics of the 4 treatment groups. For example, the mean age of the metformin group is younger than the other groups and the duration of disease is shortest in metformin (average 1.5 yrs) and longest with insulin (average 6.2 yrs). Long-term complications of diabetes are also more prevalent in the insulin group than metformin. These differences likely reflect how these different drugs are used along the spectrum of diabetes disease progress. For example, metformin is considered by most as the preferred first line therapy for T2DM. But as disease progresses, many patients will have inadequate glycemic control requiring the addition of other agents. Insulin initiation in T2DM is often the last resort when patients have failed a variety of oral anti-diabetic therapies. These differences in Baseline patient characteristics make it difficult to interpret differences in cancer incidence since some of the characteristics likely influence the risk of developing cancer. To what extent factoring in these covariates in the overall analysis correct for the imbalance is not known.

The overall incidence of all solid tumors was lowest in the metformin group compared to the other three treatment groups with the SU monotherapy group having the highest crude incidence rate/yr. After adjusting for age, sex, smoking status, and prior cancer, the metformin group still had the lowest incidence of tumor but insulin-based regimens now had the highest risk of progression to solid tumor, although the 95% CI overlapped with the SU only group. The following table summarizes the HRs relative to metformin in the adjusted analyses for solid tumors.

**Adjusted analyses for progression to solid tumors relative to metformin-only**

	HR (95% CI)
SU only	1.36 (1.19-1.54)
Met plus SU	1.08 (0.96-1.21)
Insulin-based	1.42 (1.27-1.60)

The authors noted that the signal for cancer may not be due to some adverse property of the insulin formulation since insulin secretagogues, which increase circulation of endogenous insulin, appear to have a similar risk of increase for solid tumors.

With respect to whether any particular regimen was associated with an increase risk for a specific cancer, there did not appear to be a difference in progression to breast cancer in women and prostate cancer in men across the 4 treatment groups. However, colorectal and pancreatic cancer risks were significantly

higher in the SU only and insulin-based treatment groups compared to metformin-only. Interestingly, a non-significant reduction in pancreatic cancer risk was noted in the Met plus SU group, suggesting a protective effect that was recently hypothesized in a non-clinical study evaluating sitagliptin in a diabetic rat model.

Overall, the authors noted the lower risk of cancer with metformin therapy that was similar to the cohort of diabetic patients not receiving any pharmacologic intervention. While these data should not be interpreted as a cancer-protective effect of metformin (especially since the database shows a generally younger and healthier population of metformin-only users), these findings support the general recommendation for metformin as first-line therapy. The findings of increased cancer risk w/ SU and insulin compared to metformin are concerning but the authors conclude in a very balanced statement that it is premature to assume a causal relationship between insulin therapy and cancer risk and that even if such a relationship exists, there are “life-giving” benefits of insulin.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21081	SUPPL-34	SANOFI AVENTIS US LLC	LANTUS
NDA-21081	SUPPL-34	SANOFI AVENTIS US LLC	LANTUS

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/s/

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MARY H PARKS  
09/09/2009

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**NDA 021081/S-034**

**CROSS DISCIPLINE TEAM LEADER REVIEW**

## Cross-Discipline Team Leader Review

<b>Date</b>	February 10, 2009
<b>From</b>	Hylton V. Joffe, M.D., M.M.Sc.
<b>Subject</b>	Cross-Discipline Team Leader Review
<b>NDA/BLA #</b>	NDA 21-081
<b>Supplement#</b>	S-034
<b>Applicant</b>	sanofi-aventis
<b>Date of Submission</b>	December 21, 2007
<b>PDUFA Goal Date</b>	October 19, 2008
<b>Proprietary Name / Established (USAN) names</b>	Lantus Insulin glargine
<b>Dosage forms / Strength</b>	Solution for subcutaneous injection; 100 units/mL
<b>Proposed Indication(s)</b>	Improve glycemic control in patients with diabetes mellitus
<b>Recommended:</b>	<i>Approval, pending agreement on labeling</i>

### 1. Introduction

Lantus (insulin glargine) was approved in 2000 for the control of hyperglycemia in patients with diabetes mellitus. At the time of approval, a postmarketing commitment was established for the sponsor to compare once daily Lantus to twice daily NPH insulin with respect to the percentage of patients with type 2 diabetes who develop  $\geq 3$ -step progression in the Early Treatment Diabetic Retinopathy Scale (ETDRS). The results from this completed clinical trial, which are reviewed in this memorandum, were submitted in December 2007, delayed from the April 2005 due date listed in the approval letter for the Lantus NDA.

### 2. Background

The following text is included under the Adverse Reactions section in the currently approved Lantus package insert:

Retinopathy was evaluated in the clinical studies by means of retinal adverse events reported and fundus photography. The numbers of retinal adverse events reported for LANTUS and NPH treatment groups were similar for patients with type 1 and type 2 diabetes. Progression of retinopathy was investigated by fundus photography using a grading protocol derived from the Early Treatment Diabetic Retinopathy Study (ETDRS). In one clinical study involving patients with type 2 diabetes, a difference in the number of subjects with  $\geq 3$ -step progression in ETDRS scale over a 6-month period was noted by fundus photography (7.5% in LANTUS group versus 2.7% in NPH treated group). The overall relevance of this isolated finding cannot be determined due to the small number of patients involved, the short follow-up period, and the fact that this finding was not observed in other clinical studies.

As explained in Dr. Robert Misbin's clinical review, retinal exams were incorporated into the Lantus premarketing phase 3 clinical trials because Lantus has more insulin-like growth factor (IGF)-1 activity than does human insulin and IGF-1 may play a role in diabetic retinopathy.

The finding described in the label text above was limited to a single trial and was discordant with other retina-related findings in the same trial (e.g., there was no difference between the treatment groups with respect to development of proliferative retinopathy or need for photocoagulation for proliferative retinopathy). Nonetheless, to definitively evaluate this potential safety signal, the Division requested a postmarketing commitment, which is the focus of this memorandum.

### **3. CMC/Device**

This supplement does not contain new chemistry data.

### **4. Nonclinical Pharmacology/Toxicology**

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

### **5. Clinical Pharmacology/Biopharmaceutics**

This supplement does not contain new clinical pharmacology data.

### **6. Clinical Microbiology**

Not applicable.

### **7. Clinical/Statistical- Efficacy**

#### **Study 4016: "Evaluation of diabetic retinopathy progression in subjects with type 2 diabetes mellitus treated with insulin"**

The primary objective of this trial was to assess the proportion of Lantus-treated patients and NPH insulin-treated patients who developed  $\geq 3$ -step progression in the ETDRS retinopathy scale from baseline to endpoint.

Secondary objectives included proliferative retinopathy, macular edema, HbA1c, fasting plasma glucose (FPG), hypoglycemia, insulin doses, and overall safety.

This was an open-label, multicenter (39 centers in the United States and 16 centers in Canada), non-inferiority retinopathy trial that randomized (1:1) patients with type 2 diabetes to 5 years

of treatment with once daily Lantus or twice daily NPH insulin. Randomization was stratified by investigational center and by baseline HbA1c ( $\leq 9\%$  vs.  $>9\%$ ).

Study assessments included fundus photographs/eye exams (screening, Months 3, 6, 12, then yearly), vital signs and body weight (screening, Months 0, 1.5, 3, then every 3 months), HbA1c (screening, baseline, then every 3 months), standard safety labs (screening and Month 12; serum creatinine also at Month 24 and study end), urine microalbumin/creatinine ratios (yearly starting with Month 12), and lipids (screening, Months 1.5, 3, 6, 12, then yearly).

The 7-field fundus photographs were obtained at centers certified and monitored by the central reading center (Fundus Photograph Reading Center at the University of Wisconsin). This is the same diabetic retinopathy assessment tool and same facility used in the landmark Diabetes Control and Complications Trial. These photographs were used to assess for diabetic retinopathy, macular edema, and proliferative retinopathy outcomes.

Each photograph was evaluated by 2 independent graders, blinded to treatment and blinded to other photographs from the same individual. A senior grader blinded to treatment resolved discrepancies between these 2 graders. A senior director blinded to treatment performed a side-by-side review of all photographs from patients classified as having a 3-step progression to verify whether or not the 3-step progression was present at study endpoint.

HbA1c, plasma glucose, complete blood count, serum creatinine, liver transaminases, urine creatinine, urine microalbumin, and lipids were measured in a central laboratory.

For patients not previously treated with insulin, the starting dose of Lantus or NPH insulin was 10 units daily (the NPH insulin dose could be divided twice daily, if clinically appropriate). Patients who were already treated with NPH insulin either continued on the same total daily NPH insulin dose or started Lantus at a dose that was 80% of the total previous NPH insulin dose.

Patients were asked to measure FPG daily

(b) (4)

After the April 2005 protocol amendment (implemented approximately 3 years into the trial), insulin doses were titrated to target a FPG  $\leq 100$  mg/dL and HbA1c  $\leq 7\%$ . This protocol amendment also established an algorithm to permit patients to self-titrate their Lantus and NPH insulin doses. Study personnel continued to use the algorithm in Table 1 for those patients who did not wish to self-titrate their insulin doses.

After the Lantus or NPH insulin dose was optimized, other anti-diabetic agents, including pre-meal insulin were to be adjusted or added.

<b>Table 1. Sliding-scale algorithm for patients not self-titrating</b>	
<b>Mean fasting plasma glucose</b>	<b>Lantus or NPH insulin dose adjustment</b>
100-119 mg/dL	Increase by 0-2 units at investigator's discretion
120-139 mg/dL	Increase by 2 units
140-179 mg/dL	Increase by 4 units
≥180 mg/dL	Increase by 6-8 units at investigator's discretion
*For the last 2 consecutive days with no plasma glucose <72 mg/dL NPH dose increase split between the morning and bedtime doses as clinically appropriate Decreases of 2-4 units were permitted for readings <56 mg/dL or hypoglycemia	

The protocol did not permit the use of insulin lispro, insulin aspart, repaglinide, or nateglinide.

Major study inclusion criteria included:

- Type 2 diabetes for at least 1 year with HbA1c 6-12%
- Age 30-70 years
- Women of childbearing potential using reliable contraception
- Stable oral anti-diabetic and/or insulin regimen (≤10% change in basal insulin dose) for ≥3 months prior to screening

Major study exclusion criteria included:

- Moderate or severe diabetic retinopathy on the ETDRS retinopathy scale
- Laser photocoagulation or vitrectomy for diabetic retinopathy prior to study entry or therapy expected within 1 year of study entry
- Use of Humalog or NovoLog within 3 months prior to screening
- Blood pressure >150/95 mmHg
- Hypoglycemia unawareness
- Pregnancy or breastfeeding
- Prior treatment with Lantus
- Pre-specified laboratory abnormalities (e.g., liver transaminases >2x ULN, serum creatinine ≥1.5 mg/dL in men or ≥1.4 mg/dL in women)

Efficacy endpoints: The primary efficacy variable is the binary indicator (yes/no) of whether a patient had ≥3-step progression in diabetic retinopathy on the ETDRS scale from baseline to endpoint. Patients with change less than 3 steps were still considered a ≥3-step progressor if they received pan-retinal photocoagulation for retinopathy, local photocoagulation for new vessels, or vitrectomy for diabetic retinopathy.

Secondary endpoints included ≥3-step progression in retinopathy at other timepoints during the trial, proliferative retinopathy, clinically significant macular edema, proportion of patients achieving HbA1c targets (<7%, <8%), fasting plasma glucose, hypoglycemia, insulin doses, and overall safety.

Statistics: Please see Dr. Cynthia Liu's biostatistics review for further details.

The per-protocol population was defined as patients without major protocol violations who either had an evaluable fundus photograph taken at least 4.5 years after the start of study medication or who had  $\geq 3$ -step progression of retinopathy at study endpoint.

The sponsor's primary analysis tested non-inferiority (10% margin) in the per-protocol population with respect to  $\geq 3$ -step progression in diabetic retinopathy from baseline to endpoint using the ETDRS scale. If non-inferiority was shown in the per-protocol population, the sponsor then proposed testing for non-inferiority in the intent-to-treat population followed by a test for superiority. The intent-to-treat population was used for all secondary analyses.

Of note, our biostatistics team prefers using the intent-to-treat population for the primary analysis in non-inferiority trials. Therefore, the intent-to-treat analysis will carry significant weight in this review.

The sponsor asked patients who prematurely discontinued from the trial to return for a follow-up visit (including fundus photographs, ophthalmology exam) at least 4.5 years after randomization. Investigators, at a minimum, called twice and sent a certified letter in an attempt to re-establish contact with patients lost to follow-up.

The Sponsor used the Cochran-Mantel-Haenszel test stratified by pooled center to test the hypothesis of no difference between treatment groups for the retinopathy findings, HbA1c responder analyses, and hypoglycemia. To calculate changes from baseline in HbA1c and FPG, the Sponsor used ANCOVA with fixed effect terms for treatment, pooled center, and HbA1c stratum.

## RESULTS

Disposition: Approximately, 72% of patients in both treatment groups completed the trial (Table 2). The most common reasons for premature discontinuation were withdrawal of consent (7.8% of Lantus-treated patients and 10.0% of NPH-treated patients) and loss to follow-up (5.4% of Lantus-treated patients and 6.9% of NPH-treated patients). Deaths and discontinuations due to adverse events are discussed in the safety section of this memorandum. Each of the other listed reasons for discontinuation occurred infrequently (each <2% of patients).

	<b>LANTUS N (%)</b>	<b>NPH N (%)</b>
Randomized and treated	513	504
Completers	374 (72.6)	364 (71.5)
Withdrawals	139 (27.0)	140 (27.5)
No longer meets study criteria	7 (1.4)	2 (0.4)
Lack of efficacy	4 (0.8)	2 (0.4)
Adverse event	17 (3.3)	12 (2.4)
Non-compliance	6 (1.2)	7 (1.4)
Withdrawal of consent	40 (7.8)	51 (10.0)
Lost to follow-up	28 (5.4)	35 (6.9)
Administrative reasons	5 (1.0)	4 (0.8)
Protocol violation	1 (0.2)	0
Death	11 (2.1)	11 (2.2)
Investigator discretion	7 (1.4)	6 (1.2)
Hypoglycemia	1 (0.2)	1 (0.2)
Other	12 (2.3)	9 (1.8)

Approximately one-fourth of patients in both treatment groups had a major protocol violation, most of whom were treated for <4 years or dropped out before 4.5 years, and, as a result, did not have fundus photographs after 4.5 years (Table 3).

	<b>LANTUS N (%)</b>	<b>NPH N (%)</b>
Any deviation	139 (27.1)	141 (28.0)
No post-baseline fundus photo within 30 days after last dose of study drug	16 (3.1)	21 (4.2)
Treated for <4 years*	118 (23.0)	119 (23.6)
No fundus photographs after 4.5 years*	131 (25.5)	136 (27.0)
Dropout before 4.5 years*	122 (23.8)	120 (23.8)
*and not censored because of $\geq 3$ -step progression in retinopathy		

**Demographics:** The baseline demographic data are summarized in Table 4. The randomized patients had a mean age of 55 years, mean body mass index of approximately 34 kg/m<sup>2</sup>, and mean baseline HbA1c of 8.3-8.4%. Most patients were Caucasian. A majority of patients had type 2 diabetes for at least 5 years with a median duration of insulin use of 3 years. At baseline, in each treatment group, nearly one-half of patients were taking metformin, one-fourth were taking sulfonylurea, and 15% were taking a thiazolidinedione. A baseline history of retinopathy was slightly more prevalent in the Lantus group (15.6% vs. 12.1%), which also had a higher prevalence of clinically significant macular edema at baseline.

<b>Table 4. Patient demographics – intent-to-treat population</b>		
	<b>LANTUS</b>	<b>NPH</b>
Age, years, mean±SD	54.9±8.8	55.3±8.5
<65 years old	429 (84%)	427 (85%)
Male, n (%)	278 (54%)	270 (54%)
Race, n (%)		
Caucasian	446 (87%)	422 (84%)
Black	49 (10%)	62 (12%)
Other	18 (3%)	20 (4%)
Body weight, kg, mean±SD	100.2±22.7	98.7±22.3
Body mass index, kg/m <sup>2</sup> , mean±SD	34.5±7.2	34.1±7.2
Duration of diabetes, years, median (min-max)	10 (1-38)	10 (1-51)
0 to <5 years	89 (17%)	78 (16%)
5 to <10 years	165 (32%)	163 (32%)
10 to <20 years	199 (39%)	220 (44%)
≥20 years	60 (12%)	43 (9%)
Duration of treatment with insulin, years, mean±SD	3 (0-37)	3 (0-32)
HbA1c, %, mean±SD	8.4±1.4	8.3±1.4
Fasting plasma glucose, mg/dL, mean±SD	190±66	180±61
Microvascular disease, n (%)		
Retinopathy	80 (15.6%)	61 (12.1%)
Nephropathy	60 (11.7%)	48 (9.5%)
Neuropathy	245 (47.8%)	241 (47.8%)
Baseline ETDRS score		
Mean±SD	3.0±2.2	2.9±2.0
Median (min-max)	2.0 (1.0-12.0)	2.0 (1.0-9.0)
Definite clinically significant macular edema		
Right eye	10 (2.7%)	3 (0.9%)
Left eye	12 (3.2%)	3 (0.8%)
Baseline use of oral anti-diabetic therapy, n (%)		
Metformin	211 (41%)	213 (42%)
Sulfonylurea	140 (27%)	131 (26%)
Thiazolidinedione	77 (15%)	77 (15%)
Other	7 (1.4%)	13 (2.6%)

**Primary efficacy endpoint:** As shown in Table 5, a smaller proportion of Lantus-treated patients met the primary efficacy endpoint (≥3-step progression in ETDRS or requiring pre-specified eye procedures) compared to NPH insulin-treated patients in the intent-to-treat, per-protocol, and completers populations. None of the comparisons were statistically significant.

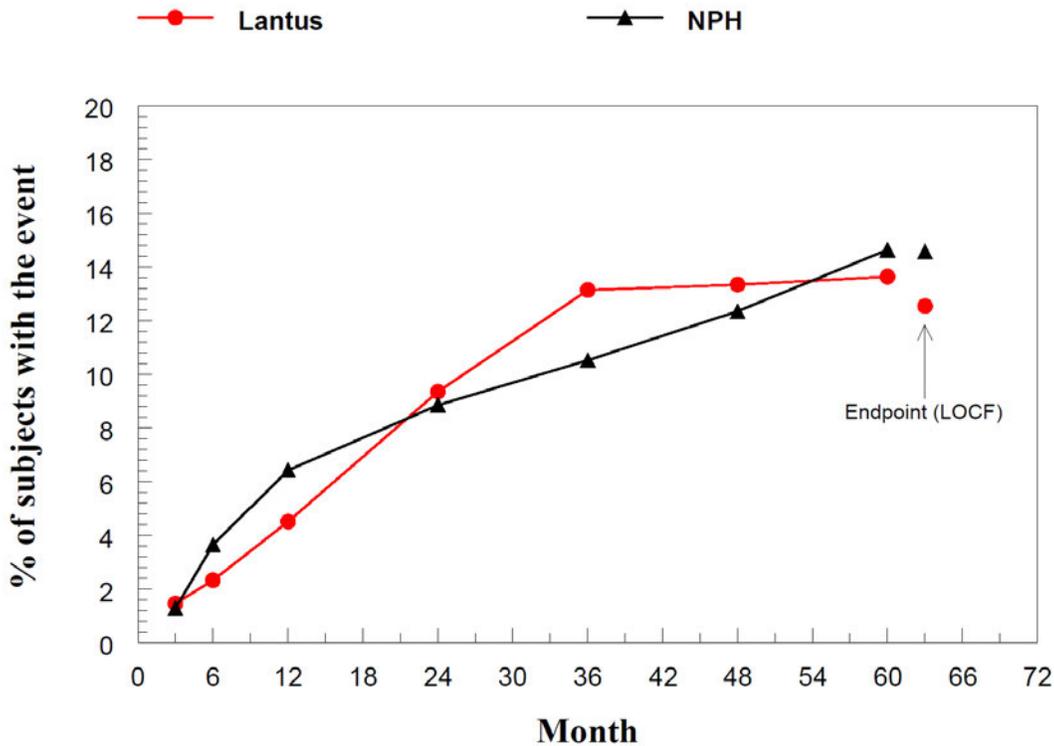
Non-inferiority is established because the upper bound of the 95% confidence interval for the treatment difference between Lantus and NPH insulin was less than the pre-specified non-inferiority margin of 10%.

<b>Endpoint</b>	<b>Lantus n/N (%)</b>	<b>NPH n/N (%)</b>	<b>Treatment difference ± SE</b>	<b>p-value</b>	<b>95% confidence interval</b>
ITT, LOCF	63/502 (12.5)	71/487 (14.6)	-2.1% ± 2.1%	0.33	(-6.3%, 2.1%)
PP	53/374 (14.2)	57/363 (15.7)	-2.0% ± 2.6%	0.44	(-7.0%, 3.1%)
Completers	52/374 (13.9)	54/364 (14.8)	-1.2% ± 2.5%	0.62	(-6.2%, 3.7%)

ITT = intent-to-treat; LOCF = last observation carried forward; PP = per-protocol

Figure 1 shows the time course of the proportion of patients in each treatment group meeting the primary efficacy endpoint. The curves cross twice, with the initial treatment period favoring Lantus, the middle treatment period favoring NPH insulin, and the ending treatment period again favoring Lantus.

**Figure 1. Primary efficacy endpoint (intent-to-treat population) adapted from Dr. Liu’s biostatistics review**



As shown in Table 6, 53.3% of Lantus-treated patients and 56.0% of NPH insulin-treated patients had improvement or no change in the ETDRS score from baseline to endpoint. There were numerically more Lantus-treated patients with a 1 or 2 step increase in ETDRS score compared to NPH insulin-treated patients (23.5% vs. 19.1% for 1-step increase; 12.2% vs. 10.9% for 2-step increase). However, there were numerically fewer Lantus-treated patients with a  $\geq 3$ -step increase in ETDRS compared to NPH-treated patients, and there was no statistical difference in the distribution of changes between the 2 treatment groups ( $p=0.67$ ).

**Table 6. Distribution of changes from baseline in ETDRS score at endpoint (intent-to-treat population)  
Adapted from Dr. Liu's biostatistics review**

Change	-4	-3	-2	-1	0	1	2	3	≥4
Lantus, n (%)	1(0.2)	6 (1.2)	14 (2.8)	62 (12.4)	184 (36.7)	118 (23.5)	61 (12.2)	28 (5.6)	28 (5.6)
NPH, n (%)	2 (0.4)	5 (1.0)	11 (2.3)	64 (13.1)	191 (39.2)	93 (19.1)	53 (10.9)	35 (7.2)	33 (6.8)

Dr. Liu noted that the primary efficacy findings are consistent across subgroups of age (<65 years vs. ≥65 years), gender, race (Caucasian, black, other), baseline HbA1c (≤9% vs. >9%), country (United States vs. Canada), and baseline diabetic retinopathy (yes vs. no). Dr. Liu noted a nominally significant interaction (p=0.06) across subgroups of body mass index (≤29 vs. 29-38.6 vs. >38.6 kg/m<sup>2</sup> representing the 25<sup>th</sup> and 75<sup>th</sup> percentiles of the data), although the low event rates in the ≤29 kg/m<sup>2</sup> and >38.6 kg/m<sup>2</sup> groups limit conclusions.

**Table 7. Number (%) of patients with ≥3-step progression in ETDRS by baseline body mass index (intent-to-treat population)**

Body Mass Index	≤29 kg/m <sup>2</sup> n/N (%)	29-38.6 kg/m <sup>2</sup> n/N (%)	>38.6 kg/m <sup>2</sup> n/N (%)
Lantus	11/119 (9.2%)	35/246 (14.2%)	17/133 (12.8%)
NPH	26/129 (20.2%)	30/245 (12.2%)	15/112 (13.4%)

Select secondary efficacy endpoints:

### 1. Clinically significant macular edema

A comparable proportion of patients in both treatment groups developed clinically significant macular edema (13.8% with Lantus vs. 14.1% with NPH; p=0.88), defined as progression in either or both eyes in the four-step scale for macular edema from a baseline grade of A or B to an on-treatment grade of C or D (based on fundus photograph analysis) or requiring photocoagulation.

### 2. Proliferative diabetic retinopathy

Patients were classified as having developed proliferative diabetic retinopathy if the ETDRS score progressed to level 12 or there was a requirement for pan-retinal photocoagulation for diabetic retinopathy, local photocoagulation for new vessels, or vitrectomy for diabetic retinopathy. This endpoint differs slightly from the primary efficacy endpoint, which was defined as a ≥3-step progression in the ETDRS score or a requirement for one of the 3 procedures described above.

In the intent-to-treat population, 25 (5.0%) Lantus-treated patients and 16 (3.3%) NPH-treated patients developed proliferative diabetic retinopathy, as defined above. Of note, this difference was not statistically significant (p=0.21), may be driven by the imbalance in reported history of diabetic retinopathy at baseline (15.6% of patients randomized to Lantus vs. 12.1% of patients randomized to NPH insulin), and is not corroborated by the results of the primary

efficacy endpoint (which was numerically less frequent with Lantus). In addition, the Lantus group began the study with a numerically higher mean baseline ETDRS score (3.1) than did the NPH group (2.9). Because the mean ETDRS score increased to the same extent in both groups (0.9), it is expected that more of the Lantus patients would have crossed the defining threshold score of level 12.

**3. Glycemic control**

At baseline, the mean HbA1c was 8.4% in the Lantus group and 8.3% in the NPH group. In the intent-to-treat population, the LS mean reduction in HbA1c from baseline to endpoint was 0.6% in the Lantus group and 0.8% in the NPH group (p=0.005 favoring NPH for the treatment difference) (Table 8). The LS mean reduction in FPG was approximately 45 mg/dL in both treatment groups, although mean baseline FPG values were higher in the Lantus group (190 mg/dL vs. 180 mg/dL).

<b>Table 8. HbA1c and fasting plasma glucose (intent-to-treat population with last-observation-carried-forward)</b>		
	<b>Lantus N=513</b>	<b>NPH N=504</b>
<b>HbA1c (%)</b>		
Baseline, mean±SD	8.4±1.4	8.3±1.4
LS mean change±SE	-0.6±0.1	-0.8±0.1
LS mean difference (95% confidence interval); p-value	0.2 (0.06, 0.35); p=0.005	
<b>Laboratory measured fasting plasma glucose (mg/dL)</b>		
Baseline, mean±SD	190±66	180±61
LS mean change±SE	-45±3	-44±3
LS mean difference (95% confidence interval); p-value	-1 (-8, 6); p=0.84	

Consistent with the findings for change from baseline in HbA1c, numerically fewer Lantus-treated patients compared to NPH insulin-treated patients achieved HbA1c ≤7% at various timepoints during the trial (Table 9). Of note, 20-30% of patients did not have HbA1c data during the later years of the treatment period, limiting robustness and interpretability of these data.

<b>Table 9. Proportion of patients achieving HbA1c ≤7% (intent-to-treat population)</b>		
	<b>Lantus N=513</b>	<b>NPH N=504</b>
Baseline	77/512 (15%)	91/504 (18%)
Month 12	161/462 (35%)	183/459 (40%)
Month 24	178/422 (42%)	192/420 (46%)
Month 36	154/401 (38%)	168/394 (43%)
Month 48	148/386 (38%)	154/369 (42%)
Month 60	121/364 (33%)	148/348 (43%)
Endpoint	157/498 (32%)	189/487 (39%)

In contrast to the HbA1c findings, a slightly greater proportion of Lantus-treated patients achieved the target FPG of  $\leq 100$  mg/dL compared to NPH insulin-treated patients, although most patients in both treatment groups did not achieve the FPG goal (Table 10). Of note, 20-55% of patients did not have laboratory-measured FPG values during the trial, which limits the robustness and interpretability of these data.

<b>Table 10. Number (%) achieving titration goal (intent-to-treat population) (laboratory measured fasting plasma glucose <math>\leq 100</math> mg/dL)</b>		
	<b>Lantus N=513</b>	<b>NPH N=504</b>
Baseline	33/512 (6%)	39/504 (8%)
Month 12	42/223 (19%)	34/233 (15%)
Month 24	116/389 (30%)	88/380 (23%)
Month 60	105/348 (30%)	89/327 (27%)
Endpoint	143/502 (29%)	121/498 (24%)

As discussed by Dr. Misbin, the median total daily insulin dose at endpoint was 71 units among the Lantus-treated patients and 80 units among the NPH-treated patients. Patients on NPH insulin tended to use more basal insulin (median dose at endpoint 63 units vs. 54 units for Lantus). At endpoint, approximately 67% of Lantus-treated patients and 69% of NPH-treated patients were using pre-meal insulin, although the amount of pre-meal insulin used at endpoint by the Lantus group was more than that used by the NPH group (median dose 30 units vs. 22 units). Slightly more Lantus-treated patients started oral anti-diabetic medications post-randomization (Table 11).

<b>Table 11. Use of oral anti-diabetic agents started post-randomization (intent-to-treat population)</b>		
	<b>LANTUS N (%)</b>	<b>NPH N (%)</b>
Sulfonylureas	104 (20.3%)	79 (15.7%)
Metformin	93 (18.1%)	78 (15.5%)
Thiazolidinedione	35 (6.8%)	31 (6.2%)
Other	2 (0.4%)	1 (0.2%)

Efficacy conclusions: A smaller proportion of Lantus-treated patients compared to NPH-treated patients developed the primary retinopathy endpoint. This difference was not statistically significant but reassuring, particularly because (1) a slightly greater proportion of patients in the Lantus group had a reported history of diabetic retinopathy at baseline, (2) the Lantus group had slightly higher mean baseline HbA1c values (8.4% vs. 8.3%), and (3) the Lantus group had a slightly smaller reduction in HbA1c over the course of the trial (0.6% vs. 0.8%).

Although most patients did not achieve the target FPG of  $\leq 100$  mg/dL and HbA1c  $\leq 7\%$ , the median daily Lantus and NPH insulin doses at endpoint were 54 units and 63 units,

respectively. Therefore, the retinopathy evaluation occurred in patients on reasonable doses (approximately 0.5-0.6 units/kg) of these insulin therapies.

In this trial, the Lantus regimen had less glycemic efficacy compared to the NPH insulin regimen based on mean changes in HbA1c and the proportion of patients achieving HbA1c  $\leq 7\%$ , although a greater proportion of Lantus-treated patients achieved laboratory-measured FPG  $\leq 100$  mg/dL. These findings are likely explained by the lower total daily insulin doses among the Lantus-treated patients compared to the NPH insulin-treated patients (median 71 units vs. 80 units at endpoint). Of note, the higher insulin dose in the NPH group is still consistent with the FPG results because NPH was administered twice daily and only the evening NPH dose would have a meaningful impact on FPG. Besides the open-label design, an important limitation of the glycemic efficacy results is that a substantial proportion of patients had missing data. For example, 20-30% of patients did not have HbA1c data during the later years of the treatment period, and up to 55% of patients did not have laboratory-measured FPG values at various time points during the trial.

## 8. Safety

Both treatment groups had a similar duration of exposure to study medication (mean 4.2 years; median 5.0 years). Only approximately one-fourth of patients in both treatment groups had at least 4 years and 10 months exposure to study medication.

Deaths: During the treatment and post-treatment periods, there were 15 deaths (2.9%) in the Lantus group and 15 deaths (3.0%) in the NPH insulin group. As expected, most of the deaths during this 5-year trial were attributed to cardiac causes.

The following deaths were reported among the Lantus-treated patients: 4 unknown causes (presumably sudden death), 3 cardiac arrests, 2 myocardial infarctions, 1 heart failure, 1 colon cancer, 1 pancreatic cancer, 1 breast cancer, 1 intracranial hemorrhage, and 1 pneumonia with multi-organ failure.

The following deaths were reported among the NPH-treated patients: 3 cardiac arrests, 3 myocardial infarctions, 1 unknown cause (presumably sudden death), 1 sudden death, 1 heart failure, 1 ruptured aortic aneurysm, 1 acute renal failure, 1 esophageal cancer, 1 patient with both cholangiocarcinoma and lung cancer, 1 patient with lung cancer, and 1 patient with glioblastoma.

Therefore, 10 Lantus-treated patients (1.9%) and 9 NPH insulin-treated patients (1.8%) died of cardiac causes. Please see the Major Adverse Cardiovascular Events (MACE) analyses below for further details.

Serious adverse events: Serious adverse events were reported in 211 Lantus-treated patients (41.1%) and 215 NPH-treated patients (42.7%). Please see the section on adverse events of special interest for a discussion of cardiovascular (including stroke) serious adverse events, hypoglycemia, and hypersensitivity reactions.

Besides the findings described below, there were no notable differences between treatment groups for the remaining serious adverse events.

- Twelve Lantus-treated patients (2.3%) developed cellulitis (reported as a serious adverse event, typically because of hospitalization and inpatient antibiotics) compared to six NPH-treated patients (1.2%). This finding is not likely to be of significance because (1) the absolute difference is only 6 patients in this clinical trial of over 1,000 patients, (2) when all events of cellulitis are considered (serious plus non-serious), this difference between treatment groups narrows considerably (5.8% of Lantus-treated patients vs. 5.2% of NPH-treated patients), (3) the Lantus group is favored for other types of serious infections (for example, pneumonia reported as a serious adverse event occurred in 2.1% of Lantus-treated patients compared to 2.8% of NPH-treated patients), and (4) the overall incidence of serious adverse events in the Infections and Infestations System-Organ-Class was comparable in the two treatment groups (9.7% for Lantus and 9.1% for NPH insulin).
- Three Lantus-treated patients (0.6%) developed iron deficiency anemia as a serious adverse event compared to no NPH-treated patients. However, 2 of these cases have alternative explanations (status-post gastric bypass surgery and metastatic colon cancer); therefore, these cases do not raise concerns for a signal of iron deficiency anemia with Lantus.
- Three Lantus-treated patients (0.6%) developed pulmonary embolism as a serious adverse event compared to no NPH-treated patients. However, all 3 cases have alternative explanations (status-post knee surgery, status-post hip surgery, status-post coronary artery bypass grafting); therefore, these cases do not raise concerns for a signal of pulmonary embolism with Lantus.
- There were 3 serious adverse events potentially related to significant hepatic impairment. One Lantus-treated patient was reported to have developed hepatic hemorrhage, but this event was a complication of an elective cholecystectomy. One NPH insulin-treated patient was reported to have developed liver failure, but this patient had terminal esophageal cancer. There was also one case of hepatic encephalopathy reported in an NPH insulin-treated patient, but this event was attributed to baclofen, which had recently been started in a patient with a history of cryptogenic cirrhosis. Therefore, these cases do not raise concerns for a signal of hepatic injury with Lantus or NPH insulin.

Adverse events leading to premature discontinuation: In the safety population, 17 (3.3%) Lantus-treated patients and 12 (2.4%) NPH insulin-treated patients discontinued due to adverse events (Table 12). As shown below, almost all of the adverse events leading to premature discontinuation occurred in at most one (0.2%) Lantus or NPH insulin-treated patient. The most common adverse event leading to premature withdrawal was rash, occurring in only 3 (0.6%) Lantus-treated patients and 1 (0.2%) NPH-treated patient. The table below contains pertinent details for some of the adverse events leading to withdrawal. There are no new safety signals with Lantus or NPH insulin based on review of these adverse events.

<b>Table 12. Treatment-emergent adverse events leading to withdrawal (safety population)</b>		
<b>Preferred term</b>	<b>LANTUS N=514 n (%)</b>	<b>NPH N=503 n (%)</b>
<b>Any event</b>	<b>17 (3.1)</b>	<b>12 (2.2)</b>
<b>Neoplasms benign, malignant, and unspecified</b>	<b>3 (0.6)</b>	<b>4 (0.8)</b>
Breast cancer	1 (0.2)	1 (0.2)
Colon cancer	1 (0.2)	0
Endometrial cancer	1 (0.2)	0
Bile duct cancer	0	1 (0.2)
Lung cancer metastatic	0	1 (0.2)
Pancreatic carcinoma	0	1 (0.2)
<b>Metabolism and nutrition disorders</b>	<b>2 (0.4)</b>	<b>0</b>
Hyperglycemia (Day 681)	1 (0.2)	0
Obesity	1 (0.2)	0
<b>Psychiatric disorders</b>	<b>2 (0.4)</b>	<b>0</b>
Mental disorder	1 (0.2)	0
Schizophrenia	1 (0.2)	0
<b>Nervous system disorders</b>	<b>2 (0.4)</b>	<b>2 (0.4)</b>
Cognitive disorder (cognitive decline on Day 1464)	1 (0.2)	0
Dementia Alzheimer's type (Day 503)	1 (0.2)	0
Grand mal convulsion (Day 1709; no glucose data)	0	1 (0.2)
Hypoglycemic encephalopathy <sup>1</sup>	0	1 (0.2)
<b>Eye disorders</b>	<b>1 (0.2)</b>	<b>0</b>
Macular edema (Day 123) <sup>2</sup>	1 (0.2)	0
<b>Cardiac disorders / vascular disorders</b>	<b>1 (0.2)</b>	<b>3 (0.6)</b>
Myocardial infarction	1 (0.2)	0
Cardiac failure congestive	0	1 (0.2)
Cardio-respiratory arrest	0	1 (0.2)
Aortic aneurysm	0	1 (0.2)
<b>Gastrointestinal disorders</b>	<b>1 (0.2)</b>	<b>1 (0.2)</b>
Lower gastrointestinal hemorrhage (due to colon cancer)	1 (0.2)	0
Small intestinal obstruction (due to Meckel diverticulum)	0	1 (0.2)
<b>Skin and subcutaneous disorders</b>	<b>3 (0.6)</b>	<b>1 (0.2)</b>
Rash/rash generalized/rash pruritic/urticaria generalized <sup>3</sup>	3 (0.6)	1 (0.2)
<b>General disorders and administration site conditions</b>	<b>2 (0.4)</b>	<b>1 (0.2)</b>
Injection site reaction (Day 30; mild in intensity)	1 (0.2)	0
Edema peripheral	1 (0.2)	0
Multi-organ failure	0	1 (0.2)

<sup>1</sup>Hypoglycemic encephalopathy – coma and confusion due to hypoglycemic event (all resolved)  
<sup>2</sup>Clinically significant macular edema occurred in 13.8% of Lantus- and 14.1% of NPH-treated patients  
<sup>3</sup>Pruritic rash involving the upper body and upper extremities occurred on Day 2 (Lantus); whole body rash occurred on Day 12 (Lantus); supra-mammary rash occurred on Day 12 (Lantus); urticarial rash occurred on Day 170 (NPH)

Common adverse events: Table 13 summarizes the most common (incidence  $\geq 5\%$ ) treatment-emergent adverse events occurring with an absolute difference  $\geq 1\%$  between treatment groups. Almost all of these adverse events do not occur more than  $\sim 2$  percentage points higher in one treatment group compared to the other treatment group. Exceptions include cough (12.1% with Lantus vs. 7.4% with NPH insulin), hyperlipidemia (7.2% with Lantus vs. 4.4% with NPH insulin - please see the objective lipid data below), hypoglycemia (7.0% with Lantus vs. 9.5% with NPH insulin – please see the adverse events of special interest section below), and sleep apnea syndrome (4.9% with Lantus vs. 7.8% with NPH-insulin, which is difficult to interpret because sleep apnea is a substantially underdiagnosed condition and was not systematically assessed in all patients).

<b>Table 13. Common treatment-emergent adverse events (safety population) (incidence <math>\geq 5\%</math> in either treatment group and absolute difference <math>\geq 1\%</math> between treatment groups)</b>		
<b>Preferred term</b>	<b>LANTUS N=514 n (%)</b>	<b>NPH N=503 n (%)</b>
Any event	490 (95.3)	479 (95.2)
Upper respiratory tract infection	149 (29.0)	169 (33.6)
Edema peripheral	103 (20.0)	114 (22.7)
Nasopharyngitis	95 (18.5)	88 (17.5)
Cataract	93 (18.1)	80 (15.9)
Bronchitis	78 (15.2)	71 (14.1)
Arthralgia	73 (14.2)	81 (16.1)
Cough	62 (12.1)	37 (7.4)
Headache	53 (10.3)	47 (9.3)
Muscle spasms	47 (9.1)	35 (7.0)
Musculoskeletal pain	44 (8.6)	51 (10.1)
Nausea	44 (8.6)	34 (6.8)
Gastroesophageal reflux disease	41 (8.0)	34 (6.8)
Gastroenteritis viral	41 (8.0)	30 (6.0)
Fatigue	41 (8.0)	30 (6.0)
Dizziness	38 (7.4)	29 (5.8)
Hyperlipidemia	37 (7.2)	22 (4.4)
Hypoglycemia	36 (7.0)	48 (9.5)
Chest pain	32 (6.2)	41 (8.2)
Pneumonia	30 (5.8)	36 (7.2)
Pharyngolaryngeal pain	29 (5.6)	35 (7.0)
Osteoarthritis	29 (5.6)	37 (7.4)
Dyspnea	27 (5.3)	33 (6.6)
Sensory disturbance	27 (5.3)	17 (3.4)
Anxiety	26 (5.1)	18 (3.6)
Sleep apnea syndrome	25 (4.9)	39 (7.8)
Myalgia	21 (4.1)	30 (6.0)
Carpal tunnel syndrome	21 (4.1)	29 (5.8)
Ear infection	18 (3.5)	26 (5.2)

Adverse events of special interest:

1. Major adverse cardiovascular events (MACE)

In July 2008, the Endocrinologic and Metabolic advisory committee recommended that all sponsors who are developing non-insulin drugs and biologics for the treatment of type 2 diabetes be required to show that these products do not cause an unacceptable increase in cardiovascular risk. The Division issued letters to all sponsors of anti-diabetic drugs (except insulin products) in November 2008 detailing the expectations for assessing cardiovascular risk and issued a final guidance document on this topic in December 2008.

In the near future, the Division plans to ask sponsors of all currently approved drugs for the treatment of type 2 diabetes to also conduct a cardiovascular assessment using their entire controlled premarketing and postmarketing clinical trial databases. In the interim, we asked sanofi-aventis to evaluate the MACE endpoint in the retinopathy safety trial given the scope of this trial (5-year treatment duration; 1,000-patient trial).

For the MACE composite of cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke, 33 events occurred among the Lantus-treated patients (6.4%) compared to 27 events among the NPH insulin-treated patients (5.4%) (Table 14). Of note, the hazard ratios comparing Lantus to NPH insulin for the MACE composite and for the individual components of cardiovascular death and non-fatal myocardial infarction exceed 1.0 with upper bounds of the 95% confidence intervals all exceeding 2.0 (Table 14). None of the MACE analyses were statistically significant with the smallest p-value being 0.28. In addition, conclusions are limited by the low numbers of events, particularly for the individual components of the MACE endpoint (and, consequently, wide confidence intervals) and lack of prospective adjudication.

In this single trial, the upper bound of the hazard ratio for MACE exceeds the 1.3 and 1.8 values discussed in the new cardiovascular guidance. However, the aggregate data from all controlled clinical trials of Lantus needs to be evaluated. As mentioned above, in the near future we will be asking sponsors of all currently approved drugs developed for the treatment of type 2 diabetes to further explore cardiovascular safety using their entire database of controlled clinical trials. In addition, cardiovascular data will be coming in a few years from the ongoing ORIGIN trial (Outcome Reduction with Initial Glargine Intervention), which is evaluating whether Lantus can reduce cardiovascular morbidity and mortality in high risk people with impaired fasting glucose, impaired glucose tolerance, or early type 2 diabetes when compared to standard care. One interim analysis of the primary outcome data by an independent data monitoring committee has not noted reasons for premature trial discontinuation. Recently, the sponsor has requested that the study be extended by 2 years from a previously proposed mean follow-up of 4.5 years (b) (4)

Although this

trial is being conducted in a lower risk patient population, the size and scope of the trial will provide important cardiovascular data on Lantus.

<b>Table 14. MACE analyses</b>			
<b>Endpoint</b>	<b>LANTUS N=513 n (%)</b>	<b>NPH N=504 n (%)</b>	<b>p-value</b>
MACE	33 (6.4%)	27 (5.4%)	0.46
Cardiovascular death	11 (2.1%)	10 (2.0%)	0.87
Non-fatal myocardial infarction	18 (3.5%)	12 (2.4%)	0.28
Non-fatal stroke	4 (0.8%)	5 (1.0%)	0.72
<b>Time-to-event analyses</b>	<b>Hazard ratio (95% CI)</b>		<b>p-value</b>
MACE	1.21 (0.73-2.01)		0.47
Cardiovascular death	1.07 (0.46-2.52)		0.88
Non-fatal myocardial infarction	1.49 (0.72-3.09)		0.28
Non-fatal stroke	0.78 (0.21-2.91)		0.71

2. Retina events

Table 15 summarizes retinopathy findings reported as adverse events. Most of these events were reported in a slightly greater proportion of Lantus-treated patients compared to NPH-insulin treated patients. However, a baseline history of retinopathy was reported in a slightly higher proportion of Lantus-treated patients compared to NPH insulin-treated patients. In addition, the objective data from retinal photographs do not support a concern for a retinal safety signal with Lantus. Please see the discussion of the primary retinopathy findings in the efficacy portion of this memorandum.

<b>Table 15. Treatment-emergent retinopathy events occurring in &gt;1 patient in either treatment group (safety population)</b>		
<b>Preferred term</b>	<b>LANTUS N=514 n (%)</b>	<b>NPH N=503 n (%)</b>
Any retina event	55 (10.7)	40 (8.0)
Diabetic retinopathy	25 (4.9)	19 (3.8)
Macular edema	23 (4.5)	16 (3.2)
Maculopathy	6 (1.2)	2 (0.4)
Retinal hemorrhage	3 (0.6)	2 (0.4)
Retinal aneurysm	2 (0.4)	2 (0.4)
Retinal exudates	0	3 (0.6)

3. Hypoglycemia

The sponsor pre-specified 4 definitions for hypoglycemia:

1. Clinically important hypoglycemia – symptoms with an accompanying plasma glucose  $\leq 36$  mg/dL or requiring the assistance of another person

2. Symptomatic hypoglycemia – symptoms with or without confirmatory plasma glucose <72 mg/dL
3. Nocturnal hypoglycemia
4. Severe hypoglycemia – symptoms requiring the assistance of another person that was either associated with a plasma glucose  $\leq 56$  mg/dL or resolved with oral carbohydrate, intravenous glucose, or glucagon. Severe hypoglycemia was to be recorded as a serious adverse event.

As shown in Table 16, the Lantus-treated patients had numerically fewer reports in each of the hypoglycemia categories compared to the NPH insulin-treated patients. Although there is a potential mechanistic explanation for these findings (i.e., the pharmacokinetic peak of NPH insulin that is absent with Lantus), the hypoglycemia data are confounded by the lower glycemic efficacy and lower insulin doses in the Lantus-treated patients compared to the NPH-treated patients.

Categories of hypoglycemia as defined in the protocol	Lantus N=513			NPH N=504		
	n (%)	Events	Rate	n (%)	Events	Rate
Symptomatic hypoglycemia	393 (76.6%)	11984	5.34	409 (81.2%)	15554	7.31
Symptomatic nocturnal hypoglycemia	289 (56.3%)	662	1.62	306 (60.7%)	1324	2.15
Clinically important hypoglycemia	198 (38.6%)	3772	0.41	240 (47.6)	4564	0.70
Severe hypoglycemia	40 (7.8%)	88	0.04	60 (11.9%)	120	0.08
Rate (number of episodes per year) = 365.25 x number of episodes of hypoglycemia on treatment / days on treatment. Data presented as means.						

#### 4. Hypersensitivity reactions

The clinical study report includes a table summarizing systemic hypersensitivity reactions (Table 17). None of these reported reactions were listed as serious adverse events or resulted in premature withdrawal from the trial. However, this list may not be all-inclusive. Additional adverse events that could be consistent with systemic hypersensitivity reactions include:

- Rash: 33 (6.4%) with Lantus vs. 29 (5.8%) with NPH insulin
- Urticaria: 10 (1.9%) with Lantus vs. 6 (1.2%) with NPH insulin
- Angioedema: 1 (0.2%) with Lantus vs. 1 (0.2%) with NPH insulin
- Rash generalized: 1 (0.2%) with Lantus vs. 1 (0.2%) with NPH insulin
- Urticaria generalized: 0 with Lantus vs. 1 (0.2%) with NPH insulin
- Anaphylactic reaction: 0 with Lantus vs. 1 (0.2%) with NPH insulin

However, even with these other terms, the incidence of potential hypersensitivity reactions is low and comparable between treatment groups.

**Table 17. Treatment-emergent hypersensitivity (safety population)**

Preferred term	LANTUS N=514 n (%)	NPH N=503 n (%)
Any hypersensitivity event	5 (1.0)	19 (3.8)
Dermatitis allergic	2 (0.4)	4 (0.8)
Drug hypersensitivity	2 (0.4)	6 (1.2)
Hypersensitivity	1 (0.2)	10 (2.0)
Drug eruption	0	1 (0.2)

Injection site reactions were reported in 12 (2.3%) Lantus-treated patients and 7 (1.4%) NPH insulin-treated patients. The only injection site reactions occurring in more than 1 patient in either treatment group were injection site bruising (4 with Lantus vs. 3 with NPH insulin), injection site atrophy (3 with Lantus vs. 0 with NPH insulin), and injection site hypertrophy (2 with Lantus vs. 1 with NPH insulin).

Laboratory data:

Anti-insulin antibodies were not measured in this trial.

Neither treatment group had clinically meaningful changes in mean values from baseline to endpoint for any of the hematologic parameters or serum transaminases.

1. Serum creatinine

For serum creatinine, an increase in serum creatinine of  $\geq 0.4$  mg/dL was the “predefined change abnormal”. A slightly greater proportion of Lantus-treated patients compared to NPH-insulin treated patients met this criterion (62/514 or 12.1% vs. 50/503 or 9.9%). Of note, this finding is not statistically significant ( $p=0.32$ ) and may partly be explained by the higher proportion of Lantus-treated patients (11.7%) compared to NPH-insulin treated patients (9.5%) who reported a history of nephropathy at baseline.

In addition, several other analyses of renal function do not confirm the presence of a safety signal. For example, over the 5-year trial, there was a similar, minor increase in mean serum creatinine concentrations in both treatment groups (Table 18). Also, for the pre-defined “clinically noteworthy change” in serum creatinine (increase  $\geq 0.4$  mg/dL and at least a doubling of the baseline serum creatinine value), only 3 patients (0.6%) in each treatment group met this criterion. Finally, a similar proportion of patients in both treatment groups had normal serum creatinine at baseline but elevated serum creatinine at endpoint (11% with Lantus; 10% with NPH). Therefore, in aggregate, there is no evidence for a differential effect of the two treatments on renal function.

<b>Table 18. Mean (<math>\pm</math>SD) serum creatinine concentrations (mg/dL) over the course of the trial</b>							
		<b>Change from baseline</b>					
	<b>Baseline</b>	<b>Month 12</b>	<b>Month 24</b>	<b>Month 36</b>	<b>Month 48</b>	<b>Month 60</b>	<b>Endpoint</b>
Lantus	514 0.8 $\pm$ 0.2	461 0.0 $\pm$ 0.1	426 0.0 $\pm$ 0.2	399 0.1 $\pm$ 0.2	383 0.1 $\pm$ 0.2	373 0.2 $\pm$ 0.2	494 0.1 $\pm$ 0.2
NPH	502 0.9 $\pm$ 0.2	455 0.0 $\pm$ 0.1	417 0.0 $\pm$ 0.2	385 0.1 $\pm$ 0.2	357 0.1 $\pm$ 0.2	362 0.2 $\pm$ 0.2	476 0.1 $\pm$ 0.2

## 2. Urine microalbumin/creatinine ratio

Table 19 summarizes the proportion of patients with at least one abnormal post-baseline urine microalbumin/creatinine ratio  $>$ ULN,  $>2x$  ULN,  $>3x$  ULN,  $>5x$  ULN, and  $>10x$  ULN. At all timepoints, the Lantus group had a slightly higher proportion of patients meeting the various categories of abnormal ratios, with slightly wider differences between treatment groups in the later years of the trial. Of note, this analysis is somewhat limited because there are no baseline values for urine microalbumin/creatinine (collection of urine samples for this analysis was only initiated post-baseline). In addition, a greater proportion of Lantus-treated patients compared to NPH insulin-treated patients reported a history of diabetic nephropathy at baseline (11.7% vs. 9.5%). Finally, concomitant use of renal-protecting medications (angiotensin receptor blockers and angiotensin converting enzyme inhibitors) may also confound this assessment.

## 3. Lipids

Fasting lipids were measured at baseline, and at 1.5, 3, and 6 months, and at annual visits for the duration of the study. The Friedenwald formula was used to calculate LDL-C when total serum triglyceride concentrations were less than 300 mg/dL. If the serum triglyceride measurement was  $\geq 300$  mg/dL, no direct measurement of HDL-C or LDL-C was performed, and these values were not recorded for those patients and visits.

Approximately 60% of patients in both treatment groups started lipid-modifying agents during the post-randomization period, which confounds the lipid results. Nonetheless, there do not appear to be clinically important differences in lipid parameters between treatment groups.

- The LS mean change from baseline in total cholesterol was -20 mg/dL for the Lantus-treated patients and -23 mg/dL for the NPH-treated patients ( $p=0.41$ ).
- The LS mean change from baseline in LDL-cholesterol was -17 mg/dL for the Lantus-treated patients and -18 mg/dL for the NPH-treated patients ( $p=0.39$ ).
- The LS mean change from baseline in HDL cholesterol was 4 mg/dL for the Lantus-treated patients and 4 mg/dL for the NPH-treated patients ( $p=0.61$ ).
- The LS mean change from baseline in serum triglycerides was -43 mg/dL for the Lantus-treated patients and -59 mg/dL for the NPH-treated patients ( $p=0.10$ ).

<b>Table 19. Proportion of patients with at least one abnormal urine microalbumin/creatinine ratio while receiving study medication (safety population)</b>					
	<b>&gt;ULN n (%)</b>	<b>&gt;2x ULN n (%)</b>	<b>&gt;3x ULN n (%)</b>	<b>&gt;5x ULN n (%)</b>	<b>&gt;10x ULN n (%)</b>
<b>Month 12</b>					
Lantus	123 (23.9)	80 (15.6)	57 (11.1)	36 (7.0)	18 (3.5)
NPH	98 (19.5)	63 (12.5)	42 (8.3)	29 (5.8)	16 (3.2)
Difference*	4.4	3.1	2.8	1.2	0.3
<b>Month 24</b>					
Lantus	116 (22.6)	78 (15.2)	62 (12.1)	50 (9.7)	33 (6.4)
NPH	97 (19.3)	62 (12.3)	47 (9.3)	33 (6.6)	20 (4.0)
Difference*	3.3	2.9	2.8	3.1	2.4
<b>Month 36</b>					
Lantus	114 (22.2)	81 (15.8)	67 (13.0)	52 (10.1)	27 (5.3)
NPH	99 (19.7)	58 (11.5)	46 (9.1)	32 (6.4)	20 (4.0)
Difference*	2.5	4.3	3.9	3.7	1.3
<b>Month 48</b>					
Lantus	125 (24.3)	81 (15.8)	64 (12.5)	49 (9.5)	34 (6.6)
NPH	84 (16.7)	52 (10.3)	38 (7.6)	26 (5.2)	16 (3.2)
Difference*	7.6	5.5	4.9	4.3	3.4
<b>Month 60</b>					
Lantus	126 (24.5)	86 (16.7)	68 (13.2)	50 (9.7)	35 (6.8)
NPH	93 (18.5)	57 (11.3)	38 (7.6)	25 (5.0)	14 (2.8)
Difference*	6.0	5.4	5.6	4.7	4.0
ULN = upper limit of normal; defined as 30 mg/g					
*in absolute percentage points					

Vital signs: There were no clinically important differences between treatment groups with respect to changes in vital signs:

- The LS mean change from baseline in heart rate was -1 bpm for the Lantus-treated patients and -2 bpm for the NPH-treated patients (p=0.61).
- The LS mean change from baseline in systolic blood pressure was 1 mmHg for the Lantus-treated patients and 2 mmHg for the NPH-treated patients (p=0.67).
- The LS mean change from baseline in diastolic blood pressure was -2 mmHg for the Lantus-treated patients and -2 mmHg for the NPH-treated patients (p=0.67).

Both treatment groups gained body weight over the course of the trial (LS mean weight gain 3.7 kg with Lantus vs. 4.8 kg with NPH insulin) (Table 20). The lower weight gain with Lantus is most likely explained by the lower doses of insulin used in the Lantus group (median total daily insulin dose at endpoint was 71 units among the Lantus-treated patients and 80 units among the NPH-treated patients).

<b>Table 20. Body weight (kg) intent-to-treat population</b>		
	<b>Lantus N=513</b>	<b>NPH N=504</b>
Baseline, mean±SD	100.2±22.7	98.7±22.3
LS mean change±SE	3.7±0.5	4.8±0.5
LS mean difference (95% confidence interval); p-value	-1.2 (-2.3, 0.0); p=0.051	

## 9. Advisory Committee Meeting

An advisory committee meeting was not held.

## 10. Pediatrics

This study was designed to further evaluate an isolated retinopathy safety signal identified in a premarketing trial. This application does not trigger the Pediatric Research Equity Act (PREA), because it does not provide for a new active ingredient, a new indication, a new dosage form, a new dosage regimen, or a new route of administration. Of note, most children with diabetes have type 1 diabetes and the current study was conducted in patients with type 2 diabetes. Nonetheless, the current findings do not alter the risk-benefit ratio in children because the initial isolated retinopathy signal did not occur in the type 1 diabetes trials and also because the definitive retinopathy study in type 2 diabetes yielded reassuring results.

## 11. Other Relevant Regulatory Issues

Financial Disclosure: Dr. Misbin reviewed the financial disclosures of the clinical investigators and did not detect any potential financial conflicts of interest.

Clinical audits and inspections: FDA did not inspect any clinical sites.

## 12. Labeling

The current submission triggers conversion of the package insert to the Physician Labeling Rule (PLR) format. Many original sections of the label have been reworded for clarity and to satisfy the new formatting rules. The current clinical trial provides useful long-term comparative data for Lantus and NPH insulin treatment regimens. Therefore, I recommend that the retinopathy findings, HbA1c, fasting plasma glucose, insulin doses, body weight, and hypoglycemia data be incorporated into the label. Most of these data were not primary endpoints of the trial and may have other limitations (e.g., missing data) and should, therefore, be presented without p-values.

### **13. Recommendations/Risk Benefit Assessment**

I recommend APPROVAL of this application pending agreement on labeling. This recommendation is consistent with that of the other reviewers. No postmarketing risk management activities or other postmarketing study commitments or requirements are needed. This submission adequately satisfies the postmarketing commitment pertaining to retinopathy and should be noted as such in the administrative record, although the timing of the results was delayed.

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/s/

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Hylton Joffe  
2/10/2009 03:48:20 PM  
MEDICAL OFFICER

Mary Parks  
2/10/2009 03:50:50 PM  
MEDICAL OFFICER  
I concur with Dr. Joffe's recommendation. His memo will  
serve as the decisional memo for the division.

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**NDA 021081/S-034**

**MEDICAL REVIEW(S)**

## ADDENDUM TO CLINICAL REVIEW

Application Type NDA  
Submission Number 21081 S-34

Letter Date Dec 21, 2007  
Stamp Date Dec 21, 2007  
Original Review Date Oct 10, 2008

Reviewer Name Robert I Misbin MD  
Addendum Date June 29, 2009

Established Name Insulin Glargine  
Trade Name Lantus  
Therapeutic Class Insulin  
Applicant Sanofi-Aventis

Priority Designation Standard

Formulation U 100  
Indication Diabetes  
Intended Population Type 1 and Type 2

The following table (table 40) was omitted from my review of October 10, 2008.

**Table 40 - Number (%) of patients with treatment emergent adverse events, presented by primary system organ class - safety population**

<b>System organ class</b>	<b>LANTUS (N=514)</b>	<b>NPH (N=503)</b>
Any class	490 (95.3%)	479 (95.2%)
Infections and infestations	388 (75.5%)	395 (78.5%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	57 (11.1%)	62 (12.3%)
Blood and lymphatic system disorders	39 (7.6%)	29 (5.8%)
Immune system disorders	32 (6.2%)	35 (7.0%)
Endocrine disorders	17 (3.3%)	25 (5.0%)
Metabolism and nutrition disorders	134 (26.1%)	133 (26.4%)
Psychiatric disorders	123 (23.9%)	105 (20.9%)
Nervous system disorders	240 (46.7%)	234 (46.5%)
Eye disorders	207 (40.3%)	167 (33.2%)
Ear and labyrinth disorders	32 (6.2%)	35 (7.0%)
Cardiac disorders	100 (19.5%)	101 (20.1%)
Vascular disorders	138 (26.8%)	137 (27.2%)
Respiratory, thoracic and mediastinal disorders	193 (37.5%)	196 (39.0%)
Gastrointestinal disorders	224 (43.6%)	219 (43.5%)
Hepatobiliary disorders	18 (3.5%)	31 (6.2%)
Skin and subcutaneous tissue disorders	161 (31.3%)	137 (27.2%)
Musculoskeletal and connective tissue disorders	294 (57.2%)	302 (60.0%)
Renal and urinary disorders	92 (17.9%)	76 (15.1%)
Reproductive system and breast disorders	73 (14.2%)	44 (8.7%)
Congenital, familial and genetic disorders	6 (1.2%)	3 (0.6%)
General disorders and administration site conditions	215 (41.8%)	205 (40.8%)
Investigations	114 (22.2%)	94 (18.7%)
Injury, poisoning and procedural complications	176 (34.2%)	166 (33.0%)
Surgical and medical procedures	27 (5.3%)	26 (5.2%)
Social circumstances	0	3 (0.6%)

Note: % calculated using the number of safety population as the denominator.

Primary SOC listed in MedDRA order.

NPH = neural protamine hagedorn; N = population size

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/s/

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Robert Misbin  
6/30/2009 05:02:51 PM  
MEDICAL OFFICER

## CLINICAL REVIEW

Application Type NDA  
Submission Number 21081 S-34

Letter Date Dec 21, 2007  
Stamp Date Dec 21, 2007  
PDUFA Goal Date Oct 21, 2008

Reviewer Name Robert I Misbin MD  
Review Completion Date Oct 10, 2008

Established Name Insulin Glargine  
Trade Name Lantus  
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Priority Designation Standard

Formulation U 100  
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## **1 EXECUTIVE SUMMARY**

### **1.1 Recommendation on Regulatory Action**

Results of the trial submitted in this supplement satisfy the Sponsor's commitment to perform a postmarketing study to determine if Lantus promotes development of diabetic retinopathy in patients with type 2 diabetes.

The statement in the current label regarding the imbalance in progression of retinopathy in a single clinical trial in type 2 diabetes can be removed and replaced by a simple statement that there appears to be no difference between Lantus and NPH insulin with respect to progression of diabetic retinopathy. If the Sponsor wishes to describe the ophthalmological findings from the postmarketing study in detail they should include results regarding (b) (4) and proliferative retinopathy in addition to the primary endpoint, three step progression of retinopathy.

The label statement proposed by the Sponsor should be expanded to include details about control of hyperglycemia.

### **1.2 Summary of Clinical Findings**

The trial evaluated progression of diabetic retinopathy in insulin-treated patients with type 2 diabetes. The treatment period lasted five years and compared once daily Lantus to twice daily NPH insulin

#### **Retinopathy:**

There was no difference between the two arms with respect to the primary endpoint, which was 3 step or greater progressions in ETDRS score. As shown in the table below, progression was reported in 12.5% of patients on Lantus and 14.6% on NPH (ITT population). The results for the two treatment arms were not statistically different.

**Table 20 - Number (%) of patients with 3-step or greater progression in ETDRS at endpoint - ITT population**

	<b>LANTUS (N=513)</b>	<b>NPH (N=504)</b>
Subjects with 3-step or greater progression (progression rate)	63/502 (12.5%)	71/487 (14.6%)
Difference in progression rate (SE) versus. NPH <sup>a</sup>	-2.10%( 2.14%)	
95% CI versus. NPH <sup>a</sup>	(-6.29% to 2.09%)	

Note: % Calculated using number of ITT subjects with non-missing data as denominator

ETDRS = early treatment diabetic retinopathy scale; ITT = intent-to-treat; NPH = neural protamine hagedorn; N = population size

<sup>a</sup> Using a generalized linear model (SAS GENMOD) with treatment and baseline HbA1c strata as the classified independent variables, and with binomial distribution and identity link function.

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### **Glycemic Control:**

Lantus was used once daily. NPH insulin was used twice daily. The total insulin dose was about 90 units per day in both groups, but patients on NPH tended to use more basal insulin and less bolus insulin than patients on Lantus. The decrease in HbA1c from baseline to endpoint was slightly greater in patients taking NPH (8.3% to 7.6%) than for Lantus (8.4% to 7.8%). The mean FPG fell by 44.9 mg/dl in the Lantus group and 44.2 mg/dl in the NPH group.

Weight gain was somewhat greater with NPH (4.8kg) than with Lantus (3.7kg). The mean difference of 1.2 kg was of marginal statistical significance (p=0.05). Hypoglycemia was more prominent with NPH than with Lantus. There were 38 subjects (7.6%) on Lantus who experienced at least one episode of severe hypoglycemia compared to 55 (11.1%) subjects on NPH. There were a total of 83 episodes of severe hypoglycemia with Lantus compared to 113 with NPH.

## 2 INTRODUCTION AND BACKGROUND

The concern that insulin glargine might exacerbate diabetic retinopathy stemmed from a body of evidence for the role of IGF 1 in diabetic retinopathy and the reports by the Sponsor showing that glargine had more IGF-like activity than human insulin. Taken together, these results raised concern that treatment of diabetic patients with glargine might lead to exacerbation of diabetic retinopathy. For this reason, DMEDP requested that retinal exams be incorporated into the phase 3 trials.

The trials in the original NDA were open-label comparisons of glargine to NPH insulin in patients with type 1 and type 2 diabetes. In one study, 3006, there was a statistically significant difference ( $p=0.028$ ) in the number of patients who experienced a three or greater step progression of retinopathy in patients on glargine 16/213 (7.5%) vs NPH 6/220 (2.7%).

Because of this finding, FDA requested that the Sponsor convene a panel of experts to review the data and make recommendations. Of particular importance was lack of consistency for the ophthalmological findings among the various trials. Even within study 2006, the greater number of glargine patients with a three step progression of retinopathy appeared to be an isolated finding. There was not difference between glargine and NPH with respect to development of proliferative retinopathy, or need for photocoagulation for proliferative retinopathy. The Sponsor stated that the difference between glargine and NPH with respect to three step progression of retinopathy was (b) (4)

The reasons for concern that glargine might exacerbate retinopathy were not compelling. Nevertheless, the fact that the finding occurred in a controlled clinical trial led FDA to require that the finding be included in the label and that the Sponsor address the issue definitively with a post approval trial. The current label (shown below) notes the imbalance in > 3 step progression in retinopathy in one six month trial of type 2 diabetes (7.5% with LANTUS versus 2.7% with NPH)

### ADVERSE REACTIONS

The adverse events commonly associated with LANTUS include the following:

**Body as a whole:** allergic reactions (see PRECAUTIONS)

**Skin and appendages:** injection site reaction, lipodystrophy, pruritus, rash (see PRECAUTIONS)

**Other:** hypoglycemia (see WARNINGS and PRECAUTIONS)

In clinical studies in adult patients, there was a higher incidence of treatment-emergent injection site pain in LANTUS-treated patients (2.7%) compared to NPH insulin-treated patients (0.7%). The reports of pain at the injection site were usually mild and did not result in discontinuation of therapy. Other treatment-emergent injection site reactions occurred at similar incidences with both insulin glargine and NPH human insulin.

Retinopathy was evaluated in the clinical studies by means of retinal adverse events reported and fundus photography. The numbers of retinal adverse events reported for LANTUS and NPH treatment groups were similar for patients with type 1 and type 2 diabetes. Progression of retinopathy was investigated by fundus photography using a grading protocol derived from the Early Treatment Diabetic Retinopathy Study (ETDRS). In one clinical study involving patients with type 2 diabetes, a difference in the number of subjects with ≥3-step progression in ETDRS scale over a 6-month period was noted by fundus photography (7.5% in LANTUS group versus 2.7% in NPH treated group). The overall relevance of this isolated finding cannot be determined due to the small number of patients involved, the short follow-up period, and the fact that this finding was not observed in other clinical studies.

As is typically the case, patients with type 1 diabetes in the original trials had diabetes longer than patients with type 2 diabetes. Because the finding of progression of retinopathy occurred

only in a single trial in patients with type 2 diabetes, the postmarketing trial was designed to determine if Lantus affected progression of retinopathy early in its natural history.

For this reasons, patients with type 2 diabetes were studied who had no retinopathy or mild diabetic retinopathy with ETDRS score up to and including 47/47

### **3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES – N/A**

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

Debarment certification

As required by Section 306(k)(1) of the Federal Food Drug and Cosmetic Act, (21 USC 335a(k)), as amended by the Generic Drug Enforcement Act of 1992, Sanofi-Aventis U.S. LLC hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug and Cosmetic Act in connection with this application.

Financial Disclosures

Form 910-0396 certifies that the Sponsor has not entered into a financial arrangement with the listed investigators and that the listed investigators did not disclose any propriety interest of receipt of significant payment as defined in 21 CFR 54.2(b).

Compliance with good clinical practices

Patients received treatment that is consistent with the standard of practice.  
On average, glycemic control improved during the study in both treatment arms

### **5 CLINICAL PHARMACOLOGY N/A**

### **6 INTEGRATED REVIEW OF EFFICACY**

Study 4016 evaluated progression of diabetic retinopathy in insulin-treated patients with type 2 diabetes. The treatment period lasted five years and compared once daily Lantus to twice daily NPH insulin

### **Inclusion criteria:**

At screening patients had no or mild diabetic retinopathy with ETDRS score up to and including 47/47. Additional inclusion criteria are as follows:

Subjects meeting all of the following criteria will be considered for admission to the study: Male or female aged 30 to 70 years, with type 2 diabetes mellitus diagnosis for at least 1 year, treatment with oral hypoglycemic agent(s) and/or insulin for at least 1 year prior to screening, and stable oral hypoglycemic and/or insulin (not >10% change in basal) regimen for at least 3 months. Patients on Lantus were excluded. At screening, HbA1c was between 6.0% and 12.0%, inclusive. Subject either were not of childbearing potential (male, female who is surgically sterile, or postmenopausal for more than 2 years) or female who is not pregnant and agrees to use a reliable contraceptive measure for the duration of the study. Patients were randomized by two strata HbA1c 6 to 9% and >9 to 12%

### **Insulin algorithms**

Insulin naïve patients were started on 10 units per day. NPH was given 5 units bid at breakfast and bedtime. Lantus was started at 10 U at bedtime. For patients previously on insulin, the initial dose of NPH was equal to the dose of basal insulin the patients had previously been receiving. The initial dose of Lantus was 80% of the previous basal insulin dose. Insulin titration was based on FPG. Variations in dosing regimen were allowed based on clinical judgment (such as Lantus at the evening meal instead of bedtime), but basal insulin needed to be given at the same time each day.

The treatment goals of the study are for each subject to achieve and maintain both a FPG of  $\leq 100$  mg/dL (5.5 mmol/L) and a HbA1c  $\leq 7.0\%$  without hypoglycemia. This was achieved by the initial titration of basal insulin (NPH human insulin or insulin glargine). Once basal insulin titration has been optimized with the aims of achieving and maintaining both a FPG of  $\leq 100$  mg/dL (5.5 mmol/L) and a HbA1c  $< 7.0\%$  without hypoglycemia, regular insulin was added at mealtimes, in an effort to realize both of these glycemic goals. Addition of oral antidiabetic agents or changing dose of oral agents was permitted after optimization of basal insulin.

The primary efficacy analysis and several other important efficacy analyses were based on grading of standard seven-field fundus photographs performed at centers certified and monitored by the central reading center, the Fundus Photograph Reading Center (FPRC) at the University of Wisconsin, Madison WI. This is the same facility and process used in the evaluation of retinal effects of intensive versus conventional glycemic control in the Diabetes Control and Complications trial (DCCT). Photographs were reviewed for quality at the start of the study, and photographers were brought to FPRC to undergo training sessions if needed. Each photograph was graded by 2 independent graders, masked to treatment and to other photos from the same individual. A senior grader resolved discrepancies between grades from the 2 graders. All patients whose ETDRS scores demonstrated 3-step progression over baseline at any point

during the study underwent a Director's Review, in which a senior director performed a side-by-side review of all photographs of the designated patient to verify that 3-step progression was or was not present at study endpoint. Grade revisions based on Director's Reviews were entered into the database. Fundus photographs were taken at screening, and after 3, 6, 12, 24, 36, 48, and 60 months of treatment.

**Primary endpoint:** Binary indicator (Yes/No) of a 3-step or greater progression in the ETDRS retinopathy scale at study endpoint for each subject.

**Secondary endpoints:** Binary indicator (Yes/No) of a 3-step or greater progression in the ETDRS retinopathy scale after 3, 6, 12, 24, 36, 48, and 60 months, respectively, for each subject. Binary indicator of: developing proliferative retinopathy for each subject, changing scores on the ETDRS retinopathy severity scale, developing clinically significant macular edema, achieving target HbA1c  $\leq 7.0\%$ , achieving HbA1c  $\leq 8.0\%$  for each subject, number of episodes of symptomatic hypoglycemia, symptomatic nocturnal hypoglycemia, and severe hypoglycemia during treatment for each subject, Measurements of HbA1c and FPG (mean of 7 days fasting self-monitored FPG; and clinical laboratory determined FPG). Daily insulin doses (total, basal, and short-acting).

**Definitions of hypoglycemia:**

Clinically important hypoglycemia was a symptomatic event which required assistance of another person OR plasma glucose of  $< 2$  mM (36 mg/dl) was recorded.

Severe hypoglycemia was defined as an event with symptoms consistent with hypoglycemia in which the subject required the assistance of another person and which was associated with plasma glucose concentration below 56 mg/dL (3.1 mmol/L) or with prompt recovery after oral carbohydrate, intravenous glucose, or glucagon administration.

Symptomatic hypoglycemia was an event with or without glucose confirmation

**Data Sets and Patient Disposition**

Data were analyzed by the Sponsor according to the following data sets. Details about patient disposition are also found in section 3.1.3 of the FDA statistical review.



Table 6 - Datasets analyzed - randomized population

	LANTUS	NPH
Randomized population	515 (100%)	509 (100%)
Per Protocol population	374 (72.6%)	363 (71.3%)
ITT population	513 (99.6%)	504 (99.0%)
Safety population	514 (99.6%)	503 (99.0%)

Note: % calculated using the number of randomized population as the denominator  
NPH = neutral protamine hagedorn; ITT = intent-to-treat  
PGM/sas\_base3/HOEB01\_4/016/pg/rep/oth/\_dispo2.sas OUT=ouli\_dispo2.rtf (16AUG2007 - 11:55)

### Baseline Characteristics:

As shown in the two tables that follow, both treatment arms were well matched with respect to demographic characteristics and metabolic control. The mean age of patients was 55.1 years. The mean duration of DM was 10.8 years, 9 years on oral agents and 5 years of insulin. At baseline approximately half of patients used oral agents, alone or in combination. 42% used metformin, 27% a SFU and 15% a TZD. Among Lantus patients 67% were taking insulin at baseline, 70% for NPH. Use of concomitant medications (lipid lowering agents, ACE inhibitors, etc) was well matched between the two arms.

Table 7 - Demography characteristics - ITT population

	LANTUS (N=513)	NPH (N=504)	All (N=1017)
<b>Age (years)</b>			
Number	513	504	1017
Mean (SD)	54.9 (8.8)	55.3 (8.5)	55.1 (8.6)
Median	55.0	56.0	56.0
Min : Max	33 : 74	29 : 72	29 : 74
<65	429 (83.6%)	427 (84.7%)	856 (84.2%)
[65 - 75]	84 (16.4%)	77 (15.3%)	161 (15.8%)
<b>Gender n(%)</b>			
Number	513	504	1017
Male	278 (54.2%)	270 (53.6%)	548 (53.9%)
Female	235 (45.8%)	234 (46.4%)	469 (46.1%)
<b>Race n(%)</b>			
Number	513	504	1017
Asian/Oriental	9 (1.8%)	12 (2.4%)	21 (2.1%)
Black	49 (9.6%)	62 (12.3%)	111 (10.9%)
Multiracial	9 (1.8%)	8 (1.6%)	17 (1.7%)
White	446 (86.9%)	422 (83.7%)	868 (85.3%)
<b>Hispanic ethnicity n(%)</b>			
Hispanic	37 (7.2%)	28 (5.6%)	65 (6.4%)
<b>Weight (kg)</b>			
Number	512	504	1016
Mean (SD)	100.17 (22.71)	98.67 (22.26)	99.43 (22.49)
Median	97.10	97.05	97.10
Min : Max	49.5 : 183.3	48.5 : 180.1	48.5 : 183.3
<b>Height (cm)</b>			
Number	510	504	1014
Mean (SD)	170.12 (10.10)	170.07 (10.27)	170.09 (10.18)
Median	170.20	170.00	170.20
Min : Max	137.2 : 198.1	127.0 : 200.7	127.0 : 200.7

**Table 14 - Metabolic control at baseline – ITT population**

	LANTUS (N=513)	NPH (N=504)	All (N=1017)
<b>HbA1c (%)</b>			
Number	512	504	1016
Mean (SD)	8.41 (1.38)	8.31 (1.38)	8.36 (1.38)
Median	8.20	8.10	8.10
Min : Max	5.7 : 12.6	5.8 : 13.5	5.7 : 13.5
<b>Lab determined FPG (mmol/L)</b>			
Number	512	504	1016
Mean (SD)	189.66 (65.97)	179.63 (61.14)	184.69 (63.79)
Median	179.60	169.65	175.55
Min : Max	73.0 : 492.3	59.3 : 389.8	59.3 : 492.3

ITT = intent-to-treat; NPH = neutral protamine hagedom; N = population size; FPG = fasting plasma glucose  
 PGM=ses\_base3/HCE901\_4/016/pg/rep/otml\_demog4\_ses OUT=out4\_demog4\_lrf(164UG2007 - 11:59)

As shown in the following two tables, there was a small imbalance at baseline between treatment arms with respect to late complications of diabetes. Diabetic retinopathy was present in 15.6% of patients on Lantus compared to 12.1% on NPH. The mean ETDRS score was also somewhat higher in patients on Lantus than NPH .

**Table 11 – Number (%) of subjects with diabetic late complications at baseline - ITT population**

	LANTUS (N=513)	NPH (N=504)	All (N=1017)
Number of ITT subjects with at least 1 complication	308 (60.0%)	291 (57.7%)	599 (58.9%)
Diabetic retinopathy	80 (15.6%)	61 (12.1%)	141 (13.9%)
Diabetic nephropathy	60 (11.7%)	48 (9.5%)	108 (10.6%)
Diabetic neuropathy	245 (47.8%)	241 (47.8%)	486 (47.8%)
Diabetic macroangiopathy	64 (12.5%)	67 (13.3%)	131 (12.9%)

Note: % calculated using the number of ITT population as denominator  
 ITT = intent-to-treat; NPH = neutral protamine hagedom; N = population size  
 PGM=ses\_base3/HCE901\_4/016/pg/rep/otml\_mh13\_ses OUT=out1\_mh13\_lrf(164UG2007 - 11:58)

**Table 12 - Baseline ETDRS score**

	LANTUS	NPH	All
<b>PP population</b>			
Number	374	363	737
Mean (SD)	3.06 (2.17)	2.85 (2.03)	2.96 (2.10)
Median	2.00	2.00	2.00
Min : Max	1.0 : 12.0	1.0 : 9.0	1.0 : 12.0
<b>ITT population</b>			
Number	513	504	1017
Mean (SD)	2.97 (2.15)	2.85 (2.02)	2.91 (2.09)
Median	2.00	2.00	2.00
Min : Max	1.0 : 12.0	1.0 : 9.0	1.0 : 12.0

ETDRS = early treatment diabetic retinopathy scale; ITT = intent-to-treat; NPH = neutral protamine hagedom  
 PGM=ses\_base3/HCE901\_4/016/pg/rep/otml\_demog2\_ses OUT=out1\_demog2\_lrf(164UG2007 - 11:59)

In the Lantus group at baseline, 10 patients had clinically significant macular edema in the right eye and 12 in the left eye. In the NPH group, there were 3 with CSME in the right eye and 3 in the left eye.

## Results

### Retinopathy:

There was no difference between the two arms with respect to the primary endpoint, which was 3 step or greater progressions in ETDRS score. As shown in the table below, progression was reported in 12.5% of patients on Lantus and 14.6% on NPH. The results for the two treatment arms were not statistically different. Change over the course of the study is shown in the figure for the per protocol population. Additional details can be found in the FDA statistical review.

**Table 20 - Number (%) of patients with 3-step or greater progression in ETDRS at endpoint - ITT population**

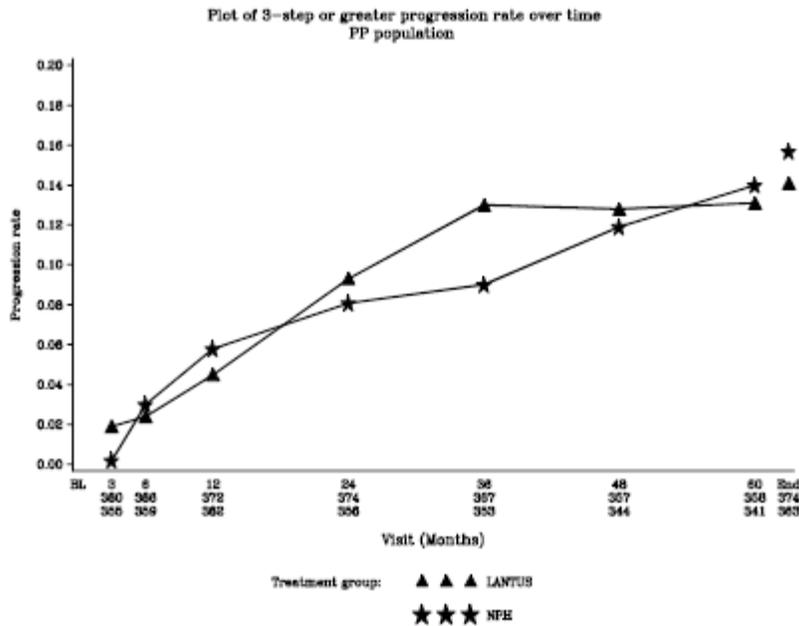
	LANTUS (N=513)	NPH (N=504)
Subjects with 3-step or greater progression (progression rate)	63/502 (12.5%)	71/487 (14.6%)
Difference in progression rate (SE) versus NPH <sup>a</sup>	-2.10%( 2.14%)	
95% CI versus NPH <sup>a</sup>	(-6.29% to 2.09%)	

Note: % Calculated using number of ITT subjects with non-missing data as denominator

ETDRS = early treatment diabetic retinopathy scale; ITT = intent-to-treat; NPH = neutral protamine hagedorn; N = population size

<sup>a</sup> Using a generalized linear model (SAS GENMOD) with treatment and baseline HbA1c strata as the classified independent variables, and with binomial distribution and identity link function.

PGM=/sas\_base3/HOE901\_4/016/pg/rep/oth/efetd1\_i.sas OUT=out/efetd1\_i.rtf (16AUG2007 - 12:05)



As noted earlier, patients in the Lantus group had somewhat more severe retinopathy at baseline. However the change from baseline to endpoint was the same in both groups. This is shown in the two tables that follow:

Table 21 - ETDRS retinopathy severity score at endpoint - PP population

ETDRS	LANTUS (N=374)	NPH (N=363)
Baseline		
Number	374	363
Mean (SD)	3.06 (2.17)	2.85 (2.03)
Median	2.00	2.00
Min : Max	1.0 : 12.0	1.0 : 9.0
Endpoint		
Number	374	363
Mean (SD)	3.86 (2.82)	3.62 (2.70)
Median	3.00	3.00
Min : Max	1.0 : 16.0	1.0 : 16.0
Change		
Number	374	363
LS Mean (SE) <sup>a</sup>	0.94 (0.104)	0.95 (0.107)
LS Mean difference (SE) versus NPH <sup>a</sup>	-0.02 (0.134)	-
95% CI versus NPH <sup>a</sup>	(-0.279 to 0.247)	-
p-value versus NPH <sup>a</sup>	0.9061	-

<sup>a</sup>Using ANCOVA (type 3) with factors: treatment, pooled center, baseline HbA1c stdev and baseline ETDRS score as covariate. Records with missing values for factors or response were excluded from statistical analyses.  
 ETDRS = early treatment diabetic retinopathy scale, PP = per-protocol; N = population size; NPH = neutral protamine hagedom  
 PGMF/ses\_base3/HOE901\_4/016/pg/rep/otn/efeld2\_p.sas OUT=ouf1\_efeld2\_p.rtf (16AUG2007 - 12:06)

**Table 22 - Distribution of changes in ETDRS at endpoint (LOCF) n(%) - PP population**

Changes in ETDRS at endpoint	LANTUS (N=374)	NPH (N=363)	P-value <sup>a</sup>
≤-4	1 (0.3%)	2 (0.6%)	0.4251
-3	5 (1.3%)	5 (1.4%)	
-2	8 (2.1%)	7 (1.9%)	
-1	49 (13.1%)	50 (13.8%)	
0	127 (34.0%)	140 (38.6%)	
1	90 (24.1%)	66 (18.2%)	
2	48 (12.8%)	38 (10.5%)	
3	23 (6.1%)	29 (8.0%)	
≥4	23 (6.1%)	26 (7.2%)	

Note: % calculated using the number of PP population as denominator.

<sup>a</sup>Using Cochran-Mantel-Haenszel test stratified by pooled center.

ETDRS = early treatment diabetic retinopathy scale; LOCF = last observation carried forward; PP = per-protocol; N = population size; NPH = neutral protamine hagedorn

PGM=ises\_base3HOE901\_4/016/pg/reploth/efeld3\_p.sas OUT=out1\_efeld3\_p.rtf (16AUG2007 - 12:07)

Findings for development of clinically significant macular edema (CSME) are shown in the following table. There was no difference between Lantus and NPH.

**Table 24 - Number (%) of who patients developed CSME during study**

	LANTUS	NPH	P-value <sup>a</sup>
<b>PP population</b>			
Number	371	362	
Patients Developed CSME during study	58 (15.6%)	53 (14.6%)	0.7674
<b>ITT population</b>			
Number	493	481	
Patients Developed CSME during study	68 (13.8%)	68 (14.1%)	0.8818

Note: % calculated using number of subjects with non-missing data as denominator.

<sup>a</sup>Using Cochran-Mantel-Haenszel test stratified by pooled center.

CSME=Clinically significant macular edema; PP = per-protocol; N = population size; NPH = neutral protamine hagedorn

PGM=ises\_base3HOE901\_4/016/pg/reploth/efcme3.sas OUT=out1\_efcme3.rtf (16AUG2007 - 12:11)

As shown in the table below, proliferative retinopathy was reported for the ITT population in 5.4% of patients on Lantus and 3.9% on NPH. The results for the two treatment arms were not statistically different. One patient (on Lantus) received laser coagulation for proliferative retinopathy.

**Table 25 - Number (%) of patients developed proliferative diabetic retinopathy during study**

	LANTUS	NPH	P-value <sup>a</sup>
PP population			
Number	373	363	
Patients developed PDR during study	20 (5.4%)	14 (3.9%)	0.5064
ITT population			
Number	496	483	
Patients developed PDR during study	25 (5.0%)	16 (3.3%)	0.2095

Note: % calculated using number of subjects with non-missing data as denominator.

<sup>a</sup>Using Cochran-Mantel Haenszel test stratified by pooled center.

PP = per-protocol; NPH = neutral protamine hagedorn; PDR = proliferative diabetic retinopathy; ITT = intent-to-treat

PGM=/sas\_base3/HOE901\_4/016/pg/rep/oth/i\_efpdr1.sas OUT=out/i\_efpdr1.rtf (16AUG2007 - 12:16)

## Glycemic Control:

### HbA1c

As shown in the following table, decrease in HbA1c from baseline to endpoint was slightly less in patients taking Lantus (8.4% to 7.8%), than in patients taking NPH (8.3% to 7.6%). The mean FPG fell by 44.9 mg/dl in the Lantus group and 44.2 mg/dl in the NPH group.

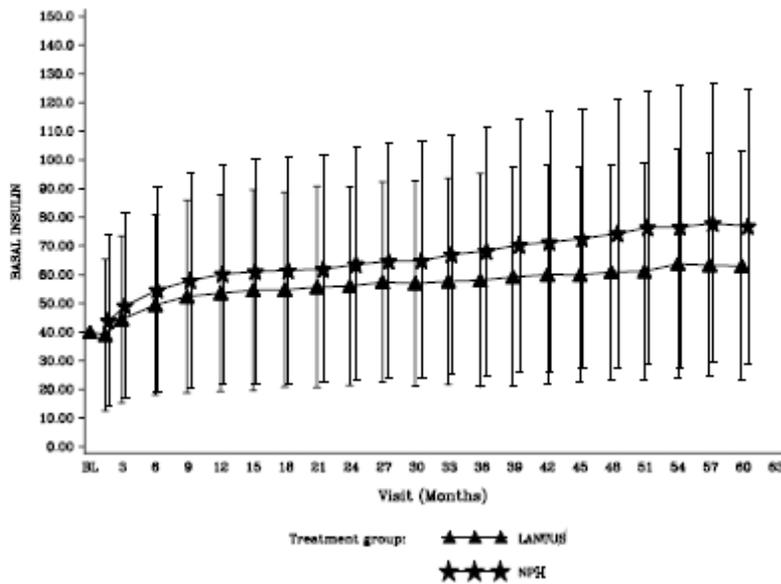
**Table 26 - Mean change from baseline in HbA1C at endpoint (LOCF) - ITT population**

HbA1c(%)	LANTUS (N=513)	NPH (N=504)
Baseline		
Number	512	504
Mean (SD)	8.41 (1.38)	8.31 (1.38)
Median	8.20	8.10
Min : Max	5.7 : 12.6	5.8 : 13.5
Endpoint		
Number	498	487
Mean (SD)	7.80 (1.33)	7.56 (1.31)
Median	7.60	7.40
Min : Max	5.1 : 13.6	4.8 : 14.2
Change		
Number	497	487
LS Mean (SE) <sup>a</sup>	-0.55 (0.061)	-0.76 (0.060)
LS Mean difference (SE) versus NPH <sup>a</sup>	0.21 (0.074)	-
95% CI versus NPH <sup>a</sup>	(0.062 to 0.354)	-
p-value versus NPH <sup>a</sup>	0.0053	-

**Insulin Dose:**

The total insulin dose was about 90 units per day at endpoint in both groups, but patients on NPH tended to use more basal insulin and less bolus insulin than patients on Lantus. These data are shown in the illustrations that follow. It should be noted that patients received Lantus once daily while patients received NPH twice daily.

**Figure 10 - Plot of basal insulin (mean + SD) over time - ITT population**



**Table 34 - Mean daily insulin dose at endpoint (LOCF) - ITT population; Displays the mean dose at endpoint for total, basal, and short-acting insulins**

Insulin Type	LANTUS (N=513)	NPH (N=504)
<b>Daily dose of basal insulin (UI) at endpoint</b>		
Number	504	498
Mean (SD)	61.84 (39.41)	72.31 (47.52)
Median	54.00	63.00
Min : Max	0.0 : 240.0	0.0 : 300.0
<b>Daily dose of short acting(UI) at endpoint</b>		
Number	345	349
Mean (SD)	43.83 (41.62)	31.81 (37.68)
Median	30.00	22.00
Min : Max	0.0 : 270.0	0.0 : 398.0
<b>Total daily dose(UI) at endpoint</b>		
Number	504	498
Mean (SD)	88.59 (65.92)	91.80 (66.36)
Median	71.00	80.00
Min : Max	0.0 : 490.0	0.0 : 452.0

LOCF = last observation carried forward; ITT = intent-to-treat; NPH = neutral protamine hagedorn; N = population size  
 PGM=/sas\_base3/HOE901\_4/016/pg/rep/oth/i\_efids2\_i.sas OUT=out/i\_efids2\_i.rtf (16AUG2007 - 12:29); N = number of patients

### Fasting Plasma Glucose (FPG) goal

The percent of patients achieving the goal of FPG<100 is shown below.

**Table 30 - Number (%) of patients achieving laboratory determined fasting plasma glucose <=100 mg/DL - ITT population**

Subjects with laboratory determined FPG <=100mg/DL	LANTUS (N=513)	NPH (N=504)
Baseline	33/512 (6.4%)	39/504 (7.7%)
Month 3	87/490 (17.8%)	70/482 (14.5%)
Month 6	99/485 (20.4%)	79/468 (16.9%)
Month 9	83/390 (21.3%)	63/385 (16.4%)
Month 12	42/223 (18.8%)	34/233 (14.6%)
Month 24	116/389 (29.8%)	88/380 (23.2%)
Month 60	105/348 (30.2%)	89/327 (27.2%)
Endpoint	143/502 (28.5%)	121/498 (24.3%)

Note: % calculated using number of subjects with non-missing data at each visit as denominator  
 ITT = intent-to-treat; N = population size; NPH = neutral protamine hagedom; FPG = fasting plasma glucose  
 PGM=isas\_base3/HOE901\_4/016/pg/rep/oth/i\_effig2\_lsas OUT=out/i\_effig2\_j.rf (16AUG2007 - 12:26)

After initial optimization of basal insulin (Lantus or NPH), patients were allowed to add regular insulin to improve glycemic control. Oral agents were allowed as well. Use of these other agents, post randomization is shown below

	% of ITT population	
	Lantus	NPH
Bolus insulin	67	69
Metformin	18	16
Sulfonylurea	16	20
Thiazolidinedione	6	6

### Body weight

Weight gain was somewhat greater with NPH (4.8kg) than with Lantus (3.7kg). The mean difference of 1.2 kg was of marginal statistically significance (p=0.05).

**Table 35 - Mean change and mean difference from baseline in body weight at endpoint (LOCF) - ITT population**

Body weight (kg)	LANTUS (N=513)	NPH (N=504)
<b>Baseline</b>		
Number	512	504
Mean (SD)	100.2 (22.7)	98.7 (22.3)
Median	97.1	97.1
Min : Max	50 : 183	49 : 180
<b>Endpoint</b>		
Number	503	500
Mean (SD)	103.2 (24.5)	103.0 (23.7)
Median	101.7	101.3
Min : Max	49 : 201	49 : 200
<b>Change</b>		
Number	502	500
LS Mean (SE) <sup>a</sup>	3.7 (0.46)	4.8 (0.46)
LS Mean difference (SE) versus NPH <sup>a</sup>	-1.2 (0.60)	-
95% CI versus NPH <sup>a</sup>	(-2.34 to 0.00)	-
p-value versus NPH <sup>a</sup>	0.0505	-

## Hypoglycemia

As shown in the following table, hypoglycemia was more prominent with NPH than with Lantus. There were 38 subjects (7.6%) on Lantus who experienced at least one episode of severe hypoglycemia compared to 55 (11.1%) subjects on NPH. There were a total of 83 episodes of severe hypoglycemia with Lantus compared to 113 with NPH. This difference with respect to hypoglycemia is consistent with the finding noted earlier that NPH was slightly more effective at lowering HbA1c than was Lantus.

**Table 36 - Summary of incidences of hypoglycemia from month 3 to the end of study - ITT population**

	LANTUS		NPH		P_value <sup>a</sup>
	Number(%) of subjects	Number of Episodes	Number(%) of subjects	Number of Episodes	
Total number of ITT subjects from month 3 to end of study	501		494		
Symptomatic hypoglycemia	370 (73.9%)	11214	385 (77.9%)	14617	0.1366
Symptomatic nocturnal hypoglycemia	281 (56.1%)	578	296 (59.9%)	1233	0.2248
Clinically important hypoglycemia	178 (35.5%)	3616	216 (43.7%)	4347	0.0083
Severe hypoglycemia	38 (7.6%)	83	55 (11.1%)	113	0.0439

Note: % calculated using total number of ITT subjects from month 3 to end of study as denominator.

<sup>a</sup>comparing number(%) of subjects using Cochran-Mantel-Haenszel test stratified by pooled center.

ITT = intent-to-treat; NPH = neutral protamine hagedom; N = population size

PGM=/sas\_base3/HOE901\_4/016/pg/rep/lothr/efhy1\_i.sas OUT=out/efhy1\_i.rtf (16AUG2007 - 12:32)

## 7 INTEGRATED REVIEW OF SAFETY

The safety population consists of over 500 patients per treatment arm with a median exposure of about five years

**Table 38 - Summary of extent of exposure – safety population**

	LANTUS (N=514)	NPH (N=503)
Cumulative exposure (subject years)	2144.0	2095.8
<b>Extent of exposure (days)</b>		
Number	514	503
Mean (SD)	1523.55 (571.77)	1521.82 (562.14)
Median	1821.50	1823.00
Min : Max	3.0 : 1958.0	1.0 : 2045.0

Treatment emergent adverse events, death, and cardiac events are shown in the next three tables. There was little, if any, difference between Lantus and NPH insulin.

All Adverse events:

**Table 39 - Number (%) of patients with treatment-emergent adverse events - safety populations**

	LANTUS (N=514)	NPH (N=503)
Patients with any TEAE	490 (95.3%)	479 (95.2%)
Patients with any treatment-emergent SAE	211 (41.1%)	215 (42.7%)
Patients with TEAE leading to death	14 (2.7%)	11 (2.2%)
Patients permanently discontinued due to TEAE	16 (3.1%)	11 (2.2%)

Note: % calculated using the number of safety population as the denominator.

NPH = neural protamine hagedorn; N = population size; TEAE = treatment-emergent adverse event; SAE= serious adverse event

PGM=/sas\_base3/HOE901\_4/016/pg/rep/oth/i\_ae1all.sas OUT=out/i\_ae1all.rtf (16AUG2007 - 12:33)

Adverse event leading to death:

**Table 43 - Number (%) of patients with treatment emergent adverse events leading to death, presented by primary system organ class and preferred term – safety population**

System Organ Class (SOC) by Preferred Term	LANTUS (N=514)	NPH (N=503)
Any class - any event	14 (2.7%)	11 (2.2%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	4 (0.8%)	2 (0.4%)
Breast cancer	1 (0.2%)	0
Colon cancer	1 (0.2%)	0
Pancreatic neoplasm	1 (0.2%)	0
Thyroid neoplasm	1 (0.2%)	0
Bile duct cancer	0	1 (0.2%)
Lung cancer metastatic	0	1 (0.2%)
Oesophageal adenocarcinoma	0	1 (0.2%)
Cardiac disorders	7 (1.4%)	6 (1.2%)
Cardiac arrest	3 (0.6%)	2 (0.4%)
Myocardial infarction	2 (0.4%)	2 (0.4%)
Cardiac failure congestive	1 (0.2%)	1 (0.2%)
Cardiomyopathy	1 (0.2%)	0
Sinus tachycardia	1 (0.2%)	0
Ventricular fibrillation	1 (0.2%)	0
Coronary artery occlusion	0	1 (0.2%)

Adverse event leading to withdrawal:

There were 17 patients on Lantus and 12 patients on NPH who withdrew because of an adverse event. As shown in table above, the adverse event was fatal in 14 patients on Lantus and 11 patients on NPH, and were unlikely to have been related to study drugs. Narratives of four patients (3 Lantus and 1 NPH) who withdrew because of skin rash are given below. Three of the patients were naïve to insulin (two on Lantus and one on NPH) and one patient (on Lantus) had received insulin previously:

Subject 1004/09, a 34-year-old male with type 2 diabetes mellitus, was diagnosed with the non-serious adverse event of a pruritic rash on 24-Jan-2002 (day 2 postrandomization) that was considered severe in intensity. Symptoms included a red, itchy rash covering the upper body and upper extremities. The subject discontinued study medication on 25-Jan-2002 and withdrew from the study due to the event. The dose of study medication was discontinued due to the event (last dose on day 3 postrandomization). The subject had been treated with study medication (insulin glargine) since 22-Jan-2002. He had also been treated with metformin and glimepiride since 01-Oct-1999 and pioglitazone since -1-Jul-2000. Relevant medical history for this subject included type 2 diabetes mellitus since 1993. Investigator's assessment: The investigator assessed the event as possibly associated with study medication.

Subject 2005/26, a 60-year-old female with type 2 diabetes mellitus, developed a rash in the supramammary region on 12-Mar-2002 (day 12 postrandomization) that was considered mild in intensity. The subject discontinued study medication on 21-Mar-2002 and withdrew from the study due to the event. No further information regarding this event is currently available. The dose of study medication was discontinued due to the event (last dose on day 21 postrandomization). The subject had been treated with study medication (insulin glargine) since 28-Feb-2002. Relevant medical history for this subject included non-insulin-dependent diabetes mellitus, hypertension, peripheral edema, transient ischaemic attack, and hyperlipidaemia. This subject had been treated with metformin and glyburide since 12-Oct-2000. Investigator's assessment: The investigator assessed the event as possibly associated with study medication

Subject 1033/27, a 39-year-old male with type 2 diabetes mellitus, developed a rash all over his body on 21-Dec-2001 (day 12 postrandomization) that was considered severe in intensity. The subject discontinued study medication on 23-Dec-2001 and withdrew from the study due to the event. No further information regarding this event is currently available. The dose of study medication was discontinued due to the event (last dose on day 14 postrandomization). The subject had been treated with study medication (insulin glargine) since 09-Dec-2001. Relevant medical history included non-insulin-dependent Diabetes mellitus and hyperlipidaemia. The subject had also been treated with Glucophage and Novalog insulin. Investigator's assessment: The investigator assessed the event as possibly associated with study medication

Subject 1017/13, a 56-year-old female with type 2 diabetes mellitus, developed a generalized urticaria on 20-Jun-2002 (day 170 postrandomization) that was considered moderate in intensity. The subject discontinued study medication on 05-Aug-2002 (day 217 postrandomization) and withdrew from the study due to the event. The subject had been treated with study medication (NPH human insulin) since 01-Jan-2002.

Treatment emergent serious adverse events occurred in 41.1% of patients on Lantus and 42.7% on NPH. The distribution of cardiac events is shown in the next table. There is little if any difference between Lantus and NPH.

**Table 44 - Number (%) of patients with treatment emergent serious adverse events occurring with an incidence  $\geq$  0.5% in any treatment group, presented by primary system organ class and preferred term – safety population**

System Organ Class (SOC) by Preferred Term	LANTUS (N=514)	NPH (N=503)
Any class - any event	211 (41.1%)	215 (42.7%)
Cardiac disorders	69 (13.4%)	59 (11.7%)
Coronary artery disease	24 (4.7%)	21 (4.2%)
Myocardial infarction	13 (2.5%)	10 (2.0%)
Cardiac failure congestive	10 (1.9%)	12 (2.4%)
Angina pectoris	8 (1.6%)	8 (1.6%)
Angina unstable	6 (1.2%)	2 (0.4%)
Atrial fibrillation	6 (1.2%)	4 (0.8%)
Acute myocardial infarction	5 (1.0%)	0
Cardiac arrest	4 (0.8%)	3 (0.6%)
Myocardial ischaemia	3 (0.6%)	1 (0.2%)
Arrhythmia	0	3 (0.6%)
Coronary artery occlusion	0	4 (0.8%)

Insulin hypersensitivity reactions and local injection site reactions are shown in the next two tables. 1.0 % of patients on Lantus and 3.8% of patients on NPH had hypersensitivity reactions. 2.3 % of patients on Lantus and 1.4% of patients on NPH had injection site reactions reactions.

**Table 46 - Number (%) of patients with treatment emergent systemic hypersensitivity reactions, presented by preferred term – safety population**

Preferred Term	LANTUS (N=514)	NPH (N=503)
Any event	5 (1.0%)	19 (3.8%)
Dermatitis allergic	2 (0.4%)	4 (0.8%)
Drug hypersensitivity	2 (0.4%)	6 (1.2%)
Hypersensitivity	1 (0.2%)	10 (2.0%)
Drug eruption	0	1 (0.2%)

Note: % calculated using the number of safety population as the denominator

<sup>1</sup>Preferred Term sorted by decreasing frequency in Lantus group

NPH = neutral protamine hagedorn; N = population size

<sup>2</sup>GM=/sas\_base3/HOE901\_4/016/pg/rep/oth/i\_ae7hyp.sas OUT=out/i\_ae7hyp.rtf (16AUG2007 - 12:38)

All 5 of Lantus patients who had systemic hypersensitivity reactions had received insulin previously. 13 of the NPH patients who had systemic hypersensitivity reactions had received insulin previously and 6 were insulin naïve. None of the systemic hypersensitivity reactions in this table were listed as serious adverse events or resulted in withdrawal.

Adverse events related to injection of study drugs are shown below:

**Table 47 - Number(%) of patients with treatment emergent adverse events, presented by preferred term - Safety population**

System Organ Class (SOC)	LANTUS (N=514)	NPH (N=503)
Any event	12 (2.3%)	7 (1.4%)
Injection site bruising	4 (0.8%)	3 (0.6%)
Injection site atrophy	3 (0.6%)	0
Injection site hypertrophy	2 (0.4%)	1 (0.2%)
Injection site infection	1 (0.2%)	0
Injection site irritation	1 (0.2%)	1 (0.2%)
Injection site mass	1 (0.2%)	0
Injection site reaction	1 (0.2%)	1 (0.2%)
Injection site nodule	0	1 (0.2%)

### Other safety findings

Doubling of baseline creatinine was observed in 0.6% in each arm

As shown in the table below, there was little change in heart rate or blood pressure during the study and no difference between the two treatments.

**Table 51 - Vital signs change from baseline to endpoint and ANCOVA analysis - ITT population**

Vital sign (SE)	LS mean change from baseline		LS mean difference	p-value <sup>a</sup>
	Lantus	NPH		
Heart Rate (bpm)	-1.27 (0.48)	-1.59 (0.48)	0.32 (0.63)	0.6097
Systolic BP (mm Hg)	1.14 (0.75)	1.55 (0.75)	-0.41 (0.97)	0.6737
Diastolic BP (mm Hg)	-2.44 (0.44)	-2.20 (0.44)	-0.24 (0.57)	0.6749

<sup>a</sup>Lantus - NPH. Change from baseline was calculated as the difference endpoint - baseline. ANCOVA with treatment and (pooled) center effects and baseline HbA1c stratum and the corresponding baseline value as covariate.  
 ANCOVA = analysis of covariance; ITT = intent-to-treat; NPH = neutral protamine hagedorn; bpm = beats per minute; BP = blood pressure

## **8 ADDITIONAL CLINICAL ISSUES - NONE**

## **9 OVERALL ASSESSMENT**

### **Conclusions:**

There was no difference between Lantus and NPH insulin with respect to progression of diabetic retinopathy. With respect to the primary endpoint, a 3 step or greater progressions in ETDRS score, progression was reported in 12.5% of patients on Lantus and 14.6% on NPH. The results for the two treatment arms were not statistically different. There was no difference between Lantus and NPH for development of clinically significant macular edema

Proliferative retinopathy was reported in 5.4% of patients on Lantus and 3.9% on NPH. The results for the two treatment arms were not statistically different. The trend against Lantus might be cause of concern, except when one considers that the frequency and severity of diabetic retinopathy was greater at baseline in patients randomized to Lantus.\*

Control of hyperglycemia was comparable between Lantus and NPH. Reduction in HbA1c was slightly better with NPH than with Lantus, but patients on NPH gained more weight. Hypoglycemia was more of a problem with NPH as well. Patients on NPH, on average, used more basal insulin than patients on Lantus. But patients on Lantus tended to use more regular insulin.

\*Diabetic retinopathy was present in 15.6 of patients randomized to Lantus compared to 12.1% randomized to NPH. The mean ETDRS score was also somewhat higher in patients randomized to Lantus (3.06) than NPH (2.85). In the Lantus group at baseline 10 patients had clinically significant macular edema in the right eye and 12 in the left eye. In the NPH group there were 3 with CSME in the right eye and 3 in the left eye.

### **Recommendation on Regulatory Action**

Results of the trial submitted in this supplement satisfy the Sponsor's commitment to perform a postmarketing study to determine if Lantus promotes development of diabetic retinopathy in patients with type 2 diabetes.

The statement in the current label regarding the imbalance in progression of retinopathy can be removed and replaced by a simple statement that there appears to be no difference between

Lantus and NPH insulin with respect to progression of diabetic retinopathy. If the Sponsor wishes to describe the ophthalmological findings of the postmarketing trial in detail, they should include results regarding macular edema and proliferative retinopathy in addition to the primary endpoint, three step progression of retinopathy.

The label statement proposed by the Sponsor should be expanded to include details about control of hyperglycemia.

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/s/

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Robert Misbin  
10/10/2008 04:27:04 PM  
MEDICAL OFFICER

Hylton Joffe  
10/13/2008 10:50:23 AM  
MEDICAL OFFICER  
Please see clinical team leader memo.

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

***APPLICATION NUMBER:***  
**NDA 021081/S-034**

**CHEMISTRY REVIEW(S)**

<b>CHEMISTS REVIEW</b>	<b>1. ORGANIZATION</b>	<b>2. NDA NUMBER</b>	
	DMEDP II, HFD-510	21-081	
<b>3. NAME AND ADDRESS OF APPLICANT</b>		<b>4. COMMUNICATION, DATE</b>	
Sanofi-aventis, U.S. LLC 55 Corporate Drive Bridgewater, NJ 08807-0977		S-034, 21-Dec-2007	
<b>5. PROPRIETARY NAME</b>	<b>6. NAME OF THE DRUG</b>	<b>7. AMENDMENTS, REPORT, DATE</b>	
Lantus	Insulin glargine, [rDNA origin] injection		
<b>8. COMMUNICATION PROVIDES FOR:</b>			
Labeling information based on clinical study HOE901/4016, titled "Evaluation of Diabetic Retinopathy Progression in Subjects with Type 2 Diabetes Mellitus Treated with Oral Agents Plus Insulin."			
<b>9. PHARMACOLOGICAL CATEGORY</b>	<b>10. HOW DISPENSED</b>	<b>11. RELATED IND, NDA, DMF</b>	
antihyperglycemic	Rx		
<b>12. DOSAGE FORM</b>	<b>13. POTENCY</b>		
Injection	100 U/mL		
<b>14. CHEMICAL NAME AND STRUCTURE</b>			
See Chemistry Review #1			
<b>15. COMMENTS</b>			
<p>The applicant has requested a categorical exclusion from the requirements to prepare an Environmental Assessment under 21 CFR, part 25 §25.31(b) for proposed action for LANTUS. Based upon marketing estimates for sales of all LANTUS products in the five years after approval of this labeling change, the estimated quantity of the active moiety insulin is expected to enter the aquatic environment of the United States below 1 part per billion (1 ppb). This supplement meets the requirements of a categorical exclusion under 21 CFR §25.31(b) since the concentration of the drug substance at the point of entry into the aquatic environment is below 1 part per billion. To the best of Sanofi-aventis's knowledge, no extraordinary circumstances exist in regards to these actions. The applicant's request for a categorical exclusion is granted.</p> <p><i>Continued on the next page.</i></p>			
<b>16. CONCLUSION AND RECOMMENDATION</b>			
A categorical exclusion from submitted an environmental assessment is granted. The PLR conversion is acceptable from a CMC standpoint. CMC recommends approval of this supplement.			
<b>17. NAME</b>	<b>18. REVIEWERS SIGNATURE</b>	<b>19. DATE COMPLETED</b>	
JANICE BROWN	See appended electronic signature sheet	24-Sept-2008	
<b>DISTRIBUTION: ORIGINAL JACKET CSO REVIEWER DIVISION FILE</b>			

15. Continued.

PLR Conversion – The following sections in the PLR are included in this review:

3. **DOSAGE FORMS AND STRENGTHS - Acceptable.** There are no text changes in this section from the currently approved labeling.

11. **DESCRIPTION – Acceptable.** Although there are some track changes in this section in the submitted summary PI, when compared to the approved label there are no changes in this section.

## 16. HOW SUPPLIED/STORAGE AND HANDLING

**16.1 How supplied – Acceptable.** The applicant converted the text describing the unit dosage to a tabular format. Included in table 1 are the current and proposed labeling changes to this section.

<b>Currently approved labeling text</b>	<b>Proposed Label</b>		
LANTUS 100 units per mL (U-100) is available in the following package size: 10 mL vials (NDC 0088-2220-33) 3 mL cartridge system*, package of 5 (NDC 0088-2220-52) *Cartridge systems are for use only in OptiClik® (Insulin Delivery Device) 3 mL SoloStar® disposable insulin device, package of 5 (NDC 0088-2220-60) Needles are not included in the packs. BD Ultra-Fine™ needles‡ to be used in conjunction with SoloStar and OptiClik are sold separately and are manufactured by BD.	Dosage Unit/Strength	Package size	NDC #00886
	10 mL vials 100Units/mL	Pack of 1	2220-33
	3 mL cartridge system* 100Units /mL	package of 5	2220-52
	3 mL SoloStar® disposable insulin device 100Units /mL	package of 5	2220-60
	*Cartridge systems are for use only in OptiClik® (Insulin Delivery Device) Needles are not included in the packs. BD Ultra-Fine™ needles‡ to be used in conjunction with SoloStar and OptiClik are sold separately and are manufactured by BD.		

**16.2 Storage – Acceptable.** There are no text changes in this section from the currently approved labeling.

**16.3 Preparation and handling – Acceptable.** There are no text changes in this section from the currently approved labeling.

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/s/

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Janice Brown  
9/24/2008 10:45:20 AM  
CHEMIST

Swapn De  
9/24/2008 10:48:00 AM  
CHEMIST  
Signed on behalf of Eric Duffy

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**NDA 021081/S-034**

**PHARMACOLOGY REVIEW(S)**

## REVIEW AND EVALUATION OF PHARMACOLOGY/TOXICOLOGY DATA

KEY WORDS: Insulin glargine: Lantus™, Diabetic complications, Insulin sensitivity and resistance, Glucose sensitivity and tolerance test, Insulin analogue

Reviewer Name: Herman Rhee, Ph.D., Pharmacology Reviewer

Division Name: Division of Metabolic and Endocrine Drug Products (DMEDP)

HFD#510

Review Completion Date: Oct. 3, 2008

Review number: 003

**IND/NDA NUMBER:** NDA21-081

Serial number/date/type of submission: 034

Information to sponsor: Yes ( ) No ( x)

Sponsor (or agent): Hoechst Marion Roussel, Inc., Kansas City, MO(Dr. Patton: (816)966-5000)

Manufacturer for drug substance: Hoechst Marion Roussel Deutschland GmbH, Frankfurt, Germany

DRUG: Insulin glargine injection

Code Name: HOE 901

Generic Name: Insulin glargine injection

Trade Name: Lantus™

Chemical Name:21<sup>A</sup>-Gly-30<sup>B</sup>a-L-Arg-30<sup>B</sup>b-L-Arg-human insulin

CAS Registry Number: 160337-95-1

Molecular Formula/ Molecular Weight: C<sub>267</sub>H<sub>404</sub>N<sub>72</sub>O<sub>78</sub>S<sub>6</sub>/606.3

Structure: Human insulin was substituted with 2 arginines at positions 31 and 32 of the β-chain of human insulin and replacing the asparagine at position 21 of the A-chain with glycine.

### Conclusion of Review:

The sponsor submitted amendment serial#034 for clinical labeling changes. There are no changes in preclinical toxicology information as indicated under item 13.1. Thus, the information on carcinogenesis, mutagenesis, and impairment of fertility should be remained the same.

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/s/

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Herman Rhee  
10/3/2008 02:55:21 PM  
PHARMACOLOGIST

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**NDA 021081/S-034**

**STATISTICAL REVIEW(S)**



U.S. Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Translational Sciences  
Office of Biostatistics

**NDA /Serial Number:** NDA 021081  
**Drug Name:** Lantus (glargine insulin)  
**Indication(s):** diabetes  
**Date(s):** Post-hoc statistical calculations: November 10, 2009  
**Biometrics Division:** Division of Biometrics II  
**Statistical Reviewer:** Janice Derr, Ph.D.  
**Concurring Reviewers:** J. Todd Sahlroot, Ph.D.  
**Medical Division:** Division of Metabolism and Endocrinology Products (DMEP)  
**Medical Reviewer:** Robert Misbin, M.D.

**Background:** Insulin glargine, marketed by Sanofi-Aventis under the trade name Lantus, is a long-acting basal insulin analogue, given once daily to control blood glucose level in diabetes. Lantus was approved by the FDA in 2000. In July 2009, the FDA released an early communication stating that the agency is in the process of evaluating four epidemiological studies that were published in June 2009, which raised concerns for the potential association between insulin glargine and the risk of cancer. The Division of Epidemiology (CDER/OSE/DEPI) was consulted by DMEP to review the epidemiological data concerning the association between insulin glargine and cancer outcomes. This review (dated October 30, 2009), assessed the strength and validity of the findings from the four recently published studies, and discussed possible reasons for the consistency and/or discrepancies between these findings and the findings of previously published epidemiologic data.

As an additional assessment of the relationship between insulin glargine and the occurrence of cancer, Dr. Misbin conducted a post-hoc evaluation of the occurrence of cancer in a five-year randomized, controlled clinical study of insulin glargine compared to NPH insulin (Study 4016). Study 4016 was designed to evaluate the progression of diabetic retinopathy in insulin-treated patients with type 2 diabetes. The treatment period lasted five years and compared once daily Lantus (n=514) to twice daily NPH insulin (n=503)<sup>1</sup>. Although Study 4016 was not designed or powered to evaluate cancer outcomes, and these outcomes were not adjudicated, the study consisted entirely of type 2 diabetic patients, and the randomized arms were reasonably balanced in the distribution of age and obesity. These are confounding factors, as noted in the Division of

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<sup>1</sup> See the clinical review of NDA 021081 S-34 dated June 29, 2009

Epidemiology review, in the assessment of the relationship between the use of insulin glargine and the occurrence of cancer.

Dr. Misbin requested assistance in calculating odds ratios and associated 95% confidence intervals from his tallies of selected cancer outcomes from Study 4016. The overall occurrence of all cancers was somewhat lower in the Lantus arm (5.8%) than in the NPH insulin arm (9.3%; Table 1). Tallies of specific types of cancer ranged from 1 to 9 (Table 1). The confidence intervals all included 1.0, which is consistent with fairly similar odds of occurrence in the two randomized arms (Table 1). These results do not support the occurrence of an increased risk of cancer associated with insulin glargine in comparison to NPH insulin in type 2 diabetic patients who are being treated with insulin. However, the limitations of the study, as noted in the previous paragraph, may have contributed to this finding.

Table 1 Odds ratios for selected cancer outcomes; post-hoc analysis of Study 4016 of Lantus (glargine insulin) compared to NPH insulin

Cancer outcome	Lantus N=514	NPH insulin N=503	Odds ratio (Lantus / NPH)	95% confidence interval
All tumors	57 (11.1%)	62 (12.3%)	0.89	(0.59, 1.33)
All cancers	30 (5.8%)	47 (9.3%)	0.60	(0.36, 0.99)
Skin (basal cell + squamous)	7 (1.4%)	9 (1.8%)	0.76	(0.24, 2.31)
Colon + rectum	3 (0.6%)	5 (1.0%)	0.59	(0.09, 3.03)
Breast	2 (0.4%)	4 (0.8%)	0.49	(0.04, 3.42)
Breast, total	3 (0.6%)	5 (1.0%)	0.59	(0.09, 3.03)
Endometrial + uterus	1 (0.2%)	4 (0.8%)	0.24	(0.01, 2.47)
Prostate	1 (0.2%)	3 (0.6%)	0.33	(0.01, 4.07)

Notes:

- (1) Odds ratios and 95% confidence intervals were obtained from the exact procedure available in StatXact 7.0™ for the odds ratio of two binomial variables. These estimates are unstratified.
- (2) The tallies for each cancer outcome were provided by Dr. Misbin.

### Signatures/Distribution List

Janice Derr, Ph.D.  
Mathematical Statistician

J. Todd Sahlroot, Ph.D.  
Statistics Team Leader and Deputy Division Director, DB2

cc: JDerr, JTSahlroot, RMisbin

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21081	SUPPL-34	SANOFI AVENTIS US LLC	LANTUS

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/s/

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JANICE A DERR  
11/17/2009

JON T SAHLROOT  
11/17/2009



DEPARTMENT OF HEALTH AND HUMAN SERVICES  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH  
OFFICE OF BIOSTATISTICS

## STATISTICAL REVIEW AND EVALUATION CLINICAL STUDIES

**NDA/Serial Number:** 21-081/SE8-034

**Drug Name:** LANTUS<sup>®</sup> Insulin glargine [rDNA origin] injection

**Indication(s):** Treatment of adult and pediatric patients with type 1 diabetes mellitus or adult patients with type 2 diabetes mellitus who require basal (long-acting) insulin for the control of hyperglycemia

**Applicant:** Sanofi-Aventis, U.S., LLC

**Date(s):** Received 12/21/07; user fee (10 months) 10/19/08

**Review Priority:** Standard

**Biometrics Division:** Division of Biometrics II (HFD-715)

**Statistical Reviewer:** Cynthia Liu, MA

**Concurring Reviewer(s):** Todd Sahlroot, Ph.D., Statistical Team Leader and Deputy Director of Biometrics II

**Medical Division:** Division of Metabolic and Endocrine Products (HFD-510)

**Clinical Team:** Robert Misbin, M.D., Medical Reviewer  
Hylton Joffe, M.D., Medical Team Leader

**Project Manager:** Rachel Hartford

**Keywords:** NDA review, clinical study

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## 1. EXECUTIVE SUMMARY

### 1.1 Conclusions and Recommendations

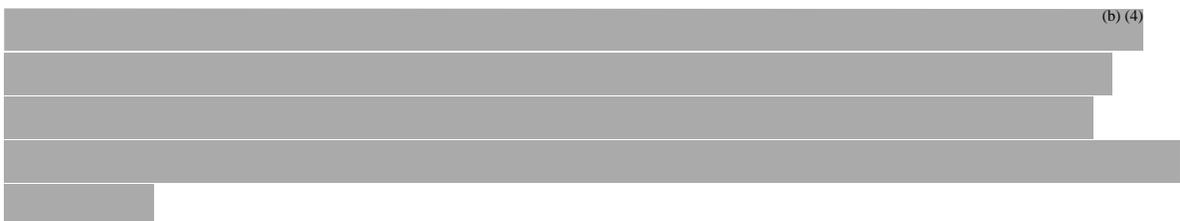
During 5 years of Lantus or NPH treatment in type 2 diabetic patients in a single open-label study, the percentages of subjects with a 3-step or greater progression in diabetic retinopathy on the ETDRS (Early Treatment Diabetic Retinopathy Study) scale over time were similar between the 2 study groups, with the Lantus group showing slightly higher progression rates in the middle of the study, but lower towards the end of the study.

At the end of the 5-year treatment period, the Lantus group had a slightly greater percentage of ITT subjects with  $\geq 1$  step change in ETDRS retinopathy score from baseline (47% vs. 44%), but a smaller percentage of subjects with  $\geq 3$  steps increase from baseline (11% vs. 14%), when compared with the NPH group.

When subjects with certain post-baseline eye procedures (i.e., pan-retinal photocoagulation for proliferative or severe nonproliferative diabetic retinopathy, local photocoagulation for new vessels, and vitrectomy for diabetic retinopathy) were also included as a 3-step progressor regardless of their changed scores from baseline, the observed percentage of ITT subjects with a 3-step or greater progression in diabetic retinopathy on the ETDRS scale (the primary endpoint) was still smaller in the Lantus group (12.5%) than in the NPH group (14.6%). The observed treatment difference (Lantus minus NPH) was -2.1% and the upper bound of the associated 95% confidence interval was 2.1%, meaning that the observed difference was consistent with 2.1% more Lantus patients with at least 3 steps progression in the ETDRS retinopathy score compared to NPH. If the sponsor's non-inferiority margin (10%) was applied, then non-inferiority of Lantus to NPH can be declared since 2.1% was less than 10%. Since the rationale of acquiring the sponsor's margin was somewhat unconventional and this reviewer could not judge the validity of this margin, whether 2.1% is clinically insignificant or not is up to the medical reviewer's discretion.

Nevertheless, Lantus was not superior to NPH in reducing the progression rate since the upper bound of the 95% confidence interval for the risk difference (Lantus minus NPH) was  $> 0\%$ .

(b) (4)

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## 1.2 Brief Overview of Clinical Studies

Sanofi-Aventis, U.S., LLC has submitted results from 1 clinical trial as a labeling supplement to NDA 21-081, to satisfy a Phase 4 post marketing study commitment for LANTUS<sup>®</sup> (insulin glargine [rDNA origin] injection), which was approved on April 20, 2000 for once-daily subcutaneous administration in the treatment of adult and pediatric patients with type 1 diabetes mellitus or adult patients with type 2 diabetes mellitus who require basal (long-acting) insulin for the control of hyperglycemia.

Study HOE901/4016 (06/18/2001 – 04/27/2007) was designed as a 5-year, open-label, NPH human insulin-controlled, stratified, randomized (1:1), parallel-group, multicenter (55), multinational (in USA and Canada), long-term safety trial, conducted in subjects aged between 29 to 74 years with type 2 diabetes mellitus. The primary objective was to compare the percentage of subjects with a 3-step or greater progression in the Early Treatment Diabetic Retinopathy Study (ETDRS) scale at study endpoint after treatment with insulin glargine (Lantus) or neural protamine hagedorn (NPH) human insulin. According to the SAP Amendment No. 1 (issued on 05/15/2007), in case a subject had any of the following eye procedures post baseline, he/she would also be treated as a 3-step progressor, even though the actual change from baseline value was less than 3.

- Pan-retinal photocoagulation for proliferative or severe nonproliferative diabetic retinopathy
- Local photocoagulation for new vessels
- Vitrectomy for diabetic retinopathy

Grading diabetic retinopathy was performed by the University of Wisconsin fundus photograph reading center blinded to treatment group, and was a multi-step process. The detailed algorithm regarding how the final ETDRS scores were obtained was described in the sponsor's SAP, Appendix III.

In general, the demographic and baseline characteristics were similar between the 2 study groups. There were slightly more males (54%) than females (46%) in this study. Approximately 85% of the patients were White and 16% were geriatrics ( $\geq 65$  years old). The overall mean BMI at entry was 34 kg/m<sup>2</sup>, ranging from 17 to 65 kg/m<sup>2</sup>, which reflected the general obesity for the type 2 diabetic population. Approximately 16% of the subjects in the Lantus group and 12% in the NPH group reported diabetic retinopathy at baseline. All subjects had been previously treated for their diabetes with either oral agent(s) and/or insulin. On the day of randomization, the use of oral antidiabetic drugs (OAD) was about 50% of the patients in each group.

### 1.3 Statistical Issues and Findings

In general, there were no serious statistical issues noted by this reviewer. My analysis results were similar to the sponsor's.

After 5 years of treatment, the observed percentage of ITT subjects with a 3-step or greater progression in diabetic retinopathy on the ETDRS scale (the primary efficacy endpoint) was smaller in the Lantus group (12.5%) than in the NPH group (14.6%). As shown in Text Table 1, the non-inferiority of Lantus to NPH was established since the upper bound (2.1%) of the 95% confidence intervals of the treatment difference was < 10% (the non-inferiority margin defined by the sponsor). However, Lantus was not superior to NPH in reducing the progression rate since the upper bound of the 95% C.I. was > 0%. Similar findings based on the PP population or completers were also observed. In addition, this reviewer also analyzed the data from the ITT population using a simpler statistical model (two-sample t-test on proportions) and found similar results (treatment difference  $\pm$  SE = -2.0%  $\pm$  2.2%, 95% C.I. = (-6.3%, **2.2%**)).

Text Table 1 – Number (%) of Subjects with a 3-step or Greater Progression in ETDRS

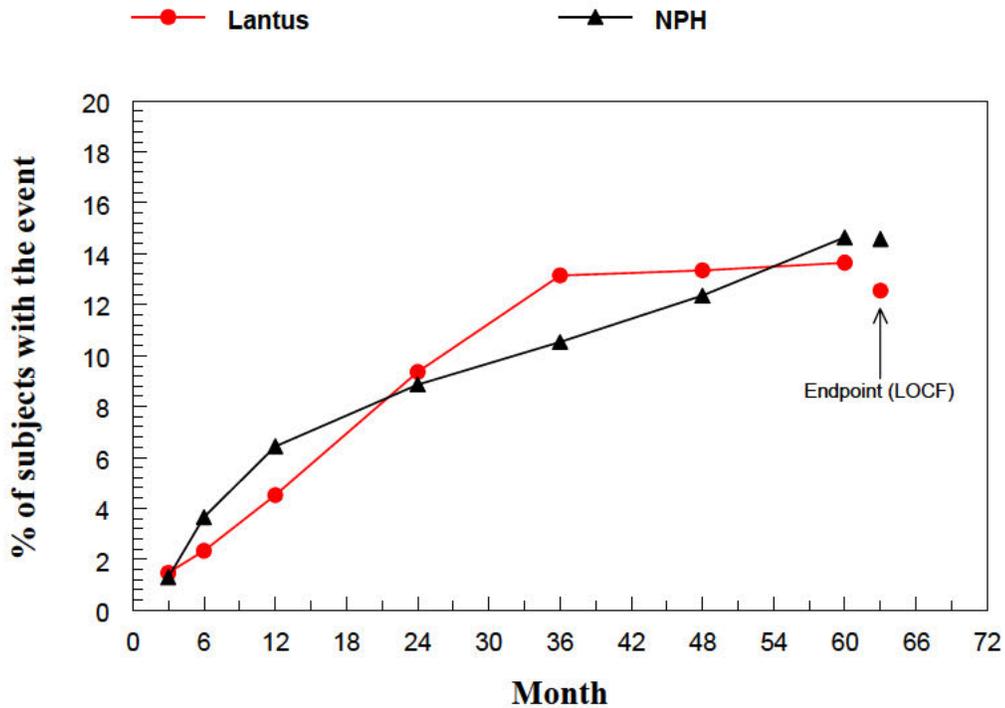
	Lantus	NPH	Treatment Difference $\pm$ SE	p-value	95% C.I.
Endpoint (ITT, LOCF)	63/502 (12.5%)	71/487 (14.6%)	-2.1% $\pm$ 2.1%	0.33	(-6.3%, <b>2.1%</b> )
Endpoint (PP)	53/374 (14.2%)	57/363 (15.7%)	-2.0% $\pm$ 2.6%	0.44	(-7.0%, <b>3.1%</b> )
Endpoint (Completers)	52/374 (13.9%)	54/364 (14.8%)	-1.2% $\pm$ 2.5%	0.62	(-6.2%, <b>3.7%</b> )

The primary efficacy endpoint was analyzed using a generalized linear model (SAS GENMOD) with treatment and baseline HbA1c strata ( $\leq$  9% or > 9 %) as the classified independent variables, and with binomial distribution and identity link function – the sponsor's model.

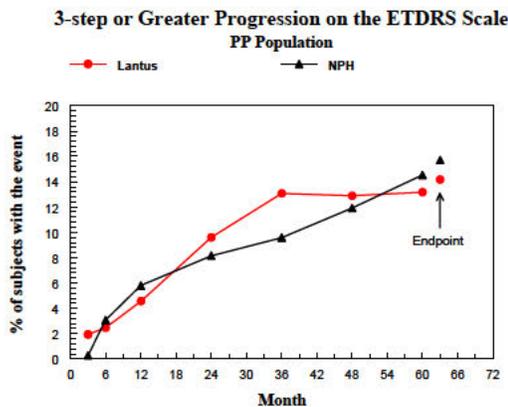
As depicted in Text Figures 1 (ITT), 2 (PP), and 3 (completers), the percentages of subjects with a 3-step or greater progressed ETDRS score over time were similar between the 2 study groups. Note that the progression rates during the middle of the study in the Lantus group were numerically higher than those in the NPH group, but they were sustained throughout the rest of the study while an increasing trend was still observed in the NPH group.

Text Figure 1 – Progression Rate over Time – ITT Population

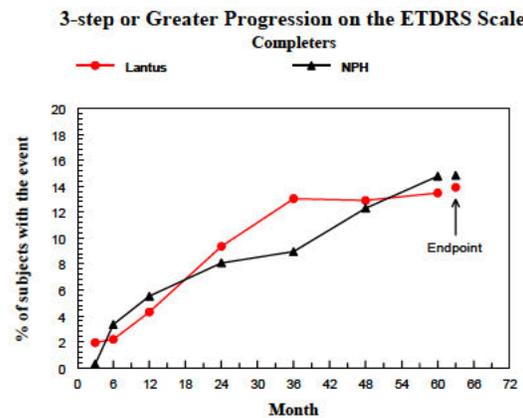
### 3-step or Greater Progression on the ETDRS Scale ITT Population



Text Figure 2  
Progression Rate over Time – PP Population



Text Figure 3  
Progression Rate over Time – Completers



As shown in Text Table 2, slightly more than half of the ITT population in each group had an improved (change  $\leq -1$ ) or no change ETDRS severity score in diabetic retinopathy after 5 years of treatment. Specifically, approximately 47% of the ITT subjects in the Lantus group

and 44% in the NPH group had at least 1 step ( $\geq 1$ ) of progression in diabetic retinopathy. There were more Lantus-treated subjects with 1 or 2 steps increase in score, but fewer with 3 or  $\geq 4$  steps increase, when compared with the respective categories of NPH-treated subjects. The Cochran-Mantel-Haenszel test stratified by baseline HbA1c strata and pooled centers did not show any difference in distribution of changes between the 2 study groups ( $p = 0.67$ ).

Text Table 2 – Distribution of Changes from Baseline in ETDRS Score at Endpoint – ITT (LOCF) Population

Change	-4	-3	-2	-1	0	1	2	3	$\geq 4$	Total
Lantus	1 (0.2%)	6 (1.2%)	14 (2.8%)	62 (12.4%)	184 (36.7%)	118 (23.5%)	61 (12.2%)	28 (5.6%)	28 (5.6%)	502
NPH	2 (0.4%)	5 (1.0%)	11 (2.3%)	64 (13.1%)	191 (39.2%)	93 (19.1%)	53 (10.9%)	35 (7.2%)	33 (6.8%)	487

Note that the combined number of subjects with a change = 3 or  $\geq 4$  in either group here is less than the number of subjects with a 3-step or greater progression shown in Text Table 1 above, which included subjects with certain eye procedures as specified in the SAP Amendment No. 1.

The mean ETDRS severity score at baseline and endpoint were both slightly higher in the Lantus group than in the NPH group. However, the mean changes from baseline in the 2 study groups after 5 years of treatment were almost identical, as shown in Text Table 3.

Text Table 3 – Summary Results for ETDRS Severity Scores at Endpoint – ITT (LOCF) Population

	Raw Mean $\pm$ SD (N)		
	Lantus	NPH	Total
Baseline	3.0 $\pm$ 2.1 (513) Median = 2 Range: 1 – 12	2.8 $\pm$ 2.0 (504) Median = 2 Range: 1 – 9	2.9 $\pm$ 2.1 (1017) Median = 2 Range: 1 – 12
Endpoint	3.7 $\pm$ 2.8 (502) Median = 3 Range: 1 – 17	3.6 $\pm$ 2.7 (487) Median = 3 Range: 1 – 16	3.7 $\pm$ 2.8 (989) Median = 3 Range: 1 – 17
Change from Baseline	0.7 $\pm$ 1.8 (502) Median = 0 Range: -4 – 14	0.8 $\pm$ 1.8 (487) Median = 0 Range: -4 – 12	0.8 $\pm$ 1.8 (989) Median = 0 Range: -4 – 14
<b>Least-squares mean <math>\pm</math> standard error (N) using the sponsor’s model</b>			
Change from Baseline	0.87 $\pm$ 0.09 (502)	0.90 $\pm$ 0.09 (487)	Treatment Diff = -0.03 p-value = 0.76 95% C.I. = (-0.26, 0.19)

The sponsor’s ANCOVA model included treatment, baseline HbA1c strata, pooled centers as factors and baseline ETDRS score as the covariate.

Treatment effects on % of subjects with a 3-step or greater progression in diabetic retinopathy on the ETDRS scale at endpoint were consistent across the subgroups defined by age (< 65 years or  $\geq$  65 years), gender, race (White, Black, or others), baseline HbA1c ( $\leq$  9% or > 9%), country (USA or Canada), and baseline diabetic retinopathy (yes or no), as no significant treatment-by-subgroup interactions were observed (all  $p > 0.10$ ). However, there was a nominally significant interaction effect seen across the subgroups defined by BMI at baseline ( $\leq$  29, between 29 and 38.6, or > 38.6 kg/m<sup>2</sup>) (treatment-by-subgroup interaction  $p = 0.0612$ , Text Table 4). The cutoff points for BMI were chosen arbitrarily by this reviewer for the purpose of subgroup analysis and they represented the 25<sup>th</sup> and 75<sup>th</sup> percentiles of the data, respectively.

Text Table 4 – Number (%) of Subjects with a 3-step or Greater Progression in ETDRS by BMI at Baseline

ITT (LOCF) Population	BMI $\leq$ 29 kg/m <sup>2</sup>	29 < BMI $\leq$ 38.6 kg/m <sup>2</sup>	BMI > 38.6 kg/m <sup>2</sup>
Lantus	11/119 (9.2%)	35/246 (14.2%)	17/133 (12.8%)
NPH	26/129 (20.2%)	30/245 (12.2%)	15/112 (13.4%)

## 2. INTRODUCTION

### 2.1 Overview

LANTUS<sup>®</sup> (insulin glargine [rDNA origin] injection) was approved on April 20, 2000 for once-daily subcutaneous administration in the treatment of adult and pediatric patients with type 1 diabetes mellitus or adult patients with type 2 diabetes mellitus who require basal (long-acting) insulin for the control of hyperglycemia. This submission is to present the results from 1 long-term safety study for satisfying a Phase 4 post marketing commitment and to seek for labeling changes to include the results of the study to the clinical section of the prescribing information.

The following paragraph, copied from the sponsor's report, states the background information regarding why the Phase 4 post marketing study was conducted.



According to the sponsor, the Phase 4 study (HOE901/4016, 06/18/2001 – 04/27/2007) was designed to overcome the deficiencies of the previous insulin glargine studies in the evaluation of eye diseases, i.e., short treatment duration and low expected event rates. The primary objective of the study was to compare the percentage of type 2 diabetic subjects with a 3-step or greater progression of retinopathy on the ETDRS scale using fundus photography after treatment with insulin glargine (Lantus) or neural protamine hagedorn (NPH) human insulin for 5 years.

## 2.2 Data Sources

The clinical study report and electronic data files are located in the sub-folders of EDR [\\FDSWA150\NONECTD\N21081\S\\_034\2007-12-21](\\FDSWA150\NONECTD\N21081\S_034\2007-12-21).

## 3. STATISTICAL EVALUATION

### 3.1 Evaluation of Efficacy

#### 3.1.1 Study Design and Endpoints

Study HOE901/4016 was a randomized, open-label, NPH human insulin-controlled, parallel-group, multicenter, multinational (in USA and Canada), long-term safety trial, to evaluate diabetic retinopathy progression in subjects with type 2 diabetes mellitus. The study consisted of a 1- to 6-week screening phase and a 5-year (60-month) treatment phase. Prior to study entry, subjects with either no or mild retinopathy were to be on their stable dose(s) of oral agent(s) and/or insulin for at least 3 months. Subjects were stratified by center and baseline HbA1c level ( $6.0\% \leq \text{HbA1c} \leq 9.0\%$  or  $9.0\% < \text{HbA1c} \leq 12.0\%$ ), and then were randomized in a 1:1 ratio to receive either insulin glargine (Lantus) or NPH human insulin as basal insulin.

Efficacy measurements included binary indicators for the progression of diabetic retinopathy on the ETDRS (early treatment diabetic retinopathy study) scale, CSME (clinically significant macular edema) score, and RTDDCIO (retinopathy thickening in disk diameters, center/inner/outer) score, HbA1c and FPG levels, body weight, insulin dose, and episodes of symptomatic hypoglycemia, clinically important hypoglycemia, nocturnal hypoglycemia, and severe hypoglycemia. Grading diabetic retinopathy was performed by the University of Wisconsin fundus photograph reading center blinded to treatment group, and was a multi-step process. The detailed algorithm regarding how the final ETDRS scores were obtained was described in the sponsor's SAP, Appendix III.

The primary efficacy variable was the binary indicator (Yes/No) whether a subject had a 3-step or greater progression in diabetic retinopathy on the ETDRS scale from baseline to study endpoint. According to the SAP Amendment No. 1 (issued on 05/15/2007), in case a subject had any of the following eye procedures post baseline, he/she would also be treated as a 3-step progressor, even though the actual change from baseline value was less than 3.

- Pan-retinal photocoagulation for proliferative or severe nonproliferative diabetic retinopathy
- Local photocoagulation for new vessels
- Vitrectomy for diabetic retinopathy

The study was conducted at 55 centers, where 39 of them were in USA and 16 in Canada.

### 3.1.2 Statistical Methods

The primary efficacy endpoint, percentage of subjects with a 3-step or greater progression in the ETDRS retinopathy scale from baseline to Year 5, was analyzed using a generalized linear model (SAS GENMOD) with treatment and baseline HbA1c strata as the classified independent variables, and with binomial distribution and identity link function (the sponsor's model). (b) (4)

The non-inferiority of Lantus to NPH was determined if the upper bound of the 95% confidence interval of the treatment difference (Lantus – NPH) was  $\leq 10\%$ . According to the sponsor's closed testing procedure, the non-inferiority of Lantus to NPH was first evaluated on a per-protocol (PP) population (the primary analysis population) and if it was established, the non-inferiority ( $\leq 10\%$ ) and superiority ( $< 0\%$ ) of Lantus over NPH based on an intention-to-treat (ITT) population were then performed. Note that in this review report, results based on the ITT population were used as the primary findings for drawing conclusions.

As stated in the sponsor's SAP, the 10% non-inferiority margin was obtained by assuming that the 5-year background event rate for at least a 3-step progression in diabetic retinopathy on the ETDRS scale was 20% and up to a 50% increase in the relative risk between NPH and insulin glargine was deemed not clinically meaningful. The 20% background rate was consistent with the results from the Diabetes Control and Complications Trial (DCCT), in which 5-year rates for at least a 3-step progression in diabetic retinopathy on the ETDRS scale in the conventional treatment group were about 20% for both the primary (no retinopathy) and the secondary (mostly 20/<20 and 20/20, i.e., microaneurysms only) cohorts. The SAP further stated that the appropriateness of using 10% as the non-inferiority margin would be conditional on the magnitude of the observed 3-step or greater progression rate in the PP population from the NPH group after the database lock. When the 90% confidence interval (CI) of the observed 5-year rate from the NPH group in the PP population excluded 20%, it may not be appropriate to use the 10% as the non-inferiority margin. Specifically, in case the observed 5-year rate in the NPH group was  $> 20\%$  and the 90% CI excluded 20%, according to the protocol, half of the observed NPH rate at 5-year may be used as the non-inferiority margin. However, if the observed 5-year rate in the NPH group was  $< 20\%$  and half of the observed rate was used as the margin, the power of demonstrating non-inferiority of Lantus to NPH may not be adequate. The rationale of how the non-inferiority margin was (or would be) determined was somewhat unconventional. Therefore, this reviewer could not judge the validity of the sponsor's margin. As a consequence,

whether Lantus was non-inferior to NPH or not may solely rely on the medical reviewer's interpretation of the final analysis results.

Since only the results from the primary efficacy endpoint were added to the labeling, this review report focused mainly on the variables related to the ETDRS score. If the on-treatment endpoint measurements for ETDRS were missing (or not valid), the end-of-5-year ETDRS data after treatment discontinuation were used in the ITT analysis. If both the on-treatment endpoint and off-treatment data were missing, the last available data were used as the endpoint.

### **3.1.3 Subject Disposition**

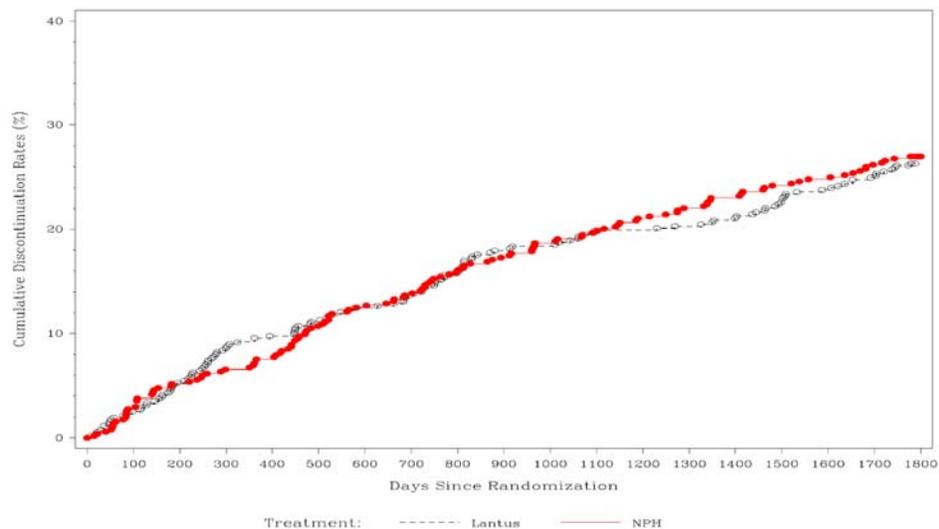
A total of 1024 subjects were randomized in the study, but 7 of them were not exposed to treatment. Among the 1017 randomized and exposed subjects, 513 of them were in the Lantus group and 504 in the NPH group. The overall withdrawal rate after 5 years of treatment was approximately 28%, which was considered a fairly low dropout rate by this reviewer. The reasons for withdrawals were similar between the 2 study groups (Table 1, copied from the sponsor's report), with subject's request and loss to follow-up being the 2 most common recorded reasons in each group. Figure 1 below (copied from the sponsor's report) also depicts that the cumulative discontinuation rates in each group were in a linear fashion over time and the 2 study groups did not differ significantly in these rates at any time points as well as overall.

Table 1 – Subject Disposition for All Randomized Subjects

	LANTUS (N=515)	NPH (N=509)
Randomized	515 (100%)	509 (100%)
Randomized but not treated	2 (0.4%)	5 (1.0%)
Reasons for withdrawal prior to treatment		
at the discretion of the Investigator	0	1 (0.2%)
the subject did not wish to continue in the study	2 (0.4%)	3 (0.6%)
the subject no longer meets the criteria to remain in the study	0	1 (0.2%)
Randomized and treated	513 (99.6%)	504 (99.0%)
Completed study	374 (72.6%)	364 (71.5%)
Premature Withdrawal	139 (27.0%)	140 (27.5%)
Reasons for Premature Withdrawal		
the subject no longer meets the criteria to remain in the study	7 (1.4%)	2 (0.4%)
new adverse event or worsening of an existing adverse event	17 (3.3%)	12 (2.4%)
lack of efficacy	4 (0.8%)	2 (0.4%)
poor compliance with treatment	6 (1.2%)	7 (1.4%)
the subject did not wish to continue in the study	40 (7.8%)	51 (10.0%)
the subject is lost to follow up	28 (5.4%)	35 (6.9%)
administrative reasons	5 (1.0%)	4 (0.8%)
protocol violation	1 (0.2%)	0
the subject died	11 (2.1%)	11 (2.2%)
at the discretion of the Investigator	7 (1.4%)	6 (1.2%)
hypoglycemia	1 (0.2%)	1 (0.2%)
other reason	12 (2.3%)	9 (1.8%)

Note: % calculated using the number of randomized population as denominator.  
 Category adverse event includes all AEs, TEAE or not

Figure 1 – Cumulative Discontinuation Rate over Time – ITT Population



The ITT population comprised all the randomized and exposed subjects (513 and 504 in the Lantus and NPH groups, respectively). The PP population comprised 374 Lantus-treated and 363 NPH-treated subjects, which excluded patients with major protocol violations, no evaluable fundus photographs taken at least 1645 days (i.e., 4.5 years) after the start of study medication, and/or no 3-step or greater progression of retinopathy at study endpoint (see more detailed definition in the sponsor's SAP). Table 2 below (copied from the sponsor's report) summarizes the number of subjects with major protocol violations that led to the exclusion from the PP population.

Table 2 – Number (%) of Subjects with Major Protocol Violations in the ITT Population

Treatment group/major protocol violation	LANTUS	NPH
Any deviation	139 (27.1%)	141 (28.0%)
Subject does not have an evaluable set of fundus photographs taken after the start of study medication and no later than 30 days after the date of last dose of study medication.	16 (3.1%)	21 (4.2%)
Subject does not remain on the assigned medication for at least 1461 days, cumulatively, unless he/she experiences a 3-step or baseline at the time of early termination.	118 (23.0%)	119 (23.6%)
Subject does not have evaluable fundus photographs taken at least 1645 days after the start medication, unless he/she experiences a 3-step or greater progression over baseline at the time of early termination.	131 (25.5%)	136 (27.0%)
Subject drops out of study earlier than 1645 days unless he/she experiences a 3-step or greater progression over baseline at the time of early termination.	122 (23.8%)	120 (23.8%)

Note: % calculated using the number of ITT population as denominator

### 3.1.4 Demographic and Baseline Characteristics

As shown in Table 3 (copied from the sponsor's report), the demographic and baseline characteristics were similar between the 2 study groups. The overall mean age at entry was 55 years (ranging from 29 to 74 years) and most of the patients (84%) were < 65 years old. There were slightly more males (54%) than females (46%) in the study. Approximately 85% of the patients were White. The overall mean BMI at entry was 34 kg/m<sup>2</sup>, ranging from 17 to 65 kg/m<sup>2</sup>, which reflected the general obesity for the type 2 diabetic population.

The mean ETDRS score, HbA1c and FPG values, and % of subjects reporting diabetic retinopathy at baseline were all slightly greater in the Lantus group than in the NPH group. However, the differences were not statistically significant (all nominal p > 0.05).

Table 3 – Demographic and Baseline Characteristics of ITT Subjects

	<b>LANTUS (N=513)</b>	<b>NPH (N=504)</b>	<b>All (N=1017)</b>
<b>Age (years)</b>			
Number	513	504	1017
Mean (SD)	54.9 (8.8)	55.3 (8.5)	55.1 (8.6)
Median	55.0	56.0	56.0
Min : Max	33 : 74	29 : 72	29 : 74
<65	429 (83.6%)	427 (84.7%)	856 (84.2%)
[65 - 75]	84 (16.4%)	77 (15.3%)	161 (15.8%)
<b>Gender n(%)</b>			
Number	513	504	1017
Male	278 (54.2%)	270 (53.6%)	548 (53.9%)
Female	235 (45.8%)	234 (46.4%)	469 (46.1%)
<b>Race n(%)</b>			
Number	513	504	1017
Asian/Oriental	9 (1.8%)	12 (2.4%)	21 (2.1%)
Black	49 (9.6%)	62 (12.3%)	111 (10.9%)
Multiracial	9 (1.8%)	8 (1.6%)	17 (1.7%)
White	446 (86.9%)	422 (83.7%)	868 (85.3%)
<b>Hispanic ethnicity n(%)</b>			
Hispanic	37 (7.2%)	28 (5.6%)	65 (6.4%)
<b>Weight (kg)</b>			
Number	512	504	1016
Mean (SD)	100.17 (22.71)	98.67 (22.26)	99.43 (22.49)
Median	97.10	97.05	97.10
Min : Max	49.5 : 183.3	48.5 : 180.1	48.5 : 183.3
<b>Height (cm)</b>			
Number	510	504	1014
Mean (SD)	170.12 (10.10)	170.07 (10.27)	170.09 (10.18)
Median	170.20	170.00	170.20
Min : Max	137.2 : 198.1	127.0 : 200.7	127.0 : 200.7
<b>BMI (kg/m<sup>2</sup>)</b>			
Number	508	503	1011
Mean (SD)	34.48 (7.24)	34.07 (7.19)	34.27 (7.22)
Median	33.50	33.40	33.50
Min : Max	20.8 : 65.4	16.9 : 63.3	16.9 : 65.4

Table 3 – Demographic and Baseline Characteristics of ITT Subjects (Continued)

	LANTUS	NPH	All
<b>Baseline ETDRS Score – PP Population</b>			
Number	374	363	737
Mean (SD)	3.06 (2.17)	2.85 (2.03)	2.96 (2.10)
Median	2.00	2.00	2.00
Min : Max	1.0 : 12.0	1.0 : 9.0	1.0 : 12.0
<b>Baseline ETDRS Score – ITT Population</b>			
Number	513	504	1017
Mean (SD)	2.97 (2.15)	2.85 (2.02)	2.91 (2.09)
Median	2.00	2.00	2.00
Min : Max	1.0 : 12.0	1.0 : 9.0	1.0 : 12.0
<b>Diabetic Retinopathy, n (%)</b>			
Number	513	504	1017
Yes	80 (15.6%)	61 (12.1%)	141 (13.9%)
No	433 (84.4%)	443 (87.9%)	876 (86.1%)
<b>HbA1c (%)</b>			
Number	512	504	1016
Mean (SD)	8.41 (1.38)	8.31 (1.38)	8.36 (1.38)
Median	8.20	8.10	8.10
Min : Max	5.7 : 12.6	5.8 : 13.5	5.7 : 13.5
<b>Lab determined FPG (mmol/L)</b>			
Number	512	504	1016
Mean (SD)	189.66 (65.97)	179.63 (61.14)	184.69 (63.79)
Median	179.60	169.65	175.55
Min : Max	73.0 : 492.3	59.3 : 389.8	59.3 : 492.3

The overall mean age at onset of type 2 diabetes in this study was 45 years and half of the study patients had more than 10 years of the disease prior to entry, as shown in Table 4 (copied from the sponsor’s table). All patients had been previously treated for their diabetes with either oral agent(s) and/or insulin. In addition, on the day of randomization, the use of oral antidiabetic drugs (OAD) was about 50% of the patients in each group.

Table 4 – Diabetic History Prior to Study Entry for the ITT Subjects

	LANTUS (N=513)	NPH (N=504)	All (N=1017)
Duration of diabetes (years)			
Number	513	504	1017
Mean (SD)	10.71 (6.87)	10.78 (6.74)	10.75 (6.81)
Median	10.00	10.00	10.00
Min : Max	1.0 : 38.0	1.0 : 51.0	1.0 : 51.0
[0,5)	89 (17.3%)	78 (15.5%)	167 (16.4%)
[5,10)	165 (32.2%)	163 (32.3%)	328 (32.3%)
[10,20)	199 (38.8%)	220 (43.7%)	419 (41.2%)
>=20	60 (11.7%)	43 (8.5%)	103 (10.1%)
Age at onset of diabetes (years)			
Number	513	504	1017
Mean (SD)	44.7 (9.2)	45.0 (9.0)	44.9 (9.1)
Median	44.0	45.0	45.0
Min : Max	20 : 67	11 : 68	11 : 68
Previous Antidiabetic treatment n(%)			
Yes	513 (100%)	504 (100%)	1017 (100%)

### 3.1.5 Efficacy Results and Discussion

After 5 years of treatment, the observed percentage of ITT subjects with a 3-step or greater progression in diabetic retinopathy on the ETDRS scale was smaller in the Lantus group (12.5%) than in the NPH group (14.6%). As shown in Table 5, the non-inferiority of Lantus to NPH was established since the upper bound (2.1%) of the 95% confidence intervals of the treatment difference was < 10% (the non-inferiority margin defined by the sponsor).

However, Lantus was not superior to NPH in reducing the progression rate since the upper bound of the 95% C.I. was > 0%. Similar findings based on the PP population or completers were also observed. In addition, this reviewer also analyzed the data from the ITT population using a simpler statistical model (two-sample t-test on proportions) and found similar results (treatment difference  $\pm$  SE = -2.0%  $\pm$  2.2%, 95% C.I. = (-6.3%, **2.2%**)).

Table 5 – Number (%) of Subjects with a 3-step or Greater Progression in ETDRS

	Lantus	NPH	Treatment Difference ± SE	p-value	95% C.I.
Endpoint (ITT, LOCF)	63/502 (12.5%)	71/487 (14.6%)	-2.1% ± 2.1%	0.33	(-6.3%, 2.1%)
Endpoint (PP)	53/374 (14.2%)	57/363 (15.7%)	-2.0% ± 2.6%	0.44	(-7.0%, 3.1%)
Endpoint (Completers)	52/374 (13.9%)	54/364 (14.8%)	-1.2% ± 2.5%	0.62	(-6.2%, 3.7%)

The primary efficacy endpoint was analyzed using a generalized linear model (SAS GENMOD) with treatment and baseline HbA1c strata ( $\leq 9\%$  or  $> 9\%$ ) as the classified independent variables, and with binomial distribution and identity link function – the sponsor’s model.

As depicted in Figures 2 (ITT), 3 (PP), and 4 (completers), the percentages of subjects with a 3-step or greater progressed ETDRS score over time were similar between the 2 study groups. Note that the progression rates during the middle of the study in the Lantus group were numerically higher than those in the NPH group, but they were sustained throughout the rest of the study while an increasing trend was still observed in the NPH group.

Figure 2 – Progression Rate over Time – ITT Population

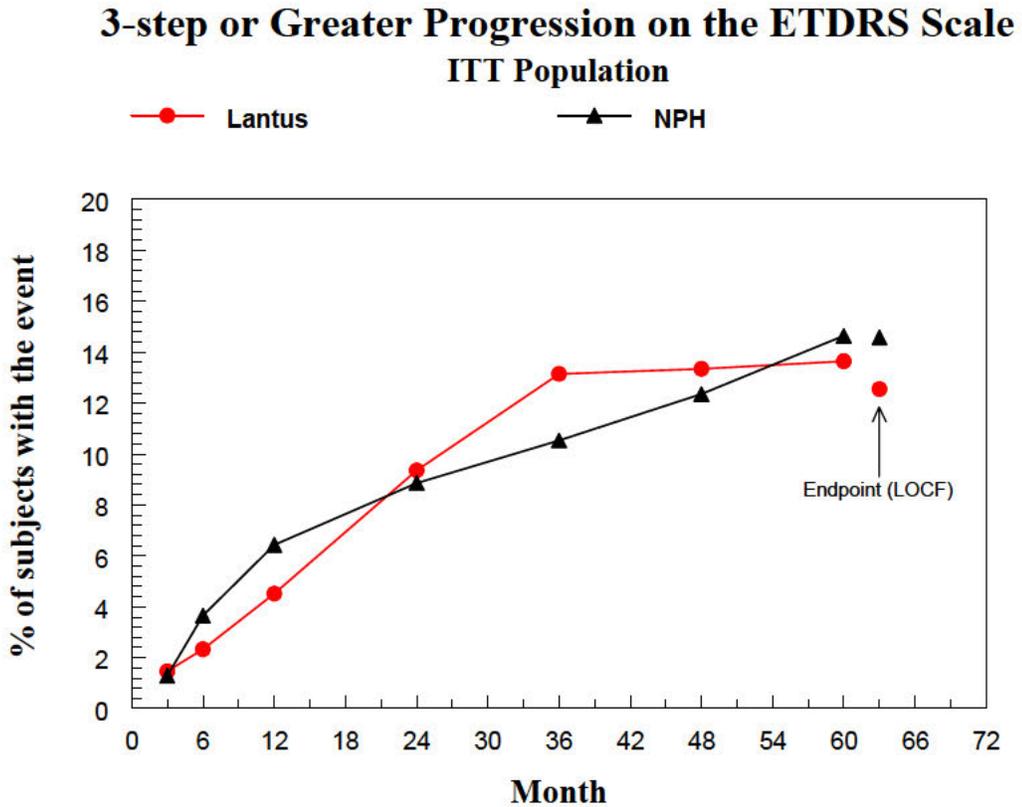


Figure 3  
Progression Rate over Time – PP Population

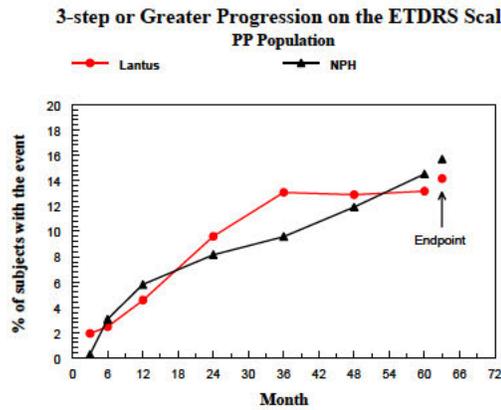
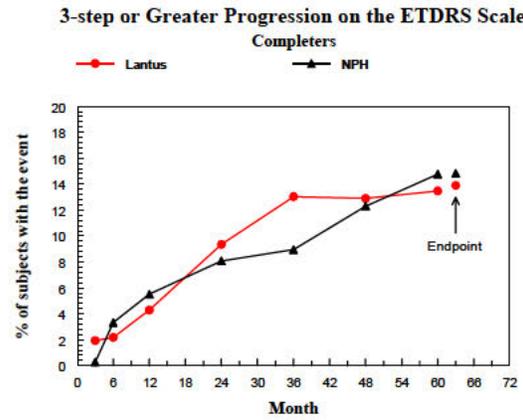


Figure 4  
Progression Rate over Time – Completers



As shown in Table 6, slightly more than half of the ITT population in each group had an improved (change  $\leq -1$ ) or no change ETDRS severity score in diabetic retinopathy after 5 years of treatment. Specifically, approximately 47% of the ITT subjects in the Lantus group and 44% in the NPH group had at least 1 step ( $\geq 1$ ) of progression in diabetic retinopathy. There were more Lantus-treated subjects with 1 or 2 steps increase in score, but fewer with 3 or  $\geq 4$  steps increase, when compared with the respective categories of NPH-treated subjects. The Cochran-Mantel-Haenszel test stratified by baseline HbA1c strata and pooled centers did not show any difference in distribution of changes between the 2 study groups ( $p = 0.67$ ).

Table 6 – Distribution of Changes from Baseline in ETDRS Score at Endpoint – ITT (LOCF) Population

Change	-4	-3	-2	-1	0	1	2	3	$\geq 4$	Total
Lantus	1 (0.2%)	6 (1.2%)	14 (2.8%)	62 (12.4%)	184 (36.7%)	118 (23.5%)	61 (12.2%)	28 (5.6%)	28 (5.6%)	502
NPH	2 (0.4%)	5 (1.0%)	11 (2.3%)	64 (13.1%)	191 (39.2%)	93 (19.1%)	53 (10.9%)	35 (7.2%)	33 (6.8%)	487

Note that the combined number of subjects with a change = 3 or  $\geq 4$  in either group here is less than the number of subjects with a 3-step or greater progression shown in Table 5 above, which included subjects with certain eye procedures as specified in the SAP Amendment No. 1.

The mean ETDRS severity score at baseline and endpoint were both slightly higher in the Lantus group than in the NPH group. However, the mean changes from baseline in the 2 study groups after 5 years of treatment were almost identical, as shown in Table 7.

Table 7 – Summary Results for ETDRS Severity Scores at Endpoint – ITT (LOCF) Population

	Raw Mean ± SD (N)		
	Lantus	NPH	Total
Baseline	3.0 ± 2.1 (513) Median = 2 Range: 1 – 12	2.8 ± 2.0 (504) Median = 2 Range: 1 – 9	2.9 ± 2.1 (1017) Median = 2 Range: 1 – 12
Endpoint	3.7 ± 2.8 (502) Median = 3 Range: 1 – 17	3.6 ± 2.7 (487) Median = 3 Range: 1 – 16	3.7 ± 2.8 (989) Median = 3 Range: 1 – 17
Change from Baseline	0.7 ± 1.8 (502) Median = 0 Range: -4 – 14	0.8 ± 1.8 (487) Median = 0 Range: -4 – 12	0.8 ± 1.8 (989) Median = 0 Range: -4 – 14
<b>Least-squares mean ± standard error (N) using the sponsor's model</b>			
Change from Baseline	0.87 ± 0.09 (502)	0.90 ± 0.09 (487)	Treatment Diff = -0.03 p-value = 0.76 95% C.I. = (-0.26, 0.19)

The sponsor's ANCOVA model included treatment, baseline HbA1c strata, pooled centers as factors and baseline ETDRS score as the covariate.

### 3.2 Evaluation of Safety

In consultation with the reviewing medical officer, there were no additional aspects of safety that required review by a statistician. See Dr. Robert Misbin's report for safety evaluation.

## 4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

### 4.1 Gender, Race, and Age

Treatment effects on % of subjects with a 3-step or greater progression in diabetic retinopathy on the ETDRS scale at endpoint were consistent across the subgroups defined by age (< 65 years or ≥ 65 years), gender, and race (White, Black, or others), as no significant treatment-by-subgroup interactions were observed (all  $p > 0.10$ ).

### 4.2 Other Special/Subgroup Populations

Treatment effects on % of subjects with a 3-step or greater progression in diabetic retinopathy on the ETDRS scale at endpoint were consistent across the subgroups defined by baseline HbA1c ( $\leq 9\%$  or  $> 9\%$ ), country (USA or Canada), and baseline diabetic retinopathy (yes or no), as no significant treatment-by-subgroup interactions were observed (all  $p > 0.10$ ). However, there were inconsistent effects seen across the subgroups defined by BMI at baseline ( $\leq 29$ , between 29 and 38.6, or  $> 38.6$  kg/m<sup>2</sup>) (treatment-by-subgroup interaction  $p = 0.0612$ , Table 8). The cutoff points for BMI were chosen arbitrarily by this reviewer for the

purpose of subgroup analysis and they represented the 25<sup>th</sup> and 75<sup>th</sup> percentiles of the data, respectively.

Table 8 – Number (%) of Subjects with a 3-step or Greater Progression in ETDRS by BMI at Baseline

ITT (LOCF) Population	BMI $\leq$ 29 kg/m <sup>2</sup>	29 < BMI $\leq$ 38.6 kg/m <sup>2</sup>	BMI > 38.6 kg/m <sup>2</sup>
Lantus	11/119 (9.2%)	35/246 (14.2%)	17/133 (12.8%)
NPH	26/129 (20.2%)	30/245 (12.2%)	15/112 (13.4%)

## 5. SUMMARY AND CONCLUSIONS

### 5.1 Statistical Issues and Collective Evidence

In general, there were no serious statistical issues noted by this reviewer. My analysis results were similar to the sponsor's. Since this review only involved 1 study and 1 efficacy variable, there is no need to re-state the findings in this section.

### 5.2 Conclusions and Recommendations

During 5 years of Lantus or NPH treatment in type 2 diabetic patients in a single open-label study, the percentages of subjects with a 3-step or greater progression in diabetic retinopathy on the ETDRS scale over time were similar between the 2 study groups, with the Lantus group showing slightly higher progression rates in the middle of the study, but lower towards the end of the study.

At the end of the 5-year treatment period, the Lantus group had a slightly greater percentage of ITT subjects with  $\geq 1$  step change in ETDRS retinopathy score from baseline (47% vs. 44%), but a smaller percentage of subjects with  $\geq 3$  steps increase from baseline (11% vs. 14%), when compared with the NPH group.

When subjects with certain post-baseline eye procedures (i.e., pan-retinal photocoagulation for proliferative or severe nonproliferative diabetic retinopathy, local photocoagulation for new vessels, and vitrectomy for diabetic retinopathy) were also included as a 3-step progressor regardless of their changed scores from baseline, the observed percentage of ITT subjects with a 3-step or greater progression in diabetic retinopathy on the ETDRS scale (the primary endpoint) was still smaller in the Lantus group (12.5%) than in the NPH group (14.6%). The observed treatment difference (Lantus minus NPH) was -2.1% and the upper bound of the associated 95% confidence interval was 2.1%, meaning that the observed difference was consistent with 2.1% more Lantus patients with at least 3 steps progression in the ETDRS retinopathy score compared to NPH. If the sponsor's non-inferiority margin (10%) was applied, then non-inferiority of Lantus to NPH can be declared since 2.1% was less than 10%. Since the rationale of acquiring the sponsor's margin was somewhat

unconventional and this reviewer could not judge the validity of this margin, whether 2.1% is clinically insignificant or not is up to the medical reviewer's discretion.

Nevertheless, Lantus was not superior to NPH in reducing the progression rate since the upper bound of the 95% confidence interval for the risk difference (Lantus minus NPH) was  $> 0\%$ .

(b) (4)



Primary Statistical Reviewer: Cynthia Liu, MA

Concurring Reviewer: Todd Sahlroot, Ph.D.  
Statistical Team Leader and Deputy Director of Biometrics II

CC: HFD-510/RHartford, HJoffe, RMisbin  
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HFD-700/LPatrician

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Todd Sahlroot  
10/8/2008 03:58:32 PM  
BIOMETRICS

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

***APPLICATION NUMBER:***  
**NDA 021081/S-034**

**OTHER REVIEW(S)**

**Division of Metabolism and Endocrinology Products**  
**REGULATORY PROJECT MANAGER REVIEW**

**Application Number:** NDA 21-081/S034

**Name of Drug:** Lantus (insulin glargine [rDNA origin] injection)

**Applicant:** sanofi-aventis

**Material Reviewed:**

**Submission &  
Receipt Date**

June 9, 2009

**Document Type**

Proposed Package Insert

**Material Referenced:**

**Date Finalized**

April 25, 2007

**Author (Discipline)**

Enid Galliers  
Chief, Project Management Staff

**Document Type**

NDA 21-081/S-024 Approval Letter

March 26, 2009

Sam Skariah  
DDMAC Reviewer

Review of NDA 21-081/S-034 Package  
Insert submitted March 19, 2009

**Background and Summary**

Lantus (insulin glargine [rDNA origin] injection) NDA 21-081 was approved on April 20, 2000, for the treatment of adult and pediatric patients with type 1 diabetes mellitus or adult patients with type 2 diabetes mellitus who require basal (long-acting) insulin for the control of hyperglycemia. The approval included a Phase 4 commitment *“To compare the percentage of patients with type 2 diabetes with  $\geq$  3-step progression in the Early Treatment Diabetic Retinopathy Study scale during treatment with either once-daily Lantus or twice-daily NPH human insulin (March 14, 2000, submission)”* with a final Report submission date of April 2005.

Supplement -034 was submitted on December 21, 2007. It proposes adding the results from clinical study HOE901-4016, titled *“Evaluation of Diabetic Retinopathy Progression in Subjects with Type 2 Diabetes Mellitus Treated with Oral Agents Plus Insulin”* to the package insert and revision into the PLR format. Study HOE901-4016 was conducted from April 12, 2001 to April 17, 2007.

## Review

The Package Insert submitted on June 9, 2009, was compared to the currently approved Package Insert; approved on April 25, 2007. In addition to the PLR formatting the following changes have been made:

1. Deleted [REDACTED] (b) (4) from Figure 1 entitled, Activity Profile in Patients with Type 1 Diabetes.
2. In the CLINICAL STUDIES section the descriptor [REDACTED] (b) (4) for clinical trials was deleted.
3. In the Type 1 Diabetes – Adult section of CLINICAL STUDIES
  - a) The table entitled, Type 1 Diabetes Mellitus – Adult was changed from Table [REDACTED] (b) (4) to Table 8 below.



**Table 8: Type 1 Diabetes Mellitus–Adult**

Treatment duration Treatment in combination with	<u>Study A</u>		<u>Study B</u>		<u>Study C</u>	
	28 weeks Regular insulin		28 weeks Regular insulin		16 weeks Insulin lispro	
	<u>LANTUS</u>	<u>NPH</u>	<u>LANTUS</u>	<u>NPH</u>	<u>LANTUS</u>	<u>NPH</u>
Number of subjects treated	292	293	264	270	310	309
HbA1c						
Baseline HbA1c	8.0	8.0	7.7	7.7	7.6	7.7
Adj. mean change from baseline	+0.2	+0.1	-0.2	-0.2	-0.1	-0.1
LANTUS – NPH	+0.1		+0.1		0.0	
95% CI for Treatment difference	(0.0; +0.2)		(-0.1; +0.2)		(-0.1; +0.1)	
Basal insulin dose						
Baseline mean	21	23	29	29	28	28
Mean change from baseline	-2	0	-4	+2	-5	+1
Total insulin dose						
Baseline mean	48	52	50	51	50	50
Mean change from baseline	-1	0	0	+4	-3	0
Fasting blood glucose (mg/dL)						
Baseline mean	167	166	166	175	175	173
Adj. mean change from baseline	-21	-16	-20	-17	-29	-12
Body weight (kg)						
Baseline mean	73.2	74.8	75.5	75.0	74.8	75.6
Mean change from baseline	0.1	-0.0	0.7	1.0	0.1	0.5

4. In the Type 1 Diabetes – Pediatric section of CLINICAL STUDIES

- a) The table entitled, Type 1 Diabetes Mellitus – Pediatric was changed from Table (b) (4) to Table 9 below.



**Table 9: Type 1 Diabetes Mellitus–Pediatric**

	Study D 28 weeks Regular insulin	
	<u>LANTUS</u>	<u>NPH</u>
Treatment duration		
Treatment in combination with		
Number of subjects treated	174	175
HbA1c		
Baseline mean	8.5	8.8
Adj. mean change from baseline	+0.3	+0.3
LANTUS – NPH		0.0
95% CI for Treatment difference		(-0.2; +0.3)
Basal insulin dose		
Baseline mean	19	19
Mean change from baseline	-1	+2
Total insulin dose		
Baseline mean	43	43
Mean change from baseline	+2	+3
Fasting blood glucose (mg/dL)		
Baseline mean	194	191
Adj. mean change from baseline	-23	-12
Body weight (kg)		
Baseline mean	45.5	44.6
Mean change from baseline	2.2	2.5

5. In the Type 2 Diabetes – Adult section of CLINICAL STUDIES

a) Rephrased the conclusion statement for study E from i) to ii).

i. [REDACTED] (b) (4)

ii. “The rate of hypoglycemia was similar in LANTUS and NPH insulin treated patients”

b) The table entitled, Type 2 Diabetes Mellitus – Adult was changed from [REDACTED] (b) (4) to Table 9 below.

c) Added the following for the Retinopathy Study HOE901-4016:

In a randomized, controlled clinical study (Study G), patients with type 2 diabetes were randomized to 5 years of treatment with once-daily LANTUS or twice-daily NPH insulin. For patients not previously treated with insulin, the starting dose of LANTUS or NPH insulin was 10 units daily. Patients who were already treated with NPH insulin either continued on the same total daily NPH insulin dose or started LANTUS at a dose that was 80% of the total previous NPH insulin dose. The primary endpoint for this study was a comparison of the progression of diabetic retinopathy by 3 or more steps on the Early Treatment Diabetic Retinopathy Study (ETDRS) scale. HbA1c change from baseline was a secondary endpoint. Similar glycemic control in the 2 treatment groups was desired in order to not confound the interpretation of the retinal data. Patients or study personnel used an algorithm to adjust the LANTUS and NPH insulin doses to a target fasting plasma glucose  $\leq 100$  mg/dL. After the LANTUS or NPH insulin dose was adjusted, other anti-diabetic agents, including pre-meal insulin were to be adjusted or added. The LANTUS group had a smaller mean reduction from baseline in HbA1c compared to

the NPH insulin group, which may be explained by the lower daily basal insulin doses in the LANTUS group (Table 10). Both treatment groups had a similar incidence of reported symptomatic hypoglycemia. The incidences of severe symptomatic hypoglycemia are given in Table 6 [See Adverse Reactions (6.1)].

**Table 10: Type 2 Diabetes Mellitus—Adult**

Treatment duration Treatment in combination with	Study E 52 weeks		Study F 28 weeks		Study G 5 years	
	Oral agents		Regular insulin		Regular insulin	
	LANTUS	NPH	LANTUS	NPH	LANTUS	NPH
Number of subjects treated	289	281	259	259	513	504
HbA1c						
Baseline mean	9.0	8.9	8.6	8.5	8.4	8.3
Adj. mean change from baseline	-0.5	-0.4	-0.4	-0.6	-0.6	-0.8
LANTUS – NPH	-0.1		+0.2		+0.2	
95% CI for Treatment difference	(-0.3; +0.1)		(0.0; +0.4)		(+0.1, +0.4)	
Basal insulin dose*						
Baseline mean	14	15	44.1	45.5	39	44
Mean change from baseline	+12	+9	-1	+7	+23	+30
Total insulin dose*						
Baseline mean	14	15	64	67	48	53
Mean change from baseline	+12	+9	+10	+13	+41	+40
Fasting blood glucose (mg/dL)						
Baseline mean	179	180	164	166	190	180
Adj. mean change from baseline	-49	-46	-24	-22	-45	-44
Body weight (kg)						
Baseline mean	83.5	82.1	89.6	90.7	100	99
Adj. mean change from baseline	2.0	1.9	0.4	1.4	3.7	4.8

\*In Study G, the baseline dose of basal or total insulin was the first available on-treatment dose prescribed during the study (on visit month 1.5).

d) Deleted  <sup>(b) (4)</sup> explanation for ‘regardless of time of administration’.

e) Deleted  <sup>(b) (4)</sup>  
   
  from the first study under LANTUS Flexible

Daily Dosing.

- f) The trade name (b) (4) for glimepiride was deleted from the second study under LANTUS Flexible Daily Dosing.
- g) Studies were re-lettered starting with study G to accommodate the addition of the retinopathy study HOE: 901-4016.
- h) The LANTUS Flexible Daily Dosing table was changed from (b) (4) Table 11 below.



**Table 11: LANTUS Timing of Daily Dosing in Type 1 (Study H) and Type 2 (Study I) Diabetes Mellitus**

Treatment duration Treatment in combination with:	Study H 24 weeks			Study I 24 weeks		
	Insulin lispro			Glimepiride		
	LANTUS Breakfast	LANTUS Dinner	LANTUS Bedtime	LANTUS Breakfast	LANTUS Bedtime	NPH Bedtime
Number of subjects treated*	112	124	128	234	226	227
HbA1c						
Baseline mean	7.6	7.5	7.6	9.1	9.1	9.1
Mean change from baseline	-0.2	-0.1	0.0	-1.3	-1.0	-0.8
Basal insulin dose (U)						
Baseline mean	22	23	21	19	20	19
Mean change from baseline	5	2	2	11	18	18
Total insulin dose (U)				NA***	NA	NA
Baseline mean	52	52	49			
Mean change from baseline	2	3	2			
Body weight (kg)						
Baseline mean	77.1	77.8	74.5	80.7	82	81
Mean change from baseline	0.7	0.1	0.4	3.9	3.7	2.9

\*Intent to treat \*\*total number of patients evaluable for safety \*\*\*Not applicable

6. Changed the INDICATIONS AND USAGE section from a) to b).

a)  (b) (4)

b) LANTUS is indicated to improve glycemic control in adults and children with type 1 diabetes mellitus and in adults with type 2 diabetes mellitus. Important Limitations of Use: LANTUS is not recommended for the treatment of diabetic ketoacidosis. Intravenous short-acting insulin is the preferred treatment for this condition.

7. Added the following to the WARNING and PRECAUTIONS section:

- a) “Due to its long duration of action, Lantus is not recommended during periods of rapidly declining renal function because of the risk for prolonged hypoglycemia” to the Renal impairment section.
- b) “Due to its long duration of action, Lantus is not recommended during periods of rapidly declining hepatic function because of the risk for prolonged hypoglycemia” to the Hepatic impairment section.

8. Added the following to the PATIENT COUNSELING INFORMATION section:

- a) “Patients should be informed that changes to insulin regimens must be made cautiously and only under medical supervision.
- b) “Accidental mix-ups between LANTUS and other insulins, particularly short-acting insulins, have been reported. To avoid medication errors between LANTUS and other insulins, patients should be instructed to always check the insulin label before each injection.
- c) “Patients should be advised not to share disposable or reusable insulin devices or needles with other patients, because doing so carries a risk for transmission of blood-borne pathogens.

9. Added the following to Pediatric Use in the USE IN SPECIFIC POPULATIONS section:

- a) “LANTUS has not been studied in pediatric patients younger than 6 years of age with type 1 diabetes.”
- b) “LANTUS has not been studied in pediatric patients with type 2 diabetes.”
- c) “Based on the results of a study in pediatric patients, the dose recommendation when switching to LANTUS is the same as that described for adults.... As in adults, the dosage of LANTUS must be individualized in pediatric patients based on metabolic needs and frequent monitoring of blood glucose.”

10. Revised the Geriatric Use subsection in the USE IN SPECIFIC POPULATIONS section:

- a) Added the number (80) and percentage (2%) of patients greater than 75 years of age in the study.
- b)  (b) (4)

11. Changed the ADVERSE REACTIONS section from a) to b):

a) .

The adverse events commonly associated with LANTUS include the following:

**Body as a whole:** allergic reactions (see PRECAUTIONS).

**Skin and appendages:** injection site reaction, lipodystrophy, pruritus, rash (see PRECAUTIONS).

**Other:** hypoglycemia (see WARNINGS and PRECAUTIONS).

In clinical studies in adult patients, there was a higher incidence of treatment-emergent injection site pain in LANTUS-treated patients (2.7%) compared to NPH insulin-treated patients (0.7%). The reports of pain at the injection site were usually mild and did not result in discontinuation of therapy. Other treatment-emergent injection site reactions occurred at similar incidences with both insulin glargine and NPH human insulin.

Retinopathy was evaluated in the clinical studies by means of retinal adverse events reported and fundus photography. The numbers of retinal adverse events reported for LANTUS and NPH treatment groups were similar for patients with type 1 and type 2 diabetes. Progression of retinopathy was investigated by fundus photography using a grading protocol derived from the Early Treatment Diabetic Retinopathy Study (ETDRS). In one clinical study involving patients with type 2 diabetes, a difference in the number of subjects with  $\geq 3$ -step progression in ETDRS scale over a 6-month period was noted by fundus photography (7.5% in LANTUS group versus 2.7% in NPH treated group). The overall relevance of this isolated finding cannot be determined due to the small number of patients involved, the short follow-up period, and the fact that this finding was not observed in other clinical studies.

b) .

## **2. ADVERSE REACTIONS**

The following adverse reactions are discussed elsewhere:

- Hypoglycemia [See Warnings and Precautions (5.3)]
- Hypersensitivity and allergic reactions [See Warnings and Precautions (5.4)]

### **6.1 Clinical trial experience**

Because clinical trials are conducted under widely varying designs, the adverse reaction rates reported in one clinical trial may not be easily compared to those rates reported in another clinical trial, and may not reflect the rates actually observed in clinical practice.

The frequencies of treatment-emergent adverse events during LANTUS clinical trials in patients with type 1 diabetes mellitus and type 2 diabetes mellitus are listed in the tables below.

**Table 1: Treatment -emergent adverse events in pooled clinical trials up to 28 weeks duration in adults with type 1 diabetes (adverse events with frequency  $\geq 5\%$ )**

	<b>LANTUS, % (n=1257)</b>	<b>NPH, % (n=1070)</b>
Upper respiratory tract	22.4	23.1
Infection *	9.4	10.3
Accidental injury	5.7	6.4
Headache	5.5	4.7

\*Body System not Specified

**Table 2: Treatment -emergent adverse events in pooled clinical trials up to 1 year duration in adults with type 2 diabetes (adverse events with frequency  $\geq$  5%)**

	<b>LANTUS, % (n=849)</b>	<b>NPH, % (n=714)</b>
Upper respiratory tract infection	11.4	13.3
Infection *	10.4	11.6
Retinal vascular disorder	5.8	7.4

\*Body System not Specified

**Table 3: Treatment -emergent adverse events in a 5-year trial of adults with type 2 diabetes (adverse events with frequency  $\geq$  10%)**

	<b>LANTUS, % (n=514)</b>	<b>NPH, % (n=503)</b>
Upper respiratory tract infection	29.0	33.6
Edema peripheral	20.0	22.7
Hypertension	19.6	18.9
Influenza	18.7	19.5
Sinusitis	18.5	17.9
Cataract	18.1	15.9
Bronchitis	15.2	14.1
Arthralgia	14.2	16.1
Pain in extremity	13.0	13.1
Back pain	12.8	12.3
Cough	12.1	7.4
Urinary tract infection	10.7	10.1
Diarrhea	10.7	10.3
Depression	10.5	9.7
Headache	10.3	9.3

**Table 4: Treatment –emergent adverse events in a 28-week clinical trial of children and adolescents with type 1 diabetes (adverse events with frequency ≥ 5%)**

	LANTUS, % (n=174)	NPH, % (n=175)
Infection*	13.8	17.7
Upper respiratory tract infection	13.8	16.0
Pharyngitis	7.5	8.6
Rhinitis	5.2	5.1

\*Body System not Specified

- *Severe Hypoglycemia*

Hypoglycemia is the most commonly observed adverse reaction in patients using insulin, including LANTUS [See *Warnings and Precautions (5.3)*]. Tables 5 and 6 summarize the incidence of severe hypoglycemia in the LANTUS individual clinical trials. Severe symptomatic hypoglycemia was defined as an event with symptoms consistent with hypoglycemia requiring the assistance of another person and associated with either a blood glucose below 50 mg/dL (≤56 mg/dL in the 5-year trial) or prompt recovery after oral carbohydrate, intravenous glucose or glucagon administration.

The rates of severe symptomatic hypoglycemia in the LANTUS clinical trials (see Section 14 for a description of the study designs) were comparable for all treatment regimens (see Tables 5 and 6). In the pediatric phase 3 clinical trial, children and adolescents with type 1 diabetes had a higher incidence of severe symptomatic hypoglycemia in the two treatment groups compared to the adult trials with type 1 diabetes. (see Table 5) [See *Clinical Studies (14)*].

**Table 5: Severe Symptomatic Hypoglycemia in Patients with Type 1 Diabetes**

	Study A Type 1 Diabetes Adults 28 weeks In combination with regular insulin		Study B Type 1 Diabetes Adults 28 weeks In combination with regular insulin		Study C Type 1 Diabetes Adults 16 weeks In combination with insulin lispro		Study D Type 1 Diabetes Pediatrics 26 weeks In combination with regular insulin	
	LANTUS	NPH	LANTUS	NPH	LANTUS	NPH	LANTUS	NPH
Percent of patients (n/total N)	10.6 (31/292)	15.0 (44/293)	8.7 (23/264)	10.4 (28/270)	6.5 (20/310)	5.2 (16/309)	23.0 (40/174)	28.6 (50/175)

**Table 6: Severe Symptomatic Hypoglycemia in Patients with Type 2 Diabetes**

	Study E Type 2 Diabetes Adults 52 weeks In combination with oral agents		Study F Type 2 Diabetes Adults 28 weeks In combination with regular insulin		Study G Type 2 Diabetes Adults 5 years In combination with regular insulin	
	LANTUS	NPH	LANTUS	NPH	LANTUS	NPH
Percent of patients (n/total N)	1.7 (5/289)	1.1 (3/281)	0.4 (1/259)	2.3 (6/259)	7.8 (40/513)	11.9 (60/504)

- *Retinopathy*

Retinopathy was evaluated in the LANTUS clinical studies by analysis of reported retinal adverse events and fundus photography. The numbers of retinal adverse events reported for LANTUS and NPH insulin treatment groups were similar for patients with type 1 and type 2 diabetes. LANTUS was compared to NPH insulin in a 5-year randomized clinical trial that evaluated the progression of retinopathy as assessed with fundus photography using a grading protocol derived from the Early Treatment Diabetic Retinopathy Scale (ETDRS). Patients had type 2 diabetes (mean age 55 yrs) with no (86%) or mild (14%) retinopathy at baseline. Mean baseline HbA1c was 8.4%. The primary outcome was progression by 3 or more steps on the ETDRS scale at study endpoint. Patients with pre-specified post-baseline eye procedures (pan-retinal photocoagulation for proliferative or severe nonproliferative diabetic retinopathy, local photocoagulation for new vessels, and vitrectomy for diabetic retinopathy) were also considered as 3-step progressors regardless of actual change in ETDRS score from baseline. Retinopathy graders were blinded to treatment group assignment. The results for the primary endpoint are shown in Table 7 for both the per-protocol and Intent-to-Treat populations, and indicate similarity of Lantus to NPH in the progression of diabetic retinopathy as assessed by this outcome.

**Table 7. Number (%) of patients with 3 or more step progression on ETDRS scale at endpoint**

	Lantus (%)	NPH (%)	Difference <sup>a,b</sup> (SE)	95% CI for difference
Per-protocol	53/374 (14.2%)	57/363 (15.7%)	-2.0% (2.6%)	-7.0% to +3.1%
Intent-to-Treat	63/502 (12.5%)	71/487 (14.6%)	- 2.1% (2.1%)	-6.3% to +2.1%

a: Difference = Lantus – NPH

b: using a generalized linear model (SAS GENMOD) with treatment and baseline HbA1c strata (cutoff 9.0%) as the classified independent variables, and with binomial distribution and identity link function

- *Insulin initiation and intensification of glucose control*

Intensification or rapid improvement in glucose control has been associated with

a transitory, reversible ophthalmologic refraction disorder, worsening of diabetic retinopathy, and acute painful peripheral neuropathy. However, long-term glycemic control decreases the risk of diabetic retinopathy and neuropathy.

- *Lipodystrophy*

Long-term use of insulin, including LANTUS, can cause lipodystrophy at the site of repeated insulin injections. Lipodystrophy includes lipohypertrophy (thickening of adipose tissue) and lipoatrophy (thinning of adipose tissue), and may affect insulin absorption. Rotate insulin injection or infusion sites within the same region to reduce the risk of lipodystrophy. [See *Dosage and Administration (2.1)*].

- *Weight gain*

Weight gain can occur with insulin therapy, including LANTUS, and has been attributed to the anabolic effects of insulin and the decrease in glucosuria.

- *Peripheral Edema*

Insulin, including LANTUS, may cause sodium retention and edema, particularly if previously poor metabolic control is improved by intensified insulin therapy.

- *Allergic Reactions*

*Local Allergy*

As with any insulin therapy, patients taking LANTUS may experience injection site reactions, including redness, pain, itching, urticaria, edema, and inflammation. In clinical studies in adult patients, there was a higher incidence of treatment-emergent injection site pain in LANTUS-treated patients (2.7%) compared to NPH insulin-treated patients (0.7%). The reports of pain at the injection site did not result in discontinuation of therapy.

Rotation of the injection site within a given area from one injection to the next may help to reduce or prevent these reactions. In some instances, these reactions may be related to factors other than insulin, such as irritants in a skin cleansing agent or poor injection technique. Most minor reactions to insulin usually resolve in a few days to a few weeks.

*Systemic Allergy*

Severe, life-threatening, generalized allergy, including anaphylaxis, generalized skin reactions, angioedema, bronchospasm, hypotension, and shock may occur with any insulin, including LANTUS and may be life threatening.

- *Antibody production*

All insulin products can elicit the formation of insulin antibodies. The presence of such insulin antibodies may increase or decrease the efficacy of insulin and may require adjustment of the insulin dose. In phase 3 clinical trials of LANTUS, increases in titers of antibodies to insulin were observed in NPH insulin and insulin glargine treatment groups with similar incidences.

## 6.2 Postmarketing experience

The following adverse reactions have been identified during post-approval use of LANTUS. Because these reactions are reported voluntarily from a population of uncertain size, it is not

always possible to estimate reliably their frequency or establish a causal relationship to drug exposure.

Medication errors have been reported in which other insulins, particularly short-acting insulins, have been accidentally administered instead of LANTUS [*See Patient Counseling Information (17)*]. To avoid medication errors between LANTUS and other insulins, patients should be instructed to always verify the insulin label before each injection.

12. Added the following to Dosing in the DOSAGE AND ADMINISTRATION section:

- a) “Patients adjusting the amount or timing of dosing with LANTUS, should only do so under medical supervision with appropriate glucose monitoring....
- b) In patients with type 1 diabetes, LANTUS must be used in regimens with short-acting insulin.

13. The Initiation of LANTUS therapy and Converting to LANTUS from other insulin therapies subsections of the DOSAGE AND ADMINISTRATION section now contain specific and thorough instructions instead of limited descriptions of how these actions were accomplished in clinical trials.

14. The revision date was changed from March 2007 to June 2009.

### **Conclusion**

The labeling underwent numerous modifications which were cleared through all disciplines including: Clinical, Pharm/Tox, Chemistry, Clinical Pharmacology, Statistics, and DDMAC. The attached labeling is the version agreed upon by the FDA and sanofi-aventis.

An approval letter should be drafted for S-034 with the minor agreed upon change of the revision date to September 2009.

Reviewed by: Rachel Hartford  
Regulatory Project Manager

Supervisory concurrence: Lina Aljuburi, Pharm. D.  
Chief, Project Management Staff

Drafted: 14Aug09  
Revised: 26Aug09  
Finalized: 09Sep09

CSO LABELING REVIEW

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RACHEL E HARTFORD  
09/09/2009

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**NDA 021081/S-034**

**ADMINISTRATIVE and CORRESPONDENCE**  
**DOCUMENTS**

## EXCLUSIVITY SUMMARY

NDA # 21-081

SUPPL # 034

HFD # 510

Trade Name Lantus

Generic Name insulin glargine [rDNA origin] injection

Applicant Name sanofi-aventis

Approval Date, If Known 09Sep09

### PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES  NO

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3, SE4, SE5, SE6, SE7, SE8

SE8

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES  NO

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

Adds the results of clinical study HOE901/4016, titled "Evaluation of Diabetic Retinopathy Progression in Subjects with Type 2 Diabetes Mellitus Treated with Oral Agents Plus Insulin" to the PI.

d) Did the applicant request exclusivity?

YES  NO

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

YES  NO

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

No.

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES  NO

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

## **PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES**

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES  NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA

#(s).

NDA# 21-081

Lantus (insulin glargine [rDNA origin] injection)

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES  NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)  
IF "YES," GO TO PART III.

**PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS**

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If

the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES  NO

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES  NO

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES  NO

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES  NO

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES  NO

If yes, explain:

- (c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Study HOE901/4016, titled "Evaluation of Diabetic Retinopathy Progression in Subjects with Type 2 Diabetes Mellitus Treated with Oral Agents Plus Insulin"

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

- a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1      HOE901/4016      YES       NO

Investigation #2      YES       NO

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

- b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1      HOE901/4016      YES       NO

Investigation #2

YES

NO

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Study HOE901/4016, titled "Evaluation of Diabetic Retinopathy Progression in Subjects with Type 2 Diabetes Mellitus Treated with Oral Agents Plus Insulin"

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1		!
		!
IND # 49,078	YES <input checked="" type="checkbox"/>	! NO <input type="checkbox"/>
		! Explain:

Investigation #2		!
		!
IND #	YES <input type="checkbox"/>	! NO <input type="checkbox"/>
		! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1  
!  
!  
YES  ! NO   
Explain: ! Explain:

Investigation #2  
!  
!  
YES  ! NO   
Explain: ! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES  NO

If yes, explain:

=====

Name of person completing form: Rachel Hartford  
Title: Regulatory Project Manager  
Date: 13Oct09

Name of Office/Division Director signing form: Mary H. Parks, M.D.  
Title: Director, Division of Metabolism and Endocrinology Products

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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RACHEL E HARTFORD  
10/14/2009

MARY H PARKS  
10/14/2009

**PEDIATRIC PAGE**

**(Complete for all filed original applications and efficacy supplements)**

NDA/BLA#: **21-081**

Supplement Number: **034**

NDA Supplement Type (e.g. SE5): **SE8**

Division Name: Division of  
Metabolism and Endocrinology  
Products

PDUFA Goal Date:  
21Oct2008

Stamp Date: 21DEC2007

Proprietary Name: **Lantus**

Established/Generic Name: insulin glargine [rDNA origin]

Dosage Form: injection

Applicant/Sponsor: sanofi-aventis

Indication(s) previously approved (please complete this question for supplements and Type 6 NDAs only):

(1) LANTUS is indicated for once-daily subcutaneous administration for the treatment of adult and pediatric patients with type 1 diabetes mellitus or adult patients with type 2 diabetes mellitus who require basal (long-acting) insulin for the control of hyperglycemia.

(2) n/a

(3) n/a

(4) n/a

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Pediatric use for each pediatric subpopulation must be addressed for each indication covered by current application under review. A Pediatric Page must be completed for each indication.

Number of indications for this pending application(s): 0

(Attach a completed Pediatric Page for each indication in current application.)

**Indication:** no new indication

**This supplement contains the retinopathy PMC study report; it triggered PLR conversion.**

**Q1:** Is this application in response to a PREA PMR? Yes  Continue

No  Please proceed to Question 2.

If Yes, NDA/BLA#: \_\_\_\_\_ Supplement #: \_\_\_\_\_ PMR #: \_\_\_\_\_

Does the division agree that this is a complete response to the PMR?

Yes. Please proceed to Section D.

No. Please proceed to Question 2 and complete the Pediatric Page, as applicable.

**Q2:** Does this application provide for (If yes, please check all categories that apply and proceed to the next question):

(a) NEW  active ingredient(s) (includes new combination);  indication(s);  dosage form;  dosing regimen; or  route of administration?\*

(b)  No. PREA does not apply. **Skip to signature block.**

\* Note for CDER: SE5, SE6, and SE7 submissions may also trigger PREA.

**Q3:** Does this indication have orphan designation?

Yes. PREA does not apply. **Skip to signature block.**

No. Please proceed to the next question.

**Q4:** Is there a full waiver for all pediatric age groups for this indication (check one)?

- Yes: (Complete Section A.)
- No: Please check all that apply:
- Partial Waiver for selected pediatric subpopulations (Complete Sections B)
  - Deferred for some or all pediatric subpopulations (Complete Sections C)
  - Completed for some or all pediatric subpopulations (Complete Sections D)
  - Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)
  - Extrapolation in One or More Pediatric Age Groups (Complete Section F)
- (Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

<b>Section A: Fully Waived Studies (for all pediatric age groups)</b>
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Reason(s) for full waiver: (**check, and attach a brief justification for the reason(s) selected**)

- Necessary studies would be impossible or highly impracticable because:
- Disease/condition does not exist in children
  - Too few children with disease/condition to study
  - Other (e.g., patients geographically dispersed): \_\_\_\_\_
- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.
- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Justification attached.

*If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed.*

**Section B: Partially Waived Studies (for selected pediatric subpopulations)**

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):  
 Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).

			Reason (see below for further detail):				
	minimum	maximum	Not feasible <sup>#</sup>	Not meaningful therapeutic benefit <sup>*</sup>	Ineffective or unsafe <sup>†</sup>	Formulation failed <sup>Δ</sup>	
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)?  No;  Yes.

Are the indicated age ranges (above) based on Tanner Stage?  No;  Yes.

Reason(s) for partial waiver (**check reason** corresponding to the category checked above, and **attach a brief justification**):

**#** Not feasible:

- Necessary studies would be impossible or highly impracticable because:
  - Disease/condition does not exist in children
  - Too few children with disease/condition to study
  - Other (e.g., patients geographically dispersed): \_\_\_\_\_

**\*** Not meaningful therapeutic benefit:

- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of pediatric patients in this/these pediatric subpopulation(s).

**†** Ineffective or unsafe:

- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

**Δ** Formulation failed:

- Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (*Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.*)

Justification attached.

For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Sections C and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4) additional studies in other age groups that are not needed because efficacy is being extrapolated (if so, proceed to Section F). Note that more than one of these options may apply for this indication to cover all of the

pediatric subpopulations.

**Section C: Deferred Studies (for selected pediatric subpopulations).**

Check pediatric subpopulation(s) for which pediatric studies are being deferred (and fill in applicable reason below):

Deferrals (for each or all age groups):				Reason for Deferral			Applicant Certification †
Population	minimum	maximum	Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Received	
<input type="checkbox"/> Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Date studies are due (mm/dd/yy): _____							

Are the indicated age ranges (above) based on weight (kg)?  No;  Yes.

Are the indicated age ranges (above) based on Tanner Stage?  No;  Yes.

\* Other Reason: \_\_\_\_\_

† Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)

If all of the pediatric subpopulations have been covered through partial waivers and deferrals, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

**Section D: Completed Studies (for some or all pediatric subpopulations).**

Pediatric subpopulation(s) in which studies have been completed (check below):					
Population		minimum	maximum	PeRC Pediatric Assessment form attached?.	
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)?  No;  Yes.

Are the indicated age ranges (above) based on Tanner Stage?  No;  Yes.

*Note: If there are no further pediatric subpopulations to cover based on partial waivers, deferrals and/or completed studies, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.*

**Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations):**

Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:			
Population		minimum	maximum
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.

Are the indicated age ranges (above) based on weight (kg)?  No;  Yes.

Are the indicated age ranges (above) based on Tanner Stage?  No;  Yes.

*If all pediatric subpopulations have been covered based on partial waivers, deferrals, completed studies, and/or existing appropriate labeling, this Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.*

**Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and/or completed studies)**

*Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the pediatric subpopulation for which information will be extrapolated. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as*

*pharmacokinetic and safety studies. Under the statute, safety cannot be extrapolated.*

Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:					
Population		minimum	maximum	Extrapolated from:	
				Adult Studies?	Other Pediatric Studies?
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)?  No;  Yes.

Are the indicated age ranges (above) based on Tanner Stage?  No;  Yes.

*Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.*

*If there are additional indications, please complete the attachment for each one of those indications. Otherwise, this Pediatric Page is complete and should be signed and entered into DFS or DARRTS as appropriate after clearance by PeRC.*

This page was completed by:

*{See appended electronic signature page}*

\_\_\_\_\_  
Regulatory Project Manager

(Revised: 6/2008)

**NOTE: If you have no other indications for this application, you may delete the attachments from this document.**

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

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Rachel E Hartford  
10/23/2008 11:35:51 AM



NDA 021081/S-034

**INFORMATION REQUEST**

CERTIFIED MAIL  
RETURN RECEIPT REQUESTED

sanofi-aventis U.S. LLC  
Attention: Antonella Lozito, Pharm.D.  
200 Crossing Blvd., BX2-700B  
Bridgewater, NJ 08807-0890

Dear Dr. Lozito:

Please refer to your supplemental New Drug Application (sNDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lantus (insulin glargine [rDNA origin]), injection.

FDA investigators have identified significant violations to the (b) (4) requirements of Title 21, Code of Federal Regulation, Part 320 in (b) (4) studies conducted by (b) (4). The pervasiveness and egregious nature of the violative practices by (b) (4) has led FDA to have significant concerns that the (b) (4) data generated at (b) (4) from (b) (4), as part of studies submitted to FDA in New Drug Applications (NDA) and Supplemental New Drug Applications (sNDA) are unreliable. FDA has reached this conclusion for three reasons: (b) (4)

Serious questions remain about the validity of any data generated in studies by (b) (4) during this time period. In view of these findings, FDA is informing holders of approved and pending NDAs of these issues.

The impact of the data from these studies (which may include (b) (4)) cannot be assessed without knowing the details regarding the study and how the data in question were considered in the overall development and approval of your drug product. At this time, the Office of New Drugs is searching available documentation to determine which NDAs are impacted by the above findings.

<sup>1</sup> These violations include studies conducted by (b) (4) specific to the (b) (4) facility.

To further expedite this process, we ask that you inform us if you have submitted any studies conducted by [REDACTED] (b) (4) during the time period of concern ([REDACTED] (b) (4)). Please submit information on each of the studies, including supplement number (if appropriate), study name/protocol number, and date of submission. With respect to those studies, you will need to do one of the following: (a) re-assay samples if available and supported by stability data, (b) repeat the studies, or (c) provide a rationale if you feel that no further action is warranted.

**Please respond to this query within 30 days from the date of this letter.**

This information should be submitted as correspondence to your NDA. In addition, please provide a desk copy to:

Office of New Drugs  
Center for Drug Evaluation and Research  
10903 New Hampshire Avenue  
Bldg. 22, Room 6300  
Silver Spring, MD 20993-0002

If you have any questions, call Rachel Hartford, Regulatory Project Manager, at (301) 796-0331.

Sincerely,

*{See appended electronic signature page}*

Mary H. Parks, M.D.  
Director  
Division of Metabolism and Endocrinology Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

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

09/12/2011

J. Marchick signing for M. Parks

## REQUEST FOR CONSULTATION

TO (Office/Division): DDMAC (HFD-42), Sam Skariah, WO 51 Rm 3226

FROM (Name, Office/Division, and Phone Number of Requestor): Rachel Hartford, DMEP (HFD-510), x60331, WO 22 Rm 3397

DATE  
23Mar09

IND NO.

NDA NO.  
21-081

TYPE OF DOCUMENT  
sNDA

DATE OF DOCUMENT  
19Mar09

NAME OF DRUG  
Lantus

PRIORITY CONSIDERATION  
R

CLASSIFICATION OF DRUG

DESIRED COMPLETION DATE  
27Mar09

NAME OF FIRM: sanofi-aventis

### REASON FOR REQUEST

#### I. GENERAL

- |  |  |  |
|--|--|--|
| <input type="checkbox"/> NEW PROTOCOL                    | <input type="checkbox"/> PRE-NDA MEETING         | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER     |
| <input type="checkbox"/> PROGRESS REPORT                 | <input type="checkbox"/> END-OF-PHASE 2a MEETING | <input type="checkbox"/> FINAL PRINTED LABELING            |
| <input type="checkbox"/> NEW CORRESPONDENCE              | <input type="checkbox"/> END-OF-PHASE 2 MEETING  | <input type="checkbox"/> LABELING REVISION                 |
| <input type="checkbox"/> DRUG ADVERTISING                | <input type="checkbox"/> RESUBMISSION            | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE       |
| <input type="checkbox"/> ADVERSE REACTION REPORT         | <input type="checkbox"/> SAFETY / EFFICACY       | <input type="checkbox"/> FORMULATIVE REVIEW                |
| <input type="checkbox"/> MANUFACTURING CHANGE / ADDITION | <input type="checkbox"/> PAPER NDA               | <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> MEETING PLANNED BY              | <input type="checkbox"/> CONTROL SUPPLEMENT      |  |

#### II. BIOMETRICS

- |   |   |
|---|---|
| <input type="checkbox"/> PRIORITY P NDA REVIEW  | <input type="checkbox"/> CHEMISTRY REVIEW       |
| <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> PHARMACOLOGY           |
| <input type="checkbox"/> CONTROLLED STUDIES     | <input type="checkbox"/> BIOPHARMACEUTICS       |
| <input type="checkbox"/> PROTOCOL REVIEW        | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> OTHER (SPECIFY BELOW): |   |

#### III. BIOPHARMACEUTICS

- |  |  |
|--|--|
| <input type="checkbox"/> DISSOLUTION             | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE  |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS |
| <input type="checkbox"/> PHASE 4 STUDIES         | <input type="checkbox"/> IN-VIVO WAIVER REQUEST      |

#### IV. DRUG SAFETY

- |  |  |
|--|--|
| <input type="checkbox"/> PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL                | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE                       |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below)           | <input type="checkbox"/> POISON RISK ANALYSIS                                |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP         |  |

#### V. SCIENTIFIC INVESTIGATIONS

- |                                   |                                      |
|-----------------------------------|--------------------------------------|
| <input type="checkbox"/> CLINICAL | <input type="checkbox"/> NONCLINICAL |
|-----------------------------------|--------------------------------------|

**COMMENTS / SPECIAL INSTRUCTIONS:** sanofi-aventis submitted a supplement for Lantus adding the results of their PMC retinopathy study; please review the PI sent via email 19Mar09.

SIGNATURE OF REQUESTOR  
Rachel E. Hartford

METHOD OF DELIVERY (Check one)  
 DFS     EMAIL     MAIL     HAND

PRINTED NAME AND SIGNATURE OF RECEIVER

PRINTED NAME AND SIGNATURE OF DELIVERER

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/s/

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Rachel E Hartford  
3/23/2009 05:57:43 PM

**Hartford, Rachel**

---

**From:** Hartford, Rachel  
**Sent:** Monday, December 29, 2008 2:46 PM  
**To:** 'Rima.Nassar@sanofi-aventis.com'  
**Subject:** RE: Lantus ORIGIN trial/Protocol Amendment  
**Follow Up Flag:** Follow up  
**Flag Status:** Purple  
**Attachments:** Table X.doc

Rima,

We would like more information on the urine microalbumin/creatinine ratios. Please complete the attached table.

Also, it was mentioned that there was a greater incidence of diabetic nephropathy and retinopathy by history in the lantus group. Please clarify how this information was captured on the case report form and what this information specifically refers to -- e.g., was this a diagnosis reported by the patient based on what they had heard from their treating doctor, or were reports of a history of retinopathy/nephropathy corroborated with the patient's medical records, etc.

Thank you,

Rachel

---

**From:** Rima.Nassar@sanofi-aventis.com [mailto:Rima.Nassar@sanofi-aventis.com]  
**Sent:** Tuesday, December 23, 2008 4:36 PM  
**To:** Hartford, Rachel  
**Cc:** Rosalyn.Walton@sanofi-aventis.com; Alan.Kerr@sanofi-aventis.com; Caroline.Dubey@sanofi-aventis.com  
**Subject:** Lantus ORIGIN trial/Protocol Amendment

Dear Rachel,

I tried to reach you today by phone to let you know that we submitted yesterday the requested information regarding the retinopathy study for Lantus (NDA 21-081, S034) that included information on Major Adverse Cardiovascular Events (MACE) and ratio of urine albumin/creatinine. The two items were submitted together in one combined response/submission. Please let me know if you have any further comments to this response.

We also submitted today a protocol amendment for the ORIGIN trial for Lantus (IND 49,078, Serial Number 0414) to extend the trial by approximately two years [REDACTED] (b) (4) [REDACTED]. The submission included a cover letter, an amendment, and the amended protocol (clean version). I am attaching in this e-mail the amended protocol with track changes for ease of review by the Agency.

Please note that the cover letter that accompanies the ORIGIN protocol amendment includes two questions that we would like the Agency to address and respond to. We would greatly and truly appreciate the Agency's prompt response to these questions. Please let me know if you have any additional comments/questions following review of the amendment.

All the best for a joyous holiday season and a very happy and healthy New Year.

Best regards,

Rima

3/9/2009

---

Rima B. Nassar, Ph.D.  
Global Diabetes Axis Head  
Corporate Regulatory Affairs  
Tel: 908-304-6471  
Cell: (b) (6)  
E-Mail: Rima.Nassar@sanofi-aventis.com

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/s/

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Rachel E Hartford  
3/16/2009 08:23:30 PM  
CSO

## Hartford, Rachel

---

**From:** Hartford, Rachel  
**Sent:** Friday, November 07, 2008 10:01 AM  
**To:** 'Rima.Nassar@sanofi-aventis.com'  
**Subject:** Lantus NDA 21-081/S034

**Follow Up Flag:** Follow up  
**Flag Status:** Purple

Rima,

We have the following additional information requests for Lantus NDA 21-081/S034:

For each treatment group, please perform the following analyses for the urine microalbumin/creatinine ratio at each timepoint in the study:

1. Summary statistics (mean, standard deviation, median, interquartile range) for the baseline data and for change from baseline
2. Shift analyses from normal at baseline to elevated (i.e., >30 mg/g creatinine)
3. The number and proportion of patients with urine microalbumin/creatinine ratio >30 mg/g creatinine
4. The number and proportion of patients with urine microalbumin/creatinine ratio >60 mg/g creatinine
5. The number and proportion of patients with urine microalbumin/creatinine ratio >90 mg/g creatinine
6. The number and proportion of patients with urine microalbumin/creatinine ratio >150 mg/g creatinine
7. The number and proportion of patients with urine microalbumin/creatinine ratio >300 mg/g creatinine

Thank you,

Rachel

*Rachel E. Hartford*

**Regulatory Project Manager**

**Division of Metabolism and Endocrinology Products**

**Center for Drug Evaluation and Research**

**Food and Drug Administration**

[rachel.hartford@fda.hhs.gov](mailto:rachel.hartford@fda.hhs.gov)

**301-796-0331 (phone)**

**301-796-9712 (fax)**

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/s/

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Rachel E Hartford  
3/16/2009 08:22:00 PM  
CSO

**Hartford, Rachel**

---

**From:** Hartford, Rachel  
**Sent:** Monday, December 01, 2008 12:57 PM  
**To:** 'Rima.Nassar@sanofi-aventis.com'  
**Subject:** FW: Lantus NDA 21-081/S034  
**Follow Up Flag:** Follow up  
**Flag Status:** Purple

Rima,

We have the following response to your comments:

We agree with sanofi's statement that reads: "Instead it was proposed to assay collected urine for albumin and creatinine, which together with serum creatinine measurements would give useful information on progression of diabetic nephropathy, at least in the form of shift tables in which patients who progressed between stages of albuminuria from no albuminuria to microalbuminuria, or to macroalbuminuria, could be captured."

However, the data in the sNDA submission appear to be presented separately for urine microalbumin and urine creatinine. To accurately assess the extent of albuminuria, the ratio of urine microalbumin to urine creatinine is needed. Therefore, please perform the requested analyses 3 through 7 below.

Thanks,

Rachel

---

**From:** Rima.Nassar@sanofi-aventis.com [mailto:Rima.Nassar@sanofi-aventis.com]  
**Sent:** Tuesday, November 11, 2008 3:58 PM  
**To:** Hartford, Rachel  
**Cc:** Alan.Kerr@sanofi-aventis.com; [REDACTED] (b) (6)  
**Subject:** RE: Lantus NDA 21-081/S034

Dear Rachel,

In response to the additional information request contained in your e-mail of November 7, 2008, we are providing the following:

Urine was collected for albumin / creatinine analysis in the Lantus retinopathy trial only at post-baseline visits. (b) (4)

[REDACTED]

Instead it was proposed to assay collected urine for albumin and creatinine, which together with serum creatinine measurements would give useful information on progression of diabetic nephropathy, at least in the form of shift tables in which patients who progressed between stages of albuminuria from no albuminuria to microalbuminuria, or to macroalbuminuria, could be captured.

Tables 3 - 7 described in the Agency's e-mail can be prepared, but it must be recognized that baseline, ie pretreatment, values are not available. If it is still desired to show the number and percent of patients in each group who satisfy the indicated parameter at each timepoint when available, this can be performed. Please let us know your wishes in this matter or how you would like us to proceed.

Best regards,  
Rima Nassar

---

**From:** Hartford, Rachel [mailto:Rachel.Hartford@fda.hhs.gov]  
**Sent:** Friday, November 07, 2008 10:01 AM  
**To:** Nassar, Rima R&D/US  
**Subject:** Lantus NDA 21-081/S034

3/9/2009

Rima,

We have the following additional information requests for Lantus NDA 21-081/S034:

For each treatment group, please perform the following analyses for the urine microalbumin/creatinine ratio at each timepoint in the study:

1. Summary statistics (mean, standard deviation, median, interquartile range) for the baseline data and for change from baseline
2. Shift analyses from normal at baseline to elevated (i.e., >30 mg/g creatinine)
3. The number and proportion of patients with urine microalbumin/creatinine ratio >30 mg/g creatinine
4. The number and proportion of patients with urine microalbumin/creatinine ratio >60 mg/g creatinine
5. The number and proportion of patients with urine microalbumin/creatinine ratio >90 mg/g creatinine
6. The number and proportion of patients with urine microalbumin/creatinine ratio >150 mg/g creatinine
7. The number and proportion of patients with urine microalbumin/creatinine ratio >300 mg/g creatinine

Thank you,

Rachel

*Rachel E. Hartford*  
**Regulatory Project Manager**  
**Division of Metabolism and Endocrinology Products**  
**Center for Drug Evaluation and Research**  
**Food and Drug Administration**  
[rachel.hartford@fda.hhs.gov](mailto:rachel.hartford@fda.hhs.gov)  
**301-796-0331 (phone)**  
**301-796-9712 (fax)**

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/s/

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Rachel E Hartford  
3/16/2009 08:20:18 PM  
CSO

## Hartford, Rachel

---

**From:** Hartford, Rachel  
**Sent:** Monday, January 26, 2009 1:07 PM  
**To:** 'Rima.Nassar@sanofi-aventis.com'  
**Subject:** Lantus PMC study question

**Follow Up Flag:** Follow up  
**Flag Status:** Purple

Rima,

Please respond to the following clinical information request:

"In the 5-year retinopathy trial, Figure 3 (summary of patient disposition) on page 52 reports that 17 Lantus-treated patients and 12 NPH-treated patients who were randomized and exposed to study medication withdrew from the study prematurely because of an adverse event. However, Table 45 reports that 16 Lantus-treated patients and 11 NPH-treated patients in the safety population withdrew due to an adverse event. Please explain this discrepancy."

Thank you,

Rachel

*Rachel E. Hartford*

**Regulatory Project Manager**

**Division of Metabolism and Endocrinology Products**

**Center for Drug Evaluation and Research**

**Food and Drug Administration**

[rachel.hartford@fda.hhs.gov](mailto:rachel.hartford@fda.hhs.gov)

**301-796-0331 (phone)**

**301-796-9712 (fax)**

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/s/

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Rachel E Hartford  
3/16/2009 08:17:40 PM  
CSO

## Hartford, Rachel

---

**From:** Hartford, Rachel  
**Sent:** Wednesday, October 08, 2008 9:42 AM  
**To:** 'Michael.Lutz@sanofi-aventis.com'  
**Subject:** Lantus NDA 21-081 Information Request

**Follow Up Flag:** Follow up  
**Flag Status:** Purple

Mike,

Please respond as soon as possible to the information request below. Let me know if you can do it within a week.

Based on the July 1-2, 2008 Endocrinologic and Metabolic advisory committee meeting, there is interest in more extensive cardiovascular assessment of drugs and biologics developed for the treatment of type 2 diabetes. Please perform a Major Adverse Cardiovascular Event (MACE) analysis using the data from your 5-year, controlled, retinopathy trial. The MACE endpoint should be a composite of cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke. Please also present data on the individual components of this composite endpoint. Your analyses should show the number and proportion of people who experienced at least one MACE event and should include a time-to-event analysis.

Thank you,

Rachel

*Rachel E. Hartford*

**Regulatory Project Manager**

**Division of Metabolism and Endocrinology Products**

**Center for Drug Evaluation and Research**

**Food and Drug Administration**

[rachel.hartford@fda.hhs.gov](mailto:rachel.hartford@fda.hhs.gov)

**301-796-0331 (phone)**

**301-796-9712 (fax)**

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Rachel E Hartford  
3/16/2009 08:15:57 PM  
CSO

## Hartford, Rachel

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**From:** Hartford, Rachel  
**Sent:** Friday, December 05, 2008 10:14 AM  
**To:** 'Rima.Nassar@sanofi-aventis.com'  
**Subject:** Lantus NDA 21-08/S034

**Follow Up Flag:** Follow up  
**Flag Status:** Purple

Rima,

Hope you had a Happy Thanksgiving. We have reviewed your submitted Major Adverse Cardiovascular Event (MACE) analysis for your Lantus retinopathy trial and have an additional information request. Please calculate the hazard ratios with 95% confidence intervals for the MACE events using the time-to-event data from the two treatment groups. Please perform this analysis for the composite MACE endpoint (cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke). Also perform this analysis for each individual component of the MACE endpoint. In addition, provide a description of how you identified and captured all patients who experienced a MACE event in the trial. Were patients with potential cardiovascular events that were coded in non-cardiovascular System-Organ-Class categories reviewed (e.g., patients with chest pain, patients with electrocardiogram abnormalities)?

Thank you,

Rachel

*Rachel E. Hartford*

**Regulatory Project Manager**

**Division of Metabolism and Endocrinology Products**

**Center for Drug Evaluation and Research**

**Food and Drug Administration**

[rachel.hartford@fda.hhs.gov](mailto:rachel.hartford@fda.hhs.gov)

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/s/

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Rachel E Hartford  
3/16/2009 08:14:39 PM  
CSO

## Hartford, Rachel

---

**From:** Hartford, Rachel  
**Sent:** Tuesday, February 10, 2009 1:07 PM  
**To:** 'Rima.Nassar@sanofi-aventis.com'  
**Subject:** Lantus PI [REDACTED] (b) (4)

**Follow Up Flag:** Follow up  
**Flag Status:** Purple

**Attachments:** annotated\_pi\_09Feb09.doc

Rima,

Please accept all FDA tracked changes you agree with in the attached Lantus PI. Use track changes for any additional edits you make. Please return the PI via email by COB 18Feb09; let me know if you need additional time.

Thanks,

Rachel



annotated\_pi\_09Feb09.doc (1 MB...)

P.S. I just spoke with Hylton. He asked me to let you and Richard know that we plan to issue the action letter for Apidra SoloStar during the week of February 16-20. I will gladly send you a pdf of the action letter so you don't have to wait for the mail.

*Rachel E. Hartford*

**Regulatory Project Manager**  
**Division of Metabolism and Endocrinology Products**  
**Center for Drug Evaluation and Research**  
**Food and Drug Administration**  
[rachel.hartford@fda.hhs.gov](mailto:rachel.hartford@fda.hhs.gov)  
**301-796-0331 (phone)**  
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Rachel E Hartford  
3/16/2009 08:12:46 PM  
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## Hartford, Rachel

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**From:** Hartford, Rachel  
**Sent:** Wednesday, October 08, 2008 8:21 AM  
**To:** 'Michael.Lutz@sanofi-aventis.com'  
**Subject:** Lantus PI

**Follow Up Flag:** Follow up  
**Flag Status:** Purple

**Attachments:** Lantus PI 10-7-08.doc

Mike,

The Lantus PI is attached; additional edits may be forthcoming. Please accept all FDA tracked changes that you agree with and return the label in a week.

Thanks,

Rachel



Lantus PI  
10-7-08.doc (899 KB)

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/s/

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Rachel E Hartford  
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CSO

## Hartford, Rachel

---

**From:** Hartford, Rachel  
**Sent:** Friday, August 22, 2008 11:13 AM  
**To:** 'Michael.Lutz@sanofi-aventis.com'  
**Subject:** NDA 21-081/S034

**Follow Up Flag:** Follow up  
**Flag Status:** Purple

Good Morning Mike,

We have a few questions in regard to comparison between Lantus and NPH ( study 4016) with respect to events related to immunological/hypersensitivity factors.

1- Table 48 lists 5 patients on Lantus and 19 on NPH with Hypersensitivity reactions. There are four narratives ( 1004/09, 2005/26, 1033/27, 1017/13) of patients who withdrew because of this AE. Are there additional cases where patients withdrew or where the reaction was classified as an SAE? Also, please go over narrative 1004/09 to be sure that the dates are correct. The chronology of events are not clear.

2- Please review similar findings from trials 3006 and 3002, and submit a table comparing Lantus with NPH for all three trials. In addition, cases should be classified as to whether they had received insulin ( any type) or test drug ( Lantus or NPH) previously.

3- We note from table 47 that 12 patients on Lantus and 7 on NPH had injection site reactions. As requested for #2, please review similar findings from trials 3006 and 3002, and submit a table comparing Lantus with NPH for all three trials. In addition, cases should be classified as to whether they had received insulin ( any type) or test drug ( Lantus or NPH) Previously.

4- Were insulin antibodies measured in trial 4016? If no, please give the rationale for omitting this measurement.

Please contact me with any questions.

Thanks,

Rachel

*Rachel E. Hartford*

**Regulatory Project Manager**

**Division of Metabolism and Endocrinology Products**

**Center for Drug Evaluation and Research**

**Food and Drug Administration**

[rachel.hartford@fda.hhs.gov](mailto:rachel.hartford@fda.hhs.gov)

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Rachel E Hartford  
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## Hartford, Rachel

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**From:** Hartford, Rachel  
**Sent:** Thursday, July 17, 2008 3:32 PM  
**To:** 'Michael.Lutz@sanofi-aventis.com'  
**Subject:** Information Request for NDA 21-081/S034

**Follow Up Flag:** Follow up  
**Flag Status:** Purple

Mike,

Please submit a comparison of the patient populations in trials HOE901/4016 titled, "*Evaluation of Diabetic Retinopathy Progression in Subjects with Type 2 Diabetes Mellitus Treated with Oral Agents Plus Insulin*" and HOE901/3006 titled, "*28-Week Multicenter, Controlled, Randomized, Open Clinical Trial Comparing HOE901 Insulin with NPH Human Insulin in Subjects with Type II Diabetes.*" Include the following baseline characteristics: age, sex, duration of diabetes, duration of insulin use, blood pressure, (b) (4) and history of treatment for retinopathy. Also include countries of origin (% from each country) and ethnicity.

Thanks,

Rachel

*Rachel E. Hartford*

**Regulatory Project Manager**

**Division of Metabolism and Endocrinology Products**

**Center for Drug Evaluation and Research**

**Food and Drug Administration**

[rachel.hartford@fda.hhs.gov](mailto:rachel.hartford@fda.hhs.gov)

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**301-796-9712 (fax)**

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Rachel E Hartford  
3/16/2009 08:06:26 PM  
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**Hartford, Rachel**

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**From:** Hartford, Rachel  
**Sent:** Monday, July 21, 2008 9:45 AM  
**To:** 'Michael.Lutz@sanofi-aventis.com'  
**Subject:** RE: Information Request for NDA 21-081/S034  
**Follow Up Flag:** Follow up  
**Flag Status:** Purple

Mike,

I checked with the medical reviewer and it is fine if you use ETDRS score in place of [REDACTED] (b) (4)

Thanks,

Rachel

---

**From:** Michael.Lutz@sanofi-aventis.com [mailto:Michael.Lutz@sanofi-aventis.com]  
**Sent:** Friday, July 18, 2008 2:34 PM  
**To:** Hartford, Rachel  
**Subject:** RE: Information Request for NDA 21-081/S034

Hi Rachel,  
Would it be possible to use "ETDRS score" in place of [REDACTED] (b) (4) at baseline for the information request below?  
Thanks and regards,  
Mike

Michael Lutz  
Corporate Regulatory affairs  
Regulatory Development  
Diabetes Axis  
908-231-5620  
908-304-6560 (fax)  
michael.lutz@sanofi-aventis.com

---

**From:** Hartford, Rachel [mailto:Rachel.Hartford@fda.hhs.gov]  
**Sent:** Thursday, July 17, 2008 3:32 PM  
**To:** Lutz, Michael (Regulatory Affairs) R&D/US  
**Subject:** Information Request for NDA 21-081/S034

Mike,

Please submit a comparison of the patient populations in trials HOE901/4016 titled, "*Evaluation of Diabetic Retinopathy Progression in Subjects with Type 2 Diabetes Mellitus Treated with Oral Agents Plus Insulin*" and HOE901/3006 titled, "*28-Week Multicenter, Controlled, Randomized, Open Clinical Trial Comparing HOE901 Insulin with NPH Human Insulin in Subjects with Type II Diabetes.*" Include the following baseline characteristics: age, sex, duration of diabetes, duration of insulin use, blood pressure, [REDACTED] (b) (4) and history of treatment for retinopathy. Also include countries of origin (% from each country) and ethnicity.

Thanks,

Rachel

*Rachel E. Hartford*  
**Regulatory Project Manager**  
**Division of Metabolism and Endocrinology Products**

3/9/2009

**Center for Drug Evaluation and Research**

**Food and Drug Administration**

[rachel.hartford@fda.hhs.gov](mailto:rachel.hartford@fda.hhs.gov)

**301-796-0331 (phone)**

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/s/

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Rachel E Hartford  
3/16/2009 08:04:44 PM  
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## Hartford, Rachel

---

**From:** Hartford, Rachel  
**Sent:** Tuesday, September 09, 2008 3:11 PM  
**To:** 'Michael.Lutz@sanofi-aventis.com'  
**Subject:** Lantus NDA 21-081/S-034

**Follow Up Flag:** Follow up  
**Flag Status:** Purple

Mike,

We have the following requests for Lantus NDA 21-081/S034.

1. What are the differences between the ADPR.XPT and ADFU.XPT files for the ETDRS related variables?
2. The number of subjects with 3-step or greater progression in the ETDRS at each study visit (page 1792) is not always the same as the number of subjects with  $\geq 3$  change in ETDRS score (page 1798 and 1799). Was the differences caused by some patients with eye procedures? If yes, please specify who they were by treatment group and visit. Can the PRPROCDT variable in ADPR.XPT be used as an identifier for those patients?
3. The percentages **could not be reproduced** using ADPR.XPT with the PRPROG3 variable as reported on page 1792 for some visits. Also, Figure 5 in the study report looks slightly different when the numbers on page 1791 were used. **Please explain/clarify.**
4. A Lantus subject 4016/1021/00109 had a baseline visit recorded as on-treatment phase. **Please explain/clarify.**

Also, PLR requires that any FDA -approved patient labeling be appended to the PI as a separate document. Please submit all applicable FDA approved labeling. If it has already been submitted to this supplement, please indicate the date(s) of submission.

Thanks,

Rachel

*Rachel E. Hartford*  
**Regulatory Project Manager**  
**Division of Metabolism and Endocrinology Products**  
**Center for Drug Evaluation and Research**  
**Food and Drug Administration**  
[rachel.hartford@fda.hhs.gov](mailto:rachel.hartford@fda.hhs.gov)  
**301-796-0331 (phone)**  
**301-796-9712 (fax)**

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/s/

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Rachel E Hartford  
3/16/2009 08:02:38 PM  
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**Table X. Proportion of patients with at least one abnormal urine microalbumin/creatinine ratio while receiving study medication**

<b>Ratio</b>	<b>LANTUS N=514 n (%)</b>	<b>NPH N=504 n (%)</b>
Any time during the treatment period		
>30 mg/g	222 (43.2)	186 (36.9)
>60 mg/g	152 (29.6)	120 (23.9)
>90 mg/g	120 (23.3)	90 (17.9)
>150 mg/g	90 (17.5)	65 (12.9)
>300 mg/g	63 (12.3)	42 (8.3)
Month 12		
>30 mg/g		
>60 mg/g		
>90 mg/g		
>150 mg/g		
>300 mg/g		
Month 24		
>30 mg/g		
>60 mg/g		
>90 mg/g		
>150 mg/g		
>300 mg/g		
Month 36		
>30 mg/g		
>60 mg/g		
>90 mg/g		
>150 mg/g		
>300 mg/g		
Month 48		
>30 mg/g		
>60 mg/g		
>90 mg/g		
>150 mg/g		
>300 mg/g		
Month 60		
>30 mg/g		
>60 mg/g		
>90 mg/g		
>150 mg/g		
>300 mg/g		



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/s/

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Rachel E Hartford  
3/16/2009 07:57:26 PM  
CSO



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

**FILING COMMUNICATION**

NDA 21-081/S-034

sanofi-aventis, U.S. LLC  
Attention: Michael Lutz, M. Sc., MBA, RAC  
Regulatory Development  
200 Crossings Boulevard, Mailstop: BX4-206  
Bridgewater, NJ 08807-0890

Dear Mr. Lutz:

Please refer to your December 21, 2007, supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lantus, insulin glargine [rDNA origin] injection.

This supplement proposes labeling information based on clinical study HOE901/4016, titled "Evaluation of Diabetic Retinopathy Progression in Subjects with Type 2 Diabetes Mellitus Treated with Oral Agents Plus Insulin."

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application has been filed under section 505(b) of the Act on February 19, 2008 in accordance with 21 CFR 314.101(a).

At this time, we have not identified any potential filing review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

If you have any questions, call Rachel Hartford, Regulatory Project Manager, at (301) 796-0331.

Sincerely,

*{See appended electronic signature page}*

Lina AlJuburi, Pharm. D., M.S.  
Chief, Project Management Staff  
Division of Metabolism and Endocrinology Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

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/s/

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Lina Aljuburi  
2/27/2008 08:53:53 AM