Synopsis for study GLP112754

Name of finished products: Eperzan® 30 mg Pulver und Lösungsmittel zur Herstellung einer Injektionslösung in einem Fertigpen,
Eperzan® 50 mg Pulver und Lösungsmittel zur Herstellung einer Injektionslösung in einem Fertigpen,
Lantus®

Name of active substances: Albiglutid**,** Insulin glargin

Pharmaceutical entrepreneur:
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Personal identifiable data of investigators (investigator names) are not published in this report, as consent according to Section 4a of the German Federal Act on Data Protection is not available for any of the investigators.

SYNOPSIS

Study Number: GLP112754

Title: A Randomized, Open-Label, Parallel-Group, Multicenter Study to Determine the Efficacy and Long-Term Safety of Albiglutide Compared With Insulin in Subjects With Type 2 Diabetes Mellitus – Year 3 Report

Investigators: This was a multicenter study

Study centers: This study was conducted at 222 centers in 4 countries.

Publications: None at the time of this report.

Study Period: 17 Feb 2009 - 08 Mar 2013

Phase of Development: III

Objectives: The primary objective of the study was to evaluate the efficacy of albiglutide as compared with insulin glargine (in combination with metformin alone or metformin + sulfonylurea [SU]) on glycosylated hemoglobin (HbA_{1c}) change from Baseline at Week 52. (The analyses pertaining to the primary efficacy objective are not contained in the current report because these data are found exclusively in the Year 2 Report.)

Secondary efficacy objectives included the following evaluations of treatment with albiglutide as compared with insulin glargine (in combination with metformin alone or metformin + SU):

- HbA_{1c} change from Baseline over time
- Change from Baseline in fasting plasma glucose (FPG) at Week 52. (The analyses pertaining to this secondary efficacy objective are not contained in the current report because these data are found exclusively in the Year 2 Report.)
- Other measures of glycemic control, including:
  - FPG change from Baseline over time
  - Time to hyperglycemia rescue
  - Incidence of clinically meaningful levels of response in HbA_{1c} (i.e., the proportion of subjects below treatment goal of 6.5%, 7.0%, and 7.5%). Note that the protocol-designated response in HbA_{1c} levels of $\leq$6.5%, $\leq$7.0%, and $\leq$7.5%; the reporting and analysis plan and the associated statistical output used the former, noninclusive levels for the analysis. The difference is not considered to be clinically meaningful.
- Change from Baseline in body weight
- Summary measures of glycemic instability derived from a 24-hour glucose profile including hyperglycemia area under the curve. (The analyses pertaining to the

24-hour glucose profile are not contained in the current report because these data are found exclusively in the Year 2 Report.)

- The population pharmacokinetics of albiglutide and the effect of plasma concentrations of albiglutide on glycemic control (population pharmacokinetics/pharmacodynamics). (The analyses pertaining to pharmacokinetics are not contained in the current report because these data are found exclusively in the Year 2 Report.).

Exploratory objectives included the following evaluations of treatment with albiglutide as compared with insulin glargine (in combination with metformin alone or metformin + SU):

- Other measures of glycemic control, including fasting insulin and incidence of hyperglycemia rescue
- Insulin resistance and β-cell function using the corresponding Homeostasis Model Assessment (HOMA) indices
- Subject satisfaction with diabetes treatment using the Diabetes Treatment Satisfaction Questionnaire (status) (DTSQs) and Diabetes Treatment Satisfaction Questionnaire (change) (DTSQc)
- Subject response to diabetes treatment using the Impact of Weight on Quality of Life Questionnaire–Lite (IWQoL-Lite)
- Albumin/creatinine ratio
- Pharmacogenetic (PGx) sampling (analysis of PGx samples is not presented in this clinical study report (CSR) and may be conducted at a later date)
- Analysis of exploratory biomarkers associated with chronic diseases, as appropriate. Blood samples were saved and stored for this purpose (analysis of biomarker samples is not presented in this CSR and may be conducted at a later date).

In addition to evaluation of adverse events (AEs), serious AEs (SAEs), and AEs leading to discontinuation, safety and tolerability objectives included evaluations of the following:

- Safety events of special interest such as cardiovascular events, hypoglycemia events, pancreatitis, thyroid tumors, gastrointestinal (GI) events, diabetic retinopathy events, potential systemic allergic reactions, injection site reactions, and liver events
- Clinical laboratory parameters, vital sign measurements, electrocardiogram (ECG) readings, and physical examination findings
- Immunogenicity

Methodology: This was a Phase III, randomized, open-label, 2 parallel-group, multicenter study of 3 years' duration designed to evaluate the efficacy and safety of a weekly subcutaneously injected dose of 30 mg (with uptitration to 50 mg, if required) of albiglutide as compared with insulin glargine administered daily in subjects with type 2

diabetes mellitus (T2DM) whose glycemia was not adequately controlled on their current regimen of metformin (± SU).

The study comprised 4 study periods: approximately 2 weeks of Prescreening and Screening, 4 weeks of Run-In, 156-week Treatment Period including 52 weeks of treatment and evaluation for primary efficacy and safety, followed by an additional 104 weeks of treatment for additional efficacy and safety, and 8 weeks of Posttreatment Follow-up. The study was designed to run for up to 3 years to assess durability of glycemic effect, to evaluate long-term safety and tolerability, and to accrue sufficient cardiovascular events for a prespecified meta-analysis. When all subjects had completed a minimum of 2 years of treatment (or withdrew early from the study), an analysis for submission of regulatory marketing applications was completed, as agreed in consultation with the authorities. True site and subject identification numbers were "masked" for the purpose of data analysis and submission to the registration applications. The data masking process for this marketing application analysis ensured that the data were blinded to the investigator and operational study staff, including staff at GSK, for the remainder of the study; this process is described in a separate Charter for Work Process Flow for Maintaining Blind: Albiglutide Phase III Studies. This Year 3 Report describes the final cumulative 3-year efficacy data through Week 156 and safety data through to the end of the study. The primary efficacy data at Week 52 and the safety data at the primary endpoint (Week 52) will not be replicated in the current report as these data are found exclusively in the Year 2 Report. Where appropriate, the Year 2 Report has been referenced in the current report and the full document citation is provided in the list of references.

Eligible subjects were stratified based on the HbA_{1c} value obtained at the Week -1 visit (<8.0% vs ≥8.0%), history of prior myocardial infarction (MI) (yes vs no), age (<65 years vs ≥65 years), and current antidiabetic therapy (metformin alone versus metformin + SU). Adjudication and review of all major cardiovascular and pancreatitis events took place over the entire Treatment Period.

The subjects had to have received metformin (± SU) for at least 3 months before Screening and been on a stable dose for at least 8 weeks before randomization. The dose of metformin should have been ≥1500 mg of metformin unless a lower dose had been documented as the maximum tolerated dose. The subject should not have received >7 contiguous days of any antidiabetic agents other than metformin (± SU) within the 3 months before Screening. Subjects continued on their current dose of metformin (± SU) for the duration of their study participation with the exception that subjects who experienced severe or repeated events of hypoglycemia while taking an SU may have had their SU reduced or discontinued at the discretion of the investigator.

Number of subjects: Approximately 750 subjects were planned for random assignment in a 2:1 ratio to add-on treatment with albiglutide or insulin glargine. A total of 779 subjects were randomly assigned: 504 subjects to albiglutide and 241 subjects to insulin glargine.

Subject Disposition			
Number of Subjects	**Albiglutide (N=516) n (%)**	**Insulin Glargine (N=263) n (%)**	**Total (N=779) n (%)**
Randomized Population	516 (100)	263 (100)	779 (100)
Intent-to-Treat Population	496 (96.1)	239 (90.9)	735 (94.4)
Received at least 1 treatment dose (Safety Population)	504 (97.7)	241 (91.6)	745 (95.6)
Completed active treatment	308 (59.7)	164 (62.4)	472 (60.6)
Completed follow-up	304 (58.9)	163 (62.0)	467 (59.9)
Did not complete follow-up	4 (0.8)	1 (0.4)	5 (0.6)
Discontinued active treatment	193 (37.4)	77 (29.3)	270 (34.7)
Completed follow-up	104 (20.2)	27 (10.3)	131 (16.8)
Did not complete follow-up	89 (17.2)	50 (19.0)	139 (17.8)
Number of subjects rescued	221 (42.8)	98 (37.3)	319 (40.9)
Reason for discontinuing active treatment			
Adverse event	50 (9.7)	11 (4.2)	61 (7.8)
Protocol violation	12 (2.3)	3 (1.1)	15 (1.9)
Noncompliance	21 (4.1)	14 (5.3)	35 (4.5)
Severe or repeated occurrences of hypoglycaemia	1 (0.2)	0	1 (0.1)
Lost to follow-up	19 (3.7)	18 (6.8)	37 (4.7)
Subject withdrew consent from active participation	81 (15.7)	29 (11.0)	110 (14.1)
Investigator decided to discontinue study participation	6 (1.2)	1 (0.4)	7 (0.9)
Termination of study by GSK[1]	1 (0.2)	0	1 (0.1)
Other	0	1 (0.4)[2]	1 (0.1)
Reason for not completing follow-up			
Adverse event	10 (1.9)	5 (1.9)	15 (1.9)
Noncompliance	6 (1.2)	5 (1.9)	11 (1.4)
Subject lost to follow-up	38 (7.4)	22 (8.4)	60 (7.7)
Subject did not enter follow-up period	7 (1.4)	7 (2.7)	14 (1.8)
Subject withdrawn from follow-up participation	26 (5.0)	12 (4.6)	38 (4.9)
Investigator decided to discontinue study participation	2 (0.4)	0	2 (0.3)
Termination of study by GSK[2]	2 (0.4)	0	2 (0.3)
Other	2 (0.4)[3]	0	2 (0.3)

GSK = GlaxoSmithKline.

Note: Percentages were calculated using the number of subjects randomized as the denominator.

1. Includes termination of the study and termination of the study site by GSK.
2. Subject discontinued active treatment due to pregnancy.
3. Subjects withdrew consent for follow-up.

Diagnosis and main criteria for inclusion: Male and nonpregnant, nonlactating females aged ≥18 years with a historical diagnosis of T2DM who were experiencing inadequate glycemic control on their current regimen of metformin alone or metformin + SU. Subjects were required to have a body mass index ≥20 kg/m^2 and ≤45 kg/m^2; HbA_{1c} between 7.0% and 10.0%, inclusive, at Visit 5 (Week -1); baseline fasting C-peptide ≥0.8 ng/mL (≥0.26 nmol/L); baseline creatinine clearance >60 mL/min (calculated using the Cockcroft-Gault formula); and baseline hemoglobin ≥11 g/dL (≥110 g/L) for male subjects and ≥10 g/dL (≥100 g/L) for female subjects, and normal thyroid-stimulating hormone level or clinically euthyroid.

Treatment administration: The dosage and administration for each treatment group were as follows:

- Albiglutide 30 mg once per week by subcutaneous injection (with treatment uptitration to 50 mg weekly if needed)
- Insulin glargine daily by subcutaneous injection (dose titration per package insert or prescribing information)

Albiglutide was supplied as fixed-dose, fully disposable pen injector system for delivery of the investigational product from a prefilled dual chamber glass cartridge; it was intended for single use by the subject. Albiglutide was injected subcutaneously into the abdomen, alternating right and left sides of the body. When the injector pen product was reconstituted by the subject (via rotation of the pen housing parts), a neutral isotonic solution was produced. The pen delivered 30 or 50 mg of investigational product or matching placebo (for Run-In Period only) in a 0.5-mL injection volume.

Insulin glargine injection pens were provided to those subjects randomly assigned to receive insulin glargine. Subjects were instructed on reconstitution and storage requirements for insulin glargine and administered insulin glargine as prescribed by their physician.

The following table summarizes the batch numbers for albiglutide and its matching placebo (for the Run-In Period) in this study.

Investigational Product	Batch/Lot Numbers
Albiglutide 30 mg	GAHC02DA, GAHC02DB, GAHE05DA, GAHL07D1A, GAKE01DA, GAIA01DA, GAJB05D1A
Albiglutide 50 mg	GAHL08DA, GAIB02DA, GAID04DA, GAJC06DA, GAJL07DA, GAKE02DA
Placebo (for Run-In Period)	GAGJ01D1A, GAGJ01D1B, GAGJ01DA,GAHD03DA

Subjects continued on their current dose of metformin and SU throughout the study except as described previously. Site personnel confirmed that subjects were taking their dose of metformin and SU as prescribed. Adherence was monitored for the duration of the study.

Hyperglycemia rescue: After randomization, subjects who experienced persistent hyperglycemia qualified to undergo hyperglycemia rescue as per the protocol. Subjects remained in the study and continued to receive their randomly assigned study medication in addition to hyperglycemic rescue medication. Glycemic rescue criteria outlined in the protocol defined the threshold for the initiation of hyperglycemia rescue medications but not postrescue medication management. The choice of rescue drug was not strictly mandated by the protocol. Investigators were permitted to choose what was best for their specific patient. The choice of rescue medication, which could have included the further titration of insulin glargine, a prandial insulin (insulin glargine subjects only), or other glucose-lowering medications, was determined by the investigator.

Criteria for evaluation: HbA_{1c}; FPG; time to and incidence of hyperglycemia rescue; proportion of subjects achieving HbA_{1c} treatment goals; body weight; fasting insulin; HOMA insulin resistance; HOMA β-cell function; DTSQs; DTSQc; IWQoL-Lite; albumin/creatinine ratio; PGx, and biomarkers associated with chronic diseases. Safety assessments included AEs and SAEs, AEs due to withdrawal, AEs of special interest (cardiovascular events, hypoglycemia events, pancreatitis, thyroid tumors, GI events, diabetic retinopathy events, potential systemic allergic reactions, injection site reactions, liver events, and new AEs of special interest [atrial fibrillation events, atrial flutter events, and pneumonia events, which were added following review of the Phase III integrated safety data]), clinical laboratory parameters, vital sign measurements, 12-lead ECG readings, physical examination findings, and immunogenicity.

Statistical methods: The primary analysis of the HbA_{1c} change from Baseline response at Week 52 was addressed in the Year 2 Report and is not included in this report.

For the Year 3 data, the continuous secondary efficacy endpoints (HbA_{1c} change from Baseline over time and the FPG and body weight changes over time) were summarized both descriptively and using an analysis of covariance model using the Intent-to-Treat (ITT) Population. Both the observed case (OC) without rescue algorithm, where only observed prehyperglycemic rescue data were used, and the OC with rescue algorithm, where all observed data including posthyperglycemic rescue results were used, were applied to the HbA_{1c} analysis. Unless specified, the rest of the efficacy endpoints were based on the OC without rescue algorithm.

For the Year 3 analysis, the time to hyperglycemia rescue was considered the most robust measurement for long-term efficacy in a comparative setting. Time to hyperglycemic rescue was calculated as the number of days between the date of first dose of study medication and the date of first hyperglycemia rescue, plus 1. Subjects who did not experience hyperglycemia rescue were censored at the date of the Week 156 visit or the date of the early termination visit if the subject terminated the study early. The between-group differences in time to hyperglycemia rescue were compared using pairwise log-rank tests. Median time to hyperglycemia rescue for each treatment group was also summarized. The proportion of subjects with hyperglycemia rescue up to Week 156 (Day 1092) based on Kaplan-Meier estimates was displayed in the summary table. Kaplan-Meier curves of the times to hyperglycemia rescue for each treatment group were presented.

The safety analyses included comparative summaries of vital sign measurements, laboratory values, physical examination findings, and AE incidence rates computed from Baseline to the end of the study (events are described before the addition of hyperglycemia rescue medication and overall, including rescue medications). Incidence of GI AEs such as nausea, vomiting, and diarrhea were summarized and analyzed in addition to AE summaries.

The ITT Population included all randomly assigned subjects who received at least 1 dose of study medication and had a baseline assessment and at least 1 postbaseline assessment (scheduled or unscheduled) of the primary endpoint, HbA_{1c}. The ITT subjects were analyzed according to randomly assigned treatment. The Safety Population included all

randomly assigned subjects who received at least 1 dose of study medication. The safety subjects were analyzed according to treatment received.

Summary:

The following table summarizes the baseline and demographic characteristics for subjects in this study:

Demographic and Baseline Characteristics (Safety Population)				
	Albiglutide (N=504)	**Insulin Glargine (N=241)**	**Total (N=745)**	**p-value[1]**
Age at randomization (years)				0.1468
n	504	241	745	
Mean (SD)	55.8 (9.33)	54.7 (9.75)	55.5 (9.48)	
Median	56.0	55.0	56.0	
Minimum, Maximum	27, 81	26, 83	26, 83	
Age category, n (%)				0.9141
n	504	241	745	
<65 years	424 (84.1)	202 (83.8)	626 (84.0)	
≥65 years	80 (15.9)	39 (16.2)	119 (16.0)	
Sex, n (%)				0.6115
n	504	241	745	
Female	218 (43.3)	109 (45.2)	327 (43.9)	
Male	286 (56.7)	132 (54.8)	418 (56.1)	
Race[2], n (%)				
n	504	241	745	
African American/African Heritage	130 (25.8)	64 (26.6)	194 (26.0)	
American Indian or Alaskan Native	3 (0.6)	1 (0.4)	4 (0.5)	
Asian - Central/South Asian Heritage	7 (1.4)	5 (2.1)	12 (1.6)	
Asian - East Asian Heritage	2 (0.4)	1 (0.4)	3 (0.4)	
Asian - Japanese Heritage	0	1 (0.4)	1 (0.1)	
Asian - Southeast Asian Heritage	16 (3.2)	8 (3.3)	24 (3.2)	
Native Hawaiian or Other Pacific Islander	1 (0.2)	0	1 (0.1)	
White - Arabic/North African Heritage	7 (1.4)	2 (0.8)	9 (1.2)	
White - White/Caucasian/European Heritage	342 (67.9)	158 (65.6)	500 (67.1)	
Other	2 (0.4)	1 (0.4)	3 (0.4)	
Ethnicity, n (%)				0.9157
n	504	241	745	
Hispanic/Latino	81 (16.1)	38 (15.8)	119 (16.0)	
Not Hispanic/Latino	423 (83.9)	203 (84.2)	626 (84.0)	
Weight (kg)				0.7290
n	504	241	745	
Mean (SD)	95.08 (19.66)	94.55 (19.08)	94.91 (19.46)	
Median	93.10	91.00	92.80	
Minimum, Maximum	46.1, 151.5	57.4, 151.4	46.1, 151.5	
Body mass index (kg/m^2)				0.6519
n	504	241	745	
Mean (SD)	33.18 (5.56)	32.98 (5.44)	33.12 (5.52)	
Median	33.00	32.00	33.00	
Minimum, Maximum	20.0, 46.0	20.0, 45.0	20.0, 46.0	

Demographic and Baseline Characteristics (Safety Population)				
	Albiglutide (N=504)	**Insulin Glargine (N=241)**	**Total (N=745)**	**p-value[1]**
Body mass index category, n (%)				0.3098
n	504	241	745	
<25 kg/m^2	26 (5.2)	8 (3.3)	34 (4.6)	
≥25 to <30 kg/m^2	116 (23.0)	63 (26.1)	179 (24.0)	
≥30 to <35 kg/m^2	155 (30.8)	83 (34.4)	238 (31.9)	
≥35 kg/m^2	207 (41.1)	87 (36.1)	294 (39.5)	

SD = standard deviation.
1. The p-value was for testing the null hypothesis that the summary statistics (mean or proportion) were equal among treatment groups. All tests were 2-sided.
2. Subjects could have been counted in more than 1 category.

Efficacy:

- A total of 779 subjects were randomly assigned to study treatment in this study (516 subjects in albiglutide group and 263 subjects in the insulin glargine group). At Week 156, 123 subjects in the albiglutide group and 88 subjects in the insulin glargine group completed treatment without requiring hyperglycemic rescue.

- At Week 52 (primary endpoint), a statistically significant decrease in HbA_{1c} from Baseline to Week 52 was observed in both the albiglutide and the insulin glargine treatment groups, with a model-adjusted change from baseline LS mean of -0.67% in the albiglutide group and -0.79% in the insulin glargine group. The treatment difference (albiglutide minus insulin glargine) of 0.11% at Week 52, using the last observation carried forward algorithm, was not statistically significant (p=0.1463) and the upper bound of the confidence interval was below the prespecified noninferiority margin of 0.3% (95% CI: -0.04, 0.27), indicating noninferiority of albiglutide to insulin glargine.

- Among those subjects who remained in the study without the need for hyperglycemic rescue, the HbA_{1c}-lowering effect seen at Week 52 for both treatments was maintained through Week 156. The reduction in HbA_{1c} from Baseline over time was similar between the 2 treatment groups. The observed mean change from Baseline in HbA_{1c} at Week 156 (the end of the 3-year treatment period) was -0.83% in albiglutide group and -1.00% in the insulin glargine group.

- Per the protocol, subjects received hyperglycemic rescue medication if prespecified hyperglycemic rescue criteria were met. Subjects who were rescued continued to have HbA_{1c} levels monitored, which allowed for evaluation of glycemic control over the entire duration of the study. Using the OC algorithm and including postrescue values (i.e., all HbA_{1c} values regardless of whether subjects were rescued), glycemic control was maintained in both treatment groups throughout the 3-year duration of the study.

- Results for change from Baseline in FPG, among those subjects who remained in the study without the need for hyperglycemic rescue, showed durability of the FPG-lowering effect. The observed mean change from Baseline in FPG at Week 156

was -0.83 mmol/L in the albiglutide group and -2.19 mmol/L in the insulin glargine group. This difference between treatments in change in FPG from Baseline to Week 156 significantly favored the insulin glargine-treated subjects.

- By Week 156, a similar proportion of subjects in the albiglutide and insulin glargine group required hyperglycemia rescue (44.6 % and 41.0%, respectively). A higher probability of hyperglycemia rescue among subjects in the albiglutide group was evident from approximately Week 52. By Week 156, the probability of hyperglycemia rescue was 56.2% in the albiglutide group and 48.0% in the insulin glargine group. The most commonly used rescue medication in both treatment groups was insulin (insulin glargine in the albiglutide group and insulin lispro in the insulin glargine group).

- Albiglutide demonstrated sustained glycemic control over the 3-year duration of the study. By Week 156, using the OC algorithm and excluding postrescue values, 59 of 123 subjects (48.0%) in the albiglutide group and 46 of 88 subjects (52.3%) in the insulin glargine group achieved a treatment goal of HbA_{1c} <7.0%. The number of subjects achieving a treatment goal of <6.5% at Week 156 was higher for albiglutide-treated subjects, and those achieving the treatment goal of <7.5% was higher for insulin glargine-treated subjects.

- Using the OC algorithm and excluding postrescue values, body weight loss was observed in the albiglutide group and weight gain was observed in the insulin glargine group. The observed mean change from Baseline in weight at Week 156 was -3.47 kg in the albiglutide group and 0.90 kg in the insulin glargine group. The treatment difference (albiglutide minus insulin glargine) was statistically significant in favor of albiglutide at each time point from Week 1 through Week 156.

- Using the OC algorithm and excluding postrescue values, mean fasting insulin increased through Week 1 and then decreased to near baseline levels by Week 156. In the insulin glargine group, mean values increased to Week 12 and then maintained a plateau to Week 104 before increasing again through Week 156. Results in the insulin glargine group should be interpreted with caution as the insulin assay employed detected both endogenous and exogenous insulin.

- Changes from Baseline over time in HOMA insulin resistance and HOMA β-cell function, using the OC algorithm and excluding postrescue values, were lower in the albiglutide group than in the insulin glargine group. HOMA insulin resistance generally decreased over time to Week 156 in the albiglutide group, whereas there was an initial increase in the insulin glargine group to Week 24, a steady decrease to Week 104, and then an increase to Week 156. HOMA β-cell function increased from Baseline in both treatment groups at Week 156; however, there was a lower increase from Baseline in the albiglutide group than in the insulin glargine group. These results should be interpreted with caution given that the insulin assay employed detected both endogenous and exogenous insulin.

- Overall, improvements in treatment satisfaction as measured by the DTSQs and IWQoL-Lite were durable and maintained through Week 156 in both groups. Both

groups showed improved DTSQs total scores from Baseline to Week 156, with no significant difference between the treatment groups. The mean values of IWQoL-Lite–transformed total scores increased in both albiglutide and insulin glargine groups. Numerically, the increase was greater for albiglutide at each time point tested up to Week 156, but the differences were not statistically significant.

Safety:

- The proportion of subjects reporting AEs was similar between the 2 treatment groups, although the event rate was higher in the albiglutide group than in the insulin glargine group.

Overview of Adverse Events (Safety Population)				
	Albiglutide (N=504)		**Insulin Glargine (N=241)**	
Description	**n (%)**	**Number of AEs[1]**	**n (%)**	**Number of AEs[1]**
Any AE[2]	453 (89.9)	3953	208 (86.3)	1714
Any fatal AE	12 (2.4)	12	5 (2.1)	5
Any serious AE (fatal and nonfatal)	98 (19.4)	181	50 (20.7)	75
Any related AE[3]	164 (32.5)	722	39 (16.2)	111
Any AE leading to withdrawal of active treatment	48 (9.5)	48	10 (4.1)	10
Any AE by maximum intensity[4]				
Mild	140 (27.8)	2623	70 (29.0)	1106
Moderate	196 (38.9)	1115	94 (39.0)	537
Severe	116 (23.0)	212	43 (17.8)	69
Not applicable	1 (0.2)	3	1 (0.4)	2
Any AE by therapy phase				
Pre-therapy	150 (29.8)	247	73 (30.3)	128
On-therapy	443 (87.9)	3585	201 (83.4)	1567
Post-therapy	50 (9.9)	150	13 (5.4)	31
On-therapy AE incidence rate[5]		298.48		253.86

AE = adverse event.

Note: Hypoglycemic events were excluded from this table except in serious AE and pre-therapy AE counts.

1. Number of AEs = the total number of AEs at each level of summarization.
2. Unless otherwise stated, the number of events in this table is for the pre-therapy, on-therapy, and post-therapy periods combined.
3. Adverse events that were missing investigator-assigned relationship to study medication were considered related and included in this summary.
4. A subject was counted once according to the maximum intensity experienced if the subject reported 1 or more AEs. The AEs with missing intensity were considered severe in this summarization.
5. The on-therapy AE incidence rate per 100 person-years = 100*(number of AEs divided by person-years), where person-years is defined as the cumulative study treatment exposure duration (in years) for all subjects in the treatment group during the on-therapy treatment period.

- In both treatment groups, the Medical Dictionary for Regulatory Activities (MedDRA) system organ classes (SOCs) in which on-therapy AEs were most frequently reported were Infections and Infestations, GI Disorders, and Musculoskeletal and Connective Tissue Disorders. The incidence of events in the GI Disorders SOC was greater in the albiglutide group than in the insulin glargine group, with nausea, diarrhea, and constipation all reported at a higher incidence and event rate in the albiglutide group; the incidence of vomiting was similar between the treatment groups. Although, the incidence of other commonly occurring AEs was

generally similar between the treatment groups, small numerical imbalances were observed for nausea, diarrhea, constipation, musculoskeletal pain, and cough. Additionally, events related to "injection site" were more common in the albiglutide group.

- The most common (i.e., ≥10% incidence) on-therapy AEs in the albiglutide group were upper respiratory tract infection (16.5%), nausea (13.3%), hypertension (13.3%), nasopharyngitis (10.9%), and diarrhea (10.9%). The most common on-therapy AEs in the insulin glargine group were upper respiratory tract infection (15.4%), hypertension (12.4%), bronchitis (11.2%), cough (12.0%), and nasopharyngitis (10.0%).
- Most on-therapy AEs in both treatment groups were mild or moderate in intensity, with a similar incidence of each in both treatment groups. The incidence of severe AEs was greater in the albiglutide group (21.4%) than in the insulin glargine group (16.6%). In the albiglutide group, with the exception of severe osteomyelitis and severe anemia, which were each reported for 4 subjects, no individual severe AE was experienced by more than 3 subjects. In the insulin glargine group, no individual severe AE was experienced by more than 2 subjects.
- The overall incidence of on-therapy AEs considered by the investigator to be related to study medication was higher in the albiglutide group than in the insulin glargine group (32.1% vs 15.8%), with injection site reactions and nausea being the most frequently reported related events in the albiglutide group.
- A total of 17 deaths were reported (12 in the albiglutide group [8 on-therapy and 4 post-therapy] and 5 in the insulin glargine group [4 on-therapy and 1 post-therapy]). Four deaths were cardiac in nature, and 3 deaths were due to cancer. No death was considered related to the study medication. Eight deaths were reported since the data cutoff for the Year 2 Report (6 in the albiglutide group [2 on-therapy and 4 post-therapy] and 2 in the insulin glargine group [1 on-therapy and 1 post-therapy]).
- The overall incidence and event rate of SAEs (fatal and nonfatal) was similar between the albiglutide and insulin glargine groups (incidence: 18.3% vs 19.1%; event rate: 12.16 vs 11.18). Most SAEs occurred in the Infections and Infestations SOC in the albiglutide group and in the Cardiac Disorders SOC in the insulin glargine group. Most SAEs were noted for 1 subject in each treatment group. Forty-nine new on-therapy fatal and nonfatal SAEs (35 events in the albiglutide group and 14 events and in the insulin glargine group) were reported since the data cutoff for the Year 2 Report.
- The incidence of AEs leading to withdrawal of active treatment was higher in the albiglutide group (9.5%) than in the insulin glargine group (4.1%). The most common AE leading to study medication withdrawal was injection site reaction, which only occurred in albiglutide-treated subjects. Seven new AEs leading to the withdrawal of active treatment were reported since the data cutoff for the Year 2 Report: 4 events in the albiglutide group and 3 events in the insulin glargine group.
- The AE profile for on-therapy AEs was similar before and after hyperglycemia rescue in both the albiglutide and insulin glargine groups.

- The incidence of subjects with prerescue on-therapy severe hypoglycemia events was similar between the treatment groups (0.6% and 0.8% in the albiglutide and insulin glargine groups, respectively). All severe events occurred in subjects taking background metformin + SU therapy. The incidence of prerescue documented symptomatic hypoglycemia events was lower in the albiglutide group (18.5%) than in the insulin glargine group (30.3%). The between-treatment difference in the event rate of documented symptomatic hypoglycemia was statistically significant in favor of albiglutide. One subject in the insulin glargine group experienced a prerescue SAE of hypoglycemia, and another subject in the insulin glargine group had study medication withdrawn as a result of a prerescue hypoglycemic event. A total of 143 new prerescue, on-therapy hypoglycemic events were reported since the data cutoff for the Year 2 Report: 50 events in the albiglutide group and 93 events in the insulin glargine group
- On-therapy injection site reaction events (events either with the preferred term of "injection site reaction" or other preferred terms that were classified by investigators as injection site reactions) occurred in more subjects in the albiglutide group (88 of 504 subjects, 17.5%) compared with the insulin glargine group (24 of 241 subjects, 10.0%). No injection site reactions were considered serious; 5 injection site reactions (all in the albiglutide group) were severe in intensity. Thirteen subjects in the albiglutide group and no subjects in the insulin glargine group were withdrawn due to an injection site reaction event. The majority of events resolved without sequelae. In both groups, the majority of subjects experienced only 1 or 2 events. Fourteen subjects with injection site reactions tested positive for anti-albiglutide antibodies. Twenty-four new injection site reaction events were reported since the data cutoff for the Year 2 Report: 22 events in the albiglutide group and 2 events in the insulin glargine group.
- The incidence of potential systemic allergic reactions was 2.2% in the albiglutide group and 0.4% in the insulin glargine group for investigator-identified events and 1.6% and 2.1% for Standard MedDRA Query (SMQ)-identified events in the albiglutide and insulin glargine groups, respectively. One albiglutide-treated subject reported an SAE of anaphylactic reaction and 1 albiglutide-treated subject reported a nonserious angioedema event. No events of pharyngeal edema or laryngeal edema were observed. Two of 17 albiglutide subjects who experienced a potential systemic allergic reaction tested positive for anti-albiglutide antibodies. Since the data cutoff for the Year 2 Report, 8 investigator-identified potential systemic allergic reactions were reported in the albiglutide group and 1 SMQ-identified potential systemic allergic reaction (urticaria in the albiglutide group) was reported. There were no new events in the insulin glargine group.
- No subjects reported thyroid cancer. The proportion of subjects experiencing thyroid AEs during the study and those with new thyroid nodules after Screening were similar in both treatment groups. There was no clinically meaningful increase in mean calcitonin levels during the study and no subjects in either group had increased postbaseline calcitonin values of clinical concern. Since the Year 2 Report, 3 subjects in the albiglutide group reported 5 new thyroid nodules and 9 new thyroid AEs were reported (7 events in the albiglutide group and 2 events in the insulin glargine group).

- Four subjects experienced 4 AEs requiring adjudication by the pancreatitis adjudication committee (3 subjects in the albiglutide group and 1 subject in the insulin glargine group). Of these, an event of pancreatitis in the albiglutide group was adjudicated as probable pancreatitis with at least a possible relationship to study treatment. There were no new on-therapy pancreatitis events, but 1 new post-therapy pancreatitis event was reported in the albiglutide group since the data cutoff for the Year 2 Report.
- More subjects in the albiglutide group experienced on-therapy pneumonia events (20 subjects [4.0%]; 20 events) compared with the insulin glargine group (5 subjects [2.1%]; 5 events). No events were considered by the investigator to be related to study medication, and no subject was withdrawn from study medication due to pneumonia. Seven SAE events were reported in the albiglutide group versus none in the insulin glargine group. Five new on-therapy pneumonia events were reported since the data cutoff for the Year 2 Report: 3 events in the albiglutide group and 2 events in the insulin glargine group.
- More subjects experienced on-therapy atrial fibrillation or atrial flutter in the albiglutide group (12 subjects [2.4%]; 16 events) compared with the insulin glargine group (1 subject [0.4%]; 1 event). No event led to the withdrawal of study medication or withdrawal from the study or was considered by the investigator to be related to study medication. Four SAE events were reported in the albiglutide group versus none in the insulin glargine group. One new event of atrial fibrillation (in the albiglutide group) was reported since the data cutoff for the Year 2 Report.
- The incidence of other prespecified events of interest, including diabetic retinopathy, cardiovascular events, was low and similar between the treatment groups.
- There was 1 report of liver enzymes meeting the prespecified laboratory criteria for an SAE (ALT $\geq$3 $\times$ the upper limit of normal [ULN] with concurrent total bilirubin $\geq$2 $\times$ ULN) in the albiglutide group. This subject subsequently had a diagnosis of hepatitis B and was withdrawn from study.
- Changes in vital sign measurements, ECG readings, and physical examination findings were generally unremarkable. No clear treatment-related trend was observed for chemistry or hematology parameters.

Conclusions:

Albiglutide is effective in lowering blood glucose levels as an adjunct to oral antidiabetic medications (metformin ± SU) that have proven unsatisfactory. Results for the secondary endpoints of proportion of subjects meeting clinically relevant HbA_{1c} treatment goals and time to hyperglycemia rescue were similar between treatment groups. In a more "real world-like" setting than is frequently utilized for a clinical trial, where doctors adjust insulin according to their practice standards, the comparison of albiglutide with insulin glargine therapy showed that albiglutide was statistically noninferior to insulin treatment with regards to HbA_{1c} and demonstrated that albiglutide could be used as an alternative to insulin therapy in patients with late-stage T2DM. Despite comparable glucose lowering, albiglutide therapy was associated with less hypoglycemia than insulin glargine and with weight loss rather than weight gain compared with the addition of insulin (model-adjusted treatment difference of 4.2 kg at Week 156).

Albiglutide was generally well tolerated with few fatal events and rates of SAEs similar between treatment groups. The percentage of subjects reporting on-therapy AEs was similar in the albiglutide and insulin glargine groups. Gastrointestinal symptoms, commonly observed with glucagon-like peptide-1 receptor agonists, were observed to a greater extent with albiglutide than insulin glargine; however, the incidence of vomiting was similar for both treatment groups. The proportion of subjects developing anti-albiglutide antibodies was low.

Overall, these data show that, when added on to metformin (± SU), albiglutide provides similar and durable glycemic control compared with insulin glargine and has the potential to reduce the burdensome requirements of insulin therapy while maintaining efficacy and reducing the risk of hypoglycemia.

Effective Date: 24-JUL-2013

Appendix 1 to Synopsis for study GLP112754

Overview of Protocol Amendments

Excerpt from protocol including final amendment version 01 dated 06-Aug-2009.

Division: Worldwide Development
Retention Category: GRS019
Information Type: Protocol Amendment

Title:	A Randomized, Open-Label, Parallel-Group, Multicenter Study to Determine the Efficacy and Long-Term Safety of Albiglutide Compared With Insulin in Subjects With Type 2 Diabetes Mellitus

Compound Number: GSK716155

Development Phase III

Effective Date: 06-AUG-2009

Protocol Amendment Number: 01

Description: This randomized, open-label, parallel-group, multicenter study evaluates the efficacy and long-term safety of a weekly subcutaneously injected dose of albiglutide as compared with insulin (insulin glargine) in subjects with type 2 diabetes mellitus. Subjects with a historical diagnosis of type 2 diabetes mellitus who are inadequately controlled on their current regimen of metformin alone or metformin + sulfonylurea will be recruited into the study.

Subject: Type 2 Diabetes Mellitus

Revision Chronology:

CM2008/00119/00	2008-DEC-28	Original
CM2008/00119/01	2009-AUG-06	Amendment No.: 01 This study was amended to clarify sections of the protocol and more closely define activities surrounding the investigation of albiglutide.

Appendix 2 to Synopsis for study GLP112754

List of study sites

Worldwide Study Centres GLP112754

Country Name	Centre Status	Clinical Site Institution Name	Clinical Site Street	Clinical Site ZIP Code	Clinical Site City
Russian Federation	Concluded	Research Centre of Family Health Problem and Man Reproduction of SD RAMS	Ulitsa Timiryazeva, 16	664003	Irkutsk
Russian Federation	Concluded	Smolensk State Medical Academy	Ulitsa Kirova, 46a	214019	Smolensk
Russian Federation	Concluded	Saratov State Medical University	Ulitsa Bolshaya Gornaya, 43	410030	Saratov
Russian Federation	Concluded	Nizhegorodskaya Regional Clinical Hospital n.a. N.A. Semashko	Ulitsa Rodionova, 190	603126	Nizhniy Novgorod
South Africa	Concluded	Wits Donald Gordon Clinical Trial Site	18 Eton Road	2193	Parktown
South Africa	Concluded	Wits Chris Hani Baragwanath Clinical Trial Site	Old Potchefstroom Road	2013	Johannesburg
South Africa	Concluded	Tread Research	Fransie van Zyl Dr	7505	Parow
South Africa	Concluded	ClinResco Centre	22 Pine Avenue	1619	Kempton Park
South Africa	Concluded	Dr GE Ellis & Dr HO Wellmann Clinical Trials Partnership	Sir Lowrys Pass Road	7129	Somerset West
South Africa	Concluded	Mercantile Hospital	Durban Road	6014	Port Elizabeth
South Africa	Concluded	Deepak Lakha, MBCHB., Private Practice	1644 Starling Street	01820	Johannesburg
South Africa	Concluded	Intercare Medical and Dental Centre	43 Old Oak Road	7530	Cape Town
South Africa	Concluded	Hermant Makan - Private Practice	80 Gemsbok Ave	1827	Lenasia
South Africa	Concluded	Practice		4068	Phoenix
South Africa	Concluded	Pretoria Heart Hospital	Cnr Park & Hamilton Street	00083	Pretoria
South Africa	Concluded	Tiervlei Trial Centre	Mike Pienaar Boulevard	7530	Cape Town
United Kingdom	Concluded	King's College London	Stamford Street	SE1 9NH	London
United Kingdom	Concluded	University Hospital Coventry	Clifford Bridge Road	CV2 2DX	Coventry
United States	Concluded	Radiant Research, Inc.	5251 South Green Street	84123	Murray
United States	Concluded	Holston Medical Group, Weber City	1754 US Hwy 23 N	24290	Weber City
United States	Concluded	Clinical Investigation Specialists, Inc.	1800 Nations Drive	60031	Gurnee
United States	Concluded	Meridian Clinical Research, LLC	3319 North 107th Street	68134	Omaha
United States	Concluded	Southwest Memorial Physician Associates	7777 Southwest Freeway	77074	Houston
United States	Concluded	Northeast Clinical Research of San Antonio, LLC	5000 Schertz Parkway	78154	Schertz
United States	Concluded	Ialum Clinical Research, LLC	3290 Memorial Drive	30032	Decatur
United States	Concluded	Destiny Clinical Research, LLC	991 Kenmore Drive	47714	Evansville
United States	Concluded	Alzohaili Medical Consultants	1331 Monroe Street	48124	Dearborn
United States	Concluded	Manassas Clinical Research Cente	9001 Digges Road	20110	Manassas
United States	Concluded	University of Hawaii	677 Ala Moana Blvd	96813	Honolulu
United States	Concluded	International Clinical Research Network	855 Third Avenue	91911	Chula Vista
United States	Concluded	MedStar Research Institute	6525 Belcrest Road	20782	Hyattsville
United States	Concluded	Columbus Clinical Research Inc	99 North Brice Road	43213	Columbus
United States	Concluded	Advance Metabolic Care Research Institute Incorporated	700 West El Norte Parkway	92026	Escondido
United States	Concluded	Professional Clinical Research, Inc.	1975 Stirling Drive	49643	Interlochen
United States	Concluded	Mission Internal Medical Group	26800 Crown Valley Parkway	92691	Mission Viejo
United States	Concluded	43rd Medical Associates	7725 North 43rd Avenue	85051	Phoenix
United States	Concluded	Mobile Medical and Diagnostic Center	2261 Cstarides Street	36617	Mobile
United States	Concluded	Gainesville Family Physicians	6900 Northwest 9th Boulevard	32605	Gainesville
United States	Concluded	Benefis Physician Associates	1401 25th Street South	59405	Great Falls
United States	Concluded	Private Practice		60525	La Grange
United States	Concluded	Atlanta Diabetes Association	77 Collier Road, Northwest	30309	Atlanta
United States	Concluded	Medical Associates Clinic	1000 Langworthy Street	52001	Dubuque
United States	Concluded	Holston Medical Group-Clinical Research	240 Medical Park Blvd	37620	Bristol
United States	Concluded	Hillcrest Clinical Research LLC	717 South East Main Street	29681	Simpsonville
United States	Concluded	Laureate Medical Group - Clinical Research Group, Suite 1550	550 Peachtree Street , NE	30308	Atlanta
United States	Concluded	Osvaldo Brusco	613 Elizabeth Street	78404	Corpus Christi
United States	Concluded	Galenos Research	12200 Park Central Dr.	75251	Dallas
United States	Concluded	Twin Cities Clinical Research	6200 Shingle Creek Parkway	55430	Brooklyn Center
United States	Concluded	Executive Health and Research Associates, Inc.	1100 Johnson Ferry Road	30342	Atlanta
United States	Concluded	Jefferson City Medical Group	1241 West Stadium Blvd	65109	Jefferson City
United States	Concluded	Northside Internal Medicine	6120 North Mayfair Ave	99208	Spokane
United States	Concluded	KRK Medical Research	6750 Hillcrest Plaza Drive	75230	Dallas
United States	Concluded	Long Beach Center for Clinical Research	2865 Atlantic Ave	90806	Long Beach
United States	Concluded	Nevada Access to Research and Education Society	701 Shadow Lane	89106	Las Vegas
United States	Concluded	Calabash Medical Center	10081 Beach Drive SW	28467	Calabash
United States	Concluded	The Family Doctors	8383 Millicent Way	71115	Shreveport
United States	Concluded	Hope Research Institute LLC	13832 North 32nd Street	85032	Phoenix
United States	Concluded	COR Clinical Research LLC	1211 North Shartel	73103	Oklahoma City
United States	Concluded	Coulter Clinic	941 Summers Avenue	29115	Orangeburg
United States	Concluded	Cotton-O'Neil Clinical Research Center	823 Southwest Mulvane Street	66606	Topeka
United States	Concluded	Venture Resource Group	5799 Broadmoor Street	66202	Mission
United States	Concluded	Florida Institue for Clinical Research	7200 Curry Ford Road	32822	Orlando
United States	Concluded	Advanced Medical Research	6450 Wheatstone Court	43537-9402	Maumee

United States	Concluded	Four Rivers Clinical Research, Inc.	225 Medical Center Drive	42003	Paducah
United States	Concluded	West Houston Clinical Research Services	2026 Wirt Road	77055	Houston
United States	Concluded	DeGarmo Institute of Medical Research	404 Memorial Drive Extension	29651	Greer
United States	Concluded	Clinical Trials of America Inc	1730 North Center Street	28601	Hickory
United States	Concluded	Integrated Medical Research PC	148 E. Hersey St.	97520	Ashland
United States	Concluded	Clinical Trials of Texas	7940 Floyd Curl Drive	78229	San Antonio
United States	Concluded	Gulf Coast Endocrine & DM Center	417 Corbett Street	33756	Clearwater
United States	Concluded	DiGiovanna Family Care Center	1061 North Broadway	11758	North Massapequa
United States	Concluded	Discovery Clinical Trials	7500 Barlite	78224	San Antonio
United States	Concluded	Primecare Medical Group	929 Gessner Road	77024	Houston
United States	Concluded	Jacksonville Center for Clinical Research	810 Lane Avenue, South	32205	Jacksonville
United States	Concluded	Renaissance Clinical Research and Hypertension	5959 Harry Hines Boulevard	75235	Dallas
United States	Concluded	Pharmacotherapy Research Associates Inc.	3620 Court Drive	43701	Zanesville
United States	Concluded	Southeastern Research Associates	4501 Old Spartanburg Road	29687	Taylors
United States	Concluded	Evergreen Medical LTD	2850 W. 95th Street	60805	Evergreen Park
United States	Concluded	Empirical Clinical Trials	118 South Second Street	98942	Selah
United States	Concluded	Top A1 Research	4362 Thousand Oaks Drive	78217	San Antonio
United States	Concluded	The Research Group of Lexington	1401 Harrodsburg Road	40504	Lexington
United States	Concluded	Horizon Clinical Research Associates, PLLC	2730 South Val Visita Drive	85295	Gilbert
United States	Concluded	Kandra Fierer Kuskin Associates Ltd	1199 Colonial Road	17112	Harrisburg
United States	Concluded	Private Practice		92117	San Diego
United States	Concluded	Diabetes Endocrinology Specialists	222 South Woods Mill Road	63017	Chesterfield
United States	Concluded	East/West Medical Research Institute	1585 Kapiolani Blvd	96814	Honolulu
United States	Concluded	Clinical Research Center of Nevada	7425 West Azure	89130	Las Vegas
United States	Concluded	Saint Lukes Medical Center	4320 Wornall Road	Not Defined	Kansas City
United States	Concluded	Talbert Medical Group	19066 Magnolia Street	92646	Huntington Beach
United States	Concluded	Burke Internal Medicine Inc.	9243 Old Keene Mill Road	22015	Burke
United States	Concluded	North Hills Family Practice, P.A.	4351 Booth Calloway Road	76180	North Richland Hills
United States	Concluded	NEA Clinic	311 East Mathews	72401	Jonesboro
United States	Concluded	Baylor College of Medicine	6620 Main Street	77030	Houston
United States	Concluded	UMDNJ-SOM	42 East Laurel Road	08084	Stratford
United States	Concluded	Cadillac Clinical Research, LLC	520 Cobbs St	49601	Cadillac
United States	Concluded	St. Jude Heritage Medical Group	100 East Valencia Mesa Drive	92835	Fullerton
United States	Concluded	Fox Valley Clinical Research Center	2088 Ogden Ave	60504	Aurora
United States	Concluded	Safe Harbor Clinical Research	450 Veterans Mem. Parkway	02914	East Providence
United States	Concluded	Coastal Biomedical Research Inc	2001 Santa Monica Blvd	90404	Satna Monica
United States	Concluded	Eastside Clinical Research Associates	4755 E. Cesar Chavez Ave	90022	Los Angeles
United States	Concluded	Sonterra Clinical Research	414 Navarro Street	78205	San Antonio
United States	Concluded	MultiCare Health System	1901 S. Cedar Street	98405	Tacoma
United States	Concluded	Sun Research Institute	303 East Quincy Street	78215	San Antonio
United States	Concluded	Middle Tennessee Clinical Research	108 Medical Center Blvd., Suite G-50	37334	Fayetteville
United States	Concluded	Midwestern Endocrinology, P.A.	5401 College Boulevard	66211	Overland Park
United States	Concluded	Medex Healthcare Research Inc	100 N. Euclid Avenue	63108	St. Louis
United States	Concluded	Desert Medical Advances	72855 Fred Waring Drive	92260	Palm Desert
United States	Concluded	Grunberger Diabetes Institute	43494 Woodward Ave	48302	Bloomfield Hills
United States	Concluded	American Institute of Research	1127 Wilshire Boulevard	90017	Los Angeles
United States	Concluded	Private Practice		06611	Trumbull
United States	Concluded	Mint Hill Family Practice	11304 Hawthorne Dr	28227	Mint HIll
United States	Concluded	Advocare Heights Primary Care	318 White Horse Pike	08035	Haddon Heights
United States	Concluded	Oakwell Clinical Research, LLC	3338 Oakwell Court	78218	San Antonio
United States	Concluded	National Clinical Research	2809 Emerywood Parkway	23294	Richmond
United States	Concluded	Shores Medical Research	346 North Ridgewood Avenue	32132	Edgewater
United States	Concluded	Baylor University Medical Center	3600 Gaston Avenue	75246	Dallas
United States	Concluded	Metabolic Research Institute Inc	1515 North Flagler Dr.	33401	West Palm Beach
United States	Concluded	Harrisburg Family Medical Center / Clinical Research Connection	802 N. Illinois Street	72432	Harrisburg
United States	Concluded	PHP - Center for Clinical Research	2912 Springboro West	45439	Dayton
United States	Concluded	State of Franklin Healthcare Associates, PLLC	3114 Browns Mill Road	37604	Johnson City
United States	Concluded	Ialum Clinical Research, LLC	3300 Memorial Drive	30032	Decatur
United States	Concluded	Allegiance Research Specialists	2645 North Mayfair Road	53226	Milwaukee
United States	Concluded	Community Healthcare Center	944 E. Cherry Street	44614	Canal Fulton
United States	Concluded	Jackson Clinic	29 South Fourth Street	39159	Rolling Fork
United States	Concluded	Interlink Research Institute	4050 Katella Ave.	90720	Los Alamitos
United States	Concluded	Radiant Research	8122 Datapoint Dr	78229	San Antonio
United States	Concluded	Clinical Medica LaRoss	15381 7th St.	92395	Victorville
United States	Concluded	Sonora Clinical Research, LLC	1520 West State Street	83702	Boise
United States	Concluded	Jones Family Practice	113 East Grover Street	28150	Shelby

United States	Concluded	Eclipse Clinical Research	75 West Calle De Las Tiendas	85614	Green Valley
United States	Concluded	Kaner Medical Group	1305 Airport Freeway	76201	Bedford
United States	Concluded	Clinical Research Authority, LLC	912 Inlet Square Drive	29576	Murrells Inlet
United States	Concluded	Private Practice		77024	Houston
United States	Concluded	Private Practice		76104	Fort Worth
United States	Concluded	Private Practice		85032	Phoenix
United States	Concluded	Clinical Trials of America Inc	1801 Fairfield Avenue	71101	Shreveport
United States	Concluded	Private Practice		80209	Denver
United States	Concluded	KMED Research	25200 Little Mack Avenue	48081	St Clair Shores
United States	Concluded	Atlanta Clinical Research Ctre	5673 Peachtree Dunwoody Road	30342	Atlanta
United States	Concluded	Pri-Med Care	502 N Valley Parkway	75067	Lewisville
United States	Concluded	Springfield Medical Centre	3808 East 3rd Street	32401	Panama City
United States	Concluded	Rainier Clinical Research Center, Inc.	723 SW 10th Street	98057	Renton
United States	Concluded	LaPorte Medical Group	900 I Street	46350	La Porte
United States	Concluded	Clinical Research of West Florida	2147 NE Coachman Road	33765	Clearwater
United States	Concluded	ClinSearch	6035 Shallowford Road	37421	Chattanooga
United States	Concluded	Suncoast Research Group, LLC	2128 W. Flagler St.	33135	Miami
United States	Concluded	Juno Research, LLC	1911 S. Gessner	77074	Houston
United States	Concluded	Progressive Clinical Research	2067 West Vista Way	92083	Vista
United States	Concluded	Utica Park Clinic	1145 South Utica Avenue	74104	Tulsa
United States	Concluded	Arlington Family Research	707 North Fielder Road	76012	Arlington
United States	Concluded	Irvine Center For Clinical Research	16275 Laguna Canyon Road	92618	Irvine
United States	Concluded	Mutigen, LLC	711 North Atlantic Street	37398	Tullahoma
United States	Concluded	Meridien Research	4751 66th Street, North	33709	St. Petersburg
United States	Concluded	Columbus Research Foundation	2425 Brookstone Centre Parkway	31904	Columbus
United States	Concluded	Georgia Clinical Research	2121 Fountain Drive	30078	Snellville
United States	Concluded	Integrated Research Center	4282 Genesee Ave	92117	San Diego
United States	Concluded	Tipton Medical & Diagnostic Center	334 Route 220	16684	Tipton
United States	Concluded	Rocky Mountain Diabetes and Osteoporosis Center	3910 Washington Parkway	83404	Idaho Falls
United States	Concluded	Southern California Endocrine Center	50 Bellefontaine Street	91105	Pasadena
United States	Concluded	Encompass Clinical Research	10225 Austin Drive	91978	Spring Valley
United States	Concluded	San Diego Sports Medicine and Family Health Center	6699 Alvarado Road	92120	San Diego
United States	Concluded	Diabetes & Endocrinology Consultants	611 North 35th Street	28557	Morehead City
United States	Concluded	Alta Clinical Research Center, LLC	1704 W. Anklam Road	85745	Tucson
United States	Concluded	Clinical Research of West Florida, Inc.	5115 N. Armenia Avenue	33603	Tampa
United States	Concluded	Discovery Clin. Trials	20658 Stone Oak Parkway	78258	San Antonio
United States	Concluded	Homestead Clinical Research Group	11285 Southwest 211 Street	33189	Cutler Bay
United States	Concluded	San Diego Managed Care Group	11777 Bernardo Plaza Court	92128	San Diego
United States	Concluded	West Broadway Clinic	1701 West Broadway	51501	Council Bluffs
United States	Concluded	Castlerock Clinical Research Consultants, LLC	6804 South Canton	74136	Tulsa
United States	Concluded	Private Practice		32927	Cocoa
United States	Concluded	East Coast Clinical Research, Inc.	One Water Street	01830	Haverhill
United States	Concluded	Hampton Family Practice	9 Manhattan Square	23666	Hampton
United States	Concluded	Berma Research Group	1625 Southeast 3rd Avenue	33316	Fort Lauderdale
United States	Concluded	Private Practice		33317	Plantation
United States	Concluded	Deer Park Family Clinic	2910 Center Street	77536	Deer Park
United States	Concluded	Wetlin Research Associates INC	6367 Alvarado Court	92120	San Diego
United States	Concluded	Kentucky Diabetes Endocrinology Center	1760 Nicholasville Road	40503	Lexington
United States	Concluded	Quality of Life Medical & Research Center	5390 East Erickson Drive	85712	Tucson
United States	Concluded	Central Nebraska Medical Clinic	145 Memorial Drive	68822	Broken Bow
United States	Concluded	The Methodist Hospital	18400 Katy Freeway	77094	Houston
United States	Concluded	Medex Healthcare Research Inc	1034 South Brentwood Boulevard	63117	St. Louis
United States	Concluded	Partners in Research, LLC	470 White Pond Drive	44320	Akron
United States	Concluded	Southern Clinic, PC	1901 Melba Drive	36301	Dothan
United States	Concluded	DHARMA, LLC	11332 Mountain View Drive	92354	Loma Linda
United States	Concluded	Commonwealth Biomedical Research	240 East Ayr Parkway	42431	Madisonville
United States	Concluded	Spokane Internal Medicine	1215 N. McDonald Rd.	99216	Spokane
United States	Concluded	Personal Physician Care	4800 Linton Boulevard	33445	Delray Beach
United States	Concluded	Valley Research	550 E. Herndon Ave	93720	Fresno
United States	Concluded	Indiana University Health Arnett, Inc.	2600 Ferry Street	47904	Lafayette
United States	Concluded	Central Jersey Medical Research Center	240 Williamson Street	07202	Elizabeth
United States	Concluded	MD Medical Research	6357 Oxon Hill Road	20745	Oxon Hill
United States	Concluded	Gulfside Clinical Research LLC	3300 15th Str.	39501	Gulfport
United States	Concluded	Searcy Medical Center	2900 Hawkins Drive	72143	Searcy
United States	Concluded	Lincoln Internal Medicine Associates	3901 Pine Lake Rd	68516	Lincoln
United States	Concluded	Permian Research Foundation	315 East 5th Street	79761	Odessa
United States	Concluded	Kentucky Medical Research Center	354 Waller Avenue	40504	Lexington
United States	Concluded	Family Medical Center	26740 Towne Centre Drive	92610	Foothill Ranch
United States	Concluded	Wells Institute for Health Awareness	513 East Stroop Road	45429	Kettering

United States	Concluded	Southeaster Research	4501 Old Spartanburg Road	29687	Taylors
United States	Concluded	Private Practice		33026	Pembroke Pines
United States	Concluded	Alpha Medical Research	2984 Alafaya Trail	32765	Oviedo
United States	Concluded	Eastern Research	760 East 49th Street	33013	Hialeah
United States	Concluded	Advanced Medical Research	5220 Clark Avenue	90712	Lakewood
United States	Concluded	Diagnostic & Critical Care Medicine PC	411 Laurel Street	50314	Des Moines
United States	Concluded	Philander Clinical Research	2481 Professional Court	89128	Las Vegas
United States	Concluded	The Whittier Institute for Diabetes	9894 Genesee Avenue	92037	LaJolla
United States	Concluded	Integrated Research Group	4646 Brockton Avenue	92506	Riverside
United States	Concluded	Magnolia Research Group Inc.	2203 SE Third Avenue	34471	Ocala
United States	Concluded	WellMed Clinical Research	7622 Louis Pasteur Drive	78229	San Antonio
United States	Concluded	Community Research	4460 Red Bank Expressway	45227	Cincinnati
United States	Concluded	Fletcher Allen Health Care	62 Tilley Drive	05403	South Burlington
United States	Concluded	Breco Research, Ltd	16659 Southwest Freeway	77479	Sugar Land
United States	Concluded	Upstate Pharmaceutical Research	30 Pointe Circle	29615	Greenville
United States	Concluded	Medex Healthcare Research	401 East 55th Street	10022	New York
United States	Concluded	Private Practice		23434	Suffolk
United States	Concluded	Research Protocol Management Specialists (RPMS)	1050 Bower Hill	15243	Pittsburgh
United States	Concluded	Creighton Diabetes Center	601 N 30th Street	68131	Omaha
United States	Concluded	R & D Clinical Research Inc	461 This Way Street	77566	Lake Jackson
United States	Concluded	Clinical Study Center of Asheville, LLC	15 Yorkshire St., Suite 202	28803	Asheville
United States	Concluded	Little Rock Family Practice Clinic	701 N University Ave Suite 202	72205	Little Rock
United States	Concluded	Diabetes/Lipid Management and Research Center	18821 Delaware Street	92648	Huntington Beach
United States	Concluded	Dallas Diabetes & Endocrine Center	7777 Forest Lane	75230	Dallas
United States	Concluded	Private Practice		79925	El Paso
United States	Concluded	New Mexico Clinical Research & Osteoporosis Center	300 Oak Street Northeast	87106	Albuquerque
United States	Concluded	Westside Family Medical Centre	6565 West Main Street	49009	Kalamazoo
United States	Concluded	Internal Medicine and Pediatric Associates	13100 East 136th Street	46037	Fishers
United States	Concluded	Professional Clinical Research, Inc.	6227 Frankfort Highway	49616	Benzonia
United States	Concluded	Cedar Valley Clinical Research Center, LLC	220 West Ridgeway Avenue	50701	Waterloo
United States	Concluded	Valley Internal Medicine, Inc.	2149 Valleygate Drive	28304	Fayetteville
United States	Concluded	Interspond, LLC	8615 Knott Avenue	90620	Buena Park
United States	Concluded	Private Practice		70433	Covington
United States	Concluded	PhysiqueMed Clinical Trials	1593 Yanceyville Street	27405	Greensboro
United States	Concluded	Heartland Research Associates, LLC	510 West Radio Lane	67005	Arkansas City
United States	Concluded	UMDNJ - Robert Wood Johnson Medical School	1 Robert Wood Johnson Place	08903	New Brunswick
United States	Concluded	St. Johns Center for Clinical Research	141 Hilden Rd	32081	Ponte Verda
United States	Concluded	Green and Seidner Family Practice	826 N. Broad St.	19446	Landsdale
United States	Concluded	University Clinical Investigators, Inc.	2492 Walnut Avenue	92780	Tustin
United States	Concluded	Associates In Medicine	4543 Post Oak Place	77027	Houston
United States	Concluded	South Florida Clinical Research Center	6448 Pembroke Road	33023	Hollywood
United States	Concluded	Radiant Research, Inc	2081 West Frye Road	85224	Chandler
United States	Concluded	Ialum Clinical Research, LLC	4850 Redan Road	30088	Stone Mountain
United States	Concluded	Novellus Research Sites, Inc.	11190 Warner Avenue	92708	Fountain Valley
United States	Concluded	Cutting Edge Research Group	6613 North Meridian Avenue	73116	Oklahoma City
United States	Concluded	Alpha Clinical Research	279 Clear Sky Ct.	37043	Clarksville
United States	Concluded	University Of Iowa	200 Hawkins Dr.	52243	Iowa City
United States	Concluded	Pennsylvania Research Institute	2846 Knights Road	19020	Bensalem
United States	Concluded	WVVA Healthcare Alliance	3738 Davis Stuart Road	24901	Lewisburg
United States	Concluded	Leavitt Medical Associates of Florida Incorporated	725 West Granada Boulevard	32174	Ormond Beach
United States	Concluded	Chase Medical Center	500 Chase Pkway	06708	Waterbury
United States	Concluded	Kernodle Clinic, Inc.	1234 Huffman Mill Road	27215	Burlington
United States	Concluded	Panhandle Family Care Associates & Emerald Coast Research Group, Inc.	4284 Kelson Ave	32446	Marianna
United States	Concluded	Metobolic Research Institute, Inc.	8200 Jog Road	33437	Boynton Beach
United States	Concluded	American Health Network	5250 East US 36	46123	Avon
United States	Concluded	PICR, Inc.	1745 Old Spring House Lane	30338	Atlanta
United States	Concluded	Burke Pharmaceutical Research	3633 Central Avenue	71913	Hot Springs
United States	Concluded	Great Lakes Research Group	200 South Wenona Street	48706	Bay City
United States	Concluded	Protenium Clinical Research LLC	1725 Chadwick Court	76054	Hurst
United States	Concluded	Cedar Crosse Research Center	800 S Wells Street	60607	Chicago
United States	Concluded	Internal Medicine of Delaware, LLC	102 Sleepy Hollow Drive	19709	Middletown
United States	Concluded	Options Health Research LLC	1245 South Utica Av.	74104	Tulsa
United States	Concluded	Alegent Health Research	7710 Mercy Road	68124	Omaha
United States	Concluded	PMI Health Research Group	285 Boulevard Northeast	30312	Atlanta
United States	Concluded	Ted Thorp MD Professional Corporation	2801 West Charleston Boulevard	89102	Las Vegas
United States	Concluded	River Birch Research Alliance, LLC	101 Riverstone Vista	30513	Blue Ridge
United States	Concluded	Ireland Road Medical Group	1815 East Ireland Road	46614	South Bend
United States	Concluded	Juno Research, LLC	607 S. Mason Road	77450	Katy
United States	Concluded	Innovative Clinical Trials	1020 26th Street South	35205	Birmingham

United States	Concluded	Southeastern Medical Research Institute	2100 North Avenue	31904	Columbus
United States	Concluded	National Institute of Clinical Research	5701 South Eastern Avenue	90040	Commerce
United States	Concluded	Tucker Family Medical - Clinical Research Connections	505 Hillcrest Street	72619	Bull Shoals
United States	Concluded	Catalina Research Institute LLC	14726 Ramona Avenue	91710	Chino
United States	Concluded	Borgess Research Institute	1722 Shaffer Street	49048	Kalamazoo
United States	Concluded	Abraham Research, PLLC	2300 Chamber Center Drive	41017	Fort Mitchell
United States	Concluded	Wade Family Medicine	557 West 2600 South	84010	Bountiful
United States	Concluded	Investigative Clinical Research of Indiana, LLC	6920 Parkdale Place	46254	Indianapolis
United States	Concluded	Bayou City Clinical Research	8408 Bellaire Boulevard	77036	Houston
United States	Concluded	Accurate Clinical Research	12553 Gulf Freeway	77034	Houston
United States	Concluded	Deerfield Beach Cardiology Associates	1874 West Hillsboro Boulevard	33442	Deerfield Beach
United States	Concluded	Clinical Trials North Houston	18220 State Highway 249	77070	Houston
United States	Concluded	SouthCoast Medical Group	1326 Eisenhower Dr	31406	Savannah
United States	Concluded	Mountain Diabetes and Endocrine Center	1998 Hendersonville Road	28803	Asheville
United States	Concluded	SUNY Upstate Medical University	505 Irving Ave.	13210	Syracuse
United States	Concluded	Private Practice		45040	Mason
United States	Concluded	Baptist Diabetes Associates	7867 N. Kendall Drive	33156	Miami
United States	Concluded	ProHealth Clinical Studies	3104 17th Str.	34769	St. Cloud
United States	Concluded	MD Clinical		33009	Hallandale Beach
United States	Concluded	Achieve Clinical Research, LLC	100 Rice Mine Road Loop	35406	Tuscaloosa
United States	Concluded	Private Practice		77479	Sugarland
United States	Concluded	Rapid Medical Research, Inc	3619 Park East Drive	44122	Cleveland
United States	Concluded	ICR at Wolfson & Klein Medical Center	6767 West Tropicana Avenue	89103	Las Vegas
United States	Concluded	Northern California Research	3840 Watt Avenue	95821	Sacramento
United States	Concluded	Spring Clinical Research	9898 Bissonnet Street	77036	Houston
United States	Concluded	Internal Medicine Clinical Research, P.A.	5959 Harry Hines Blvd	75235	Dallas