Summary ID# 9632

Clinical Study Summary: Study H7U-MC-IDBA

A Phase 3, Open-Label, Three-Group Parallel Study to Evaluate the Efficacy and Safety of Human Insulin Inhalation Powder (HIIP) in Patients with Type 2 Diabetes Treated with Once-Daily Insulin Glargine

Date summary approved by Lilly: 01 May 2009

Title of Study: A Phase 3, Open-Label, Three-Group Parallel Study to Evaluate the Efficacy and Safety of Human Insulin Inhalation Powder (HIIP) in Patients with Type 2 Diabetes Treated with Once-Daily Insulin Glargine	
Investigators: This multicenter study included 103 principal investigators.	
Study Centers: This study was conducted at 101 study centers in 11 countries.	
Publications Based on the Study: None at this time.	
Length of Study: Date first patient enrolled (randomized): 18 September 2006 Date last patient completed (study terminated early): 30 May 2008	**Phase of Development:** 3

Objectives: This parallel study involved 3 treatment groups: patients continuing insulin glargine on an intensified regimen ("intensified glargine"); patients stopping once-daily insulin glargine and starting mealtime HIIP ("HIIP only"); and patients continuing once-daily insulin glargine, but adding mealtime HIIP ("HIIP + intensified glargine"). In all groups, the oral antihyperglycemic medications used prior to randomization were continued at the doses used at screening.

Primary Objectives:

The primary objective of this study was to compare, in patients who at study entry had type 2 diabetes not optimally controlled by one or more oral antihyperglycemic medications plus once-daily insulin glargine, the following hypotheses with respect to mean change in HbA_{1c} from baseline to 24 week endpoint:

- Noninferiority with respect to mean change in HbA_{1c} from baseline to 24 week endpoint in "HIIP only" group minus "intensified glargine" group, with noninferiority margin of 0.4%,
- Superiority with respect to mean change in HbA_{1c} from baseline to 24 week endpoint in "HIIP + intensified glargine" group minus "intensified glargine" group,
- Superiority with respect to mean change in HbA_{1c} from baseline to 24 week endpoint in "HIIP only" group minus "intensified glargine" group.

Superiority with respect to HbA_{1c} would be concluded if the upper limit of the 95% confidence interval for a specified treatment difference ("HIIP only" minus "intensified glargine or "HIIP + intensified glargine" minus "intensified glargine") was less than zero. Noninferiority was concluded if this upper limit was less than 0.4%, but greater than or equal to 0.0%.

These hypotheses were tested using the following fixed-sequence approach: (1) the tests were carried out in the order listed above and (2) all previous tests must have demonstrated a statistically significant result at the 0.05 level before conducting the next test in the list. The fixed-sequence approach controlled the overall type 1 error rate at a 0.05 level. The study was considered to have achieved its primary objective(s) if at least the first of the hypotheses was achieved.

Secondary Objectives:

- To compare the "HIIP only" group versus the "intensified glargine" group, "HIIP + intensified glargine" group versus the "intensified glargine" group, and the "HIIP + intensified glargine" group versus the "HIIP only" group, with respect to the following after 24 weeks and 52 weeks (if applicable) of treatment:
  - mean change in HbA_{1c} from baseline to various time points (including comparison for change in HbA_{1c} from baseline to 24 week endpoint for "HIIP + intensified glargine" versus "HIIP only" groups),
  - the proportion of patients achieving HbA_{1c} <7.0% and, in a separate analysis, achieving HbA_{1c} ≤6.5%,
  - the proportion of patients who required rescue therapy,
  - 8-point self-monitored blood glucose (SMBG) profiles (blood glucose measurements before the morning, midday, and evening meals; 2 hours after the start of the morning, midday, and evening meals; at bedtime; and at 3 a.m.),
  - insulin dose requirements (total insulin and, where applicable, basal or prandial insulin),
  - standard fasting lipid profile (high-density lipoprotein cholesterol [HDL-C], total cholesterol, triglycerides, and low-density lipoprotein cholesterol [LDL-C]) (only collected at 24 weeks),
  - hypoglycemia (rate, incidence, nocturnal, severe),
  - patient-reported evaluation of the following: insulin delivery system satisfaction, lifestyle impact of insulin delivery system, ease of dosing; diabetes treatment satisfaction; energy, positive well-being, negative well-being; fatigue, cognitive distress symptoms, hyperglycemia symptoms, hypoglycemia symptoms; perceived effectiveness; willingness to continue current insulin system,
  - body weight,
  - treatment-emergent adverse events,
  - safety as assessed by insulin antibody levels; pulmonary function testing (PFT), including forced expiratory volume in 1 second (FEV_1), forced vital capacity (FVC), total lung capacity (TLC), and diffusing capacity of the lung for carbon monoxide (DL_{CO}); Pulmonary Symptoms Questionnaire (PSQ).
- To assess inhaler reliability in patients randomized to treatment with HIIP.

Exploratory Objectives

- To explore the relationship between HbA_{1c} and GlycoMark blood test.
- To assess health status with patient-reported outcomes questionnaire (EQ-5D).
- To collect data regarding resource utilization (that is, hospitalizations and emergency room visits).

Study Design: This parallel study randomized patients to 3 treatment groups: patients who continued insulin glargine on an intensified regimen ("intensified glargine"); patients who stopped once-daily insulin

glargine and starting mealtime HIIP ("HIIP only"); and patients who continued once-daily insulin glargine, but added mealtime HIIP ("HIIP + intensified glargine"). In all groups, the oral antihyperglycemic medications used prior to randomization were continued at the doses used at screening (unless safety concerns mandated dosage change). Hemoglobin A_{1c} was used to assess overall glycemic efficacy. The primary efficacy endpoint was assessed at 24 weeks; and safety endpoints were examined at 24 weeks and at 52 weeks of treatment.

Number of Patients:

Planned: 510 Actual: 560

Randomized: 222 "HIIP only", 115 "HIIP + intensified glargine", 223 "intensified glargine"

Completed 24-week Treatment Period:

148 "HIIP only", 80 "HIIP + intensified glargine", 163 "intensified glargine"

Completed 52-week Treatment Period*:

45 HIIP only, 25 HIIP + intensified glargine, 54 intensified glargine

*On 7 March 2008, the sponsor announced the decision to terminate the development of the AIR Insulin program due to increasing uncertainties in the regulatory environment and after a thorough evaluation of the evolving commercial and clinical potential of the product compared with existing therapies. The decision was not a result of any observations during AIR Insulin trials relating to the safety of the product.

Diagnosis and Main Criteria for Inclusion: Male or female nonsmoking patients 18 years of age or older; type 2 diabetes mellitus for at least 6 months at study entry treated with one or more oral antihyperglycemic medications on a stable dose for at least 6 weeks (3 months for thiazolidinediones [TZDs]) and once-daily insulin glargine for at least 4 months; FEV_1 and DL_{CO} >70% predicted; HbA_{1c} $\geq$7.5% and $\leq$10.5% at screening.

Test Product, Dose, and Mode of Administration: Human Insulin Inhalation Powder (HIIP) delivered to the deep lung using the commercial version of the Lilly/Alkermes insulin inhaler (AIR® Insulin Inhaler System). Doses were titrated according to the protocol and administered preprandially as combinations of inhaled low-dose and mid-dose strengths (equivalent to approximately 2U and 6U of injectable insulin). Patients continued their prestudy oral antihyperglycemic medication dose and regimen throughout the study.

Duration of Treatment: 52-week treatment period.

Reference Therapy, Dose, and Mode of Administration: Injectable insulin glargine (of recombinant DNA origin, 100U/mL) administered at the same time of day as at study entry. Dosage was determined based on individual needs and was intensified according to the protocol. Injectable insulin lispro (of recombinant DNA origin, 100U/mL) if necessary for rescue therapy, beginning at the 24-week visit. Patients continued their prestudy oral antihyperglycemic medication dose and regimen throughout the study.

Variables:

Efficacy: The primary efficacy measure was the difference in the change in mean HbA_{1c} from baseline to endpoint (24 weeks). The secondary measures of the study were to compare the three treatment groups after 24 weeks and 52 weeks with respect to the following parameters: mean change in HbA_{1c} from baseline to timepoints, 8-point SBGM profiles; proportion of patients who achieved HbA_{1c} $\leq$6.5% and <7.0%; proportion of patients who required rescue therapy; daily insulin dose; fasting lipid profile; and, insulin inhaler reliability.

Safety Measures: Insulin antibody levels; chest x-rays; electrocardiograms; change from baseline in PFTs (FEV_1, FVC, FEV_1/FVC, TLC, DL_{CO}); difference from baseline in cough and other pulmonary symptoms using the PSQ; hypoglycemia; "for cause" evaluations, treatment-emergent adverse events; laboratory tests; vital signs (body temperature, systolic and diastolic blood pressure, pulse and respiratory rate); and weight.

Health Outcomes: Patient-reported general well-being, diabetes-associated symptoms, diabetes treatment satisfaction, and evaluation of insulin delivery systems using the 12-item Well-Being Questionnaire

(W-BQ12); the Cognitive Distress, Fatigue, Hyperglycemia, and Hypoglycemia Subscales of the Diabetes Symptom Checklist-Revised (DSC-R); the Diabetes Treatment Satisfaction Questionnaire Status Version ($DTSQ_s$); and the Insulin Delivery System Questionnaire (IDSQ), and the EQ-5D.

Evaluation Methods:

The evaluation of the primary efficacy analysis consisted of three tests in a fixed sequence using gatekeeping to preserve type I error rate: noninferiority of "HIIP only" to "intensified glargine", superiority of "HIIP + intensified glargine" to "intensified glargine only", superiority of "HIIP only" to "intensified glargine". The sample size in the "HIIP only" and "intensified glargine" treatment groups was first chosen so that the comparison between the 2 groups after 24 weeks would have approximately 90% power to show superiority of "HIIP only" to "intensified glargine" assuming the HbA_{1c} treatment difference between these groups in HbA1c change from baseline was -0.40% and a 15% dropout rate over 24 weeks). Noninferiority of "HIIP only" to "HIIP + intensified glargine" was tested in a similar manner. For efficacy variables (HbA_{1c}, SBGM level, daily insulin dose, standard fasting lipid profile) and for continuous safety measures, an analysis of covariance (ANCOVA) model was performed for treatment comparisons which included terms for treatment, insulin secretagogue strata, country, and corresponding baseline. HbA_{1c} strata were included as a term in all continuous models except for HbA_{1c}. For proportion of patients who had an HbA_{1c} $\leq$6.5% and <7.0%, and proportion of patients requiring rescue therapy, a logistic regression analysis was utilized. For pulmonary function test the ANCOVA model also included terms for PFT baseline values, baseline height, age, and sex. No adjustments for missing data were performed with the exception of the last observation carried forward (LOCF) when earlier observations on treatment were available. All tests of treatment effects were conducted at a two-sided alpha level of 0.05 and/or two-sided 95% confidence interval, with no multiplicity adjustment. For categorical data, Fisher's exact test for pairwise comparisons (or Freeman-Halton for comparison of 3 groups) or Chi-square test was used. Baseline value used for the analysis was the last scheduled baseline value obtained for each patient prior to randomization. Summary statistics were calculated for efficacy and safety measures.

Summary:

A total of 1246 patients signed informed consent for the study, all of whom completed Visit 1. Of these 1246 patients, 686 patients did not meet the entry criteria and 560 patients were randomly assigned to a treatment group (222 patients on "HIIP only", 115 patients on "HIIP + intensified glargine", and 223 patients on "intensified glargine") at the randomization visit. Of the 560 randomized patients, 124 (22.1%) patients completed the 52-week treatment period for this study (45 patients on "HIIP only", 25 patients on "HIIP + intensified glargine", and 54 patients on "intensified glargine") and 115 (20.5%) patients (42 patients on "HIIP only", 25 patients on "HIIP + intensified glargine", and 48 patients on "intensified glargine") completed the study. Of 560 randomized patients, 391 (69.8%) patients completed the 24-week treatment period for this study (148 patients on "HIIP only", 80 patients on "HIIP + intensified glargine", and 163 patients on "intensified glargine"). The most common reasons for study discontinuation in both groups were sponsor decision and patient decision.

The intent-to-treat (ITT) study population represented a population of individuals with type 2 diabetes inadequately controlled by one or more oral antihyperglycemic medications and once-daily insulin glargine. The average duration of prior insulin use was 2.41 years. The patient demographic data were similar among the 3 treatment groups. The only statistically significant difference was mean age (p=.041), which was statistically significantly higher in the "intensified glargine" group (57.8±9.8) compared with the "HIIP only" group (55.9±9.5).

After 24 weeks of treatment, the change from baseline to LOCF endpoint in HbA_{1c} in the "HIIP only" group compared with the "intensified glargine" group was -0.20% (95% CI: -0.39, -0.02; p=.032). The change in HbA_{1c} in the "HIIP + intensified glargine" group compared with the "intensified glargine" group

was -0.35% (95% CI: -0.57, -0.13; p=.002). The difference between the "HIIP + intensified glargine" group and "HIIP only" group (-0.15%) was not statistically significant (p=.198). The study met all 3 levels of its primary objective, demonstrating that preprandial HIIP treatment provides a statistically significantly greater reduction in HbA_{1c} than intensified once-daily insulin glargine treatment when combined with oral antihyperglycemic agents in patients inadequately controlled on once-daily insulin glargine plus oral antihyperglycemic agents.

In subgroup analyses of HbA_{1c} (%) change from baseline to 24-week and 52-week LOCF endpoints by baseline HbA_{1c} category, "HIIP only" treatment was superior to "intensified glargine" treatment in the 7.5% – 8.5% baseline HbA_{1c} category at both the 24- and 52-week LOCF endpoints. At the 52-week LOCF endpoint, "HIIP + intensified glargine" treatment was superior to "intensified glargine" treatment in the 7.5% – 8.5% baseline HbA_{1c} category.

At the 24-week LOCF endpoint, the percentage of patients in each group achieving an HbA_{1c} of <7.0% were 27.5% in the "HIIP only" group, 25.2% in the "HIIP + intensified glargine" group, and 14.7% in the "intensified glargine" group. The percentage of patients in each group achieving an HbA_{1c} of ≤6.5% were 14.0% in the "HIIP only" group, 12.6% in the "HIIP + intensified glargine" group, and 4.1% in the "intensified glargine" group. There were statistically significantly greater percentages of patients achieving either HbA_{1c} target in the "HIIP only" group compared with the "intensified glargine" group at the 24-week and 52-week LOCF endpoints. There were statistically significantly greater percentages of patients achieving either HbA_{1c} target in the "HIIP + intensified glargine" group compared with the "intensified glargine" group at the 24-week and 52-week LOCF endpoints. The differences between the "HIIP + intensified glargine" and "HIIP only" groups were not statistically significant at LOCF endpoints.

There were greater improvements from baseline of the overall 2-hour postprandial blood glucose in the "HIIP only" group compared with the "intensified glargine" group and in the "HIIP + intensified glargine" group compared with the "intensified glargine" group but not in the "HIIP + intensified glargine" group compared with the "HIIP only" group. These improvements were statistically significant. Consistent results were obtained for the other postprandial timepoints and for the overall daily average blood glucose. One exception was at the evening postprandial timepoint where the "HIIP only" group had a larger decrease compared with the "HIIP + intensified glargine" group at the 24-week LOCF endpoint.

In contrast to the postprandial and overall blood glucose differences between treatment arms, the morning fasting glucose analyses demonstrated less worsening from baseline in the "intensified glargine" group compared with the "HIIP only" group and compared with the "HIIP + intensified glargine" group. The "HIIP only" group had greater worsening compared with the "HIIP + intensified glargine" group. These differences were statistically significant. No statistically significant differences between treatment groups were observed for the midday preprandial, evening preprandial, or 3 a.m. timepoints.

At the 24-week LOCF endpoint based on MODD, there was a statistically significantly greater decrease from baseline in the inter-day blood glucose variability in the "HIIP only" and "HIIP + intensified glargine" groups compared with the "intensified glargine" group. The differences in changes from baseline in the "HIIP + intensified glargine" and "HIIP only" groups were not statistically significant.

The mean daily weight adjusted total insulin dose at the 24-week LOCF endpoint in the "HIIP only" group was 0.77 U/kg, in the "HIIP + intensified glargine" was 1.00 U/kg, and in the "intensified glargine" was 0.57 U/kg. At the 52-week LOCF endpoint, the mean daily weight adjusted total insulin dose in the "HIIP only" group was 0.84 U/kg, in the "HIIP + intensified glargine" group was 1.05 U/kg, and in the "intensified glargine" group was 0.61 U/kg. The mean total daily weight adjusted insulin doses were

statistically significantly different between all 3 treatment groups and for each pairwise comparisons at both 24-week and 52-week LOCF endpoints (p<.007).

Because no significant difference between the "HIIP only" and "intensified glargine" groups was observed on the IDSQ insulin delivery satisfaction domain at the 24-week LOCF endpoint, no further statistical comparisons in any of the questionnaires were evaluated for superiority of HIIP to intensified glargine. Patients in the "intensified glargine" group had statistically significant greater improvements in IDSQ lifestyle impact domain scores compared with those in the "HIIP + intensified glargine" group at the 24-week and 52-week LOCF endpoints. Patients in the "intensified glargine" group also had statistically significant greater improvements in DTSQ treatment satisfaction scores compared with those in the "HIIP only" group at all LOCF endpoints.

Of the 2451 inhalers dispensed, none of the 15 inhalers returned for complaint during the study were found to be faulty.

There were 2 deaths during the study (cardiac arrest in a "HIIP + intensified glargine" patient and myocardial infarction in a "HIIP only" patient). A total of 30 patients experienced one or more SAEs, 18 patients in the "HIIP only" group, 5 patients in the "HIIP + intensified glargine" group, and 6 patients in the "intensified glargine" group. One patient reported an SAE prior to being assigned to a treatment group. A total of 6 patients (4 patients in the "HIIP only" group and 2 patients in the "HIIP + intensified glargine" group) discontinued the study due to an adverse event. One event each of dyspnea, cough, and allergic hypersensitivity were considered to be related to study procedure. The event of allergic hypersensitivity was also considered to be related to the study device. One event of cough was considered to be related to study device, study medication, and study procedures.

Overall, 132 (59.5%) patients in the "HIIP only" group, 76 (66.1%) patients in the "HIIP + intensified glargine" group, and 131 (59.3%) patients in the "intensified glargine" group experienced at least one TEAE during the study. Table 1 shows the TEAEs reported by at least 2% of patients in the safety population. The most frequently reported TEAEs in the groups with HIIP exposure were nasopharyngitis, cough, and headache and in the group with "intensified glargine" exposure was nasopharyngitis. In the system organ class of general disorders and administration site conditions, there were statistically significant differences between the "HIIP + intensified glargine" group and the "intensified glargine" group (p=.002) and between the "HIIP + intensified glargine" group and the "HIIP only" group (p=.017). For headache, the rate in the "HIIP only" group was higher than the rate in the "intensified glargine" group (p=.016). In the system organ class of respiratory, thoracic, and mediastinal disorders, there were statistically significant differences between the "HIIP only" and "intensified glargine" groups (p=.013) and between the "HIIP + intensified glargine" and "intensified glargine" groups (p=.002). There was statistically significantly more cough in the "HIIP only" group versus the "intensified glargine" group (p=.046). In the system organ class of ear and labyrinth disorders, there was a statistically significantly higher number of patients with one or more TEAE within the overall category in the "HIIP + intensified glargine" group compared with the "HIIP only" group (p=.019).

There were no statistically significant differences between any of the treatment comparisons in change from baseline of FEV_1, FVC, FEV_1/FVC, TLC, and corrected DL_{CO} at the 24-week LOCF endpoint in analyses adjusted for patient characteristics. At the 52-week visit and at isolated visits, there were statistically significantly greater declines from baseline of FEV_1, FVC, and corrected DL_{CO} measurements in either the "HIIP only" or "HIIP + intensified glargine" groups compared with the "intensified glargine" groups. At the follow-up visit, the only statistically significant difference between treatment groups for any of the pulmonary function tests was a decline in corrected DL_{CO} in the "intensified glargine" group compared with a slight increase in the "HIIP only" group.

There were no statistically significant differences between the treatment groups in the incidence or rate per 30 days of hypoglycemic episodes or nocturnal hypoglycemic episodes at the LOCF endpoints. At individual visits, there were higher incidences of hypoglycemia and/or nocturnal hypoglycemia in the "intensified glargine" group compared with the "HIIP only" group. There were higher incidences and/or rates of hypoglycemia in the "HIIP + intensified glargine" group compared with either the "HIIP only" group or the "intensified glargine" group. There were higher incidences and rates of nocturnal hypoglycemia in the "intensified glargine" group compared with the "HIIP + intensified glargine" group and in the "HIIP + intensified glargine" group compared with the "HIIP only" group. There were statistically significantly higher percentages of patients with at least one severe hypoglycemic episode in the "HIIP only" group compared with the "intensified glargine" group at the 24-week (p=.036) and 52-week (p=.032) LOCF endpoints.

There were statistically significant differences overall between the 3 treatment groups at all treatment phase visits (p<.001) for cross-reactive antibodies during the study. Patients in the "HIIP only" and "HIIP + intensified glargine" groups had greater increases from baseline compared with the "intensified glargine" group. For insulin-specific antibodies, there was a greater increase from baseline in the "HIIP + intensified glargine" group as compared with the other 2 treatment groups. For lispro-specific antibodies, there were no statistically significant differences between the treatment groups.

There were no clinically significant differences at endpoint between the treatment groups for systolic blood pressure, diastolic blood pressure, heart rate, respiratory rate, body temperature, or change from baseline in body weight.

Analyses of the study data led to the following conclusions:

- The study met the primary objectives, demonstrating that preprandial HIIP treatment was statistically superior with respect to mean change in HbA_{1c} from baseline to the 24-week endpoint in the "HIIP only" and the "HIIP + glargine" groups minus "intensified glargine", respectively.
- There were statistically significant greater proportions of patients achieving either <7.0% or ≤6.5% HbA_{1c} target in the "HIIP only" and "HIIP + glargine" compared with the "intensified glargine" groups at the 24- and 52-week LOCF endpoints, but this difference was not seen in the "HIIP only" compared with "HIIP + glargine" groups.
- The "HIIP only" and "HIIP + glargine" groups showed greater decreases from baseline in the overall 2-hour postprandial blood glucose, overall daily average blood glucose levels, and most postprandial timepoints compared with the "intensified glargine", but not for preprandial or 3 a.m. timepoints.
- The mean total daily weight adjusted insulin doses were statistically significantly different between all 3 treatment groups and for each pairwise comparison at the endpoints with "HIIP + glargine" group taking the highest dose and "intensified glargine" group taking the lowest dose.
- There were more severe hypoglycemic episodes in the "HIIP only" group compared with the "intensified glargine" group at the LOCF endpoints. Early in the treatment period, there were more hypoglycemic and/or nocturnal hypoglycemic episodes in the "intensified glargine" group compared with the "HIIP only" group and there were more nocturnal hypoglycemic episodes in the "intensified glargine" group compared with the "HIIP + intensified glargine" group.
- There was no significant difference between the "HIIP only" and "intensified glargine" groups on the IDSQ insulin delivery satisfaction domain at the 24-week LOCF endpoint. However, patients in the "intensified glargine" group compared with patients in the "HIIP + intensified glargine" group had greater improvements in IDSQ at the 24-week LOCF endpoint.

- Patients in the “intensified glargine” group had greater improvement in the DTSQ treatment satisfaction scores at both LOCF endpoints than did the “HIIP only” group.
- None of the safety findings in this study changed the known safety profile of HIIP.

Table 1. Summary of Treatment-Emergent Adverse Events Reported in at Least 2% of Patients by Decreasing Frequency
Safety Population

Preferred Term	Treatment Group: 1) HIIP Only (N=222) n (%)	2) HIIP + Intensified Glargine (N=115) n (%)	3) Intensified Glargine (N=221) n (%)	p-Values: Overall	1) - 3)	2) - 3)	2) - 1)
Patients with >= 1 TEAE	132 (59.5)	76 (66.1)	131 (59.3)	.423	>.999	.239	.240
Patients with No TEAE	90 (40.5)	39 (33.9)	90 (40.7)	.423	>.999	.239	.240
NASOPHARYNGITIS	34 (15.3)	13 (11.3)	29 (13.1)	.610	.587	.729	.407
COUGH	31 (14.0)	17 (14.8)	17 (7.7)	.053	.046	.055	.870
HEADACHE	23 (10.4)	9 (7.8)	9 (4.1)	.032	.016	.200	.558
INFLUENZA	13 (5.9)	8 (7.0)	14 (6.3)	.901	.846	.820	.813
PHARYNGOLARYNGEAL PAIN	13 (5.9)	7 (6.1)	5 (2.3)	.106	.090	.117	>.999
ARTHRALGIA	13 (5.9)	5 (4.3)	14 (6.3)	.796	.846	.620	.621
UPPER RESPIRATORY TRACT INFECTION	12 (5.4)	9 (7.8)	9 (4.1)	.382	.656	.200	.476
BACK PAIN	12 (5.4)	8 (7.0)	11 (5.0)	.742	>.999	.463	.629
PAIN IN EXTREMITY	10 (4.5)	4 (3.5)	6 (2.7)	.613	.446	.740	.779
DIARRHOEA	8 (3.6)	6 (5.2)	9 (4.1)	.762	.811	.781	.567
HYPERTENSION	8 (3.6)	2 (1.7)	2 (0.9)	.154	.105	NA	.504
VOMITING	6 (2.7)	7 (6.1)	5 (2.3)	.151	>.999	.117	.142
PYREXIA	6 (2.7)	3 (2.6)	2 (0.9)	.326	.285	NA	>.999
SINUSITIS	6 (2.7)	3 (2.6)	7 (3.2)	.947	.787	>.999	>.999
MYALGIA	6 (2.7)	1 (0.9)	3 (1.4)	.538	.503	NA	.430
URINARY TRACT INFECTION	4 (1.8)	4 (3.5)	8 (3.6)	.486	.260	>.999	NA
NAUSEA	4 (1.8)	3 (2.6)	8 (3.6)	.494	.260	.755	NA
ANXIETY	3 (1.4)	1 (0.9)	6 (2.7)	.496	.338	.429	NA
OSTEOARTHRITIS	2 (0.9)	0	5 (2.3)	.196	.285	.170	NA
DYSPEPSIA	1 (0.5)	4 (3.5)	5 (2.3)	.054	.122	.498	NA
TOOTHACHE	1 (0.5)	3 (2.6)	6 (2.7)	.111	.068	>.999	NA
NASAL CONGESTION	1 (0.5)	2 (1.7)	6 (2.7)	.116	.068	.720	NA
PHARYNGITIS	1 (0.5)	1 (0.9)	6 (2.7)	.127	.068	.429	NA

Abbreviations: HIIP = Human Insulin Inhalation Powder; N = number of patients; TEAE = treatment-emergent adverse event.