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Clinical Study Summary: Study H7U-MC-IDAS

A Pivotal, Open-Label, Parallel Study to Evaluate the Safety and Efficacy of Human Insulin Inhalation Powder (HIIP) Compared to Injectable Insulin in Patients with Diabetes and COPD or Asthma

Date summary approved by Lilly: 01 May 2009

Title of Study: A Pivotal, Open-Label, Parallel Study to Evaluate the Safety and Efficacy of Human Insulin Inhalation Powder (HIIP) Compared to Injectable Insulin in Patients With Diabetes and COPD or Asthma	
Investigator(s): This multicenter study included 186 principal investigators.	
Study Center(s): This study was conducted at 159 study centers in 15 countries.	
Publication(s) Based on the Study: None at this time.	
Length of Study: Date first patient enrolled: 21 Nov 2005 Date last patient completed: 26 May 2008	**Phase of Development:** 3

Objectives: This trial consisted of two similar studies with different patient populations (patients with diabetes and chronic obstructive pulmonary disease [COPD] or patients with diabetes and asthma). Each study was analyzed separately for the primary objective. The primary objective of these studies was to test the hypothesis that the glycemic control achieved with preprandial HIIP is noninferior to that achieved with injectable insulin, as measured by mean change from baseline to endpoint in hemoglobin A1c (HbA_{1c}) after approximately 12 months. A noninferiority margin of 0.4% for HbA_{1c} was used.

The secondary objectives were as follows:
1) To compare the effects of preprandial HIIP and injectable insulin on the following parameters after approximately 12 months:

- forced expiratory volume in 1 second (FEV_1) and forced vital capacity (FVC) before and after inhalation of bronchodilator
- the response to bronchodilator as measured by change between pre- and post-bronchodilator FEV_1 and FVC
- DL_{CO} (pre-bronchodilator)
- total lung capacity (TLC) (pre-bronchodilator)

Objectives (concluded):

- safety as assessed by insulin antibody levels, adverse events (AEs), and episodes of hypoglycemia
- safety as assessed by chest x-rays
- safety as assessed by the St. George's Respiratory Questionnaire
- safety as assessed by the Six-Minute Walk Test with the Borg CR10 Scale
- proportion of patients who achieved or maintained HbA_{1c} of ≤6.5% and who achieved or maintained HbA_{1c} of <7.0%
- proportion of patients with type 2 diabetes on oral agent(s) randomized to HIIP only or glargine only who did not achieve an HbA_{1c} <7.5% after at least 6 months
- glycemic control as assessed by the 8-point self-monitored blood glucose (SMBG) profiles (blood glucose measurements before and 2 hours after the start of the morning, midday, and evening meals, and blood glucose measurements at bedtime and 0300 hours)
- insulin dose requirements (including total, basal, and/or bolus insulin)
- patient-reported outcomes questionnaires to assess general health status
- resource utilization (for example, hospitalizations and emergency room visits).

2) To assess insulin inhaler reliability in patients randomized to treatment with HIIP.
3) To explore the impact of HIIP on peak flow and peak flow variability in the study with asthma patients.

Study Design: These open-label, randomized, active-comparator, 2-arm parallel studies assessed the safety and efficacy of HIIP compared with injectable insulin for treatment of diabetes in approximately 300 patients with asthma and 300 patients with COPD for 12 months. These studies comprised of a 4-week screening and lead-in period, a 12-month treatment period, and an 8-week follow-up period. During the screening and lead-in period, baseline data were collected and patients were switched to study insulin if necessary. During the treatment period, patients were randomly assigned to 1 of 2 treatment groups: Treatment 1: Preprandial HIIP (with or without glargine); Treatment 2: Injectable insulin (insulin glargine, insulin glargine + regular human insulin, insulin glargine + insulin lispro) with or without oral anti-hyperglycemic medication (OAM). Following the treatment period, patients randomized to HIIP were switched to injectable insulin (insulin glargine, insulin glargine + regular human insulin, insulin glargine + insulin lispro) with or without OAMs.

Number of Patients in the Asthma Population:

Planned: 300
Randomized: 232 total patients, 118 preprandial HIIP, 114 preprandial injectable insulin
Completed treatment period*: 145 total patients, 76 preprandial HIIP, 69 preprandial injectable insulin
Completed the study*: 122 total patients, 64 preprandial HIIP, 58 preprandial injectable insulin

Number of Patients in the COPD Population:

Planned: 300
Randomized: 66 total patients, 34 preprandial HIIP, 32 preprandial injectable insulin
Completed treatment period*: 37 total patients, 16 preprandial HIIP, 21 preprandial injectable insulin
Completed the study*: 31 total patients, 14 preprandial HIIP, 17 preprandial injectable insulin

* 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 patients 30 years of age or older for those with COPD, 18 years of age or older for those with asthma; had type 1 diabetes mellitus for at least 24 months at study entry or had type 2 diabetes mellitus and were taking insulin or were appropriate candidates for insulin therapy, as judged by the investigator; met disease (diabetes) diagnostic criteria as defined by the World Health Organization (WHO); had an HbA_{1c} ≤11% at screening; nonsmokers and had been diagnosed with asthma or COPD. Additionally, they must have had an FEV_1, FVC, and DL_{CO} >50% predicted per local pulmonary function testing (PFT) lab. Asthma and COPD populations are defined as follows:

Asthma Population:

To be included in the asthma population for this protocol, a patient must:

- have a documented history of reversible airway obstruction based on either a post-bronchodilator change in FEV_1 of ≥12%, or a previously conducted positive metacholine challenge test (per ATS guidelines)

OR

- have, at Visit 1, a post-bronchodilator change in FEV_1≥12%.

COPD Population:

Patients must meet the following criteria at Visit 1 to be included in the COPD population:

- smoking history ≥15 pack years
- post-bronchodilator change in FEV_1<12%
- FEV_1/FVC <70% (post-bronchodilator).

Test Product, Dose, and Mode of Administration: Human Insulin Inhalation Powder (HIIP) was administered preprandially to the deep lung by the Lilly/Alkermes insulin inhaler using a combination of 2 dose strengths, low (2U-equivalent) and mid (6U-equivalent). Dosage was determined based on individual needs.

Duration of Treatment: 12-month treatment period

Reference Therapy, Dose, and Mode of Administration: Injectable insulin (insulin glargine, insulin glargine + regular human insulin, insulin glargine + insulin lispro) with or without OAMs was administered daily per the directions for use. Dosage was determined based on individual needs.

Variables:

Efficacy: The primary efficacy measure was the HbA_{1c} change from baseline to endpoint. The secondary measures of the study were as follows: 8-point blood glucose profiles; daily insulin dose requirements; and in patients randomized to HIIP, insulin inhaler reliability as assessed by a sampling of returned used inhalers without complaint and all inhalers returned due to patient complaint.

Safety measures: The St. George's Respiratory Questionnaire (SGRQ), FEV_1, and FVC before and after inhalation of bronchodilator, TLC, DL_{CO}, 6-Minute Walk Test (6MWT) with Borg CR10 Scale, insulin antibody titers, chest x-rays, 'for cause' evaluation, hypoglycemia, and adverse events. Additional safety measures included vital signs (body temperature, systolic and diastolic blood pressure, pulse respiratory rate), body weight, general physical examination and directed cardiopulmonary exam, and carboxyhemoglobin levels (COPD population only).

Peak Flow Assessment: Peak flow data were collected but are not reported here.

Health Outcomes: Patient-reported health status and insulin delivery system satisfaction were collected using the EuroQol (EQ-5D) instrument but are not reported here.

Statistical Methods:
The primary efficacy outcome was HbA_{1c} change from baseline to the endpoint. Additional secondary variables included 8-point blood glucose profiles and insulin dose requirements. For most continuous safety variables (vital signs and antibodies), an analysis of covariance (ANCOVA) model with effects for treatment, country, and diabetes stratum at entry (type 1 diabetes, type 2 diabetes insulin taking, or type 2 diabetes insulin-naive), and baseline as a covariate was performed for treatment comparisons, while a similar nonparametric analysis was used to analyze hypoglycemia rate. Percent of patient achieving HbA1c targets (≤6.5%, <7.0%) used a logistic regression. For PFT variables, the ANCOVA model also included age, baseline height, sex, and baseline value. All tests of treatment effects were conducted at a two-sided alpha level of 0.05. Last observation carried forward (LOCF) was used for missing data. Summary statistics were calculated for all variables.

Summary: The 2 parts of the study (Asthma and COPD) will be discussed separately below.

Asthma

Of 291 patients with diabetes and asthma who signed informed consent for the study, 232 patients were randomly assigned to either HIIP treatment (118 patients) or injectable insulin treatment (114 patients). Of these 232 randomized patients, 145 patients completed the treatment period specified for the primary analysis (76 patients, HIIP group; 69 patients, injectable insulin group). There was no statistically significant difference between groups for the percentage completing at that time point. The most common reasons for early patient discontinuations were sponsor decision, patient decision, and lost to follow-up.

Of the 232 randomized patients in the ITT population, 86 (37.1%) were male and 146 (62.9%) were female; one-half of all randomized patients (116 patients, 50.0%) were Caucasian. The average age (mean±SD) was 55.5±12.0 years with a minimum age of 19 years and maximum age of 85 years. The average baseline body weight was 81.3±21.8 kg and the average baseline height was 162.1±10.9 cm. Of the 232 randomized patients, 64 (27.6%) were past smokers with an average number of years smoked of 20.1±12.3 years. Patients had a mean duration of diabetes of 11.4±8.7 years and a mean duration of asthma of 20.6±17.0 years. The patient demographic data were similar between the treatment groups.

Noninferiority to preprandial injectable insulin in change from baseline HbA_{1c} to endpoint was not demonstrated as the upper limit of the 95% CI was >0.4% (95% CI was -0.053, 0.555). The difference between the preprandial HIIP group and the preprandial injectable insulin group in change from baseline HbA_{1c} to endpoint was 0.251 (p=.105).

In an analysis of HbA_{1c} change from baseline to endpoint by FEV_1 subgroup, the subgroup with the lowest FEV_1 at baseline showed a difference between the treatment groups with patients in the injectable insulin group having greater decreases in HbA_{1c} from baseline than the HIIP group (p=.001). In addition, the test for the interaction of HbA_{1c} change from baseline between treatment group and FEV_1 percentage of predicted value at baseline was also significant (p=.026). These results suggest that very poor pulmonary function in patients with diabetes and asthma may adversely affect the ability of HIIP to lower glucose.

There were no statistically significant differences between the treatment groups for the percentage of patients in each group able to achieve the HbA_{1c} goal of <7.0%. However, there were statistically significant differences between the treatment groups in mean change from baseline to endpoint for the overall 2-hour postprandial, evening 2-hour postprandial, and bedtime SMBG levels with the HIIP group having a larger decrease from baseline. Although the HIIP group tended to have slightly higher HbA_{1c} values, these occurred with the HIIP group receiving nominally higher insulin doses. There were

statistically significant differences in change from baseline to endpoint of weight-adjusted prandial insulin doses (with imputation) at morning (p=.003), midday (p=.007), and evening (p=.027) time points, and for total prandial dose (p=.002). None of the inhalers dispensed during the study was found to be faulty.

One patient in the injectable insulin group died of sudden death. A total of 47 patients experienced one or more SAEs, 20 patients in the HIIP group and 27 patients in the injectable group. A total of 2 patients in the HIIP group and 1 patient in the injectable insulin group had an AE that resulted in study discontinuation after randomization. No AEs that resulted in discontinuation were considered possibly study drug or study procedure related.

Overall, 80 (67.8%) patients in the HIIP group and 81 (71.7%) patients in the injectable insulin group experienced at least one TEAE during the study. There was no statistically significant difference between the 2 groups in the percentage of patients reporting one or more TEAE. Table 1 shows the TEAEs reported by at least 2% of the safety population. There was a statistically significant difference between the 2 treatment groups for dyspnea (p<.001).

There were no statistically significant differences between treatment groups for the change from baseline in pre-bronchodilator FEV_1 and the change from baseline for the difference in pre- to post-bronchodilator FEV_1 values at any visit or at endpoint. FVC showed similar results. The change from baseline in the FEV_1/FVC ratio was significantly different at the 3-month visit (p=.025) with the HIIP group experiencing a larger decrease. A similar difference was observed at LOCF endpoint (p=.006). There was a statistically significant difference in change from baseline between the 2 treatment groups in DL_{CO} measurements at LOCF endpoint (p=.028) with the HIIP group experiencing a larger decrease. The statistically significant difference between treatment groups for DL_{CO} was no longer present at the follow-up visit. Other pulmonary assessments such as the St Georges Questionnaire, the 6-Minute Walk Test and the Borg CR10 scale did not reveal any statistically significant differences between the treatment groups. The 'for cause' process did not identify clinically significant differences in pulmonary abnormalities among patients exposed to HIIP versus injectable insulin.

There were no statistically significant differences between treatment groups for any the vital signs collected during the study although there were statistically significant differences in body weight between the 2 treatment groups at Visits 6 through 9, at endpoint (p<.001), and at follow-up (p=.020) with patients in the HIIP group having less weight gain.

There were statistically significant differences between the 2 treatment groups at all treatment phase visits (where insulin antibody samples were collected) for cross-reactive and insulin-specific antibodies, with patients in the HIIP group having greater increases from baseline for both types of antibodies. This difference was not seen for the lispro-specific antibody assay.

There were no statistically significant differences between the HIIP group and the injectable insulin group in the incidence or rate of overall and nocturnal hypoglycemia at LOCF endpoint, and no apparent difference in the percent of patients with at least 1 severe hypoglycemic episode during the study.

Analysis of the study data for the asthma population led to the following conclusions:

- The study did not meet the primary objective of demonstrating that the glycemic control (mean change in HbA_{1c} from baseline to 12-month LOCF endpoint) achieved with preprandial HIIP was noninferior to that achieved with injectable insulin.
- The 2 treatment groups were not different with respect to the percentage of patients achieving HbA_{1c} levels of <7% or ≤6.5% or in the percentage of patients who qualified for or initiated rescue therapy.

- The risk of hypoglycemia did not differ between the treatment groups.
- There were significant baseline to endpoint increases in the human insulin-specific antibody and cross-reactive antibody percent binding in the HIIP group.
- The HIIP group experienced larger decreases in DL_{CO} during the study that were no longer present at the follow-up visit. There were no significant differences between the 2 groups in FEV_1, FVC, TLC, or response to bronchodilator.
- The safety profile of HIIP in patients with asthma was consistent with the safety profile previously observed in patients without asthma.

COPD

Of 92 patients with diabetes and COPD who signed informed consent for the study, 66 patients were randomly assigned to either HIIP treatment (34 patients) or injectable insulin treatment (32 patients). Of these 66 randomized patients, 37 patients, completed the treatment period specified for the primary analysis (16 patients, HIIP group; 21 patients, injectable group). There was no statistically significant difference between groups for the percentage of patients completing the primary endpoint visit. The most common reasons for early patient discontinuations were sponsor decision.

Of the 66 randomized patients in the ITT population, 50 (75.8%) were male and 16 (24.2%) were female; the majority of randomized patients (59.1%) were Caucasian. The average age (mean±SD) was 64.8±8.7 years with a minimum age of 33 years and maximum age of 83 years. The average baseline body weight was 90.8±23.7 kg and the average baseline height was 168.1±10.9 cm. Of the 66 randomized patients, 64 (97.0%) were past smokers with an average number of years smoked of 31.7±10.9 years. Patients had a mean duration of diabetes of 13.4±9.2 years and a mean duration of COPD of 8.9±10.8 years. The patient demographic data were similar between the HIIP and injectable insulin groups

Noninferiority to preprandial injectable insulin in change from baseline HbA_{1C} to endpoint was not demonstrated as the upper limit of the 95% CI was >0.4% (95% CI -0.415, 0.650). The difference between the preprandial HIIP group and the preprandial injectable insulin group in change from baseline HbA_{1c} to endpoint was not statistically significant.

There were no statistically significant differences between the treatment groups for the percentage of patients in each group able to achieve the HbA_{1c} goal of <7.0%. The change from baseline of overall 2-hour postprandial blood glucose (mg/dL) levels for the ITT population was statistically significantly different between the 2 treatment groups at Visit 7 (p=.013), but not at endpoint. The change from baseline of morning 2-hour postprandial blood glucose (mg/dL) levels was statistically significantly different between the 2 treatment groups at Visit 9 (p=.020), but not at endpoint. The change from baseline of evening 2-hour postprandial blood glucose (mg/dL) levels for the ITT population was statistically significantly different between the 2 treatment groups at Visit 7 (p=.023), but not at endpoint. The other SMBG time points did not show a statistically significant difference between the 2 treatment groups at any visit or at endpoint. None of the inhalers dispensed during the study was found to be faulty.

Two patients in the injectable insulin group died: 1 renal failure and 1 myocardial infarction. A total of 14 patients experienced one or more SAEs, 4 patients in the HIIP group and 10 patients in the injectable group. Two patients in the HIIP group and 3 patients in the injectable insulin group had an AE that resulted in study discontinuation after randomization. One discontinuation event of dyspnea was considered by the investigator to be related to study drug. No other AEs that resulted in discontinuation were considered possibly study drug or study procedure related.

Overall, 22 (64.7%) patients in the HIIP group and 21 (67.7%) patients in the injectable insulin group experienced at least one TEAE during the study. There was no statistically significant difference between

the 2 groups in the percentage of patients reporting 1 or more TEAE. Table 2 shows the TEAEs reported by at least 2% of the safety population. There were no statistically significant differences between the 2 treatment groups for any single TEAE.

There was a statistically significant difference in change from baseline between the 2 treatment groups in DL_{CO} measurements at follow-up (p=.021) with patients in the HIIP group had larger decreases in DL_{CO}. There was also a statistically significant difference between the 2 treatment groups in FEV_1 changes from baseline at Visit 6 (p=.014) and at the unadjusted analysis LOCF endpoint (p=.010), where the HIIP group had a larger decrease. These differences were not observed at follow-up. There was a difference between treatment groups for the change in FVC values from pre- to post-bronchodilator use at the LOCF endpoint (p=.037) with the HIIP group increasing from baseline and the injectable insulin group decreasing. Similarly, there was a greater increase in the HIIP group for change in FEV_1 values from pre- to post-bronchodilator use at the unadjusted analysis LOCF endpoint (p=.026) with the HIIP group increasing from baseline and the injectable insulin group decreasing. There were no other significant differences between the treatment groups for FEV_1, FVC, and TLC. Other pulmonary assessments such as the St. Georges Questionnaire, the 6-Minute Walk Test and the Borg CR10 scale did not reveal any statistically significant differences between the treatment groups. There were no abnormalities that led to a 'for cause' evaluation.

There were no statistically significant differences between treatment groups for any the vital signs collected during the study or for body weight.

There was a statistically significant difference between the treatment groups in the overall percent of patients with at least 1 nocturnal hypoglycemic episode during the study (p=.034) with patients in the injectable insulin group experiencing a higher incidence of nocturnal hypoglycemic episodes. There were no other observed differences between the treatment groups with respect to risk of hypoglycemia.

The only statistically significant difference between the treatment groups for the insulin antibody assays was for the lispro-specific assay at the LOCF endpoint (p=.034) with patients in the injectable group having a larger decrease from baseline.

Very little can be concluded from the COPD portion of this study regarding glycemic control due to the low number of patients randomized. However, the following conclusions were made:

- The study did not meet the primary objective of demonstrating that the glycemic control (mean change from baseline to endpoint in HbA_{1c}) achieved with preprandial HIIP was noninferior to that achieved with injectable insulin after approximately 12 months in patients with diabetes and COPD.
- There was no effect of HIIP treatment on the percentage of patients achieving HbA_{1c} levels of $<7\%$ or $\leq 6.5\%$, SMBG levels, weight-adjusted insulin dose, or the percentage of patients who qualified for or initiated rescue therapy.
- Patients in the injectable insulin group experienced a greater overall incidence of nocturnal hypoglycemic episodes.
- Although there were isolated statistically significant differences between treatment groups in FEV_1 and FVC, there was not a consistent pattern that allowed conclusions to be drawn from the data.
- The safety profile of HIIP in patients with COPD was consistent with the safety profile previously observed in patients without COPD.

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

	Treatment Group		
	HIIP (N=118)	Injectable Insulin (N=113)	
Preferred Term	n (%)	n (%)	p-Value
Patients with >= 1 TEAE	80 (67.8)	81 (71.7)	.568
Patients with No TEAE	38 (32.2)	32 (28.3)	
COUGH	18 (15.3)	14 (12.4)	.572
NASOPHARYNGITIS	16 (13.6)	15 (13.3)	>.999
ASTHMA	11 (9.3)	11 (9.7)	>.999
DYSPNOEA	11 (9.3)	0	<.001
HEADACHE	10 (8.5)	10 (8.8)	>.999
UPPER RESPIRATORY TRACT INFECTION	8 (6.8)	8 (7.1)	>.999
URINARY TRACT INFECTION	8 (6.8)	3 (2.7)	.216
DIARRHOEA	7 (5.9)	6 (5.3)	>.999
INFLUENZA	7 (5.9)	4 (3.5)	.540
BACK PAIN	7 (5.9)	3 (2.7)	.334
PYREXIA	6 (5.1)	6 (5.3)	>.999
ARTHRALGIA	6 (5.1)	5 (4.4)	>.999
HYPOGLYCAEMIA	6 (5.1)	2 (1.8)	.281
TOOTHACHE	6 (5.1)	2 (1.8)	.281
PAIN IN EXTREMITY	4 (3.4)	8 (7.1)	.246
SINUSITIS	4 (3.4)	5 (4.4)	.744
MUSCULOSKELETAL PAIN	4 (3.4)	2 (1.8)	NA
RESPIRATORY TRACT CONGESTION	4 (3.4)	2 (1.8)	NA
BRONCHITIS	3 (2.5)	8 (7.1)	.129
OEDEMA PERIPHERAL	3 (2.5)	4 (3.5)	NA
NECK PAIN	3 (2.5)	3 (2.7)	NA
WHEEZING	3 (2.5)	3 (2.7)	NA
SINUS CONGESTION	3 (2.5)	2 (1.8)	NA
CHEST DISCOMFORT	3 (2.5)	1 (0.9)	NA
CHOLELITHIASIS	3 (2.5)	1 (0.9)	NA
NEUROPATHY PERIPHERAL	3 (2.5)	1 (0.9)	NA
CARPAL TUNNEL SYNDROME	3 (2.5)	0	NA
MUSCLE SPASMS	3 (2.5)	0	NA
PRODUCTIVE COUGH	3 (2.5)	0	NA
RESPIRATORY TRACT INFECTION	3 (2.5)	0	NA
VOMITING	3 (2.5)	0	NA
PHARYNGOLARYNGEAL PAIN	2 (1.7)	5 (4.4)	.272
DIZZINESS	2 (1.7)	3 (2.7)	NA
LOWER RESPIRATORY TRACT INFECTION	2 (1.7)	3 (2.7)	NA
NAUSEA	2 (1.7)	3 (2.7)	NA
FATIGUE	1 (0.8)	4 (3.5)	NA
GASTRITIS	1 (0.8)	3 (2.7)	NA
PNEUMONIA	1 (0.8)	3 (2.7)	NA

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

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

	Treatment Group		
Preferred Term	HIIP (N=34) n (%)	Injectable Insulin (N=31) n (%)	p-Value
Patients with >= 1 TEAE	22 (64.7)	21 (67.7)	>.999
Patients with No TEAE	12 (35.3)	10 (32.3)	
BRONCHITIS	6 (17.6)	4 (12.9)	.736
CHRONIC OBSTRUCTIVE PULMONARY DISEASE	4 (11.8)	2 (6.5)	NA
PAIN IN EXTREMITY	3 (8.8)	0	NA
RESPIRATORY TRACT CONGESTION	3 (8.8)	0	NA
DYSPNOEA	2 (5.9)	4 (12.9)	NA
COUGH	2 (5.9)	3 (9.7)	NA
UPPER RESPIRATORY TRACT INFECTION	2 (5.9)	2 (6.5)	NA
DIARRHOEA	2 (5.9)	1 (3.2)	NA
DIZZINESS	2 (5.9)	1 (3.2)	NA
INFLUENZA	2 (5.9)	1 (3.2)	NA
INFLUENZA LIKE ILLNESS	2 (5.9)	1 (3.2)	NA
BACK PAIN	2 (5.9)	0	NA
DEPRESSION	2 (5.9)	0	NA
CARDIAC FAILURE	0	2 (6.5)	NA
OEDEMA PERIPHERAL	0	2 (6.5)	NA
SKIN ULCER	0	2 (6.5)	NA
TOOTH FRACTURE	0	2 (6.5)	NA

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