

ABSTRACT

We conducted a prespecified analysis review across all studies of subjects with type 2 diabetes mellitus (T2DM) from controlled Phase 2/3 clinical trials of Technosphere® Insulin (TI) and one uncontrolled long-term extension trial (for HRCT). In all, 1795 subjects received TI, and 1345 received comparator—either sc insulin (953) or oral agents (392). In the TI group, 838 subjects completed 1 year of treatment and 533 completed 2 years. In both groups, mean age was 56 years. Mean BMI was 31 kg/m²; 51% of subjects were male.

Hypoglycemia was the most common adverse event (AE) in all insulin-treated subjects. The incidences of hypoglycemia and severe hypoglycemia were significantly lower with TI than comparator sc injected insulins.

Mild cough occurred more frequently with TI (25.8% vs 5.4%). Only 2.6% of TI subjects withdrew due to cough. Small declines in FEV₁ and DL_{CO} occurred in both groups over 2 years of treatment, with greater initial decline in TI-treated subjects. Differences were small, nonprogressive, and disappeared within 3 months of stopping TI.

Of 667 subjects with HRCT, 494 received TI and 72 received comparator. There were no differences in the rates of clinically significant abnormal findings between groups.

In patients with T2DM who received TI:

- The most common AEs were hypoglycemia and mild transient cough.
- The incidence of hypoglycemia and of severe hypoglycemia was reduced compared with sc insulin.
- There was no increase in cardiovascular risk.
- There was a small reduction in pulmonary function that was nonprogressive and resolved on discontinuation.
- There was no difference in the rate of clinically significant radiological findings in HRCT between groups.

INTRODUCTION/BACKGROUND

AFREZZA™ (Technosphere® Insulin) is a rapid acting inhaled insulin being developed for the treatment of adult subjects with diabetes mellitus. Afrezza contains recombinant human insulin adsorbed onto Technosphere® microparticles (T Powder). Technosphere microparticles are formed by the acid-induced self-assembly of fumaryl diketopiperazine (FDKP) molecules, a novel and metabolically inert excipient. Upon inhalation into deep lung, Technosphere particles dissolve rapidly at the prevailing physiological pH in lungs allowing rapid absorption of insulin in systemic circulation. The resultant insulin pharmacokinetic profile mimics the early mealtime insulin release observed in healthy subjects. The main objective of this review of the Phase 2/3 clinical trials was to characterize the safety profile of Afrezza in patients with type 2 diabetes mellitus (T2DM).

MATERIALS AND METHODS

All Phase 2/3 completed, controlled randomized clinical studies of Afrezza with duration of 14 days or greater in adults with T2DM were pooled for the analysis. Pooled safety analysis was conducted in the Safety population. The Safety population was defined as all randomized patients who received at least 1 dose of the study drug. All safety data were presented according to the actual treatment that patients received.

Seven controlled clinical trials with durations ranging between 3 months and 2 years contributed to the pooled analysis of safety in type 2 diabetes. Two studies of 3 months' duration were double blind placebo controlled where Afrezza was used in combination with oral treatment or basal sc insulin, and compared with placebo with or without sc basal insulin. Five studies with durations ranging between 6 months and 2 years were open label with active controls where Afrezza was used alone or in combination with oral agents and/or sc basal insulin. The pooled analysis of pulmonary function included only 2 studies with duration of treatment of 1 year or more. In addition, follow-up pulmonary function tests (PFTs) were obtained at 1 month and 3 months after completion of the comparative phase of the parent trials to evaluate the changes in lung functions after discontinuation of Afrezza.

Mean age was 56 years for both treatment groups. The distribution by sex was approximately 51% male and 49% female in each treatment group. In both treatment groups, close to 80% of patients were Caucasian, 10% were Hispanic, close to 5% were black, and less than 2.6% of subjects in both groups were classified "other." Mean BMI was 31 kg/m² for both groups. In both treatment groups duration of the diabetes was 11 years.

Safety data included general safety [adverse events (AE), serious adverse events (SAEs) and deaths], special safety events [cardiovascular, and cerebrovascular], identified through an independent blinded MedDRA search strategy; and pulmonary function tests [forced expiratory volume in one second (FEV₁), forced vital capacity (FVC), total lung capacity (TLC), and lung diffusion capacity for carbon monoxide (DL_{CO})]. Pulmonary function tests were performed only at certified PFT laboratories according to American Thoracic Society (ATS) guidelines and submitted for a central, independent, real-time review and interpretation.

In addition, results of all chest high resolution computerized tomography (HRCT) images from the controlled studies and from a long-term safety extension study were included in the safety analysis. In trials, MKC-TI-005 (N=217; 174 Afrezza group, 43 T Powder group) and PDC-INS-0008 (N=121; 60 Afrezza group, 61 T Powder group), patients had chest HRCTs obtained at baseline and at the end of the treatment period. After completion of these two trials, 206 patients continued in the uncontrolled open-label extension trial (MKC-TI-010) and underwent annual chest HRCTs (or magnetic resonance imaging [MRI] in Germany) for up to 4 years. In addition, subsets of patients participating in trial MKC-TI-030 [n=127; 55 Afrezza group, 72 usual care (UC) group] were also randomized to an annual chest HRCT during the 24-month treatment period. All chest HRCT images were reviewed centrally following a pre-specified adjudication protocol by an independent, blinded, board-certified radiologist. All images for any subject with chest HRCT findings, other than normal, underwent secondary joint review by an independent board-certified radiologist (different from the primary reviewer) and an independent board-certified pulmonologist, who were blinded to the treatment group and had access to all clinical records from the patients. Images were classified as "normal," "abnormal, not clinically significant," or "abnormal, clinically significant".

RESULTS

Seven Phase 2/3 trials contributed to the pooled analyses in patients with type 2 diabetes. In total, 1795 patients received Afrezza, and 1345 received comparator—either sc insulin (953) or oral agents (392). In the Afrezza group, 838 patients completed 1 year of treatment and 533 completed 2 years. A total of 206 patients entered into an uncontrolled open-label extension trial and received Afrezza with or without other antidiabetes treatment for up to 4 years.

General Safety

The incidence of AEs, including severe AEs, deaths, and special events was comparable between treatment groups (Table 1).

Figure 1 summarizes treatment emergent adverse events (TEAE) reported in ≥5% of subjects. Hypoglycemia was the most common adverse event with incidence ≥5% in all insulin-treated patients (Table 2). The incidences and event rates (Figure 2) of total hypoglycemia and severe hypoglycemia were significantly lower with Afrezza-treated patients than comparator insulin treatment. Mild cough occurred more frequently with Afrezza (25.8% vs. 5.4%). Only 2.6% of Afrezza patients withdrew due to cough.

TABLE 1

Summary of Safety in Any Treatment Group Type 2 Patients, Safety Population – Pooled Phase 2/3 Trials		
	Afrezza n=1795 n (%)	Comparator n=1345 n (%)
All cause TEAEs	1275 (71.0)	958 (71.2)
Severe TEAEs	213 (11.9)	185 (13.8)
Serious TEAEs	122 (6.8)	108 (8.0)
Deaths	8 (0.4)	5 (0.4)
Cerebrovascular TEAEs	21 (1.2)	18 (1.3)
Cardiovascular TEAEs	167 (9.3)	136 (10.1)

*RR (95% CI), 1.02 (0.84–1.24).

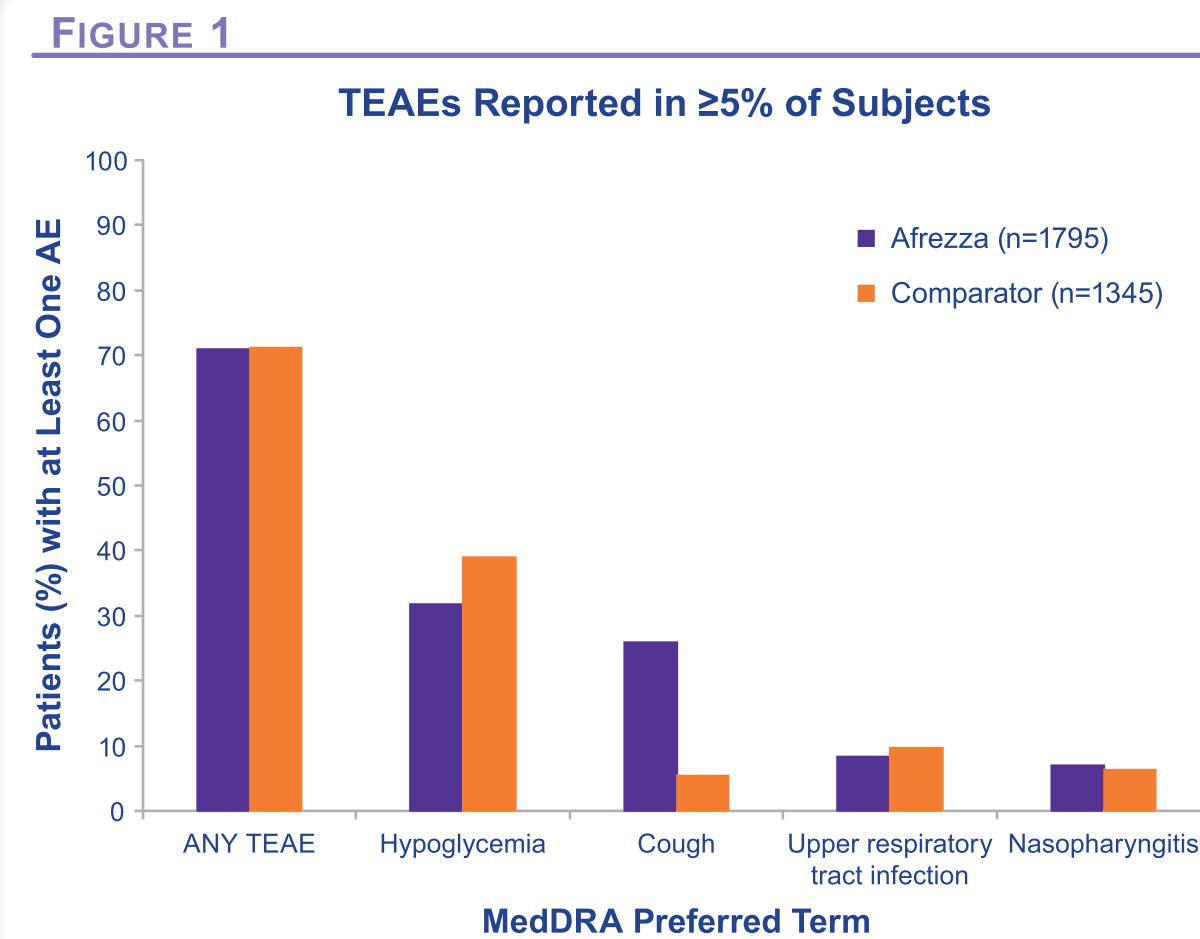
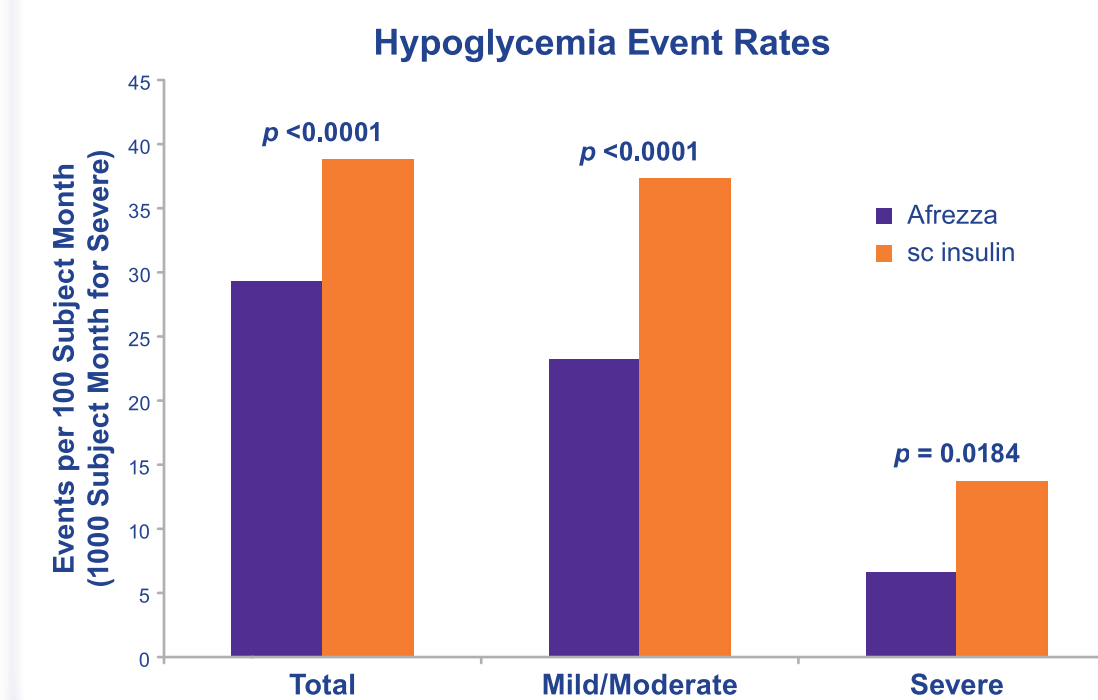


TABLE 2

Incidence and Event Rates of Hypoglycemia Type 2 Patients (Safety Population – Pooled Controlled Phase 2/3 Trials)				
	Afrezza n=1795	SC Insulin n=942	Odds Ratio	p Value
Incidence, n (%)				
Total	570 (31.8)	467 (49.6)	0.466	<0.0001
Severe	50 (2.8)	71 (7.5)	0.359	<0.0001
Event Rate, per 100 subject-month				
Total	23.9	38.8		<0.0001
Mild/Moderate	23.2	37.3		<0.0001
Severe	0.66	1.37		0.0184

FIGURE 2



RESULTS (CONTINUED)

Pulmonary Function Testing

Small declines in FEV₁ (Figure 3) occurred in both groups over 2 years of treatment, with greater initial decline in Afrezza-treated patients. Differences were small, non-progressive, and disappeared within 3 months of stopping Afrezza irrespective of the duration of exposure (Figure 4). Changes from baseline in FVC and DL_{CO} also showed a similar pattern. There was no significant difference in change from baseline in TLC between Afrezza and comparator groups.

FIGURE 3

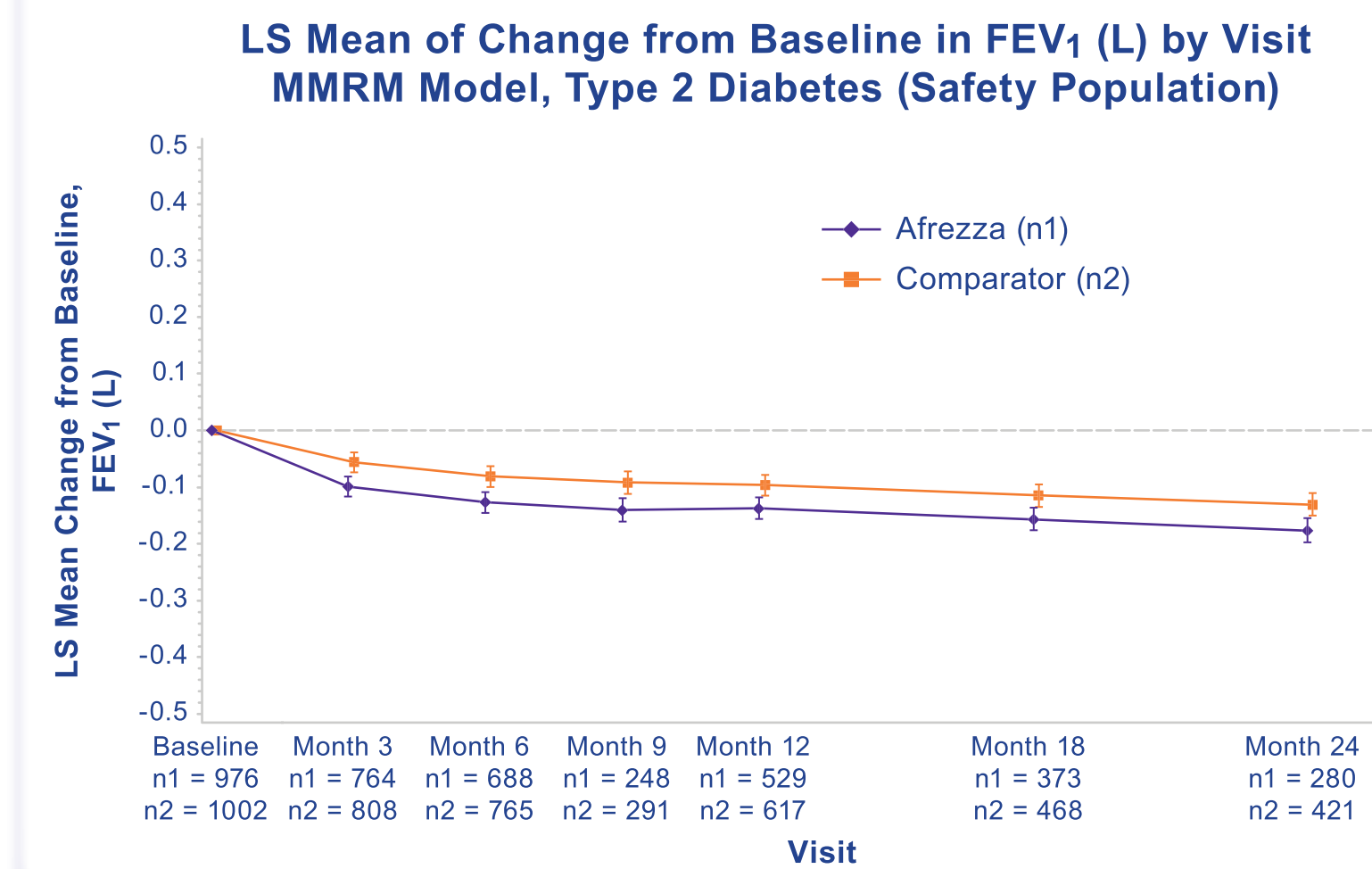
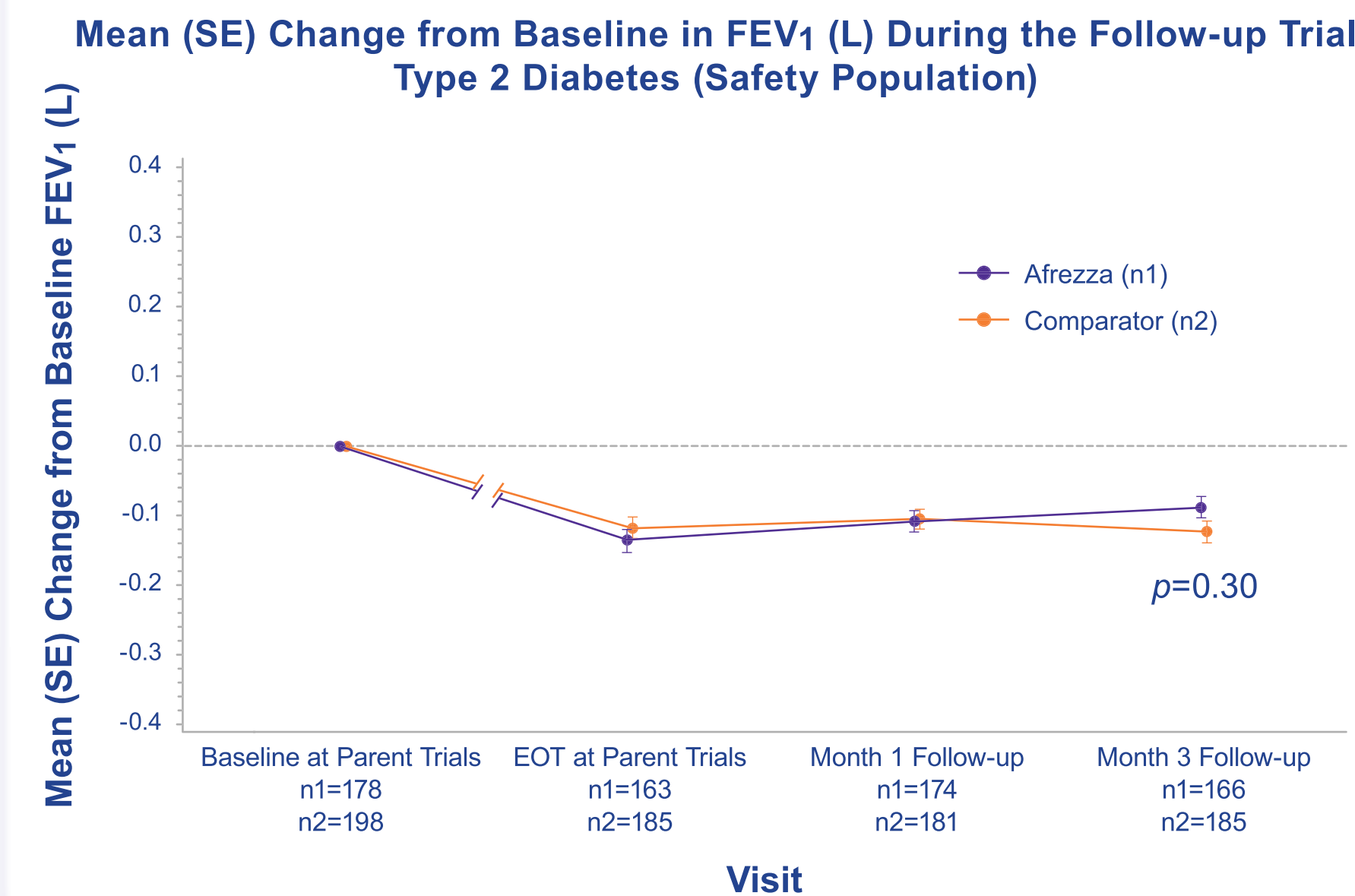


FIGURE 4



RESULTS (CONTINUED)

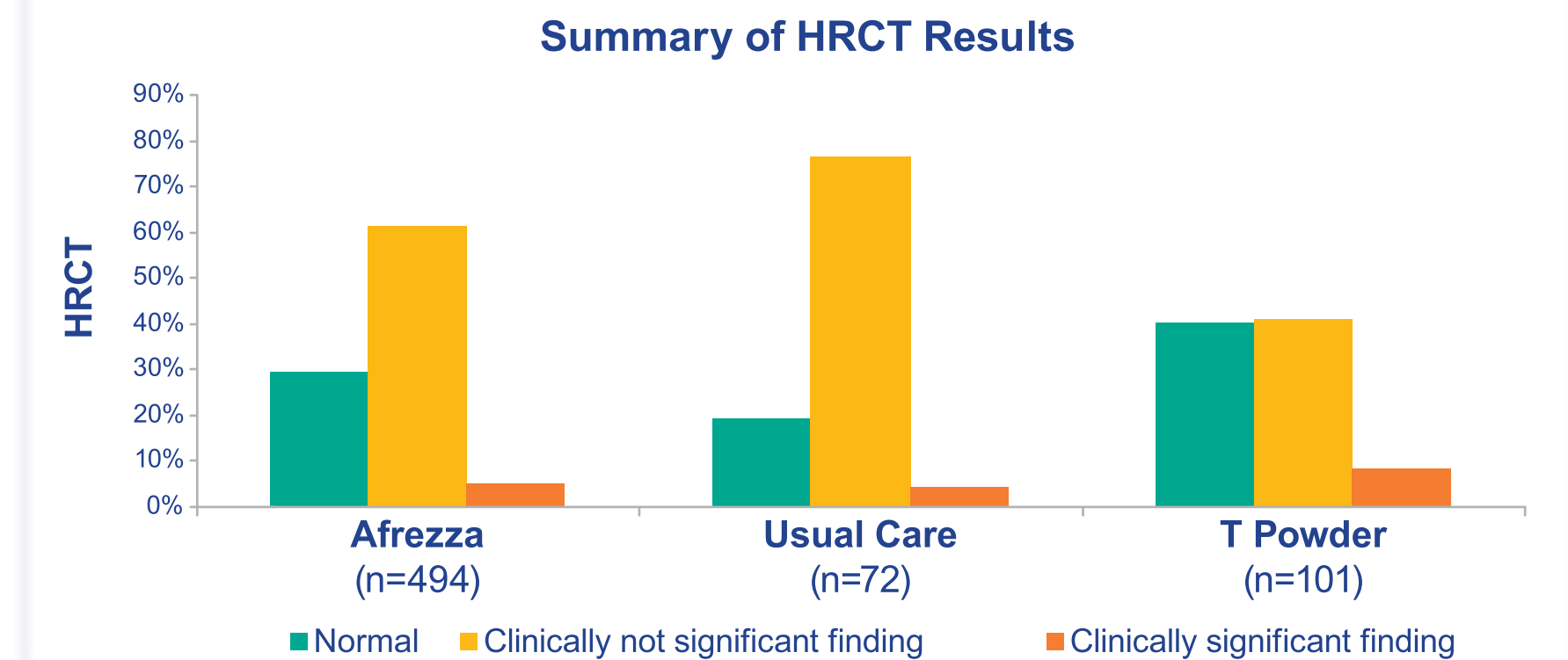
Chest HRCT Results

A total of 667 patients had a baseline and at least one postbaseline chest HRCT or MRI examination. Of these, 494 patients were treated with Afrezza, 101 were exposed to T Powder, and 72 were in the UC group with no exposure to Afrezza or T Powder.

Chest HRCTs for 94% of the Afrezza group, 92% of the T Powder group, and 96% of the UC group showed normal findings or the findings were not clinically significant (Figure 5).

Radiological findings considered abnormal and clinically significant consisted of atelectasis, septal thickening, peribronchial thickening, bronchial dilatation or mild bronchiectasis, one or more new or non-enlarging nodules, and ground glass densities; these findings were seen with comparable frequency in all three treatment groups.

FIGURE 5



CONCLUSIONS

In patients with type 2 diabetes who received Afrezza:

- The most common AEs were hypoglycemia and mild transient cough.
- The incidence of hypoglycemia and of severe hypoglycemia was lower compared with sc insulin.
- There was no increase in cardiovascular risk.
- Observed changes in pulmonary function tests were small, non-progressive and resolved on discontinuation.
- There was no difference in the rate of clinically significant radiological findings in HRCT between groups.