

Pulmonary Safety of Inhaled Technosphere® Insulin Therapy in Adults with Diabetes Using High-Resolution Computerized Tomography of the Chest

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ABSTRACT

Background and aims: Technosphere® Insulin (TI) is a rapid-acting inhaled insulin with pharmacokinetics well suited for control of postprandial plasma glucose. Because TI is intended to be administered via the pulmonary route, the TI clinical program was designed to assess possible radiological changes associated with the chronic use of TI therapy.

Materials and methods: Adult subjects with diabetes were evaluated with high-resolution computerized tomography (HRCT) of the chest during the clinical trials. In controlled clinical trials, MKC-TI-005 (N = 217; 174 TI group, 43 Technosphere® Inhalation Powder [T Powder] group) and PDC-INS-0008 (N = 121; 60 TI group, 61 T Powder group) subjects were randomized to receive TI or T Powder without insulin. Chest HRCTs were obtained at baseline and at the end of the 12-week treatment period. After completion of these two trials, 206 subjects 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 subjects with type 1 or type 2 diabetes participating in trial MKC-TI-030 (n = 127; 55 TI group, 72 usual care [UC] group) were also randomized to an annual chest HRCT during the 24-month treatment period. All HRCT images were reviewed centrally following a prespecified adjudication protocol by an independent, blinded, board-certified radiologist. All images for any subject with 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.

Results: A total of 667 subjects had a baseline and at least one post-baseline chest HRCT or MRI examination. Of these, 494 subjects were treated with TI, 101 were exposed to T Powder and 72 were in the UC group with no exposure to TI or T Powder. Chest HRCTs for 94% of the TI group, 92% of the T Powder group, and 96% of the UC group showed normal findings or the findings were not clinically significant (Table 2). Radiological findings considered abnormal and clinically significant consisted of atelectasis, septal thickening, peri-bronchial 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.

Conclusions: Overall, HRCT and MRI findings suggest that there were no clinically significant radiological changes from baseline in all three groups. Observed radiological findings were not suggestive of a safety signal with the long-term use of TI therapy.

BACKGROUND AND AIMS

MannKind Corporation is currently developing Technosphere® Insulin Inhalation Powder (TI) for the treatment of adult patients with diabetes mellitus. TI is an inhaled dry powder formulation of regular human insulin adsorbed onto Technosphere® particles with an action profile that closely mimics endogenous meal related insulin response and well suited for the control of hyperglycemia in patients with diabetes. Because TI is administered via pulmonary route, pulmonary safety was monitored using routine chest radiology in TI clinical development program. However, conventional chest radiography is less sensitive than the high resolution computed tomography (HRCT) in detection of focal and diffuse lung lesions. HRCT is a computerized tomography technique which uses thin collimation and image reconstruction with a high spatial frequency algorithm in order to obtain detailed images of lung morphology. This allows for an accurate morphologic analysis and early detection of the pathologic processes affecting the lung. HRCT currently has the best sensitivity and specificity of any imaging method for the assessment of focal and diffuse lung diseases.¹ Computed tomography (CT) detects four times as many lung cancers and six times the number of stage 1 lesions than the routine chest radiography.² Studying the morphology of nodules noted on HRCT provides high degree of sensitivity (84.2%) and specificity (96.6%) for the diagnosis of lung cancers.³ HRCT has a sensitivity of 94% and a specificity of 96% for the detection of infiltrative lung disease⁴, 97% sensitivity and 93% specificity for the diagnosis of Bronchiectasis⁵, and 91% sensitivity and 80% specificity for the detection of air trapping.⁶

Subset of patients with diabetes in the TI clinical trials were evaluated with sequential chest HRCT in order to detect any possible radiological changes associated with the chronic use of TI therapy.

MATERIALS AND METHODS

In the TI clinical development program, adults with diabetes were evaluated with Chest HRCT (or MRI in a subset of patients in Germany) in four clinical trials. In the controlled clinical trial MKC-TI-005 and PDC-INS-0008, patients were randomized to receive Technosphere® Insulin (TI) or Technosphere® Inhalation Powder (T Powder) as a placebo. Chest HRCTs were obtained at baseline and at the end of the 12-week treatment period. In the trial MKC-TI-005, 217 patients with type 2 diabetes (174 in TI group and 43 in T Powder group) and for PDC-INS-0008 trial 121 patients with type 2 diabetes (60 in TI group and 61 in T Powder group) had both a baseline and 12 week HRCT examination. 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 MRI in Germany) for up to 4 years. Subset of patients with type 1 or type 2 diabetes participating in the MKC-TI-030 pulmonary safety trial (n = 127; 55 in TI group, 72 in Usual care group) were randomized to annual chest HRCT during the 24-month comparative treatment period.

HRCT Review Process

All images were collected and centrally reviewed by an independent third party; Perceptive Informatics, Inc. All images were converted into a digital format for review using high-resolution monitors.

During the reviews, the independent radiologist was blinded to subject identity, investigator site, examination dates, sequence of examinations, reason for the imaging (scheduled or unscheduled). All available images for a given subject were reviewed during a single session. The reviewer prepared 1 electronic analysis form per imaging time point. The independent radiologist reviewer was responsible for making the following qualitative assessments of the imaging data:

1. Interlobular septal thickening
2. Ground glass opacities, diffuse or centrilobular
3. Tree-in-bud opacities or clustered centrilobular nodules
4. Parenchymal abnormalities
 - a. Consolidation
 - b. Nodules or masses
5. Bronchial abnormalities
6. Pleural abnormalities
7. Pleural effusions

Each lung was assessed in each these categories for all acquired images. Qualitative assessment response choices were provided for each category. For Interlobular septal thickening, Ground glass opacities, or Tree-in-bud opacities, the responses included:

1. Absent
2. Present, but involving < 50% of the lung
3. Involving ≥50%, but < 100% of the lung
4. Involving 100% of the lung
5. Uncertain

For parenchymal, bronchial, or pleural abnormalities or pleural effusions, the responses were limited to:

1. Absent
2. Present
3. Uncertain

Subjects found to have “absent” in all categories for both lungs in each image were deemed as “normal”. Any subject with a response other than “absent” was submitted for secondary review.

The second review was conducted by an independent board-certified radiologist (different from the primary reviewer) and an independent board-certified pulmonologist, who conducted a second joint qualitative review of radiological and clinical data. The second review included presentation of all relevant imaging and the analysis forms of the first reviewer. Subjects were re-queued and blinding of the image data was conducted as for the first review. In addition, the second reviewers were supplied with the following clinical data: subject demographics, smoking history, diabetes treatment history, exposure to pulmonary toxins or chronic irritants, family pulmonary disease history, drug and environmental allergies, medical and surgical history, respiratory infection history, abnormal central laboratory assessments, physical examination findings (for heart, lungs, and edema), abnormal vital signs, ECG results, chest x-ray reports, PFT and re-testing results, self-reported health assessments, pulmonary status update, interim visits, unscheduled visit, concomitant medications and herbal therapies, adverse events, cough and cough reports, subject summary including reason for withdrawal, and comments but were blinded to the clinical trial treatment arm. Based upon all available data the secondary reviewers wrote a joint brief narrative for each subject to provide a final interpretation of the radiology imaging. This joint interpretation included a statement of finding whether the subjects' images were “normal,” “abnormal, not clinically significant,” or “abnormal, clinically significant.”

RESULTS

The number of subjects who had a baseline and at least one post baseline chest HRCT (or MRI) examination available for the independent review is depicted in the Table 1.

494 subjects were treated with TI, 101 were exposed to T Powder, and 72 were in the UC group with no exposure to TI or T Powder. Chest HRCTs were considered normal or abnormal, clinically not significant by independent central reviewers in 94% of the TI-treated, 92% of the T Powder treated, and 96% of usual care-treated patients (Figure 1 and Table 2). Radiological findings considered abnormal and clinically significant consisted of segmental atelectasis, septal thickening, peri-bronchial thickening, bronchial dilatation or mild bronchiectasis, one or more new or non-enlarging nodules, linear or multifocal ground glass densities, reticular opacities, and scarring; these findings were seen with comparable frequency in all three treatment groups.

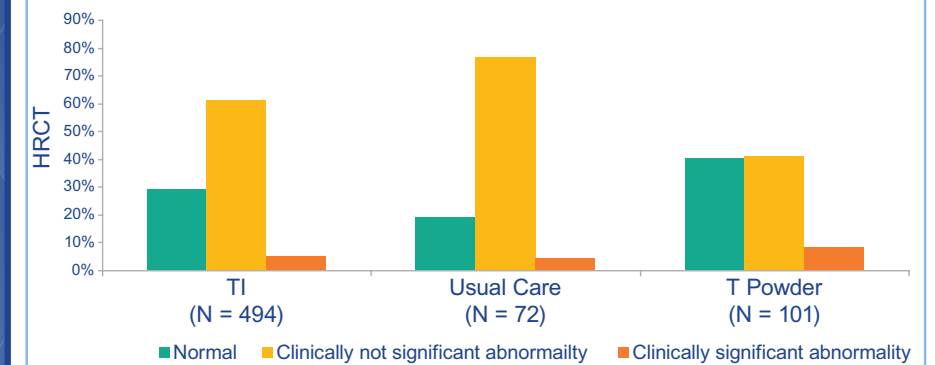
	MKCTI-005		PDC-INS-0008		MKC-TI-030		MKC-TI-010
N	217		117		127		206
Duration of Exposure	3 months		3 months		24 months		Up to 48 months
Rx Group	TI	T Powder	TI	T Powder	TI	UC	TI
	174	43	59	58	55	72	206

Table 2. Summary of High Resolution Computerized Tomography Results

HRCT Results	Technosphere® Insulin n (%)	Usual Care	Technosphere® Inhalation Powder n (%)
Normal	140 (28.3)	14 (19.4)	40 (39.6)
Abnormal, not clinically significant	325 (65.8)	55 (76.4)	53 (52.5)
Abnormal, clinically significant	29 (5.9)	3 (4.2)	8 (7.9)
Total	494	72	101

RESULTS (CONT'D)

Figure 1. Summary of HRCT Results



CONCLUSIONS

1. Overall, the results of the independent HRCT (or MRI) readings suggest that there were no differences in the rate of clinically significant radiological changes during the course of the clinical trials in patients with diabetes treated with Technosphere® Insulin, Technosphere® Inhalation Powder or the usual antidiabetic regimen.
2. Observed radiological findings were not suggestive of a safety signal.

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