# Patient Reported Outcomes in Adults with Type 2 Diabetes Using Mealtime Insulin Monomer Human (rDNA origin) Inhalation Powder (Technosphere® Insulin Inhalation Powder) or Metformin + Secretagogue or Both

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## Abstract

**Background and aims**: This study investigated whether Mealtime Insulin Monomer Human (rDNA origin) Inhalation Powder alone or in addition to Metformin + Secretagogue was associated with improved patient reported outcomes (PRO) over Metformin + secretagogue alone. **Materials and methods**: In this 24-week randomized, multicenter study adults with type 2 diabetes used Mealtime Insulin Monomer Human (rDNA origin) Inhalation Powder (MIMHIP; n = 177), Metformin + Secretagogue (MS; n = 162) or both (I+MS; n = 169). At 12 weeks, subjects not adequately controlled with MIMHIP or MS were transferred to I+MS. Patient-reported outcomes (PRO) included: the SF-36, assessing health-related quality of life (HRQOL), and the Insulin Treatment Questionnaire (assessing diabetes worries and treatment satisfaction). Intent to treat (ITT) analysis used mixed effect models to estimate differences in mean group changes in PRO from Baseline to week 12 (adjusted for baseline scores); *t* tests assessed within-group change from Baseline to 12 weeks in all groups and from 12 to 24 weeks in patients adding MIMHIP to MS. **Results**: At Week 12, SF-36 mental health composite scores (MCS) increased ($p = 0.0010$) in MIMHIP but not in MS or I+MS; the difference in change between MIMHIP and MS was not significant in ITT analysis ($p = 0.0612$), but was in the per protocol population ($p = 0.0233$). MIMHIP improved more than MS in Role-Emotional scores ($p = 0.0044$). At Week 12, SF-36 physical health composite scores (PCS) increased in MIMHIP and I+MS and declined in MS; although none of these changes were significant, the difference in change between I+MS and MS was significant ($p = 0.0084$). I+MS showed greater improvement than MS for Bodily Pain ($p = 0.0148$), Physical Functioning ($p = 0.0020$), and Role Physical scores ($p = 0.0172$); MIMHIP showed greater improvement than MS for Role-Physical scores ($p = 0.0124$). There were no changes in Diabetes Worries from Baseline to Week 12, and no differences in change. There was an increase in Treatment Satisfaction in MIMHIP ($p = 0.0003$) and TM ($p < 0.0001$); these improvements were greater than MS (MIMHIP $p = 0.0116$; I+MS $p = 0.0009$). There was no change in MCS, PCS or Diabetes Worries between Weeks 12 and 24 among subjects who added MIMHIP to MS (n = 79), but treatment satisfaction increased ($p = 0.0007$). **Conclusion**: HRQOL and treatment satisfaction improved more among those taking Mealtime Insulin Monomer Human (rDNA origin) Inhalation Powder (with or without oral medications) than those taking oral medications only. Those who added Mealtime Insulin Monomer Human (rDNA origin) Inhalation Powder to oral medications during the trial experienced increased treatment satisfaction.

## Background

Existing mealtime insulins have a number of limitations. Their onset of action is slower than endogenous postprandial insulin release and their duration of action often exceeds the postprandial rise in glucose. This can result in an initial state of postprandial hyperglycemia followed by hypoglycemia hours after injection. Mealtime insulin injections also represent a burden for patients, and may involve pain, bruising, and infection.

The ideal mealtime insulin would mimic postprandial endogenous insulin responses, providing physiologic mealtime insulin levels, both with respect to rapid onset and limited duration of action. It would also relieve patients of the burden of injecting themselves. Technosphere® Insulin (TI) Inhalation Powder (Mealtime Insulin Monomer Human [rDNA origin] Inhalation Powder) is a mealtime insulin monomer human (rDNA origin) inhalation powder that offers a new approach to administering bolus insulin which closely mimics endogenous insulin responses[1], and has been shown to improve attitudes toward insulin therapy in insulin naïve patients.[2]

## Study Aims

The purpose of this study was to assess how Technosphere® Insulin Inhalation Powder alone or in combination with metformin plus a secretagogue compared to treatment with metformin plus a secretagogue alone in terms of several PRO.

## Materials and Methods

### Design

In this 24-week prospective, randomized, multicountry, multicenter open-label study, adults with type 2 diabetes used mealtime TI or in combination with Metformin (TM) or Metformin plus a Secretagogue (MS). Technosphere® Insulin is a mealtime insulin monomer human (rDNA origin) powder that is inhaled into the deep lung using the MedTone® inhaler, a pocket-sized, breath-powered unit.

## Materials and Methods (cont'd)

Subjects in the TI Alone and Metformin + Secretagogue arms who did not achieve a predefined improvement in HbA1c at Week 12 (HbA1c > 8.5% or an HbA1c decrease from Baseline of < 1.5%) were transferred to the TI + Metformin treatment arm, per the protocol. Those who transferred from the Metformin + Secretagogue arm discontinued their secretagogue when they started TI.

### Measures

In addition to a variety of efficacy and safety measures, patients completed the SF-36 measure of health-related quality of life and the Insulin Treatment Questionnaire (ITQ) prior to beginning treatment in the study and 12 and 24 weeks later. The SF-36 measures include two composite scores: the Physical Component Summary (PCS) and the Mental Component Summary (MCS), as well as eight scale scores – four physical domain scores (Physical Functioning, Role-Physical, Bodily Pain, General Health) and four mental domain scores (Vitality, Social Functioning, Role-Emotional, Mental Health). ITQ measures include: Diabetes Worries (5 questions) and Treatment Satisfaction (3 questions).

### Analysis

Intent-to-treat analysis used mixed effect models to estimate differences in mean group changes in patient-reported outcomes (PRO) from Baseline to Week 12 (adjusted for baseline scores); *t* tests assessed within-group change from Baseline to Week 12 in all groups and from Week 12 to Week 24 in patients adding TI to MS.

### Subjects

The trial was conducted with nonsmoking adults (aged 18 years to 80 years) who had an HbA1c level of > 7.5% and ≤ 11.0% and BMI < 40 kg/m² on entry to the study (see Table 1).

**Table 1.** Demographic and Baseline Characteristics

| Baseline Characteristics | TI Alone (n = 177) | Metformin + Secretagogue (n = 162) | TI + Metformin (n = 169) |
|---|---|---|---|
| **Gender, n (%)** | | | |
| Male | 84 (47.5) | 74 (45.7) | 68 (40.2) |
| Female | 93 (52.5) | 88 (54.3) | 101 (59.8) |
| **Race, n (%)** | | | |
| Caucasian | 133 (75.1) | 114 (70.4) | 129 (76.3) |
| African American | 9 (5.1) | 8 (4.9) | 12 (7.1) |
| Asian American | 4 (2.3) | 5 (3.1) | 2 (1.2) |
| Hispanic | 26 (14.7) | 25 (15.4) | 23 (13.6) |
| Other | 5 (2.8) | 10 (6.2) | 3 (1.8) |
| **Age (years), mean (± SD)** | 57.3 (8.47) | 57.6 (9.14) | 56.8 (8.31) |
| **Weight (kg), mean (± SD)** | 86.14 (15.59) | 84.18 (16.21) | 83.87 (13.93) |
| **BMI (kg/m²), mean (± SD)** | 31.23 (4.30) | 30.73 (4.61) | 30.81 (4.40) |
| **Baseline HbA1c (%), mean (± SD)** | 8.92 (0.95) | 8.90 (0.94) | 8.95 (0.97) |
| **Fasting Plasma Glucose (mg/dL), mean (± SD)** | 193.59 (53.582) | 197.31 (47.956) | 189.39 (47.340) |

## Results

### Changes in SF-36 Scores from Baseline to Week 12

ITT results are presented in Table 2. The TI Alone group experienced a significant ($p = 0.0010$) increase in MCS scores. Mean changes in MCS scores from Baseline were not significantly different between treatment groups.

Mean changes in PCS scores showed a slight decline for the Metformin + Secretagogue group vs small improvements in the TI Alone and TI + Metformin groups; the Metformin + Secretagogue group was significantly different from the TI + Metformin group ($p = 0.0084$).

## Results (cont'd)

**Table 2.** Change from Baseline to Week 12 in SF-36 MCS and PCS

| | Statistic | TI Alone | Metformin + Secretagogue | TI + Metformin |
|---|---|---|---|---|
| **MCS** | | | | |
| | n | 132 | 145 | 102 |
| | Mean | 2.6 | 0.7 | 0.6 |
| | SD | 8.80 | 8.86 | 9.71 |
| Within Group[a] | *p* Value | 0.0010 | 0.3723 | 0.5212 |
| Between Group[b] | Comparison | **TI – MS** | **TM – MS** | **TM – TI** |
| | *p* Value | 0.0612 | 0.3761 | 0.4005 |
| **PCS** | | | | |
| | n | 132 | 145 | 102 |
| | Mean | 0.7 | -0.5 | 0.8 |
| | SD | 5.82 | 6.48 | 6.16 |
| Within Group[a] | *p* Value | 0.1561 | 0.3479 | 0.1742 |
| Between Group[b] | Comparison | **TI – MS** | **TM – MS** | **TM – TI** |
| | *p* Value | 0.0917 | 0.0084 | 0.2943 |

[a] *p* values are derived from a paired *t* test.
[b] *p* values and estimates are derived from an ANCOVA model with treatment and investigator site as class variables, and baseline SF-36 score as a covariate.
• SD = Standard Deviation, TI = TI Alone, MS = Metformin + Secretagogue, TMS = TI + Metformin.

### Change in SF-36 Subscale Scores from Baseline to Week 12

When mean changes in SF-36 subscale scores that are components of MCS were evaluated from Baseline to Week 12, the mean score for the Role-Emotional scale in the TI Alone group increased significantly ($p = 0.0096$) and there was a significant between-group difference favoring TI Alone over Metformin + Secretagogue ($p = 0.0044$).

When individual SF-36 subscales that are components of PCS were evaluated, there were significant improvements for the TI + Metformin group relative to the Metformin + Secretagogue group in mean Bodily Pain scores ($p = 0.0148$) and Physical Functioning score ($p = 0.0020$). For Role-Physical scores there were significant improvements relative to the Metformin + Secretagogue group for the TI Alone group ($p = 0.0142$) and TI + Metformin group ($p = 0.0172$).

### Changes in SF-36 Scores from Week 12 to Week 24

Subjects who transferred from Metformin plus Secretagogue to TI plus Metformin showed no significant change in mean SF-36 MCS scores from Week 12 to Week 24. No significant differences were noted for mean changes in any of the SF-36 subscales that are components of MCS.

### Changes in Insulin Treatment Questionnaire from Baseline to Week 12

ITT results are presented in Table 3. There were no significant changes from Baseline to Week 12 in mean ITQ Worries scores and no significant differences among groups in mean change.

The TI Alone and the TI + Metformin groups had significant within-group changes in ITQ Treatment Satisfaction from Baseline to Week 12 ($p = 0.0003$ and $<0.0001$, respectively).

There were significant differences among treatment groups for changes in ITQ Treatment Satisfaction; Treatment Satisfaction increased more in the TI Alone and the TI + Metformin groups than the group receiving Metformin + Secretagogue ($p = 0.0116$ and 0.0009, respectively).

### Changes in ITQ Scores from Week 12 to Week 24

Mean ITQ Worries scores showed no significant changes from Week 12 to Week 24 for the subjects who transferred from Metformin + Secretagogue to TI + Metformin.

There was a statistically significant improvement in mean Treatment Satisfaction scores from Week 12 to Week 24 for subjects who transferred from Metformin + Secretagogue to TI + Metformin ($p = 0.0007$).

## Results (cont'd)

**Table 3.** Change from Baseline to Week 12 in ITQ Diabetes Worries and Treatment Satisfaction

| | Statistic | TI Alone | Metformin + Secretagogue | TI + Metformin |
|---|---|---|---|---|
| **Diabetes Worries** | | | | |
| | n | 119 | 129 | 90 |
| | Mean | 0.0 | 0.0 | -0.1 |
| | SD | 1.00 | 1.05 | 0.76 |
| **Within Group[a]** | *p* Value | 0.6655 | 0.6343 | 0.1355 |
| **Between Group[b]** | Comparison | **TI – MS** | **TM – MS** | **TM – TI** |
| | *p* Value | 0.3947 | 0.7592 | 0.6359 |
| **Treatment Satisfaction** | | | | |
| | n | 119 | 128 | 90 |
| | Mean | 0.5 | 0.2 | 0.7 |
| | SD | 1.51 | 1.24 | 1.27 |
| **Within Group[a]** | *p* Value | 0.0003 | 0.0538 | < 0.0001 |
| **Between Group[b]** | Comparison | **TI – MS** | **TM – MS** | **TM – TI** |
| | *p* Value | 0.0116 | 0.0009 | 0.3285 |

[a] *p* values are derived from a paired *t* test
[b] *p* values and estimates are derived from an ANCOVA model with treatment and investigator site as class variables, and baseline ITQ score as a covariate
• SD = Standard Deviation, ITQ = Insulin Treatment Questionnaire

## Conclusions

- Treatment with Technosphere® Insulin Inhalation Powder was associated with improved health-related quality of life relative to those who used metformin plus a secretagogue.
- Treatment with Technosphere® Insulin Inhalation Powder was associated with significant improvement in treatment satisfaction relative to those who used metformin plus a secretagogue.

## References

1. Rave K, Heise T, Pfützner A, Boss AH. Coverage of postprandial blood glucose excursions with inhaled Technosphere Insulin in comparison to subcutaneously injected regular human insulin in subjects with type 2 diabetes. *Diabetes Care.* 2007;30:2307-8.
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