SUPPLEMENTARY DATA

**Affinity 1 Study Group**

**US**

| | | | |
|---|---|---|---|
| M. Adams, Murray, UT | R. Fink, La Mesa, CA | S. Lerman, Hollywood, FL | M. Rendell, Omaha, NE |
| A. Ahmann, Portland, OR | S. Garg, Aurora, CO | L. Loman, New Port Richey, FL | P. Rosenblit, Huntington Beach, CA |
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| J. Bridges, Vicennes, IN | T. Helmer, Edina, MN | F. Marquez, Hialeah, FL | L. Stone, Wenatchee, WA |
| M. Brown, Atlanta, GA | K. Hershon, New Hyde Park, NY | R. Mayfield, Greer, SC | L. Stonesifer, Federal Way, WA |
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| K. Castorino, Santa Barbara, CA | P. Kapsner, Albuquerque, NM | A. Miller, Dunwoody, GA | A. Sussman, Renton, WA |
| W. Cefalu, Baton Rouge, LA | W. Kaye, West Palm Beach, FL | S. Miller, San Antonio, TX | R. Tanenberg, Greenville, NC |
| R Cherlin, Los Gatos, CA | D. Klonoff, San Mateo, CA | A. Odugbesan, Lawrenceville, GA | G. Uwaifo, New Orleans, LA |
| D. Cheung, Long Beach, CA | W. Lane, Asheville, NC | R. Patel, Houston, TX | T. Wahl, Omaha, NE |
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SUPPLEMENTARY DATA

**Ex-US**

| Russia | | Ukraine | Brazil |
|---|---|---|---|
| Prof. A. Ametov, Moscow | Prof. A. Obrezan, St. Petersburg | Prof. Y. Karachentsev, Kharkiv | Dr. Denise Reis Franco, São Paulo |
| Prof. A. Gordienko, St. Petersburg | Dr. M. Pavlova, Moscow | Prof. V. Korpachev, Kiev | Dr. Jorge Luiz Gross, Porto Alegre |
| Prof. A. Gorelov, St. Petersburg | Prof. V. Podzolkov, Moscow | Prof. O. Larin, Kiev | |
| Dr. S. Grigoriev, Moscow | Prof. G. Reshedko, Smolensk | Prof. B. Mankovskyy, Kiev | |
| Dr. M. Kotelnikov, Moscow | Dr. O. Semenova, St. Petersburg | Prof. T. Pertseva, Dnipropetrovsk | |
| Dr. T. Kulagina, Petrozavodsk | Prof. S. Shustov, St. Petersburg | Prof. G. Popik / Dr. S. Kovalenko, Odessa | |
| Prof. L. Kvitkova, Kemerovo | Dr. E. Smolyarchuk, Moscow | Dr. Y. Suprun, Donetsk | |
| Prof. V. Marasaev, Yaroslavl | Dr. E. Turova, Moscow | Dr. Z. Teliatnikova, Odessa | |
| Dr. A. Mayorov, Moscow | Prof. N. Vorokhobina, St. Petersburg | Prof. M.Vlasenko, Vinnytsya | |
| Dr. T. Meleshkevich, Moscow | Prof. V. Yakusevich,Yaroslavl | Prof. Y. Karachentsev, Kharkiv | |
| Dr. E. Metkina, St. Petersburg | Dr. A. Zalevskaya, St. Petersburg | | |
| Prof. A. Ametov, Moscow | Prof. A. Obrezan, St. Petersburg | | |

SUPPLEMENTARY DATA

**Supplementary Table S1.** TI-Gen2 dose conversion

| RAA (prandial) bolus dose | Starting TI-Gen2 dose |
|---|---|
| Up to 4 U | 10 U |
| > 4–8 U | 20 U |
| > 8–12 U | 30 U |
| > 12–16 U | 40 U |
| > 16–20 U | 50 U |
| > 20–24 U | 60 U |

RAA: rapid-acting insulin analog, TI-Gen2: Technosphere Insulin delivered via the Gen2 inhaler.

**Supplementary Table S2.** Prandial dose* titrations for insulin aspart group adjusted weekly based on median of the 3 most recent measurements for each meal

| Median pre-next meal BG level[†] | Insulin aspart dose adjustment[‡] |
|---|---|
| <100 mg/dL | Decrease dose by 10% of current dose |
| ≥100 to <120 mg/dL | Maintain current dose |
| ≥120 to <140 mg/dL | Increase by 1 U |
| ≥140 to <180 mg/dL | Increase dose by 2 U |
| >180 mg/dL | Increase dose by 3 U (or 10% of dose) |

BG: blood glucose

*The total daily prandial insulin was to be approximately 40% to 60% of total daily insulin dose.

[†]Patients measured pre-next meal and bedtime BG levels at least 3 times for a given meal within each week.

[‡]Adjustment of prandial doses of insulin aspart was based on subsequent pre-meal BG values (breakfast, lunch and dinner doses were based on prelunch, predinner and bedtime BG, respectively). Additional dose adjustments/modifications (e.g., based on carbohydrate counting, meal size, self-monitored blood glucose [SMBG] results, snacks, postprandial glucose [PPG] level) were allowed.

SUPPLEMENTARY DATA

**Supplementary Table S3.** Prandial dose* titrations for TI-Gen2 group adjusted weekly based on median of the 3 most recent measurements for each meal

| Median 90-minute PPG level[†] | TI-Gen2 Inhalation Powder dose adjustment[‡] |
|---|---|
| <110 mg/dL | Decrease dose by 10 U |
| ≥110 to <160 mg/dL | Maintain current dose |
| ≥160 mg/dL | Increase dose by 10 U |

PPG: postprandial glucose, TI-Gen2: Technosphere Insulin delivered via the Gen2 inhaler

*The total daily prandial insulin was to be approximately 40% to 60% of total daily insulin dose (based on equivalent units: 4 U of prandial insulin is approximately equivalent to 10 U of TI Inhalation Powder using the Gen2 inhaler or 15 U of TI Inhalation Powder using the MedTone inhaler).

[†]Patients who had a 90-minute PPG level ≥ 180 mg/dL were to take a supplemental after-meal dose of 10 U with the Gen2 inhaler at the time of the PPG reading (i.e., same day and time). Patients who developed more than 2 episodes of hypoglycemia after taking supplemental doses of TI Inhalation Powder were instructed not to take additional supplemental doses of TI Inhalation Powder and to consult with the Principle Investigator.

[‡]The instructions were the same for the MedTone inhaler except that the dose adjustments were in increments of 15 U; 10 U from the Gen2 inhaler provides the same insulin dose as 15 U from the MedTone inhaler.

SUPPLEMENTARY DATA

**Supplementary Table S4.** Patient demographics and baseline disease characteristics (safety population)

| | Number (%) of patients | | |
|---|---|---|---|
| | TI-Gen2 (*n* = 174) | TI-MedTone (*n* = 173) | Insulin aspart (*n* = 171) |
| Age (years) | | | |
| Mean | 37.0 | 40.0 | 39.0 |
| SD | 12.42 | 13.32 | 12.67 |
| Median | 36.0 | 39.0 | 36.0 |
| Range | [18, 71] | [18, 76] | [18, 76] |
| Age group (years) | | | |
| 18–30 | 56 (32.2) | 47 (27.2) | 47 (27.5) |
| 31–49 | 93 (53.4) | 84 (48.6) | 88 (51.5) |
| 50–64 | 18 (10.3) | 33 (19.1) | 28 (16.4) |
| 65+ | 7 (4.0) | 9 (5.2) | 8 (4.7) |
| Sex | | | |
| Male | 77 (44.3) | 80 (46.2) | 74 (43.3) |
| Female | 97 (55.7) | 93 (53.8) | 97 (56.7) |
| Race | | | |
| White | 164 (94.3) | 166 (96.0) | 167 (97.7) |
| Black or African American | 8 (4.6) | 5 (2.9) | 3 (1.8) |
| American Indian or Alaska Native | 0 | 0 | 0 |
| Asian | 1 (0.6) | 1 (0.6) | 0 |
| Native Hawaiian/Other Pacific Islander | 1 (0.6) | 0 | 0 |
| Other | 0 | 1 (0.6) | 1 (0.6) |
| Country | | | |
| United States | 71 (40.8) | 68 (39.3) | 68 (39.8) |
| Russia | 45 (25.9) | 52 (30.1) | 52 (30.4) |
| Ukraine | 44 (25.3) | 38 (22.0) | 38 (22.2) |
| Brazil | 14 (8.0) | 15 (8.7) | 13 (7.6) |
| Duration of diabetes mellitus (years) | | | |
| Mean (SD) | 16.0 (10.27) | 17.7 (10.69) | 16.7 (10.01) |
| Median | 13.8 | 15.2 | 16.0 |
| Range | [1.1, 57.3] | [1.1, 49.5] | [1.0, 42.2] |
| Weight (kg) | | | |
| Mean (SD) | 75.7 (15.75) | 76.8 (14.87) | 72.6 (15.24) |
| Median | 74.4 | 76.3 | 69.7 |
| Range | [41.7, 129.4] | [47.6, 124.0] | [46.6, 120.2] |
| BMI ($kg/m^2$) | | | |
| Mean (SD) | 26.0 (4.48) | 26.2 (3.74) | 25.4 (4.10) |
| Median | 25.7 | 26.0 | 24.5 |
| Range | [16.6, 38.6] | [18.1, 36.4] | [17.4, 37.2] |
| $HbA_{1c}$ (%)* | | | |
| Mean (SD) | 7.98 (0.767) | 7.99 (0.732) | 7.88 (0.751) |
| Median | 7.90 | 8.00 | 7.90 |
| Range | [6.20, 10.60] | [6.10, 10.20] | [5.80, 10.10] |

SUPPLEMENTARY DATA

| | Number (%) of patients | | |
|---|---|---|---|
| | TI-Gen2 (*n* = 174) | TI-MedTone (*n* = 173) | Insulin aspart (*n* = 171) |
| $HbA_{1c}$ (mmol/mol) | | | |
| Mean | 63.7 | 63.8 | 62.6 |
| Median | 62.8 | 63.9 | 62.8 |
| Range | [44.3, 92.4] | [43.2, 88.0] | [39.9, 86.9] |
| Fasting plasma glucose (mg/dL) | | | |
| Mean (SD) | 155.0 (67.62) | 143.9 (60.79) | 151.6 (67.44) |
| Median | 144.5 | 137.0 | 149.0 |
| Range | [21.0, 403.0] | [43.0, 358.0] | [23.0, 375.0] |
| Basal insulin (n [%]) | | | |
| Insulin detemir | 26 (14.9) | 26 (14.9) | 26 (15.3) |
| Insulin glargine | 121 (69.5) | 122 (70.1) | 121 (71.2) |
| NPH insulin | 27 (15.5) | 26 (14.9) | 23 (13.5) |
| Basal insulin dosing frequency (n [%])[†] | | | |
| Once | 72 (42) | 83 (48) | 77 (45) |
| More than once | 99 (58) | 90 (52) | 93 (55) |

SD is standard deviation, TI-Gen2: Technosphere Insulin delivered via the Gen2 inhaler, TI-MedTone: Technosphere Insulin delivered via the MedTone inhaler

*Baseline $HbA_{1c}$ values were obtained at randomization, after run-in period

[†]Dosing frequency is based on each subject's predominant dosing frequency observed from their diary data.

SUPPLEMENTARY DATA

**Supplementary Table S5.** Analysis of the primary endpoint (per-protocol population)

| | | TI-Gen2 (*n* = 130) | Insulin aspart (*n* = 146) | Treatment difference |
|---|---|---|---|---|
| $HbA_{1c}$, % [mmol/mol] (95% CI)* | Baseline | 7.94 [63.3] | 7.92 [63.1] | |
| | Adjusted mean change | –0.21 (–0.35 to –0.08) | –0.42 (–0.54 to –0.29) | 0.20 (0.02 to 0.39) |

TI-Gen2: Technosphere Insulin delivered via the Gen2 inhaler
*Assessed using mixed-model repeated-measures analysis

**Supplementary Table S6.** Adverse events in ≥2% of patients

| | Number (%) of patients | | |
|---|---|---|---|
| | TI-Gen2 (*n* = 174) | TI-MedTone (*n* = 173) | Insulin aspart (*n* = 171) |
| Cough | 55 (31.6) | 39 (22.5) | 4 (2.3) |
| Upper respiratory tract infection | 14 (8.0) | 16 (9.2) | 12 (7.0) |
| Headache | 7 (4.0) | 5 (2.9) | 4 (2.3) |
| Dyspnea | 7 (4.0) | 0 | 0 |
| Bronchitis | 6 (3.4) | 1 (0.6) | 4 (2.3) |
| Nasopharyngitis | 5 (2.9) | 13 (7.5) | 12 (7.0) |
| Throat irritation | 5 (2.9) | 3 (1.7) | 1 (0.6) |
| Diarrhea | 4 (2.3) | 2 (1.2) | 5 (2.9) |
| Oropharyngeal pain | 3 (1.7) | 6 (3.5) | 3 (1.8) |
| Influenza | 2 (1.1) | 9 (5.2) | 3 (1.8) |
| Vomiting | 2 (1.1) | 3 (1.7) | 5 (2.9) |
| Urinary tract infection | 1 (0.6) | 6 (3.5) | 3 (1.8) |
| Nausea | 1 (0.6) | 5 (2.9) | 6 (3.5) |
| Hypoglycemic unconsciousness | 1 (0.6) | 4 (2.3) | 2 (1.2) |
| Blood creatine phosphokinase increased | 0 | 2 (1.2) | 4 (2.3) |

TI-Gen2: Technosphere Insulin delivered via the Gen2 inhaler, TI-MedTone: Technosphere Insulin delivered via the MedTone inhaler

SUPPLEMENTARY DATA

**Supplementary Table S7.** Hypoglycemic event rates during the treatment period – results from models with and without terms for the effect of treatment on $HbA_{1c}$ (safety population)

| | TI-Gen2 (*n* = 174) | Insulin aspart (*n* = 171) | Percentage reduction in event rate | TI - Insulin aspart *P*-value |
|---|---|---|---|---|
| Adjusted event rate from the original model (per 100 patient-months) | | | | |
| Total hypoglycemia | 1028 | 1503 | 31.6% | <0.000* |
| Severe hypoglycemia | 8.84 | 14.03 | 37.0% | 0.1022* |
| Adjusted event rate from the model with additional $HbA_{1c}$ terms† (per 100 patient-months) | | | | |
| Total hypoglycemia | 1035 | 1414 | 26.8% | <0.000† |
| Severe hypoglycemia | 8.66 | 15.24 | 43.2% | 0.0516† |

TI-Gen2: Technosphere Insulin delivered via the Gen2 inhaler

*Adjusted event rates and *P*-values from a negative binomial regression analysis with terms for region, basal insulin stratum, and treatment in the model with duration of treatment exposure as an offset. The event rates given in this table are model-adjusted, whereas the event rates given in Table 1 are based on the total number of events divided by the total exposure time.

†Adjusted event rates and *P*-values from a negative binomial regression analysis with terms for region, basal insulin stratum, treatment, $HbA_{1c}$ change from baseline, and $HbA_{1c}$ at end of treatment in the model with duration of treatment exposure as an offset.

**Supplementary Table S8.** Analysis of the primary endpoint (full analysis set) adjusted by basal dose

| | | TI-Gen2 (*n* = 171) | Insulin aspart (*n* = 169) | Treatment difference |
|---|---|---|---|---|
| $HbA_{1c}$, % [mmol/mol] (95% CI)* | Baseline | 7.92 [63.1] | 7.91 [63.0] | |
| | Adjusted mean change | –0.21 (–0.33 to –0.09) | –0.40 (–0.52 to –0.28) | 0.19 (0.02 to 0.36) |

TI-Gen2: Technosphere Insulin delivered via the Gen2 inhaler

*Assessed using mixed-model repeated-measures analysis with additional terms for basal dose per kg of weight (U/kg)

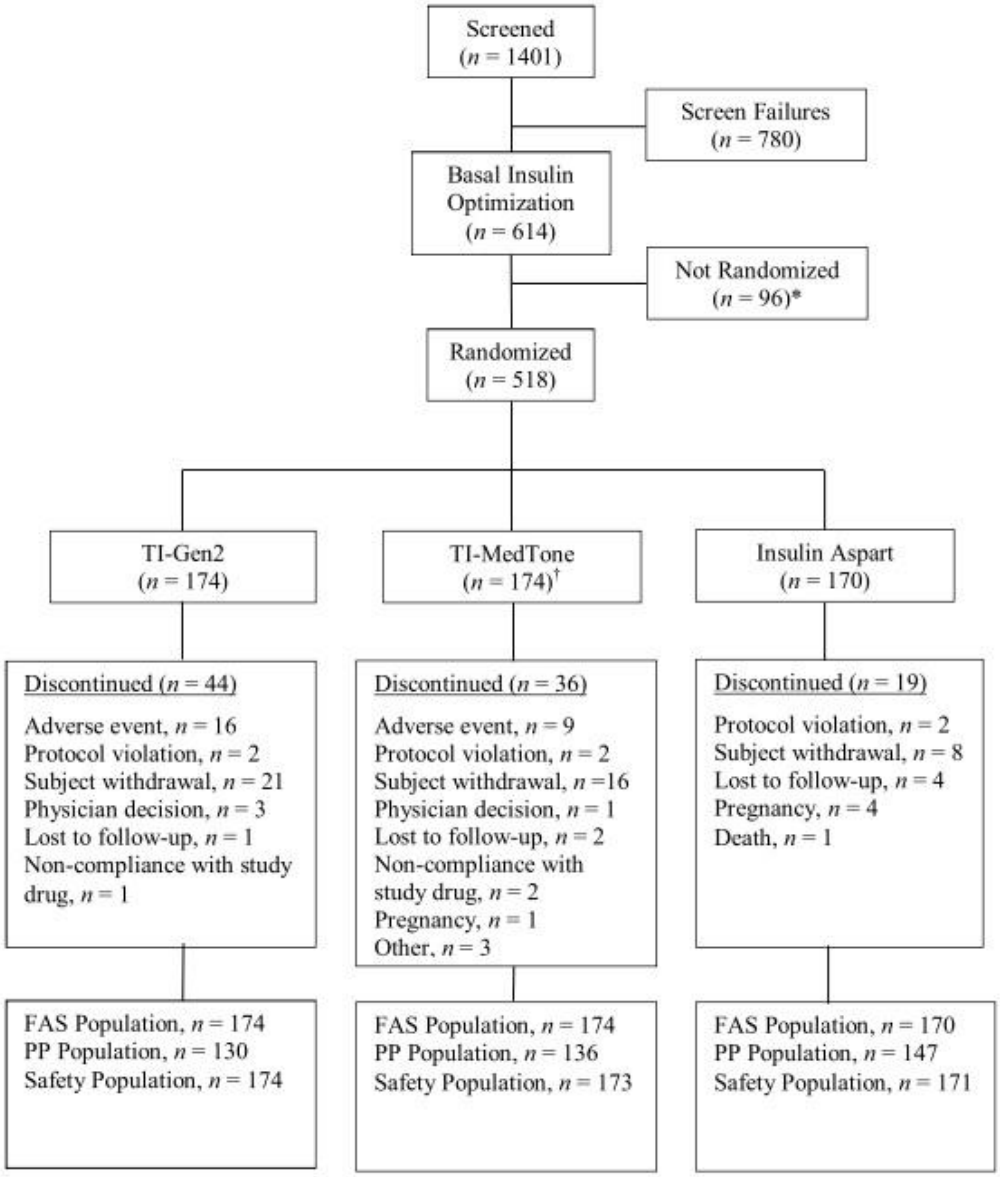
SUPPLEMENTARY DATA

**Supplementary Figure S1.** Patient disposition.

FAS: full analysis set, PP: per-protocol, TI-Gen2: Technosphere Insulin delivered via the Gen2 inhaler, TI-MedTone: Technosphere Insulin delivered via the MedTone inhaler.

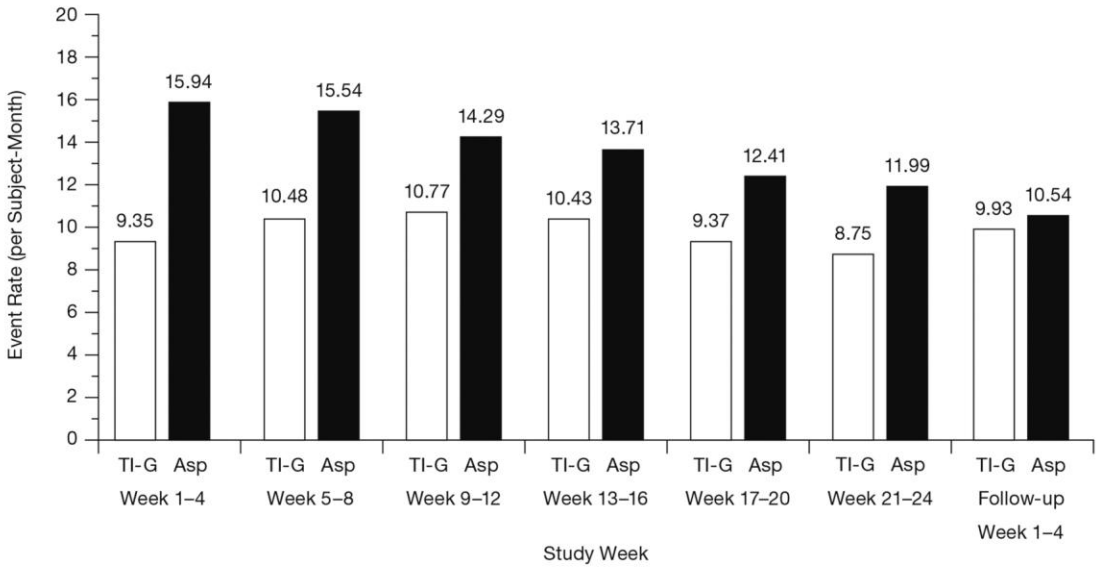
*Of the 96 patients not randomized, 32 did not complete the basal optimization phase, 44 had pre-randomization FPG values >180 mg/dL, and 20 were not randomized because, despite meeting the randomization criteria, the number of randomized patients exceeded the planned number.

†One patient randomized to the TI-MedTone group was dispensed insulin aspart from day 1 until end of study; the patient was included in the insulin aspart group for safety.



SUPPLEMENTARY DATA

**Supplementary Figure S2.** Hypoglycemia event rates during trial (Safety population).
Asp: insulin aspart, TI-Gen2 and also TI-G: Technosphere Insulin delivered via the Gen2 inhaler.




| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Exposure Time: | | | | | | | |
| TI Gen2: | 152.4 | 138.5 | 133.3 | 126.1 | 124.2 | 118.2 | 117.9 |
| Insulin aspart: | 154.6 | 151.6 | 148.4 | 144.5 | 143.4 | 138.5 | 138.5 |
| Number of events: | | | | | | | |
| TI Gen2: | 1425 | 1452 | 1435 | 1315 | 1164 | 1034 | 1170 |
| Insulin aspart: | 2464 | 2356 | 2120 | 1982 | 1780 | 1660 | 1460 |