SUPPLEMENTARY DATA

APPENDIX

Table of Contents

SUPPLEMENTARY DATA

Appendix 1: RISE Consortium Investigators

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SUPPLEMENTARY DATA

Appendix 2: Supplemental Study Methods

Inclusion Criteria

1. Fasting plasma glucose ≥5.0 mmol/L, plus 2-hour glucose ≥7.8 mmol/L on 75-gram OGTT, plus laboratory-based HbA1c ≤8.0% (64 mmol/mol) if treatment naïve. In those already taking metformin, laboratory-based HbA1c ≤7.5% (58 mmol/mol) if on metformin for <3 months and ≤7.0% if on metformin for 3-6 months
2. Age 10-19 years
3. Breast development ≥Tanner stage II in females and testicular volume >3 mL in boys
4. Body mass index (BMI) ≥85th percentile for age and sex and <50 kg/m^2
5. Diabetes duration <6 months
6. If on treatment with metformin for diabetes, <6 months in duration prior to screening

Exclusion Criteria

1. Underlying disease likely to limit life span, increase risk of intervention or limit ability to participate in outcomes assessment
2. Underlying disease, other than type 2 diabetes, that affects glucose metabolism
3. Medications that affect glucose metabolism (other than metformin in participants with diabetes)
4. Treatment with insulin for >1 week at any time prior to screening
5. Active infectious disease
6. Serum creatinine >106.1 µmol/L (1.2 mg/dL) or serum potassium <3.4 or >5.5 mmol/L
7. Hemoglobin <6.83 mmol/L (11 g/dL in girls), <7.45 mmol/L (12 g/dL) in boys
8. Known coagulopathy
9. Uncontrolled hypertension, defined as average systolic or diastolic blood pressure >99th percentile for age or >135/90 mm Hg, despite adequately prescribed antihypertensive therapy
10. Conditions that may be precipitated or exacerbated by a study drug:
    a. Serum ALT >3 times the upper limit of normal
    b. Excessive alcohol intake (3 or more alcoholic beverages daily, consumption of more than 7 alcoholic beverages within a 24-hour period)
    c. Sub-optimally treated thyroid disease
    d. Seizure disorder
11. Conditions or behaviors likely to affect conduct of the RISE Study:
    a. Participant and/or parents unable to adequately communicate with clinic staff
    b. Another household member is a participant or staff member in RISE
    c. Current, recent or anticipated participation in another intervention research project
    d. Weight loss ≥5% of body weight in the past 3 months; use of medications or other preparations intended for weight loss
    e. Likely to move away from participating clinic in next 2 years
    f. Current (or anticipated) pregnancy or lactation
    g. A pregnancy completed less than 6 months prior to screening
    h. Breast feeding within 6 months prior to screening
    i. Women with childbearing potential unwilling to use adequate contraception, including abstinence

SUPPLEMENTARY DATA

Study Medications

All study medications were dispensed by the RISE Drug Distribution Center (DDC) at Belmar Pharmacy (Lakewood, CO). Participants who experienced any side effects of medications or study procedures were instructed to call the clinical site. To minimize gastrointestinal side effects, metformin-naïve participants were titrated over four weeks (maximum of eight weeks) from a starting dose of 500 mg once daily to a maximum dose of 1000 mg twice daily. If gastrointestinal side effects were not tolerable, metformin was reduced by 500 mg to the next tolerable dose. If the side effect was still severe, the metformin was again reduced by 500 mg. Once gastrointestinal symptoms resolved, metformin was re-escalated by 500 mg per day each week. Placebo metformin pills were manufactured by Belmar Pharmacy to be identical to purchased generic metformin.

For participants randomized to glargine followed by metformin, once-daily insulin glargine was initiated in the evening (between 9:00 PM and 11:00 PM) based on weight (0.25 units/kg for participants with IGT; 0.4 units/kg for participants with type 2 diabetes) and titrated over one month, based on daily fasting morning (between 6:00 AM and 9:00 AM) self-monitoring blood glucose (SMBG), to achieve a fasting blood glucose of 4.4-5.0 mmol/L. Abbott Laboratories provided the glucose meters (FreeStyle Lite system) and test strips. Participants worked with study staff to adjust the glargine dose every 2-3 days. If at least two of the previous three fasting SMBG values were available (or average if less than three readings were available), the dose of glargine was to be adjusted according to the following algorithm:

If 2 of last 3 fasting SMBG (or average if < 3)	**Glargine Dose Adjustment**
<2.8 mmol/L	Decrease by the greater of 10% or 8 units
2.8-3.8 mmol/L	Decrease by the greater of 5% or 5 units
3.9-4.4 mmol/L	Decrease by 5 units
4.4-4.9 mmol/L	No adjustment
5.0-5.5 mmol/L	Increase by the greater of 10% or 5 units
5.5-6.1 mmol/L	Increase by the greater of 20% or 10 units
6.1-6.6 mmol/L	Increase by the greater of 25% or 15 units
≥6.7 mmol/L	Increase by the greater of 30% or 20 units

Following 3 months of insulin treatment, insulin glargine was discontinued, and metformin was initiated and titrated as described above.

Study staff monitored compliance by auditing returned medication every three months. For study procedures performed during the active phase of treatment, study medications were withheld on the morning of testing. Study medications were stopped after the 12-month visit.

SUPPLEMENTARY DATA

Safety

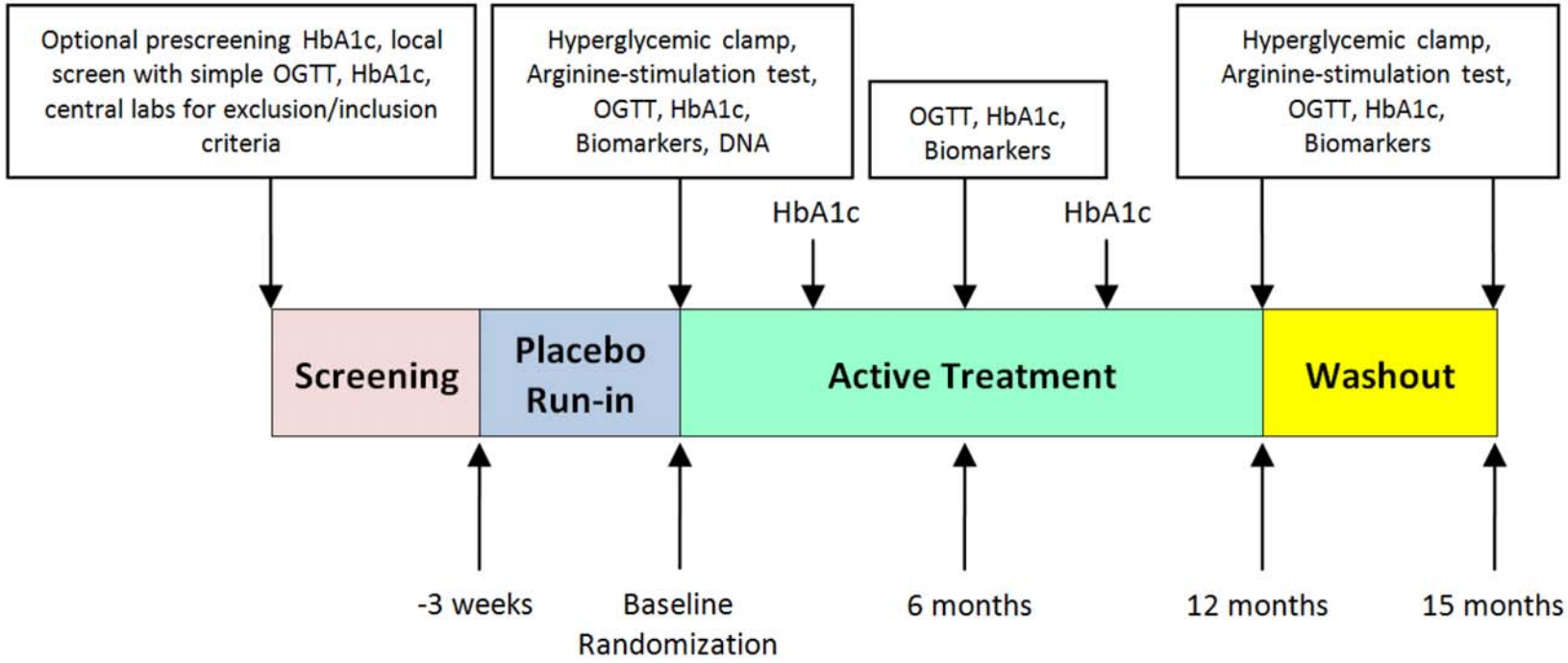
At screening all participants were provided with routine recommendations for weight loss and exercise, consistent with the US Diabetes Prevention Program recommendations, as well as standard diabetes education, glucose management and study medication management. Participants with type 2 diabetes and those randomized to glargine were asked to perform SMBG daily and whenever they had symptoms of hypoglycemia or hyperglycemia or felt ill for any reason. They were asked to report abnormal readings to clinic staff, who inquired about symptoms and requested that the participant check urine ketones. If symptoms and/or ketones were present, the participant was brought to the research clinic for interim assessment using the following algorithm:

- If participants experienced acute metabolic decompensation, rescue therapy with insulin was to be initiated. Acute metabolic decompensation was defined as hyperglycemia (plasma glucose >16.6 mmol/L accompanied by symptoms (e.g., vomiting, dehydration, lethargy) and/or moderate or large urinary ketones. Participants with diabetic ketoacidosis (DKA) were to be referred for emergent care. (No participants experienced acute metabolic decompensation.)
- If HbA1c was ≥9% (75 mmol/mol) without acute metabolic decompensation or DKA, therapy was invigorated (using frequent telephone contact and/or visits to encourage optimal medication adherence and lifestyle choices) and HbA1c was repeated within 2 weeks. If HbA1c was still ≥9% (75 mmol/mol), final outcome measurements were obtained within 2 weeks of confirmation, after which rescue therapy was initiated.
- If HbA1c was ≥8% (64 mmol/mol) but <9% (75 mmol/mol) at any visit, therapy was invigorated. HbA1c was obtained within six weeks, and if it was confirmed ≥8% (64 mmol/mol), final outcome measurements were obtained within two weeks, after which rescue therapy was initiated.
- If HbA1c was ≥7% (53 mmol/mol) but <8% (64 mmol/mol) at any visit, therapy was invigorated. HbA1c was obtained at the next quarterly visit, and if it was ≥7% (53 mmol/mol) but <8% (64 mmol/mol), frequent contact was maintained.

SUPPLEMENTARY DATA

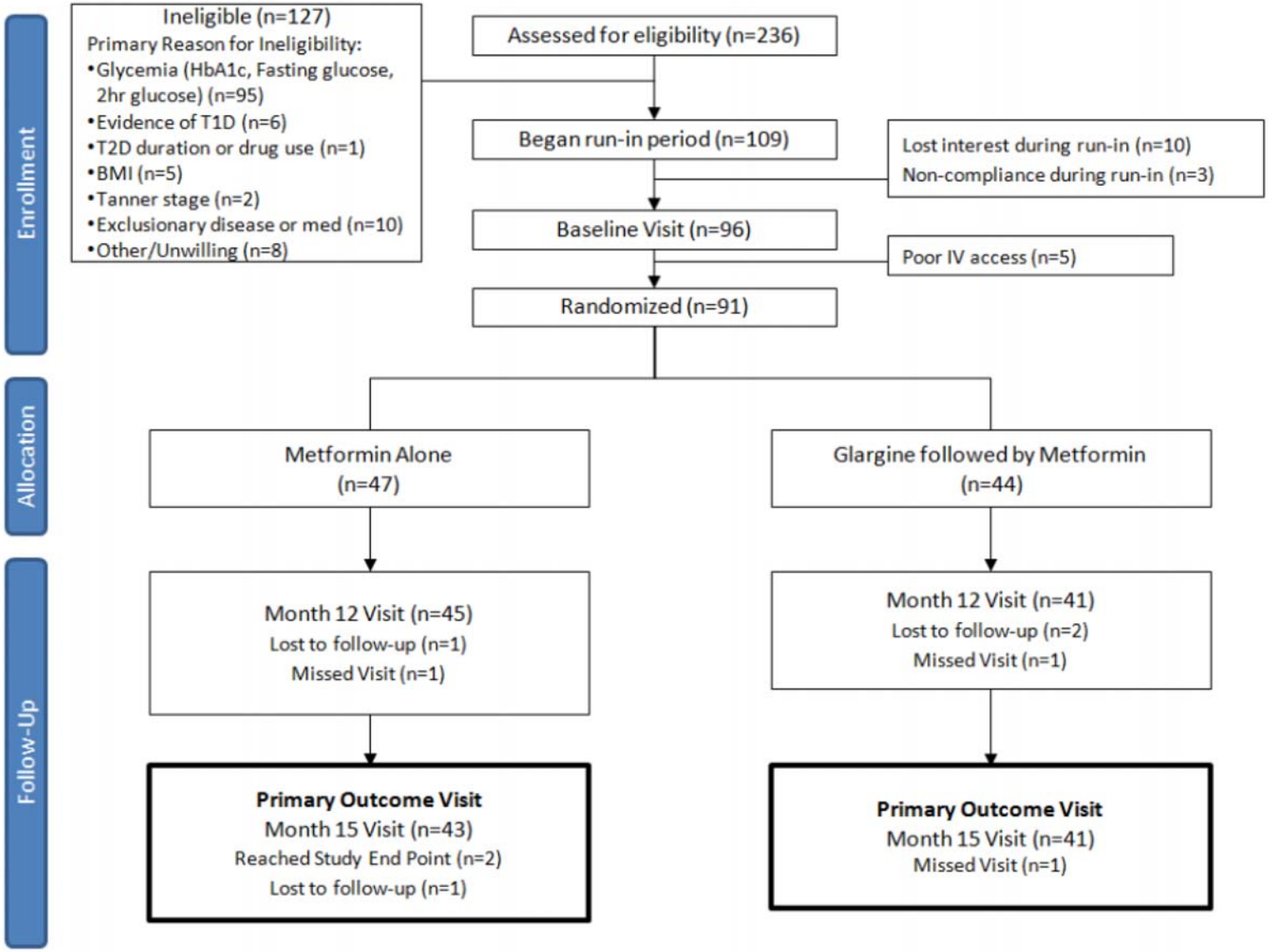
Appendix 3: Supplemental Figures

Supplementary Figure S1. Timeline for Screening, Run-in, Treatment and Washout Visits along with Procedures Performed at these Visits



SUPPLEMENTARY DATA

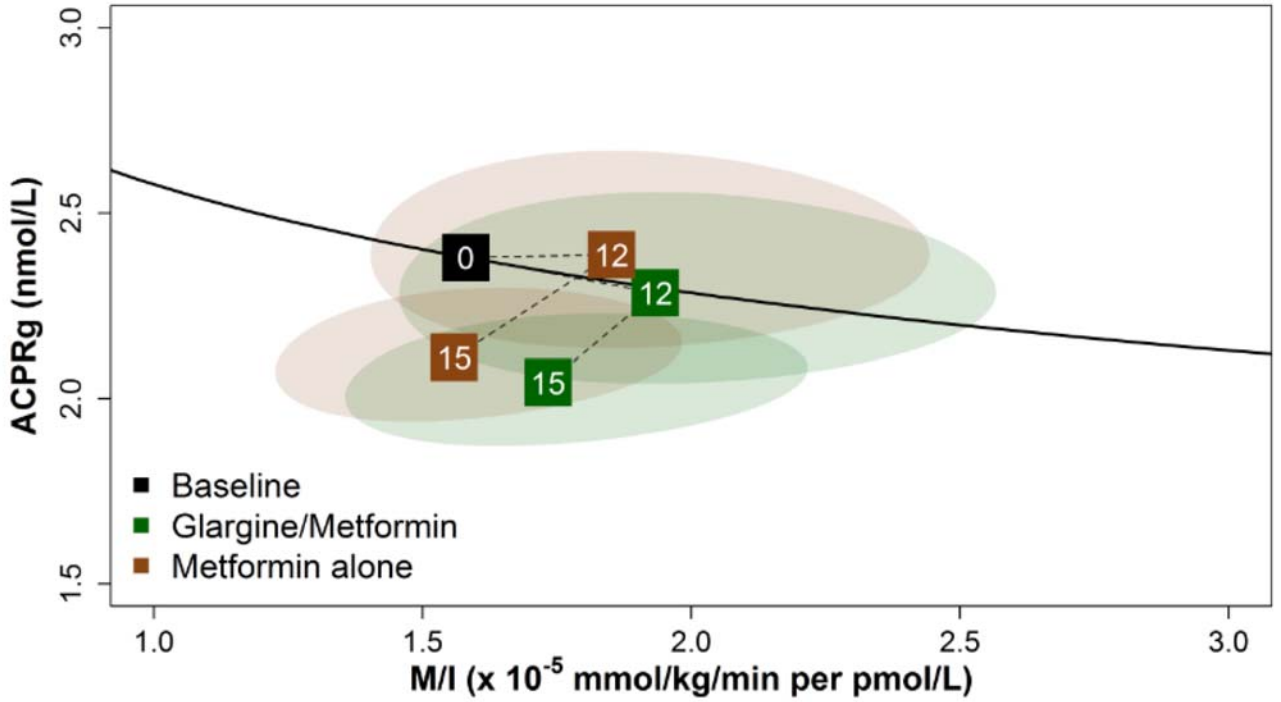
Supplementary Figure S2. RISE Pediatric Medication Study Consort Diagram



SUPPLEMENTARY DATA

Supplementary Figure S3. **Relationship of the Secondary Outcome: Hyperglycemic Clamp-derived β-cell Response (Acute C-peptide Response to Glucose, ACPRg) Paired with Insulin Sensitivity (M/I)**

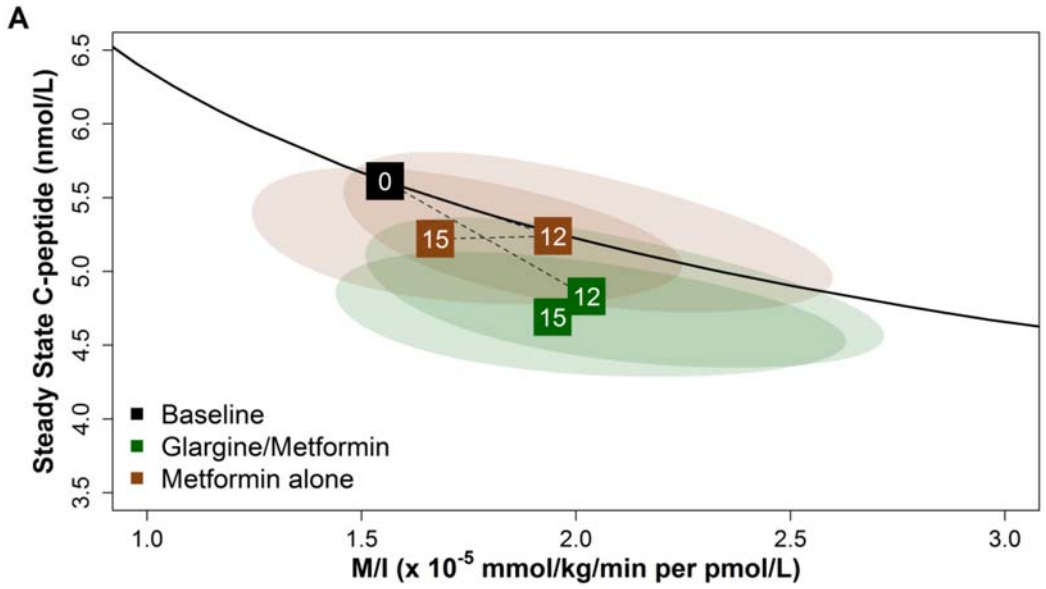
Changes from baseline at 12 and 15 months for the secondary outcome: clamp-derived β-cell response (acute C-peptide response to glucose, ACPRg) and insulin sensitivity (M/I). The black line depicts the joint relationship between β-cell response (ACPRg) and M/I at baseline for the full cohort, with the mean value indicated by the black box with 0. The dotted lines to boxes at months 12 and 15 show the trajectory of values from baseline to 12 months of intervention and then to 3 months following discontinuation of the intervention (15 months) for glargine followed by metformin in green and metformin alone in brown. Values above the black line represent improved β-cell function and values below the line represent poorer β-cell function. The ellipses depict the 95% confidence bands around the points at months 12 and 15. There were no significant differences at any timepoint between treatment arms; however, there were significant within-group declines from baseline through 15 months in both treatment arms (glargine followed by metformin: $p<0.001$, metformin alone: $p=0.014$).

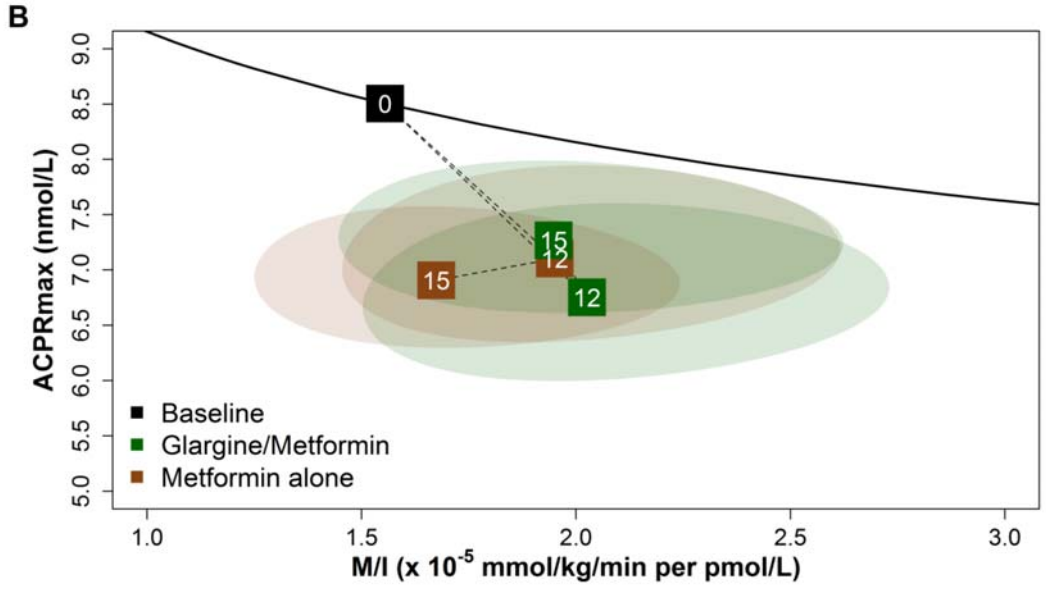


SUPPLEMENTARY DATA

Supplementary Figure S4. Relationship of the Two Co-primary Outcomes: Hyperglycemic Clamp-derived β-cell Responses (Steady-State C-peptide and Acute C-peptide Response to Arginine at Maximal Glycemic Potentiation, ACPRmax) Paired with Insulin Sensitivity (M/I) in Participants with Impaired Glucose Tolerance (IGT)

Changes from baseline at 12 and 15 months for each of the co-primary outcomes: clamp-derived β-cell responses (steady-state C-peptide [A], acute C-peptide response to arginine at maximal glycemic potentiation, ACPRmax [B]) and insulin sensitivity (M/I). The black line depicts the joint relationship between β-cell response and M/I at baseline for the IGT cohort, with the mean value at baseline for the IGT cohort indicated by the black box with 0. The dotted lines to boxes at months 12 and 15 show the trajectory of values from baseline to 12 months of intervention and then to 3 months following discontinuation of the intervention (15 months) for glargine followed by metformin in green and metformin alone in brown. Values above the black line represent improved β-cell function and value below the line represent poorer β-cell function. The ellipses depict the 95% confidence bands around the points at months 12 and 15.





SUPPLEMENTARY DATA

Appendix 4: Supplemental Tables

Supplementary Table S1. Hyperglycemic Clamp-derived Measurements over Time

Clamp Variables	Glargine Followed by Metformin: Baseline (n=44)	Glargine Followed by Metformin: 12 months (n=41)	Glargine Followed by Metformin: 15 months (n=41)	Metformin Alone: Baseline (n=47)	Metformin Alone: 12 months (n=45)	Metformin Alone: 15 months (n=43)
Steady-State C-peptide (nmol/L)	5.22 (2.44, 11.16)	4.37 (1.75, 10.94)	4.18 (1.74, 10.08)	5.09 (2.32, 11.19)	4.78 (2.09, 10.94)	4.82 (2.07, 11.23)*
ACPRmax (nmol/L)	7.29 (3.29, 16.16)	5.79 (2.49, 13.46)	5.95 (2.17, 16.37)	8.12 (3.42, 19.26)	6.95 (3.16, 15.28)	6.92 (2.81, 17.03)
ACPRg (nmol/L)	1.06 (0.1, 11.66)	1.03 (0.05, 21.73)	1.12 (0.15, 8.35)	1.14 (0.14, 9.02)	1.06 (0.1, 11.33)	1.11 (0.14, 8.56)
M/I (x 10^{-5} mmol/kg/min per pmol/L)	1.607 (0.35, 7.43)	1.929 (0.30, 12.50)	1.704 (0.25, 11.54)	1.544 (0.35, 6.76)	1.516 (0.17, 13.48)	1.478 (0.29, 7.63)

Data displayed are geometric means (95% CI).
ACPRmax = acute C-peptide response to arginine at maximal glycemic potentiation, ACPRg = acute C-peptide response to glucose, M/I = steady-state glucose infusion/steady-state insulin
*p=0.04 for difference between glargine followed by metformin vs. metformin alone at 15 months. No other values were significantly different between treatment groups at 12 or 15 months.

Supplementary Table S2. Targeted Adverse Events

	Through Month 12		Through Month 15	
Event	Glargine Followed by Metformin	Metformin Alone	Glargine Followed by Metformin	Metformin Alone
N	44	46	44	46
SMBG <3.9 mmol/L*	16 (36.4%)	--	--	--
Skin rash†	4 (9.1%)	5 (10.9%)	5 (11.4%)	6 (13%)
Gastrointestinal discomfort	16 (36.4%)	16 (34.8%)	17 (38.6%)	16 (34.8%)
Polyuria or polydipsia‡	8 (18.2%)	9 (19.6%)	10 (22.7%)	11 (23.9%)

* Blood glucose <3.9 mmol/L per self-monitoring blood glucose (SMBG) meter download during the 12 weeks of glargine treatment
†p-value determined from Fisher exact test
‡Defined as "nocturia more than once a night on a regular basis, enuresis, increased thirst, urinating more often than usual"
All p=ns