# Antisense Inhibition of Protein Tyrosine Phosphatase 1B With IONIS-PTP-1B$_{Rx}$ Improves Insulin Sensitivity and Reduces Weight in Overweight Patients With Type 2 Diabetes

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## OBJECTIVE

**To evaluate safety and efficacy of IONIS-PTP-1B$_{Rx}$, a second-generation 2′-*O*-methoxyethyl antisense inhibitor of protein tyrosine phosphatase 1B, as add-on therapy in overweight patients with type 2 diabetes inadequately controlled with metformin with or without sulfonylurea therapy.**

## RESEARCH DESIGN AND METHODS

**In this phase II, double-blind, randomized, placebo-controlled, multicenter trial, overweight and obese patients (BMI ≥27 kg/m$^2$) with type 2 diabetes (HbA$_{1c}$ ≥7.5% [58 mmol/mol] and ≤10.5% [91 mmol/mol]) on a stable dose of metformin alone or with sulfonylurea were randomized 2:1 to IONIS-PTP-1B$_{Rx}$ 200 mg (*n* = 62) or placebo (*n* = 30) once weekly for 26 weeks.**

## RESULTS

**Mean baseline HbA$_{1c}$ was 8.6% (70 mmol/mol) and 8.7% (72 mmol/mol) in placebo and active treatment, respectively. At week 27, IONIS-PTP-1B$_{Rx}$ reduced mean HbA$_{1c}$ levels by −0.44% (−4.8 mmol/mol; *P* = 0.074) from baseline and improved leptin (−4.4 ng/mL; *P* = 0.007) and adiponectin (0.99 μg/mL; *P* = 0.026) levels compared with placebo. By week 36, mean HbA$_{1c}$ was significantly reduced (−0.69% [−7.5 mmol/mol]; *P* = 0.034) and accompanied by reductions in fructosamine (−33.2 μmol/L; *P* = 0.005) and glycated albumin (−1.6%; *P* = 0.031) versus placebo. Despite both treatment groups receiving similar lifestyle counseling, mean body weight significantly decreased from baseline to week 27 with IONIS-PTP-1B$_{Rx}$ versus placebo (−2.6 kg; *P* = 0.002) independent of HbA$_{1c}$ reduction ($R^2$ = 0.0020). No safety concerns were identified in the study.**

## CONCLUSIONS

**Compared with placebo, IONIS-PTP-1B$_{Rx}$ treatment for 26 weeks produced prolonged reductions in HbA$_{1c}$, improved medium-term glycemic parameters, reduced leptin and increased adiponectin levels, and resulted in a distinct body weight–reducing effect.**


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Despite a number of drugs that have been approved to treat type 2 diabetes, many of the current therapies do not adequately address one of the root causes of the disease, insulin resistance. Improving insulin sensitivity would be ideal for patients with type 2 diabetes because it could effectively reverse the course of the disease as well as prevent the development of diabetic complications. However, there is still a large unmet demand for safe and effective insulin sensitizers because of the safety concerns of current approved therapies such as thiazolidinediones (TZDs).

TZDs have been shown to moderately improve glycemic control in randomized controlled studies without increasing the risk of hypoglycemia (1,2). However, TZDs have many recognized side effects, including weight gain, fluid retention leading to edema, and bone fractures (3,4). Rosiglitazone has been shown to have significantly higher odds of adverse cardiovascular effects, such as congestive heart failure and myocardial infarction, compared with pioglitazone (5,6). Although pioglitazone is available in most countries, its use is restricted because of possible associations with urinary bladder cancer (7); therefore, this class of drugs has been restricted or withdrawn from clinical use in the U.S. and European Union as a result of various safety concerns (5–9).

Protein tyrosine phosphatase 1B (PTP-1B) has been identified as a negative regulator of both insulin and leptin signaling pathways (10). In insulin signaling, PTP-1B dephosphorylates the insulin receptor, including its primary substrates, whereas in leptin signaling, the downstream Janus kinase 2 is the primary target for dephosphorylation (11). The result is a disruption of the insulin and leptin signaling pathways, leading to decreased sensitivity to both these hormones. Studies have shown that insulin resistant conditions are associated with increased expression and activity of PTP-1B in insulin sensitive tissues (12,13). Disruption and pharmacological inhibition of the PTP-1B gene results in improved glycemic control and resistance to diet-induced obesity in mice (14,15). In addition, single-nucleotide polymorphisms in the PTP-1B gene in humans are associated with a reduced risk of diabetes, further lending to the evidence that PTP-1B is involved in human glucose metabolism (16,17). The glucose-lowering effects, improvements in insulin sensitivity, and resistance to high-fat diet observed with reductions/deletions in PTP-1B make this gene an attractive therapeutic target that could effectively address the underlying etiology of type 2 diabetes.

Second-generation antisense oligonucleotides (ASOs) have been developed to reduce the expression of PTP-1B specifically in both animals and humans (18). This class of RNA therapeutic drugs selectively bind mRNA through Watson-Crick base pair interactions, leading to RNase H1-mediated degradation (19). In mice treated with a species-specific ASO, dose-dependent reductions in hepatic and adipose PTP-1B protein levels were observed with an associated decrease in plasma glucose and improvement in insulin sensitivity (20,21). Initial evidence of a PTP-1B ASO treatment in humans comes from a pilot study in patients with type 2 diabetes that demonstrated glucose-lowering effects and improvements in leptin and insulin sensitivity (22). IONIS-PTP-1B$_{Rx}$ is a 2′-*O*-methoxyethyl (2′-MOE)–modified second-generation ASO designed as a more potent inhibitor of PTP-1B mRNA expression in humans. This phase II study was conducted to further explore the safety and efficacy of inhibiting PTP-1B with 200 mg of IONIS-PTP-1B$_{Rx}$ as an add-on therapy in overweight patients with type 2 diabetes unable to maintain glycemic control with stable metformin alone or in combination with sulfonylurea.

## RESEARCH DESIGN AND METHODS

### Clinical Trial Design and Participants

A phase II, double-blind, randomized, placebo-controlled trial was conducted between August 2013 and January 2015 at 18 sites in three countries (Argentina, Canada, and South Africa) to evaluate the effects of IONIS-PTP-1B$_{Rx}$ in combination with one or two oral antidiabetic drugs (OADs) (defined as a stable dose of metformin with or without sulfonylurea) in overweight or obese adult patients with type 2 diabetes. Written informed consent was obtained from all patients before study participation. The clinical trial protocol was approved by institutional review boards and an independent ethics committee (Ontario, Canada; Alberta, Canada; Pretoria, South Africa; Rosario, Argentina) and complied with the guidelines of the 2002 Declaration of Helsinki and the International Conference on Harmonization Tripartite Guidelines on Good Clinical Practice.

Eligible patients were 18–70 years old; had a clinically confirmed diagnosis of type 2 diabetes, fasting C-peptide $\geq$500 pmol/L, uncontrolled hyperglycemia defined as HbA$_{1c}$ $\geq$7.5% (58 mmol/mol) and $\leq$10.5% (91 mmol/mol), and BMI $\geq$27 kg/m$^2$; and were on a stable dose of metformin $\geq$1,000 mg/day alone or in combination with a stable dose of sulfonylurea ($\geq$10 mg/day of glibenclamide, 4 mg/day of glimepiride, or 80 mg/day of gliclazide). Patients were excluded if they had diabetic complications (e.g., painful neuropathy, nephropathy, proliferative retinopathy, foot ulcers); confirmed reduction in fasting plasma glucose levels $>$40 mg/dL before treatment; low platelet counts; blood on urinalysis; New York Heart Association class III or IV heart failure; more than three episodes of severe hypoglycemia within 6 months of screening; a reduction in body weight $\geq$5% during screening; and treatment with other antidiabetic drugs, nonselective β-blockers, or lipid-lowering therapy (except statins at stable doses) within 3 months of screening. All patients received counseling, were advised on maintaining their current diet and exercise regimen, and agreed to conduct home fasting blood glucose testing and seven-point glucose profiles.

The trial consisted of four periods (Supplementary Fig. 1): screening, pretreatment (3 weeks), treatment (26 weeks [days 1–176]), and posttreatment evaluation (12 weeks [days 177–260]). Eligible patients from screening returned to the study center for pretreatment evaluations to assess their final eligibility. During this period, patients also received a calibrated glucometer for their home-based glucose monitoring. Eligible patients were then randomized 2:1 to receive IONIS-PTP-1B$_{Rx}$ 200 mg to placebo subcutaneously once weekly for 26 weeks. After treatment completion or early termination, patients transitioned to the 12-week follow-up period where they continued to be monitored for safety and pharmacology.

### End Point Assessments

The primary efficacy end point was the change from baseline (defined as the last value before the first dose) to week 27 in plasma HbA$_{1c}$. Key secondary end points were change and percent change from baseline (defined as the average of day −7 and day 1 predose values) in markers of medium-term glycemic control (fructosamine and glycated albumin),

fasting plasma glucose, leptin, total adiponectin, high–molecular weight adiponectin, and body weight.

### Safety

Safety assessments included adverse events (AEs), vital signs, clinical laboratory tests (Medpace Reference Laboratories, Cincinnati, OH), physical examinations, electrocardiograms, and use of concomitant medications.

### Statistical Analysis

Sample size was determined to provide 80% power to detect a net 0.7% difference in reduction in $HbA_{1c}$ by using the two-sided *t* test at a significance level of 0.05 under the assumption of a 1.0% reduction for patients treated with IONIS-PTP-$1B_{Rx}$, a 0.3% reduction for patients treated with placebo, and a common SD of 0.9%.

The safety population comprised all patients who were randomized and received at least one dose of study drug. The per-protocol population comprised patients who received at least 13 doses of study drug within 15 weeks of the first dose, completed at least 23 doses, had not missed 3 consecutive doses, had no dose adjustments of OADs, and had no significant protocol deviations that would affect their pharmacodynamics assessment. The primary efficacy analysis compared absolute change from baseline to week 27 (or early termination) in $HbA_{1c}$ between the IONIS-PTP-$1B_{Rx}$–treated and placebo group in the per-protocol population. An exploratory post hoc analysis compared change in $HbA_{1c}$ in patients with different baseline hyperglycemic status (as measured by $HbA_{1c}$), and a second analysis compared the magnitude of change in $HbA_{1c}$ at week 36 versus change in body weight at week 27. The data were analyzed by using ANOVA or the Wilcoxon rank sum test where appropriate.

## RESULTS

### Study Population

Ninety-two patients were randomized 2:1 to receive either 200 mg of IONIS-PTP-$1B_{Rx}$ (*n* = 62) or placebo (*n* = 30). Baseline demographics and characteristics are shown in Table 1. Most patients were black (53%) and female (63%). Mean ± SD age was 56.7 ± 8.2 years, and mean ± SD BMI was 34.4 ± 5.6 kg/$m^2$. At baseline, 51 of 92 patients (55%) were taking sulfonylurea medication on top of metformin. There was a slightly higher percentage of patients taking sulfonylurea plus metformin in the active treatment group compared with placebo (Table 1). Baseline $HbA_{1c}$ levels were similar and all other characteristics generally well balanced between the two treatment groups.

**Table 1—Demographics and baseline characteristics**

| Characteristic | Placebo | IONIS-PTP-$1B_{Rx}$ |
|---|---|---|
| *n* | 30 | 62 |
| Sex, *n* (%) | | |
| Male | 16 (53.3) | 18 (29.0) |
| Female | 14 (46.7) | 44 (71.0) |
| Race, *n* (%) | | |
| Black | 15 (50.0) | 34 (54.8) |
| White | 12 (40.0) | 18 (29.0) |
| Asian | 1 (3.3) | 6 (9.7) |
| Other | 2 (6.7) | 4 (6.5) |
| Age (years), mean (SD) | 57.3 (7.3) | 56.4 (8.6) |
| BMI (kg/$m^2$), mean (SD) | 35.1 (5.8) | 34.1 (5.5) |
| OAD therapy, *n* (%) | | |
| Metformin | 30 (100.0) | 62 (100.0) |
| Sulfonylurea | 14 (46.7) | 37 (59.7) |
| Gliclazide | 8 (26.7) | 21 (33.9) |
| Glibenclamide | 4 (13.3) | 14 (22.6) |
| Glimepiride | 2 (6.7) | 2 (3.2) |
| Full analysis set, *n** | 29 | 61 |
| Fasting glucose (mg/dL), mean (SD) | 183.1 (38.2) | 171.2 (40.8) |
| $HbA_{1c}$ (%), mean (SD) | 8.6 (1.0) | 8.7 (1.0) |
| $HbA_{1c}$ (mmol/mol), mean (SD) | 70 (10.9) | 72 (10.9) |

*Includes all patients in safety population who had a valid baseline and at least one postbaseline $HbA_{1c}$ measurement.

There were 17 early terminations during the treatment period, with 12 (19.4%) in the active treatment and 5 (16.7%) in the placebo group (Supplementary Fig. 2). Reasons for dose discontinuation included AEs (hyperglycemia, injection site pain, injection site swelling, injection site bruising, injection site erythema, injection site induration, hypersensitivity, angioedema, and/or tachycardia), ineligibility, voluntary withdrawal, or protocol deviation. All AE-related discontinuations occurred in the first half of the treatment period and were considered possibly related or related to study drug; cases of hyperglycemia were considered unrelated to study drug. All 92 patients were included in the safety analysis, and 69 (46 active and 23 placebo) were included in the per-protocol population. Patient disposition is shown in Supplementary Fig. 2.

### Efficacy

The addition of 200 mg of IONIS-PTP-$1B_{Rx}$ to OAD therapy resulted in a mean ± SEM reduction from baseline in $HbA_{1c}$ levels at week 27 (−0.44 ± 0.12% [−4.8 ± 1.3 mmol/mol]) compared with placebo with OAD (−0.07 ± 0.16% [−0.8 ± 1.7 mmol/mol]; *P* = 0.074). $HbA_{1c}$ levels continued to decrease after cessation of IONIS-PTP-$1B_{Rx}$ dosing, reaching statistical significance by week 36 with a mean ± SEM reduction from baseline of −0.69 ± 0.14% (−7.5 ± 1.5 mmol/mol) versus placebo (−0.18 ± 0.19% [2.0 ± 2.1 mmol/mol]; *P* = 0.034). Greater $HbA_{1c}$ reductions from baseline were observed with IONIS-PTP-$1B_{Rx}$ treatment compared with placebo beginning week 13 and continued through the end of the study (Fig. 1*A*).

In the analyses of secondary outcomes, significant body weight reduction was observed with IONIS-PTP-$1B_{Rx}$ treatment versus placebo at week 27 (mean decrease 2.6 vs. 0.2 kg, respectively; *P* = 0.002) (Fig. 1*B*). These changes were sustained at the end of the follow-up period (week 36) and remained significant versus placebo (*P* = 0.012). Consistent with the mechanism of PTP-1B reduction, IONIS-PTP-$1B_{Rx}$ versus placebo treatment improved leptin sensitivity at week 27 (mean reduction −4.4 vs. 0.4 ng/mL, respectively; *P* = 0.007) (Fig. 1*C*). We also observed improved levels of adiponectin at week 27 in patients treated with IONIS-PTP-$1B_{Rx}$ but not with placebo

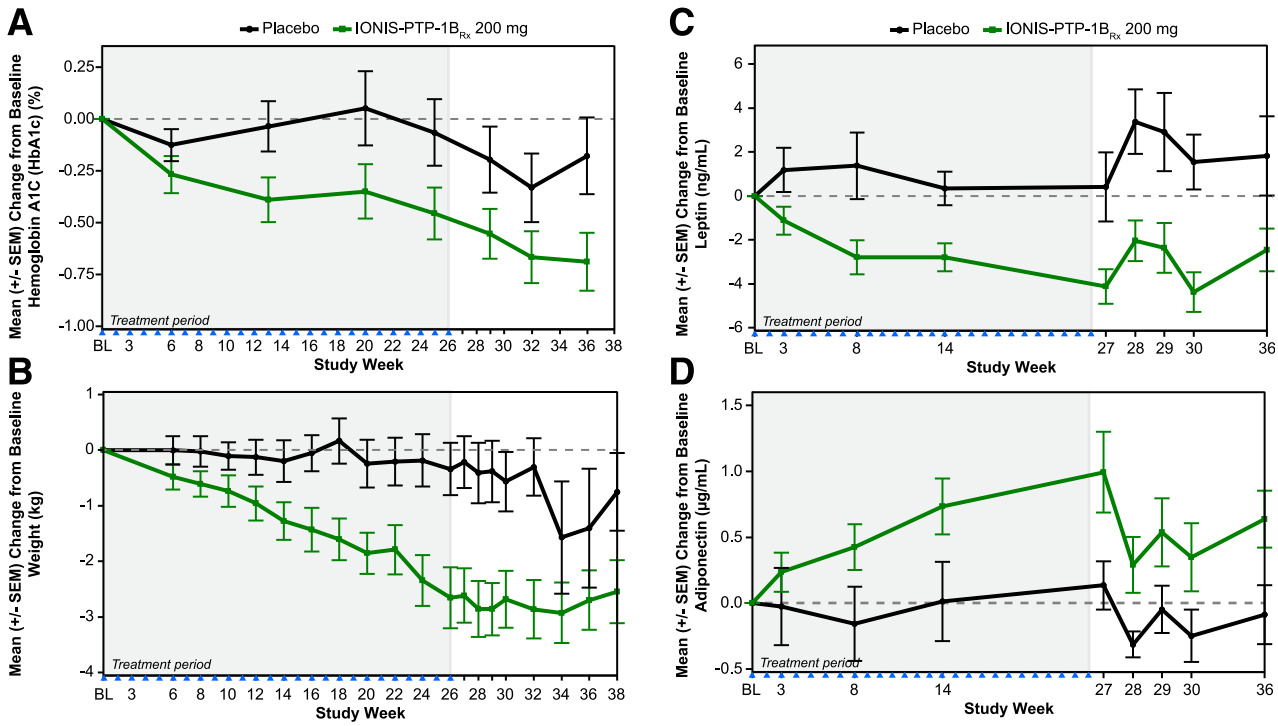


**Figure 1**—Effect of IONIS-PTP-1B$_{Rx}$ 200 mg on HbA$_{1c}$, leptin, adiponectin, and body weight over time. *A*: HbA$_{1c}$. *B*: Body weight. *C*: Leptin. *D*: Adiponectin. Data are mean change from baseline (BL). Error bars represent ± SEM. Shaded region, treatment period; ▲, days that a patient received the study drug.

(mean increase from baseline 1.0 vs. 0.1 µg/mL, respectively; $P = 0.020$) (Fig. 1*D*). Concomitant improvements in high–molecular weight adiponectin was also observed (Table 2). IONIS-PTP-1B$_{Rx}$ treatment also led to significant reductions from baseline versus placebo in the medium-term glycemic parameters fructosamine (mean −33.2 vs. −3.7 µmol/L, respectively; $P = 0.005$) and glycated albumin (mean −1.6% vs. 0.05%, respectively; $P = 0.031$) at week 36. Full results, including change from baseline at weeks 27 and 36 in the primary and secondary outcomes, are shown in Table 2.

To evaluate whether the severity of hyperglycemia at baseline may potentially have an effect on the glucose-lowering effects of IONIS-PTP-1B$_{Rx}$, we performed an exploratory post hoc analysis comparing different hyperglycemic status at baseline as measured by HbA$_{1c}$. We observed that patients with higher baseline HbA$_{1c}$ levels had slightly greater reductions in HbA$_{1c}$ by week 27 (Supplementary Table 1 and Supplementary Fig. 3). In a second analysis, no correlation was observed between the magnitude of change from baseline of HbA$_{1c}$ levels at week 36 compared with the change in body weight from baseline to week 27 ($R^2$ = 0.0020) (Supplementary Fig. 4).

### Safety

The incidence of treatment-emergent serious AEs (SAEs) was comparable between the two treatment groups (three [10.0%] placebo vs. six [9.7%] active), and all events were considered unrelated to study drug. All SAEs occurred during the posttreatment follow-up period, except for two (umbilical hernia and osteoarthritis), which occurred during treatment in two patients receiving IONIS-PTP-1B$_{Rx}$. Two SAEs (gastritis and extrapyramidal disorder) persisted at the end of the study as non-SAEs in three patients treated with IONIS-PTP-1B$_{Rx}$, and all other SAEs resolved without sequelae. One death by accident was reported during the follow-up period as a result of craniocerebral injury in a patient who received IONIS-PTP-1B$_{Rx}$ that was considered by the investigator to be unrelated to study drug.

Outside injection site reactions, the most common AE was urinary tract infection, with a slightly greater incidence in the placebo group. Myalgia (one patient treated with placebo) and headache (one patient treated with IONIS-PTP-1B$_{Rx}$) were the only AEs considered possibly related or related to study drug (Table 3). Overall, a mean of 10% of IONIS-PTP-1B$_{Rx}$ injections were accompanied by local cutaneous reactions at the injection site (LCRIS) (Table 3). No influenza-like reactions were observed in this trial as defined by the Medical Dictionary of Regulatory Activities–preferred terms influenza-like illness or pyrexia plus two of the following: chills, myalgia, or arthralgia, all starting within 2 days after study drug injection. No severe cases of hypoglycemia, defined as a patient requiring assistance of another person to obtain treatment for the event and plasma glucose levels <60 mg/dL, were observed in this study. Mild hypoglycemia occurred in five patients treated with IONIS-PTP-1B$_{Rx}$ and one patient treated with placebo, all of whom were on sulfonylurea background therapy. All patients recovered after consumption of food and drink or sulfonylurea dose reduction. No clinical evidence of prothrombotic effects or bleeding episodes (23,24) were observed. There were no clinically significant changes in laboratory parameters, including no significant reductions in platelet counts and no significant treatment-related changes in liver or renal function.

## CONCLUSIONS

Reducing PTP-1B with IONIS-PTP-1B$_{Rx}$ in overweight and obese patients with

**Table 2—Primary and secondary efficacy end point results**

| Parameter | Placebo | IONIS-PTP-1B$_{Rx}$ | *P* value |
|---|---|---|---|
| *n* | 23 | 46* | |
| $HbA_{1c}$ (%) | | | |
| Baseline | 8.4 (0.9) | 8.8 (1.0) | |
| Week 27 change from baseline | −0.1 (0.8) | −0.4 (0.8) | 0.074† |
| Week 36 change from baseline | −0.2 (0.9) | −0.7 (0.9) | 0.034† |
| $HbA_{1c}$ (mmol/mol) | | | |
| Baseline | 68.2 (10.0) | 72.4 (10.8) | |
| Week 27 change from baseline | −0.7 (8.4) | −4.8 (9.1) | 0.074† |
| Week 36 change from baseline | −1.9 (9.7) | −7.5 (10.2) | 0.034† |
| Fasting plasma glucose (mg/dL) | | | |
| Baseline | 179.5 (37.9) | 169.5 (40.7) | |
| Week 27 change from baseline | −17.3 (34.5) | −11.3 (40.4) | 0.547† |
| Week 36 change from baseline | −7.7 (37.5) | −15.9 (50.1) | 0.494† |
| Fructosamine (μmol/L) | | | |
| Baseline | 315.3 (55.7) | 319.6 (50.0) | |
| Week 27 change from baseline | −23.7 (42.5) | −26.6 (36.2) | 0.772† |
| Week 36 change from baseline | −3.7 (40.4) | −33.2 (39.2) | 0.005† |
| Glycated albumin (%) | | | |
| Baseline | 19.0 (4.5) | 19.6 (4.4) | |
| Week 27 change from baseline | −1.0 (2.9) | −1.7 (3.0) | 0.399† |
| Week 36 change from baseline | 0.1 (3.6) | −1.6 (3.4) | 0.031‡ |
| Leptin (ng/mL) | | | |
| Baseline | 14.1 (9.4) | 16.5 (10.8) | |
| Week 27 change from baseline | 0.4 (7.5) | −4.4 (5.5) | 0.007‡ |
| Week 36 change from baseline | 1.8 (8.6) | −2.5 (6.5) | 0.089‡ |
| Adiponectin (μg/mL) | | | |
| Baseline | 4.7 (2.4) | 5.5 (3.5) | |
| Week 27 change from baseline | 0.1 (0.9) | 1.0 (2.0) | 0.020‡ |
| Week 36 change from baseline | −0.1 (1.1) | 0.6 (1.4) | 0.037† |
| High–molecular weight adiponectin (μg/mL) | | | |
| Baseline | 3.0 (2.0) | 3.6 (3.0) | |
| Week 27 change from baseline | 0.03 (0.9) | 0.7 (1.4) | 0.019‡ |
| Week 36 change from baseline | 0.01 (0.8) | 0.7 (1.1) | 0.015‡ |
| Body weight (kg) | | | |
| Baseline | 96.0 (17.5) | 91.5 (18.7) | |
| Week 27 change from baseline | −0.2 (2.2) | −2.6 (3.3) | 0.002‡ |
| Week 36 change from baseline | −1.4 (5.1) | −2.7 (3.6) | 0.012‡ |

Data are mean (SD) and represent the per-protocol population (patients who received at least 13 doses of study drug within 15 weeks of the first dose, completed at least 23 doses, had not missed three consecutive doses, had no dose adjustments of OAD, and did not have any significant protocol deviations that would be expected to bias the patients' pharmacodynamics assessments). Week 27 includes early termination. Baseline $HbA_{1c}$ is defined as the last nonmissing value before the first dose. Baseline for all other parameters is defined as the average of day −7 and day 1 predose values. *$n$ = 45 for all week 36 values. †$P$ value determined by ANOVA. ‡$P$ value determined by Wilcoxon rank sum test.

type 2 diabetes unable to achieve or maintain glycemic control with OAD therapy led to distinct reductions in $HbA_{1c}$ and body weight. The reductions in $HbA_{1c}$ began at week 13 with IONIS-PTP-1B$_{Rx}$ and continued until the end of the follow-up period. By week 36, a statistically significant reduction in $HbA_{1c}$ levels of 0.69% (7.5 mmol/mol) was observed versus placebo ($P$ = 0.034). The markers of medium-term glycemic control, fructosamine, and glycated albumin responded similarly to IONIS-PTP-1B$_{Rx}$ treatment, also achieving statistical significance versus placebo at week 36. In line with the dual mechanism of PTP-1B, antisense inhibition by IONIS-PTP-1B$_{Rx}$ demonstrated significant mean reductions in body weight and reductions in plasma leptin levels. Body weight reduction also was accompanied by a significant increase in adiponectin levels. The reduced body weight was maintained until the end of the study.

The continued reduction in $HbA_{1c}$ for up to 3 months after treatment cessation in this study can be explained by the relatively long half-life of ASOs and is consistent with previous observations of other 2′-MOE ASOs in the clinic (25,26). Therefore, a study with a longer treatment duration possibly would have shown an even greater reduction in $HbA_{1c}$ levels. Additional factors that may have contributed to a delay (>26 weeks) in reaching maximal efficacy are *1*) that the dose of the drug corresponded to an approximate median effective dose and was chosen on the basis of previous clinical experience with other 2′-MOE ASOs (27,28), suggesting that a higher dose may have reached maximal efficacy sooner, and *2*) that $HbA_{1c}$ is a marker that represents an ∼3-month delay from plasma glucose levels.

As shown in Table 2, treatment with IONIS-PTP-1B$_{Rx}$ did not result in a significant effect on fasting glucose levels compared with the placebo group, despite significant reductions in fructosamine and $HbA_{1c}$ levels. Table 2 shows the mean glucose data collected once a week; we also evaluated the changes in weekly fasting glucose levels by self-monitoring of blood glucose from glucometer data collected daily (and averaged for the week) and observed an ∼15–20 mg/dL drop in the IONIS-PTP-1B$_{Rx}$ group compared with the placebo group. Inhibition of PTP-1B with an antisense drug is associated with a robust effect on fasting and postprandial glucose excursions both preclinically and clinically (22,29). The effects on fasting glucose become significant when the baseline glucose levels show severe hyperglycemia (>200 mg/dL). Overall, these data are consistent with what would be expected with an insulin sensitizer because the drug would work better in the presence of higher postprandial insulin levels compared with low insulin levels seen after an overnight fast. In addition, the observed decrease in fasting glucose levels in the placebo group was greater than anticipated, further contributing to the lack of an effect on this parameter.

Patients with higher baseline $HbA_{1c}$ have been shown to have larger reductions in $HbA_{1c}$ with a variety of noninsulin glucose-lowering products, such as sulfonylureas, metformin, and TZDs (30,31). Similarly, an unplanned exploratory analysis in the current study suggested potentially greater glycemic improvement with IONIS-PTP-1B$_{Rx}$ treatment in patients with a greater baseline $HbA_{1c}$ level than in those with a lesser baseline $HbA_{1c}$ level (Supplementary Table 1 and

**Table 3—Summary of treatment-emergent AEs in >5% of total patients***

| Preferred term | Placebo (*n* = 30) | IONIS-PTP-1B$_{Rx}$ (*n* = 62) |
|---|---|---|
| Urinary tract infection | 9 (30.0) | 13 (21.0) |
| Influenza | 6 (20.0) | 11 (17.7) |
| Headache | 4 (13.3) | 7 (11.3) |
| Upper respiratory tract infection | 2 (6.7) | 7 (11.3) |
| Nasopharyngitis | 3 (10.0) | 6 (9.7) |
| Sinusitis | 1 (3.3) | 5 (8.1) |
| Back pain | 4 (13.3) | 5 (8.1) |
| Hypoglycemia | 1 (3.3) | 5 (8.1) |
| Severe† | 0 (0.0) | 0 (0.0) |
| Gastritis | 1 (3.3) | 4 (6.5) |
| Musculoskeletal pain | 4 (13.3) | 1 (1.6) |
| Myalgia | 2 (6.7) | 3 (4.8) |
| Other AEs of interest | | |
| LCRIS‡ | 1 (3.3) | 20 (32.3) |
| Percentage of injections leading to LCRIS, mean (SD) | 0.13 (0.73) | 10.0 (23.1) |
| Hyperglycemia | 1 (3.3) | 2 (3.2) |
| Severe§ | 0 (0.0) | 0 (0.0) |

Data are *n* (%) unless otherwise noted. *Excludes injection site reactions. †Defined as requiring assistance of another person to obtain treatment for the event and has plasma glucose levels <60 mg/dL. ‡Defined as injection site erythema, swelling, pruritus, pain, or tenderness that started on the day of injection and persisted for at least 2 days. §Defined as fasting plasma glucose levels >270 mg/dL on two consecutive study visits.

Supplementary Fig. 3). Future randomized controlled studies will assess whether these observations can be confirmed by evaluating the precise effects of the drug on hepatic and peripheral insulin sensitivity in patients with various degrees of insulin resistance and $HbA_{1c}$ levels.

Modest reduction in body weight has been shown to be a significant factor in improving glycemic and metabolic control in patients with type 2 diabetes (32). Unlike some other available or discontinued insulin sensitizing agents on the market in which one of the major side effects is weight gain in conjunction with fluid retention and edema (1,33,34), IONIS-PTP-1B$_{Rx}$ demonstrated significant weight loss on top of achieving moderate glycemic control versus placebo. The reason why an insulin sensitizer mimics the glucose-lowering effects of insulin but not the effects on weight (i.e., weight gain) can be partly attributed to PTP-1B playing a distinct role versus insulin in liver versus adipose tissue. PTP-1B reductions in adipose tissue reportedly decrease adiposity in association with reduced fat triglycerides and downregulate several important genes involved in lipogenesis (29). This decrease in weight did not correlate with reductions in $HbA_{1c}$ levels in the current study (Supplementary Fig. 4*A*), suggesting that the dual roles of PTP-1B in regulating insulin signaling and leptin pathway signaling are likely independent of each other. Our observation shows that therapeutic inhibition of PTP-1B in humans can provide significant advantages over the current available therapies in addressing the many markers of type 2 diabetes as well as obesity.

IONIS-PTP-1B$_{Rx}$ was generally well tolerated, and there was no evidence of severe hypoglycemia or clinically significant treatment-related changes in laboratory tests. The incidence of AEs leading to discontinuations were higher in patients treated with IONIS-PTP-1B$_{Rx}$ (11%) than with placebo (3%) and could likely be attributed to initial tolerability of the study drug injections. Aside from hyperglycemia, which was considered unrelated to the study drug, most of the discontinuations from AEs were due to injection tolerability–related AEs within the first 2 months of initiating treatment. Of note, no patients discontinued because of injection-related AEs after being on treatment for >3 months. One possible reason for this could be related to the study population, which may not have had experience with receiving an injectable drug and suffered initial anxiety from needle phobia. However, consistent with our broader experience involving >15,000 injections with this drug class, educating the sites and patients about proper injection technique and addressing their initial fears can significantly mitigate such discontinuations, as evidenced by no patients terminating during the last 3 months of the current study.

No treatment-associated safety issues were identified in the current study. Minor hypoglycemia was observed in six patients, all of whom were on sulfonylurea background therapy, which is known to cause hypoglycemia (35,36). LCRIS primarily were mild erythema, which occurred in 10% of all administered injections, and had a lower incidence than other ASOs of similar dose tested in the clinic for 26 weeks (26). Because antisense compounds, such as IONIS-PTP-1B$_{Rx}$, are not metabolized by the cytochrome P450 system, no drug-drug interactions are expected between IONIS-PTP-1B$_{Rx}$ and metformin, sulfonylurea, or statins. Consequently, no dose adjustments of any allowed concomitant medications were needed (37).

Recent advances in the ligand-conjugated ASOs, more specifically conjugations to N-acetylgalactosamine, have shown significantly improved potency of up to 30-fold compared with the respective parent compound when dosed in patients (38,39). Because N-acetylgalactosamine–conjugated compounds are more rapidly and specifically taken up by the hepatocytes through the asialoglycoprotein receptor, it would be an attractive follow-on for IONIS-PTP-1B$_{Rx}$ because of the relatively high levels of PTP-1B in the liver among other tissues (40). In addition, improved potency likely would mean a lower dose being administered to patients—thus further increasing the therapeutic index—or a reduction in the frequency of administrations from weekly to potentially monthly or quarterly.

A limitation of this study included the relatively small sample size, which should be taken into consideration when interpreting the statistical analyses of the data. The study population comprised mainly African American patients, making the data difficult to translate across other populations, such as Caucasians, or to compare with previous studies with TZDs. Furthermore, it is possible that the mechanism of PTP-1B inhibition requires longer treatment duration to demonstrate maximal efficacy. Post hoc data suggest that PTP-1B inhibition may work better in patients with more-severe insulin resistance.

In the current study, we evaluated the effects of IONIS-PTP-1B$_{Rx}$ in a group of patients who were unresponsive to metformin alone or metformin plus sulfonylurea to evaluate the safety profile, including lack of severe hypoglycemia after administration of IONIS-PTP-1B$_{Rx}$, in patients with type 2 diabetes. The initial intended target population for this drug is patients with severe insulin resistance who are obese and taking high doses of insulin therapy. Therefore, future studies with IONIS-PTP-1B$_{Rx}$ would focus on patients who are insulin insensitive (i.e., unresponsive to conventional insulin therapy) because the mechanism of PTP-1B improving insulin sensitivity would likely be most beneficial for this group. In addition, IONIS-PTP-1B$_{Rx}$ conceivably could be used solely as an antiobesity therapy in individuals who have not yet developed diabetes, potentially addressing the link between obesity and diabetes.

In conclusion, antisense inhibition of PTP-1B with a second-generation 2′-MOE ASO shows improvements in $HbA_{1c}$ levels over placebo in patients who were not well controlled by one or two OADs. No severe hypoglycemia was observed, and no unexpected safety findings were reported. Treatment with IONIS-PTP-1B$_{Rx}$ also demonstrated significant weight reductions compared with placebo, which offers increased therapeutic benefit over other classes of insulin sensitizers. The dual mechanism of action of IONIS-PTP-1B$_{Rx}$ would be advantageous for a large unmet population of obese patients with diabetes who are not benefiting from current standard therapies, including insulin, as a result of poor insulin sensitivity. The incorporation of a controlled regimen of diet and exercise alongside IONIS-PTP-1B$_{Rx}$ could yield even more robust reductions in weight and further improve glycemic control in these patients.

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**Author Contributions.** A.D., N.C.P., L.M.W., E.S.M., B.F.B., R.S.G., and S.B. analyzed and/or interpreted the data. A.D., L.M.W., and S.B. contributed to the study design and conduct. N.C.P. drafted the manuscript. S.W.J. provided statistical support. All authors were involved in the critical revision of the manuscript. S.B. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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