Can a Selective PPARγ Modulator Improve Glycemic Control in Patients With Type 2 Diabetes With Fewer Side Effects Compared With Pioglitazone?

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OBJECTIVE
INT131 besylate is a potent, nonthiazolidinedione, selective peroxisome proliferator–activated receptor γ (PPARγ) modulator (SPPARM) designed to improve glucose metabolism while minimizing the side effects of full PPARγ agonists. This placebo-controlled study compared the efficacy and side effects of INT131 besylate versus 45 mg pioglitazone HCl in subjects with type 2 diabetes (T2D).

RESEARCH DESIGN AND METHODS
This was a 24-week randomized, double-blind, placebo- and active-controlled study of 0.5–3.0 mg INT131 versus 45 mg pioglitazone or placebo daily in 367 subjects with T2D on sulfonylurea or sulfonylurea plus metformin. The primary efficacy analysis was the comparison of change from baseline to week 24 in hemoglobin A1c (HbA1c) across treatment groups. Fluid status was assessed with a prospective scoring system for lower-extremity pitting edema.

RESULTS
INT131 had a steep dose response for efficacy as measured by changes in HbA1c. After 24 weeks’ treatment, the 0.5-mg dose demonstrated minimal efficacy (HbA1c $-0.3 \pm 0.12\%$) and the 2-mg dose demonstrated near-maximal efficacy (HbA1c $-1.1 \pm 0.12\%$), which was not statistically different from the efficacy of 45 mg pioglitazone. (HbA1c $-0.9 \pm 0.12\%; P < 0.01$ for noninferiority). With the 1-mg dose, INT131 provided significant improvements in glycemic control (HbA1c $0.8 \pm 0.12\%; P < 0.001$ vs. placebo) but with less edema, weight gain, and hemo-dilution than observed with 45 mg pioglitazone.

CONCLUSIONS
INT131 demonstrated dose-dependent reductions in HbA1c equivalent to 45 mg pioglitazone, but with less fluid accumulation and weight gain, consistent with its SPPARM design.

Insulin resistance is a key etiologic factor in type 2 diabetes (T2D). Peroxisome proliferator–activated receptor (PPAR)y activation is associated with significant improvement in insulin resistance, hyperglycemia, endothelial function, and markers of inflammation (1,2). However, clinical use of thiazolidinediones (TZDs) has been limited by their side effect profile, namely, fluid retention, congestive
heart failure (CHF), adipogenic weight gain, and a decrease in bone mineral density associated with fractures (2–9).

INT131 besylate is a selective PPARγ modulator (SPPARM) (10,11). Chemically, INT131 is structurally distinct from the TZDs and represents a new class of non-TZD PPARγ ligands (12). INT131 was specifically designed to retain the insulin-sensitizing and glucose-lowering actions of the PPARγ full agonists while mitigating or eliminating their undesirable side effects (12,13).

The SPPARM properties of INT131 have been shown by the favorable separation of efficacy and side effect profile in both nonclinical and clinical studies. In rodent models of T2D, INT131 demonstrated similar insulin-sensitizing and glucose-lowering activity as full-agonist TZDs with little or none of the fluid retention, weight gain, or cardiomegaly produced by TZDs (12). The typical dose-limiting adverse effects of full PPARγ agonists are observed in toxicology studies of TZDs in healthy animals at low multiples of clinically efficacious drug exposures (five- to sixfold exposures over that observed at the highest clinical doses of the two U.S. Food and Drug Administration–approved TZDs, rosiglitazone and pioglitazone, and –unapproved muraglitazar) (14,15). In contrast, INT131 besylate demonstrated no significant weight gain, edema, cardiac hypertrophy, or adipocyte replacement of bone marrow in 6-month safety studies in rodent and monkey at exposures exceeding 200-fold the clinical exposure that provides comparable therapeutic effect (16).

Based on this favorable preclinical profile, a 4-week placebo-controlled phase 2a study in untreated patients with T2D was undertaken (17). The 1-mg dose of INT131 demonstrated improvements in fasting plasma glucose (FPG) that were consistent with mathematical modeling of maximal dose of the full agonist rosiglitazone but was not associated with typical TZD side effects (weight gain, edema, and decreases in hematocrit). These data supported further study of INT131 to more fully characterize the clinical efficacy and side effect profile. A 24-week study was conducted comparing four doses (0.5–3 mg) of INT131 to maximal dose pioglitazone and placebo.

**RESEARCH DESIGN AND METHODS**

This study was a 24-week randomized, double-blind, placebo- and active-controlled efficacy and safety study of 0.5–3.0 mg INT131 besylate versus 45 mg pioglitazone HCl or placebo daily in 367 subjects with poorly controlled T2D on sulfonylurea or sulfonylurea plus metformin. Subjects were males or females 30–75 years old with T2D ≥6 months on a stable dose (≥3 months) of sulfonylurea with or without metformin, HbA1c 7.5–10%, and FPG <240 mg/dL. Subjects were excluded if they had significant concomitant disease (e.g., CHF, ischemic heart disease, cardiac electrophysiology abnormalities, renal impairment, liver disease, uncontrolled hypertension, prior malignancy, or morbid obesity). After a 2-week screening/lead-in period, eligible subjects were randomly assigned 1:1:1:1:1:1 to the following 24-week daily dosing regimens: 0.5, 1, 2, or 3 mg INT131; 45 mg pioglitazone; or placebo.

The primary efficacy analysis was a comparison between treatment groups in change from baseline to week 24 in hemoglobin A1c (HbA1c). Secondary end points included change in levels of FPG, insulin, serum lipids (total cholesterol, triglycerides, LDL cholesterol [LDL-C], HDL cholesterol [HDL-C]), body weight, and edema at 12 and 24 weeks.

Safety end points included adverse events (AEs), physical examination, blood chemistry and hematology, and electrocardiograms. Edema was measured prospectively because of its recognized association with the PPARγ full agonists and the potential that AE reporting of edema can be misleading owing to impression and lack of standardization. In addition, imbalances in baseline edema across treatment groups can lead to reporting bias, and fluctuations in edema throughout the course of the study may result in multiple reports of edema. For this study, we developed an assessment tool for lower-extremity pitting edema, which was used to collect an edema assessment (present or absent) at baseline and at 12 and 24 weeks at three distinct sites in the lower extremities (mid-foot, ankle, and mid-predictia). A total edema score for each subject was determined by assigning a 0, 1, 2, or 3 for the number of sites that were positive for pitting edema.

**Statistical Analysis**

The primary efficacy analysis was the comparison of INT131 treatment groups with placebo with respect to least squares mean (LSM) change from baseline to week 24 in HbA1c. A step-down testing procedure was followed using the fixed-testing order 3 mg, 2 mg, 1 mg, and 0.5 mg INT131 to address multiple comparisons. The subsequent hypothesis for each dose of INT131 was tested only if all previously tested null hypotheses were rejected (i.e., lower doses of INT131 were only tested when higher doses were shown to have larger HbA1c changes compared with placebo). Dunnett test was used for the adjustment of multiple comparisons from the ANCOVA model as an exploratory analysis for the primary efficacy analysis. The ANCOVA model used for the primary efficacy variable was used for analysis of all secondary efficacy variables. Summary statistics were provided for each efficacy variable at each assessment time point and for change from baseline at each assessment. Comparisons of pioglitazone with INT131 were completed to assess relative efficacy (no comparisons between pioglitazone and placebo were made).

Efficacy analyses were performed using the intent-to-treat (ITT) population (all randomized subjects who had at least one efficacy baseline assessment took at least one dose of study medication and had at least one postbaseline efficacy measurement) and the per-protocol population (all subjects in the ITT population who completed the 24-week double-blind treatment period without any major deviations from the protocol requirements as determined by a blinded data review prior to database lock). The per-protocol population analysis is reported here because it is a better estimate of the magnitude of the effect of drug therapy. The most common reasons for exclusion from the per-protocol population were early withdrawal from the study, change in background therapy, low compliance, missing HbA1c measurement at week 24, medication dispensed in error, and use of contraindicated medication.

The safety population was defined as all randomized subjects who received at least one dose of study drug.
Ethics and Good Clinical Practice
All participants provided written informed consent. The protocol was approved by an independent review board, and the study was conducted in accordance with the Declaration of Helsinki and following good clinical practice.

RESULTS
Subject Demographics and Baseline Characteristics
Demographic and baseline characteristics of the study population were similar across treatment groups (Table 1). Three hundred and sixty-seven subjects discontinued participation in the study during the treatment period: 17 (4.6%) were withdrawn owing to persistent hyperglycemia, 17 (4.6%) withdrew from placebo (HbA1c −0.2 ± 0.13; P < 0.001). The 2- and 3-mg doses of INT131 were not statistically different from 45 mg pioglitazone (HbA1c −0.9 ± 0.12%; P < 0.01 for noninferiority). Changes in FPG across the dose range studied were consistent with insulin-sensitizing activity of INT131 (Table 2). Changes in fasting insulin levels were similar to placebo with all doses of INT131 but less than the decrease with pioglitazone. INT131 increased adiponectin in a dose-dependent manner, which was similar to the increase in pioglitazone (Table 2).

Side Effects
After 24 weeks of treatment with INT131, the change from baseline in average total edema score for pitting edema was not statistically different from placebo for any dose group of INT131 and was significantly lower than the pioglitazone group for INT131 at 0.5, 1, and 2 mg (Fig. 2). Changes in hemoglobin and hematocrit (also indicative of fluid retention) were modest in all groups and not significantly different from placebo at INT131 doses of 0.5 and 1 mg and comparable with pioglitazone at higher doses. Body weight gain was dose responsive and greater than placebo for all doses of INT131 but significantly less than pioglitazone at the 0.5 and 1 mg INT131 doses (Table 2).

Changes in total cholesterol, LDL-C, triglycerides, and HDL-C are shown in Table 2. Pioglitazone demonstrated a slight increase in LDL-C and HDL-C and a marked decrease in triglycerides. INT131 demonstrated a similar dose-responsive pattern of change but appeared to be less effective at lowering triglycerides.

Although this study was not powered to assess changes in bone turnover markers, assessment of markers of bone turnover, which reflect bone remodeling rate and thus may be associated with changes in bone quality, showed numerically greater increases in C-telopeptide type 1 collagen (a marker of bone degradation) and osteocalcin (a marker of osteoblast activity) after treatment with 45 mg pioglitazone compared with treatment with INT131 (Table 2). None of these changes were statistically significant.

No other consistent treatment- or dose-related trends were noted in other laboratory parameters, vital signs, or electrocardiograms for subjects treated with INT131.

Safety and Tolerability
Nine of 366 (2.5%) subjects discontinued study medication owing to an AE (no significant difference between study groups). Treatment-emergent AEs (TEAEs)
were reported for 38 (62%) subjects taking placebo, 27 (45%) subjects taking 0.5 mg INT131, 37 (61%) subjects taking 1 mg INT131, 41 (65%) subjects taking 2 mg INT131, and 38 (63%) subjects taking 45 mg pioglitazone. There were no clinically meaningful differences between treatment groups in the incidences of serious AEs, severe AEs, or AEs that led to discontinuation from the study. The most common system organ classes of TEAEs were infections and infestations, musculoskeletal and connective tissue disorders, gastrointestinal disorders general disorders, and administration site conditions. There was no significant difference in TEAEs between INT131, placebo, or pioglitazone treatment groups. The most common TEAEs were peripheral edema (11.0% INT131, 10.0% pioglitazone), urinary tract infection (6.5% INT131, 6.7% pioglitazone), hypoglycemia (6.1% INT131, 0.0% placebo, 11.7% pioglitazone), and headache (5.3% INT131, 8.2% placebo, 5.0% pioglitazone).

**CONCLUSIONS**

INT131 was designed as a SPPARM to address concerns with current full-agonist PPARy drugs. Both nonclinical and clinical studies have supported the potential to separate insulin-sensitizing actions and undesirable side effects. PPARy activation is associated with significant improvement in insulin resistance, hyperglycemia, endothelial function, and markers of inflammation (1,2). Full activation of PPARy with TZDs is associated with a range of receptor responses in a linked fashion resulting in a number of undesirable effects with a dose response that appears to be similar to that of beneficial effects (18–20). These side effects include fluid retention, CHF, adipogenic weight gain, and a decrease in bone mineral density associated with fractures (2,6). Based on the detailed understanding of PPARy receptor activation, the opportunity exists to selectively modulate specific activities of the receptor (12,21). A SPPARM would allow separation of the insulin-sensitizing actions of PPARy activation from the unwanted activities (22,23).

INT131 besylate was specifically designed as a SPPARM to retain the...
For 1 year demonstrated excellent TZD side effects. Rodents studied for also demonstrated the lack of typical accumulation.

Insulin target tissues without stimulation, in rodents and healthy subjects increased after INT131 treatment in DIO mediated Akt phosphorylation also in INT131 therapy. Concurrently, insulin-stimulated adiponectin, a marker of PPARγ activation, in rodents and healthy subjects (10,24). With use of the DIO mouse model of obesity and insulin resistance, treatment with INT131 enhanced systemic insulin sensitivity independent from changes in adiposity (11). Insulin-stimulated phosphatidylinositol 3-kinase activity in skeletal muscle and adipose tissue of DIO mice was significantly reduced by ~50–65%, but this was restored completely by INT131 therapy. Concurrently, insulin-imediated Akt phosphorylation also increased after INT131 treatment in DIO mice (11). Thus, preclinical studies suggest that INT131 normalizes obesity-related defects in insulin signaling and action in insulin target tissues without stimulating preadipocyte stimulation or lipid accumulation.

Long-term safety studies with INT131 also demonstrated the lack of typical TZD side effects. Rodents studied for up to 2 years and monkeys studied for 1 year demonstrated excellent glucose lowering of PPARγ activation without the adipogenic properties of the full agonist. INT131 is a novel, selective PPARγ modulator that is not structurally related to the glitazone class of PPARγ full agonists and has distinctive binding properties in the nuclear receptor-binding pocket (10,12). INT131 does not stimulate rodent or human preadipocytes to differentiate or accumulate lipid (12) and has equal or greater efficacy to stimulate adiponectin, a marker of PPARγ activation, in rodents and healthy subjects (10,24).

With exposure multiples >40 times the clinical exposure (1 mg q.d.) without weight gain, edema, cardiac hypertrophy, and adipocyte replacement of bone marrow (16). This differentiation was specifically evident in the carcinogenicity studies, which did not reveal any evidence of cardiovascular or carcinogenic concerns over 2 years in mice and rats. Based on this safety and efficacy profile of INT131 in nonclinical pharmacology and toxicology studies, as well as evidence for efficacy and safety in clinical studies in healthy subjects (24) and subjects with T2D (17), a 6-month dose-ranging study in subjects with T2D was undertaken to determine the optimal dose of INT131 to demonstrate the separation of efficacy and side effects compared with a full agonist TZD.

This current study demonstrated dose-responsive improvements in 
HbA1c with INT131 that were comparable with 45 mg pioglitazone. Pioglitazone at the maximal marketed dose of 45 mg/day reduced 
HbA1c by 0.9% with expected concomitant side effects including fluid retention, demonstrated by worsening lower-extremity edema, alterations in bone turnover markers, and significant weight gain. The 1-mg dose of INT131 reduced 
HbA1c by 0.8% with no clinically significant hemodilution (estimated by changes in hemoglobin and hematocrit) or change in incidence of edema, and minimal weight gain (the weight gain in subjects taking 1 mg INT131 was significantly less than in those taking pioglitazone at the end of the study). The 2-mg dose of INT131 reduced 
HbA1c by 1.1% with minimal change in edema but caused weight gain only slightly less than was associated with pioglitazone. Edema was identified as an AE of special interest owing to the recognized association of the PPARγ full agonists with fluid retention. The percentage of subjects with reported AEs of peripheral edema was similar between INT131 and pioglitazone. However, because potential imbalances in baseline edema across treatment groups can lead to reporting bias and fluctuations in edema throughout the course of the study may result in multiple AE reports of edema, we developed a prespecified assessment tool for pitting edema. The change in average total edema score from baseline for any INT131-treated group was not statistically different from placebo and was significantly less than pioglitazone for the 0.5-, 1-, and 2-mg INT131 groups. This finding, along with no significant difference in changes in hemoglobin or hematocrit in the 1-mg INT131 compared with placebo group, supports the conclusion that INT131 has less fluid retention than pioglitazone at doses that produce similar efficacy.

Increases in body weight were dose dependent and greater than placebo for all doses of INT131 but significantly less than pioglitazone at the 1-mg INT131 doses. The body weight gain with the 2- and 3-mg doses of INT131 were not significantly different from that associated with 45 mg pioglitazone. Whether similar differences in weight gain compared with efficacy would have been observed if the 30-mg dose of pioglitazone was used needs to be tested. These results emphasize that preclinical studies do not always predict clinical trial results.

In summary, INT131 was well tolerated and significantly improved 
HbA1c compared with placebo in subjects with T2D not adequately controlled on metformin and sulfonylureas or sulfonylurea alone. A dose response for most secondary efficacy parameters was also observed, as well as less edema, fluid retention, and body weight gain compared with pioglitazone. The

**Figure 2**—Average total edema score: mean change from baseline at 24 weeks for safety population. Values are LSMS and SEs for the safety population.
results of this study confirm that INT131 shifts the dose response profile of side effects to the left in relation to the efficacy dose response curve. When taken together with the previously described in vitro and in vivo characterization of the molecule, these results are consistent with the SPPARM design of INT131.

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Author Contributions. A.M.D. designed the study, researched data, and wrote the manuscript. L.S.H., R.R.H., and C.M. contributed to the design of the study and interpretation of data and reviewed and edited the manuscript. F.L.D. contributed to the design of the study and interpretation of data and wrote the manuscript. A.M.D. 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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