

INT131: A Selective PPAR γ Modulator (SPPARM) for Type 2 Diabetes Mellitus (T2D)

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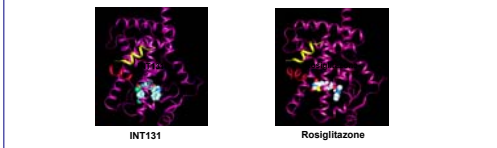
ABSTRACT

INT131 (formerly T0903131 and AMG 131) is a potent non-thiazolidinedione (TZD), selective peroxisome proliferator-activated receptor modulator (SPPARM) being developed for treatment of T2DM. Specifically, INT131 is a novel chemical entity which acts to selectively modulate PPAR γ activity differentially from the full agonist action of the TZDs. INT131 has demonstrated consistent unique properties in functional assays for receptor activation compared with multiple PPAR γ full agonists providing support for the SPPARM concept. Preclinical studies with INT131 demonstrate similar glucose lowering with fluid retention, weight gain and cardiomyopathy than currently available TZDs in similar studies. In early clinical experience, INT131 has been shown to be a potent inducer of adiponectin in normal subjects without evidence of fluid retention. Based on these non-clinical and clinical data, a 4 week Phase 2a multi-center, randomized, double blind, placebo controlled study was conducted to establish the glucose lowering activity of INT131 besylate in subjects with T2DM. Two doses of INT131 besylate (1 and 10 mg OD) or placebo were given over 4 weeks in 69 subjects with T2DM not receiving pharmacotherapy for their hyperglycemia. The primary efficacy endpoint was change from baseline of fasting plasma glucose at week 4. Baseline fasting glucose in the placebo, 1mg, and 10mg groups were 165 mg/dL, 163 mg/dL, and 184 mg/dL respectively. Mean FPG increased in the placebo group 8 mg/dL after 4 weeks. Mean change from baseline to week 4 for subjects treated with 1 mg INT131 was -22 mg/dL (p<0.05) and for subjects treated with 10 mg INT131 was -46 mg/dL (p<0.0001). The pattern of reduction of FPG over time would suggest continued lowering beyond 4 weeks, consistent with glucose lowering associated with PPAR γ activity. Both doses of INT131 besylate were well tolerated and there were no serious adverse events. We conclude that 4 weeks of treatment with INT131 besylate was well tolerated and significantly improves fasting glucose compared to placebo at doses of 1 and 10 mg daily in subjects with T2DM. INT131 offers the potential for significant glucose lowering without the recognized side effects of the TZDs. INT131 besylate is currently being tested in a longer-term multi-center phase 2b study to confirm and extend these findings.

INTRODUCTION

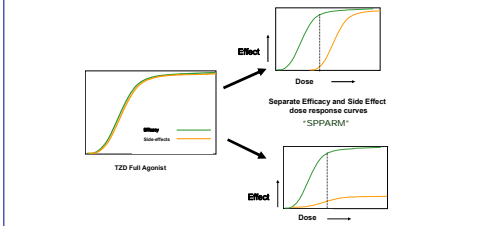
PPAR γ is a ligand-activated transcription factor that plays a critical role in the regulation of glucose and lipid homeostasis. PPAR γ activation is associated with significant improvement in insulin resistance, hyperglycemia, endothelial function, nonalcoholic steatohepatitis (NASH), polycystic ovarian syndrome (PCOS), and markers of inflammation. INT131 (formerly T0903131 (T131) and AMG 131) is a novel, selective PPAR γ modulator which is not structurally related to the thiazolidinedione (TZD) class of PPAR γ full agonists and has distinctive binding properties in the nuclear receptor binding pocket (Fig 1).

Figure 1: Ribbon diagram of INT131 and rosiglitazone in the PPAR γ binding pocket demonstrating distinct binding properties, particularly with respect to the activation helix (in red).



Full PPAR γ activation with the TZDs is associated with a number of undesirable effects that appear to share a dose response with their beneficial effects. These effects include fluid retention and CHF, adipogenic weight gain, and bone resorption associated with fractures. Based on the detailed understanding of PPAR γ receptor activation, the opportunity exists to selectively modulate specific activities of the receptor. A Selective PPAR γ Modulator (SPPARM) may allow separation of the insulin sensitizing actions of PPAR γ activation from the unwanted activities (Fig 2).

Figure 2: Conceptual approaches to selective PPAR γ modulation



INT131 was specifically designed to retain the efficacy of PPAR γ activation without the unwanted side effects. INT131 has been shown to lack the adipogenic properties of the full agonist TZDs on both rodent and human pre-adipocytes (Fig 3) while maintaining equal or greater efficacy to stimulate adiponectin in rodents and healthy human subjects (Fig 4).

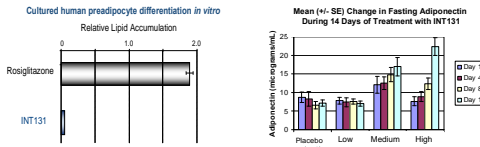


Figure 3: Relative lipid accumulation in cultured human pre-adipocytes. Human pre-adipocytes were cultured in the presence of 3 μ M rosiglitazone or 3 μ M INT131, and assayed after 10 days for differentiation as measured by lipid accumulation with Nile Red staining.

Given the safety and efficacy profile of INT131 in non-clinical pharmacology and toxicology studies (Li et. al. ADA 2004), as well as its safety and evidence for potent efficacy in initial Phase 1 clinical studies (Kersey et. al. ADA 2004, Floren et. al. 2003), INT131 was advanced into a Phase 2a study in subjects with T2DM. This study was designed to investigate efficacy for INT131 as measured by a change in FPG over 4 weeks.

PHASE 2A OBJECTIVE:

The primary objective of this study was to investigate whether 4 weeks of INT131 would improve glycemic control in subjects with T2DM inadequately controlled on no diabetes medications.

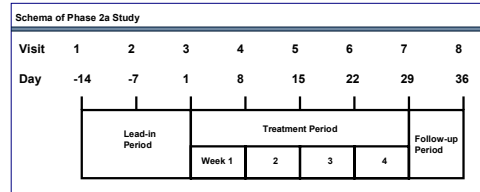
PHASE 2A STUDY DESIGN:

A Randomized, Double-blind, Placebo-controlled, 4-Week Study to Evaluate the Safety and Efficacy of INT131 Besylate in Subjects with Type 2 Diabetes Mellitus (Study T0903131-004)

- Multi-center trial (21 sites in U.S.)
- 70 Subjects (male and female) with T2DM
 - Stable but inadequately controlled on diet and exercise alone
 - HbA1c 6.5-10% / Fasting glucose between 126 and 240 mg/dL
 - 1 and 10 mg INT131 besylate and placebo
 - Treatment duration 4 weeks

- Endpoints
- Primary efficacy parameter: fasting plasma glucose
 - Secondary efficacy parameters: Fasting insulin, HOMA-IR, NEFA & lipids, adiponectin
- Safety assessments were performed frequently during study conduct. Assessments included:
- Serum chemistry panel
 - Complete hematology panels
 - Urinalysis
 - Cardiac monitoring (ECG)
 - Vital signs
 - Physical examinations

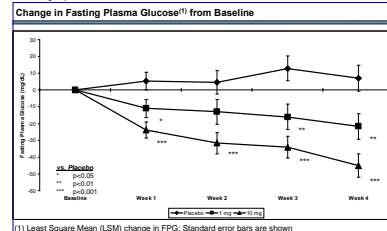
Adverse events were assessed throughout the study.



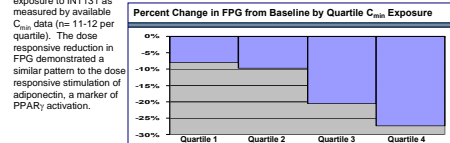
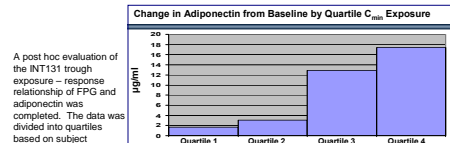
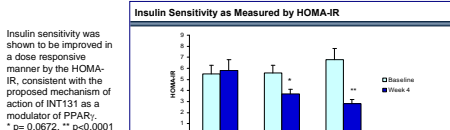
RESULTS

	Placebo	1 mg	10 mg
Age (SD)	52.8 (8.2)	54.7 (11.3)	51.6 (8.2)
Sex (M/F)	10/10	12/13	15/9
BMI (SD)	32.2 (4.9)	32.1 (6.5)	32.1 (5.0)
Caucasian (n)	17	21	24
African AM (n)	3	4	0
Hispanic (n)	9	11	7
Duration of Diabetes (yr)	3.9 (3.4)	3.8 (3.6)	4.3 (3.9)
HbA1c (%)	8.0 (1.1)	7.6 (0.7)	8.2 (1.2)
FPG (mg/dl)	165 (38)	163 (42)	184 (44)
Insulin (μ U/ml)	13.4 (6.2)	15.1 (9.9)	15.6 (9.4)
Adiponectin (μ g/ml)	7.5 (2.2)	7.4 (3.7)	8.1 (3.5)

The dose groups were well balanced overall.



- A significant change in FPG was demonstrated in both the 1 mg and 10 mg INT131 dose arms.
- The decrease in FPG from baseline was rapid and dose related.
- The dose related reduction in FPG was maintained throughout the study with substantial reductions from baseline and placebo at week 4 in FPG at both 1 mg and 10 mg.

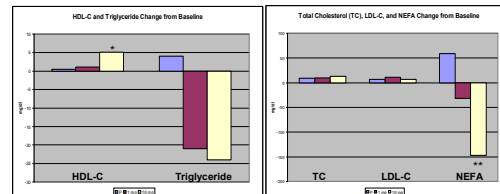


A post hoc evaluation of the INT131 through exposure - response relationship of FPG and adiponectin was completed. The data was divided into quartiles based on quantiles exposure to INT131 as measured by available C₁₆₆ data (n= 11-12 per quartile). The dose responsive reduction in FPG demonstrated a similar pattern to the dose responsive stimulation of adiponectin, a marker of PPAR γ activation.

Lipid Parameters

Lipid profiles were assessed at baseline and after 4 weeks of INT131 besylate and demonstrated:

- Dose responsive increase in HDL-C
- Non-dose responsive trend in triglyceride (TG) decrease
- No significant change in total cholesterol or LDL-C
- Dose responsive decrease in non-esterified fatty acids (NEFA)



LSM Change from Baseline
* p = 0.0236 compared with placebo
** p = 0.0002 compared with placebo

SUMMARY OF SAFETY ASSESSMENTS

- There were no SAEs reported throughout the study.
- No subject withdrew due to an AE.
- There were no clinically significant changes in laboratory tests (including hematology and liver functions tests), physical examination, vital sign measurement, or ECG recording.

DISCUSSION

- The primary objective of this study was to investigate whether 4 weeks of INT131 would improve glycemic control in subjects with T2DM inadequately controlled on no diabetes medications. FPG was chosen as the primary assessment parameter, since it is widely accepted as an effective marker of the pharmacodynamic activity for PPAR γ activation.
- INT131 was well tolerated with no safety issues over 4 weeks.
- The 1 mg and 10 mg doses of INT131 both demonstrated potent insulin sensitizing activity with significant rapid glucose lowering and adiponectin stimulating activity. The speed of onset and the magnitude of glucose lowering was substantial, particularly given the known latency of glucose lowering with PPAR γ full agonist (TZDs) and the modest baseline FPG of the subject population.
- The exposure response relationship analysis (identified by C₁₆₆ Quartiles) suggests that FPG reduction and adiponectin stimulation were associated. Further, the data appear to allow prediction of doses of INT131 for continued study that will provide significant glucose lowering efficacy, while minimizing the potential for the known safety and tolerability concerns of the full agonist TZDs with respect to weight gain and fluid retention.
- INT131 exposure over 4 weeks was also associated with overall positive lipid changes (elevation in HDL, reduction in NEFA, a trend in TG lowering, and no change in LDL). This is important for a T2DM therapeutic given the known increased risk of CV disease in this population.
- Taken together these data support the potential of INT131 as a potent SPPARM with significant glucose lowering and insulin sensitizing activity.

CONCLUSIONS

- Four weeks of treatment with INT131 besylate significantly improved fasting plasma glucose compared to baseline and placebo at doses of 1 mg and 10 mg daily in subjects with T2DM on no drug therapy. The changes in FPG were accompanied by improvements in insulin sensitivity and an increase in adiponectin.
- INT131 was safe and well tolerated, without evidence of weight gain or fluid retention at a dose that provides glycemic improvement as good or better than the full agonist TZDs.
- As a potent non-TZD SPPARM with specifically designed PPAR γ modulatory activity, INT131 besylate offers the potential for significant glucose lowering and adiponectin stimulation without the recognized side effects of the TZDs. INT131 besylate is currently being tested in a 6-month multi-center phase 2b study to further evaluate these findings and define the differential safety and tolerability profile in direct comparison to pioglitazone.

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