

# Impact of INT131 Besylate, a Selective PPAR $\gamma$ Modulator (SPPARM), on Glycemic Control in Patients with Type 2 Diabetes in a 24-Week Phase 2b Study (INT131-007)

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## ABSTRACT

**Background and aims:** Insulin resistance is a key etiologic factor in Type 2 Diabetes Mellitus (T2DM). INT131 besylate is a novel, potent, non-TZD selective PPAR $\gamma$  modulator (SPPARM) designed to improve insulin sensitivity and glucose metabolism while minimizing the typical side effects of the full PPAR $\gamma$  agonists: excessive weight gain, increased fluid retention (edema), and CHF. In rodent models of T2DM, INT131 besylate demonstrated similar insulin sensitizing and glucose lowering activity as full agonist TZDs with little or no side effects. Further, 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 high multiples of projected clinical exposures. A 4-week Phase 2a study of 1 and 10 mg INT131 besylate QD used as monotherapy in T2DM patients previously demonstrated potent insulin sensitizing activity and glucose lowering. The magnitude of glucose lowering of 1 mg INT131 besylate in that study was consistent with modeled glucose lowering of 45 mg QD pioglitazone HCl, but without typical TZD side effects. Based on these data, a 24-week head-to-head dose-finding clinical study of INT131 besylate compared to 45 mg pioglitazone HCl and placebo was carried out.

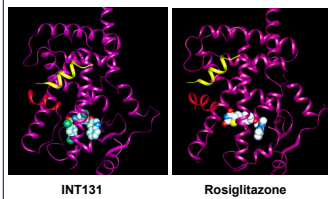
**Materials and methods:** INT131-007 is a 24-week double blind, placebo and active controlled Phase 2b study with either INT131 besylate (0.5, 1, 2, or 3 mg QD), pioglitazone HCl 45 mg QD, or placebo in patients with inadequately controlled T2DM (HbA1c 7.5-10.0) on a stable dose of sulfonylurea with or without metformin. Enrollment across the US and Mexico of 367 patients was completed on March 10, 2009. Patients underwent 2 screening visits separated by 1 week followed by a 1 week lead-in period with home glucose monitoring. A glucose rescue algorithm focusing on FPG and HbA1c was monitored throughout the 24-week study.

**Results:** Baseline characteristics ( $\pm$  SD) for the INT131-007 study patients include: age 55.8  $\pm$  9.5 yrs, duration of diabetes 8.4  $\pm$  6.2 yrs, 46% women, BMI 32.0  $\pm$  5.5, FPG 9.59  $\pm$  1.95 mmol/l (172.6  $\pm$  35.0 mg/dl), and HbA1c 8.33  $\pm$  0.72%. The objective of the study was to assess change from baseline in glycemic control (FPG and HbA1c) after 24 weeks of INT131 besylate (0.5, 1, 2, and 3 mg QD), or full dose (45mg QD) pioglitazone HCl or placebo.

**Conclusion:** Available data support the potential of INT131 to function as a SPPARM to provide potent insulin sensitization and glucose reduction in patients with poorly controlled T2DM separate from the undue effects of full-agonist TZDs such as weight gain and fluid retention. The design of the trial, baseline demographics, adverse events, and key efficacy assessments are presented.

## INTRODUCTION

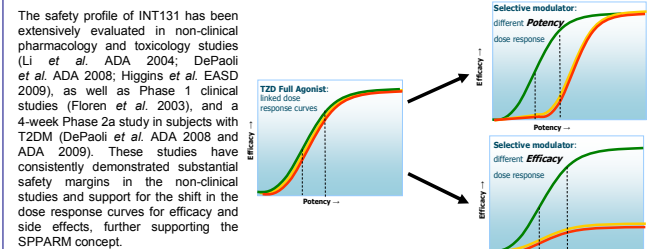
Ribbon diagrams of INT131 or rosiglitazone show distinct interactions with PPAR $\gamma$  binding pocket (activation function helix in red)



PPAR $\gamma$  is a ligand-activated transcription factor that plays a critical role in the regulation of glucose and lipid homeostasis. PPAR $\gamma$  activation in animals and humans is associated with significant improvement in insulin resistance, hyperglycemia, endothelial function, nonalcoholic steatohepatitis (NASH), and markers of inflammation. Unfortunately, the thiazolidinedione (TZD) class of PPAR $\gamma$  full agonists, represented by pioglitazone and rosiglitazone, is also associated with significant tolerability and safety concerns (weight gain, edema, fluid retention and bone fracture) in the clinic. INT131 [formerly T0903131 (T131) and AMG 131] is a novel, selective PPAR $\gamma$  modulator which is not structurally related to the TZD class of PPAR $\gamma$  full agonists and has distinctive binding properties in the nuclear receptor binding pocket.

## Conceptual Approaches to Selective PPAR $\gamma$ Modulation

Based on a detailed understanding of PPAR $\gamma$  ligand binding and receptor activation, a moiety can be specifically designed which interacts uniquely within the binding pocket to selectively modulate the receptor. Two possible approaches to PPAR $\gamma$  Selective Modulation (SPPARM) are depicted below, with shift in either potency or efficacy of the dose response curves. INT131 was specifically designed as a SPPARM to retain PPAR $\gamma$  activation in terms of efficacy while altering the dose responses of the unwanted side effects.



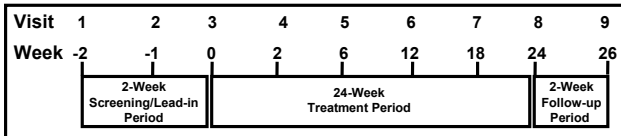
## PHASE 2b OBJECTIVES

- Primary objective: To investigate whether 24 weeks of INT131 besylate improves glycemic control in subjects with T2DM inadequately controlled on sulfonylurea monotherapy or sulfonylurea plus metformin combination therapy.
- Key secondary objective: Compare the efficacy (HbA1c) and side effects (body weight gain, lower extremity edema and hematocrit change) of INT131 besylate to 45 mg pioglitazone HCl.

## PHASE 2b STUDY DESIGN

INT131-007 was a 28-week, multi-center, randomized, double-blind, double-dummy, placebo-controlled study with a 2-week screening/lead-in period, a 24-week double-blind treatment period, and a 2-week follow-up period conducted at 60 sites in the US and 7 sites in Mexico.

- Primary objective: Evaluate the ability of 0.5 mg, 1 mg, 2 mg, and 3 mg of INT131 besylate to reduce HbA1c over 24 weeks of repeat daily dose administration
  - Primary endpoint: Change in HbA1c from baseline
  - Secondary efficacy parameters: Fasting insulin, HOMA IR, lipids, adiponectin
- Patients with T2DM were studied
  - Stable diabetes therapy on either sulfonylurea monotherapy or sulfonylurea plus metformin combination
  - HbA1c 7.5-10%
  - Fasting plasma glucose  $\leq$  240 mg/dL
- Treatment duration: 24 weeks
  - 0.5, 1, 2, 3 mg INT131 besylate, placebo, or 45 mg pioglitazone HCl daily prior to the morning meal
- Safety assessments performed during the study included:
  - Home glucose monitoring for hypoglycemia (< 60 mg/dl) or excess hyperglycemia (> 240 mg/dL)
  - Safety labs: Serum chemistry panel / Complete hematology panels / Urinalysis
  - Vital signs with careful attention to body weight (calibration of scales)
  - Physical examinations including a prospective clinical assessment of edema
- Adverse events were assessed throughout the study



## RESULTS

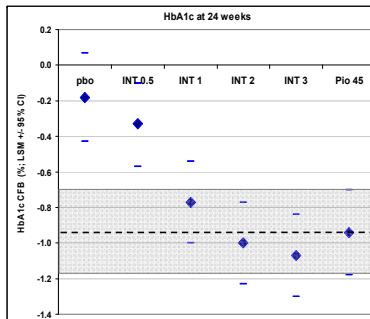
### Baseline Demographics

	Placebo	0.5 mg	1 mg	2 mg	3 mg	45 mg Pio
Number of Subjects (n)	61	60	61	63	61	60
Age (SD)	55.3 (10.9)	54.9 (8.5)	58.0 (9.2)	56.1 (8.0)	54.8 (9.8)	55.8 (10.4)
Sex (M/F)	33 / 28	36 / 24	32 / 29	31 / 32	36 / 25	28 / 32
BMI (SD)	31.8 (5.7)	31.9 (5.8)	32.6 (5.6)	31.7 (5.5)	31.4 (5.4)	32.7 (5.4)
Caucasian (n)	50	49	54	48	52	47
African AM (n)	6	7	4	10	6	9
Hispanic (n)	31	29	31	29	32	28
Duration of Diabetes (yr)	8.9	8.2	7.9	8.4	9.0	8.2
% HbA1c (SD)	8.4 (0.8)	8.3 (0.8)	8.3 (0.7)	8.5 (0.7)	8.3 (0.7)	8.2 (0.7)
FPG, mg/dL (SD)	176.8 (34)	171.3 (40)	172.5 (32)	175.4 (39)	166.6 (31)	172.5 (34)
Metformin Users (%)	49 (80.3)	49 (81.7)	50 (82.0)	50 (79.4)	49 (80.3)	48 (80.0)

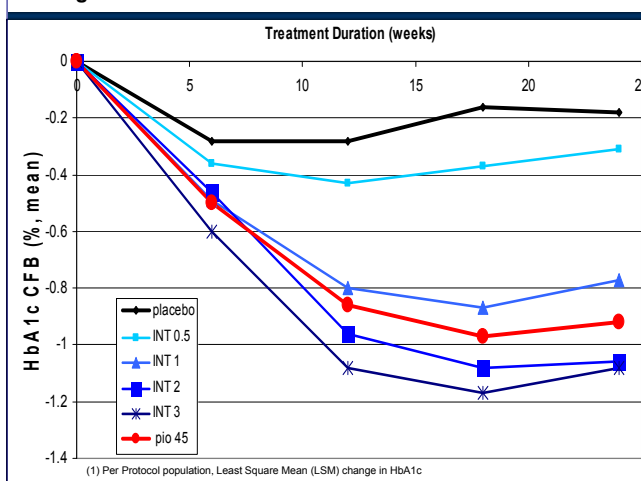
**Subject disposition:** 366 subjects received study drug and 299 completed the study. The study had a glycemic rescue criteria that identified 17 subjects for discontinuation due to persistent hyperglycemia. Nine subjects withdrew for adverse events. Overall the completion rates across the study drug dose groups were balanced. The per protocol population was all subjects who completed study without major protocol violations.

### Primary Efficacy Profile: Change in HbA1c from Baseline

- The primary endpoint of the study was least square mean (LSM) change from baseline HbA1c at 24 weeks. Results are shown in the figure at right expressed as change from baseline (LSM)  $\pm$  95% confidence interval (CI). The 95% CI for is shaded, and dashed line through LSM for the pioglitazone HCl group for ease of comparison for other groups.
- A statistically significant change in HbA1c from baseline to week 24 [LSM (95% CI)] compared to placebo was demonstrated in the 1-mg 2-mg and 3-mg INT131 besylate and the 45 mg pioglitazone HCl dose groups.
- The reduction in HbA1c at week 24 relative to baseline seen in the 1-mg, 2-mg, and 3-mg INT131 besylate dose groups were not different than that seen with 45 mg of pioglitazone HCl based on the 95% confidence intervals.

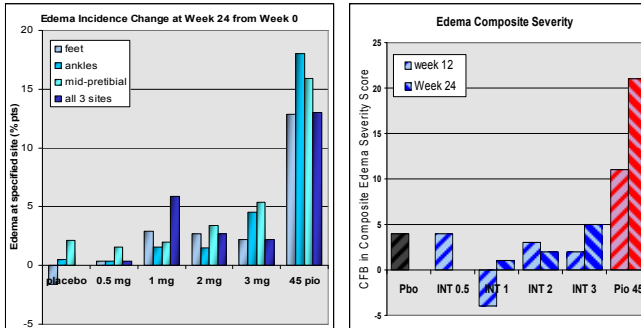


## Change in HbA1c from Baseline (1)



## Side Effect Profile: Edema Evaluations, Body Weight, Hematocrit and Creatinine

Edema was evaluated using a pre-specified clinical edema scale. This assessment tool consisted of a systematic evaluation of the presence or absence of pitting edema at the level of the mid-foot, ankle and mid-pretibia. These assessments were collected at baseline, 12 wks, and 24 wks. **Left Panel:** Summary of change from Week 0 at Week 24. **Right Panel:** A composite edema severity score was calculated based on presence of edema at one site (1 point), two sites (2 points) and three sites (3 points). The change from baseline for INT131 besylate at all doses was not different from placebo, while the 45 mg pioglitazone HCl group showed the expected increase in edema severity.



Hematocrit (Hct) and body weight were evaluated at each visit during the study. Body weight was assessed using calibrated scales across sites to ensure accuracy. Baseline body weight and hematocrit were defined as the average of measurements at Week 0 and the last measurement within 15 days prior to Week 0 to obtain a stable baseline. Creatinine was measured as part of routine safety surveillance and closely monitored as increased creatinine is associated with some PPAR $\gamma$  full agonists.

	Placebo	INT131 0.5 mg	INT131 1 mg	INT131 2 mg	INT131 3 mg	Pio 45 mg
Body Weight CFB to 24 Wks Relative to Pioglitazone, kg (SD)	-	-1.54 (0.59)*	-1.94 (0.59)**	-0.21 (0.58)	0.64 (0.59)	-
Hematocrit CFB to 24 Wks Relative to Pioglitazone, % (SD)	-	0.75 (0.36)***	0.58 (0.36)*	-0.46 (0.36)	0.01 (0.36)	-
Creatinine Mean CFB to 24 Wks, mg/dL (SD)	-0.016 (0.0926)	-0.021 (0.0876)	-0.018 (0.0774)	-0.007 (0.1055)	-0.010 (0.1056)	0.010 (0.0912)

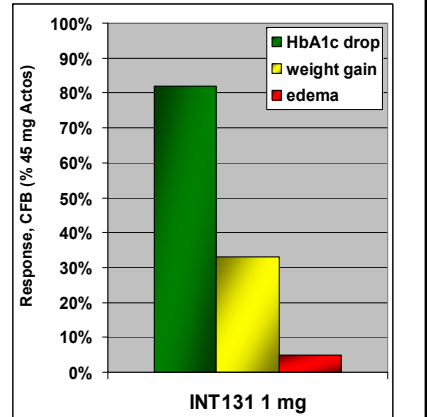
\*p=0.0095, \*\*p=0.0011, \*\*\*p=0.04, ^ NS; p=0.11

## SUMMARY OF SAFETY ASSESSMENTS

- The overall adverse event profile was consistent with a study of patients with T2DM.
- There were 16 SAEs reported in 12 patients throughout the 24 week study. None were deemed by the investigator as related to study drug.
- The most common AEs included peripheral edema, urinary tract infections, headache, hypoglycemia, diarrhea, and upper respiratory tract infection.
- Overall there were no clinically important changes in laboratory tests (including hematology, liver function, and creatinine).
- Clinical parameters including vital sign measurement, physical examination, and ECG have not demonstrated any significant findings and are currently being analyzed.

## Comparison of 1 mg INT131 Besylate to 45 mg pioglitazone

As a non-TZD selective modulator of PPAR $\gamma$ , INT131 was specifically designed to provide comparable efficacy to the full agonist TZDs but with significantly less of the side effects associated with the TZD class. In non-clinical safety studies, INT131 besylate has not demonstrated the typical toxicities of the full PPAR $\gamma$  agonists (Higgins et al. 2009). A Phase 2a study demonstrated that 1 mg of INT131 besylate provided comparable efficacy to 45 mg pioglitazone HCl with minimal side effects for 4 weeks (DePaoli et al. 2009). The figure at right provides the relative efficacy and side effect measures of 1 mg INT131 besylate compared to 45 mg pioglitazone HCl in the current study. These Phase 2b data confirm and extend the Phase 2a findings, and demonstrate that the reduction in HbA1c seen with 1 mg of INT131 besylate is comparable to 45 mg pioglitazone HCl, while the side effects of weight gain and new or worsening edema are substantially mitigated.



## DISCUSSION AND CONCLUSIONS

- The primary objective of this study was to investigate effect of INT131 besylate on glycemic control (HbA1c) in subjects with T2DM inadequately controlled on an SU +/- metformin after 24 weeks of treatment.
- INT131 besylate demonstrated substantial HbA1c reduction, which was comparable to 45 mg pioglitazone HCl at the 1-, 2-, and 3-mg doses.
- INT131 besylate was well tolerated, with no safety issues based on AEs, laboratory assessments, and clinical findings.
- There was no difference in incidence or severity of edema in any INT131 besylate dose group compared to placebo, while an expected frequency and severity of edema was observed in the pioglitazone HCl group.
- INT131 besylate at 1 mg provided potent glucose lowering with minimal body weight gain, Hct reduction, or evidence of edema, confirming the results of the 4-week Phase 2a study.
- Ongoing analyses will fully define the profile of INT131 besylate as a potential diabetes therapeutic.
- These data confirm the activity of INT131 besylate as a potent selective PPAR $\gamma$  modulator (SPPARM) with significant glucose lowering properties but without the degree of body weight gain or the edema seen with pioglitazone HCl.

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