PIOGLITAZONE: HEMODILUTION/CARDIAC EFFECTS

1. Increased heart weights all species. Consistent between experiments.
2. Plasma volume expansion.
3. Hemodilution (↓ HCT, HB, RBC in mouse, rat, dogs; ↓ reticulocytes and platelets in rats and mice). Splenic extramedullary hematopoiesis.
4. Hydrothorax (rats); hydropericardium (dogs), atrial thrombosis (rats and mice).
5. Cardiac changes associated with plasma volume expansion. Not associated with functional changes.

PIOGLITAZONE: LIVER EFFECTS

1. Increased liver weights (rats, mice, dogs, monkeys); not found consistently.
2. No histological or clinical chemical correlates in rats and mice. Occasional centrilobular hypertrophy in dogs and monkeys. Necrosis and subacute hepatitis observed in one dog ~50X human dose.
3. Increased ALT (2.5X at ~11 times clinical exposure; 1.4X at ~3 times clinical exposure based on mg/m^2) in dogs. Sporadic elevations noted in some rat and monkey studies. Decreases in albumin and total protein in dogs indicate functional effects.

SUMMARY (PRECLINICAL) FOR PIOGLITAZONE

1. Cardiac findings are generally attributable to responses to plasma volume expansion and occur at relatively low multiples of human exposure.
2. Increases in liver weight were not consistently found in preclinical studies. The finding of elevated ALT in the chronic dog toxicology study provides a signal for liver toxicity at relatively low doses.

PIOGLITAZONE: EXPOSURE COMPARISONS OF MINIMUM EFFECT LEVEL IN ANIMAL STUDIES TO HUMAN DOSE (mg/m^2)

TOXICITY	SPECIES	ANIMAL:HUMAN RATIO
CARDIAC HYPERTROPHY	MOUSE	5
	RAT	1.3
	DOG	3.2
	MONKEY	6
HEMODILUTION	MOUSE	51
	RAT	5.1
	DOG	3.2
	MONKEY	90
↑ ALT	DOG	3.2
HEPATIC HYPERTROPHY	MOUSE	0.5
	RAT	20
	DOG	11
	MONKEY	6

CONCLUSION

The potential for cardiac and hepatic toxicity must be considered in the clinical safety evaluation of Pioglitazone.

Echocardiographic Studies

- TRG 600 mg vs. Glynase max dose **96 weeks**
- RSG 8 mg vs. Glyburide max dose **52 weeks**
- PIO 7.5-45 mg vs. Placebo **26 weeks**

ALT elevations with Troglitazone

	Continued	Withdrawn	Total (n=2510)
>3xULN	25	23	48 (1.9%)
>5xULN	22	20	42 (1.7%)
>8xULN	8	14	22(0.9%)
30xULN	0	5	5 (0.2%)

Pioglitazone ALT elevations

	Continued	Withdraw	Total (n=3610)
>3x ULN	5	7	12 (0.33%)
>5x ULN	4	5	9 (0.25%)
>8x ULN	1	0	1 (0.03%)
>30x ULN	0	0	0

ALT > 3xULN (Controlled Trials)

	Active drug	Placebo
PIO USA	0.3% (4/1526)	0.3% (2/793)
PIO Japan	0.7% (4/570)	0.7% (2/280)

ALT > 3xULN (Controlled Trials)

Trial:	Duration	Patients	ALT > 3xULN
Acarbose	6-12 m	Placebo	0.6% (5/865)
Miglitol	6-12 m	Placebo	0.6% (3/545)
Metformin	29 weeks	Placebo, Glyburide Metformin	0.4% (4/921)