Abiraterone decanoate (PRL-02): Pharmacology of a single intramuscular (IM) depot injection compared to oral abiraterone acetate (AA) in intact male rats (Abstract #160)

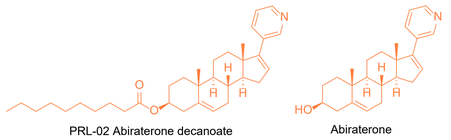
William Moore[1], Matthew Sharp[1], Joel Eisner[2], Caroline Bell[3], Stuart Freeman[4], Tony Leesnitzer[5], Robert Schotzinger[6]

[1]Propella Therapeutics, Inc., Pittsboro, NC; [2]Consultant, Chapel Hill, NC; [3]PharmaFacts, Phoenixville, PA; [4]Consultant, Surrey, UK; [5]OpAns LLC, Durham, NC; [6]Consultant, Raleigh, NC

BACKGROUND

- PRL-02 is a long-acting IM formulation of the novel prodrug abiraterone decanoate (**Fig. 1**)
- PRL-02 was designed to produce prolonged androgen lowering activity without the highly variable PK and safety issues associated with AA
- In a castrate monkey model, single doses of PRL-02 delivered low and controlled abiraterone plasma exposures and suppressed androgens for greater than 14 weeks (Moore et al, Abstract 319635, 2021 ASCO GU)
- In the present intact rat study, tissue exposures and activity of single-dose PRL-02 were compared with a clinically-equivalent daily oral AA regimen at 14 days after treatment initiation

Figure 1: Structures of Abiraterone Decanoate and Abiraterone



METHODS

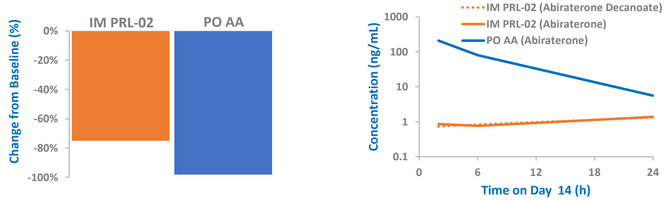
- Four groups (n=4/group) of sexually mature intact male rats were administered a single IM dose of PRL-02 (90 mg/kg) or IM vehicle (VEH) or daily oral AA (90 mg/kg) or oral VEH for 14 days
- Blood and tissue samples were collected on Day 14 at 2, 6 and 24h post final dose of AA
- Drug and androgen concentrations in blood and tissues were determined by LC/MS/MS
- Tissue drug concentrations and *ex vivo* CYP17 hydroxylase activity were measured in treated and VEH testicular microsomes isolated on Day 14

Table 1: Study Treatment Schedule

Treatment Group	Treatment Day													
	1	2	3	4	5	6	7	8	9	10	11	12	13	14
PO VEH	x	x	x	x	x	x	x	x	x	x	x	x	x	x
PO AA	x	x	x	x	x	x	x	x	x	x	x	x	x	x
IM VEH	x													
IM PRL-02	x													

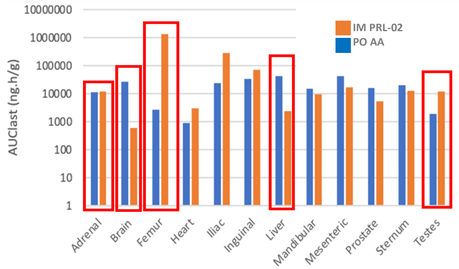
RESULTS

Figure 2: Day 14 Serum Testosterone Change from Baseline (Left) and Plasma Pro-Drug and Abiraterone Concentrations (Right)

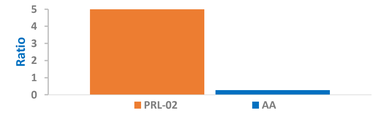


- A single IM dose of PRL-02 or repeat daily doses of PO AA resulted in a profound reduction in serum testosterone at Day 14
- Abiraterone decanoate and abiraterone plasma concentrations were comparable from PRL-02; abiraterone acetate was not detected following AA administration

Figure 3: Day 14 Concentrations of 'Abiraterone Equivalents' Across Target Tissues (Top) and Ratio of Adrenal:Liver 'Abiraterone Equivalents' (Bottom)

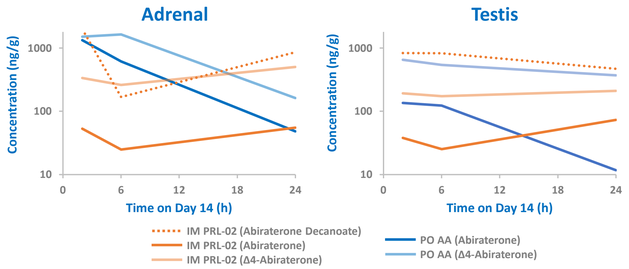


Day 14 Adrenal:Liver AUC Ratio of Total Abiraterone Equivalents



- Abiraterone equivalents (i.e., abiraterone + prodrug concentrations) were greater from PRL-02 compared to AA in target tissues (e.g., adrenal, testis, lymph nodes and bone) and lower than AA in off-target tissues (e.g., liver and brain)
- PRL-02 has a predicted Safety Margin that is ~18.5-fold greater than AA based upon relative AUCs of abiraterone equivalents in the adrenal vs. the liver

Figure 4: Day 14 Concentrations of Prodrugs and Active Metabolites in the Adrenal and Testis



- Abiraterone concentrations from AA in adrenal and testis decreased consistently following dosing on Day 14; abiraterone and abiraterone decanoate concentrations from PRL-02 remained relatively constant
- Both PRL-02 and oral AA regimens produced high concentrations of the Δ4-abiraterone metabolite, a more potent CYP17 inhibitor than abiraterone (Li et al, Nature. 523(7560) 347-351 (2015)), in the adrenal and testes

Figure 5: Day 14 *Ex Vivo* Testicular CYP17 Activity

Treatment		IM PRL-02				PO AA			
Timepoint		2h	6h	24h	VEH	2h	6h	24h	VEH
Concentration in Microsomes	Abiraterone (ng/mL)	7.6	6.4	7.3	-	21.6	13.1	3.6	-
	Δ4-Abiraterone (ng/mL)	85.9	103	112	-	412	296	225	-

- There was no measurable CYP17 hydroxylase activity in testicular microsomes isolated from rats treated with IM PRL-02 or PO AA at 2, 6, or 24h on Day 14
- Consistent with testes results, concentrations of abiraterone and Δ4-abiraterone decreased throughout Day 14 for PO AA but remained relatively constant from IM PRL-02

SUMMARY AND CONCLUSIONS

- Both the IM PRL-02 and PO AA dosing regimens produced large reductions in serum testosterone levels along with complete inhibition of testicular CYP17 on Day 14 in intact male rats
- Single dose IM PRL-02 delivered through the lymphatic system provides durable androgen suppression that is comparable to that from much larger cumulative doses of daily oral AA
- The tissue origin of the serum testosterone measured on day 14 is apparently not the testes and remains to be identified
- Both PRL-02 and PO AA dosing produced higher concentrations of the active metabolite, Δ-4 abiraterone, than of abiraterone in the adrenal and testes
- Total abiraterone exposures were greater from IM PRL-02 in therapeutic target tissues (e.g., adrenal, testes, lymph, bone) whereas exposures from PO AA were greater in plasma and off-target tissues (e.g., liver, brain)
- The relative increase in on-target to off-target exposures of abiraterone equivalents from IM PRL-02 compared to PO AA may provide an improved therapeutic index in man, which could lead to an improved safety and efficacy profile in patients with advanced prostate cancer
- Results from the current study, along with those from prior non-human primate models and ongoing clinical study findings, support the continued clinical development of PRL-02

FUTURE RESEARCH DIRECTIONS

- Experiments are ongoing to more fully understand the contribution of abiraterone and Δ4-abiraterone in PRL-02 pharmacologic activity and to determine whether the inhibition of tissue CYP17 by PRL-02 is reversible or irreversible
- A Phase 1/2a clinical study of IM PRL-02 in patients with metastatic castration-sensitive prostate cancer (mCSPC) and metastatic castration-resistant prostate cancer (mCRPC) is ongoing (NCT04729114)
- Results from the ongoing Phase 1 study will be reported at a future conference

For more information or to request a copy of the poster use the QR code or contact: wmoore@propellatx.com

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