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

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ABSTRACT AND CONCLUSIONS

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• 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 319653, 2021 ASCO GI).

• 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.

Both 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, Δ4-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.

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METHODOLOGY

• 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 24 h 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 treated testicular microsomes isolated on Day 14.

• Abiraterone equivalents (i.e., abiraterone + prodrug concentrations) were greater from PRL-02 compared to AA in target tissues (e.g., adrenal, testes, 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.

• 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 24 h on Day 14.

• Consistent with tests 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

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• 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.

• 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.

• 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-resistant prostate cancer (mCSPC) and metastatic castration-dependent prostate cancer (mCPRC) is ongoing (NCT04729114).

• Results from the ongoing Phase 1 study will be reported at a future conference.