Nano-amorphous Abiraterone acetate formulation with improved bioavailability and eliminated food effect

Tamás Solymosi[1], Zsolt Ötvös[1], Réka Angi[1], Orsolya Basa-Dénes[1], Tamás Jordán[1], Hristos Glavinas[1]

[1]NanGenex Inc, Budapest, Hungary

Abstract

Abiraterone acetate (AA) is a poorly water soluble drug molecule indicated for metastatic castration resistant prostate cancer. The drug product Zytiga possesses the highest food effect of all marketed drugs. Despite of the extremely poor absorption of AA in fasted conditions, Zytiga is to be taken strictly without food.

We have developed a nano-amorphous Abiraterone acetate formulation prepared by controlled precipitation followed by lyophilization. The formulation exhibited higher apparent solubility and passive permeability when compared to either the crystalline AA or Zytiga. DLS measurements and filtration experiments yielded particle size in the 100-200 nanometer range when the solid formula was reconstituted in water. The active ingredient in the formulation was amorphous by XRD. Beagle dog studies showed 10-fold increase in exposure from the novel formulation when compared to the marketed drug. Also, the marked food effect seen with Zytiga was not observed for the nano-amorphous AA. A first-in-human clinical trial was conducted with a lyophilized powder-in-bottle formulation in healthy male volunteers. The active ingredient was rapidly absorbed in both the fasted and the fed states. Based on the PK analysis a 250 mg dose of the novel formulation is predicted to give the same exposure as 1000 mg Zytiga in the fasted state. As in preclinical studies, the significant positive food effect was eliminated. Moreover, variability of exposure was reduced when compared to Zytiga.

In conclusion we have developed a novel nano-amorphous AA formulation that significantly outperformed the marketed product in *in vitro* and *in vivo* tests. Ultimately, the formulation might allow a 75% dose reduction and negate the restriction of a food label.

Image

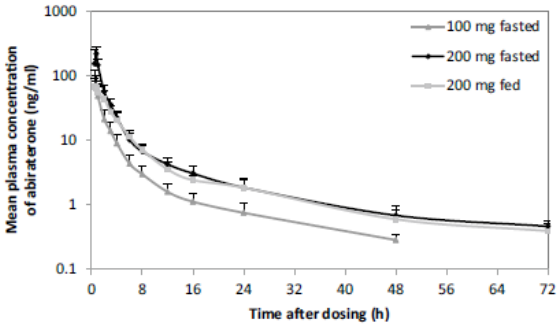


Fig. 1 The mean (SD) of plasma abiraterone concentrations

Recent Publications

1. Solymosi T (2017) Novel formulation of abiraterone acetate might allow significant dose reduction and eliminates substantial positive food effect, Cancer Chemotherapy and Pharmacology
2. Solymosi T (2017) Development of an abiraterone acetate formulation with improved oral bioavailability guided by absorption modeling, International Journal of Pharmaceutics
3. Goldwater R (2017) Comparison of a Novel Formulation of Abiraterone Acetate vs. the Originator Formulation in Healthy Male Subjects: Two Randomized, Open-Label, Crossover Studies, Clinical Pharmacokinetics
4. Papangelou A (2017) The Effect of Food on the Absorption of Abiraterone Acetate from a Fine Particle Dosage Form: A Randomized Crossover Trial in Healthy Volunteers, Oncology and Therapy
5. Chi K N (2015) Food Effects on Abiraterone Pharmacokinetics in Healthy Subjects and Patients With Metastatic Castration-Resistant Prostate Cancer, The Journal of Clinical Pharmacology

Biography

Tamás Solymosi has been working at NanGenex Inc for 9 years, gaining experience in the formulation of poorly water soluble active ingredients. He holds an MSc degree in chemical engineering and currently writing his PhD thesis about the formulation of Abiraterone acetate. He is interested in the physicochemical background of nanoformulation and bioavailability increasing technologies.

Tel: +36301971517
Email: tamas.solymosi@nangenex.com
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