# RAPID ABSOPRITON OF NANO-AMOPHOUS ABIRATERONE ACETATE IS DRIVEN BY IMPROVED DISSOLUTION AND ACCELERATED CONVERSION OF THE DRUG TO ABIRATERONE IN THE INTESTINE

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## Introduction and objectives

• Abiraterone acetate (AA) is indicated for patients with metastatic castration resistant prostate cancer. It is a prodrug, which is converted to abiraterone *in vivo*, an androgen biosynthesis inhibitor [1]. The oral dose is high; 1,000 mg which is administered once daily as 4x250 mg Zytiga® tablets. The absolute bioavailability of abiraterone following the administration of Zytiga® is estimated to be below 10% in the fasted state with a 10-fold (AUC) and up to a 17-fold ($C_{max}$) increase following a high-fat meal [2]. AA is converted to abiraterone in the intestinal lumen by the enzyme cholesterol esterase yielding supersaturated abiraterone concentrations, which is believed to be the driving force of the absorption process [3].

• The objective of this work was to develop an AA formulation with improved absorption in the fasted state, which could allow the reduction of the dose and could eliminate food effect.

## Methods

• AA formulations produced by different methods exhibiting different particle size and crystalline structure were tested.
• In vitro solubility, dissolution and permeability measurements were performed in biorelevant media.
• Absorption modelling was performed to predict fraction dose absorbed.
• AA hydrolysis was assayed by the incubation of samples with porcine pancreatic cholesterol esterase.
• Beagle dog studies and a phase I clinical study were conducted to characterize in vivo pharmacokinetics and food effect.

## Results

• Absorption modelling based on biorelevant dissolution tests showed that the concurrent increase of solubility and dissolution rate is necessary for improved absorption [5].
• This could only be achieved by a nano-amorphous formulation produced by controlled precipitation [5].
• In dogs, nano-amorphous AA exhibited >10-times higher AUC and $C_{max}$ in the fasted state when compared to Zytiga® and eliminated the food effect [5].
• The higher apparent solubility of AA resulted in its faster enzymatic hydrolysis. Co-administration of an inhibitor of cholesterol esterase in dogs showed that improved absorption is indeed dependent on the prior hydrolysis of AA to abiraterone.
• In healthy volunteers AUC following the administration of 200 mg of the novel formulation was 81% of the AUC for 1,000 mg Zytiga®. Inter-individual variability was low and the extensive positive food effect was not observed [6].

## Conclusions

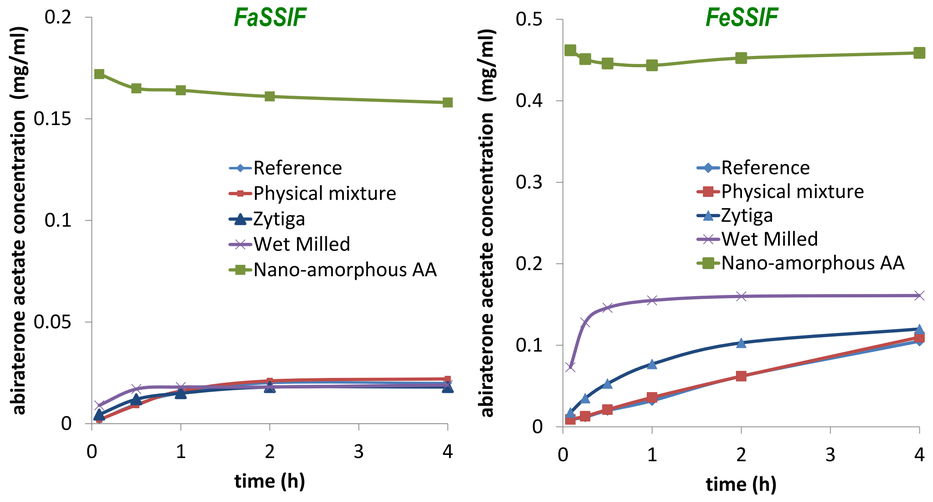
• A 250 mg oral dose of the nano-amorphous formulation is expected to result in the same exposure as 1,000 mg Zytiga® in the fasted state.
• Food effect was eliminated and variability reduced.
• The proposed mechanism behind the improvement is the immediate transfer of AA to bile micelles in the intestine followed by rapid conversion of AA to abiraterone by cholesterol esterase.

## References

[1] M. Acharya, A. Bernard, M. Gonzalez, J. Jiao, R. De Vries, and N. Tran, "Open-label, phase I, pharmacokinetic studies of abiraterone acetate in healthy men," *Cancer Chemother. Pharmacol.*, vol. 69, no. 6, pp. 1583–1590, 2012.
[2] K. N. Chi *et al.*, "Food effects on abiraterone pharmacokinetics in healthy subjects and patients with metastatic castration-resistant prostate cancer," *J. Clin. Pharmacol.*, vol. 55, no. 12, pp. 1406–1414, 2015.
[3] J. Stappaerts *et al.*, "Rapid conversion of the ester prodrug abiraterone acetate results in intestinal supersaturation and enhanced absorption of abiraterone: In vitro, rat in situ and human in vivo studies," *Eur. J. Pharm. Biopharm.*, vol. 90, pp. 1–7, 2015.
[4] G. L. Amidon, H. Lennernäs, V. P. Shah, and J. R. Crison, "A Theoretical Basis for a Biopharmaceutic Drug Classification: The Correlation of in Vitro Drug Product Dissolution and in Vivo Bioavailability," *Pharm. Res. An Off. J. Am. Assoc. Pharm. Sci.*, vol. 12, no. 3, pp. 413–420, 1995.
[5] T. Solymosi *et al.*, "Development of an abiraterone acetate formulation with improved oral bioavailability guided by absorption modeling based on in vitro dissolution and permeability measurements," *Int. J. Pharm.*, vol. 532, no. 1, pp. 427–434, 2017.
[6] T. Solymosi *et al.*, "Novel formulation of abiraterone acetate might allow significant dose reduction and eliminates substantial positive food effect," *Cancer Chemother. Pharmacol.*, vol. 80, no. 4, pp. 723–728, 2017.

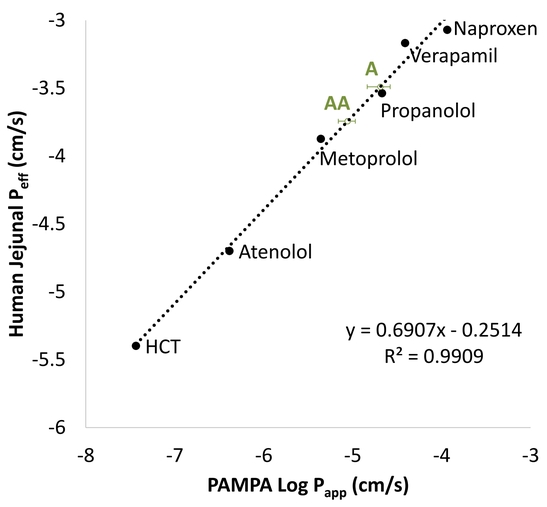
## Dissolution in biorelevant media

**Comparison Zytiga® with the unformulated reference and with the wet-milled, the nano-amorphous formulation and a physical mixture with the same composition (18% AA, 71% Soluplus, 11% SDC)**




## PAMPA permeability

**Permeability of abiraterone acetate, abiraterone and the validation set. Test items were dissolved in FeSSIF biorelevant media**



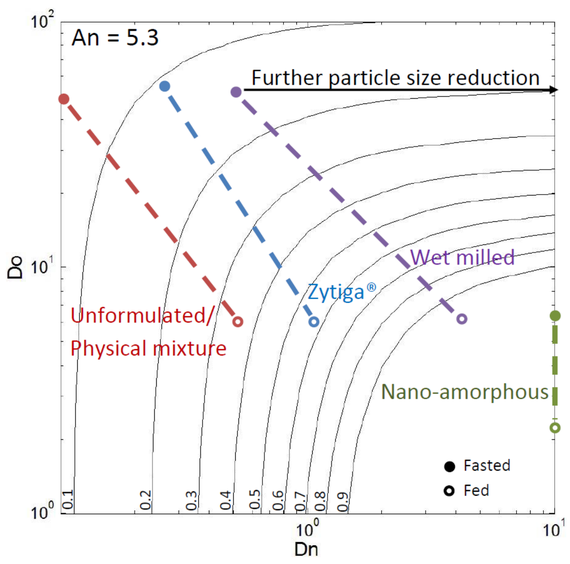

**Formulation method, particle size and crystal structure of the formulations**

| | Unformulated AA | Zytiga® | Wet Milled AA | Nano-amorphous AA |
|---|---|---|---|---|
| **Formulation method** | Not applicable | Jet milling | Wet milling | Continuous flow precipitation |
| **Particle size* (range or $d_{50}$, µm)** | 50-100 | 3-10 | 0.497 | 0.186 |
| **Crystal structure (pXRD)** | Crystalline | Crystalline | Crystalline | Amorphous |

* Determined microscopy or by DLS.

## Absorption modelling

**Estimation of fraction dose absorbed ($f_a$) in the fasted and in the fed states based on Do, Dn and An calculated from in vitro dissolution and permeability experiments**



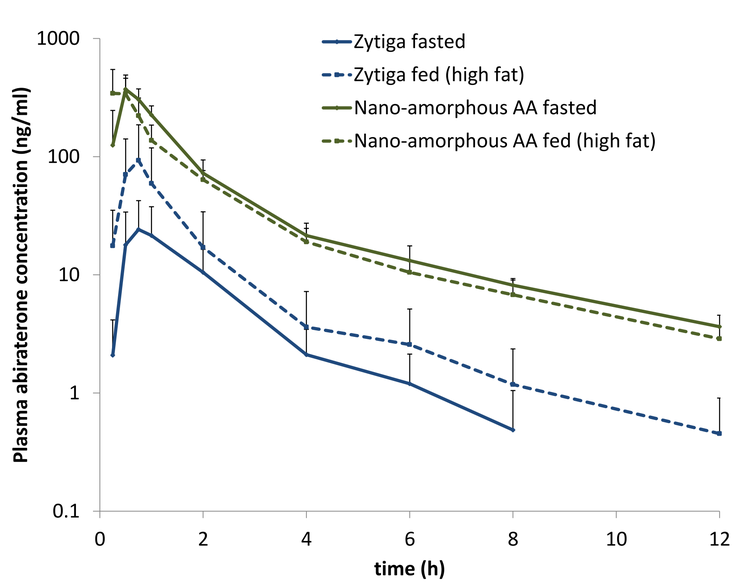

**The observed relative AUC values and the corresponding calculated $f_a$ values.**

| | Observed relative $AUC_{last}$ | Calculated relative $f_a$ |
|---|---|---|
| **Zytiga® food effect*** | 5.7 | 5.6 |
| **Nano-amorphous AA food effect*** | 0.85 | 1.0 |
| **$F_{rel}$ Zytiga®/Nanostuctured AA fasted**** | 11.5 | 9.1 |
| **$F_{rel}$ Zytiga®/Nanostuctured AA fed**** | 1.7 | 1.6 |

*Ratio of observed $AUC_{last}$ and calculated $f_a$ in the fed and fasted states.
**Ratio of $AUC_{last}$ and calculated $f_a$ for Zytiga® and nano-amorphous AA.

## Beagle dog pharmacokinetics

**Plasma concentrations following the oral administration of 50 mg Zytiga® or nano-amorphous AA to beagle dogs in the fasted and fed states. N=4**



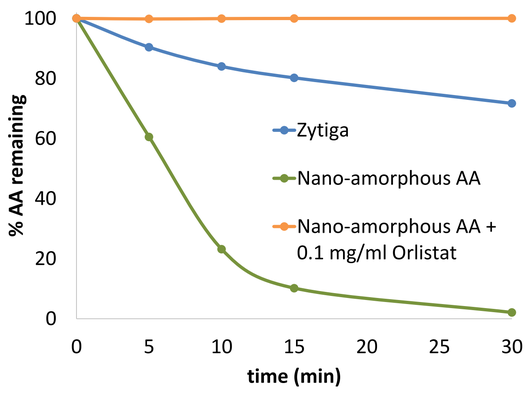

**Pharmacokinetic parameters following the oral administration of 50 mg Zytiga® or nano-amorphous AA to beagle dogs. N=4**

| Test article | Feeding condition | $t_{max}$ (h) | $C_{max}$ (ng/mL) | $AUC_{last}$ (h*ng/mL)* |
|---|---|---|---|---|
| **Zytiga®** | **Fasted** | 1.06 ± 0.63 | 27 ± 13 | 48 ± 26 |
| | **Fed, high fat** | 0.81 ± 0.13 | 154 ± 75 | 270 ± 104 |
| **Nano-amorphous AA** | **Fasted** | 0.50 ± 0 | 371 ± 76 | 551 ± 119 |
| | **Fed, high fat** | 0.38 ± 0.13 | 379 ± 151 | 470 ± 152 |

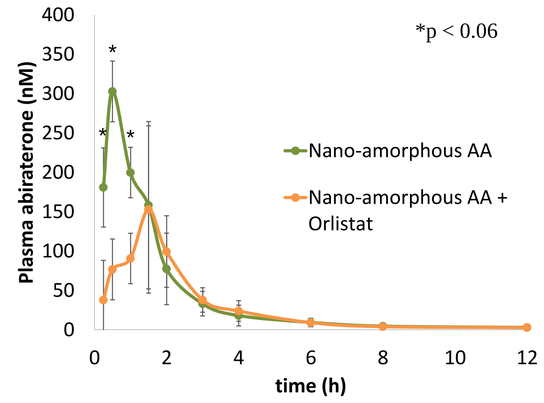
*Food effect: p < 0.005 for Zytiga®, p > 0.5 for nano-amorphous AA; relative exposure for Zytiga® and nano-amorphous AA: p < 0.01 for the fasted state, p < 0.1 for the fed state

## Cholesterol esterase hydrolysis of AA and its inhibition in vitro and in vivo

**Enzymatic hydrolysis of AA (1 mg/ml) by cholesterol esterase in vitro for Zytiga® and nano-amorphous AA with or without Orlistat in FaSSIF media**

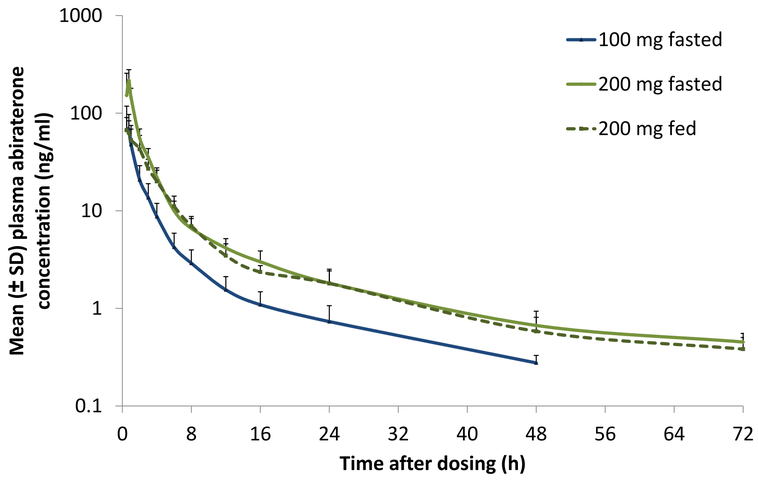



**Plasma concentrations following the oral administration of 50 mg nano-amorphous AA with or without 1 mg/kg Orlistat to beagle dogs in the fasted state. N=4**




## Clinical pharmacokinetics

**Plasma concentrations following the oral administration of nano-amorphous AA to healthy volunteers at different doses and prandial states**




**Pharmacokinetic parameters following the oral administration of nano-amorphous AA to healthy volunteers compared to historic Zytiga® PK data**

| Parameter | 100 mg fasted (N=10) | 200 mg fasted (N=9) | 200 dose fed (N=9) | 1000 mg Zytiga fasted (N=433)* |
|---|---|---|---|---|
| **$C_{max}$ (ng/ml), mean (CV%)** | 82.1 (48) | 206 (41) | 84.2 (39) | 93.5 (63) |
| **$t_{max}$ (h)** | ≤1 | ≤1 | ≤2 | 2 (1 - 8) |
| **$AUC_{last}$ (hg*h/ml), mean (CV%)** | 158 (39) | 397 (28) | 292 (23) | N.A. |
| **$AUC_{inf}$ (hg*h/ml), mean (CV%)** | 164 (38) | 408 (29) | 301 (23) | 503 (59) |
| **$t_{1/2}$ (h), mean (CV%)** | 13.6 (31) | 14.4 (21) | 15.5 (21) | 15.2 (26) |

*NDA 202-379, Clinical Pharmacology and Biopharmaceutics Review(s), 2011: p. 20