Improved Bioavailability of a Novel Abiraterone Acetate Formulation is Driven by Immediate Transfer of the Drug from Amorphous Nanoparticles to Bile Micelles Followed by its Rapid Conversion to Abiraterone in the Intestine

Druggability Technologies Inc.
NanGenex zRt.

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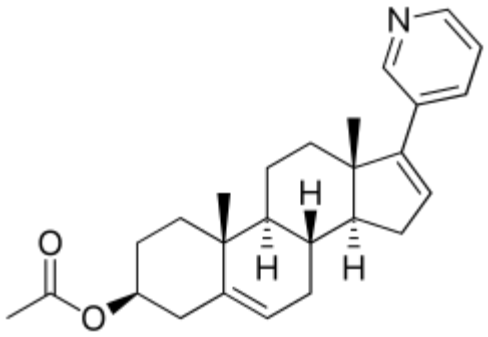
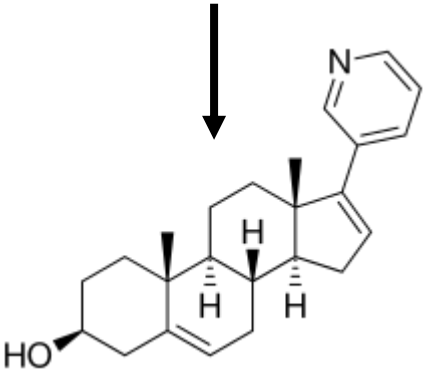
Introduction and objectives



Abiraterone acetate



Abiraterone

- Abiraterone acetate (AA , trade name Zytiga®) is indicated for patients with metastatic castration resistant prostate cancer [1].
- It is a prodrug, which is converted to abiraterone (A) *in vivo*, an androgen biosynthesis (CYP17A) inhibitor.
- Both AA and A are highly lipophilic (LogP > 5 ALOGPS), both are insoluble in water.
- 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].
- Zytiga® has to be taken on an empty stomach at very high dose (1,000 mg).
- Absorption is highly variable and no increase in AUC is observed above the currently used 1,000 mg dose.
- Zytiga absorption is at least partially driven by the conversion of AA to A by the enzyme cholesterol esterase in the intestinal lumen by the enzyme cholesterol esterase yielding supersaturated abiraterone concentrations [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.

[1] M. Acharya et al., *Cancer Chemother. Pharmacol.*, vol. 69, no. 6, pp. 1583–1590, 2012.
[2] K. N. Chi *et al, J. Clin. Pharmacol.*, vol. 55, no. 12, pp. 1406–1414, 2015.
[3] J. Stappaerts *et al.*, *Eur. J. Pharm. Biopharm.*, vol. 90, pp. 1–7, 2015.

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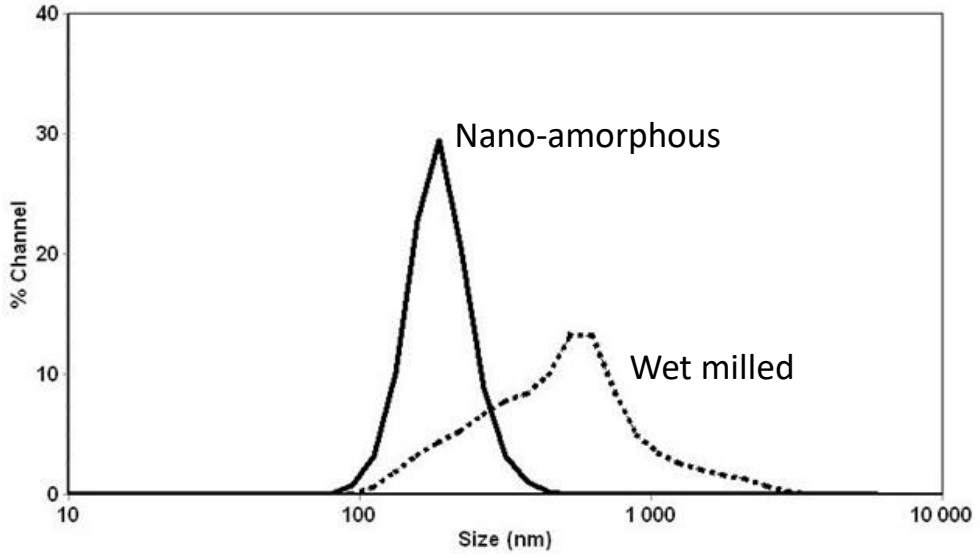
Properties of the test formulations

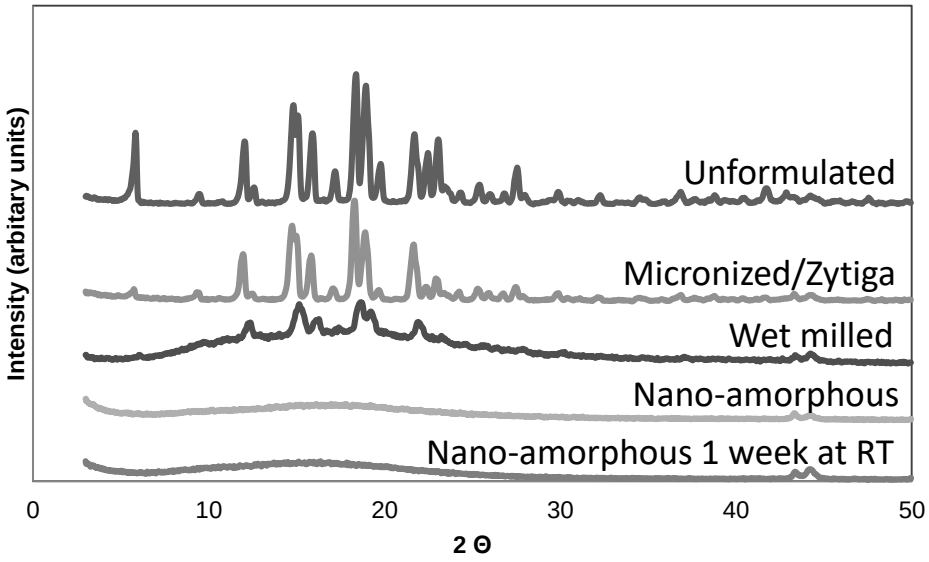
	Formulation method	Particle size (range/d_{50}, µm)	API Crystal structure (pXRD)
Unformulated AA	Not applicable	50-100*	Crystalline
Zytiga®	Jet milling	3-10**	Crystalline
Wet Milled AA	Wet milling	0.497	Crystalline
Nano-amorphous AA	Continuous flow precipitation	0.186	Amorphous
Physical mixture	Not applicable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

The wet-milled, the nano-amorphous formulation and the physical mixture had the same composition (18% AA, 71% Soluplus, 11% SDC)

Partcle size by DLS



Crystal structure by pXRD



Solymosi *et al.*, *Int. J. Pharm.*, vol. 532, no. 1, pp. 427–434, 2017.

*Determined by microscopy
**Assessment Report For Zytiga (abiraterone) Procedure No.: EMEA/H/C/002321

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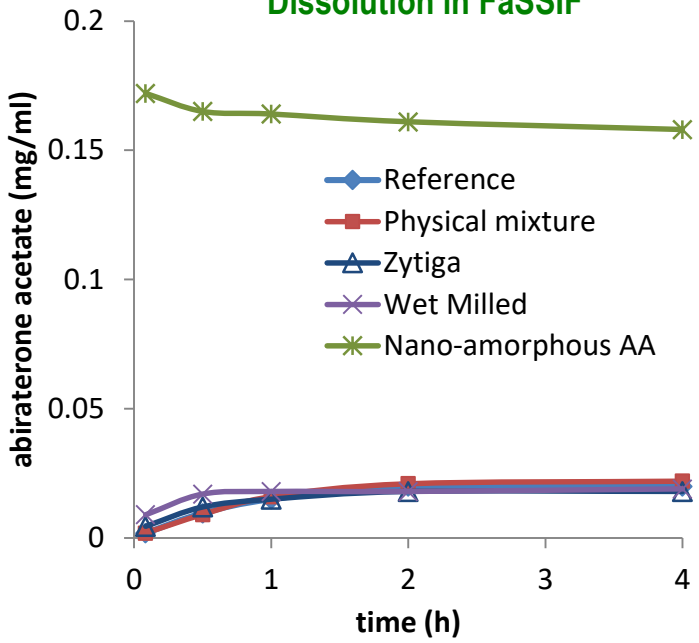
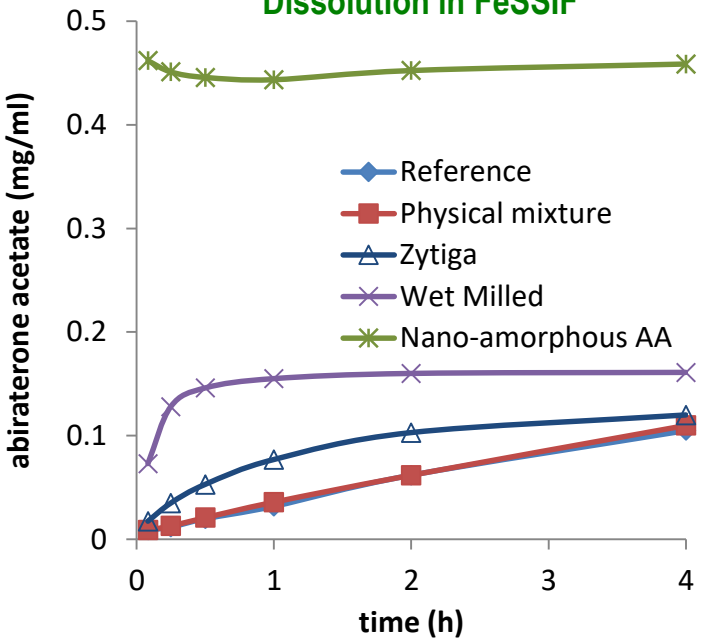
In vitro pharmacokinetics

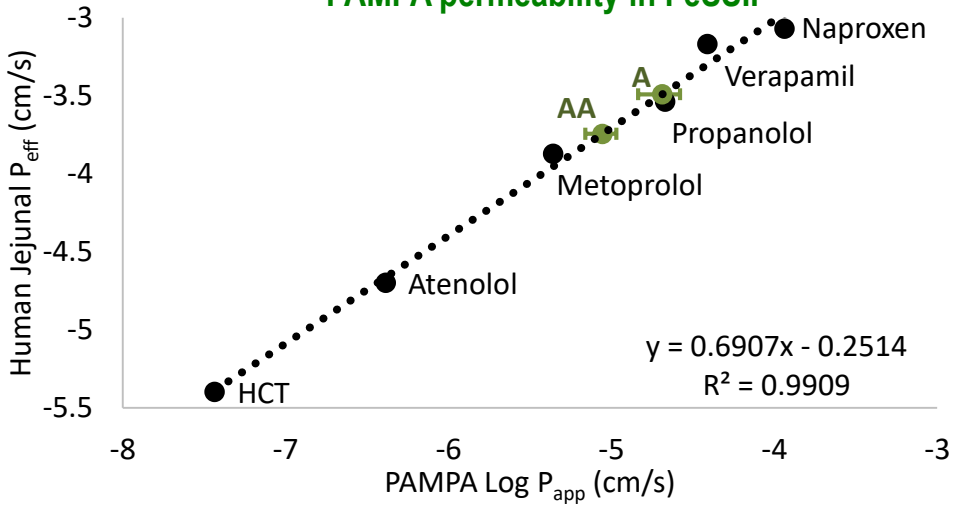
Dissolution in FaSSIF



Dissolution in FeSSIF



PAMPA permeability in FeSSIF



Particle size reduction improves t_{diss}, but leaves C_s the same. The nano-amorphous formulation improves both t_{diss} and C_s.

Permeability does not appear to be a rate limiting parameter of the absorption process.

Solymosi *et al.*, *Int. J. Pharm.*, vol. 532, no. 1, pp. 427–434, 2017.

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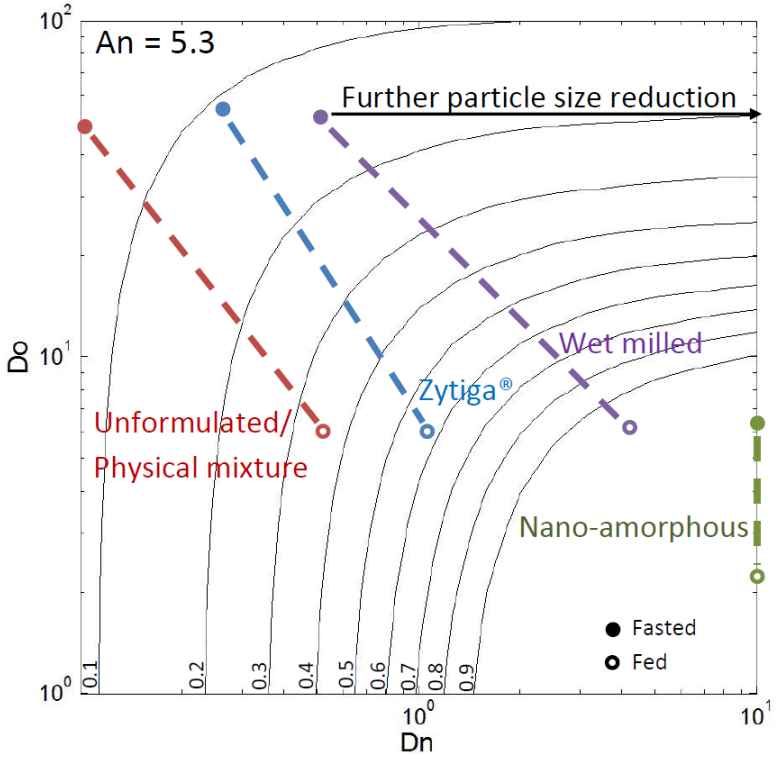
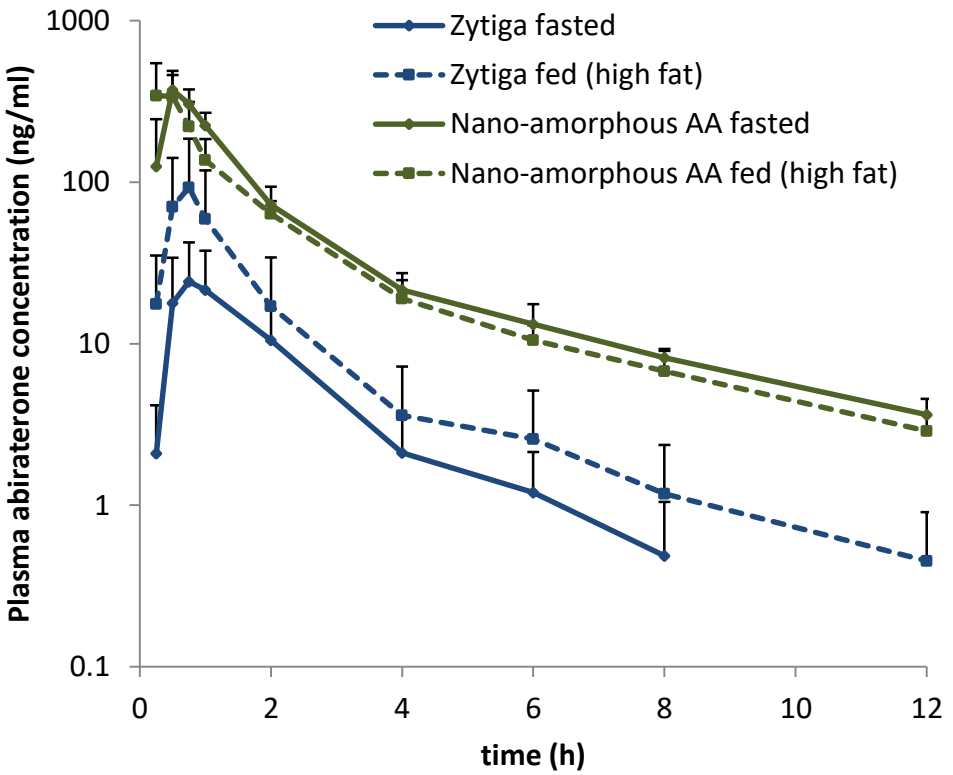
Absorption modelling and pharmacokinetics in beagle dogs





The concurrent increase of C_s (Do↓) and decrease of t_{diss} (Dn↑) is necessary for improved absorption in the fasted state.

	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} Nano-amorphous AA/ Zytiga® fasted	11.5	9.1
F_{rel} Nano-amorphous AA/ Zytiga® fed	1.7	1.6

Solymosi *et al.*, *Int. J. Pharm.*, vol. 532, no. 1, pp. 427–434, 2017.

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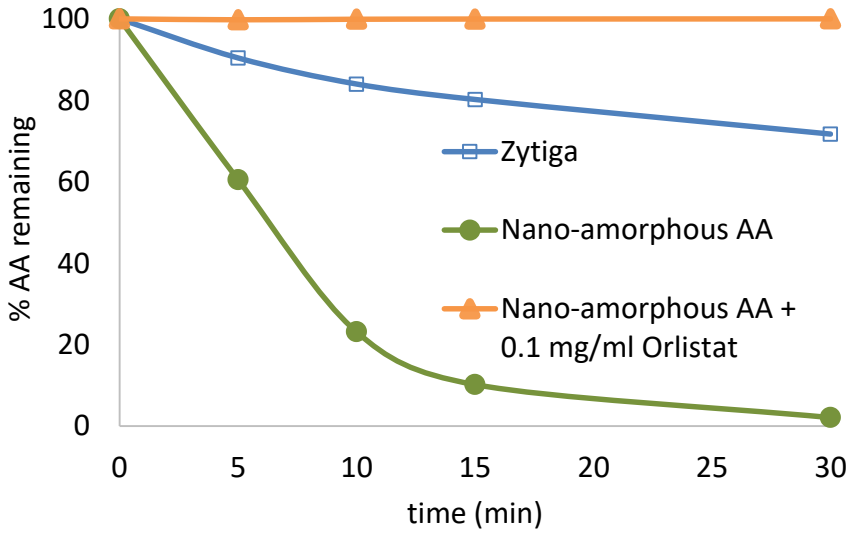
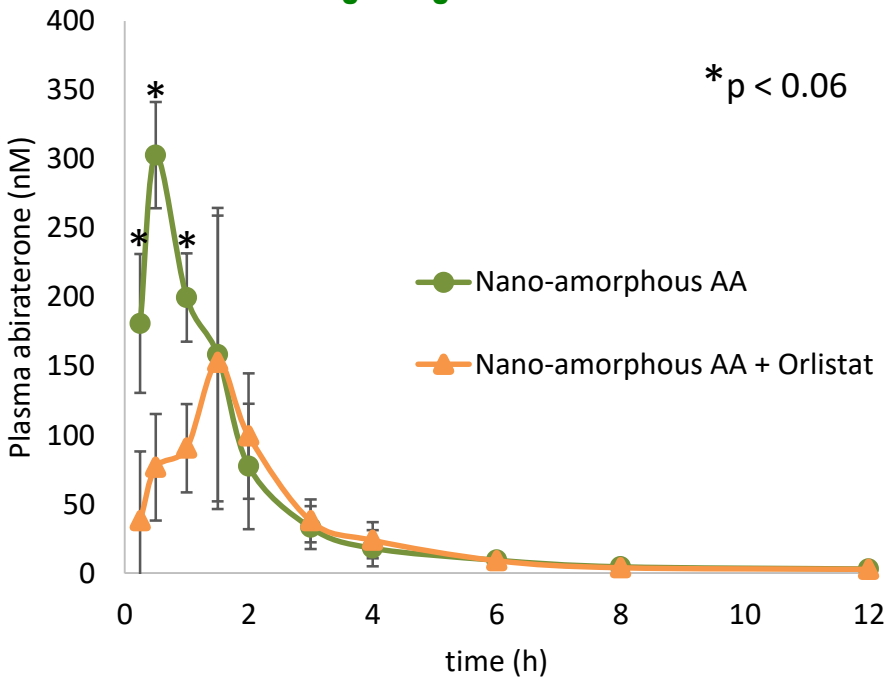
Cholesterol esterase (CE) hydrolysis and its inhibition in vitro and in vivo

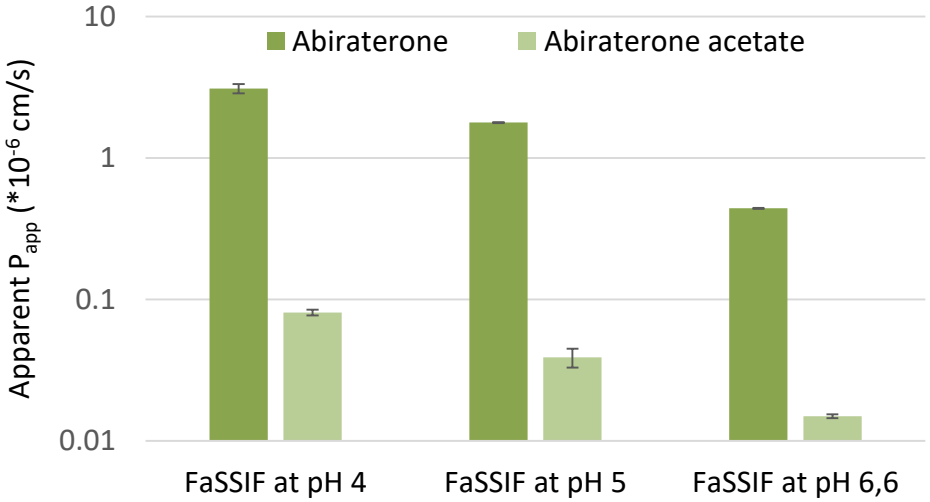
Enzymatic hydrolysis of AA (1 mg/ml) by 1 U/ml CE in vitro for Zytiga® and nano-amorphous AA with or without Orlistat in FaSSIF media



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



Apparent PAMPA permeability of A and AA when nano-amorphous AA is supplemented with 1 U/ml CE



Abiraterone acetate is rapidly converted to abiraterone in the intestine. The rapid absorption is dependent on this process.

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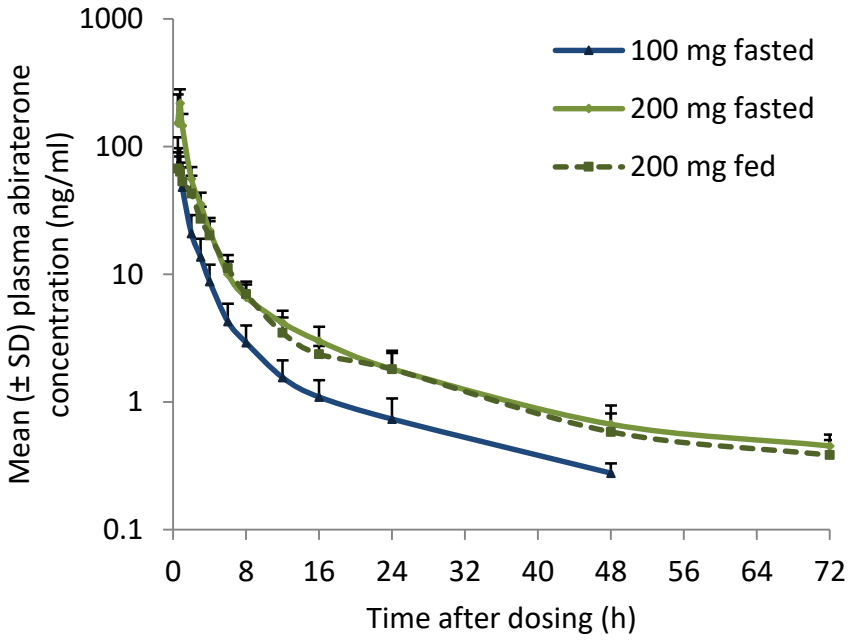
Clinical pharmacokinetics in comparision with historic Zytiga® data

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

200 mg oral dose of the nano-amorphous formulation resulted in 80 % of the AUC of 1,000 mg Zytiga. Food effect was eliminated and variability was reduced.

Solymosi *et al.*, *Cancer Chemother. Pharmacol.*, vol. 80, no. 4, pp. 723–728, 2017.

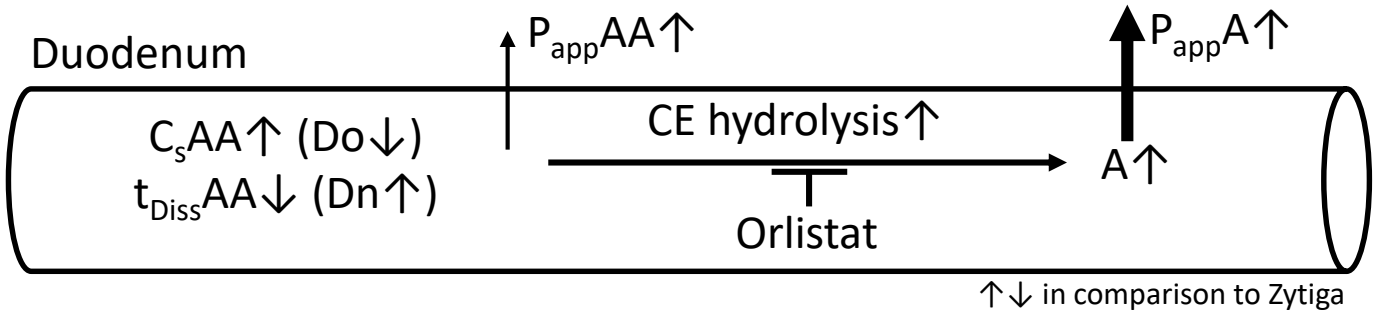
Conclusions

Objectives

- 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.

- In humans 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.

Mechanism



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Thank you for your attention!