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Development, preclinical evaluation and first-in-human clinical trial of a nano-amorphous abiraterone acetate formulation

Summary of PhD dissertation

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1. Introduction

33% of the drugs listed in the US Pharmacopeia are considered to be poorly water soluble. At a first glance this is not a huge number. However, if we consider the drugs in development and the new chemical entities, these numbers are 75% and 90%, respectively.[1] Conventional oral dosage forms containing the unformulated poorly soluble compounds usually exhibit low bioavailability due to the low solubility and slow dissolution of the API in aqueous media.

We can differentiate three methods to formulate poorly soluble active ingredients. First, the stable crystal structure of the active ingredient that is barely accessible to water molecules can be modified. This includes different salt formation methods, cocrystal development or simply the application of higher energy polymorphs or even the amorphous form. The second option is the reduction of particle size. With micronization the dissolution rate can be increased while with nanonization both apparent solubility and dissolution rate can be enhanced. The third option is the solubilization of the active ingredient. This involves the use of formulations in which the API is dissolved in some polymer matrix, surfactant or lipid or cyclodextrin complexes are formed. It is important to note that formulation methods may overlap or sometimes combinations of formulation methods are used.

Controlled precipitation is a simple method for producing nanoparticles of poorly soluble compounds. The core material (active ingredient) is dissolved in a water miscible organic solvent together with excipients and an antisolvent is added rapidly. As the equilibrium solubility of the solute decreases in the new medium, it gets supersaturated and precipitates out of solution. The supersaturated API and the stabilizers assemble in diffusion limited aggregation. Optimally, the excipients (preferably amphiphilic polymers, surfactants, etc…) applied prevent the growth of macroscopic crystals and a colloidal suspension is produced. The precipitation process is fast, nanoparticles are usually formed in the 10-millisecond time scale. Therefore, extremely fast mixing is desired to obtain homogenous supersaturation (and hence narrow particle size distribution) throughout the system. Usually nanoprecipitation processes yield particles with sub-200 nm average particle size.[2]

The nanosuspensions formed are not thermodynamically stable in most of the cases and Ostwald ripening will occur. Therefore, solidification is desired. Regular technologies, e.g.

[1] M. Rodriguez-Aller, D. Guillarme, J. L. Veuthey, and R. Gurny, "Strategies for formulating and delivering poorly water-soluble drugs," *J. Drug Deliv. Sci. Technol.*, vol. 30, pp. 342–351, 2015

[2] R. F. Pagels, J. Edelstein, C. Tang, and R. K. Prud'homme, "Controlling and Predicting Nanoparticle Formation by Block Copolymer Directed Rapid Precipitations," *Nano Lett.*, vol. 18, no. 2, pp. 1139–1144, 2018.

lyophilization or spray drying are available to create solid formulations of the precipitated colloids enabling the development of solid dosage forms and greatly increasing the stability.[3]

The technology is advantageous as it does not require an expensive instrument, process scale-up is very simple and the precipitation is performed at ambient temperature and pressure. However, for certain APIs (e.g. with logP < 6) Ostwald ripening is prominent and very high excipient:API ratios have to be used. Also, depending on the solid content of the suspensions produced, lyophilization or spray drying can be long and energy consuming, rendering a promising formulation industrially unviable.

Despite of its simplicity only one commercialized drug product has been formulated with precipitation: the active ingredient vemurafenib (Zelboraf®) was coprecipitated with the polymer HPMCAS, increasing the exposure in humans five-fold when compared to the crystalline drug.[4]

1.1. Abiraterone acetate in the treatment of prostate cancer

Prostate cancer is the most common non-skin cancer diagnosed in men in the EU and US with approximately 1 in 7 men being diagnosed with the disease in their lifetimes. Localized PC has extremely good prognosis, 5-year overall survival is above 99%. However, roughly 3-5% of the patients is present with metastatic disease at the time of diagnosis. Treatment options for metastatic prostate cancer were – and still remain – extremely limited, less than 30% of the patients are still alive 5 years after diagnosis.

Abiraterone is an androgen synthesis inhibitor steroid used for the treatment of metastatic castration resistant prostate cancer. The drug product Zytiga® was launched in 2011 containing the acetate ester prodrug of the active ingredient. Abiraterone treatment in combination with the steroid prednisone significantly improved overall survival, progression free survival and quality of life in this difficult-to-treat patient group.[5]

Abiraterone in its stable crystalline form is not druggable due to extremely low solubility in aqueous media. Abiraterone acetate is an ester prodrug hydrolyzed rapidly in the gastrointestinal lumen, in enterocytes and in the liver into the active ingredient abiraterone. The

[3] Y. Zhang, J. Feng, S. A. McManus, H. D. Lu, K. D. Ristroph, E. J. Cho, E. L. Dobrijevic, H. K. Chan, and R. K. Prud'Homme, "Design and Solidification of Fast-Releasing Clofazimine Nanoparticles for Treatment of Cryptosporidiosis," *Mol. Pharm.*, vol. 14, no. 10, pp. 3480–3488, 2017.

[4] N. Shah *et al.*, "Improved human bioavailability of vemurafenib, a practically insoluble drug, using an amorphous polymer-stabilized solid dispersion prepared by a solvent-controlled coprecipitation process," *J. Pharm. Sci.*, vol. 102, no. 3, pp. 967–981, Mar. 2013.

[5] C. J. Logothetis, E. Efstathiou, F. Manuguid, and P. Kirkpatrick, "Abiraterone acetate," *Nat. Rev. Drug Discov.*, vol. 10, no. 8, pp. 573–574, 2011.

transformation is so fast that the circulating abiraterone acetate concentration is negligible in plasma. It was reported, that after the rapid ester cleavage abiraterone concentrations exceeded the thermodynamic solubility of the compound in intestinal fluids by an order of magnitude. It is hypothesized that this increase in apparent solubility drives the absorption of the compound.[6]

Abiraterone acetate is reported to belong to BCS 4 group with low solubility and low permeability. The drug product Zytiga® contains abiraterone acetate in micronized form in order to increase the dissolution rate and hence the bioavailability of the compound. The recommended dose of Zytiga® is 1000 mg given as four 250 mg tablets. The tablets are to be taken without food to reduce inter-patient variability. However, the drug product has up to 10-fold higher exposure and up to 17-fold maximal plasma concentration (in healthy volunteers, depending on the fat content of the food consumed) when taken with meal, the single largest food effect of all marketed drugs.

It is evident that reducing or eliminating the food effect would significantly improve the quality of life of prostate cancer patients. Moreover, an increase in bioavailability would reduce the pill burden that in turn would improve adherence to therapy and ultimately yield better therapeutic outcomes. In summary, besides the economic advantages, both better quality of life and therapeutic outcome could be achieved by either an abiraterone or an abiraterone acetate formulation with increased bioavailability and reduced food effect.

1.2. Objectives

Despite of the well-known physicochemical and pharmacokinetic issues associated with abiraterone acetate, advanced formulations are extremely scarcely reported. We started the development of an advanced abiraterone acetate formulation with the primary objectives of increasing the bioavailability in the fasted state and eliminating the food effect associated with Zytiga®. The work focused on the controlled precipitation of abiraterone acetate. The following aims and objectives were set:

- development of a versatile high throughput (HT) precipitation screening method that can be applied to any poorly soluble APIs in order to find stable nanoformulations;
- identification of the disadvantageous properties of abiraterone acetate *in vitro*. This included solubility measurements, thermoanalytical and crystallographic characterization of abiraterone acetate;

[6] J. Stappaerts, S. Geboers, J. Snoeys, J. Brouwers, J. Tack, P. Annaert, and P. Augustijns, "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

- utilization of the HT screening platform for abiraterone acetate. Scale-up and optimization of the formula and production transfer to continuous flow method;
- *in vitro* characterization of the optimized nanoprecipitated abiraterone acetate and comparison to the micronized drug product Zytiga® and to a nanomilled formulation;
- *in vivo* evaluation of the nanoprecipitated formula in dog studies and comparison to the drug product Zytiga®;
- conduction of a proof of concept Phase I clinical trial.

2. Materials and methods

2.1. Materials and production methods

The unformulated and micronized abiraterone acetate were ordered from LeapChem and Olon S.p.A., respectively. Zytiga® tablets were purchased in a local pharmacy.

2.1.1. Production of nano-amorphous abiraterone acetate formulation

The nano-amorphous formulation was prepared with controlled precipitation method in a continuous flow instrument. Abiraterone acetate was dissolved in THF together with the polymer Soluplus. The API was precipitated with aqueous sodium deoxycholate solution. The resulting colloid was lyophilized.

2.1.2. Production of the nanomilled abiraterone acetate formulation

For comparison with the nanoprecipitated formula, a nanomilled abiraterone acetate was produced by wet milling method. The composition of the wet milled sample was identical to the composition of nano-amorphous abiraterone acetate prepared by precipitation.

2.2. Analytical methods

2.2.1. HPLC assay

Chemical stability test and active content determination was performed by HPLC measurement.

2.2.2. Apparent solubility measurement

The apparent solubility of the redispersed formulations was monitored by filtration with 450 nm filter followed by quantification of the active ingredient in the filtrate.

2.2.3. Particle size analysis

Particle size of the reconstituted formulations was measured by dynamic light scattering and scanning electronmicroscopy.

2.2.4. Solid state characterization

The formulation was characterized with powder X-ray diffraction method. Moreover, thermal analysis by temperature modulated DSC was performed to investigate melting point and/or glass transition temperature of the samples.

2.2.5. Residual solvent and water content

Residual THF in the solid formula was quantified by head space gas chromatography while water content was determined by Karl-Fischer titration.

2.2.6. Passive permeability

Passive permeability of the formulation was evaluated using double sink PAMPA. The formulation was reconstituted in biorelevant media in the donor compartment. The membrane was composed of dodecane containing 20% lecithin. The receiver compartment was phosphate buffer containing 1% sodium dodecyl sulfate.

2.2.7. Dissolution tests

Dissolution of the test items was measured in fasted and fed state simulating intestinal fluids.

2.3. Absorption modeling

A mathematical model of absorption was set up using dissolution and permeability data obtained from *in vitro* tests. The fraction dose absorbed was calculated for the test items (unformulated API, the micronized API, the physical mixture of the API and the excipients, the nanomilled sample and the nano-amorphous sample prepared by precipitation).

2.4. Dog study protocol

The pharmacokinetic parameters after oral dosing of the nano-amorphous formulation and the drug product Zytiga® were evaluated in beagle dogs in fasted and fed states. The dose administered was 50 mg for both the nano-amorphous formulation and for Zytiga®.

2.5. Clinical trial

A proof of concept Phase 1 clinical trial was conducted with healthy male volunteers. The nano-amorphous abiraterone acetate formulation was administered as an oral suspension at 100 mg and 200 mg dose in the fasted state and at 200 mg dose following a standard high-fat breakfast.

3. Results and discussion

3.1. Development and characterization of the nano-amorphous abiraterone acetate

A new high throughput screening platform was developed (based on precipitation, followed by lyophilization and reconstitution of the solid product) for the formulation of poorly water-soluble compounds. The platform identified drug-excipient preformulations that dispersed well in water forming stable nanoparticles with particle size in the lower nano range. These compositions might behave as quasi-BCS 1 compounds *in vivo* after optimization and scale-up, overcoming the pharmacokinetic issues associated with poorly soluble compounds. Over 3000 compositions could be tested with only 100 mg API in two days.

The active ingredient abiraterone acetate was thoroughly characterized *in vitro*. It was concluded that absorption of the compound was hindered by extremely low solubility in biorelevant medium simulating the fasted intestine. The biorelevant solubility and permeability measurements correlated well with the huge food effect observed in clinical trials.

The HT screening platform was utilized in order to find abiraterone acetate nanoformulations that could keep the active ingredient highly supersaturated to enable absorption. A composition was found containing the polymer Soluplus and the surfactant sodium deoxycholate that exhibited increased apparent solubility and passive permeability compared to the reference API. The formulation was scaled up and a lyophilized powder-in-bottle dosage form was developed. The formulation dispersed well in water and could easily be administered orally.

The powder-in-bottle formulation was characterized using *in vitro* assays. Mean particle size of the reconstituted colloid was 140-180 nm by dynamic light scattering method. The material was amorphous by XRD. DSC measurements supported that the active was amorphous in the composition. Apparent solubility and permeability measurements showed an order of magnitude increase compared to the micronized abiraterone acetate. HPLC showed no degradation or byproducts after formulation. Residual solvent content was below 5 ppm.

Stability tests yielded identical performance at 4°C and room temperature for at least 1 month. However, storing the formulation at 40°C for two weeks resulted in the re-crystallization of abiraterone acetate from the nano-amorphous state. This could be predicted by the relatively low glass transition temperature ($T_g \approx 50°C$) of the solid formulation.

3.2. Absorption modeling

Comparative *in vitro* tests were performed on the crystalline API, the physical mixture (containing the API, Soluplus and sodium deoxycholate), the drug product Zytiga®, the nanomilled material and the nano-amorphous sample. All samples (excluding the nano-amorphous material) proved to be crystalline. Moreover, dissolution tests in biorelevant media revealed one order of magnitude higher apparent solubility for the nano-amorphous abiraterone acetate when compared to all other test items. Based on the *in vitro* results, the fraction dose absorbed was calculated. The contour plot with the test items in fasted and fed states is shown on Figure 1. The model predicted low absorbed abiraterone acetate percent in the fasted state and huge positive food effect for all samples with the exception of the nano-amorphous formulation. Based on the absorption model we expected very high fraction absorbed and eliminated food effect for the formulation.

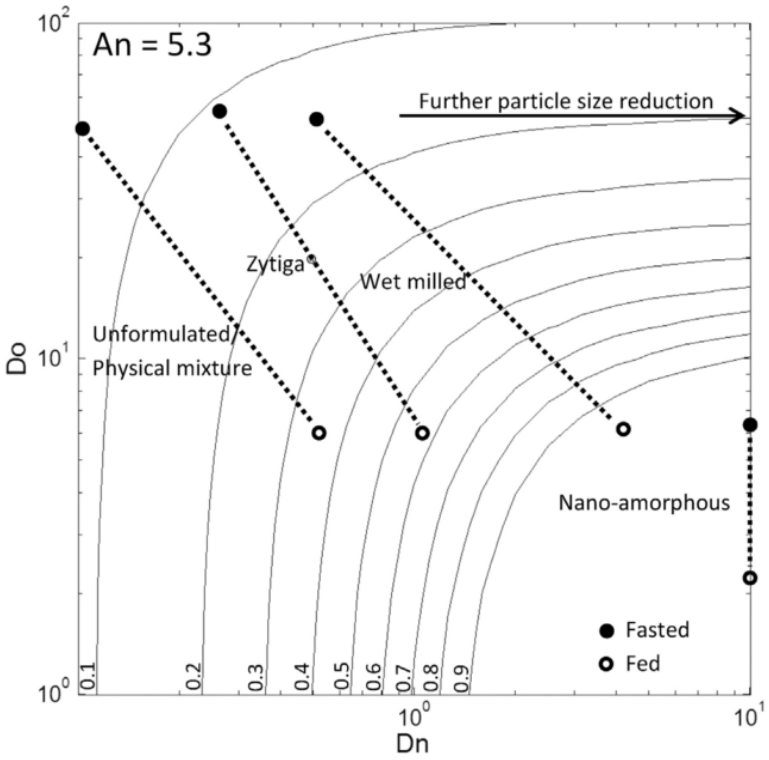

Figure 1. Contour plot of fraction dose absorbed. Corresponding fasted and fed points are connected with a dashed line.

3.3. Beagle dog study results

Zytiga® and the nano-amorphous formulation were administered to beagle dogs after overnight fasting and after standard high fat meal. Pharmacokinetic parameters are summarized in Table 1 while the PK curve is shown on Figure 2. Zytiga® yielded 5.6-fold higher exposure in the fed state compared to the fasted state exhibiting huge food effect, comparable to the one observed

in clinical trials. The nano-amorphous abiraterone acetate showed 2-fold and 11-fold exposure increase over Zytiga® in fasted and fed state, respectively.

Table 1. Pharmacokinetic parameters following the oral administration of 50 mg Zytiga® or nano-amorphous AA to beagle dogs in the fasted state or following a high-fat meal (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

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

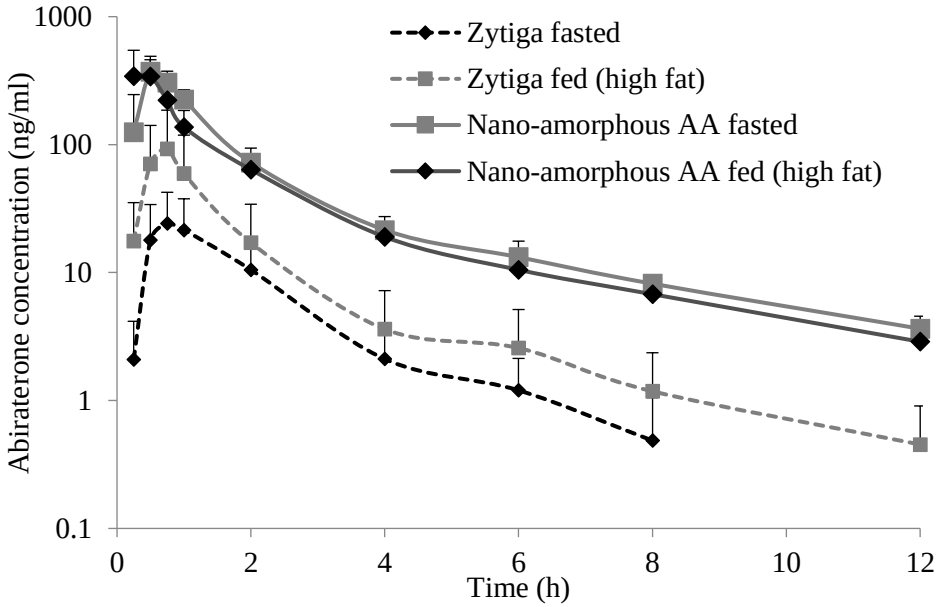

Figure 2. Mean (±S.D.) plasma concentrations of abiraterone following oral administration of 50 mg Zytiga® or nano-amorphous abiraterone acetate to beagle dogs in the fasted or fed state following a high-fat meal (N=4)

3.4. Clinical trial results

The Phase I clinical trial was completed with 9 subjects. There were no serious adverse events or deaths reported during this study. All adverse events were assessed as mild and unrelated to the drug product. Following the administration of the nano-amorphous abiraterone acetate, the mean abiraterone plasma concentrations increased rapidly to peak and declined in a biphasic

manner (Figure 3). Mean t_{max} occurred within 1 h regardless of dose or prandial status. For the 200 mg dose, abiraterone was detectable in plasma for up to 72 h (>0.2 ng/ml), while for the 100 mg dose, it was detectable for up to 48 h. The calculated pharmacokinetic parameters were compared to literature data available across multiple studies for Zytiga® (Table 2).[7]

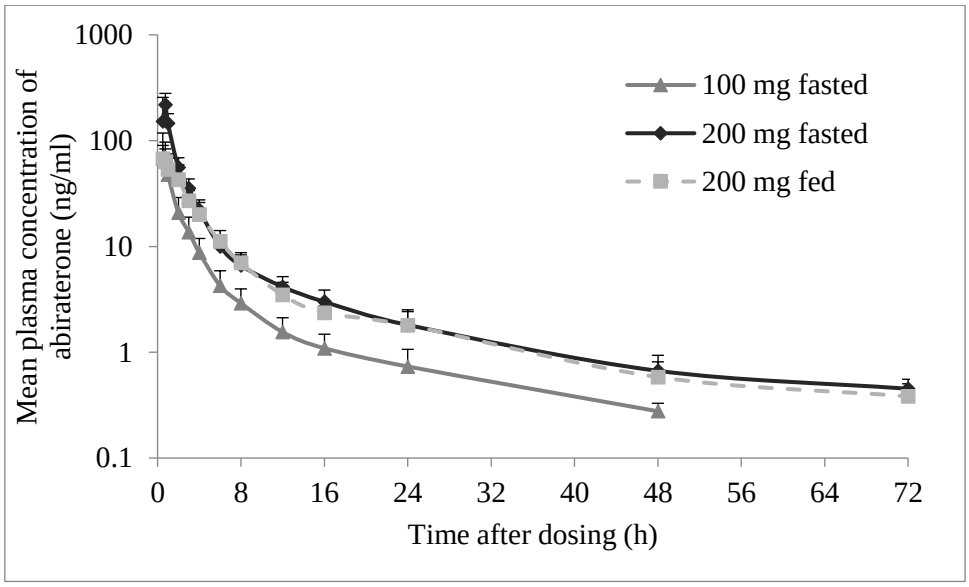

Figure 3. The mean (SD) of plasma abiraterone concentrations

Table 2. Pharmacokinetic parameters in healthy volunteers of the present study in comparison with historic pharmacokinetic data across multiple studies for 1000 mg Zytiga® administered in the fasted state

Parameter	100 mg dose fasted (N=10)	200 mg dose fasted (N=9)	200 mg 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} (ng·h/ml), mean (CV%)	158 (39)	397 (28)	292 (23)	N.A.
AUC_{inf} (ng·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)

*precise calculation of t_{max} was not possible. (N.A.: not available)

Following the administration of 100 mg of the novel formulation in the fasted state, C_{max} and AUC_{inf} were 88% and 33% of that following the administration of 1000 mg Zytiga®, respectively. At 200 mg dose of the formulation, C_{max} exceeded that of 1000 mg Zytiga® by

[7] FDA, "Abiraterone acetate - Clinical Pharmacology and Biopharmaceutics Review (NDA 202-379 Review)," 2010.

over twofold, while AUC was 81% of the 1000 mg Zytiga®. Increasing the dose from 100 mg to 200 mg resulted in a 2.5-fold increase in AUC, which was greater than dose proportional and statistically significant. Inter-subject variability was also reduced from 59% (Zytiga®) to 38% (100 mg dose) and 29% (200 mg dose). Food slightly delayed absorption. Interestingly a slight, albeit statistically significant food effect was observed, C_{max} and AUC were reduced by 59% and 26%, respectively, when dosing in the fed state.

Although the proof-of-concept study reported here was not a direct comparison to the marketed drug, it allowed the estimation of the improvement the novel formulation could deliver in exposure, variability and food effect. Overall, we expect 250 mg dose of the nano-amorphous formulation to yield identical exposure to 1000 mg Zytiga® with lower variability and reduced or eliminated food effect.

4. Theses

1. A new platform was developed based on controlled precipitation for the formulation of poorly water soluble active ingredients. The process was scaled-up from high throughput screening to pilot plant scale production. Numerous active ingredients were successfully formulated using the technology.
   Related papers: I, V
   Related patents: VIII, X, XI
2. We identified the physicochemical reasons of the poor bioavailability and significant food effect of abiraterone acetate. A nanoformula was developed based on controlled precipitation that outperformed both the crystalline active and the marketed drug product Zytiga® in apparent solubility, apparent permeability and biorelevant dissolution tests.
   Related papers: II, IV
   Related patent: IX
3. Mathematical simulation of the absorption process showed that that simply increasing the dissolution rate of abiraterone acetate is insufficient to increase the bioavailability of the formulation. Increase in apparent solubility is required to reach a meaningful increase in bioavailability of the active ingredient.
   Related paper: IV
4. The *in vitro* results were validated in beagle dog pharmacokinetic studies. The novel formula showed one order of magnitude higher bioavailability in the fasted state when compared to the marketed drug product Zytiga®.
   Related paper: IV
   Related patent: IX
5. The advantageous properties of the novel formulation were translated from *in vitro* and preclinical *in vivo* tests to a first-in-human Phase I clinical trial. The bioavailability of the novel formulation containing 250 mg abiraterone acetate was practically identical to 1000 mg Zytiga® with no positive food effect. Interestingly, a slight, but statistically significant negative food effect was observed.
   Related paper: III

5. Application of the results

A universal high throughput screening method has been developed for the rapid precipitation screening of poorly soluble compounds. It was shown that the technology is scalable and the resulting drug product can outperform commercial drug formulations.

A novel abiraterone acetate formulation has been described with detailed *in vitro* and *in vivo* evaluation. Based on the Phase 1 study results approximately 250 mg dose of the novel formulation is predicted to result in the same exposure as 1000 mg Zytiga® in the fasted state. The substantial positive food effect seen for Zytiga® is expected to be eliminated. This might allow the reduction of the dose and could eliminate the requirement of taking the drug on an empty stomach. Also, the novel formulation is expected to exhibit smaller variability when compared to Zytiga®. Recent clinical studies indicate that there is a relationship between steady state abiraterone trough concentrations and progression free survival in metastatic prostate cancer patients. In general, higher abiraterone concentrations result in more efficient treatment. The novel formulation might allow the increase of abiraterone acetate dose with more precise control of abiraterone plasma levels. This could not be achieved with Zytiga®, as exposure showed a plateau at the 750-2000 mg dose range. In conclusion, treatment outcomes of metastatic prostate cancer patients using the abiraterone acetate formulation developed might be superior compared to the currently available therapies.

6. Publications

6.1. Original research papers in peer reviewed journals:

I. T. Solymosi, R. Angi, O. Basa-Dénes, S. Ránky, Z. Ötvös, H. Glavinas, G. Filipcsei, and G. Heltovics, "Sirolimus formulation with improved pharmacokinetic properties produced by a continuous flow method," *Eur. J. Pharm. Biopharm.*, vol. 94, pp. 135–140, 2015., IF = 4.51

II. T. Solymosi, O. Basa-Dénes, R. Angi, F. Tóth, J. Orosz, T. Jordán, Z. Ötvös, and H. Glavinas, "Solubility measurement, thermoanalytical and crystallographic characterization of abiraterone and abiraterone acetate," *J. Chem. Eng. Data,* vol. 63, no. 12, 2018., IF = 2.32

III. T. Solymosi, Z. Ötvös, R. Angi, B. Ordasi, T. Jordán, L. Molnár, J. McDermott, V. Zann, A. Church, S. Mair, G. Filipcsei, G. Heltovics, and H. Glavinas, "Novel formulation of abiraterone acetate might allow significant dose reduction and eliminates substantial positive food effect," *Cancer Chemother. Pharmacol.*, vol. 80, no. 4, pp. 1–6, Aug. 2017., IF = 2.81

IV. T. Solymosi, Z. Ötvös, R. Angi, B. Ordasi, T. Jordán, S. Semsey, L. Molnár, S. Ránky, G. Filipcsei, G. Heltovics, H. Glavinas, L. Molnár, G. Filipcsei, G. Heltovics, and H. Glavinas, "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, Sep. 2017., IF = 4.22

V. R. Angi, T. Solymosi, Z. Ötvös, B. Ordasi, H. Glavinas, G. Filipcsei, G. Heltovics, and F. Darvas, "Novel continuous flow technology for the development of a nanostructured Aprepitant formulation with improved pharmacokinetic properties," *Eur. J. Pharm. Biopharm.*, vol. 86, no. 3, pp. 361–368, 2014., IF = 4.51

VI. R. Angi, T. Solymosi, N. Erdősi, T. Jordán, B. R. Kárpáti, O. Basa-Dénes, A. Ujhelyi, J. McDermott, C. Roe, S. Mair, Z. Ötvös, L. Molnár, and H. Glavinas, "Characterization, pre-clinical and clinical evaluation of a novel rapidly absorbed celecoxib formulation," *AAPS PharmSciTech,* vol. 20, no. 2, pp. 90, 2019., IF = 2.67

VII. O. Basa-Dénes, T. Solymosi, Z. Ötvös, R. Angi, A. Ujhelyi, T. Jordán, G. Heltovics, and H. Glavinas, "Rapid dissolution and absorption of a nano-amorphous abiraterone acetate formulation is driven by elevated intestinal conversion to abiraterone," *Eur. J. Pharm. Sci.,* vol. 129, pp. 79-86., 2019., IF = 3.47

6.2. Patents granted:

VIII. R. Angi, T. Solymosi, R. B. Kárpáti, Z. Fenyvesi, Z. Ötvös, L. Molnár, H. Glavinas, G. Filipcsei, K. Ferenczi, G. Heltovics: Complexes of Fulvestrant and its derivatives, process for the preparation thereof and pharmaceutical compositions containing them; Priority date: 12 November 2013; WO2015/071836A1; Granted in the EU

IX. R. Angi, T. Jordán, O. Basa-Dénes, T. Solymosi, Z. Ötvös, H. Glavinas, G. Filipcsei: Complexes of Abiraterone acetate, process for the preparation thereof and pharmaceutical compositions containing them; Priority date: 9 February 2015; WO2016/128891; Granted in the US, EU and Singapore

X. R. Angi, T. Solymosi, R. B. Kárpáti, Z. Fenyvesi, Z. Ötvös, L. Molnár, H. Glavinas, G. Filipcsei, K. Ferenczi, G. Heltovics: Complexes of Sirolimus and its derivatives, process for the preparation thereof and pharmaceutical compositions containing the the them; Priority date: 14 February 2014; WO2015/121836; Granted in Australia

XI. R. B. Kárpáti, G. Patyi, O. Basa-Dénes, R. Angi, T. Jordán, T. Solymosi, H. Glavinas, G. Filipcsei: Complexes of ivacaftor and its salts and derivatives, process for the preparation thereof and pharmaceutical compositions containing them; Priority date: 25 April 2016, WO2017/187336; Granted in the US

6.3. Presentations:

XII. T. Solymosi, L. Molnár: *Nanoformulációk nagy áteresztőképességű (HT) szűrése*, MTA Kolloidkémiai Munkabizottság Ülés, Velence, Hungary, 4-5 June 2015

XIII. T. Solymosi, O. Basa-Dénes, R. Angi, T. Jordán, Zs. Ötvös, H. Glavinas: *Nano-amorf abirateron acetát formula növekedett biohasznosulással és eliminált ételhatással*, MKE Kristályosítási Kerekasztal, Balatonszemes, Hungary, 4-5 May 2018

XIV. T. Solymosi, Zs. Ötvös, R. Angi, O. Basa-Dénes, T. Jordán, H. Glavinas: *Nano-amorphous abiraterone acetate formulation with improved bioavailability and eliminated food effect*, 12th Nano Drug Delivery 2018, Dublin, Ireland, 16-18 August 2018

6.4. Conference posters:

XV. R. Angi, T. Solymosi, Zs. Ötvös, B. Ordasi, H. Glavinas, G. Filipcsei, G. Heltovics and F. Darvas, *Physicochemical and in vitro pharmacokinetic comparison of traditional nanomilled and novel NanoActive drug formulations*, 8th World Meeting on Pharmaceutics, Biopharmaceutics and Pharmaceutical Technology, 19-22 March 2012, Istambul, Turkey

XVI. R. Angi, T. Solymosi, Zs. Ötvös, B. Ordasi, H. Glavinas, G. Filipcsei, G. Heltovics and F. Darvas, *Pharmacokinetic evaluation of novel formulations of poorly soluble drugs prepared by controlled continuous flow precipitation*, 3rd International Congress BioNanoMed, 2 March 2012, Krems, Austria

XVII. T. Solymosi, R. Angi, T. Jordán, B. Szabóné, B. Kárpáti, Zs. Ötvös, L. Molnár, H. Glavinas, G. Filipcsei, *Scalable continuous flow technology for the development of pharmaceutical nanoformulations*, 5th Conference on Frontiers in Organic Synthesis Technology, Budapest, Hungary, 21 - 23 October 2015

XVIII. H. Glavinas, T. Solymosi, R. Angi, O. Basa-Dénes, T. Jordán, Zs. Ötvös, G. Heltovics: *Rapid absorption of nano-amorphous abiraterone acetate is driven by improved dissolution and accelerated conversion of the drug to abiraterone in the intestine,* 11th World Meeting on Pharmaceutics, Biopharmaceutics and Pharmaceutical Technology, Granada, Spain, 19 - 22 March 2018