NANO-AMORPHOUS ORAL SIROLIMUS FORMULATION EXHIBITS LOW INTER-INDIVIDUAL VARIABILITY AND IMPROVED EXPOSURE

Orsolya Basa-Dénes[1], Réka Angi[1], Balázs Kárpáti[1], Tamás Jordán[1], Tamás Solymosi[1], John McDermott[2], Chris Roe[2], Litza McKenzie[2], Gábor Heltovics[3] and Hristos Glavinas[1]

[1]NanGenex Inc., H-1138 Budapest, Madarász V. u. 47-49., Hungary

[2]Quotient Sciences Ltd., Mere Way, Ruddington, Nottingham, NG11 6JS, United Kingdom

[3]Druggability Technologies Holdings Ltd., Regional Business Centre, University Heights, Msida MSD, 1751, Malta

Introduction and objectives

- Sirolimus (SIR) is indicated for the prophylaxis of organ rejection in patients receiving renal transplants. The marketed formulation (Rapamune®) exhibits low bioavailability, high variability and a moderate food effect. This makes therapeutic blood monitoring of sirolimus levels necessary for patients. Also, reaching the therapeutic blood sirolimus concentrations in renal cancer patients was found to be challenging when the marketed drug was administered alone, therefore, temsirolimus, a prodrug of sirolimus is administered intravenously in these patients [1], [2].
- The objective of this work was to develop a SIR formulation with improved bioavailability in the fasted state which could eliminate the variability, food effect and could be an oral alternative to intravenous temsirolimus.

Methods

- SIR formulation was compared to (Rapamune®) by in vitro and in vivo tests.
- In vitro solubility, permeability and stability measurements were performed in biorelevant media.
- In vivo pharmacokinetic studies in rats and in humans were conducted.

Results

- Particles size of the redispersed colloid solution were less than 100 nm.
- Stable amorphous solid form
- Improved apparent solubility and permeability when compared to Rapamune®.
- The solid form redispersed instantaneously in water and was stable in biorelevant media.
- Improved pharmacokinetics following oral administration to rats [3].
- In a phase I clinical dose escalation study roughly dose proportional increases of C_{max} and $AUC_{0\text{-}48h}$ up to 10 mg.
- Mean AUC_{inf} at the 40 mg dose in the fasted state was 28% higher than AUC reported following the administration of 90 (2x45) mg Rapamune® and 11% higher than the exposure reported for 25 mg intravenous temsirolimus.
- Variability observed was significantly lower than for Rapamune®.

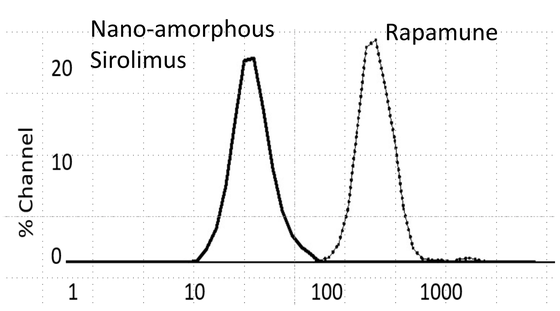
Conclusions

- The PK properties of the nano-amorphous formulation were improved when compared to the marketed formulation.
- The low variability observed might make therapeutic blood monitoring unnecessary.
- Increased exposure could allow the replacement of intravenous temsirolimus with an oral sirolimus alternative for cancer patients.

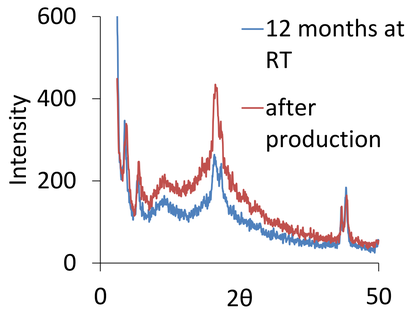
References

[1] Sehgal SN. et al., Transplant Proc. 2003;35:7S–14S.
[2] Cohen EEW, et al., Clin Cancer Res. 2012;18:4785–93.
[3] Solymosi T, et al., Eur, J. Pharm. Biopharm. 2015, 94, 135–140.
[4] Jimeno et al., J Clin Oncol. 2008 Sep 1;26(25):4172-9.
[5] Böttiger et al., Clin Pharmacol Ther. 2001 Jan;69(1):32-40.

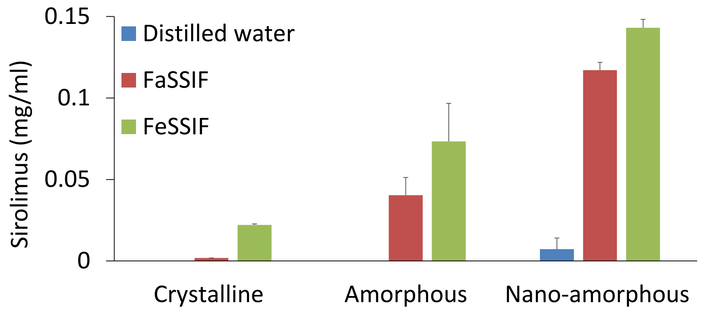
Particle size



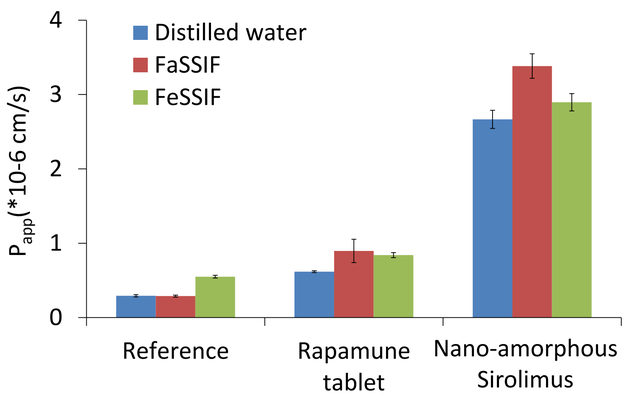
Solid form stability



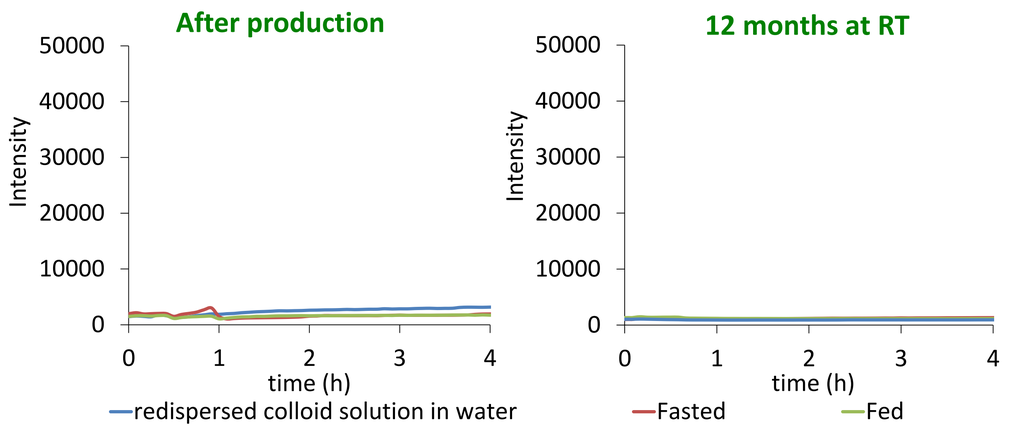
Apparent solubility



PAMPA permeability

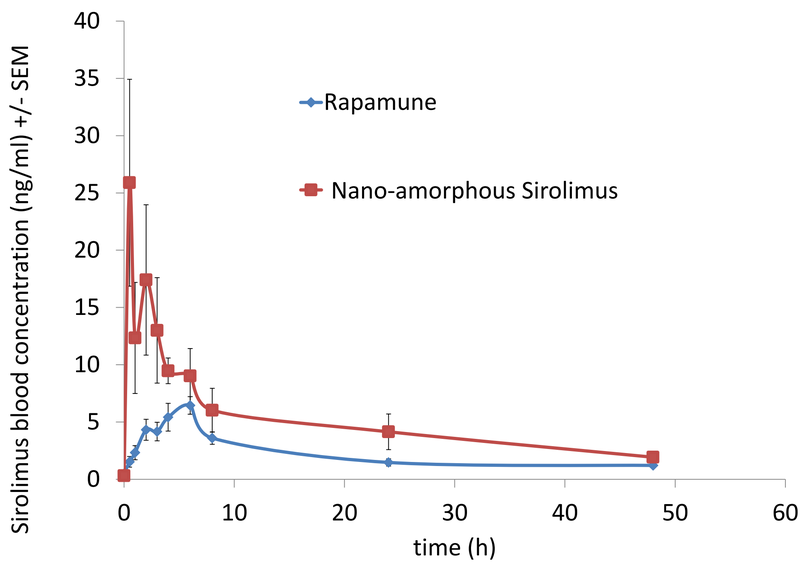


Colloid stability in biorelevant media*



*measured by nephelometry

Rat pharmacokinetics in comparision with Rapamune®

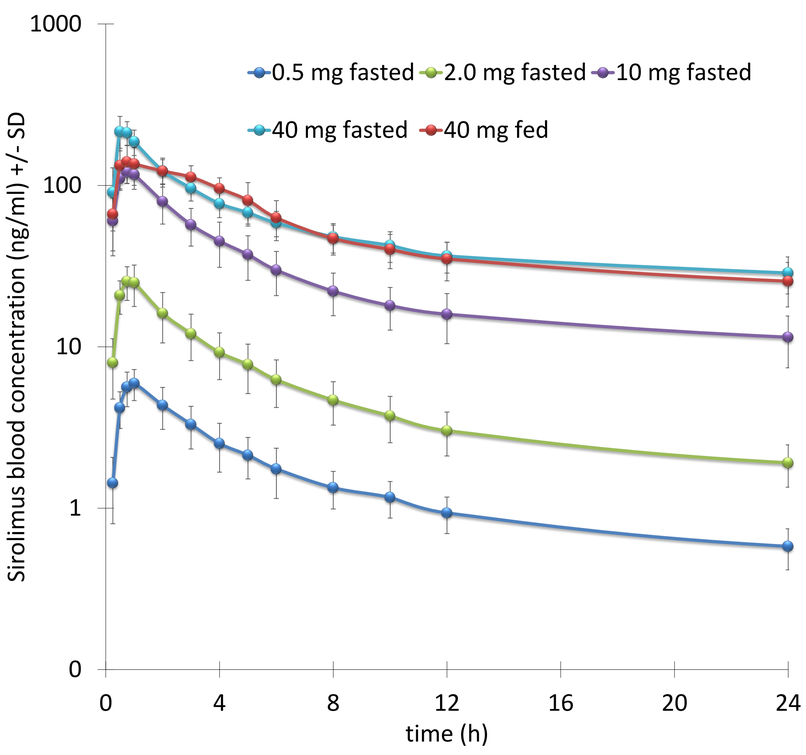


Pharmacokinetic parameters following the oral administration of 1 mg/kg Rapamume® or nano-amorphous SIR to rats. N=4

Test compound	C_{max} (ng/ml)	$C_{24h(trough)}$ (ng/ml)	t_{max} (h)	AUC_{inf} (ng/ml*h)	F_{rel} (%)
Rapamume®	6.9±0.3	1.47±0.31	4.8±0.4	144±14	
Nano-amorphous Sirolimus	25.9±9.0*	4.15±1.55**	0.5±0.0***	307±59*	209

*: $p < 0.05$ **: $p < 0.1$ ***: $p < 0.005$

Clinical pharmacokinetics in comparision with Rapamune® literature data



Oral Nano-amorphous Sirolimus		Oral Rapamune		Intravenous Temsirolimus	
Doses	$AUC_{0\text{-}inf}$ (h*ng/ml)	Doses	$AUC_{0\text{-}inf}$ (h*ng/ml)	Doses	$AUC_{0\text{-}inf}$ (h*ng/ml)
2mg	278 ± 86	2mg	65.3 ± 69.1 [4]		
10mg	1497 ± 578	10mg	736 (317-1487) [5] 615(130) [2]		
40mg	4300 ± 1083 (unfed)	60mg	3,142 (1,680) [2] 2,054 (1,123) [2][1]	25mg	3810
	3922 ± 1226 (fed)		3,677 (1,460) [2][2]		
		90mg	3,356 (138)[3]		

Note: All Super-Sirolimus data is from the Phase I trial, all Rapamune data is from published literature [4] [5] [6]
1- Two doses of 30mg delivered 4 hours apart
2- Two doses of 30mg delivered 24 hours apart
3 – Two doses of 45mg delivered 24 hours apart