EUROPEAN HEMATOLOGY ASSOCIATION
haematologica
Journal of the European Hematology Association

Phase I study of the heparanase inhibitor Roneparstat: an innovative approach for multiple myeloma therapy

by Monica Galli, Manik Chatterjee, Mariella Grasso, Giorgina Specchia, Hila Magen, Hermann Einsele, Ivana Celeghini, Paola Barbieri, David Paoletti, Silvia Pace, Ralph D. Sanderson, Alessandro Rambaldi, and Arnon Nagler

Haematologica 2018 [Epub ahead of print]

Citation: Monica Galli, Manik Chatterjee, Mariella Grasso, Giorgina Specchia, Hila Magen, Hermann Einsele, Ivana Celeghini, Paola Barbieri, David Paoletti, Silvia Pace, Ralph D. Sanderson, Alessandro Rambaldi, and Arnon Nagler. Phase I study of the heparanase inhibitor Roneparstat: an innovative approach for multiple myeloma therapy.
Haematologica. 2018; 103:xxx
doi:10.3324/haematol.2017.182865

Phase I study of the heparanase inhibitor Roneparstat: an innovative approach for multiple myeloma therapy

Monica Galli[1], Manik Chatterjee[2], Mariella Grasso[3], Giorgina Specchia[4], Hila Magen[5], Hermann Einsele[2], Ivana Celeghini[3], Paola Barbieri[6], David Paoletti[6], Silvia Pace[7], Ralph D. Sanderson[8], Alessandro Rambaldi[1,9] and Arnon Nagler[5]

[1]Hematology and Bone Marrow Transplant Unit, Azienda Ospedaliera Papa Giovanni XXIII, Bergamo, Italy

[2]Universitätsklinik Würzburg, Medizinische Klinik und Poliklinik II, Würzburg, Germany

[3]S.C Ematologia, ASO S.Croce e Carle, Cuneo, Italy

[4]U.O Complessa di Ematologia con Trapianto, A.O. Universitaria Policlinico Consorziale di Bari, Italy

[5]Division of Hematology, Chaim Sheba Medical Center, Tel Hashomer, Israel

[6]Leadiant Biosciences SA, Mendrisio, Switzerland

[7]Alfasigma SpA, Pomezia (Rome), Italy

[8]University of Alabama at Birmingham, USA

[9]Department of Oncology and Hematology-Oncology, University of Milan, Italy

Corresponding author: monicagalli@asst-pg23.it

The role that bone marrow microenvironment plays in differentiation, migration, proliferation, survival and drug resistance of malignant plasma cells has attracted significant attention in the attempt to identify new druggable targets in multiple myeloma (MM).[1]

Heparanase is an endo-ß-d-glucuronidase that trims the heparan sulfate (HS) chains of proteoglycans, impacting cell signaling, gene expression and promoting extracellular matrix (ECM) remodeling within the tumor microenvironment.[2-4]

Heparanase is highly upregulated in the great majority of MM patients and associated with elevated micro vessel density and enhanced shedding of the HS proteoglycan syndecan-1[5], events that are highly relevant to disease progression.[6, 7]

In preclinical models of MM, heparanase was shown to be a master regulator of aggressive tumor behavior and bortezomib or melphalan were found to enhance heparanase expression and secretion. High heparanase expressing MM cells are less susceptible to cytotoxic effects of bortezomib or melphalan.[8-10]

Roneparstat (laboratory codes: G4000, SST0001; Leadiant Biosciences, formerly sigma tau Research Switzerland SA) is a chemically modified 100% N-desulphated, N-reacetylated and 25% glycol-split heparin with very low anticoagulant activity and a molecular weight between 15.000 and 25.000 Da. It is a very potent and pure competitive HPSE inhibitor.[11, 12]

Roneparstat showed a significant anti-myeloma effect in murine models, either alone or in combination with dexamethasone, bortezomib or melphalan.[10,13]

Based on this preclinical evidence an open-label, multicenter, phase I first-in-human study was designed to assess the safety and tolerability profile of Roneparstat in patients with relapsed/refractory MM. (EudraCT number 2012-001127-12 and clinicaltrials.gov identifier: NCT01764880).

Patients with advanced relapsed/refractory MM were eligible to be enrolled. Two treatment schedules were used: every day for 5 days (schedule A) and every day for 5 days week 1 and week 2 (schedule B), in a cycle of 28 days, according to a 3+3 design (see Table 1); Roneparstat was administered subcutaneously.

Dose Limiting Toxicities (DLTs) were characterized as per National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.0. Safety assessment of the drug was based on adverse events (AE), local

tolerability evaluation, physical examination, vital signs and laboratory tests. Patients could receive a standard supportive therapy with dexamethasone. Use and doses of dexamethasone were upon physician's judgment.
Blood samples were collected during cycle 1, on Day 1 over 24 h, and on the last day of treatment (Day 5 or Day 12) over 72 h. Pharmacokinetic (PK) sampling was performed during the first cycle. Plasma samples were analysed by a fluorescent probe assay (Heparin Red).[14]
The anti-MM activity assessment was based on a surrogate parameter, the monoclonal protein modifications in serum and urine, evaluated accordingly to IMWG (International Myeloma Working Group) Guidelines.
Nineteen patients with advanced relapsed/refractory MM were enrolled into the study and completed a total of 57 cycles (514 doses), with a median of 2 cycles (range 1-11). Four patients received > 5 cycles. Baseline patients' characteristics and enrolment by cohort of treatment are reported in Table 1.
Roneparstat was well tolerated and safe at all doses tested.
Seventeen patients reported a total of 88 AEs. Most common AEs in at least 10% of patients are reported in Table 2. Most of the AEs were grade 1 or 2 and unrelated, except for 3 treatment-related AEs in three patients (viral infection, injection site reaction, abdominal pain), assessed as Grade 1/2, transient and recovered with conservative therapy.
Grade 3/4 AEs included general physical health deterioration (3 patients, 15.8%), anemia, thrombocytopenia and bone pain (2 patients each, 10.5%); neutropenia, gastric hemorrhage, and hyperglycemia (1 patient each, 5.3%). None of these events were assessed by the investigators as related to study treatment.
Five patients experienced 6 serious adverse events (SAEs), only one (viral infection) was assessed as related to study drug, although correlation with the concomitant treatment with dexamethasone could not be excluded. The remaining SAEs were unrelated: general physical health deterioration in 2 patients, pneumonia in one patient, a suspected gastrointestinal hemorrhage in one patient (that the endoscopic evaluation did not confirm) and gastric hemorrhage in one patient (the patient was enrolled with a gastric myeloma lesion and presented progressive disease while on Roneparstat therapy). SAEs were transient, patients recovered with conventional therapy except one general physical health deterioration, ongoing at end of study.
No patients succumbed due to toxicity of the study drug. Nine patients died during the study, all from tumor progression.
Fifteen patients reported 31 local reactions at the injection site. Local side effects were < Grade 2, transient and resolved with conventional therapy, when needed. Only one was Grade 2 (redness).
Due to Roneparstat similarity with heparin, the risk of bleeding was carefully monitored. TT and INR indicated that there was no evident relationship with Roneparstat administration following single or repeated dosing. For aPTT there was no association with dose upon single dosing; after repeated dosing aPTT pharmacodynamic parameters (Emax and AUEC0-t) were higher at 200 and 400 mg/day than at lower doses, without reaching clinically meaningful levels.
The coagulation results by worst CTCAE Grade did show one Grade 1 in one patient (5.3%) for aPTT and one grade 1 and one grade 2 in 1 (5.3%) and 4 patients (21.1%), respectively, for INR.
In the 17 patients evaluable for DLTs, no clinically relevant toxicities occurred and no DLTs were observed, a true MTD was not reached. Dose escalation was stopped based on safety and PK data, indicating patients could be exposed to the study drug at dose levels of 200 and 400 mg/day without any clinically relevant toxicities.
Reproducible plasma levels of Roneparstat were measurable at cycle 1 at the two highest dose levels, as shown in Supplementum Figure S1 depicting single patient plasma concentration at day 1 and day 12 (single and repeat dosing, respectively). There was a dose-related increase in mean Cmax between 200 mg/day and 400 mg/day, both on day 1 (1.67 µg/mL vs 2.45 µg/mL) and day 12 (2.07 µg/mL vs 5.95 µg/mL). The mean exposure (AUC0-t) at day 1 after repeated dosing was 16.2 µg.h/mL and 37.25 µg.h/mL, while at day 12 it was 15.4 µg.h/mL and 133µg.h/mL for 200 mg and 400 mg/day, respectively. Upon repeated dosing, tmax was achieved at approximately 3-hour post-dose. On Day 12 and at 400 mg/day, the estimated T1/2 was approximately 14-20 h (2 patients).
Seventeen patients that received at least 1 cycle of Roneparstat were evaluable for overall response assessment (Table 3). One PR (5.9%) and 9 SD (52.9%) were observed. The remaining patients (41.2%) presented PD. The PR occurred in a patient receiving Roneparstat 50 mg, who relapsed after 3 prior therapy lines with a continuous increase of the monoclonal component. Response was characterized by a rapid decrease of the monoclonal component, from 1.75 g/dL at baseline to 0.99 g/dL at cycle 1, 0.71 g/dL at cycle 6. The patient remained on therapy until cycle 9 with sustained clinical benefit. Two of the 9 SDs were sustained with significant clinical benefit (10 and 7 months) following 200 mg and 400 mg of Roneparstat. The PR and one prolonged SD patients received low dose of concomitant dexamethasone (up to 40 mg/week), while the other prolonged SD did not receive any dexamethasone.

This is the first trial evaluating an heparanase inhibitor in hematological malignancies. Heparanase represents an increasingly studied but still largely unexploited target for anticancer therapy. Our data show that Roneparstat presents an excellent safety profile, without clinically relevant systemic reactions, and an excellent tolerability profile. Systemic exposure appears measurable in a reproducible and linear fashion at 200 and 400 mg. This study allowed identification of doses within the range from 300 to 400 mg/day as suitable for further development of the drug.
Roneparstat showed little efficacy in this specific experimental setting. Heparanase inhibition is not expected to yield tumor cell kill directly and evidence of efficacy was beyond the main scope of this trial also given the advanced heavily treated patient population, the trial size, and the design allowing a concomitant administration of dexamethasone. However, the safe and well tolerated profile of Roneparstat that can be learnt from this clinical experience combined with the extensive preclinical evidence on the ability of heparanase inhibition to influence the bone marrow microenvironment in myeloma patients, and the synergistic effect of Roneparstat when associated with bortezomib or melphalan suggest the possibility to capitalize and improve the role of heparanase inhibition in myeloma treatment. In fact, the involvement of heparanase in regulating the cross talking between the tumor and the host myeloma microenvironment and Roneparstat preclinical activity in combination regimens[8-10] have been widely described (see Supplementum 1). Of particular interest, Ramani et al[10] reported a very significant effect on tumor burden when Roneparstat was combined with bortezomib or melphalan to treat mice bearing an aggressive myeloma in vivo model formed by CAG human myeloma cells expressing high levels of heparanase (CAG-HPSE cells). Therefore, even though this phase I study does not provide evidence on the potential direct anti-myeloma effect of Ronepartstat in humans, exploration of Roneparstat in combination regimens for the treatment of MM is justified and should be the next step to move the field.

References

1. Kawano Y, Moschetta M, Manier S, Glavey S, et al. Targeting the bone marrow microenvironment in multiple myeloma. Immunol Rev. 2015;263(1):160-172.
2. Vlodavsky I, Singh P, Boyango I, et al. Heparanase: from basic research to therapeutic applications in cancer and inflammation. Drug Resist Updat. 2016;29:54-75.
3. Sanderson RD, Elkin M, Rapraeger AC, Ilan N, Vlodavsky I. Heparanase regulation of cancer, autophagy and inflammation: new mechanisms and targets for therapy. FEBS J. 2017;284(1):42-55.
4. Masola V, Secchi MF, Gambaro G, Onisto M. Heparanase as a target in cancer therapy. Curr Cancer Drug Targets. 2014;14(3):286-293.
5. Kelly T, Miao HQ, Yang Y, et al. High heparanase activity in multiple myeloma is associated with elevated microvessel density. Cancer Res. 2003;63(24):8749-8756.
6. Yang Y, Yaccoby S, Liu W, et al. Soluble syndecan-1 promotes growth of myeloma tumors in vivo. Blood. 2002;100(2):610-617.
7. Yang Y, Macleod V, Miao HQ, et al. Heparanase enhances syndecan-1 shedding: a novel mechanism for stimulation of tumor growth and metastasis. J Biol Chem. 2007;282(18):13326-13333.
8. Purushothaman A, Chen L, Yang Y, Sanderson RD. Heparanase stimulation of protease expression implicates it as a master regulator of the aggressive tumor phenotype in myeloma. J Biol Chem. 2008;283(47):32628-32636.
9. Ramani VC, Vlodavsky I, Ng M, et al. Chemotherapy induces expression and release of heparanase leading to changes associated with an aggressive tumor phenotype. Matrix Biol. 2016;55:22-34.
10. Ramani VC, Zhan F, He J, et al. Targeting Heparanase overcomes chemoresistance and diminishes relapse in Myeloma. Oncotarget. 2016;7(2):1598-1607.
11. Naggi A, Casu B, Perez M, et al. Modulation of the Heparanase-inhibiting activity of heparin through selective desulfation, graded N-acetylation, and glycol splitting. J Biol Chem. 2005;280(13):12103-12113.
12. Pala D, Rivara S, Mor M, et al. Kinetic analysis and molecular modeling of the inhibition mechanism of Roneparstat (SST0001) on human Heparanase. Glycobiology. 2016;26(6):640-654.
13. Ritchie JP, Ramani VC, Ren Y, et al. SST0001, a chemically modified Heparin, inhibits myeloma growth and angiogenesis via disruption of the heparanase/syndecan-1 axis. Clin Cancer Res. 2011;17(6):1382-1393.
14. Nobili L, Goegan M, Pezzetta D, Pace S, Barbieri P, Molinari A. Validation of a homogeneous fluorescence quenching assay for the direct quantification of a heparin-like compound in human plasma. EBF. November 19-21, 2014; abstract.

Tables

Table 1
Baseline patients' characteristics, patient enrolment by cohort of treatment and cycles administered.

		No. of patients	No. of cycles
Age, years, median (range): 68 (51-81)			
Male/Female		8 / 11	
SCHEDULE A: every day for 5 days, week 1			
Dose 1st cohort: 25 mg		4*	6
SCHEDULE B: every day for 5 days, week 1 and week 2			
Dose 2nd cohort: 25 mg		3	8
Dose 3rd cohort: 50 mg		2**	11
Dose 4th cohort: 100 mg		3	4
Dose 5th cohort: 200 mg		3	15
Dose 6th cohort: 400 mg		4*	13
Salmon & Durie staging	I	1	
	II	2	
	III	16	
International Staging System	I	13	
	II	4	
	III	2	
No prior lines, median, range: 4 (1-8)			
Prior PI/IM/RT PI = proteasome inhibitor; IM = immune modulatory drugs; M = Melphalan; RT = Radiotherapy.		PI/IM: 12 M/IM: 1 PI: 1 PI/IM/RT: 5	
Prior Autologous/Allogeneic transplant		AUTO: 13 Both: 2 NO transplant: 4	
ECOG	0	11	
	1	7	
	2	1	
DLTs in cycle 1 defined as: grade ≥3 non-hematological toxicities, grade ≥3 reactions at the site of injection, grade ≥3 hematological toxicities lasting > 7 days and/or requiring therapy, febrile neutropenia, aPTT ≥1.5 to 2.5 times the upper limit of normal (ULN) (≥Grade 2) and inability to retreatment or to receive at least 75% of study drug.			
*1 pt received one day of treatment for early PD, one additional patient (pt) enrolled, to get 3 pts evaluable for DLTs. **1 additional pt had intra-patient dose escalation from 25 (2nd cohort) to 50 mg (3rd cohort) at cycle 4 and 5, approval granted by the local Ethical Committee. Although pt started in 2nd cohort, the protocol requirement of 3 different patients in the 3rd cohort is met.			

Table 2
Unrelated and related AEs in the safety population, consisting of 19 patients; the number of patients per cohort is reported as (N).

	Schedule A	Schedule B				
Patients presenting with at least one **unrelated or related AE**. For each dose level it is reported the number of patients (n) and the percentage of patients (%), based on N, presenting an AE, and the number of events (E).						
	25 mg/day (N=4) n (%) E	25 mg/day (N=3) n (%) E	50 mg/day (N=2) n (%) E	100 mg/day (N=3) n (%) E	200 mg/day (N=3) n (%) E	400 mg/day (N=4) n (%) E
Patients with at least one RELATED OR UNRELATED AE (all causality)	2 (50) 7	3 (100) 16	2 (100) 19	3 (100) 12	3 (100) 20	4 (100) 14
Patients with at least one RELATED AE (type of AE)	0 0	0 0	1 (50) 1 (Viral infection)	1 (33.3) 1 (Injection site reaction)	1 (33.3) 1 (Upper abdominal pain)	0 0
Most common **unrelated or related AEs** reported in **at least 10 % of patients**: percentages based on N. A patient with multiple events within a Preferred Term (PT) is counted only once in the PT						
AE Preferred term (PT)	25 mg/day (N=4) n (%)	25 mg/day (N=3) n (%)	50 mg/day (N=2) n (%)	100 mg/day (N=3) n (%)	200 mg/day (N=3) n (%)	400 mg/day (N=4) n (%)
Anemia	0	1 (33.3)	0	1 (33.3)	2 (66.7)	0
Thrombocytopenia	1 (25.0)	0	0	0	0	2 (50.0)
Upper abdominal pain	0	1 (33.3)	0	0	1 (33.3)	0
Diarrhoea	0	0	1 (50.0)	0	0	1 (25.0)
Nausea	0	2 (66.7)	0	0	0	0
Asthenia	0	2 (66.7)	0	0	0	1 (25.0)
Fatigue	1 (25.0)	0	0	0	1 (33.3)	0
General Physical Health Deterioration	1 (25.0)	1 (33.3)	0	0	0	1 (25.0)
Arthralgia	0	0	1 (50.0)	0	1 (33.3)	0
Back Pain	0	1 (33.3)	1 (50.0)	1 (33.3)	1 (33.3)	0
Bone Pain	0	0	0	2 (66.7)	0	0
Insomnia	0	0	0	1 (33.3)	0	1 (25.0)
Cough	0	0	0	0	2 (66.7)	0
Epistaxis	1 (25.0)	0	0	1 (33.3)	0	1 (25.0)

Table 3
Response rates in the efficacy population, consisting of 17 patients.

	CR	VGPR	PR	MR	SD	PD
OVERALL RESPONSES (all cohorts) – n/17 (%)	0/17	0/17	1/17 (5.9 %)	0/17	9/17 (52.9%)	7/17 (41.2%)
RESPONSES BY DOSING COHORTS – n/N (%)						
Schedule A						
25 mg (N= 3)	0/3	0/3	0/3	0/3	0/3	3/3 (100%)
Schedule B						
25 mg (N= 3)	0/3	0/3	0/3	0/3	2/3 (66.7%)	1/3 (33.3%)
50 mg (N= 2)	0/2	0/2	1/2 (50%)	0/2	1/2 (50%)	0/2
100 mg (N= 3)	0/3	0/3	0/3	0/3	1/3 (33.3%)	2/3 (66.7%)
200 mg (N= 3)	0/3	0/3	0/3	0/3	2/3 (66.7%)	1/3 (33.3%)
400 mg (N= 3)	0/3	0/3	0/3	0/3	3/3 (100%)	0/3

CR: complete response; VGPR: very good partial response; PR: partial response; SD: stable disease; PD: progressive disease
n: number of responses; N: number of patients evaluable for efficacy.

Phase I study of the heparanase inhibitor Roneparstat: an innovative approach for multiple myeloma therapy

Monica Galli, Manik Chatterjee, Mariella Grasso, Giorgina Specchia, Hila Magen, Hermann Einsele, Ivana Celeghini, Paola Barbieri, David Paoletti, Silvia Pace, Ralph D. Sanderson, Alessandro Rambaldi and Arnon Nagler

SUPPLEMENTUM 1

Roneparstat did show a very good activity when combined with dexamethasone.[1] Roneparstat (60 mg/kg/day for 14 days) and dexamethasone (1 mg/kg/day for 14 days) combination therapy was tested against subcutaneous Myeloma tumor growth in SCID mice (using human MM.1R Myeloma cells) and in Balb/c mice (using murine MPC-11 Myeloma cells), thereby representing drug-resistant and immuno-competent models of Myeloma, respectively. In both settings, the combination therapy significantly inhibited tumor growth more effectively than single agent therapy alone. In the drug-resistant MM.1R model, combination therapy inhibited tumor growth by 80% and in the syngeneic model, combination therapy inhibited tumor growth by 97%. In both cases, assessment of the combination of Roneparstat and dexamethasone revealed a synergistic effect in inhibiting Myeloma tumor growth (Table S1).

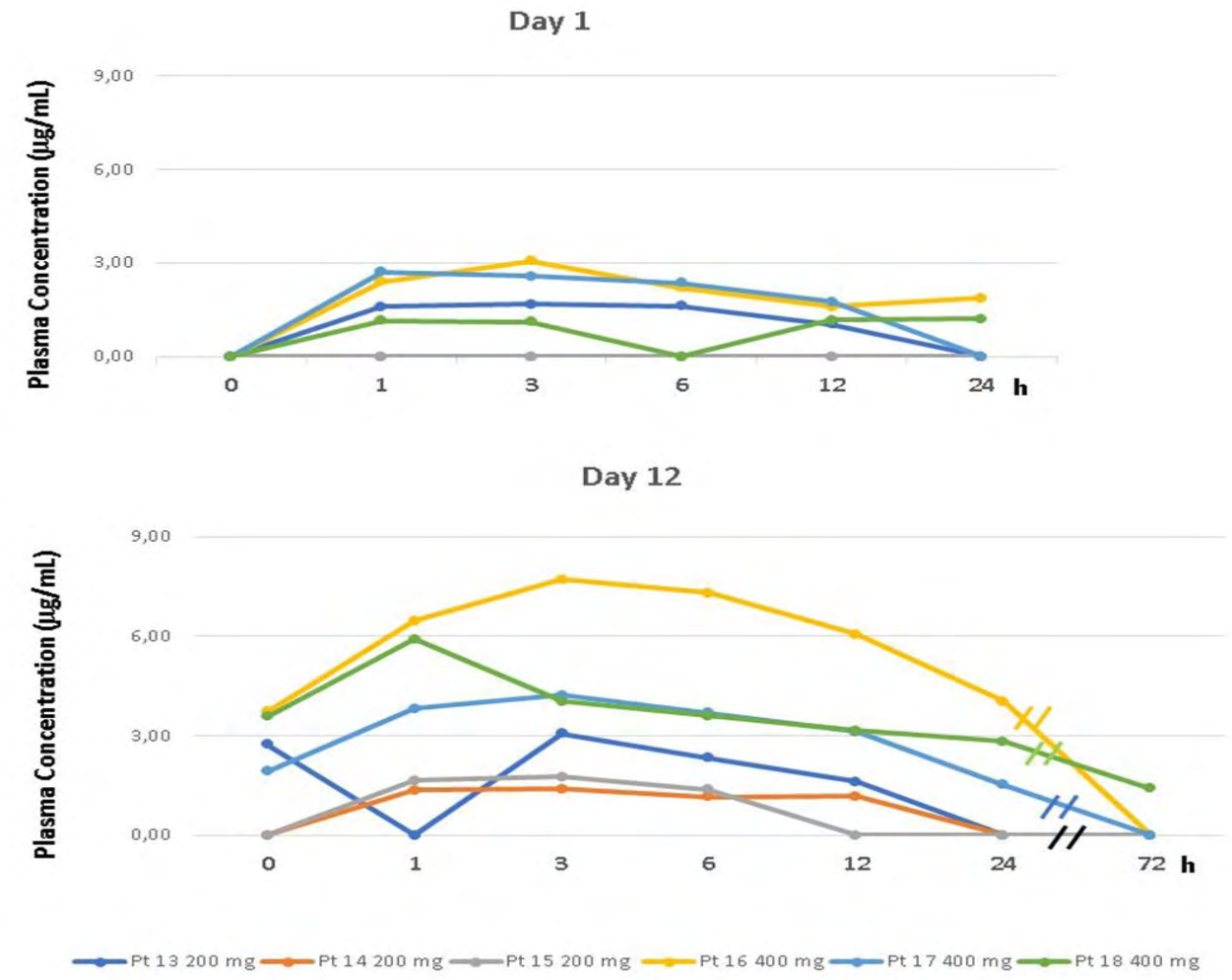
Table S1 - Roneparstat in combination, preclinical models.

Model	**Dose**	**Results**	
		TVI %	**κ chains % inhibition**
MM.1R model, tumour cells injected sc [1] SCID mice	60 mg/kg/day sc injection + dexamethasone 1 mg/kg/day	**80**	-
Syngeneic (MPC-11) model cells injected sc [1] Balb/c mice	60 mg/kg/day sc injection + dexamethasone 1 mg/kg/day	**97**	-
CAG HPSE high cells model Cells intravenously injected in mouse tail veins [2] SCID mice	120 mg/kg/day sc injection + bortezomib 0.5 mg/kg/twice a week	**75%-80%** (Tumour burden reduction by bioluminescence assay)	**70** (only 3/10 animals had detectable levels of serum κ)
CAG HPSE high cells model Cells intravenously injected in mouse tail veins [2] SCID mice	60 mg/kg/day sc injection + melphalan 1 mg/kg/week	**90%-95%** (Tumour burden reduction by bioluminescence assay)	**100**
TVI: tumour volume inhibition; k: human kappa light chain; SCID: Severe Combined Immunodeficiency; sc: subcutaneous			

A preclinical in vivo combination experiment evaluated CAG human Myeloma cells expressing high levels of HPSE (CAG HPSE cells), intravenously injected in mouse tail veins.[2] The CAG HPSE cells are very aggressive, they home to and grow rapidly and almost exclusively in the mouse bones (21 days post-injection), as evidenced by bioluminescence signal, mimicking the late stages of Myeloma. Tumor burden was evaluated by measurement of kappa-levels and bioluminescence after combination treatment with Roneparstat (120 mg/kg/day for 14 days) plus bortezomib (0.5 mg/kg/twice a week for 14 days) (Table S1) or Roneparstat (60 mg/kg/day for 14 days) plus melphalan (1 mg/kg/week for 14 days) (Table S1). Results showed that bortezomib and melphalan efficacy in tumour inhibition was substantially increased when they were combined with Roneparstat. This was evident both from kappa-levels and bioluminescence imaging data; a decrease in the former was always paralleled by a decrease of the latter. This increased efficacy was shown also when Roneparstat was given as sequential therapy after Melphalan.[2]
Positive data of Roneparstat efficacy when combined with Bortezomib or Melphalan are supported by the fact that chemotherapies are known to increase HPSE expression.[3]
Roneparstat also showed activity in tumors other than Myeloma. In particular, an antitumor effect was reported in lymphomas when given alone (60 mg/kd/day) or in combination with Cyclophosphamide, Rituximab or Bevacizumab.[4] Similarly, a strong inhibitory effect was reported in sarcomas models at 60mg/kg/twice daily, especially when combined with 50 mg/kg/day Irinotecan.[5]

Supplementary Figure S1 reports the plasma profiles of individual patients receiving 200 mg and 400 mg. Plasma levels of Roneparstat were quantifiable at cycle 1 at the two highest dose levels after single (day 1) and repeated (day 12) dosing using fluorescent probe assay (Heparin Red).[6]
Systemic exposure appears reproducible, linear but slightly over-proportional with the dose. These data seem to reflect preclinical PK (rat & monkey).[7]
With all the caution due to the translation from preclinical to clinical findings, the reported plasma levels are coherent with preclinical data showing that the inhibitory ability of the drug is in the nanomolar range, with an IC_{50} value corresponding to 0,06 µg/mL.[8] Moreover, a non-clinically significant increase of aPTT and of TT was detected in one and two patients receiving 400 mg, respectively, thus further showing patient exposure to the drug.
The effect on coagulation occurring in the patients who received 400 mg suggested this as the highest dose level to be explored. In combination phase I/II studies the dose identified to be used will be 300-400 mg/day.

Figure S1 - Day 1 and Day 12 plasma profiles in patients treated with Roneparstat 200 mg (3 patients) and 400 mg (3 patients).



References

1. Ritchie JP, Ramani VC, Ren Y, et al. SST0001, a chemically modified Heparin, inhibits myeloma growth and angiogenesis via disruption of the heparanase/syndecan-1 axis. *Clin Cancer Res*. 2011;17(6):1382-1393.
2. Ramani VC, Zhan F, He J, et al. Targeting Heparanase overcomes chemoresistance and diminishes relapse in Myeloma. *Oncotarget.* 2016;7:1598-1607.
3. Ramani VC, Vlodavsky I, Ng M, et al. Chemotherapy induces expression and release of heparanase leading to changes associated with an aggressive tumor phenotype. *Matrix Biol*. 2016;55:22-34.
4. Di Nicola M, Zunino F, Rossini A, et al. Microenvironment modulation and enhancement of cytotoxic therapy by the heparanase inhibitor Roneparstat against human B-non Hodgkin lymphomas. *AACR*. 2016; Abstract #3289.
5. Cassinelli G, Favini E, Dal Bo L, et al. Antitumor efficacy of the heparan sulfate mimic roneparstat (SST0001) against sarcoma models involves multi-target inhibition of receptor tyrosine kinases. *Oncotarget*. 2016;7(30):47848-47863.
6. Nobili L, Goegan M, Pezzetta D, Pace S, Barbieri P, Molinari A. Validation of a homogeneous fluorescence quenching assay for the direct quantification of a heparin-like compound in human plasma. *EBF*. November 19-21, 2014; abstract.
7. Leadiant Biosciences SA. *Investigator's Brochure* (Data on file). 2014.
8. Rivara S, Milazzo FM, Giannini G. Heparanase: a rainbow pharmacological target associated to multiple pathologies including rare diseases. *Future Med Chem.* 2016;8(6):647-80.