SEL-212: Enhanced Serum Uric Acid Control in Hyperuricemic Patients through Selective Mitigation of Anti-Drug Antibodies against Pegsitacase

THU 0402

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Abstract

Background: Recent EULAR recommendations for refractory gout treatment with pegylated uricase (pegloticase) acknowledge the risk of allergic reactions related to the development of anti-drug antibodies (ADAs) [1]. ADAs also affect the efficacy of treatment [2]. As a novel approach to treatment, we have previously demonstrated that co-administration of pegsitacase (another pegylated uricase) with a synthetic vaccine particle encapsulating rapamycin (SVP-Rapamycin) showed improved control of serum uric acid (sUA) in uricase-deficient mice by inducing antigen-specific immune tolerance to pegsitacase [3]. Here we describe the impact of SEL-212, a combination product of SVP-Rapamycin and pegsitacase, on ADA formation and sUA levels in a Phase 1 single ascending dose clinical trial in hyperuricemic patients and in an ongoing Phase 2 multiple ascending dose clinical trial in patients with hyperuricemia and symptomatic gout .

Objectives: To assess the initial safety and impact on sUA levels and ADA formation of SEL-212, which is designed to be the first non-immunogenic uricase therapy for chronic severe gout.

Methods: In the Phase 1 trial, hyperuricemic (sUA ≥6 mg/dL) patients consented to a single dose of pegsitacase alone, SVP-Rapamycin alone, or SEL-212 (combination of pegsitacase co-administered with SVP-Rapamycin). In the Phase 2 trial, patients with symptomatic gout and hyperuricemia consented to a repeated dose study of pegsitacase alone or SEL-212. The effects of treatment on ADAs, serum pegsitacase activity and sUA were evaluated.

Results: Sixty-three patients were enrolled in an open label multi-center US Phase 1 trial with a median age of 49.4 years. Mean baseline sUA was 7.4 ± 1.3 mg/dL. Patients dosed with pegsitacase alone showed an immediate drop in sUA, which returned to baseline levels by 14-21 days in 4 of 5 subjects, correlating with the induction of ADA titers >1:1000. As expected, patients treated with SVP-Rapamycin alone showed no meaningful change in sUA. In contrast, patients treated with SEL-212 showed a dose-dependent inhibition of anti-uricase ADAs and a corresponding decrease in sUA levels through at least day 30 after a single injection. Seven of 10 patients treated with SEL-212 at an SVP-Rapamycin dose of 0.1 mg/kg showed no detectable sUA at day 30, and all 10 subjects dosed with SEL-212 at SVP-Rapamycin doses of 0.15 or 0.3 mg/kg showed sustained control of sUA (<6mg/dL) through at least day 30. There was a strong correlation between maintenance of low uric acid levels at day 30 with low or no ADA titers.

As of June 12, 2017, 60 patients had been dosed in an ongoing open label Phase 2 multiple ascending dose clinical study in symptomatic gout patients with hyperuricemia at 11 US centers. Control patients administered 0.4 mg/kg pegsitacase alone were unable to maintain control of sUA for more than 14-21 days, as expected. In contrast, patients administered monthly doses of 0.08 mg/kg of SVP-Rapamycin + 0.4 mg/kg of pegsitacase have maintained control of sUA levels for up to 133 days, defining the minimal effective dose.

SEL-212 has been generally well tolerated at clinically active dose levels of SEL-212.

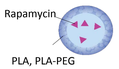
Conclusions: These data suggest that the addition of SVP-Rapamycin to pegsitacase (SEL-212) can inhibit the formation of ADAs in a dose-dependent manner resulting in sustained control of serum uric acid levels after a single dose in hyperuricemic patients and with repeated dosing in patients with symptomatic gout and hyperuricemia. SEL-212 has the potential to address a substantial unmet need for patients with chronic severe gout and tophaceous gout.

Background

Pegsitacase

- Uricases have been shown to be very effective in significantly reducing serum uric acid levels in patients with chronic refractory gout [2]
- The currently marketed uricase, Krystexxa (pegloticase), is highly immunogenic, compromising its safety and efficacy [2]
- Pegsitacase is a different pegylated uricase enzyme that is being developed in combination with SVP-Rapamycin to mitigate its immunogenicity

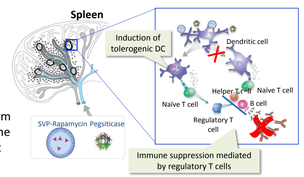
SVP-Rapamycin



- SVP-Rapamycin is a biodegradable nanoparticle that encapsulates rapamycin, an mTOR inhibitor [3]
- Intravenous injection of SVP-Rapamycin results in selective accumulation in the spleen and liver, where it is endocytosed by dendritic cells (DC) and macrophages
- SVP-Rapamycin is designed to be co-administered with biologic drugs to prevent the formation of anti-drug antibodies (ADAs) through the induction of immune tolerance and thus enable sustained therapeutic activity of the biologic

SEL-212

- SEL-212 is a combination drug comprised of pegsitacase and SVP-Rapamycin, which is designed to enable sustained reduction of serum uric acid (sUA) levels by inducing the formation of regulatory T cells that prevent the formation of ADAs



Phase 1b Clinical Trial

Single ascending dose clinical trial design

Study description

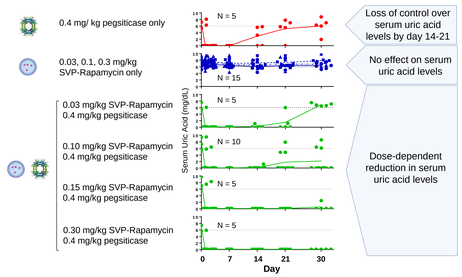
- Evaluate the safety, pharmacokinetics, pharmacodynamics and immunogenicity of a single IV dose of SEL-212 in patients with elevated serum uric acid (SUA) levels (>6 mg/dL)
- Cohorts of patients administered single IV infusions of pegsitacase, SVP-Rapamycin, or SEL-212 (combination of pegsitacase + SVP-Rapamycin)
- Monitored for safety, sUA levels, uricase pharmacodynamic activity, and anti-uricase-antibodies (ADAs)
- Male or female subjects ages 21 to 75 inclusive

Dosing cohorts

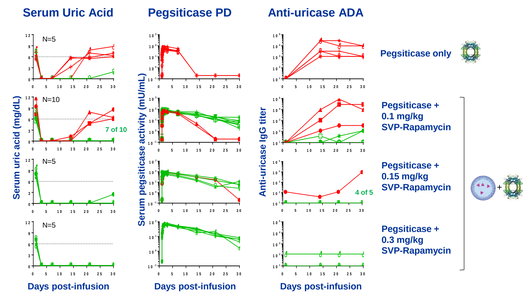
- Pegsitacase only cohort: 0.4 mg/kg pegsitacase
- SVP-Rapamycin alone cohorts: 0.03, 0.1, 0.3, or 0.5 mg/kg SVP-Rapamycin
- SEL-212 cohorts: 0.03, 0.1, 0.15, or 0.3 mg/kg of SVP-Rapamycin in combination with a fixed dose of 0.4 mg/kg pegsitacase

Clinicaltrials.gov NCT02648269

Dose-dependent reduction of sUA with SEL-212 in hyperuricemic patients



Correlation of ADA titers with sUA and pegsitacase PD



Safety and tolerability of SEL-212

SVP-Rapamycin alone

- 17x dose range tested to determine maximum tolerated dose (MTD)
- At 0.5 mg/kg, two SAEs (stomatitis) observed, a known side effect of rapamycin. Resolved

SEL-212 (combination of SVP-Rapamycin and pegsitacase)

- Generally well tolerated at clinically active dose levels (0.1, 0.15 or 0.3 mg/kg SVP-Rapamycin + 0.4 mg/kg pegsitacase). No dose-dependent trends
- At 0.1 mg/kg SVP-Rapamycin + pegsitacase there was one SAE (grade 2 rash). Resolved
- No SAEs at 0.15 or 0.3 mg/kg SVP-Rapamycin + pegsitacase

Ongoing Phase 2 Clinical Trial

Clinical trial design – Multiple ascending dose

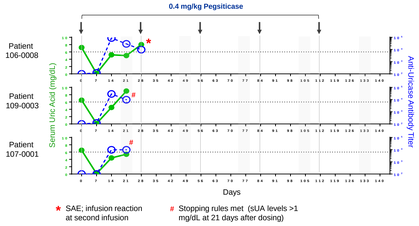
Study description

- Evaluate the safety, pharmacokinetics, pharmacodynamics and immunogenicity of repeated monthly IV infusions of SEL-212 in patients with symptomatic gout and elevated serum uric acid (sUA) levels (>6 mg/dL)
- Cohorts of patients administered three q28 day IV infusions of 0.2 or 0.4 mg/kg pegsitacase in combination with ascending doses of SVP-Rapamycin followed by two q28 day IV infusions of 0.2 or 0.4 mg/kg pegsitacase alone
- Monitored for safety, uric acid levels, uricase pharmacodynamic activity, and anti-uricase-antibodies (ADAs)
- Male or female subjects ages 21 to 75 inclusive
- Patients with established or symptomatic gout (≥1 tophus, ≥ 1 gout flare in last 6 months, or chronic gouty arthropathy) with hyperuricemia (> 6mg/dL sUA)

Clinicaltrials.gov NCT02959918

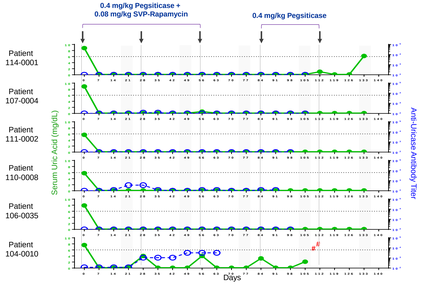
Cohort	Treatment Weeks 0, 4, 8		Treatment Weeks 12 + 16	Status
	Pegsitacase	SVP-Rapamycin	Pegsitacase	
1	0.2 mg/kg	None	0.2 mg/kg	Enrollment terminated
2	0.4 mg/kg	None	0.4 mg/kg	Enrollment terminated
3	0.2 mg/kg	0.05 mg/kg	0.2 mg/kg	Dosing completed
4	0.4 mg/kg	0.05 mg/kg	0.4 mg/kg	Dosing completed
5	0.2 mg/kg	0.08 mg/kg	0.2 mg/kg	Dosing completed
6	0.4 mg/kg	0.08 mg/kg	0.4 mg/kg	Ongoing
7	0.2 mg/kg	0.1 mg/kg	0.2 mg/kg	Ongoing
8	0.4 mg/kg	0.1 mg/kg	0.4 mg/kg	Ongoing
9+	Under design			Planned

Pegsitacase alone is highly immunogenic



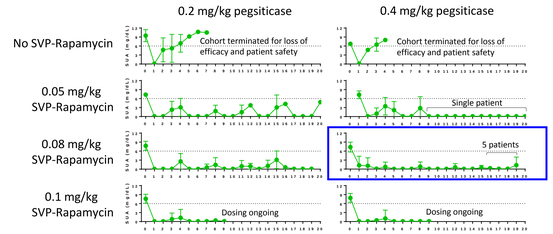
- Control of sUA levels is lost by day 14-21
- Loss of sUA control correlates with formation of ADAs
- Allergic reactions observed with second dose
- Further enrollment terminated for loss of efficacy and patient safety

Data show that SVP-Rapamycin mitigates immunogenicity of pegsitacase and enables repeat dosing with sustained control of sUA



- Sustained reduction of sUA after two injections of pegsitacase alone suggests induction of immune tolerance
- Additional ADA data are pending
- Cohort being expanded to 10 evaluable patients

Minimal effective dose of pegsitacase and SVP-Rapamycin defined



Minimal effective dose: 0.08 mg/kg SVP-Rapamycin + 0.4 mg/kg pegsitacase

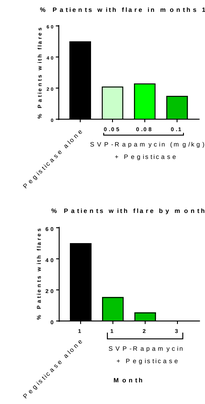
Safety and tolerability

Cohort	Entire Study	1	2	3	4	5	6	7	8
N(%)	60	3	3	9	10	6	7	10	10
≥ 1TEAE	49(81.7)	2	2	9	8	5	5	3	6
≥ SAE	8	1	1	2	0	0	1*	1*,1	1*
Death	0	0	0	0	0	0	0	0	0
Discontinuation due to TEAE	8	1	1	2	0	0	1	2	1
Specific TEAEs									
Infusion reaction	8(13.3)	1	1	2	0	0	1*,1	1	1*
Gout Flare	13(21.7)	3	0	2	2	1	2	1	2
Hyperglycemia	9(15)	0	0	2	0	3	2	1	1
Hypertriglyceridemia	4(6.7)	0	0	1	0	2	0	1	0
Infection	9(15)	0	1	4	1	1	1	0	1
Tachycardia	3(5)	0	0	2	1	0	0	0	0
Headache	3(5)	0	0	0	3	0	0	0	0
Hypophosphatemia	4(6.7)	0	0	4	0	0	0	0	0
Stomatitis or oral lesion	2(3.3)	0	0	0	0	1	0	0	1
Leukopenia	10(16.7)	0	0	2	0	2	1	2	3

*Not related to study drug *Patient incorrectly dosed

- Repeated administration of SEL-212 has been generally well tolerated at clinically active doses (0.4 mg/kg pegsitacase + 0.08 or 0.1 mg/kg SVP-Rapamycin)
- Four infusion reactions with repeat dosing were observed with pegsitacase alone and low dose SEL-212 groups – classified as SAEs
- As expected, these infusion reactions were preceded by the development of high titer ADAs and loss of control of serum uric acid (sUA) levels
- Enrollment of patients in Cohorts 1 and 2 administered pegsitacase alone was terminated early for loss of efficacy and patient safety
- Stopping rule was defined as sUA level >1mg/dL at day 21 after dosing
- One infusion reaction was observed after a repeat dose of 0.2 mg/kg pegsitacase + 0.1 mg/kg SVP-Rapamycin – classified as an SAE
- One of the new patients in the 0.4 mg/kg pegsitacase + 0.08 mg/kg SVP-Rapamycin cohort had an infusion reaction during the first administration of SEL-110 – classified as an SAE

Low incidence of gout flares



- Urate lowering therapies typically increase the incidence of flares at the beginning of therapy
- SEL-212 lowers flares compared to pegsitacase alone

References:

1. Richette P, et al., Ann Rheum Dis., 2017, 76:29-42.
2. Sundy, JS, JAMA, 2011, 306:711-720
3. Kishimoto, TK, et al., Nat Nanotechnol. 2016, 11:890-899.

Acknowledgements

We thank all of the patients that participated in these studies. We are grateful to the clinical study site investigators and their staff and the entire Selecta SEL-212 project team

Conclusions

- SEL-212 is a combination product being developed as a monthly therapy for the removal of urate crystal deposits in patients with severe uncontrolled gout while mitigating the immunogenicity of uricase
- The initial data from the ongoing Phase 2 multi-dose clinical trial indicates that 0.08 mg/kg SVP-Rapamycin + 0.4 mg/kg pegsitacase mitigates the formation of ADAs and enables sustained control of serum uric acid levels in most patients
- Data show evidence of immune tolerance was demonstrated after doses 4 and 5 of pegsitacase alone
- Lower incidence of gout flares with SEL-212 was observed compared to pegsitacase alone
- SEL-212 has been generally well tolerated at clinically active dose levels and infusion reactions were reduced with increasing doses of SVP-Rapamycin
- Available clinical data allows for initial design of the Phase 3 program
- Clinical proof of concept for SVP-Rapamycin's potential to mitigate ADAs for a wide range of biologic therapies