Initial Phase 2 Clinical Data of SEL-212 in Symptomatic Gout Patients: Monthly Dosing of a Pegylated Uricase (Pegsitcase) with SVP-Rapamycin Enables Sustained Reduction of Serum Uric Acid Levels by Mitigating Formation of Anti-Drug Antibodies

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Abstract

Background: Pegylated uricases are promising therapies for treatment of chronic severe gout, particularly for rapid resolution of tophi. However, uricases are limited by induction of anti-drug antibodies (ADAs) that can compromise efficacy and safety. SEL-212 is a novel combination product consisting of pegsitcase co-administered with synthetic vaccine particles encapsulating rapamycin (SVP-Rapamycin). Preclinical studies showed the ability of SVP-Rapamycin to induce durable, antigen-specific immune tolerance to a wide range of co-administered biologic drugs. A Phase 1 study of SEL-212 demonstrated dose-dependent mitigation of ADAs and sustained control of serum uric acid (sUA) for ≥30 days after a single dose. Here we report initial data on safety, tolerability, and effects on sUA, ADAs, and gout flares of repeated monthly doses of SEL-212 from an ongoing Phase 2 study in symptomatic gout patients.

Methods: Patients with symptomatic gout (≥1 tophus, gout flare within 6 months or gouty arthropathy) and elevated sUA (≥6mg/dL) were enrolled to SEL-212 treatment (N=6-12 patients/cohort) of fixed doses of pegsitcase (0.2mg/kg or 0.4mg/kg) alone or co-administered with SVP-Rapamycin (0.05, 0.08, 0.1, 0.125, and 0.15 mg/kg). SEL-212 was infused in 28-day cycles x3 doses followed by challenge with pegsitcase alone on 28-day cycles x2 doses. Safety, tolerability, sUA, and ADAs were monitored.

Results: As of 23 October, 2017, 79 patients had been dosed in the ongoing Phase 2 study. To date, dosing of cohorts at SVP-Rapamycin doses up to 0.1 mg/kg has been completed. Sustained control of SUA was observed in the majority of the per protocol patients treated with 0.1 mg/kg SVP-Rapamycin. SVP-Rapamycin inhibited ADAs in a dose-dependent manner, which correlated with reduction of sUA levels. The percentage of patients who experienced flares was less than 25% during the first month after treatment and continued reduction was observed during months 2-5. SEL-212 has been generally well tolerated at clinically active dose levels and infusion reactions associated with repeat dosing were reduced with increasing doses of SVP-Rapamycin. No infusion reactions were observed during the trial after treatment period 2.

Conclusion: SEL-212 has been well-tolerated, and, compared to pegylated uricase alone, has mitigated immunogenicity, reduced flare rates, and enabled repeated monthly dosing with sustained control of sUA levels. Additional cohorts are being evaluated to define the dose regimens to take forward into Phase 3.

Background

Pegsitcase

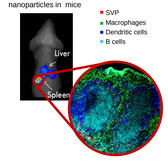
Pegsitcase

- Uricases have been shown to be very effective in significantly reducing serum uric acid levels in patients with chronic severe gout
- Uricases are highly immunogenic, compromising their safety and efficacy
- Pegsitcase is a 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
- Intravenous injection of SVP-Rapamycin results in selective accumulation in the spleen and liver, where it is endocytosed by dendritic cells (DC) and macrophages

6 hr post IV injection of fluorescent nanoparticles in mice

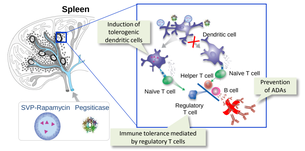


- SVP-Rapamycin is designed to be co-administered with biologic drugs to prevent the formation of ADAs through the induction of immune tolerance and thus enable sustained therapeutic activity of the biologic

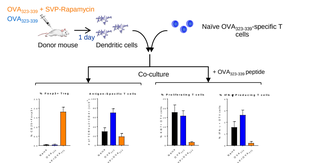
ADA Mitigation MOA

SEL-212

- SEL-212 is a combination drug comprised of pegsitcase and SVP-Rapamycin
- The co-administration of SVP-Rapamycin and pegsitcase is designed to induce the formation of regulatory T cells that prevent the formation of ADAs against pegsitcase and enable sustained reduction of serum uric acid (sUA) levels

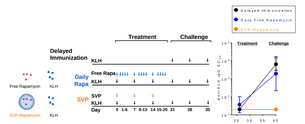


Tolerogenic dendritic cells induced in vivo by SVP-Rapamycin



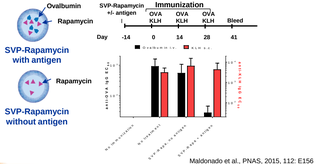
Kishimoto et al., Nature Nanotech, 2016, 11:890

Encapsulation of rapamycin is required for tolerance induction



Kishimoto et al., Nature Nanotech, 2016, 11: 890

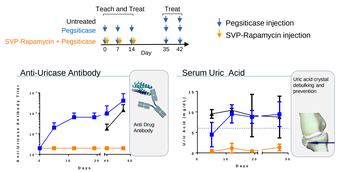
Tolerance induction is antigen-specific



Maldonado et al., PNAS, 2015, 112: E156

Preclinical Efficacy

SEL-212 prevents ADAs and lowers sUA levels in uricase-deficient mice



Phase 1b Clinical Trial

SEL-212/101 clinical trial design - Single ascending dose

Study description

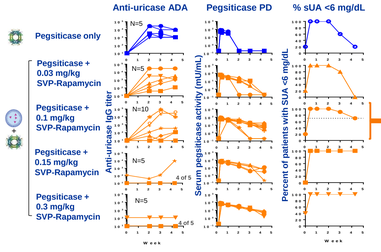
- Evaluate the safety, pharmacokinetics, pharmacodynamics and immunogenicity of a single IV dose of SEL-212 in patients with elevated serum uric acid (sUA) levels (>6 mg/dL)
- Cohorts of patients administered single IV infusions of pegsitcase, SVP-Rapamycin, or SEL-212 (combination of pegsitcase + SVP-Rapamycin)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

Dosing cohorts

- Pegsitcase only cohort: 0.4 mg/kg pegsitcase
- 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 pegsitcase

Clinicaltrials.gov NCT02648269

Correlation of ADA titers with sUA and pegsitcase PD



Ongoing Phase 2 Clinical Trial

SEL-212/201 clinical trial design – Multiple ascending dose

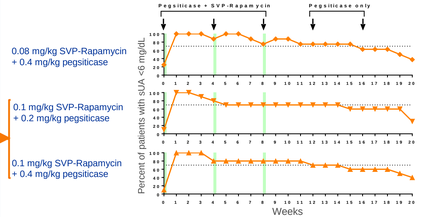
Study description

- 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 pegsitcase in combination with ascending doses of SVP-Rapamycin followed by two q28 day IV infusions of 0.2 or 0.4 mg/kg pegsitcase alone
- Monitored for safety, uric acid levels, uricase pharmacodynamic activity, and anti-uricase-antibodies (ADAs)
- Male or female subjects ages 21 to 75 inclusive
- Demographics
  - Patients with established or symptomatic gout (≥1 tophus, ≥ 1 gout flare in last 6 months, or chronic gouty arthropathy) with hyperuricemia (> 6mg/dL sUA)
  - Average sUA at enrollment/screening: 8.2 mg/dL
  - Average age: 55.5
  - Male, 71; Female, 8
  - Caucasian, 48; African American, 23: Hispanic 5; Other (Pacific Islander/Asian) 3

Clinicaltrials.gov NCT02959918

Cohort	Treatment Weeks 0, 4, 8		Treatment Weeks 12 + 16	Status
	Pegsitcase	SVP-Rapamycin	Pegsitcase	
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	Dosing completed
7	0.2 mg/kg	0.1 mg/kg	0.2 mg/kg	Dosing completed
8	0.4 mg/kg	0.1 mg/kg	0.4 mg/kg	Dosing completed
10	0.4 mg/kg	0.125 mg/kg	0.4 mg/kg	Ongoing
11	0.2 mg/kg	0.15 mg/kg	0.2 mg/kg	Planned
12	0.4 mg/kg	0.15 mg/kg	0.4 mg/kg	Ongoing

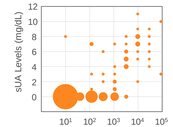
Sustained control of sUA levels with pegsitcase + SVP-Rapamycin



Percent per protocol patients with serum uric acid levels <6 mg/dL at indicated time points. 70% response at day 30 observed in Phase 1b after a single dose of 0.1 mg/kg SVP-Rapamycin + 0.4 mg/kg pegsitcase was sustained with multiple doses of SEL-212 (SVP-Rapamycin + pegsitcase) in Phase 2.

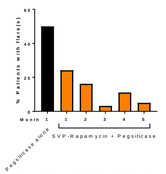
Impact of SEL-212 on ADAs and gout flares

Correlation of sUA and ADA Titers



Serum uric acid levels vs anti-uricase IgG titers at 21 days after each dose for all patients in cohorts 1-8

% Patients with Flare(s) by Month



Percent flares with SEL-212 treatment trended downwards over the treatment period.

Safety

- SEL-212 has been generally well tolerated at clinically active doses following repeated administrations
- SAEs reported in the SEL-212/201 trial:
  - Four SAEs were determined to be not related or unlikely to be related to study drug. Two patients with a history of gall stones experienced cholecystitis (inflammation of gall bladder caused by impacted gall stones) which were determined to be not related to study drug. The third patient experienced a post-Micturition autonomic response during the infusion which was determined to be not related to study drug. The fourth patient experienced peripheral edema which was reported as unlikely to be related to study drug.
  - Seven infusion reactions, four of which were in cohorts receiving pegsitcase alone or pegsitcase in combination with the lowest dose of SVP-Rapamycin, as anticipated, and two of which were due to protocol deviations related to dosing errors. One infusion reaction was observed during a repeat dose of SEL-212 in Cohort 7 and was classified as an SAE.
  - No infusion reactions were observed during the trial after treatment period 2.
- All SAEs were successfully treated and resolved without further issues

Cohort	Entire Study	1	2	3	4	5	6	7	8	10^A	12^A
N	79	3	3	9	10	6	11	11	12	10	4
≥ 1TEAE	63	2	2	6	8	6	10	10	12	7	0
≥ SAE	11	1	1	2	0	0	2(1*, 1*†)	1	4(3*, 1*†)	0	0
Death	0	0	0	0	0	0	0	0	0	0	0
Discontinuation due to TEAE	15	1	1	2	0	0	3	2	4	2	0
Specific TEAEs											
Infusion reaction	11	1	1	2	0	0	2(1*, 1)	2	2(1*, 1)	1	0
Gout Flare	37	3	0	2	2	3	3	9	12	3	0
Hyperglycemia†	8	0	0	1	0	2	2	1	1	1	0
Hypertriglyceridemia†	11	0	0	1	0	3	1	1	2	3	0
Infection†	15	0	1	7	1	1	1	1	3	0	0
Tachycardia†	4	0	0	3	0	0	0	0	0	1	0
Anemia†	13	0	0	1	0	2	3	2	3	2	0
Headache†	14	0	0	0	4	1	1	5	1	2	0
Hypophosphatemia†	5	0	0	5	0	0	0	0	0	0	0
Stomatitis or oral lesion†	10	0	0	0	0	1	1	0	5	3	0
Leukopenia†	15	0	0	2	0	4	1	2	5	1	0

*Dosing for cohorts 10 and 12 are still ongoing
#Not related to study drug *Patient incorrectly dosed
† TEAEs were single data points and transient in nature

Conclusions

- SEL-212 is a monthly combination product being developed as a therapy for the removal of urate crystal deposits in patients with chronic severe gout
- The initial data from the ongoing Phase 2 multi-dose clinical trial indicate that doses of 0.1 mg/kg SVP-Rapamycin administered with 0.2 or 0.4 mg/kg pegsitcase enable sustained control of serum uric acid levels in most patients
- SVP-Rapamycin inhibited the formation of ADAs in a dose-dependent manner which correlated with control of sUA levels
- Evidence of immune tolerance was observed in some patients after doses 4 and 5 of pegsitcase alone. It may be possible to maintain tolerance in a majority of subjects with enhanced or continuous dosing regimens of SEL-212
- The percentage of patients who experienced flares was less than 25% during the first month after treatment and continued reduction was observed during months 2-5. Percent of patients experiencing gout flares typically increases during the first month after the initiation of urate lowering therapies.
- SEL-212 has been generally well tolerated at clinically active dose levels and infusion reactions associated with repeat dosing were reduced with increasing doses of SVP-Rapamycin. No infusion reactions were observed during the trial after treatment period 2.
- Available clinical data is encouraging and allows for design of the Phase 3 program
- SEL-212 provides clinical proof of concept for SVP-Rapamycin's potential to mitigate immunogenicity for a wide range of biologic therapies where ADAs may be a limiting factor for efficacy or approvability

Acknowledgements

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

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