Initial Data from a Phase 2 Multiple Ascending Dose Clinical Trial of SEL-212: Monthly Dosing of SEL-212 Mitigates the Formation of Anti-Drug Antibodies and Enables Sustained Control of Serum Uric Acid in Symptomatic Gout Patients

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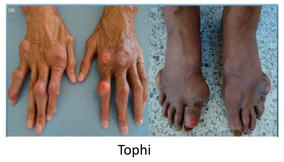
Abstract

The currently available pegylated uricase treatment for refractory gout is compromised by the development of anti-drug antibodies (ADAs) for most patients, which adversely affects efficacy and safety. We have developed synthetic vaccine particles encapsulating rapamycin (SVP-Rapamycin) that are capable of inducing antigen-specific immunological tolerance to biologic drugs (Kishimoto et al., Nature Nanotech, 2016, 11:890). Here, we report on initial data from a Phase 2 open label multiple ascending dose clinical study of SEL-212, the combination of SVP-Rapamycin and the pegylated uricase enzyme, pegsitricase, in symptomatic gout patients with hyperuricemia. The primary and secondary endpoints for this trial include the safety, tolerability and pharmacokinetics of repeated monthly doses of SEL-212; sustained reduction of serum uric acid levels (sUA); and prevention of ADAs. As of June 12, 2017, a total of 60 patients had been dosed at 11 U.S. clinical sites. Control patients administered pegsitricase alone were unable to maintain control of sUA for more than 14-21 days, as expected. In contrast, patients administered 0.08 mg/kg of SVP-Rapamycin + 0.4 mg/kg of pegsitricase have thus far maintained control of sUA levels for up to 133 days following three q28 day IV infusions of SEL-212 (Pegsitricase + SVP-Rapamycin) followed by two q28 day IV infusions of pegsitricase alone. SEL-212 has been generally well tolerated at this active dose level of SEL-212. These data suggest that SVP-Rapamycin may significantly enhance the activity of pegsitricase and potentially address a substantial unmet need for patients with chronic severe gout and tophaceous gout.

Unmet Medical Need

Disease burden of chronic severe and tophaceous gout

- Severe uncontrolled gout is caused by unabated deposition of urate crystals in joints, soft tissues and organs in patients
- Urate crystals can cause painful joint inflammation, destructive arthritis and the formation of debilitating nodules called tophi
- The therapeutic goal in gout is to reduce serum uric acid (sUA) levels below 6 mg/dL, which is below its limit of solubility of 6.8 mg/dL
- Gout is associated with cardiovascular, renal, and metabolic co-morbidities
- Patients with tophaceous gout have a increased risk of mortality (Perez-Ruiz et al, Ann Rheum Dis, 2014, 73:177; Choi et al Arthr Rheumatol, 2016, 68 suppl 10; Vincent et al, J Rheumatol, 2017, 44:368)



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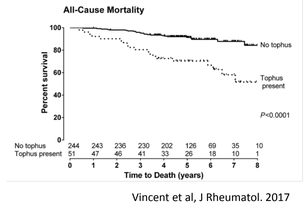
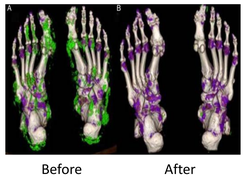


Vincent et al, J Rheumatol. 2017

Role for uricase therapies in chronic severe and tophaceous gout



Before After

Resolution of tophi (green) with uricase therapy (Araujo et al, RMD Open, 2015, e000075)

- Uricases are enzymes that rapidly metabolize uric acid
- Uricase therapy has shown the potential to rapidly resolve tophi
- However the currently marketed uricase, Krystexxa (pegloticase), is highly immunogenic (Sundy et al, JAMA 2011)
- Ph 3 clinical trials show that 92% of patients develop anti-drug antibodies to Krystexxa
  - 58% lose efficacy
  - 26% and 6.5% of patients experienced infusion reactions and anaphylaxis, respectively

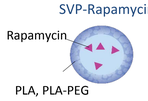
Ongoing SEL-212 Phase 2 Clinical Trial

SEL-212: Design of a monthly combination product to mitigate the immunogenicity of uricase

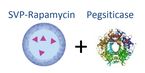
Pegsitricase

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

SVP-Rapamycin

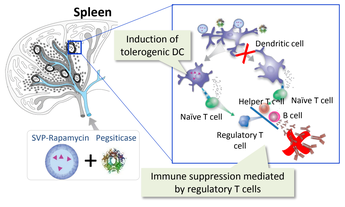


- SVP-Rapamycin is a biodegradable nanoparticle that encapsulates rapamycin, an mTOR inhibitor
- Designed to stay intact after injection until taken up by immune cells
- Intravenous injection of SVP-Rapamycin results in selective accumulation in the spleen and liver, where it is endocytosed by dendritic 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 is a combination drug comprised of pegsitricase and SVP-Rapamycin

The co-administration of SVP-Rapamycin and pegsitricase is designed to induce the formation of regulatory T cells that prevent the formation of anti-drug antibodies (ADAs) against pegsitricase and to enable sustained reduction of serum uric acid (sUA) levels



Clinical trial design – Monthly doses of SEL-212

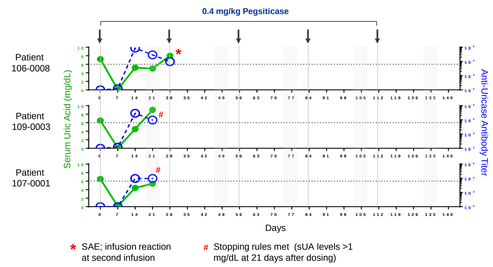
Study description

- 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 pegsitricase in combination with ascending doses of SVP-Rapamycin followed by two q28 day IV infusions of 0.2 or 0.4 mg/kg pegsitricase 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

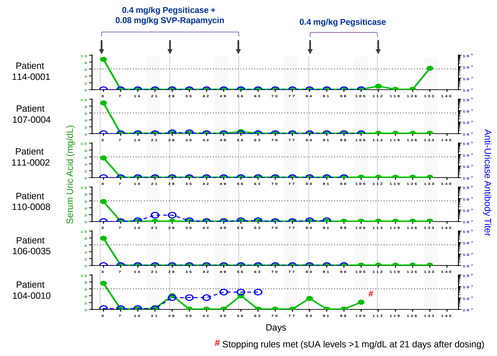
Cohort	Treatment Weeks 0, 4, 8		Treatment Weeks 12 + 16	Status
	Pegsitricase	SVP-Rapamycin	Pegsitricase	
1	0.2 mg/kg	None	0.2 mg/kg	Enrollment terminated
2	0.4 mg/kg	None	0.4 mg/kg	Enrollment terminated
3	0.2 mg/kg	0.05 mg/kg	0.2 mg/kg	Dosing completed
4	0.4 mg/kg	0.05 mg/kg	0.4 mg/kg	Dosing completed
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

Pegsitricase alone is highly immunogenic



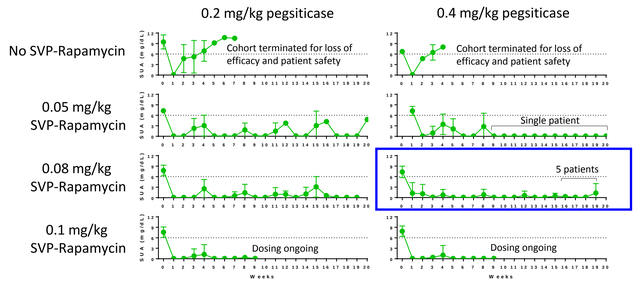
- Control of uric acid levels is lost by day 14-21
- Loss of sUA control correlates with formation of ADAs
- Allergic reactions observed with second dose
- Further enrollment terminated for loss of efficacy and patient safety

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



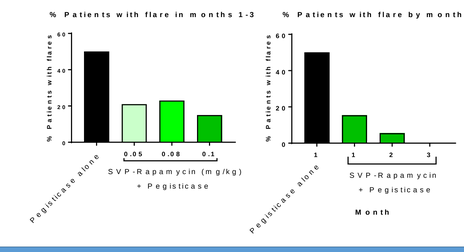
- Sustained reduction of sUA after two injections of pegsitricase alone suggests induction of immune tolerance
- Additional ADA data are pending
- Cohort being expanded to 10 evaluable patients

Minimal effective dose of pegsitricase and SVP-Rapamycin defined



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

Low incidence of gout flares with SEL-212 treatment



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

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 pegsitricase + 0.08 or 0.1 mg/kg SVP-Rapamycin)
- Four infusion reactions with repeat dosing were observed with pegsitricase 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 pegsitricase 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 pegsitricase + 0.1 mg/kg SVP-Rapamycin – classified as an SAE
- One of the new patients in the 0.4 mg/kg pegsitricase + 0.08 mg/kg SVP-Rapamycin cohort had an infusion reaction during the first administration of SEL-110 – classified as an SAE

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 pegsitricase mitigates the formation of ADAs and enables sustained control of serum uric acid levels in most patients
- Evidence of immune tolerance was demonstrated after doses 4 and 5 of pegsitricase alone
- Lower incidence of gout flares with SEL-212 was observed compared to pegsitricase 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

Acknowledgements: We thank all of the patients that participated in this trial. We are very grateful to the clinical trial site investigators and the entire Selecta SEL-212 project team