Initial Phase 2 Clinical Data of SEL-212 in Symptomatic Gout Patients: Monthly Dosing of a Pegylated Uricase (Pegadricase) with SVP-Rapamycin Enables Sustained Reduction of Acute Gout Flares

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Abstract

Background: Pegylated uricases are therapies for treatment of severe chronic gout, particularly for rapid tophi resolution. 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 pegadricase (formerly known as pegsitricase) co-administered with synthetic vaccine particles encapsulating rapamycin (SVP-Rapamycin). We report initial data on gout flares from an ongoing Phase 2 study in symptomatic gout patients.

Gout is caused by the deposition of monosodium urate (MSU) crystals in joints due to chronic hyperuricemia. Long term treatment focuses on reducing serum uric acid (SUA) levels, thus allowing MSU crystals to dissolve. Rapid dissolution of MSU crystals during initial phase of urate lowering therapy (ULT) is associated with an increased frequency of acute gout flares, which can contribute to poor treatment compliance. During ULT initiation, colchicine, NSAIDs or corticosteroids are used for gout flare prophylaxis.

Methods: Patients with symptomatic gout (≥1 tophus, gout flare within 6 months or gouty arthropathy) and elevated serum uric acid SUA (≥6 mg/dL) were treated with monthly doses of pegadricase (0.2 mg/kg or 0.4 mg/kg) alone or in combination with SVP-Rapamycin (0.05 to 0.15 mg/kg). SEL-212 was infused in 28-day cycles x3 doses followed by challenge with pegadricase alone on 28-day cycles x2 doses, or in 28-day cycles x5 combination doses of SVP-Rapamycin and pegadricase. Safety, tolerability, SUA, and ADAs were monitored.

All randomized patients received colchicine (1.2 mg as loading dose, 0.6 mg QD for the remainder of their participation in the trial) as premedication for gout flare prevention. If colchicine was contraindicated, patients received ibuprofen 600 mg TID or equivalent dose of a NSAID. If colchicine and NSAIDs were contraindicated, patients did not receive any premedication.

Results: As of 09 Oct 2018, demographics of the 152 treated patients were as follows: 23 - 75 years old (mean 54.8 years), male 90.8%, and white 67.8%. The mean BMI at baseline was 34.8 kg/m^2. 71.7% of patients were obese with mean duration of established or symptomatic gout as 10.8 years.

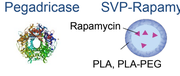
Flare incidence was 32.9% in months 1-3 and 11.1% in months 4-5. In these patients flare frequency was 0.62 flares/patient in months 1-3 and 0.17 flares/patient in months 4-5. Mean duration of the gout flares was 11.6 days, with majority of the gout flares (64.1%) being categorized as mild, 32.0% as moderate and 3.8% (4 cases) as severe in intensity. Adjustments to gout flare prevention medication were not required for 34% of the patients. No gout flares resulted in a patient discontinuation or were reported as a serious adverse event.

Conclusion: SEL-212 has been generally well-tolerated, and, compared to pegylated uricase alone, has mitigated immunogenicity, shown low flare rates, and enabled repeated monthly dosing with sustained control of SUA levels.

Background

SEL-212

- SEL-212 is a combination drug candidate comprised of pegadricase and SVP-Rapamycin
- SVP-Rapamycin is designed to induce the formation of regulatory T cells that mitigate the formation of anti-drug antibodies (ADAs)
- Ongoing Phase 2 clinical trial of SEL-212 has demonstrated low incidence of ADAs resulting in sustained reduction of serum uric acid (SUA) with monthly dosing (see Abstract 2254)



Gout Flares

- Acute gout attacks are characterized by a rapid onset of pain in the affected joint followed by warmth, swelling and pain[1]
- 69% of gout patients describe the pain of an attack as “miserable”, 23% of patients compare the pain of a gout attack to shattered glass piercing their skin, 28% to breaking a bone, 34% to a severe burn[2]
- Most people with gout will experience repeated bouts over the years

[1]www.uptodate.com/contents/treatment-of-gout-flares
[2]www.webmd.com/arthritis/news/20100611/gout-survey-offers-peek-at-the-pain

Effect of Urate Lowering Therapies on Gout Flares

- Dispersion of MSU crystals during the initial phase of deposit dissolution exposes the patient to an increased rate of acute flares
- Increased gout flare can adversely affect patient compliance[3]
- Pegylated uricase therapy, which rapidly debulks tissue uric acid, has been reported to induce gout flares in 75% of patients in the first months after initiation of therapy[4]

[3]Becker MA et al., Nucleic Acids 2008 27:585-91
[4]Sundy et al, JAMA, 306 7:711-720

Results

SEL-212/201: Ongoing Phase 2 Clinical Trial

Study description

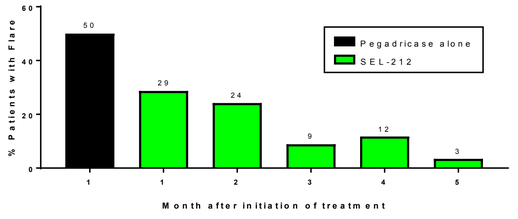
- Evaluate the safety, pharmacokinetics, pharmacodynamics and immunogenicity of repeated monthly IV infusions of SEL-212 in patients with symptomatic gout and elevated SUA levels (>6 mg/dL)
- Cohorts of patients administered either three q28 day IV infusions of 0.2 or 0.4 mg/kg pegadricase in combination with ascending doses (0.05 – 0.15 mg/kg) of SVP-Rapamycin followed by two q28 day IV infusions of 0.2 or 0.4 mg/kg pegadricase alone; or five q28 day IV infusions of 0.2 mg/kg pegadricase in combination with 0.1 - 0.15 mg/kg doses of SVP-Rapamycin
- Monitored for safety, SUA levels, uricase pharmacodynamic activity, and ADAs
- Male or female subjects ages 21 to 75 inclusive
- Demographics
  - 152 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: 8.1 mg/dL
  - Average age: 54.8 (range 23-75)
  - Male, 138 (90.8%); Female, 14 (9.2%)
  - Caucasian, 103 (67.8%); African American, 40 (26.3%); Asian 4 (2.6%) and Other 5 (3.3%)
  - Mean BMI at baseline: 34.8 kg/m^2 (71.7% of patients moderately obese)
  - Mean duration of established or symptomatic gout: 8.0 years.

Clinicaltrials.gov NCT02959918

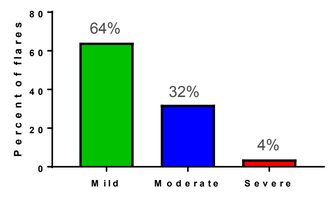
SEL-212 Treatment Cohorts

Cohort	Treatment Weeks 0, 4, 8 (months 1, 2, 3)		Treatment Weeks 12 + 16 (months 4, 5)		Status
	Pegadricase	SVP-Rapamycin	Pegadricase		
1	0.2 mg/kg	None	0.2 mg/kg		Dosing completed
2	0.4 mg/kg	None	0.4 mg/kg		Dosing completed
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		Dosing completed
11	0.2 mg/kg	0.15 mg/kg	0.2 mg/kg		Dosing completed
12	0.4 mg/kg	0.15 mg/kg	0.4 mg/kg		Dosing completed
Cohort	**Treatment Week 0**		**Treatment Weeks 4, 8, 12, 16**		**Status**
	Pegadricase	SVP-Rapamycin	Pegadricase	SVP-Rapamycin	
13	0.2 mg/kg	0.15 mg/kg	0.2 mg/kg	0.15 mg/kg	Ongoing
15	0.2 mg/kg	0.15 mg/kg	0.2 mg/kg	0.1 mg/kg	Ongoing
17	0.2 mg/kg	0.1 mg/kg	0.2 mg/kg	0.1 mg/kg	Ongoing

Low Gout Flare Rates with Reduction in Frequency During SEL-212 Therapy



Gout Flare Classification



Summary

- SEL-212 is a monthly combination product candidate being developed as a therapy for the sustained control of SUA leading to removal of urate crystal deposits in patients with chronic severe gout
- The percentage of patients who experienced flares was 29% during the first month after treatment and continued reduction was observed during months 2-5
- 96% of gout flares were mild or moderate in severity, and no new patient experienced a flare after the 2nd month
- Unlike with other urate lowering therapies that typically increase the incidence of flares at the beginning of treatment, the incidence of gout flares substantially decreases after the first and subsequent treatments with SEL-212
- Gout flares represented 13% of the total number of treatment-emergent adverse events (TEAEs) reported up to October 9, 2018 (708 days of follow up from the start of the study)
- No gout flares were classified as SAEs nor resulted in study drug discontinuations

Acknowledgements

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Disclosures

Authors are employees and shareholders of Selecta Biosciences

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