SAFETY & EFFICACY OF SEL-212 IN PATIENTS WITH GOUT REFRACTORY TO CONVENTIONAL TREATMENT: OUTCOMES FROM TWO RANDOMIZED, DOUBLE BLIND, PLACEBO-CONTROLLED, MULTICENTER PHASE III STUDIES

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Disclosures

- **Herbert S.B. Baraf** Speakers bureau: Horizon Pharmaceuticals, Grant/research support from: Horizon Pharmaceuticals, Swedish Orphan Biovitrum
- **Alan Kivitz** Consultant of: AXDEV Group, Amgen, Pfizer, Janssen, Boehringer Ingelheim, AbbVie, Flexion, Gilead, Grünenthal, Orion, Regeneron, Sun Pharma Advance Research, and ECOR1, Speakers bureau: Merck & Co, Eli Lilly, Novartis, Pfizer, Flexion, AbbVie, Amgen, Genentech, Regeneron, UCB, Horizon, and GSK, Shareholder of: Pfizer, GSK, Gilead, Novartis, and Amgen
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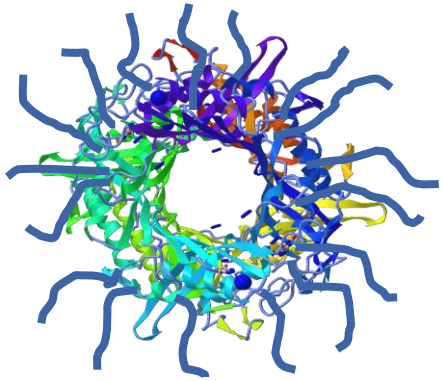
Patients with refractory gout have limited effective therapeutic options

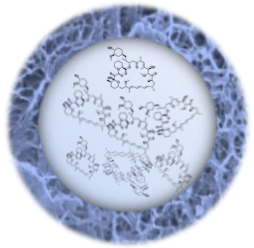
- **ACR 2020 guidelines "strongly recommend"** uricase-based therapy for gout patients who:[1]
  - *"have failed to achieve uric acid lowering targets"*
    AND
  - *"continue to have frequent gout flares…"*
    OR
  - *…nonresolving tophi*"
- Uricase-based therapy is effective for refractory gout but:
  "comes with …, twice-monthly infusions, and the potential for serious allergic reactions"[1]
- Immunogenicity of the one US-approved uricase-based treatment can impair efficacy and increase the incidence of infusion reactions[2]
  - May contribute to the 29-58% treatment failure rate with uricase therapy[3-5]
- This presentation includes top line data from DISSOLVE Phase 3 studies of SEL-212, which is being explored as a potential new uricase-based therapy

[1]Fitzgerald JD, et al. Arthritis Care Res 2020;72(6):744-60; [2]KRYSTEXXA® (pegloticase) prescribing information: Available at: https://www.hzndocs.com/KRYSTEXXA-Prescribing-Information.pdf. Accessed May 2023; [3]Sundy et. al JAMA 2011;306(7):711-720; [4]Botson J, et al. Arthritis Rheumatol 2022; 74(suppl 9); [5]Botson J, et al. Ann Rheum Dis 2022;81:112-113.

SEL-212 is a monthly 2-component infusion therapy designed to treat refractory gout



SEL-037 – Pegadricase (a PEGylated uricase)



SEL-110 – Rapamycin encapsulated in biodegradable polymeric nanoparticles

- Pegadricase (**SEL-037**) is a potent pegylated uricase that converts uric acid to soluble and readily excreted allantoin[1,2]
- Pegadricase, like most uricases, elicits a vigorous ADA response, limiting its use as a monotherapy[2]
- **SEL-110**, an immune-tolerizing nanoencapsulated rapamycin, administered 30 minutes before pegadricase, has demonstrated dose dependent inhibition of anti-pegadricase antibodies in phase 1 and phase 2 trials[1,2]
- **SEL-212** is the combination of the sequential infusion of these 2 components

ADA, anti-drug antibodies; sUA, serum uric acid

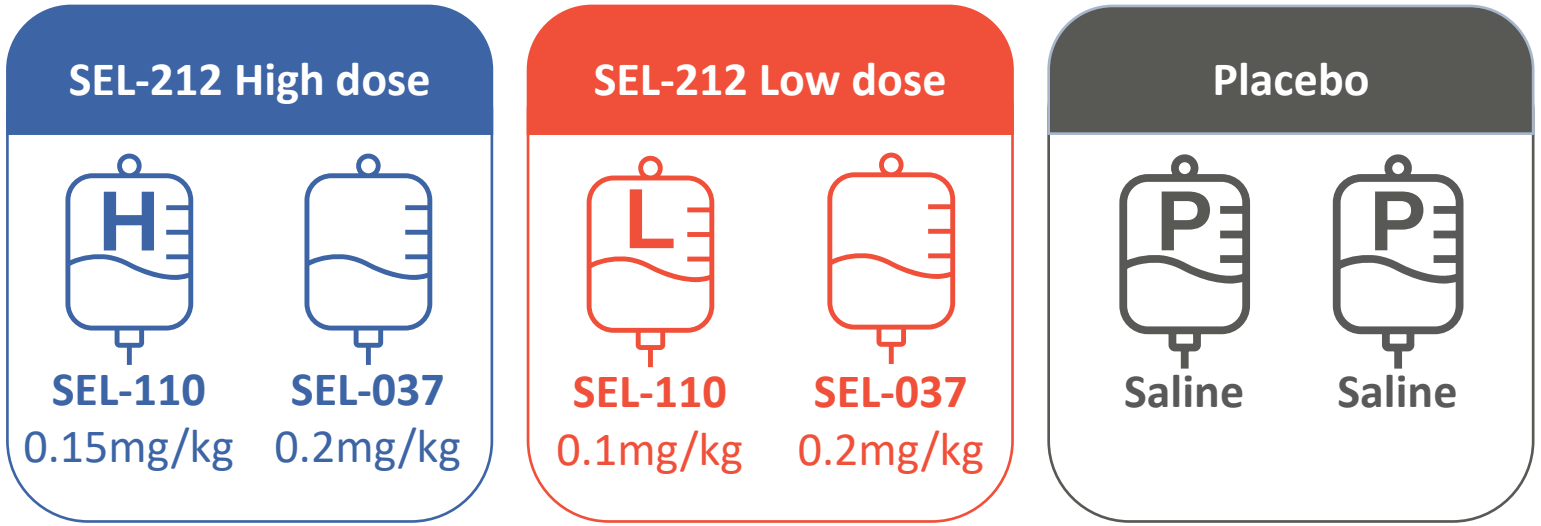
[1]Sands et al. Nature Communications 2022. 13:272; [2]Kivitz A, et. al. Rheumatol Ther.2023. doi: 10.1007/s40744-023-00546-0

DISSOLVE I & II study design: Two replicate, double blind, placebo-controlled trials

Participants were:

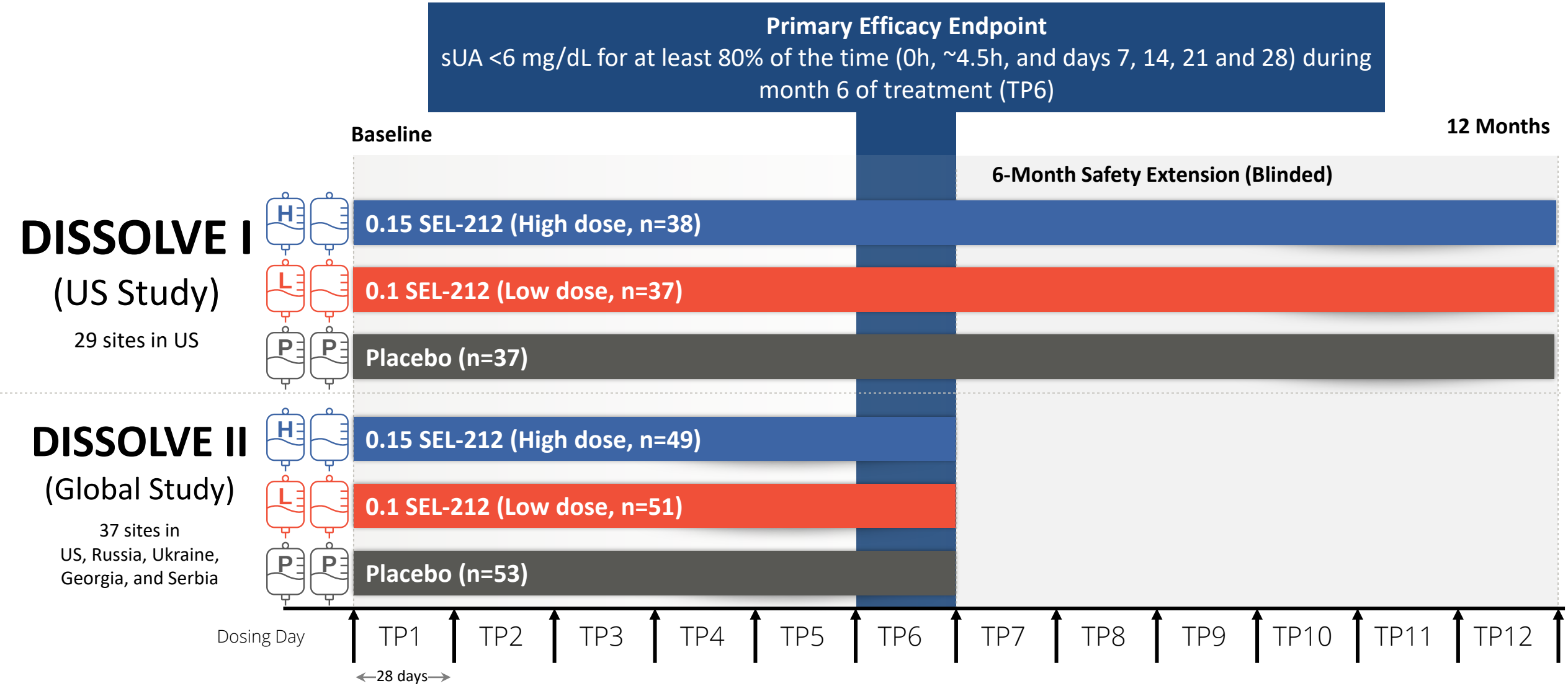
Allocated into 3 study arms, randomized 1:1:1

Administered sequential infusions every 28 days



- Treatment arms differed in the dose level of SEL-110 (0.15 vs 0.1 mg/kg)
- Patients in both treatment arms received 0.2 mg/kg of pegadricase (SEL-037)
- Placebo patients received sequential infusions of saline
- Prophylaxis against infusion reactions and gout flares were given to all participants

DISSOLVE I & II study design



IV, intravenous; sUA, serum uric acid; TP, treatment period

DISSOLVE I & II study design: Participant selection

Key inclusion criteria

- Adults with history of symptomatic gout
  - ≥3 gout flares within 18 months prior to screening, **OR**
  - or ≥1 tophus, **OR**
  - current diagnosis of gouty arthritis
- History of chronic refractory gout:
  - Failure to normalize sUA and control symptoms with any xanthine oxidase inhibitor
- Screening sUA ≥7 mg/dL

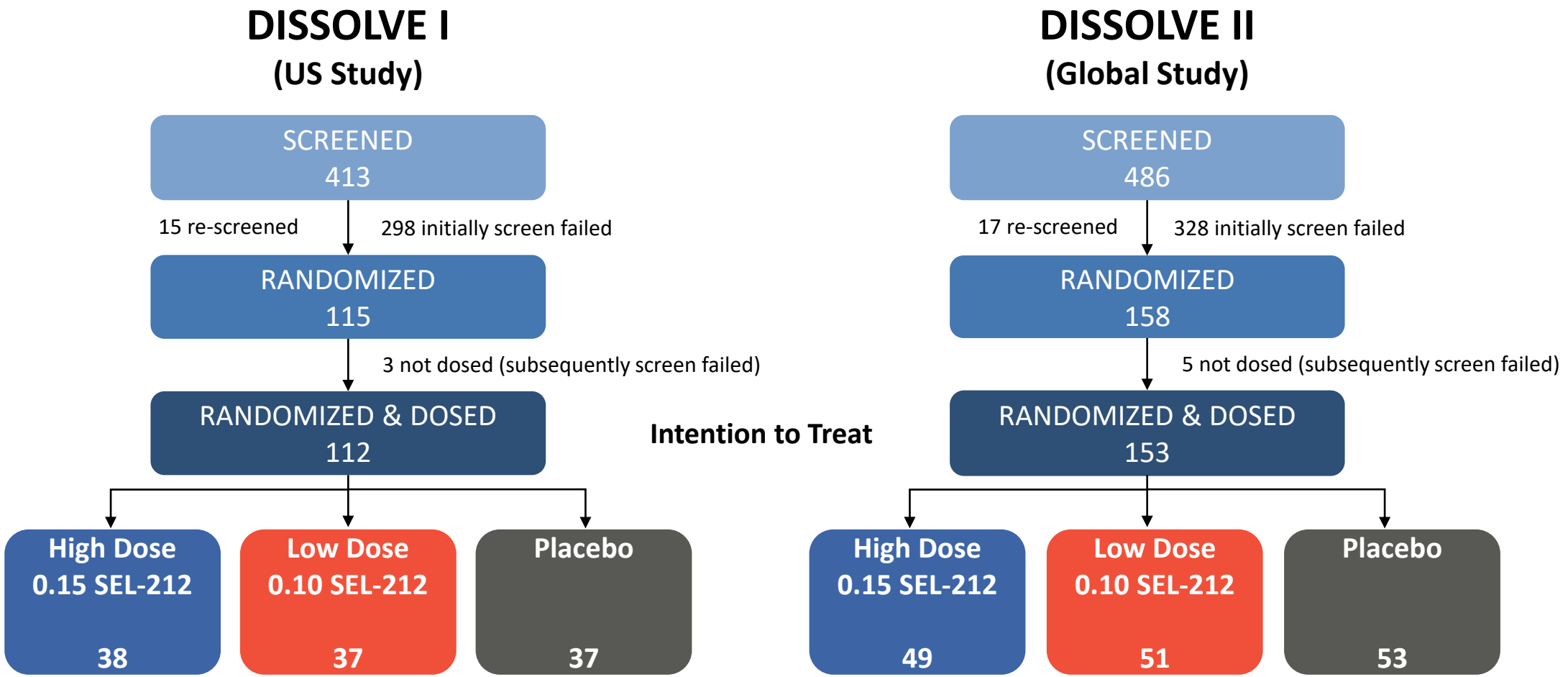
Key exclusion criteria

- History of anaphylaxis, severe allergic reactions, or severe atopy
- Allergy to PEGylated products
- Requires drugs known to interact with rapamycin
- Uncontrolled diabetes or hypertension
- Unstable cardiovascular/cerebrovascular disease or congestive heart failure (NY Heart Association Class III or IV)
- Prior exposure to experimental or marketed uricase therapy
- G6PD deficiency

Stringent stopping rules were implemented to minimize the risk of infusion related adverse events

G6PD, glucose-6-phosphate dehydrogenase; IV, intravenous; NY, New York; sUA, serum uric acid; TP, treatment period

Subject flow



ITT, intention to treat

Baseline demographics

	DISSOLVE I (US Study)			DISSOLVE II (Global Study)		
	High dose (38)	Low dose (37)	Placebo (37)	High dose (49)	Low dose (51)	Placebo (53)
Age in years, mean (SD)	54 (12)	55 (10.6)	54 (10.6)	56 (9.7)	53 (10.6)	57 (10.1)
Age ≥50 years, %	66	73	60	76	61	79
BMI, mean (SD)(kg/m²)	35 (6.4)	34 (7.5)	33 (6.3)	33 (5.2)	32 (6.3)	33 (6.2)
Gender, %						
Male	92	95	100	96	96	98
Race, %						
White	71	76	59	96	88	83
Region, n (%)						
United States	38 (100)	37 (100)	37 (100)	14 (29)	18 (35)	24 (45)
Russia, Ukraine, Serbia, Georgia	-	-	-	35 (71)	33 (65)	29 (55)

- Balanced for age, BMI, and sex across treatment groups in both studies
- Racial imbalances were noted in both studies
- ~15% of DISSOLVE II patients were from Russia and Ukraine

BMI, body mass index; n, number; SD, standard deviation

Disease characteristics

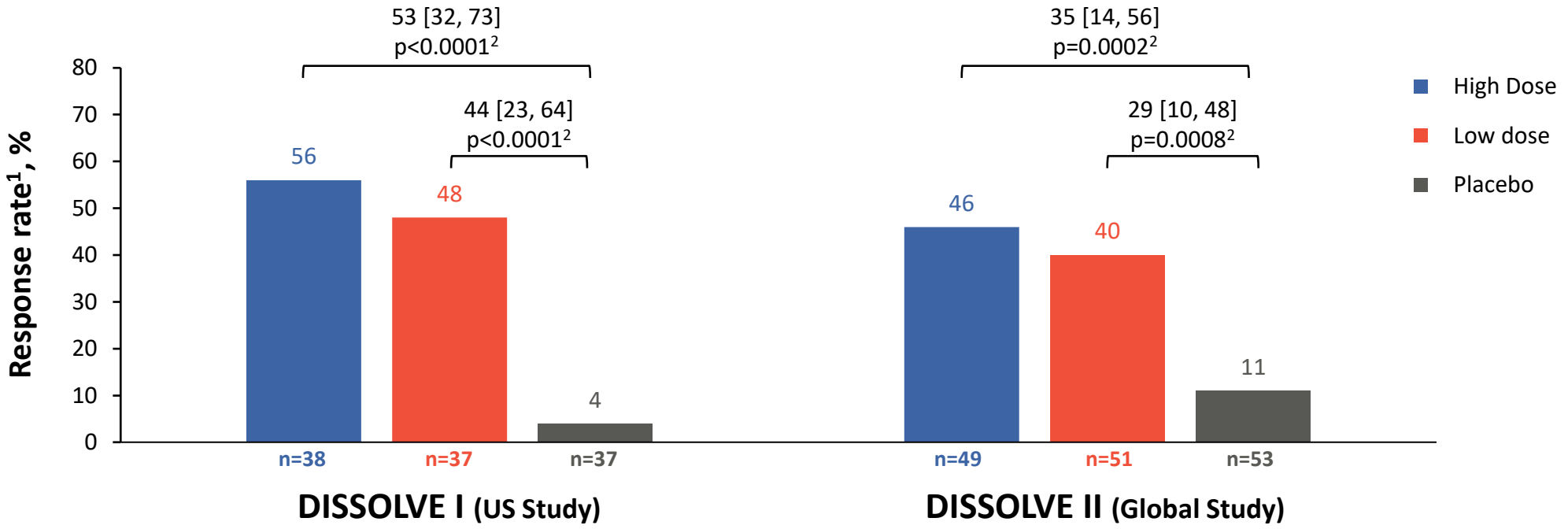
	DISSOLVE I (US Study)			DISSOLVE II (Global Study)		
	High dose (38)	Low dose (37)	Placebo (37)	High dose (49)	Low dose (51)	Placebo (53)
Duration of gout diagnosis, years	14.3 (10.5)	11.9 (10.0)	12.4 (9.6)	10.8 (9.0)	11.6 (9.0)	10.5 (7.5)
Participants with tophi at baseline: n (%)	22 (57.9)	21 (56.8)	21 (56.8)	33 (67.3)	34 (66.7)	36 (67.9)
sUA (mg/dL)	8.7 (1.4)	8.2 (1.9)	8.3 (1.5)	8.4 (1.7)	8.6 (1.5)	9.1 (1.6)
Tender joints	1.9 (5.1)	3.5 (6.4)	2.6 (9.9)	11.6 (11.5)	11.1 (12.8)	10.6 (11.5)
Swollen joints	2.0 (4.3)	3.6 (7.5)	1.0 (3.4)	6.9 (10.4)	4.4 (8.1)	7.0 (9.0)

- Gout severity was numerically greater in **DISSOLVE II** as evidenced by a higher baseline incidence of tophi, tender joints and swollen joints

Data are represented as mean (standard deviation) unless otherwise stated.

sUA, serum uric acid

Primary endpoint: Response to SEL-212 versus placebo



Primary efficacy endpoints were met for both studies and doses

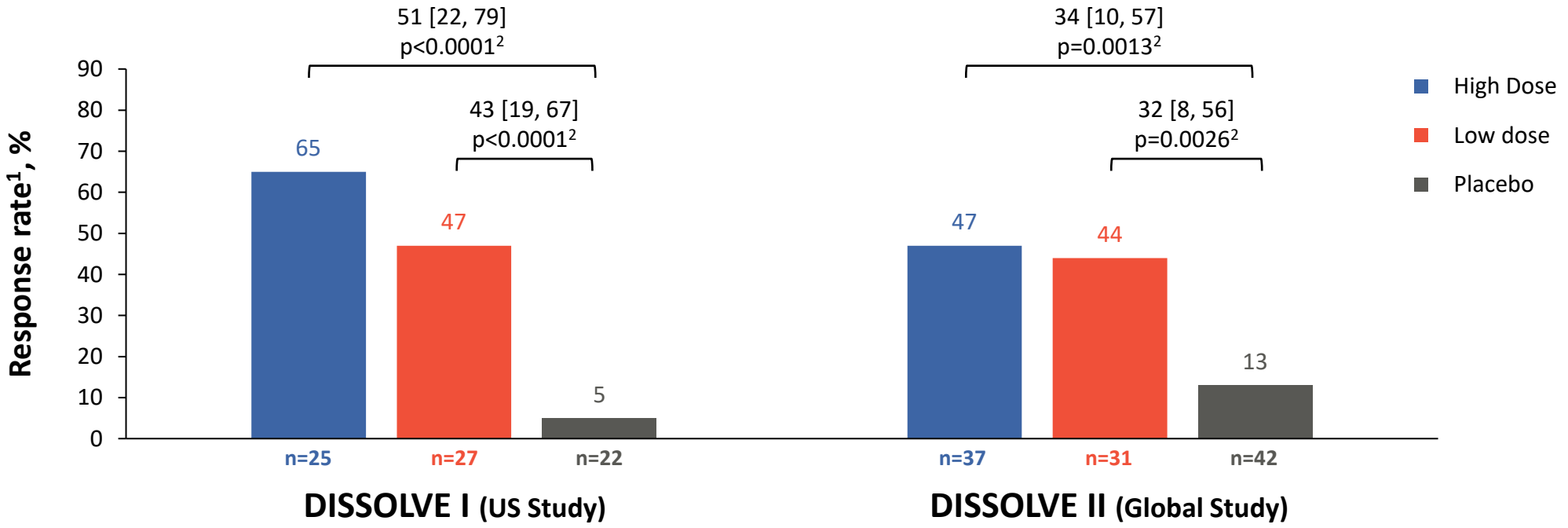
- In the high dose group, **56%** and **46%** of patients responded to treatment in DISSOLVE I & II, respectively
- In the low dose group, **48%** and **40%** of patients responded to treatment in DISSOLVE I & II, respectively

CI, confidence interval of the risk difference

[1]Responders were defined as subjects with sUA levels <6mg/dL for at least 80% of the time during month 6 of therapy (TP6). Subjects who dropped from study due to stopping rule, AE, and COVID were considered non-responders. Percentages shown are averaged over multiple imputed datasets for missing sUA for withdrawal of consent, lost to follow-up, and other as per FDA guidance.

[2]Difference vs placebo [97.5% CI] and p-value versus placebo group for each treatment group are indicated above each bracket

SEL-212 versus placebo in patients aged ≥50 years



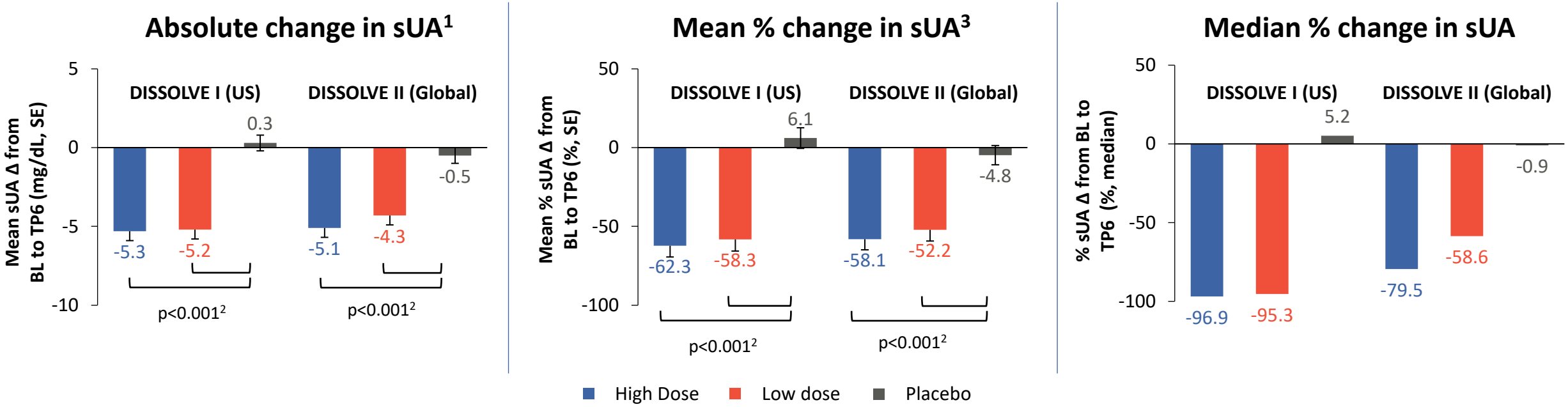
- A pre-specified subanalysis of patients aged ≥50 years showed response rates[1] of **65%** and **47%** in the high dose group for the US & Global Studies, respectively

CI, confidence interval

[1]Responders were defined as subjects with sUA levels <6mg/dL for at least 80% of the time during month 6 of therapy (TP6). Subjects who dropped from study due to stopping rule, AE, and COVID were considered non-responders. Percentages shown are averaged over multiple imputed datasets for missing sUA for withdrawal of consent, lost to follow-up, and other as per FDA guidance.

[2]Difference vs placebo [97.5% CI] and p-value versus placebo group for each treatment group are indicated above each bracket

Significant reduction of serum uric acid from baseline to TP6



- Significant reductions in sUA were observed for all treatment groups compared to placebo
- Analyses include all available patient data, including those withdrawn from treatment
- Median % change estimates indicate very large reductions in at least half of patients
- Analyses of secondary endpoints are ongoing

BL, baseline; sUA, serum uric acid; TP, treatment period

[1]Reduction of mean sUA as computed by subtracting the Baseline (BL) sUA level from the mean sUA during Treatment Period 6 (TP6) defined as the area under the time curve divided by the corresponding time interval.

[2]Analysis using ANCOVA model with reduction or percent reduction of mean sUA at TP6 from baseline as dependent variable and randomization stratum and baseline sUA as covariates. Missing values of change or percent change from baseline were multiple imputed by using the Recursively Partitioned Mixture Model. The means of treatment groups are pooled estimates after multiple imputation and 2-sided p-values.

[3]Percent reduction mean sUA as computed by subtracting Baseline (BL) sUA level from the mean sUA during TP6 divided by the Baseline and reported as either absolute difference or percent difference.

All Adverse Events of Special Interest (AESI)[1]

Safety Set	Pooled Studies at 6-Month Primary Endpoint		
	High dose (87) n (%)	Low dose (88) n (%)	Placebo (90) n (%)
≥1 Treatment-emergent AESI	55 (63.2)	60 (68.2)	49 (54.4)
Gout Flares	38 (43.7)	40 (45.5)	39 (43.3)
Infections (including viral)	20 (23.0)	16 (18.2)	15 (16.7)
COVID-19[2]	6 (6.9)	5 (5.7)	6 (6.7)
Infusion-related AEs (24h)	6 (6.9)	6 (6.8)	2 (2.2)
Infusion reactions (1h) incl. anaphylaxis	3 (3.4)	4 (4.5)	0 (0)
Hypertriglyceridemia[3]	7 (8.0)	8 (9.1)	6 (6.7)
Stomatitis[4]	8 (9.2)	3 (3.4)	0 (0)
Proteinuria/renal impairment/ ↑ creatinine	1 (1.1)	2 (2.3)	3 (3.3)
Thromboembolism	0 (0)	1 (1.1)	0 (0)
Leukopenia	0 (0)	2 (2.3)	0 (0)
Miscellaneous[5]	0 (0)	0 (0)	2 (2.2)

[1] AESIs included in protocol as agreed with FDA; No other TEAEs ≥5%
[2] There were no other individual infections >2%
[3] Dyslipidemia/hypertriglyceridemia/hyperlipidemia
[4] Stomatitis/oral ulcer/aphthous ulcer; 67% mild, 33% moderate
[5] Influenza-like (1), ↑LDL (1)

- No increase in gout flares between active treatment and placebo groups
- Low incidence of infusion reactions in high and low dose groups
- All IRs occurred with the first three infusions and resolved when infusions were stopped
- Stomatitis in treatment groups were all mild to moderate intensity and did not result in withdrawal of any patient

AE, adverse event; AESI, adverse event of special interest; FDA, Food & Drug Administration; IRs, infusion reactions; LDL, low-density lipoprotein; TEAE; treatment emergent adverse event

Serious Adverse Events (SAEs)

	Pooled Studies at 6-Month Primary Endpoint		
	High dose (87) n (%)	Low dose (88) n (%)	Placebo (90) n (%)
Subjects with ≥1 SAE	6 (6.9)	13 (14.8)	2 (2.2)
Subjects with treatment-related SAE	3 (3.4) [1]	3 (3.4) [2]	0 (0)
Primary per Patient			
Infections	0 (0)	4 (4.5) [3]	1 (1.1) [4]
Anaphylaxis	2 (2.3)	2 (2.3)	0 (0)
Gout Flare	1 (1.1)	1 (1.1)	0 (0)
GI, Renal, Liver, & Neuro	2 (2.3) [5]	4 (4.5) [6]	1 (1.1) [7]
Cardio & Vascular	1 (1.1) [8]	2 (2.3) [9]	0 (0)

[1] **US:** Gout flare (1), **Global:** Anaphylaxis (2);
[2] **US:** Anaphylaxis (2), Gout Flare (1)
[3] **US**: Periodontal infection/cellulitis (1), C. diff colitis (1), **Global:** Pneumonia/Resp Failure/Sepsis (1); infected tophus (1)
[4] **Global:** COVID-19 (1)
[5] **US:** GI bleed (1) **Global:** Acute Renal Injury (1)

[6] **US:** Presyncope (1), Cholelithiasis (1), Post Traumatic Subarachnoid Hemorrhage (1),
Global: Enteritis (1)
[7] **Global**: Diverticular Hemorrhage (1)
[8] **Global**: Angina Pectoris (1)
[9] **Global:** Pulmonary Embolism (1) Acute myocardial infarction (1)

- Six patients (3.4%) in the pooled active treatment groups had an SAE related to treatment (n=4 anaphylaxis, n=2 gout flares)
- No other SAEs were evaluated as treatment-related

GI, gastrointestinal; SAE, serious adverse event

Conclusions

- For all treatment groups, the DISSOLVE studies **met the primary efficacy endpoint** of achieving and maintaining a sUA <6 mg/dL for ≥80% of the time during the sixth treatment period.
- The response rate[1] and sUA reduction were statistically significant against placebo with **once-monthly SEL-212**
- The high dose response rate was **56%** in DISSOLVE I and **46%** in DISSOLVE II
- **For patients ≥50 years old,** the high dose response rate was **65%** and **47%** in DISSOLVE I & II, respectively
- Infusion reaction incidence was **3.4%** in the combined **high dose** groups
- The **efficacy and safety of SEL-212** in these Phase 3 trials indicate that **targeted immunomodulation with nanoencapsulated rapamycin** may have the potential to provide a **new once-monthly uricase-based treatment option** for patients with refractory gout.

sUA, serum uric acid

[1]Defined as the % of patients who achieved and maintained a sUA < 6 mg/dL for at least 80% of the time during the sixth 28-day treatment period (TP6).

Thank you to the entire team

most importantly

participating patients & their families