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A randomized, placebo-controlled trial of long-acting dexamethasone viscous gel delivered by transforaminal injection for lumbosacral radicular pain

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Abstract

Epidural steroid injections are used to treat lumbosacral radicular pain. However, there are no Food and Drug Administration–approved corticosteroids for lumbosacral radicular pain and all currently available injectable corticosteroids carry safety warnings about their use in epidural steroid injection procedures. SP-102 (dexamethasone injectable viscous gel) was developed to provide a safer option with extended local effect. In a randomized, double-blind, placebo-controlled, multicenter trial, 401 patients with moderate-to-severe leg pain from unilateral intervertebral lumbar disc herniation were randomized (1:1) to receive transforaminal SP-102 or sham intramuscular (IM) placebo injection and followed for 24 weeks. If clinically warranted, a repeat open-label SP-102 injection was allowed between 4 and 20 weeks for both groups. Primary and key secondary end points were change in average daily pain on the Numeric Pain Rating Scale in the affected leg and disability measured by Oswestry Disability Index over 4 weeks. Other secondary end points included time to repeat injection, pain, and quality of life assessments. Over 4 weeks, SP-102 demonstrated statistically significant pain relief compared with placebo (least-squares mean group difference −0.52 [SE 0.163] [$P = 0.002$]) in the intent-to-treat population. Oswestry Disability Index mean improvement was −3.38 (1.388) (least-squares mean group difference [SE]) for SP-102 vs placebo ($P = 0.015$). Median time to repeat injection was 84 days for SP-102 vs 58 days for placebo ($P = 0.001$). Most other secondary end points were statistically significant for SP-102 compared with placebo. There were no serious adverse events related to study medication or procedure, no adverse events leading to death, and no AEs of special interest (paraplegia, hematoma, or infection).

Trial Registration

ClinicalTrials.gov Identifier: NCT03372161.

Keywords: Epidural Steroid Injections, ESI, Epidural, Anesthesia, Dexamethasone, sciatica, Lumbar radiculopathy, SP-102, Dexamethasone injectable viscous gel, Lumbosacral radiculopathy, LSR

In a randomized, double-blind, placebo-controlled trial, involving 401 patients with lumbosacral radicular pain, SP-102 (dexamethasone injectable viscous gel) transforaminal injection demonstrated significant pain relief compared with placebo.

1. Introduction

Lumbosacral radicular pain (LRP), "sciatica," is a common debilitating disorder associated with persistent morbidity and impact on

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daily function. It can lead to short-term and long-term disability, increased healthcare costs, and is a leading cause of work-related disability in the Western World.[17,20,38] Lumbosacral radicular pain has an annual incidence and prevalence of 1% to 5% and 9.8%, respectively, accounting for a lifetime incidence of 13% to 40%.[17,18,20] There are several conservative treatments used initially, with few regimens shown to be effective. These therapeutic approaches include oral corticosteroids, nonsteroidal anti-inflammatory drugs, acupuncture, spinal manipulations, traction therapy, physical therapy, and psychological treatments.[7,24,44] When conservative treatments fail, patients are often referred by their primary care physicians for further interventions including epidural steroid injections (ESIs) and eventually surgery.[1,27,41] In systematic reviews, ESIs have been shown to prevent surgery in selected patients for up to 1 year, suggesting that longer-lasting formulations might further prevent need for surgery.[6,21]

There are no pharmaceutical products, oral or parenteral, approved by the Food and Drug Administration (FDA) for the treatment of LRP. Whereas corticosteroid injectables are often used off-label to treat LRP, currently available corticosteroids have not demonstrated safety or efficacy in well-controlled clinical trials and may confer neurologic risks including death, as listed on the product labels.[4,10,33,34,43]

Based on an analysis from the FDA Adverse Event Reporting System database and reports in the medical literature of serious neurologic AEs associated with ESIs, FDA issued a warning on April 23, 2014, that the injection of corticosteroids into the epidural space of the spine *"may result in rare, serious adverse events (SAEs) including the loss of vision, stroke, paralysis, and death."*[15] As a result of the FDA warning, a multidisciplinary working group from 13 societies formulated safety guidelines for ESIs and recommended the use of nonparticulate steroid products for transforaminal (TF) ESI.[36] The rationale for the latter was that rare but severe neurological complications with ESI are more often associated with TF injections of particulate corticosteroids (suspension products).[5]

SP-102 (10 mg of dexamethasone sodium phosphate in 2 mL of viscous gel solution) is an investigational injectable product designed to produce an immediate effect while increasing the residence time of dexamethasone at the site of epidural injection without an increase in systemic drug exposure or use of particulates or preservatives.[45] Thus, treatment with this unique formulation may result in a longer duration of benefit and an improved safety profile relative to currently used corticosteroids. The Corticosteroid Lumbosacral Epidural Analgesia for Radiculopathy (CLEAR) trial was designed to investigate the safety and efficacy of single and repeat SP-102 TF injections compared with a placebo sham intramuscular (IM) injection in patients with LRP.

2. Methods

2.1. Trial oversight

The CLEAR trial (ClinicalTrials.gov Identifier: NCT03372161) was a double-blind, randomized, placebo-controlled, multicenter trial that was conducted at clinical sites in the United States under an investigational new drug application submitted to FDA. The study was approved by Copernicus Group Independent Review Board on November 27, 2017, and performed in accordance with the principles of the Declaration of Helsinki and good clinical practices under the International Conference on Harmonization.

2.2. Trial population

Patients aged 18 to 70 years were screened for current episodes of LRP and enrolled across 37 sites between January 2018 and January 2022. Key inclusion criteria were a Numeric Pain Rating Scale (NPRS) of 4 to 9 in the affected leg and ≤3 NPRS in the nonaffected leg over 12 hours that was present for at least 6 weeks but not more than 9 months, clinical symptoms consistent with magnetic resonance imaging (ie, unilateral nerve root impingement at one lumbosacral level secondary to a herniated disc), and highest pain rating in the affected leg greater than the highest pain rating in the lower back in the 3 days before screening. Patients were required to discontinue the use of nonsteroidal anti-inflammatory drugs for treating radicular pain symptoms but were allowed to continue a stable dose of oral nonopioid analgesics for indications other than radicular pain. Key exclusion criteria were patients who were morbidly obese (ie, body mass index ≥40 kg/m^2), have evidence of spinal cord tumor(s), epidural or intrathecal abscess, systemic infection, history of lumbosacral surgery, significant lumbosacral disease, significant motor impairment, have fibromyalgia, already undergoing ESI treatment for the current episode, have insulin-dependent diabetes mellitus, use of any investigational drug and/or device, or had a clinical history of other pain conditions that might confound efficacy assessments. Patients who were taking low-dose opioids within 30 days before screening were allowed to participate in this study if they agreed to discontinue opioid therapy. At screening, patient demographic information was collected, including race and ethnicity (self-identified), age, weight, height, and body mass index.

2.3. Trial procedures

The study compared the effect of a TF injection of SP-102 against placebo sham IM injection in the treatment of LRP. Other design considerations included the use of an active comparator as a positive control such as a TF injection of a commercially available corticosteroid, which was problematic given lack of standard TF ESI therapy relative to corticosteroid, dose, injection volume, and coadministration with local anesthetics (eg, lidocaine).[19]

The use of a commercially available corticosteroid would also involve a comparator product specifically labeled with warnings of serious neurologic reactions associated with the exact epidural administration that it would be used in the study. Specifically, patients would need to consent to potential administration of a comparator product that is warned of the following: "serious neurologic events, some resulting in death, have been reported with epidural injection of corticosteroids. Specific events reported include, but are not limited to, spinal cord infarction, paraplegia, quadriplegia, cortical blindness, and stroke. These serious neurologic events have been reported with and without use of fluoroscopy. The safety and effectiveness of epidural administration of corticosteroids have not been established, and corticosteroids are not approved for this use."[4,10,33,34,44] Relative to patient risk, it was prudent to control the study with an IM placebo injection vs the use of an active comparator that is not recognized to be effective and presents significant safety risks that would be challenging to reconcile in an informed consent.

Before study participation, study-related information was presented in an informed consent form containing all essential elements in accordance with the Code of Federal Regulations. Study assessments were organized and completed in temporal order at each study visit according to the schedule of assessment in the protocol. Patient reported outcomes were collected directly from patients in electronic diaries (eDiaries), and all other data

collection was entered into an electronic data capture system by study staff delegated their responsibilities by the principal investigator at each site.

After meeting eligibility criteria, patients were randomized using an Interactive Web Response System to receive a course of treatment of single SP-102 TF dose or placebo IM injection in a blinded fashion and followed for 24 weeks (**Fig. 1**). A schedule involving a block randomization technique, randomly assigned participants on a 1:1 allocation ratio. The randomization schedule was stratified by study site. The investigational product (IP) was provided to the pharmacy in a blinded fashion. From the pharmacy, after randomization assignment and before the injection procedure, a single drug package was dispensed to site staff. The outer packaging was a white box, marked with an IP label and IP Kit identification. The inner contents of the white box included a silver sealed pouch containing a prefilled syringe of active drug or placebo. The contents of the drug package remained unopened until the unblinded Physician was prepared to begin the injection. Only the Injection Physician and other designated unblinded staff were unblinded to the contents of the silver pouch upon dosing of each subject when he/she opened the pouch. All other site staff entirely avoided visibility to the contents of the silver pouch when opened by the Injection Physician, during the injection, and after the injection to ensure they remained blinded to each subject's drug assignment. After injection, the Injection Physician returned the used active or placebo syringe to the silver pouch, sealed it with tamper-evident tape, and the silver pouch was then returned to the outer white box; thus, ensuring the contents of the used drug package remained blinded from any staff handling and accounting for the dispensed IP.[22]

Using fluoroscopic guidance in multiple views and verification of epidural contrast spread, the SP-102 TF initial injection was made at the affected nerve root corresponding to the site of disc herniation, whereas the placebo was given IM into the posterior multifidus muscle to avoid risks associated with neuraxial injection. All patients were blinded to treatment assignment, and there were no reports of patients becoming unblinded during the study.

Patients were contacted 2 days after each injection to discuss progress, review their medication list, and determine whether they had any AEs. All patients were seen at the clinic on day 15 and every 4 weeks after the initial injection. If the patient continued to experience an NPRS average daily pain of 4 to 9 in the affected leg between weeks 4 and 20, they were considered for an optional open-label repeat injection of SP-102 at the investigator's discretion. The repeat injection was made optional for all patients regardless of receiving SP-102 or placebo as the initial treatment. Patients receiving a repeat injection were also seen in clinic 14 days after the injection and continued with regularly planned visits. Patients completed their eDiary twice daily for 12 weeks after the initial injection.

For participants who experienced inadequate control of radicular pain postinjection, up to 3 g/day of acetaminophen could be taken as rescue medication. To avoid confounding the pain assessment, patients were instructed to avoid use of acetaminophen within 6 hours before recording an NPRS score.

2.4. Outcome measures

The primary efficacy end point was the change of the mean NPRS average pain score over the first 4 weeks in the affected leg. The key secondary end point was change in Oswestry Disability Index (ODI)[13] total score from baseline to week 4. Other secondary end points included time to repeat injection, proportion of patients receiving a repeat injection, mean change in PainDETECT,[16] mean change in Brief Pain Inventory-Short Form (BPI-SF) score, proportion of patients achieving reductions (30%, 50%, and 75%) in mean NPRS average pain score in the affected leg, mean change in NPRS lower back pain, Patient Global Impression of Change (PGIC), Clinical Global Impression of Change (CGIC), cumulative use of rescue medication, time to first rescue medication dose, and proportion of patients requiring rescue medications.

The safety end points included AEs, changes in laboratory parameters, vital signs, and neurological examinations.

2.5. Statistical analysis plan

A prospective statistical analysis plan was finalized before unblinding and data analyses. The "all randomized" population was the same as that of the intent-to-treat (ITT) population. The safety analysis population included all randomized patients who received a study drug injection. The modified ITT (mITT) population was the primary population and included all randomized patients who received a verified initial injection of SP-102 or placebo. For this mITT population, a verified injection for the SP-102 group were patients for whom the spread of iodinated contrast is confirmed through imaging to be in the epidural space. A verified injection for the placebo group were patients for whom the needle placement was confirmed through imaging to be in the muscle. Review of fluoroscopy imaging data was conducted by an independent interventional pain physician and radiologist, not associated with investigative sites or clinical data collection.

The prespecified primary and secondary end points were analyzed using a restricted maximum likelihood–based mixed model for repeated measures with fixed effects for treatment (SP-102 or placebo), week, site, Pain Catastrophizing Scale group (<30 or ≥ 30), baseline averaged daily leg pain score, and treatment-by-week interaction. Study week was included in the model as a categorical variable (weeks 1 through 4) along with the treatment-by-week interaction. The unstructured covariance was used for the analysis. The primary comparison used a linear contrast of the least squares (LS) means comparing the mean weekly mean scores up to week 4 (average of weeks 1, 2, 3, and 4 change from baseline LS means estimated from the model). A pattern-mixture model with control-based pattern imputation

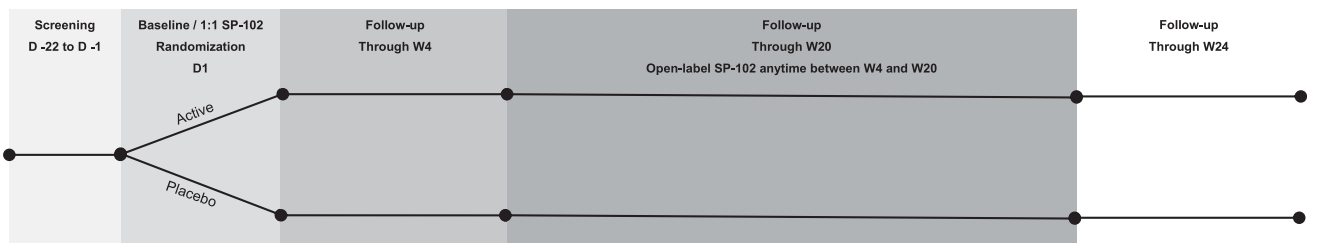

Figure 1. Corticosteroid Lumbosacral Epidural Analgesia for Radiculopathy trial schema.

was used as a sensitivity analysis. For the group of patients receiving repeat injections, PGIC, CGIC, NPRS responder analyses, and proportion of patients requiring rescue medications, chi square tests were performed. Time to repeat injection and first rescue medication dose were analyzed using Kaplan–Meier survival analysis. Cumulative use of rescue medication was analyzed using an analysis of variance model with treatment as the effect. Two identical sets of analyses for all efficacy end points were performed in randomized (ITT) and mITT populations.

The sample size was calculated to provide 90% power to detect a 1-point difference in change from baseline in the mean NPRS average daily leg pain score in the affected leg over 4 weeks between the 2 treatment groups using a Student's *t*-test with a 2-sided 0.05 significance level assuming a SD of 2.8. The minimal perceptible difference for group comparison against placebo was selected based on Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials recommendations.[12] This resulted in a requirement of 166 completers per treatment group through week 4.

To account for an anticipated 15% dropout rate, approximately 400 patients were targeted for enrollment at 45 sites. These estimates were based on published reviews of relevant clinical data.[8,37,46]

Cohen's d is presented as the standardized effect size (SES) for the primary result and is determined by calculating the mean difference between the active and placebo groups (ie, Group A mean–Group B mean) and then divided by the pooled SD. Cohen's d is commonly used for the SES because it relates the mean difference to the variability, similar to a signal-to-noise ratio (ie, a large Cohen's d indicates the mean difference is large compared with the variability). This is also the best metric to compare across studies and different products for similar indications.[12,25,42]

3. Results

3.1. Patient disposition and baseline demographics

A total of 401 patients were enrolled (ITT/Safety population; SP-102: n = 202; placebo: n = 199) across 37 sites and the baseline demographics were balanced between treatment groups. Most patients were female (59.4%), and the mean age of all patients was 51.4 years (range of 21-70). For racial breakdown, most patients were White (80.3%) followed by African Americans (17.5%) and Asians (1.7%; **Table 1**). There were 58 patients (48 SP-102, 10 placebo) for whom injections were unverifiable (could not be confirmed through fluoroscopy imaging; mITT population; SP-102: n = 154; Placebo: n = 189; **Fig. 2**). Among these, there were 9 patients (5 SP-102, 4 placebo) who terminated this study early, with 4 patients (3 SP-102, 1 placebo) lost to follow-up and the remaining 5 patients (2 SP-102, 3 placebo) withdrawing from this study.

After the primary analysis period (week 4), and if the patients continued to experience an NPRS average daily leg pain between 4 and 9, a repeat injection of open-label SP-102 was made optional at the investigator's discretion. A total of 354 patients received at least a single injection of SP-102 with 134 patients receiving both the initial and repeat injections. The remainder of the patients received a single SP-102 injection (n = 68) or repeat injection after the placebo injection (n = 152). Forty-seven patients received only a placebo injection (**Fig. 3**).

3.2. Primary and secondary outcomes

For the ITT population, the primary end point of change in average daily NPRS pain in the affected leg over 4 weeks after the initial injection of SP-102 demonstrated LS mean treatment difference (SE) of −0.52 (0.163) units (95% confidence interval [CI]: −0.84 to −0.20) compared with placebo ($P = 0.002$). The change from

Table 1

Baseline characteristics at screening--intent-to-treat population.

	ITT population		
	SP-102 (n = 202)	Placebo (n = 199)	Overall (n = 401)
Age (y), mean (SD)	51.2 (9.83)	51.7 (10.36)	51.4 (10.09)
Gender			
Female, n (%)	116 (57.4)	122 (61.3)	238 (59.4)
Male, n (%)	86 (42.6)	77 (38.7)	163 (40.6)
Ethnicity			
Hispanic or Latino, n (%)	34 (16.8)	35 (17.6)	69 (17.2)
Not Hispanic or Latino, n (%)	168 (83.2)	164 (82.4)	332 (82.8)
Race			
White, n (%)	160 (79.2)	162 (81.4)	322 (80.3)
Black or African American, n (%)	37 (18.3)	33 (16.6)	70 (17.5)
Asian, n (%)	4 (2.0)	3 (1.5)	7 (1.7)
American Indian or Alaska Native, n (%)	0	0	0
Native Hawaiin/Other Pac Islander, n (%)	0	0	0
Multiple races, n (%)	1 (0.5)	1 (0.5)	2 (0.5)
Weight (kg), mean (SD)	86.33 (17.812)	85.51 (16.679)	85.92 (17.242)
BMI (kg/m^2), mean (SD)	29.90 (5.303)	29.79 (5.035)	29.85 (5.166)
Height (cm), mean (SD)	169.76 (10.556)	169.32 (9.882)	169.54 (10.217)
Fertility status*			
Childbearing potential, n (%)	32 (27.6)	34 (27.9)	66 (27.7)
Postmenopausal, n (%)	44 (37.9)	56 (45.9)	100 (42.0)
Surgically sterile, n (%)	40 (34.5)	32 (26.2)	72 (30.3)

* Percentages are based on the number of female patients in the safety analysis population by treatment group and overall.
BMI, body mass index; ITT, intent-to-treat; n, number of patients.

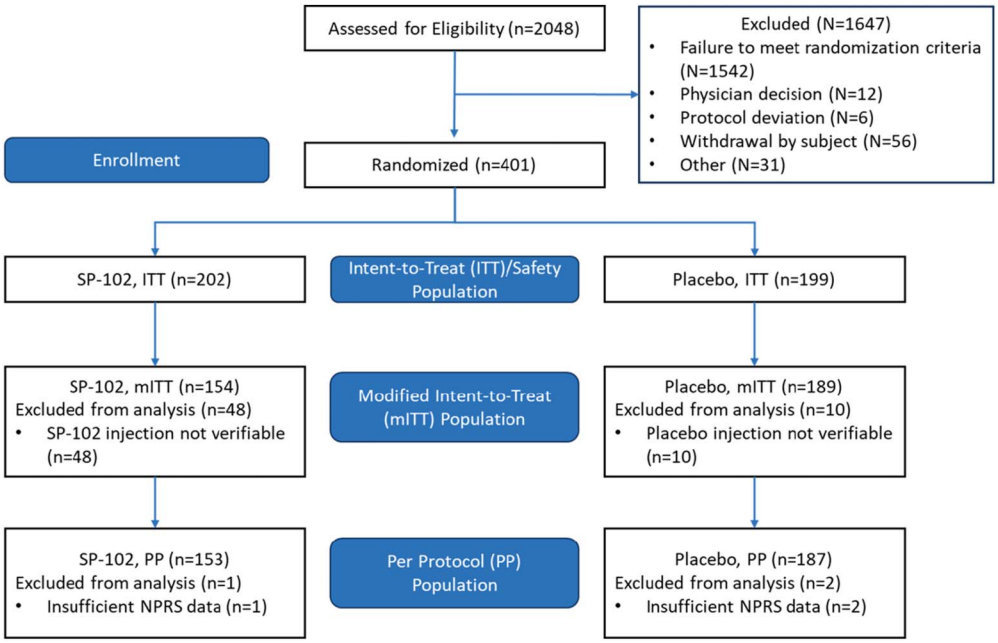

Figure 2. Consort diagram primary analysis period (week 4).

baseline to week 4 in the mean daily average NPRS pain score (SD) in the affected leg was −1.81 (1.896) for SP-102 vs −1.29 (1.814) in the placebo group. The calculated SES associated with the ITT population is 0.28. A statistically significant difference in the mean daily average NPRS pain change between SP-102 and placebo was observed at week 1 with a mean change from baseline of −1.49 (1.519) for SP-102 and −1.02 (1.472) for placebo ($P = 0.002$), which was maintained through week 4 (**Fig. 4**). These highly significant differences between SP-102 and placebo were also observed following sensitivity analyses for fixed effects.

Similarly, most of the secondary end points for the ITT population at 4 weeks also demonstrated statistically significant results. For the key secondary end point of mean change in ODI from baseline, the LS mean treatment difference (SE) for SP-102 was −3.38 (1.388) units (95% CI: −6.11 to −0.65) compared with placebo ($P = 0.015$). SP-102 treatment resulted in a −8.88 point reduction from baseline, which exceeds the minimal clinically important difference of −8 established in a lower back pain study.[30] Additional secondary end points with statistically significant results include worst pain in affected leg at week 4 ($P = 0.004$) and over 4 weeks ($P = 0.001$), current pain in the affected leg ($P = 0.009$), average pain in lower back ($P = 0.035$), BPI-SF for pain severity ($P = 0.003$), and pain interference ($P = 0.049$; **Table 2**), PGIC ($P < 0.001$) and CGIC ($P < 0.001$; **Table 3** and **Figs. 5 and 6**), proportion of patients achieving a response of 30% ($P = 0.002$) (**Table 4** and **Fig. 7**). Statistically significant results were not observed for SP-102 relative to placebo for

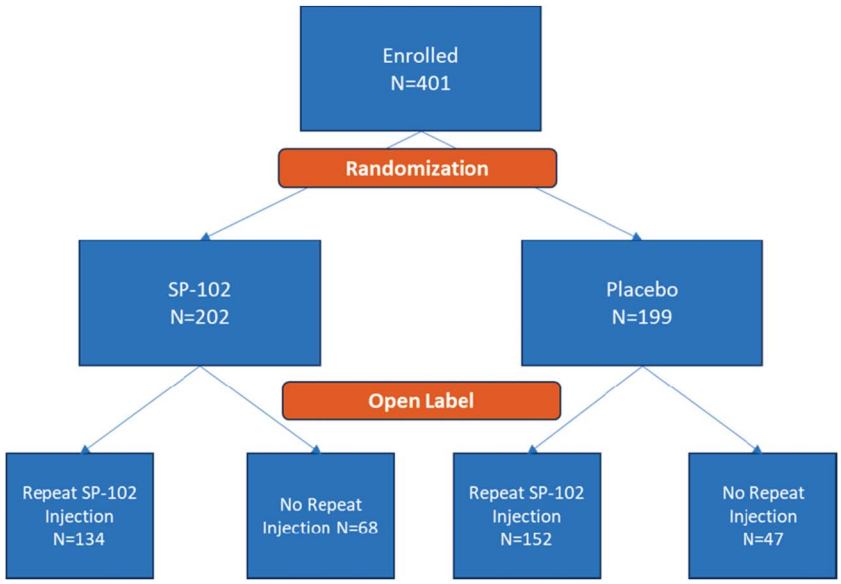

Figure 3. Subjects receiving repeat SP-102 injection.

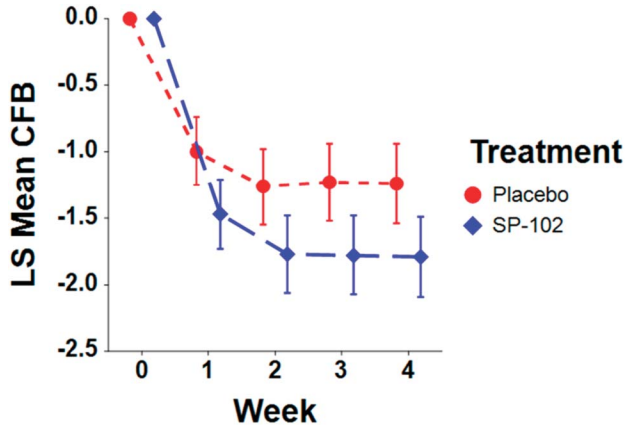

Figure 4. Mean NPRS average pain score (SE) in the affected leg over time in the ITT population. SP-102 vs placebo weeks 1-4: $P = 0.002$, 0.005, 0.003, 0.003. Overall treatment effect (mean SP-102 vs placebo difference): diff = −0.52, SE = 0.163, $P = 0.002$. Error bars: 95% confidence limits. ITT, intent-to-treat; LS mean: least squares means; NPRS, Numeric Pain Rating Scale.

PainDETECT, rescue medication use and number of patients who used rescue medication, and responder analysis for patients experiencing a 50% and 75% reduction in pain in the affected leg (**Tables 4 and 5** and **Fig. 7**).

The time to repeat injection (50th quantile [95% CI]) for the ITT population was 84 (71-100) days for SP-102 vs 58 (50-69) days for placebo ($P = 0.001$) (**Table 6** and **Fig. 8**).

The primary end point group mean difference, associated SES, and statistical significance were improved for the mITT population (ie, −1.08 [0.171], SES = 0.68, $P < 0.001$), which was also observed at week 1 and improved through week 4. Similarly, the mITT population was observed to have improved and mostly highly statistically significant outcomes for SP-102 over placebo for the secondary efficacy end points. In contrast to the ITT population, the mITT population observed to have statistically significant PainDETECT for SP-102 over placebo ($P = 0.037$) as well as number of patients experiencing a 50% reduction in pain in the affected leg ($P < 0.001$). Similar to the ITT population, there were no significant differences in rescue medication use for the mITT population or patients experiencing 75% reduction in pain. For the mITT population, the time to repeat injection was 99 (78-129) days for SP-102 vs 57 (49-67) days for placebo.

The 8-week and 12-week efficacy data (both ITT and mITT populations) were mixed and uninterpretable, which was expected due to bias introduced by the optional open-label repeat injection allowed to all patients after week 4.

3.3. Adverse events

There were no SAEs related to study medication or procedure, no AEs leading to death, and no AEs of special interest (ie, paraplegia, hematoma, or infection at the injection site). There were 4 patients (1.4%) experiencing SAEs and 1 patient (0.3%) experiencing an AE leading to early withdrawal after receiving SP-102. Two patients (1.0%) experienced an SAE, with 1 (0.5%) each experiencing an AE leading to early withdrawal and death after placebo (**Table 7**). The fatal SAE was considered unrelated to study medication and study procedure, as were the SAEs leading to early withdrawal.

In general, a slightly higher proportion of patients in the SP-102 group had treatment emergent AEs (TEAEs) than in the placebo group, (60 [29.7%] patients vs 42 [21.1%] patients with any TEAE). The most common TEAEs by system organ class were nervous system disorders: 20 (9.9%) in the SP-102 group, 16 (8.0%) in the placebo group, and 20 (7.0%) in the SP-102 repeat injection group. The most common TEAEs by preferred term were headache, reported in 13 patients (6.4%) in the SP-102 group, 11 patients (5.5%) in the placebo group, and 10 patients (3.5%) in the SP-102 repeat injection group (**Table 7**).

Overall, headaches were more commonly reported in patients exposed to SP-102 than in patients not exposed to

Table 2

Primary and secondary outcomes: Numeric Pain Rating Scale average leg pain in affected leg, Oswestry Disability Index total score, mean daily Numeric Pain Rating Scale (worst, current, and lower back), PainDETECT, Brief Pain Inventory-Short Form (change from baseline to 4 weeks; intent-to-treat population).

End point	SP-102 (N = 202)	Placebo (N = 199)	LSM (SE)	95% CI	*P*
	Mean change from baseline	Mean change from baseline			
NPRS average pain score in the affected leg (primary end point)*	−1.81 (1.896)	−1.29 (1.814)	−0.55 (0.187)	−0.92 to −0.18	0.003
Standardized effect size of primary (Cohen's d)	0.28				
ODI total score (key secondary end point)†	−8.88 (14.684)	−5.48 (13.083)	−3.38 (1.388)	−6.11 to −0.65	0.015
Worst pain in the affected leg at week 4*	−1.88 (2.014)	−1.33 (1.946)	−0.57 (0.198)	−0.96 to −0.18	0.004
Worst pain in the affected leg over 4 weeks*			−0.56 (0.173)	−0.90 to −0.22	0.001
Current pain in the affected leg*	−1.8 (2.28)	−1.2 (2.41)	−0.6 (0.23)	−1.1 to −0.2	0.009
Average pain in the lower back*	−0.7 (2.54)	−0.2 (2.48)	−0.5 (0.23)	−0.9 to 0.0	0.035
PainDETECT†	−2.7 (6.47)	−2.5 (6.07)	−0.3 (0.62)	−1.5 to 0.9	0.642
BPI-SF score (pain severity)†	−1.56 (1.952)	−0.98 (1.928)	−0.59 (0.200)	−0.98 to −0.20	0.003
BPI-SF score (pain interference)†	−1.16 (2.413)	−0.71 (2.095)	−0.44 (0.221)	−0.87 to 0.00	0.049

Baseline NPRS score is the mean of at least 5 days and no more than 7 days of scores from the screening visit until treatment randomization. For the current pain, baseline is the last score before treatment. Baseline ODI is defined as the last ODI assessment score before the first dose on day 1.

* The analysis uses a REML-based MMRM with fixed effects for treatment (SP-102 or placebo), week, site, Pain Catastrophizing Scale group (<30 or ≥30), baseline score, and treatment-by-week interaction.

† The analysis uses an analysis of covariance model with fixed effects for treatment (SP-102 or placebo), site, Pain Catastrophizing Scale group (<30 or ≥30), and baseline score.

ANCOVA, analysis of covariance; ANOVA, analysis of variance; BPI-SF, Brief Pain Inventory-Short Form; CI, confidence interval; ITT, intent-to-treat (randomized population); LSM, least squares mean; MMRM, mixed model for repeated measures; NPRS, Numeric Pain Rating Scale; ODI, Oswestry Disability Index; REML, restricted maximum likelihood.

Table 3

Patient global impression of change and clinical global impression of change—intent-to-treat population.

	SP-102 (N = 202)		Placebo (N = 199)
PGIC responders (no. of patients who responded with "very much improved" or "much improved"*)	71 (35.1%)		39 (19.6%)
χ^2		$P < 0.001$	
Logistic regression (odds ratio [95% CI])†		2.25 (1.42-3.54)	
		$P < 0.001$	
CGIC responders (no. of patients assessed as "very much improved" or "much improved"*)	76 (37.6%)		39 (19.6%)
χ^2		$P < 0.001$	
Logistic regression (odds ratio [95% CI])†		2.49 (1.58-3.91)	
		$P < 0.001$	

* Seven-point scale rating patient's overall improvement. Patient change is rated from "very much improved," "much improved," "minimally improved," "no change," "minimally worse," "much worse," or "very much worse."
† Logistic regression models with treatment (SP-102 or placebo), site, and Pain Catastrophizing Scale group (<30 or ≥30) as factors.
CGIC, Clinical Global Impression of Change; CI, confidence interval; ITT, intent-to-treat (randomized population); PGIC, Patient Global Impression of Change.

SP-102 through 12 weeks (6.5% vs 2.1%). Headaches were generally mild, transient, and associated with the epidural injection. Pain at the site of injection was only reported for patients receiving SP-102 after the initial injection (2.0%) and repeat injection (0.7%). Otherwise, TEAEs occurring ≥2% of patients were low and balanced between SP-102 and placebo (**Table 7**). Treatment emergent AEs occurring with an incidence ≥2% remained low after the repeat injection. There were no meaningful differences observed in physical examinations, vital signs, or laboratory parameters between treatment groups.

4. Discussion

Epidural steroid injections are commonly used for treating LRP, with lumbosacral transforaminal epidural steroid injections (TFESI) growing 15% annually in Medicare beneficiaries between 2000 and 2018.[29] However, corticosteroids currently used for ESIs have neither been rigorously studied in large randomized controlled studies, nor approved for epidural use by FDA, and contain safety warnings in their labels for ESI administration. Thus, there is a significant unmet need for an injectable steroid product designed to provide a safety and efficacy profile demonstrated with the rigor of a multicenter clinical study that can support an FDA approval.[9]

Although multiple systematic reviews and meta-analyses show lumbar TFESIs are effective for LRP,[5,19,39] most studies have relatively small sample sizes, with the largest study enrolling 120 patients.[28] The CLEAR trial presents the first large, multicenter, randomized, controlled study determining the safety and efficacy of a corticosteroid product intended for treatment of LRP through TF epidural injection. In the CLEAR trial, SP-102 demonstrated clinically meaningful pain relief with statistically significant differences vs placebo for the primary and most secondary end points over the 4-week primary analysis period for the ITT population. Highly significant differences ($P < 0.01$) were observed for the primary end point, worst pain in the affected leg at and over 4 weeks, current pain in the affected leg, BPI-SF (pain severity), PGIC, CGIC, time to repeat injection, and patients experiencing 30% reduction in pain.

Although not defined specifically for LRP, clinically meaningful pain relief in individual patients with chronic pain has been generally defined as ≥30% improvement (associated with "Much Improved") and ≥50% improvement (associated with "Very Much Improved"; NPRS, 0-10 point scale) in conjunction with PGIC responses of "Very Much Improved," "Much Improved," or "Minimally Improved."[11] Although there is not an accepted definition for clinically meaningful differences between groups, generally SESs (Cohen's d) are examined in the context of the overall risk-benefit profile of the product and also can be looked at in comparison with other used analgesic products that are currently approved for use.[11] Evaluation of the ITT population demonstrated that the number of patients in the SP-102 group that experienced a clinically meaningful reduction in pain[12,14] was greater than for placebo (responder analyses: ≥30% reduction SP-102: 88 [43.6%] vs placebo: 57 [28.6%], $P = 0.002$ and ≥50% reduction SP-102: 58 [28.7%] vs placebo: 41 [20.6%], $P = 0.060$), there was a higher number of PGIC responders for the SP-102 group (71 [35.1%]) vs for the placebo group (39 [19.6%]; $P < 0.001$), and a - 0.28 SES (Cohen's d calculated as the group mean difference divided by the pooled SD) for the group mean differences in the primary end point that is comparable or surpasses results from modern analgesic clinical trials.[31,40] Based on the criteria for within-subject data, a significantly higher proportion of patients were classified as experiencing clinically meaningful pain relief in the

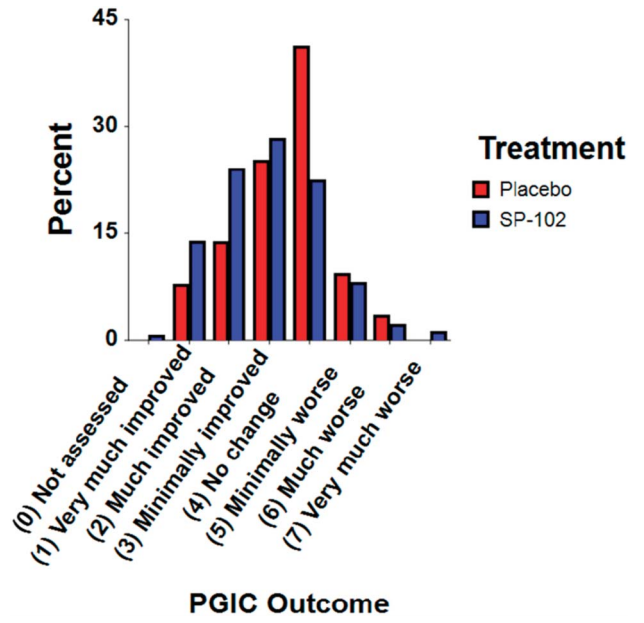

Figure 5. Summary of patient global impression of change (PGIC) responses at week 4—ITT Population. N: SP-102 = 202, placebo = 199. PGIC, Patient Global Impression of Change; ITT, intent-to-treat.

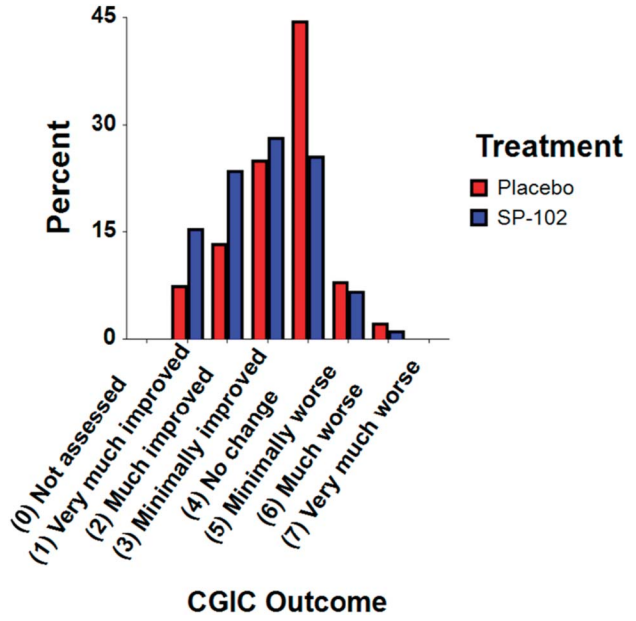

Figure 6. Summary of CGIC responses at week 4—ITT Population. N: SP-102 = 202, placebo = 199. ITT, intent-to-treat; CGIC, Clinical Global Impression of Change.

SP-102 group (35.1%) over the placebo group (21.6%) (odds ratio [95% CI]: 1.96 [1.26-3.07]; $P = 0.003$ for both logistic regression and χ^2 test).[12] In addition, SP-102 treatment resulted in an ODI −8.88 point reduction from baseline, which exceeds the minimal clinically important difference of −8 established in a lower back pain study.[30] Taken together, the results indicate that SP-102 demonstrated both statistically significant and clinically meaningful separation from placebo on several key metrics.

As the largest prospective, double-blind, randomized study, the CLEAR trial demonstrated a meaningful SES (SES for ITT population = 0.28 and for the mITT population 0.68) compared with the observed trend of decreasing effect sizes (average SES of 0.38 [CI: 0.308-0.451] overall, and a mean SES of approximately 0.30 for the most recent published chronic pain trials) according to a meta-analysis of all chronic pain trials from 1980 to 2016.[40]

The CLEAR trial is also the first formal clinical study to evaluate and confirm the importance of correct needle placement and verified contrast flow for the TF epidural injection, which is demonstrated by the improvement in efficacy responses observed for the mITT population across the primary, key secondary, and most secondary end points when patients receive a verifiable injection. The quality of TF injections in CLEAR trial is consistent with observations reported in literature,[44,45] which highlights the complexity of anatomical structures affected by disc herniation and other pathology, challenges of TF approach to epidural space, and underscores the importance of technical skills of a physician performing the injection.

Despite safety risks, clinicians are still using particulate steroids for TFESI because multiple studies show nonparticulate dexamethasone is less effective with a shorter duration of action than particulate steroids.[3,23,35] In the CLEAR trial, SP-102 demonstrated a longer time to repeat injection (84 days) relative to placebo (58 days). These results suggest that SP-102 could play a major role in the treatment of LRP as a nonparticulate steroid with an enhanced safety profile compared with particulate steroids but a longer duration of benefit. This may facilitate the compliance of clinicians with the limits that Center for Medicare and Medicaid Services established for ESI and limit steroid and procedure exposure for patients.[26]

4.1. Limitations

Limitations of this study include lack of an active control which is attributed to the absence of drugs approved for the treatment of LRP and the labeled warnings for corticosteroids routinely used off-label for TFESI. Intramuscular saline was selected as the control group to mimic experience of ESI without incurring unnecessary risks of epidural injection of the placebo. The efficacy analyses of the ITT population showed significant differences across the primary, key secondary, and most secondary end points; however, the increased effect size in the mITT population illustrates the importance of quality in correct needle placement during ESI procedures. Notably, the number of incorrect needle placement formally documented in this study was in line with those reported in the literature (ie, ~25%-30%).[2, 32] Because placebo injection required a simple IM injection, there were an expectedly lower number of unverifiable injections in the placebo arm.

4.2. Conclusions

The CLEAR trial is the first large, multicenter, randomized, controlled clinical study evaluating TF epidural injection of a corticosteroid. The results of the CLEAR trial suggest that TF epidural injection of SP-102 in patients with radicular pain

Table 4

Responder analysis (change from baseline in mean Numeric Pain Rating Scale, average daily pain in affected leg)*—intent-to-treat population.

	SP-102 (N = 202)		Placebo (N = 199)
30% reduction	88 (43.6%)		57 (28.6%)
χ^2		$P = 0.002$	
Logistic regression† (odds ratio [95% CI])		1.96 (1.28-2.98)	
		$P = 0.002$	
50% reduction	58 (28.7%)		41 (20.6%)
χ^2		$P = 0.060$	
Logistic regression† (odds ratio [95% CI])		1.58 (0.99-2.52)	
		$P = 0.055$	

* Patients who discontinued or have missing scores at week 4 were considered nonresponders.

† Logistic regression models with treatment (SP-102 or placebo), site, and Pain Catastrophizing Scale group (<30 or ≥30) and baseline averaged daily pain score as factors were used to compare the treatment groups at each week.

CI, confidence interval; ITT, intent-to-treat (randomized population).

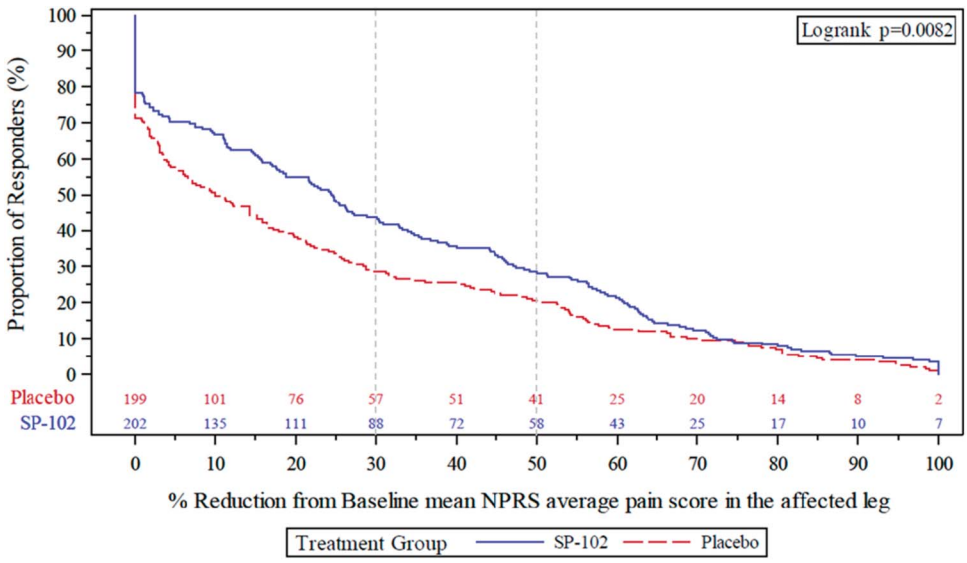

Figure 7. Cumulative proportion of responders analysis graph of reduction from baseline in mean NPRS average pain score in the affected leg at week 4—ITT population. ITT, intent-to-treat; NPRS, Numeric Pain Rating Scale.

associated with lumbar intervertebral disc herniation is well-tolerated and results in significant reduction in leg pain and associated disability during the first 4 weeks after treatment.

Conflict of interest statement

Dr. Miller A.M. reported serving as a consultant for Scilex Holding Company. K.D.C. reported receiving payments for expert testimony. N.N.K. reported serving as a consultant for Scilex Holding Company, Tris Pharma, and Esai Inc. D.S. reported serving on the Speaker Bureau for AbbVie and serving as a consultant for Scilex Holding Company. S.H. reported receiving payments for expert testimony. N.K. was a paid consultant for Scilex Holding Company and his employer at the time of the study, WCG (www.wcgclinical.com) provided supportive services for the CLEAR Trial. R.H.D. has received research grants and contracts from the US FDA and the US National Institutes of Health, and compensation for serving on advisory boards or consulting on clinical trial methods from Abide, Acadia, Adynxx, Analgesic Solutions, Aptinyx, Aquinox, Asahi Kasei, Astellas, Beckley, Biogen, Biohaven, Biosplice, Boston Scientific, Braeburn, Cardialen, Centrexion, Chiesi, Chromocell, Clexio,

Table 5

Rescue medication use—intent-to-treat population.

	SP-102 (N = 202)		Placebo (N = 199)
Cumulative use of rescue medication (mg) through week 4, mean (SD)*	6768.3 (10,950.39)		8281.0 (15,106.48)
LSM (SE)		−1513.6 (1317.39)	
95% CI		−4103.5 to 1076.4	
		$P = 0.251$	
No. of patients who used rescue medication during the first 4 weeks	141 (69.8%)		132 (66.3%)
No. of patients who did not require rescue medication	61 (30.2%)		67 (33.7%)
χ^2		$P = 0.456$	
Time (days) to the first rescue medication dose during the first 4 weeks†			
N	141		132
Mean (SD)	4.6 (6.25)		4.9 (5.94)
Median	2.0		2.0
Min, max	1-28		1-24
25th quantile (95% CI)	1 (NE-NE)		2 (1-2)
50th quantile (95% CI)	4 (2-8)		6 (4-11)
75th quantile (95% CI)	NE (27-NE)		NE (NE-NE)
Hazard ratio (95% CI)†		1.13 (0.89-1.43)	
		$P = 0.316$	

* Cumulative use of rescue medication (mg of acetaminophen) was analyzed using an analysis of variance model with fixed effects for treatment (SP-102 or placebo), site, and Pain Catastrophizing Scale group (<30 or ≥30).
† A Cox proportional hazards model was used to test the treatment difference while adjusting for site and Pain Catastrophizing Scale (<30 or ≥30).
CI, confidence interval; ITT, intent-to-treat (randomized population); LSM, least squares mean; NE, not estimable.

Table 6

Time to repeat injection—intent-to-treat population.

	SP-102 (N = 202)		Placebo (N = 199)
No. of patients with repeat injection of SP-102 (patients who received open-label SP-102 between 4 and 20 weeks after initial injection)	134 (66.3%)		152 (76.4%)
No. of censored patients*	68 (33.7%)		47 (23.6%)
χ^2		$P = 0.026$	
Time (d) to repeat injection			
N	134 (66.3%)		152 (76.4%)
Mean (SD)	67.0 (33.31)		57.8 (31.69)
Median	57.5		43.0
Min-max	27-143		26-148
25th quantile (95% CI)†	45 (43-57)		36 (34-40)
50th quantile (95% CI)†	84 (71-100)		58 (50-69)
75th quantile (95% CI)†	143 (141-143)		126 (87-146)
Comparison to Placebo‡ (hazard ratio [95% CI])		0.68 (0.54-0.86) $P = 0.001$	

* Censored subjects are the following: (1) subjects who do not receive a repeat injection of SP-102 and (2) subjects who discontinued the study before week 20 without receiving a repeat injection.
† Quartiles are estimated using Kaplan–Meier estimation.
‡ A Cox proportional hazards model was used to test the treatment difference while adjusting for site and Pain Catastrophizing Scale (<30 or ≥30).
CI, confidence interval; ITT, intent-to-treat (randomized population).

Collegium, CoimbiGene, Confo, Decibel, Editas, Eli Lilly, Endo, Ethismos (equity), Eupraxia, Exicure, GlaxoSmithKline, Glenmark, Gloriana, Hope, Juca, Kriya, Lotus, Mainstay, Merck, Mind Medicine (also equity), Neumentum, Neurana, NeuroBo, Novaremed, Novartis, Orion, OliPass, Oxford, Cannabinoid Technologies, Pfizer, Q-State, Reckitt Benckiser, Regenacy (also equity), Rho, Sangamo, Sanifit, Scilex, Semnur, SIMR Biotech, Sinfonia, SK Biopharmaceuticals, Sollis, SPRIM, Teva, Theranexus, Vertex, Vizuri, and WCG. S.P.C. reported receiving research funding to his institution and serving as a consultant for Scilex Holding Company and Avanos. He also reported serving as a consultant for SPR Therapeutics, CLEARING, Persica, SWORD, Releviate (inactive), and CLEARING (inactive). He has also received payments for expert testimony. J.P.R. reported receiving NIH grant funding for NIH 1U24NS113850-01; he has also received payment for serving as Chair of the Clinical Events Committee for the ReActivat B international clinical trial for Mainstay, LLC, and other financial interests as Chief, Enterprise Anesthesiology, Mass General Brigham. D.J.L. reported serving as a consultant for Scilex Holding Company. E.S., K.V., and M.J. were paid consultants for Scilex Holding Company during the CLEAR Trial. C.A. and D.L. were employees of Scilex Holding Company. The remaining authors have no conflict of interest to declare.

The data that support the findings of this study are available from the corresponding author (D.L.), upon reasonable request.

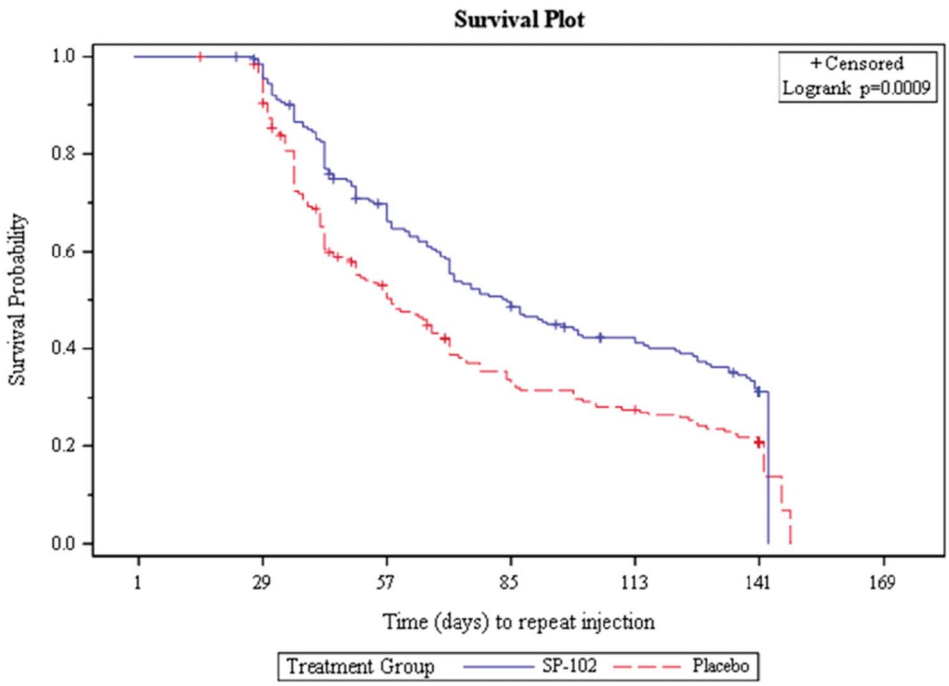

Figure 8. Survival plot of time (days) to repeat injection—ITT population. Censored subjects are the following: (1) subjects who do not receive a repeat injection of SP-102 and (2) subjects who discontinued the study before week 20 without receiving a repeat injection. ITT, intent-to-treat.

Table 7

Overview of treatment-emergent adverse events for the entire treatment period.*

	SP-102 (N = 354)‡		Placebo (N = 199)‡	
	Patients, n (%)	Events, n	Patients, n (%)	Events, n
Any TEAE	125 (35.3)	277	42 (21.1)	68
Any treatment-related† TEAE	32 (9.0)	56	12 (6.0)	15
Any study medication-related TEAE	16 (4.5)	27	10 (5.0)	13
Any study procedure-related TEAE	23 (6.5)	34	5 (2.5)	5
Any serious TEAE	4 (1.1)	5	2 (1.0)	2
Any serious study medication-related AE	0	0	0	0
Any serious study procedure-related AE	0	0	0	0
Any TEAE leading to early withdrawal	1 (0.3)	1	1 (0.5)	1
Any TEAE leading to death	0	0	1 (0.5)	1

Treatment-emergent adverse events occurring ≥2% of patients before or after repeat injection

	Before repeat injection SP-102 (N = 202)‡		Placebo (N = 199)‡		After repeat injection SP-102 or placebo/SP-102 (N = 286)‡	
System organ class preferred term	Patients, n (%)	Events, n	Patients, n (%)	Events, n	Patients, n (%)	Events, n
Any TEAE	60 (29.7)	104	42 (21.1)	68	85 (29.7)	173
Gastrointestinal disorders	10 (5.0)	12	3 (1.5)	3	10 (3.5)	18
General disorders and administration site conditions	6 (3.0)	8	3 (1.5)	4	7 (2.4)	7
Injection site pain	4 (2.0)	4	0	0	2 (0.7)	2
Infections and infestations	14 (6.9)	15	12 (6.0)	17	23 (8.0)	27
Sinusitis	4 (2.0)	4	0	0	3 (1.0)	3
Upper respiratory tract infection	2 (1.0)	2	4 (2.0)	4	7 (2.4)	8
Injury, poisoning, and procedural complications	6 (3.0)	7	6 (3.0)	7	6 (2.1)	7
Investigations	5 (2.5)	5	4 (2.0)	4	15 (5.2)	37
Musculoskeletal and connective tissue disorders	7 (3.5)	8	4 (2.0)	4	17 (5.9)	17
Nervous system disorders	20 (9.9)	28	16 (8.0)	16	20 (7.0)	27
Headache	13 (6.4)	17	11 (5.5)	11	10 (3.5)	16
Psychiatric disorders	2 (1.0)	2	3 (1.5)	4	7 (2.4)	7
Vascular disorders	6 (3.0)	6	2 (1.0)	3	5 (1.7)	6
Hypertension	4 (2.0)	4	1 (0.5)	2	4 (1.4)	5

* From randomization to the end of study participation.
† Study medication-related and/or study procedure-related TEAE.
‡ Treatment-emergent AEs starting while on placebo but before repeat injection were recorded in the placebo group; TEAEs starting on or after repeat injection were recorded in the SP-102 group. TEAEs that started while on placebo and that worsened in severity on or after the repeat injection were assigned to SP-102; therefore, patients can be counted in both the placebo and SP 102 columns.
AE, adverse event; N, number of patients in the treatment group; n, number of patients in the sample; TEAE, treatment-emergent AE.

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