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CLINICALLY MEANINGFUL RADICULAR LEG PAIN MANAGEMENT VIA NOVEL DEXAMETHASONE EXTENDED-RELEASE MICROSUSPENSION (SX600)–PH1/2 RESULTS

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Introduction

Management of lumbar radicular pain remains challenging. Although not FDA-approved for this use, epidural steroid injections (ESIs) are commonly administered for lumbosacral radiculopathy treatment. However, need for repeated injections is common and there is a risk, particularly with corticosteroid suspensions, of serious neurologic events. SX600, dexamethasone acetate microspheres for extended-release injectable micro-suspension, is a sustained-release formulation of dexamethasone acetate incorporated into biodegradable poly-lactic-co-glycolic acid (PLGA) microspheres being developed for management of radicular leg pain secondary to lumbar disc herniation. This formulation provides 90 days of dexamethasone exposure and, thus, may provide long term pain relief. Key SX600 microsphere design characteristics (small diameter [≤ 50% of RBCs], spherical, non-aggregating microspheres), take into consideration reports of serious neurologic sequelae with ESIs attributable to inadvertent intravascular administration.

Materials and Methods

The SALIENT trial was a randomized, double-blind, placebo-controlled parallel-group trial to assess the safety and efficacy of SX600, an investigational drug, administered by lumbosacral transforaminal epidural injection (TF-EI) in patients with unilateral radicular leg pain. SALIENT was conducted in Australia under a Clinical Trial Notification (equivalent to an US IND) and was approved by a Human Research Ethics Committee (i.e. IRB). Key eligibility criteria included disc herniation affecting L4-5 or L5-S1 with involvement of L4, L5, or S1 nerve roots unilaterally, mean worst daily leg pain (WDLP) score of ≥ 5 to ≤ 9 on an 11-point NRS scale, failed conservative therapy, and 1-6 months pain. Following screening and patient informed consent, patients were randomized 1:1:1 to receive a single injection of SX600 12.5 mg: SX600 25 mg: placebo (0.9% NaCl) administered by fluoroscopically-guided TF-EI to the epidural space at the L4-L5, L5-S1 level, or S1 nerve root on Day 0. Patients were followed for ≤ 180 days (14, 30, 60, 90, 120, 150, and 180 day visits post-dose) for assessment of safety, efficacy, and pharmacokinetics (PK).
The primary efficacy endpoint was proportion of 50% responders (≥ 50% improvement in WDLP from baseline) at 60 days post-dosing. Secondary efficacy endpoints included 50% responders at each visit, change in function (Oswestry Disability Index [ODI], quality of life (QOL; Short Form [SF] – 36), patient impression of efficacy (Patient Global Impression of Change [PGIC]), and rescue medication use. Safety assessments included collection of adverse events

(AEs), physical exam, vital signs, electrocardiograms (ECGs), and clinical labs.

Results/Case Report

Due to the impact of COVID-19 on enrollment, SALIENT was terminated with a total sample size of 56 randomized patients (SX600 25 mg, 17; SX600 12.5 mg, 21; placebo, 18). Fifty-one (91.1%) completed the trial; 5 were withdrawn, none due to AEs. The mean age was 48 years, the majority (66.1%) were male, and the most common nerve root of involvement was L5 (53.6%) or S1 (35.7%).

A higher proportion of patients who received SX600 (25 mg, 71.4%; 12.5 mg, 52.6%), were 50% responders compared with placebo (12.5%) at 60 days (Figure 1). This represented a large treatment effect over placebo with an absolute increase of 58.9% with SX600 25 mg and 40.1% with SX600 12.5 mg. SX600 25 mg was associated with durable pain relief to a high proportion of patients after a single TF-EI, with ≥ 64% of subjects experiencing ≥ 50% improvement in their baseline WDLP from Day 30-180. Rescue medication was used less frequently in SX600 groups (25 mg, 17.6%; 12.5 mg, 14.3%) compared with placebo (38.9%). Mean baseline ODI scores (scale, 0–100) were generally similar with the majority within each group reporting moderate disability scores (Table 1). At Day 60 the mean change from baseline (CFB) in ODI score was -16.3, -18.1, and -10.4 for SX600 25 mg, SX600 12.5 mg, and placebo groups, respectively. Further, 80% of patients in the 25-mg group reported minimal disability scores at Day 60 compared with 65% and 59% in the 12.5-mg and placebo groups, respectively. Similarly, at Day 60 improvements in QOL across all 8 domains of the SF-36 were observed for the SX600 groups and were greater than CFBs observed in the placebo group (Figure 2). Finally, patients who believed that their status was Very Much Improved/Much Improved was highest in the SX600 25-mg group at Day 60 (SX600 25 mg, 60%; SX600 12.5 mg, 45%; placebo, 24%).

Of the patients with PK results from sampling at scheduled visits, 37.5% patients in the 12.5-mg group and 78.6% in the 25-mg group had low systemic dexamethasone exposure through the Day 90 Visit.

SX600 was generally well tolerated. In total, 45 (82%) patients reported ≥ 1 treatment-emergent AE (TEAE: SX600 25 mg, 88%; SX600 12.5 mg, 76%; placebo, 83%) and the vast majority were mild in severity. The most commonly reported TEAE was back pain (SX600 25 mg, 12.5%; SX600 12.5 mg, 9.5%; placebo, 27.8%). No TEAE led to study withdrawal. Four serious AEs (SAEs) were reported in 4 patients and there were no deaths. SAEs of radiculopathy and back pain occurred in 1 placebo patient each. An SAE of likely low back pain/radicular leg pain was reported in a patient who received SX600 25 mg. An SAE of small intestinal obstruction was reported a patient with a history of recurrent small intestinal obstruction who received SX600 25 mg. No clinically meaningful differences relative to placebo, signals, patterns, or trends in physical findings, laboratory parameters, ECGs, or vital signs were detected across treatment groups over the trial duration.

Discussion

SX600 provided clinically meaningful reduction in unilateral radicular leg pain. A substantially higher proportion of patients who received SX600 had ≥ 50% improvement from baseline in WDLP compared with placebo at 60 days (primary endpoint/assessment time). This magnitude of pain reduction (i.e. ≥ 50%) is considered substantial by the IMMPACT group as well as clinically relevant for patients with sciatica.1,2 This effect was durable and provided clinically relevant pain relief to a high proportion of patients after a single TF-EI. Improvements in pain relief were accompanied by improvements in function and QOL outcomes, patient impression of efficacy, and reductions in rescue medication use. The overall safety profile of a single dose SX600 administered by TF-EI was favorable and comparable to placebo.

References

1. Giraudeau B, Rozenberg S, Valat JP. Assessment of the clinically relevant change in pain for patients with sciatica. Ann Rheum Dis. 2004;63(9):1180-1.

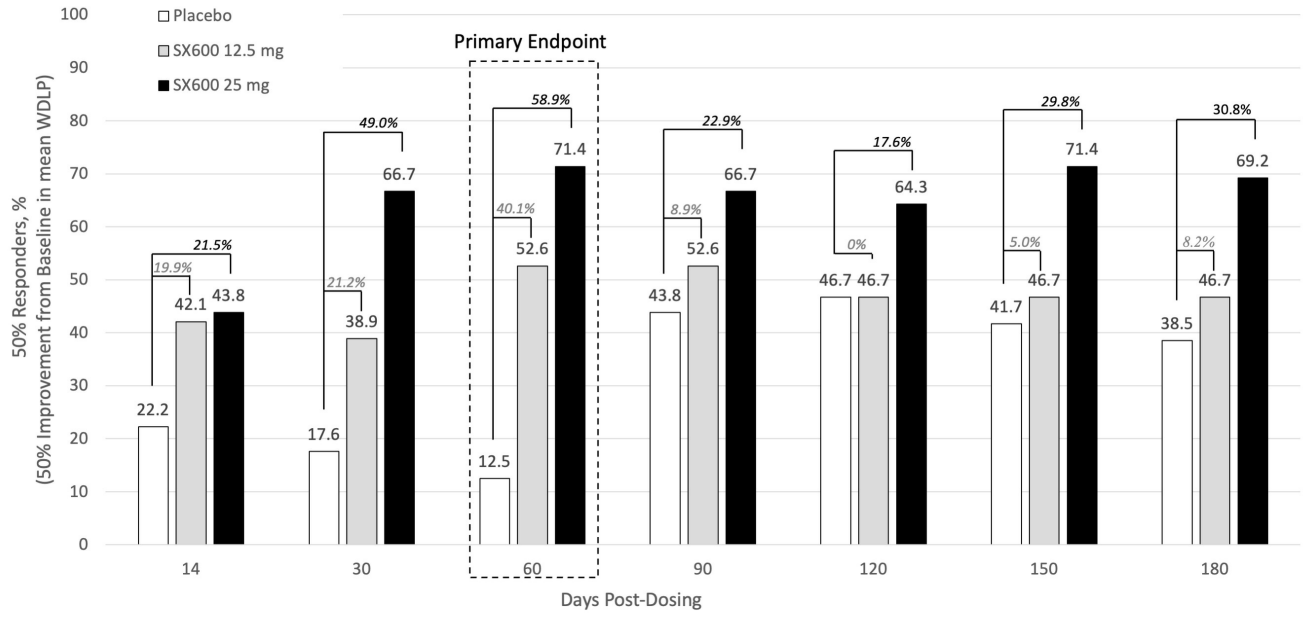
2. Dworkin RH, Turk DC, Wyrwich KW, et al. Interpreting the clinical importance of treatment outcomes in chronic pain clinical trials: IMMPACT recommendations. J Pain. 2008 Feb;9(2):105-21.

Disclosures

Yes

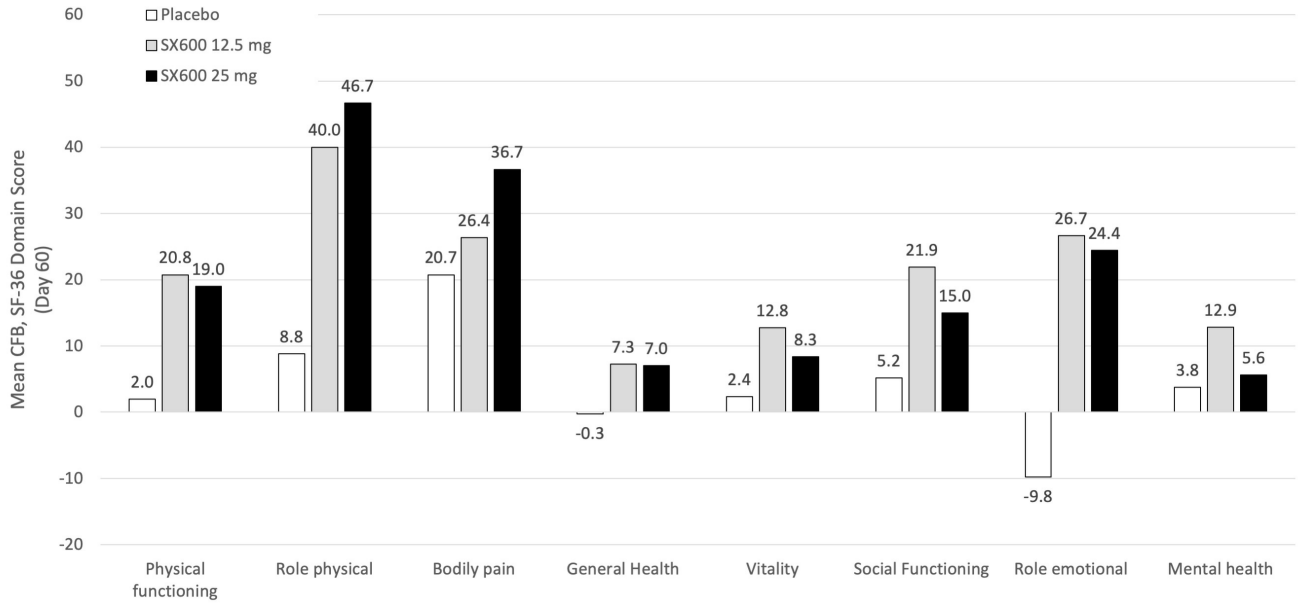
Tables / Images

Figure 1. Proportion of 50% Responders and Treatment Effect at 14, 30, 60, 90, 120, and 180 Days Post-Dosing (mITT Population, Phase 1/2 SALIENT Trial)



mITT = Modified intent-to-treat.

Figure 2. Short Form 36 (SF-36) Change from Baseline Scores at 60 Days Post-Dosing (mITT Population, Phase 1/2 SALIENT Trial)



CFB = Change from baseline; mITT = Modified intent-to-treat; SF = Short form.

Table1: Oswestry Disability Index Scores (mITT Population, Phase 1/2 SALIENT Trial)

	Baseline			Day 60		
	Placebo (N=17)	**SX600 12.5 mg (N=21)**	**SX600 25 mg (N=16)**	**Placebo (N=17)**	**SX600 12.5 mg (N=20)**	**SX600 25 mg (N=15)**
Score, mean (SD)	27.99 (9.525)	35.21 (12.844)	32.83 (16.113)	17.64 (11.306)	16.5 (13.839)	15.31 (19.237)
Interpretation of Scores, n (%)						
0% to 20%: Minimal Disability	4 (23.5)	3 (14.3)	4 (25.0)	10 (58.8)	13 (65.0)	12 (80.0)
21% to 40%: Moderate Disability	11 (64.7)	12 (57.1)	8 (50.0)	7 (41.2)	6 (30.0)	2 (13.3)
41% to 60%: Severe Disability	2 (11.8)	6 (28.6)	3 (18.8)	0	1 (5.0)	0
61% to 80%: Crippling Back Pain	0	0	1 (6.3)	0	0	1 (6.7)
81% to 100%: Bed-Bound or Exaggerating Their Symptoms	0	0	0	0	0	0
Change from baseline, mean (SD)	-	-	-	-10.36 (13.501)	-18.08 (15.058)	-16.25 (9.717)

ABBREVIATIONS: mITT = Modified Intent-to-Treat; SD = Standard Deviation.

Percentages are based on the number of non-missing values at the time of visit for the Modified Intent-to-Treat Population. Baseline is defined as the value collected on Day 0 visit.