Interpreting Clinical Meaningfulness of SP-102 for the Treatment of Lumbosacral Radicular Pain (LRP): A Post-hoc Analysis of the CLEAR-1 Trial and A Systematic Review of Literature

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BACKGROUND

Analgesic clinical studies performed for the purposes of FDA approval produce results that require interpretation to fully understand their clinical meaningfulness. The results of these studies are often misinterpreted with the most common source of confusion arising when the magnitude of group differences are conflated with the determination of the magnitude of improvement within subjects that can be considered clinically important[1,2,3]. While there has been consensus on what constitutes a clinically meaningful change with-in individual subjects, group differences should include evaluations based on the overall risk-benefit profile of the treatment within the context of other available treatments for the indication[4].

Lumbosacral radicular pain (LRP), is a common and debilitating disorder that affects millions of Americans in their lifetime (13 to 40%)[5], leading to short- and long-term disability and increased healthcare costs[5,6]. There are no products approved by FDA to treat LRP. Therapeutic approaches include oral corticosteroids, non-steroidal anti-inflammatory drugs (NSAIDs), and non-pharmacologic approaches[7]. When conservative methods fail, patients are often referred for epidural steroid injections (ESIs) as a last line before surgery[8]. ESIs are used off-label in the absence of any Class I data and are associated with significant risks, including neurological complications and death, as outlined in the product labels.

SP-102 (10 mg of dexamethasone sodium phosphate in 2 mL of viscous gel solution) is an investigational non-particulate, preservative-free injectable product designed to increase the residence time of dexamethasone at the site of injection without increasing systemic exposure[9]. Recently, the CLEAR Trial (Corticosteroid Lumbosacral Epidural Analgesia for Radiculopathy) investigated the safety and efficacy of single and repeat SP-102 transforaminal injection (TFI) compared to a placebo sham intramuscular (IM) injection in subjects with LRP[9].

OBJECTIVE

Interpret the clinical meaningfulness of the magnitude of group mean differences (GMD) of the CLEAR-1 Trial by comparing to the effects observed for other analgesic products and in the context of overall safety.

METHODS

CLEAR Trial Population and Procedures:

- The CLEAR Trial was a double-blind, randomized, placebo-controlled, multicenter study conducted in the US (January 2018 - January 2022). The primary results were previously reported[9]. Subjects were screened for current episodes of LRP and randomized (1:1) to receive either a TFI of SP-102 (active) or an intramuscular (IM) placebo injection and followed for 24 weeks. If clinically warranted, a repeat open-label SP-102 injection was allowed between 4-20 weeks for both groups. Fluoroscopic guidance and verification of epidural contrast spread was used to confirm study drug administration. Subjects that did not have verified needle placement and contrast spread were excluded from the modified intent-to-treat (mITT) analyses (pre-defined in the statistical analysis plan (SAP). The intent-to-treat (ITT) population included all randomized subjects.

CLEAR Trial Endpoints:

- The primary endpoint was change in average daily pain on the Numeric Pain Rating Scale (NPRS) in the affected leg over 4 weeks. This publication also includes results from other pre-defined and post-hoc endpoints: (1) responder analysis, (2) Oswestry Disability Index (ODI) group mean comparisons, and (3) Brief Pain Inventory (BPI) Pain Interference group mean comparisons. The ODI and BPI clinically meaningful cutoff comparisons are post-hoc, the remainder were pre-defined.

Systematic Reviews:

Comparison to Other Approved Analgesics

- Because there are no approved products for LRP, Phase 3 efficacy results for existing analgesic products used to treat chronic low back pain (CLBP) were collected through database searches of: FDALabel (https://nctr-crs.fda.gov/fdalabel/ui/search), Centerwatch "FDA Approved Drugs", and PubMed. Identified products were further evaluated by searching in Drugs@FDA database for a product label. Once all products were identified every effort was made to find the results of their Phase 3 study(ies) by searching for publications, data presented in their product label, FDA summary basis of approvals, and clinicaltrials.gov. When multiple studies/ doses were identified for a single product, data were selected for presentation based on pre-defined criteria (in order of descending importance): (1) parallel designed studies (i.e., no enriched-enrollment randomized withdrawal [EERW]), (2) fixed-dose, (3) dose/ data presented in the product label, (4) if 2 studies were available the highest standardized effect size (SES; Cohen's D) was selected and if three studies were available the middle SES was selection (the group mean differences are presented for the corresponding SES), and (5) if multiple doses were included in the study the highest approved dose in the product label is presented.

Comparison to Other Transforaminal Epidural Steroid Injections

- There are no products approved for the treatment of LRP and while ESIs are commonly used, it is exclusively off-label. A recent Cochrane review examined the efficacy of ESIs using various administration techniques, including transforaminal[10]. All studies stated that fluoroscopic imaging was used and all injections were confirmed to be given successfully (i.e., a population most similar to the mITT population from the CLEAR Trial). The primary publications were reviewed and primary endpoint data from the closest timepoint to the CLEAR Trial (Week 4) was analyzed when available. Due to potential differences in efficacy, only studies using TFI were included.

Statistical Analyses:

- The primary endpoint comparison used a linear contrast of the least square (LS) means comparing the weekly mean scores up to Week 4 (average of Weeks 1, 2, 3, and 4 change from baseline LS means estimated from the model). Responder analyses for NPRS Responder, ODI, and BPI Pain Inventory utilized chi square tests.
- Cohen's D was used for SES calculations and is determined by calculating the mean difference between the active and placebo groups (i.e., Group A mean – Group B mean) and then divided by the pooled standard deviation (SD). When publications only presented standard error (SE), SD was calculated by multiplying the SE by the square root of the N for each group.

RESULTS

The CLEAR Trial demonstrated a statistically significant difference between SP-102 and placebo for the primary endpoint and many secondaries for both populations (mITT and ITT) and supported the overall safety of the product[9] (Table 1).

Clinically Meaningful With-in Subject Results:

Responder analyses

- A ≥30% and/or ≥50% reduction in pain represents a clinically meaningful reduction in an individual subject based on the correlation to patient reported outcomes of "Much Improved" and "Very Much Improved" from the PGIC measure[4]. This is referred to as the responder analysis and the percentage of subjects reporting ≥30% and ≥50% is presented in Table 1.

Oswestry Disability Index

- Results from the CLEAR Trial demonstrated a statistically significant difference in change from baseline to Week 4 in ODI for both the mITT and the ITT population (Table 1). General consensus suggests that a ≥10 point change from baseline or ≥30% improvement represents the minimum clinically meaningful change with-in subjects[11]. These results are presented in Table 1.

Brief Pain Inventory – Pain Interference

- In the mITT population, a statistically significant difference in the BPI-SF Pain Interference was observed for the GMD, and a similar trend was observed for the ITT population. Clinically meaningful improvement (>1 point improvement) is presented in Table 1.

Table 1. Secondary endpoint results at Week 4

Outcome	Endpoint	mITT Population			ITT Population		
		SP-102 n=154	Placebo n=189	p-value	SP-102 n=202	Placebo n=199	p-value
NPRS Responder Analysis	≥30% improvement n(%)	86 (55.8)	49 (25.9)	**<0.001**	88 (43.6)	57 (28.6)	**0.002**
	≥50% improvement n(%)	58 (37.7)	35 (18.5)	**<0.001**	58 (28.6)	41 (20.6)	0.055
Oswestry Disability Index	LS Mean Difference (SE)	-6.28 (1.49)		**<0.001**	-3.38 (1.39)		**0.015**
	≥10 point improvement n(%)	70 (45.5)	58 (30.7)	**0.005**	79 (39.1)	65 (32.7)	0.179
	≥30% improvement n(%)	62 (40.3)	49 (25.9)	**0.005**	70 (34.7)	57 (28.6)	0.196
Brief Pain Inventory: Pain Interference	LS Means Difference (SE)	-1.01 (0.24)		**<0.001**	-0.44 (0.22)		**0.049**
	≥1 point improvement n(%)	85 (55.2)	60 (31.7)	**<0.001**	95 (47.0)	68 (34.2)	**0.009**

Abbreviations: ITT = intent to treat; mITT = modified intent to treat; SE = standard error
Chi square tests for statistical significance were used.

Clinically Meaningful Between Group Differences:

Comparison of SESs for Currently Approved Analgesics:

- The most appropriate way to compare the results of the primary endpoint is by comparing the SES (Cohen's D)[4]. However, the NPRS GMD between active and placebo across products were also compared (Figure 1a and 1b).

Figure 1a
Comparison of Standardized Effect Size In Chronic Low Back Pain Studies for the Primary Endpoint

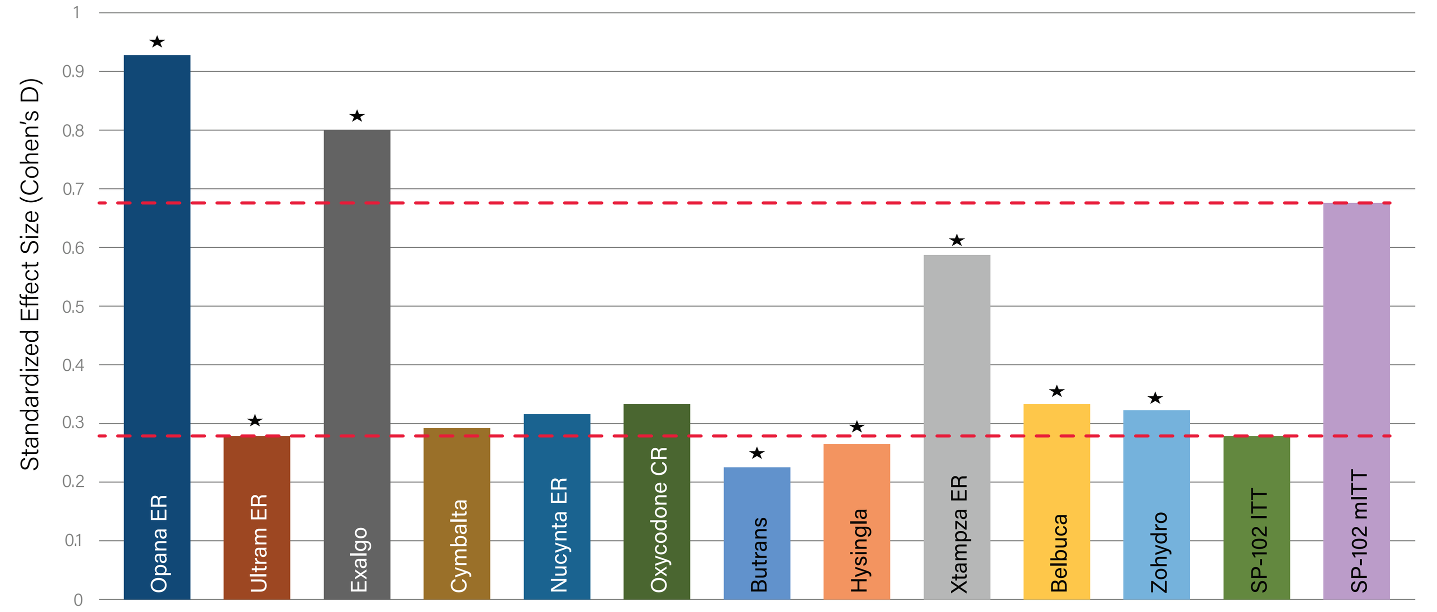
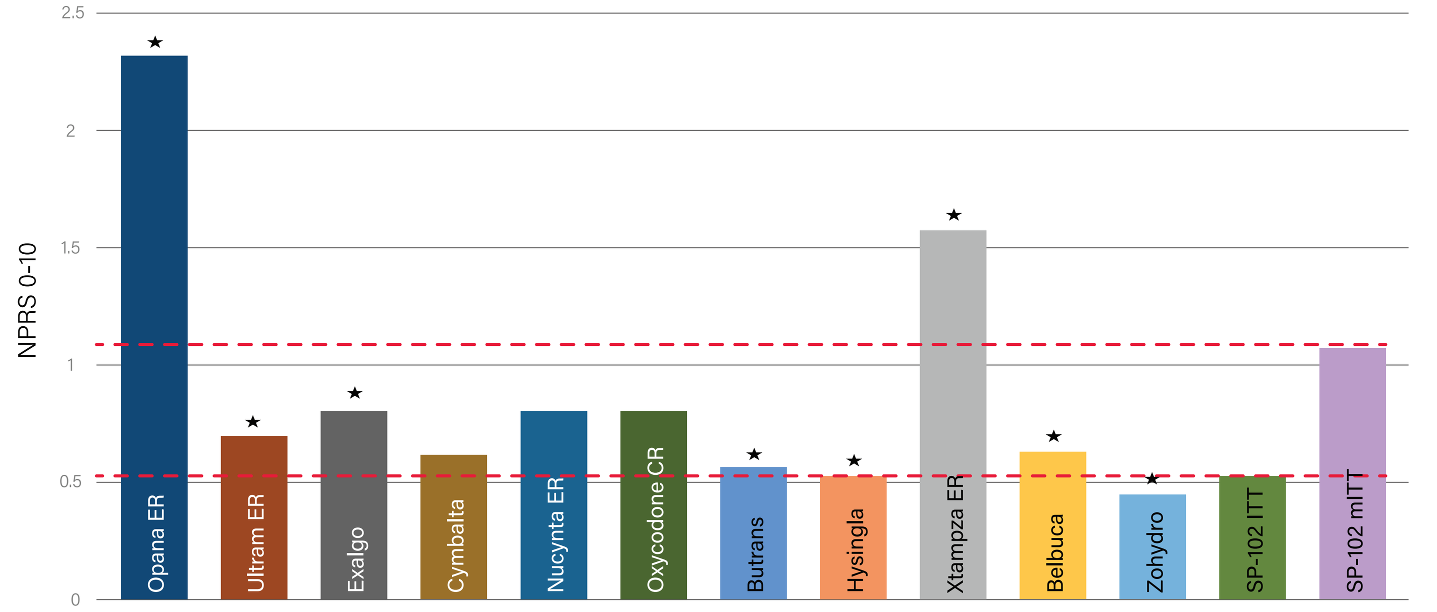


Figure 1b
Comparison of Between Mean Group Differences in Chronic Low Back Pain Studies on NPRS Scale at Primary Timepoint



Results for the mITT population (SES = 0.68) for SP-102 produced the 4th highest SES among currently approved analgesics (Figure 1A). In the ITT population, the SES was aligned with other products (SES = 0.28) (Figure 1A). Results were similar when NPRS GMD were compared, with results for the mITT population ranking 3rd (1.08-point difference) and the ITT population result being comparable to other analgesic products (0.52-point difference) (Figure 1B). If these approved products are assumed to be clinically meaningful analgesics, it can be concluded that SP-102 (both analysis populations) is also a clinically meaningful analgesic.

Clinically Meaningful Between Group Differences:

Comparison of SESs for Studies of Off-Label Use of TFI Administered Steroids:

- As there are no products approved for treatment of LRP, there are limited high quality data available for comparison. All four 4 studies included in this analysis reported that all subjects included had fluoroscopic confirmation of a successful injection (i.e., a population most similar to the mITT).

Figure 2a
Comparison of Standardized Effect Size

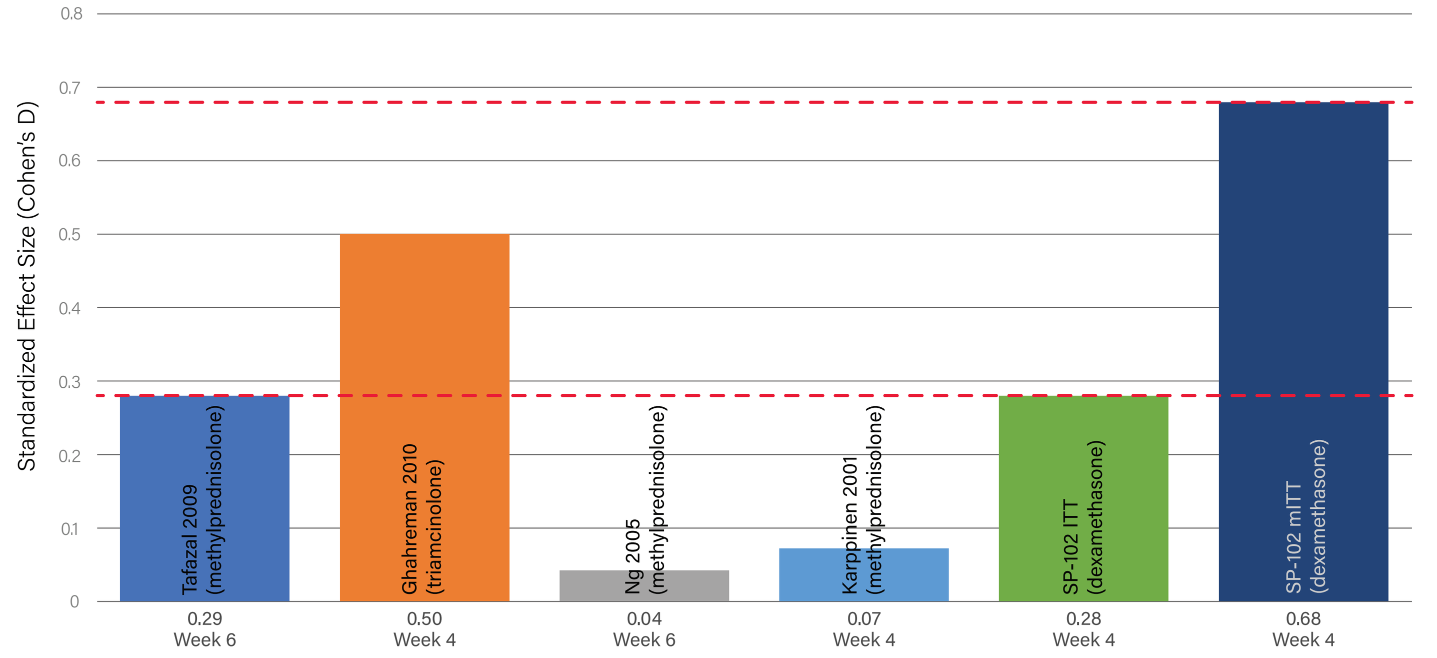
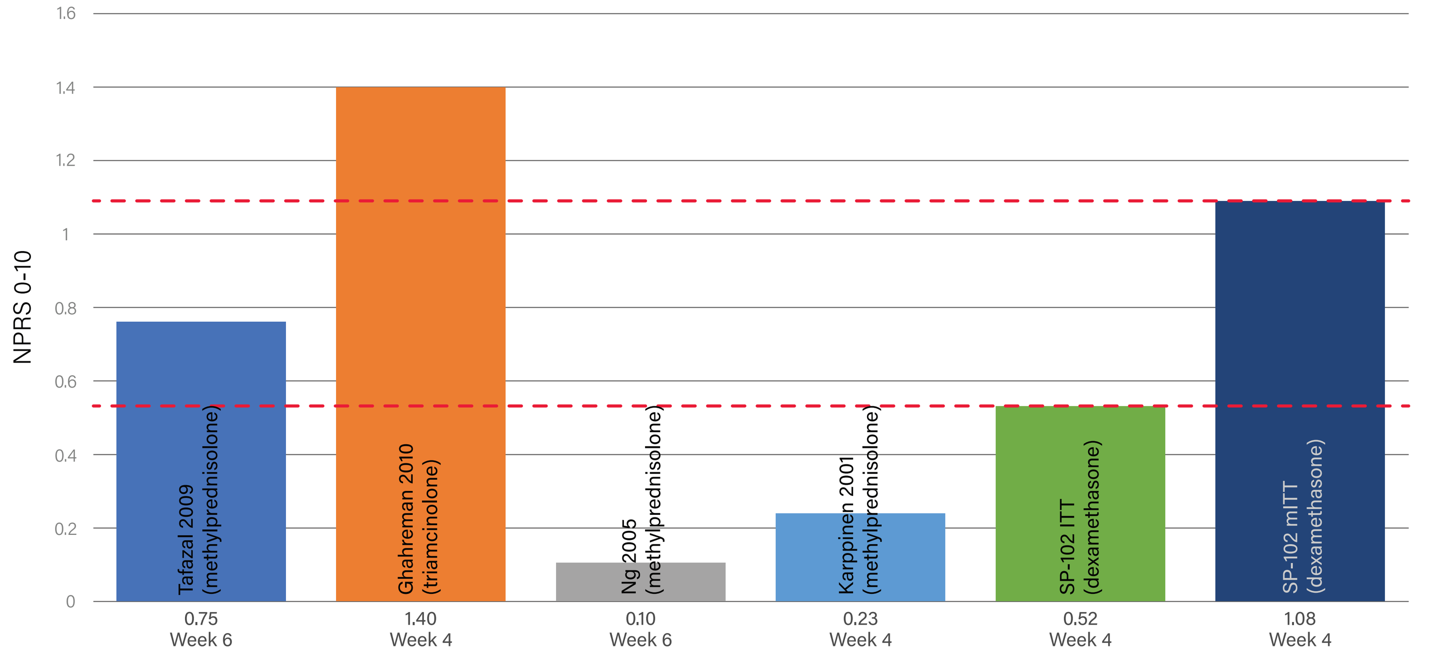


Figure 2b
Comparison of Between Mean Group Differences on NPRS Scale at Primary Timepoint



Results for the mITT population (SES = 0.68) for SP-102 produced the highest SES among the studied TFIs (Figure 2A). In the ITT population, the SES (SES = 0.28) was smaller than one study, similar to one study and greater than two studies (Figure 2A). Results were similar when the NPRS GMD were compared with SP-102 showing the second highest separation in the mITT population and 3rd highest for the ITT (Figure 2B). Results suggest SP-102 may have greater and or longer efficacy than products used off-label.

DISCUSSION

- Interpretation of the clinical meaningfulness of results requires consideration of primary and secondary endpoints assessed with-in subject based on consensus benchmarks, and the between group differences in the context of the overall risk-benefit and in comparison to other approved products for similar indications.
- The results of the CLEAR Trial show clear clinically meaningful separation between SP-102 and placebo in multiple with-in subject endpoints (NPRS Responder Analyses, ODI and BPI Pain Interference). This result is enhanced when solely considering the mITT population.
- This trend is also observed in the magnitude of GMD, particularly when the SESs of SP-102 is compared to other marketed and approved analgesics for CLBP, as well as other TSIs.
- The SP-102 formulation was intentionally created to offer a safer alternative to current off-label use of products that contain warnings of the potential dangerous and life-threatening AEs associated with epidural administration.
- Collectively, the benefit-risk profile presented supports SP-102 being a safe and efficacious product that has the potential to offer a much-needed therapy for the treatment of LRP.

1. Dworkin, R.H., Contemp Clin Trials 2016. 46(11). 2. Smith, S., et al., Pain 2020. 161; S3-S13. 3. Smith, S., et al. Pain 2020; 2446-2461. 4. Dworkin, R., et al. Pain 2009; 238-244. 5. Frymoyer, J.NEJM 1988; 291-300. 6. Frymoyer, J. Instr Course Lect 1992; 217-223. 7. Koes, B., et al. BMJ 2007 8. Stafford, M., et al. Br J Anaesth 2007; 461-473. 9. Miller, A., et al., Pain, 2024. 10. Oliveira, C., et al., Cochrane Database of Systematic Reviews 2020. 11. Ostelo, R., et al., Spine 2008; 90-94.