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The pharmacokinetics and pharmacodynamics of dexamethasone following epidural SP-102 or intravenous dexamethasone sodium phosphate injection in subjects with lumbosacral radicular pain

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Key words
steroids – pharmacokinetics – pharmacodynamics – dexamethasone

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Trial Registration: Australian New Zealand Clinical Trials Registry (registration number ACTRN12619000448145).

Abstract. Objectives: To evaluate the pharmacokinetics, pharmacodynamics (PD), safety, and tolerability of epidural SP-102 (10 mg dexamethasone sodium phosphate injectable gel) compared to an intravenous injection of 10 mg dexamethasone sodium phosphate, USP (IV USP). Materials and methods: Subjects with lumbosacral radiculopathy received a single dose of epidural SP-102, followed by a single dose of IV USP 4 weeks later. Dexamethasone plasma levels, cortisol levels, white blood cells (WBC), and blood glucose levels were assessed. Results: Twelve subjects entered and completed the study. The mean total dexamethasone exposure (AUC_{last} and AUC_{inf}) following SP-102 by epidural injection was equivalent to the total exposure following IV USP. A lower mean plasma C_{max} (~ 50% lower) was observed following epidural administration compared to IV injection. PD parameters were similar between treatments. Adverse events (AEs) were mild, with no serious AEs or study discontinuations due to AEs. Conclusion: In this small study, epidural SP-102 injection was well tolerated, was not associated with greater systemic dexamethasone exposure than IV USP, and both treatments had similar PD effects on cortisol suppression, blood glucose, and WBC levels.

What is known about this subject

- Epidural steroid injections (ESIs), the current standard of care, are not approved by the Food and Drug Administration (FDA) for managing lumbosacral radicular pain.
- SP-102 is being developed to address the serious complications associated with ESIs. SP-102 is a sterile dexamethasone sodium phosphate viscous gel solution of 10 mg dexamethasone for epidural administration. It does not contain neurotoxic preservatives or surfactants and is particulate-free, which is anticipated to reduce the risk of embolic events in case of inadvertent intra-arterial uptake during epidural injection. The viscous gel formulation was also designed to prolong the dexamethasone absorption at the injection site.
- There is no known published literature on the PK-PD and safety profiles of an epidural viscous dexamethasone gel.

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What this study adds

– This study was conducted to understand the preliminary PK-PD characteristics and safety profile of an epidural dexamethasone drug product, SP-102.

Introduction

Epidural injections of corticosteroids are a common procedure in the U.S. for managing lumbosacral radicular pain predominantly caused by disc herniation [1, 2, 3, 4]. They have been shown to be effective in reducing pain, restoring function, and reducing or eliminating the need for other healthcare, including surgery [1, 4]. Despite the commonality of epidural steroid injection (ESI) in the U.S., ESIs are an off-label use of licensed injectable corticosteroids as their injection into the epidural space is not approved by the Food and Drug Administration (FDA). In 2014, the FDA required a class warning on all injectable corticosteroids to include information about the risk of serious neurologic events with ESI [5]. This action was taken due to cases of paraplegia, quadriplegia, spinal cord infarction, stroke, and death, which were associated with injection of a suspension of steroid-containing particulates [6]. By contrast, few cases involving temporary symptoms were seen with soluble glucocorticoids such as dexamethasone [6]. Accordingly, the injection of these soluble glucocorticoids over particulate steroids was recommended by an FDA-convened multidisciplinary working group [7]. Consequently, randomized clinical trials are needed to further evaluate the efficacy and safety of ESIs to determine the benefit/risk balance and provide evidence to support an application for regulatory approval [8].

SP-102 is being developed to address the potential serious complications (such as paralysis and death) associated with currently available injectable corticosteroid formulations. SP-102 is a sterile dexamethasone sodium phosphate viscous gel solution of 10 mg dexamethasone at a 5 mg/mL concentration for epidural administration. It does not contain neurotoxic preservatives or surfactants and is particulate-free, which is anticipated to reduce the risk of embolic events in case of inadvertent intra-arterial uptake during epidural injection, especially via transforaminal approach [7]. The viscous gel formulation was designed to prolong the absorption of dexamethasone at the injection site. SP-102 is an investigational drug and is not currently approved for any indication in the U.S.. It is being developed under the 505(b)(2) regulatory pathway, which permits use of certain information required for the New Drug Application (NDA) approval from the Agency's prior findings and/or any information found in the public domain for the reference listed drug (RLD), dexamethasone sodium phosphate, USP.

Given the novel dosage form of SP-102 and the local route of delivery, this phase I study was designed to evaluate the pharmacokinetics (PK), pharmacodynamics (PD), safety, and tolerability of epidural SP-102 (10 mg dexamethasone sodium phosphate injectable gel) compared to an intravenous (IV) injection of 10 mg dexamethasone sodium phosphate, USP, in subjects with lumbosacral radicular pain. PD endpoints included change in white blood cell (WBC) and blood glucose levels, and cortisol suppression time.

Materials and methods

This phase I study was reviewed and approved by Health and Disability Ethics Committees (Wellington, Australia). Written informed consent was obtained from all subjects. The trial was registered with the Australian New Zealand Clinical Trials Registry (registration number ACTRN12619000448145). This trial was conducted according to the ethical principles stated in the Declaration of Helsinki (version 13).

Study participants

Study participants had a diagnosis of lumbosacral radicular pain radiating unilaterally or bilaterally into the leg(s), with a minimum 2-month duration of radicular pain in the current episode. Eligible subjects were aged 18 – 70 years old, with cortisol, WBC count, and glucose levels within the normal ranges. Key exclusion criteria included a body mass index ≥ 40 kg/m^2; any significant medical condition that could be affected by dexamethasone use, including infection, renal, hepatic, or cardiovascular disease; use of

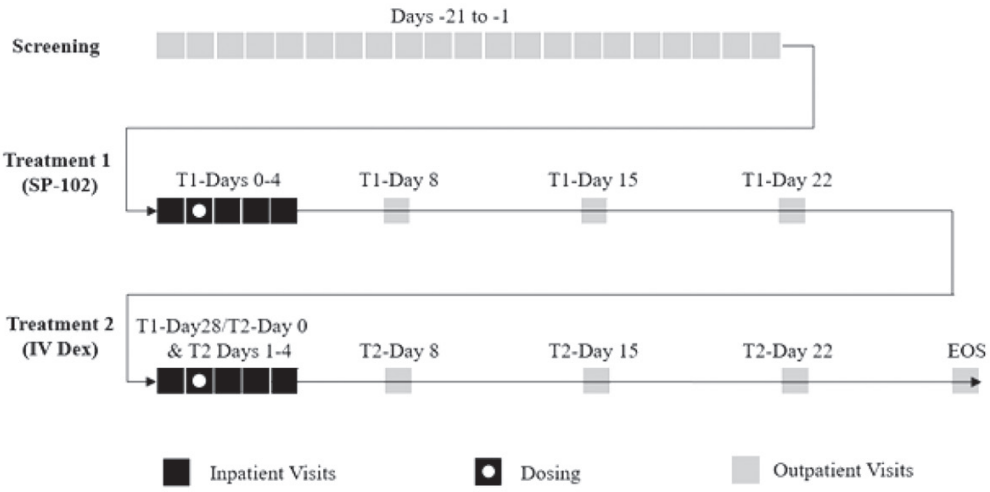

Figure 1. Study design. EOS = end of study; IV Dex = intravenous dexamethasone.

anticoagulants in the last 7 days; if female, pregnant, lactating, or breastfeeding. Any history of a cortisol production disorder or malignancy, other than successfully treated basal or squamous cell carcinoma of the skin or cervical intra-epithelial neoplasia, was also a reason for exclusion.

Study design and interventions

The study was conducted at Christchurch Clinical Studies Trust (Christchurch, New Zealand). After a screening period of up to 21 days, subjects underwent sequential treatment with a washout period of ~ 4 weeks between treatments. All subjects received the two treatments in a fixed sequence: first the SP-102 epidural injection, then the USP IV injection. Treatments were administered as follows:

– Treatment 1 (T1): SP-102 epidural injection: interlaminar epidural administration of 2.0 mL SP-102 (10 mg dexamethasone) using a sterile, computerized tomography (CT)-guided technique with a Siemens Definition CT (Siemens AG, Erlangen, Germany). Translaminar epidural access was gained using 90-mm, 22-gauge terumo spinal needles, with air contrast confirmation of epidural needle tip position. Cutaneous or subcutaneous local anesthetic (1% lignocaine) was administered before epidural injection and no intra-epidural local anesthetic was used.
– Treatment 2 (T2): Dexamethasone sodium phosphate injection, USP (USP IV injection); manufactured by Fresenius Kabi, Lake Zurich, IL, USA; LLC: Intravenous administration of 1.2 mL dexamethasone sodium phosphate injection, USP (10 mg dexamethasone).

The screening visit occurred between day −21 and day −1 (Figure 1) and the baseline visit (T1Day 0) took place the day before T1 was administered (T1Day 1). Ahead of both treatments, subjects were admitted to the clinical research unit (CRU) the evening before the doses were given and required to fast for at least 10 hours prior to administration. After T1 and T2, subjects were discharged from the CRU following the collection of the first post-dose sample for PD assessment and the 24-hour post-dose PK blood sample. They then returned to the CRU to provide all subsequent samples, including the 48-hour PK blood sample and remaining post-dose samples for PD assessment, laboratory tests, and other required assessments at 2, 3, and 7 days after dosing, with further visits at ~ 2, 3, and 4 weeks after dosing. During the fourth weekly visit after T1 (T1Day 28/T2Day 0), subjects were evaluated for further participation in the study. Subjects in T2 were dosed at the same time of day (± 10 minutes) as their T1 dose time, prior to noon. The fourth weekly visit after T2 was the end of study (EOS) visit. From the time of informed consent to the EOS visit, the total study duration for each subject was ~ 3 months.

Table 1. Subject demographics and baseline characteristics.

Characteristic		N = 12
Age, median years (IQR)		51.0 (36.0 – 63.5)
Gender, n male (%)		6 (50%)
Race, n (%)	Asian	0
	Black	0
	White	11 (91.7%)
	Pacific Islander	0
	Australian Aborigine/ Torres Strait Islander	0
	Other	1 (8.3%)
Ethnicity, n (%)	Hispanic or Latino	0 (0%)
	Not Hispanic or Latino	12 (100%)
Height, median cm (IQR)		169.5 (162.0 – 179.0)
BMI, median kg/m^2 (IQR)		31.7 (28.8 – 33.8)
Straight leg raise, L5-S1, n, (%)	Negative	4 (33.3%)
	Positive	8 (66.7%)
Femoral stretch, L3-L4, n (%)	Negative	7 (58.3%)
	Positive	5 (41.7%)

BMI = body mass index; IQR = interquartile range.

Study endpoints and assessments

The primary objective in this study was to assess the overall PK profile of each treatment after a single dose. Secondary objectives included assessment of the PD of the two treatments based on plasma cortisol levels, glucose levels, WBC count, and the safety and tolerability of SP-102 epidural injection.

Blood for PK assessment at each treatment was collected in pre-chilled K_2EDTA tubes at the following timepoints: 8 AM (± 10 minutes) pre-dose, and 0.25, 0.50, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, 20, 24, and 48 hours post-dose. The blood samples were centrifuged at 3,200×g and 2 to 8 °C for 15 minutes. Plasma samples was collected and frozen at –20 °C until analysis. A validated liquid chromatography/tandem mass spectrometry (API 5000, SCIEX, Framingham, MA, USA) using electrospray ionization and positive ion mode (m/z 393.3) with protein-precipitation extraction was used for the analysis of dexamethasone in plasma. The linear range of the assay for dexamethasone was 1 – 1,000 ng/mL. The intra-assay accuracy and precision was 6.0 – 13.0% and 7.4 – 10.0%, respectively. The inter-assay accuracy and precision was –2.8% –2.2% and 3.3% – 8.3%, respectively. Dexamethasone-d_4 was used as the internal standard. PK sample bioanalysis was performed by Covance Laboratories (Durham, NC, USA).

PK parameters were estimated using non-compartmental methods from plasma samples for dexamethasone. Time from end of injection was used in all estimates. C_{max} and t_{max} data were directly taken from the measured data.

Blood for PD assessment was drawn at the following timepoints: at 8 AM (± 10 minutes) pre-dose on day 1, then at 8 AM (± 10 minutes) on days 2, 3, 4, 8, 15, 22, and 28 (EOS visit for T2). The pre-dose morning values were used as baseline in PD assessments. Dexamethasone-induced hypothalamic pituitary adrenal (HPA) suppression was assessed based on the observed total plasma cortisol level, glucose levels, and WBC count. Cortisol levels were measured by Canterbury Health Laboratories (Canterbury Health Laboratories, Christchurch, New Zealand) and based on a reference range of 250 – 800 nmol/L. The reference range for WBC count was 4 – 11 × 10^9/L, while that for fasting glucose was 3.5 – 6.0 mmol/L, and both tests were performed by Christchurch Clinical Studies Trust.

Adverse events (AEs) were coded using MedDRA terms and monitored throughout the study from the time the subject signed the informed consent and until 28 days after the last dose of study drug. AEs were collected in accordance with good clinical practice (GCP) standards, i.e., non-leading questions and spontaneous reporting. AE severity was classified as mild, moderate, severe,

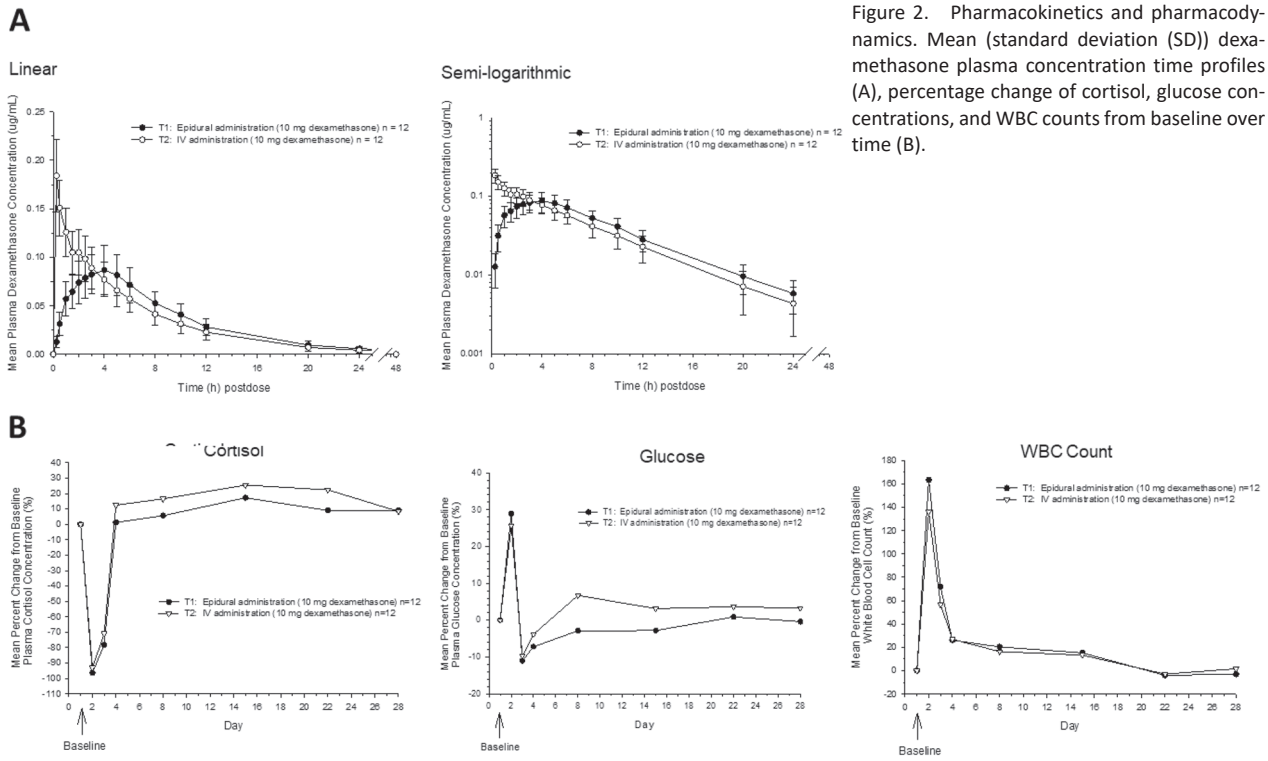

Figure 2. Pharmacokinetics and pharmacodynamics. Mean (standard deviation (SD)) dexamethasone plasma concentration time profiles (A), percentage change of cortisol, glucose concentrations, and WBC counts from baseline over time (B).

Table 2. Summary of dexamethasone pharmacokinetic parameters by treatment.

Treatment	AUC_{inf} (µg×h/mL)	C_{max} (µg/mL)	t_{max} (h)	$T_{1/2}$ (h)
T1 (N = 12)	0.916 (0.225)	0.091 (0.027)	4.00 (2.00 – 5.05)	5.16 (0.90)
T2 (N = 12)	0.943 (0.229)	0.184 (0.037)	0.25 (0.25 – 0.5)	4.64 (0.91)

Arithmetic mean (standard deviation); median (range). T1 = treatment 1 (SP-102 epidural injection); T2 = treatment 2 (dexamethasone USP IV injection).

life-threatening, or death, with the last two grades qualifying as serious AEs (SAEs). The likelihood of association with treatment was also recorded. All AEs that occurred after the time of treatment with the study drug were considered to be treatment-emergent AEs (TEAEs).

Statistical analysis

The sample size for this study was based on clinical and practical considerations and not on a formal statistical power calculation.

To assess relative bioavailability, natural log transformed maximum plasma concentration (C_{max}) and area under the plasma concentration-time curve (AUC_{last}, and AUC_{inf}) of dexamethasone were separately analyzed using a linear mixed-effects model with treatment as the fixed effect and subject as a random effect. In all comparisons between treatments, T2 was used as the reference treatment. Transformed back from the logarithmic scale, geometric least-squares means (LSMs) with corresponding 2-sided, 95% confidence intervals (CIs) were estimated for C_{max}, AUC_{last}, and AUC_{inf}. Ratios of geometric LSMs (T1/T2) with 2-sided, 90% CIs were estimated, and bioequivalence was concluded if the 90% CIs for these ratios were contained within the range of 80 – 125%.

PK parameters were derived using non-compartmental methods with Phoenix WinNonlin Version 6.4 (Pharsight, a Certara Company, Princeton, NJ, USA) and SAS Version 9.4, SAS Institute, Inc., Cary, NC, USA). All descriptive and inferential statistical computations were performed using SAS Version 9.4. Mean PK figures were developed using SigmaPlot Version 12.5 (Systat Software, Inc, San Jose, CA, USA).

Table 3. Statistical comparison of dexamethasone pharmacokinetic parameters.

Parameter (unit)	Treatment[a]	n	Geo LSM	Comparison of SP-102 epidural vs. USP IV	
				Ratio (%)	90% CI
AUC_{inf} (µg×h/mL)	T1	12	0.8873	97.04	(92.37, 101.95)
	T2	12	0.9143		
AUC_{last} (µg×h/mL)	T1	12	0.8515	96.23	(91.61, 101.09)
	T2	12	0.8848		
C_{max} (µg/mL)	T1	12	0.0877	48.46	(41.89, 56.07)
	T2	12	0.1809		

T1 = treatment 1 (SP-102 epidural injection); T2 = treatment 2 (dexamethasone USP IV injection). AUC_{inf} = area under the plasma concentration-time curve from zero to infinity; AUC_{last} = area under the plasma concentration-time curve from zero to the last quantifiable concentration; CI = confidence interval; C_{max} = maximum plasma concentration; IV = intravenous; Geo = geometric; LSM = least-squares mean; n = number of subjects; USP = United States Pharmacopeia; vs = versus. Results are based on a linear mixed-effects model for PK parameters on log-scale with treatment as fixed effect and subject as a random effect. Geo least-square means and ratios are calculated by anti-log transformation of the least square estimates.

Table 4. TEAEs reported during the study.

TEAE type	TEAEs experienced by ≥ 1 subject, n (%)	
	SP-102 Epidural	USP IV
Any TEAE	12 (100)	10 (83.3)
Headache	5 (41.7)	3 (25.0)
Transient radicular pain[a]	3 (25.0)	0 (0.0)
Back pain	3 (25.0)	1 (8.3)

IV = intravenous; TEAE = treatment-emergent adverse events; USP = United States Pharmacopeia. [a]Reported term: exacerbation of sciatica.

Results

Study subjects and administration

Study participants were enrolled between January 22 and October 6, 2016. Twelve subjects were enrolled, with a median age of 51 years. Subject demographics and characteristics at baseline are shown in Table 1. All subjects completed the study.

Pharmacokinetics

Mean (standard deviation (SD)) dexamethasone plasma concentration time profiles are shown in Figure 2A. The initial portion of the curves are different due to the route of administering study drug, but from 3 hours post-dose onwards, the mean dexamethasone concentrations were similar for both treatments, declining monoexponentially.

PK parameters are summarized by treatment in Table 2. The geometric mean dexamethasone AUC_{inf} was similar between the two treatments. The geometric mean dexamethasone C_{max} was lower after SP-102 epidural injection compared with USP IV injection, which is to be expected given that USP IV dexamethasone was immediately available in the plasma while SP-102 epidural injection was not. The median t_{max} values were 4 hours (range 2.00 – 5.05 hours) after SP-102 epidural injection and 0.25 hours (range 0.25 – 0.50 hours) after USP IV injection. Arithmetic mean (SD) dexamethasone $T_{1/2}$ was 5.163 (0.9030) hours after SP-102 epidural injection and 4.641 (0.9080) hours after USP IV injection.

Statistical comparisons of dexamethasone AUC_{inf}, AUC_{last}, and C_{max} between the two treatments are summarized in Table 3. The geometric LSM ratios comparing SP-102 epidural injection with USP IV injection for dexamethasone AUC_{last}, AUC_{inf}, and C_{max} were 96.23% (0.8515/0.8848), 97.04% (0.8873/0.9143), and 48.46% (0.0877/0.1809), respectively. The 90% CIs of the geometric LSM ratios for AUC_{last} and AUC_{inf} ratio was within the predefined limit of 80 – 125%. This demonstrated that the difference in mean total dexamethasone exposure (AUC_{last} and AUC_{inf}) following SP-102 epidural injection compared to the total exposure following USP IV injection was non-significant. However, the mean maximal dexamethasone exposure (C_{max}) following SP-102 epidural injection was ~ 50% lower than that of USP IV injection and did not meet the criteria for bioequivalence.

Pharmacodynamics

The percentage change of cortisol and glucose concentrations and WBC counts from baseline over time are shown in Figure 2B. On the day after treatment administration, mean plasma cortisol concentrations decreased by ~ 96 and 93% for epidural SP-102 and IV USP, respectively. Mean cortisol concentrations then returned to within the normal by about day 4 post-dose. Average plasma glucose concentrations increased by day 2 by ~ 29 and 26% for epidural SP-102 and IV USP, respectively, before returning to the normal range on day 3. Average WBC counts showed an initial increase of ~ 163% and 136% for epidural SP-102 and IV USP, respectively, by day 2, before returning to the normal range on day 3.

Safety

The proportion of subjects with TEAEs was slightly higher with SP-102 epidural compared with USP IV (Table 4). The most commonly reported TEAEs were headache, back pain, and transient radicular pain. All AEs were mild or moderate. No new unexpected TEAEs were observed. There were no clinically meaningful changes in hematology, blood chemistry, and coagulation parameters during either treatment, nor were there any clinically relevant changes in vital signs, ECG, or physical examinations during the study. There were no deaths or SAEs or premature treatment discontinuations during the study.

Discussion

This was an open label, non-randomized, fixed sequential dose PK and PD study. All subjects received both T1 and T2, with a washout period of ~ 4 weeks between doses. Administration of both treatments to each subject allowed for within-subject observations. PK sampling time was appropriate, given the reported 2- to 4-hour terminal half-life of dexamethasone [11]. The fixed sequential dose design was used to control pain by epidural injection in subjects with lumbosacral radicular pain when indicated. Therefore, epidural injection was administered first, followed by an IV injection after a washout period.

The PK profile of SP-102 epidural injection suggests that the resulting systemic exposure to dexamethasone was equivalent to those observed with USP IV injection, as indicated by AUC.

The PK profile of the SP-102 epidural injection showed a lower mean plasma C_{max} (~ 50%) than the USP IV injection and a delayed median t_{max}.

Although USP IV injection resulted in higher initial plasma dexamethasone concentrations compared to SP-102 epidural administration, the systemic effects of dexamethasone on HPA suppression were comparable between both treatments as evidenced by similar transient decreases in cortisol levels, increases in glucose levels, and increases in WBC counts. The data suggests that dexamethasone-mediated PD effects appear to be entirely related to total exposure (i.e., AUC) rather than maximum exposure (C_{max}). Furthermore, epidural injection of SP-102 in this small study appeared to be well tolerated, associated with no significant injection-site reactions, and appeared to demonstrate a similar safety profile to USP IV. The most commonly reported TEAEs reported in this study of headache, back pain, and transient radicular pain are commonly reported with epidural injections [9].

The limitations of this study include the fact that the treatments were administered in a fixed sequence to all subjects and that the different injection routes precluded any blinding of subjects or clinicians to treatments. In addition, no radiological assessment was conducted to confirm the diagnosis of lumbosacral radicular pain in the patient population; the number of subjects was small, and the study was reasonably short in duration because the primary objective of the study was to assess the single-dose PK following the two treatments. Therefore, any interpretation related to SP-102 clinical safety should be treated as preliminary data.

Whilst prolonged-release gel formulations of local anesthetics are in late-stage clinical trials or have been approved by the FDA for other indications [13], there are few other published data on the use of gel formulations of steroids or other drugs in epidural injections for lumbosacral radicu-

lopathy in humans [12]. This is the first publication of the PK characteristics of an epidural dexamethasone drug product, therefore comparison of dexamethasone PK following epidural administration across other studies are not possible.

In conclusion, PK data from this study indicate that 10 mg of dexamethasone released from a novel viscous SP-102 formulation delivered epidurally does not predispose patients to higher systemic exposure than 10 mg USP dexamethasone delivered intravenously. This study suggests that both treatments had similar PD effects on cortisol suppression, blood glucose, and WBCs levels. SP-102 injections in this small study appeared generally safe and well tolerated, with no unexpected AEs from epidural administration.

Ethnicity

It is unknown if there is an ethnicity-related differences in dexamethasone delivery via an epidural injection.

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Authors' contributions

Richard Robson helped with data collection from study subjects, performed safety assessments, and served as the Principal Investigator.

Elizabeth Stannard helped to manage and organize the study.

Shiyin Yee helped to oversee scientific integrity of the study, pharmacokinetic data collection and analysis.

Ritu Lal helped develop the study methodology and design.

Dmitri Lissin helped to design the study and to interpret study data, directed the study, and oversaw study conduct.

All authors contributed to development of the manuscript and approved the final draft.

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Conflict of interest

Shiyin Yee, Elizabeth Stannard, and Ritu Lal received consultancy fees from Scilex Pharmaceuticals, Inc. during and outside of the conduct of the study. Dmitri Lissin is an employee of Scilex Pharmaceuticals, Inc. and holds shareholder status in the company.

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