Integrating Hybrid Blinding, Algorithmic Pain Endpoints, and Pharmacokinetic Characterization in a First-in-Human Trial of an Extended-Release Epidural Corticosteroid

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Methodological Issue Being Addressed

Procedural CNS and pain trials involving extended-release neuraxial products face three core methodological challenges: 1) maintaining blinding when the active injectate is visually distinct from placebo, 2) deriving stable patient-reported pain endpoints from high-variability daily ratings, and 3) integrating pharmacokinetic data into a procedure-based study where systemic exposure is an indirect surrogate for local depot release. This study implements a hybrid-blinded design, an algorithmic diary-based primary endpoint, and an embedded intensive/sparse PK strategy to address these issues within a first-in-human evaluation of an extended-release epidural corticosteroid.[1] The rationale was to enhance internal validity, ensure consistent endpoint construction, and enable interpretable assessment of exposure and durability of clinical response in an early-phase setting, recognizing that analyses were descriptive and constrained by early termination during the COVID-19 pandemic.

Introduction

Extended-release neuraxial therapeutics present unique trial-design constraints, including visually distinguishable injectates, difficulty achieving uniform blinding, and the need to stabilize highly variable pain ratings. These limitations can impair internal validity and complicate interpretation of early-phase results. We developed a methodological framework combining hybrid blinding, algorithmic NRS pain endpoints, and pharmacokinetic exposure characterization to evaluate a first-in-human extended-release epidural corticosteroid formulation administered via lumbar transforaminal epidural injection for unilateral radicular leg pain. This abstract focuses on the design, implementation, and analytic performance of these methods in a procedurally complex, early-phase setting.

Methods

Adults with radicular leg pain due to single-level lumbar disc herniation were randomized 1:1:1 to two dose levels of an extended-release epidural corticosteroid formulation or placebo. Because active product reconstituted to an opaque suspension while placebo was clear, injectors were intentionally unblinded; participants, investigators, outcome assessors, and analysts remained blinded. Daily Worst Daily Leg Pain (WDLP) scores were collected electronically once per day. A prespecified algorithm calculated visit-level WDLP means by requiring at least seven diary entries within a ten-day window, trimming the highest and lowest values, and averaging the remaining scores. Missing data were not imputed. Rescue medication use or additional procedures triggered automatic classification as nonresponse for subsequent visits. Pharmacokinetic sampling included intensive 0–24 hour profiles in a subset and sparse sampling through Day 180 for all participants. Enrollment stopped early due to COVID-19 operational disruptions; all analyses followed the prespecified statistical plan and were conducted descriptively given limited event counts and reduced sample size.

Results

Fifty-six participants were randomized and treated, with 91 percent completing Day 180 follow-up. High diary compliance enabled consistent application of the algorithmic endpoint. Hybrid blinding was maintained without documented breaches. Pharmacokinetic data demonstrated prolonged, low-level systemic corticosteroid exposure in the higher-dose cohort, consistent with expectations for depot release and aligning with durability patterns observed in responder analyses. Sensitivity analyses demonstrated robustness of endpoint construction using alternative diary-processing and conservative reclassification rules yielding consistent directional patterns, supporting robustness of the methodological approach despite reduced sample size.

Conclusions

This study illustrates the feasibility and internal validity of a hybrid-blinded, algorithmically defined, pharmacokinetically integrated framework for early-phase neuraxial depot trials. The combination of intentional injector unblinding, standardized diary-based endpoint construction, and embedded pharmacokinetic assessment enabled interpretable evaluation of durability patterns despite COVID-related early termination. These design elements offer generalizable methodological advantages for CNS and pain trials involving procedural interventions, depot formulations, or patient-reported outcomes with high day-to-day variability.

References

1. Ludbrook G, Houghton W, Techner L, Meyering E, Gashwiler V, Rachfal A, Missling J. Clinically meaningful radicular leg pain management via novel dexamethasone extended release microsuspension (SX600)-Phase 1/2 Results (4710). ASRA 2024 PM Scientific Abstracts Regional Anesthesia & Pain Medicine 2024;49:381-390. doi: 10.1136 /rapm-2024-ASRA_PM_ABSTRACTS. Presented at 22nd ASRA Annual Pain Medicine Meeting, Nov 10-11, 2023, New Orleans, Louisiana.