Intradiscal linezolid (PP353) treatment for chronic low back pain associated with Modic change type 1: an international, first-in-human, randomised, sham procedure-controlled, double-blind, phase 1b clinical trial

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Summary

Background Oral amoxicillin reduced pain and disability in patients with chronic Low Back Pain (cLBP) and vertebral endplate bone oedema (Modic changes type 1; MC1) in two randomised controlled trials (RCTs), providing evidence that cLBP with MC1 may be caused by a chronic bacterial infection of the disc. Disc tissue is poorly vascularised, and oral antibiotics will not achieve optimal antibacterial concentration. Linezolid has been formulated for intradiscal administration (PP353) to deliver effective antibacterial therapy while minimising systemic exposure. This trial aimed to establish whether PP353 is safe and has the potential to treat cLBP with MC1 or mixed MC1 and Modic changes type 2 (MC2).

Methods The trial was a double blind, randomised, sham-procedure controlled phase 1b clinical trial in patients with cLBP of ≥6 months duration and MC1 or mixed MC1 and MC2 at a single lumbar level, aged 18–70 years, average Low Back Pain Numerical Rating Scale (LBP NRS) ≥ 4 on chronic pain medication or ≥ 6 if not, Roland Morris Disability Questionnaire-23 (RMDQ-23) score ≥9, low back pain greater than leg pain, and failure to adequately respond to standard of care. Interactive response technology randomly assigned participants 1:1 to PP353 (2 intradiscal doses) or placebo (2 sham procedures). The primary outcomes were the incidence of adverse events and the change in LBP NRS score at 12 months. Secondary outcomes were change in LBP NRS at intervening timepoints and change in RMDQ-23 and Oswestry Disability Index (ODI) (v2.1) at all timepoints, responder analyses ≥30% and ≥50% change from baseline and characterisation of the pharmacokinetics of two doses of PP353. The trial is registered with ClinicalTrials.gov (NCT04238676) and EudraCT (2018-004488-30), and the Universal Trial Number is U1111-1257-2567.

Findings Between December, 2021, and December, 2023, 41 participants from sites in the UK, Spain, New Zealand and Denmark were recruited, with 40 participants receiving at least one dose of PP353 (20 participants) or placebo (20 participants) and having at least one post-baseline assessment of efficacy. 29 (72.5%) participants were female. PP353 and the intradiscal procedure were well tolerated, with no severe, life-threatening or disabling adverse events

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and no overall difference in adverse events from the sham procedure. At 12 months, a statistically significant and clinically meaningful difference between PP353 and placebo in mean group change from baseline in patient-reported pain (LBP NRS −3.36 vs −2.00; 95% CI −0.19, p = 0.028), using a predefined one-sided test, was observed.

Interpretation Two intradiscal administrations of PP353 are well tolerated and could be an effective and minimally invasive, day case therapy for patients with cLBP associated with MC1 or mixed MC1 and MC2.

Funding Persica Pharmaceuticals Ltd funded the trial and was responsible for the conceptualisation, overall design, collation of data, decision to publish and the first draft of the manuscript.

Keywords: Linezolid; Modic; Vertebrogenic back pain; Intradiscal; Intervertebral disc; Chronic low back pain

Research in context

Evidence before this study

PubMed was searched from inception to May 1, 2025, with the terms "intradiscal" AND "antibiotic", and "intradiscal" AND "linezolid" without restrictions which provided 21 results. Ten were reviews or case studies of discitis. Eight were *in vitro* studies, preclinical or veterinary studies. One investigated oral antibiotic penetration into disc tissue. Two investigated prophylactic use of antibiotic or ozone to reduce discitis after discography. Only one trial investigated clinical intradiscal administration of antibiotic, the PP353 Phase 1b single-dose trial. Two oral antibiotic RCTs investigating treatment of cLBP with MC1 and 12 month follow up have been reported.

Added value of this study

This trial is the first to evaluate the safety and efficacy of two-doses of intradiscal linezolid (PP353) in participants with cLBP and MC1. This trial demonstrates that intradiscal linezolid is well tolerated and is a potentially effective therapy that reduces chronic pain and disability. Furthermore, intradiscal antibiotic administration may reduce side effects observed with oral systemic treatment.

Implications of all the available evidence

This trial provides Proof of Concept for intradiscal linezolid therapy to treat cLBP with MC1. This is the third positive antibiotic RCT exploring treatment of cLBP with MC1. The use of a different antibiotic and route of administration, with significant and meaningful reductions in pain and disability, strongly supports the hypothesis that bacterial infection can lead to cLBP with MC1.

Introduction

Chronic low back pain (cLBP) is a substantial cause of disability and major health economic burden.[1] There are multiple causes of cLBP, but using MRI, patients presenting with pain associated with vertebral bone oedema or Modic Changes type 1 (MC1) or mixed MC1 and Modic changes type 2 (MC2), hereafter summarised as MC1, can be easily identified, with an estimated prevalence of tens of millions of patients worldwide.[2–5] The presence of MC1 is associated with prolonged, severe and disabling back pain[6,7] and lack of benefit from conservative therapies.[8–10] The importance of recognising cLBP with Modic changes has led to the introduction of an MRI-based diagnostic code, ICD-10-CM-54.51.[11]

Bacterial infection of the disc has been associated with cLBP and MC1.[12] The published literature investigating the presence of pathogenic bacteria in intervertebral disc tissue is inconsistent. However, as discussed in the review article by Gilligan et al., the inconsistency may be due to a combination of methodological issues related to sample disruption, incubation conditions and duration and different lower limits of detection of bacterial burden.[4,13–19] In five well-designed and executed disc microbiology studies, 45.2% (range 34.8%–56.7%) of disc tissue samples were infected with bacteria, most frequently 36.7% (range 31.3%–39.7%) with *Cutibacterium acnes*.[12,20–23] Histological studies have visualised *in situ* bacteria embedded within disc tissue, reducing the likelihood that findings are contamination from surgical procedures.[23–26] Infection of intervertebral discs with *C. acnes* in preclinical models leads to recapitulation of MC1-like changes, bone remodelling, nerve fibre endplate in-growth, increased expression of the neurotransmitter CGRP and nociceptive hypersensitivity, confirming the hypothesis of a bacterial infective aetiology.[27,28]

Oral antibiotic treatment of 90 or 100 days of amoxicillin or co-amoxiclav, in participants with cLBP and MC1 has been evaluated in two Randomised Controlled Trials (RCTs) with 12-month follow-up.[29–31] In both trials, improvements were observed in both pain and disability measures, although the magnitude

of benefit was not consistent across trials, possibly due to differing designs.[12,29,30] Albert et al.[29] observed a dose–response using 1.5 g and 3 g amoxicillin per day. Braten et al.[30] used an intermediate dose of 2.25 g amoxicillin per day which may have contributed to the reduced magnitude of effect observed. A meta-analysis of studies investigating oral antibiotics to treat cLBP with Modic changes concluded that although oral antibiotics were statistically superior to placebo in reducing LBP-related disability in patients with cLBP and concomitant MC1, its clinical significance remains uncertain and recommended additional trials.[31]

Prolonged use of high dose oral antibiotics was poorly tolerated, with 56%[30] and 65%[29] of participants reporting gastrointestinal adverse events, and in one trial, 12% of participants discontinued or paused oral antibiotic treatment.[30] The benefit-risk assessment for prolonged high-dose oral antibiotic use to treat cLBP will always be impacted by these systemic side effects. While the oral antibiotic RCTs demonstrate potential, it is clear that they do not provide a treatment suitable for routine clinical use.

The intervertebral disc is poorly vascularised and it is not easy to ensure effective antibacterial exposure in the disc tissue using oral administration.[32,33] Intradiscal administration of antibiotic to the infected disc, provides a greater concentration of antibiotic at the infected site, reduces the amount of antibiotics used and limits systemic exposure and side-effects, thereby improving patient compliance and antibiotic stewardship when compared to oral antibiotics. However, direct administration of an intravenous formulation of an antibiotic into a degenerate intervertebral disc leads to relatively rapid dispersion out of the disc space and so the formulation needs to combine being suitable for intradiscal injection and providing extended duration of exposure. PP353 addresses both of these challenges. PP353 contains a radio-opaque dye, iohexol, which enables image-guided administration into the nucleus pulposus of the disc which can be stopped if leakage is observed, and it contains a poloxamer-based thermosensitive gel which is liquid until it warms in the body, where it forms a viscous gel that minimises leakage.

Preclinical development and Phase 1b single-dose safety and pharmacokinetics of PP353, a suspension of micronised linezolid for intradiscal administration, have been reported.[34,35] The trial reported here was conducted to assess the safety, pharmacokinetics and efficacy of two-doses of intradiscal linezolid (PP353), in participants with cLBP and MC1. Participants were followed up for a year.

Methods

Study design and participants

This randomised, placebo-controlled, investigator- and subject-blinded, third-party unblinded, international Phase 1b 12-month clinical trial was conducted across 9 trial sites (5 in the UK, 2 in Spain, 1 in New Zealand and 1 in Denmark).

The trial was sponsored by Persica Pharmaceuticals Limited and coordinated by Micron Research Limited. A Safety Review Committee (including Sponsor representatives) had oversight of the trial which was conducted according to Good Clinical Practice.

The trial is registered with ClinicalTrials.gov (NCT04238676), the World Health Organization (Universal Trial Number U1111-1257-2567 and the European Medicines Agency (EudraCT number 2018-004488-30) and is complete. The trial protocol and statistical analysis plan, redacted to be compliant with the General Data Protection Regulations (GDPR) are provided in the online supplemental information.

Participants were aged 18–70 years with cLBP associated with MC1 (vertebral body endplate oedema) or MC1 and MC2 (vertebral body endplate bone fat) at a single lumbar level. Participants must have had inadequate relief from conservative treatment, and the current cLBP episode must have lasted for ≥6-months at the time of randomisation. Detailed eligibility criteria have been published.[35]

Key pain and disability inclusion criteria were baseline LBP NRS ≥4 if taking chronic pain medication or ≥6 if not,[29,36] a score of ≥9 on the Roland–Morris Disability Questionnaire, RMDQ-23 (0–23),[29,37,38] and low back pain was greater than leg pain.

Key exclusion criteria were MC1 changes present at more than 1 lumbar level, the target lumbar disc for injection had lost more than half of its original height or was not accessible for the intradiscal injection, there was a clear alternative cause of back pain, or antimicrobial therapy had been previously used to treat the cLBP, or serious psychiatric or medical conditions that could interfere with treatment, compliance or the ability to give consent.[35]

MRI using 1.5 T scanners with T1, T2 and STIR sequences across the T8-S3 Sagittal plane with a field of view of >40 cm and Dixon Sagittal and Coronal cover across T11-S3 with a field of view >30 cm, in craniocaudal direction (4 mm) slice thickness and 10% gap, was used to assess radiological findings. A central reader confirmed subject eligibility for enrolment and confirmed no other significant spinal pathologies e.g. gross facet joint degeneration or inflammatory joint disorders, that could account for the pain symptoms.

Female participants who were pregnant or breastfeeding, or those who were of child-bearing potential and unwilling to use an acceptable method to avoid pregnancy were excluded. All trial participants provided written informed consent. Participants self-reported as either male or female. Race and ethnicity were not recorded in this study. Participants received unrestricted standard of care during the study period.

Ethics

The protocol was first approved by the UK Regulatory Authority, the Medicines and Healthcare products Regulatory Agency (MHRA), (15 April 2019), and by the Yorkshire and The Humber–Leeds East Research Ethics Committee (24 May 2019) and subsequently by Agencia Española de Medicamentos y Productos Sanitarios (AEMPS), Madrid, Spain and CEIm Hospital Universitai Vall d"Hebron, Barcelona, Spain; Medsafe, Wellington, New Zealand and Southern Health and Disability Ethics Committee, Ministry of Health, Wellington, New Zealand and the Danish Medicines Agency, Copenhagen, Denmark and De Videnskabsetiske Medicinske Komiteer (VMK), Copenhagen, Denmark. Additional country authorities and ethics committees approved the protocol but did not contribute participants.

Randomisation and masking

Eligible participants were randomly assigned in a 1:1 ratio to receive PP353 or a sham control. Sites requested treatment allocation from an independent vendor via a web-based Interactive Response Technology, and were provided with a sequential assignment based on a block size of 4. Third-parties, the administration team, comprising pharmacy, injector and support, were unblinded because of the impracticality of blinding PP353 for injection due to differences between the active and placebo injection procedures. To mitigate any risk of bias due to inadvertent unblinding, a blinding plan was developed and administration teams received training in masking the allocated procedure and acting out the administration for patients allocated to placebo so that the timing of the procedures were the same. Trial team members collecting efficacy or adverse event data were blinded to treatment allocation. Treatment assignment was not revealed to blinded trial team members until after database lock and trial unblinding. No formal assessment of masking was performed.

Procedures

Details on PP353 and the intradiscal administration procedure have been published.[35] Briefly, PP353 was prepared by combining PP353-A, a vial containing 253 mg of micronised linezolid powder, with 4.8 ml of PP353-B, a suspension vehicle containing poloxamer 407 and iohexol, under local pharmacy or procedure room conditions, yielding a final linezolid suspension concentration of 50 mg/ml[34,35] PP353-A and PP353-B were manufactured according to Good Manufacturing Practice. For participants allocated to the treatment, PP353 was injected into the nucleus pulposus of the target lumbar vertebral disc associated with adjacent endplate MC1. Participants received treatment on day 0 and day 4 ± 1. A guide needle was inserted into the deep fascia under physician selected anaesthetic, with or without mild sedation, as a day case procedure.[35] At each treatment, PP353 (50 mg/ml) was administered via a spinal needle inserted through the guide needle, with a target volume of 3 mls (total dose 150 mg) and a minimum volume of at least 2 mls to be a successful dose. PP353 is administered under image guidance to ensure the correct placement of the needle and that the dose remained in the disc and did not leak into adjacent tissue. For participants allocated a sham injection, the whole procedure was carried out by the administration team, with the administration needle inserted into the guide needle but the annulus fibrosus was not penetrated and nothing was administered. All participants were permitted to receive prophylactic antibiotic coverage for the intradiscal procedure as per standard institutional policy, with the exception of linezolid which was not permitted.

Participants were clinically and radiographically evaluated before enrolment (baseline), and clinically assessed at 1, 3, 6, 9 and 12-months. Participants had additional visits for safety assessments and to take blood samples for pharmacokinetic analyses. Clinical assessments included examinations, laboratory tests, vital signs and patient-reported outcome questionnaires, concomitant medications and adverse events.

Investigators and the trial team reviewed clinical assessments to identify potential safety signals and adverse events. The safety review committee regularly reviewed adverse events blinded to treatment allocation.

Methodology for plasma linezolid analysis has been published.[35] A Liquid Chromatography-Tandem Mass Spectrometry (LC-MS/MS) method for determining Poloxamer 407 concentration in human plasma (EDTA) samples was developed and validated at ACM Global Laboratories. Samples (50 µL) of human plasma (EDTA) containing Poloxamer 407 were extracted using a protein precipitation procedure and analysed by an HPLC equipped with an AB Sciex 6500 mass spectrometer. Positive ions were monitored in the multiple reaction–monitoring (MRM) mode. Quantification was by peak area ratio. The lower limit of quantification was 1 µg/ml Poloxamer 407. The estimation of pharmacokinetic parameters was performed by non-compartmental analysis methods using Phoenix WinNonlin software (v8.5, Certara USA, Inc., USA).

Outcomes

The primary efficacy assessment, based on the LBP NRS patient-reported questionnaire, was the mean score of 3 questions: "Low back pain intensity now"; "Worst low back pain intensity in the last 14 days"; and "Average low back pain intensity over the last 14 days". The subject assessed each question on an 11-point scale with 0 = "no pain" and 10 = "the worst possible pain you can imagine."

The primary efficacy endpoint was the change from baseline in LBP NRS at 12-months post-procedure, and the mean difference between the PP353 and placebo

groups at 12-months, analysed by a mixed model for repeated measures (MMRM).

Secondary outcomes included change from baseline LBP NRS for pain at 1, 3, 6 & 9-months; change from baseline at multiple timepoints for the RMDQ-23[37] and the Oswestry Disability Index (ODI)[39,40]; proportions of subjects achieving a pre-specified clinically relevant improvement defined, as a ≥30% or ≥50% reduction from baseline LBP NRS and RMDQ-23 scores at multiple timepoints; and characterisation of the pharmacokinetics of two doses of PP353.[41–43] Safety was assessed by the incidence, relatedness and severity of adverse events. As an exploratory endpoint, subject diary-reported analgesic use (including opioids) in the 7 days prior to a timepoint was recorded.

Statistical analysis

The statistical analysis plan was finalised and approved on 23rd December 2024 before database lock on 7th January 2025 and is provided in supplemental online information in redacted form to be GDPR compliant. The sample size calculation was based on the two oral antibiotic RCTs.[29,30] The planned sample size of 40 participants divided equally between the two groups, assuming a one-sided test of significance (treatment is better than placebo) would provide 80% power to detect a difference of 2.08 LBP NRS points between groups at 12 months, assuming a common standard deviation of 2.3, with 5% type I error and assuming 20% withdrawals or loss to follow-up.

The safety analysis was performed on participants with at least one dosing procedure. The efficacy analysis was based on the Full Analysis Set (FAS), which included participants with at least one dosing procedure and post-baseline efficacy assessment. The primary efficacy analysis used a pre-specified one-sided test at the 5% significance level. Secondary endpoints were assessed using two-tailed tests and included assessment of participants in the Per Protocol Set (PPS) of participants who had no protocol deviations which could potentially affect the efficacy of PP353, e.g. only having 1 dosing procedure. PPS results are provided in supplemental data. No adjustments for multiplicity were made due to the exploratory nature of the study. Change from baseline was assessed using a mixed model repeated measures model (MMRM) with treatment group, visit, score at baseline and treatment group by visit interaction included as fixed effects, was used to estimate the difference between groups for analyses of continuous endpoints, reported as adjusted least squares means with standard error and 95% CI. For binary variables, logistic regression, with treatment group and baseline score as explanatory variables, reported as adjusted means with standard deviation, was used. The MMRM analysis accounts for missing data by using all available observations assuming that data are missing at random, allowing for unbiased estimation of treatment effects without explicitly imputing missing values. For logistic regression, the last observation carried forward was used for missing data points. None of the primary or secondary endpoints analysed by logistic regression has sufficient missing data to perform additional sensitivity testing. PP353 group % change from placebo was estimated using the group difference divided by the placebo group observed endpoint value at the time point. Post-hoc sensitivity analyses were performed to assess the impact of potential baseline imbalances between the two groups in sex, disability (ODI), leg pain score, duration of pain and average hours of pain during the preceding 28 days. Each covariate was added individually to the primary efficacy assessment MMRM model using the FAS. Statistical analyses were performed with SAS® Version 9.4. Graphs are provided with –30% and –50% change from baseline reference lines to aid interpretation of the results. Unblinded statisticians undertook a pre-specified early readout after all subjects had completed their 6 month follow-up. The early readout was to enable Persica management to make an informed decision on the plans for the next phase of development to minimise time between results and start of the next phase of clinical development. There was no opportunity to alter the study based on the early readout. Therefore, no adjustment to the sample size was deemed necessary or planned in the protocol. Distribution of early results was limited to Persica senior management and did not alter the conduct of the study.

Role of the funding source

Persica Pharmaceuticals Limited funded the study, was involved in the study design, was represented on the Safety Review Committee, reviewed the 6-month readout and was involved in the analysis and preparation of the manuscript, but had no direct role in data collection.

Results

Through community and hospital pain clinics, referrals from other centres and social media campaigns, between December, 2021, and December, 2023, potential participants were pre-screened, leading to 136 participants assessed for eligibility, 40 of whom met the inclusion criteria were randomised and met the criteria to be included in the full analysis set (FAS); 20 to PP353 treatment and 20 to placebo (Fig. 1). The per protocol set (PPS) comprised 18 participants allocated to PP353 and 19 participants allocated a placebo, as two participants did not receive both allocated procedures, and one was considered potentially unblinded.

Baseline characteristics were not tested for statistical significance (Tables 1 and 2). Within the FAS, 72.5% percent (n = 29/40) of participants were female. There was a higher proportion of males in the PP353 group

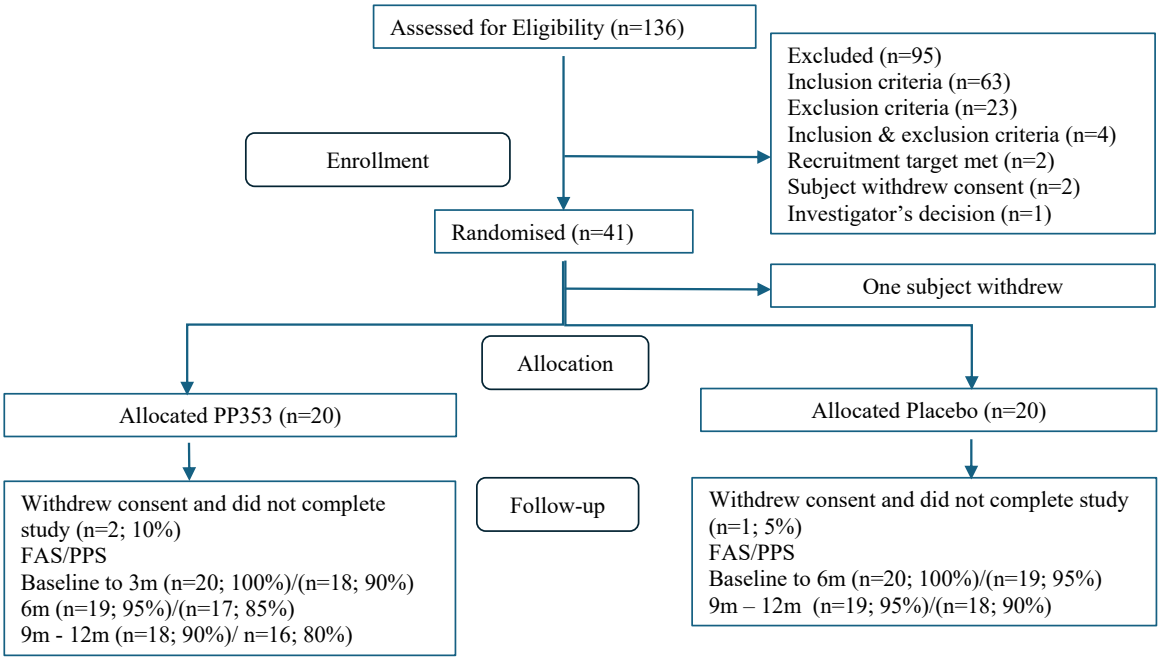

Fig. 1: **Trial profile**.

Category	Full analysis set		Per protocol set	
	PP353 n = 20	Placebo n = 20	PP353 n = 18	Placebo n = 19
Male/Female %	8/12, 40%/60%	3/17, 15%/85%	7/11, 3%/61%	3/16, 16%/84%
Age years (mean, SD)	42.9 (7.41)	44.1 (7.43)	42.8 (7.56)	43.7 (7.44)
Age range	28–54	30–56	28–54	30–56
Body Mass Index (kg/m^2, mean, SD)	26.8 (4.47)	28.5 (5.00)	26.6 (4.46)	28.6 (5.12)
Duration of episode of cLBP Years mean (SD)	4.1 (4.75)	7.1 (7.33)	4.2 (5.00)	6.3 (6.75)
LBP NRS mean (SD)	6.7 (1.02)	6.9 (1.52)	6.8 (1.05)	6.8 (1.52)
RMDQ-23 mean (SD)	14.9 (3.83)	16.2 (3.59)	15.0 (3.83)	16.3 (3.68)
ODI mean (SD)	33.0 (11.34)	40.7 (10.13)	33.3 (11.96)	40.1 (10.04)
Hours per month with pain mean (SD)	389.2 (200.0)	496.4 (155.7)	404.4 (194.3)	498.9 (159.5)
Hours per month with pain median (IQR)	448.0 (168.0–518.0)	518.0 (441.0–630.0)	448.0 (168.0–504.0)	532.0 (434.0–644.0)
Leg Pain mean (SD)	1.9 (2.39)	2.6 (2.93)	2.0 (2.48)	2.7 (2.95)
Pain Catastrophising Scale mean (SD)	25.2 (11.47)	29.2 (12.17)	24.7 9 (11.4)	29.2 (12.5)
Lumbar level of Modic changes				
L2/L3	1	1	1	1
L3/L4	1	0	1	0
L4/L5	5	6	5	6
L5/S1	13	13	11	12
Proportion inferior and superior Modic changes	20/20 (100%)	19/20 (95%)	18/18 (100%)	18/19 (95%)
Upper/Lower MC1/MC0	0	1	0	1
Upper/Lower MC1/MC1	0	3	0	3
Upper/lower MC1/MC1+2	2	0	2	0
Upper/Lower MC1+2/MC1+2	17	14	15	14
Upper/Lower MC2/MC2	0	1	0	1
Upper/Lower MC1+2/MC2	1	1	1	0

LBP NRS, Low Back Pain Numerical Ratings Scale; RMDQ-23, Roland Morris Disability Questionnaire-23; ODI, Oswestry Disability Index; MC0, No Modic Changes; MC1, Modic Changes type 1; MC2, Modic Changes type 2; MC1+2, Mixed Modic Changes type 1 and 2; SD, Standard Deviation; IQR, Interquartile Range, cLBP, chronic Low Back Pain; BMI, Body Mass Index.

Table 1: **Baseline demographic and disease characteristics.**

FAS Baseline	PP353			Placebo		
Nordic Modic score	Upper n (%)	Lower n (%)	Most severe n (%)	Upper n (%)	Lower n (%)	Most severe n (%)
n	20	20	20	20	20	20
0 (no oedema)	0 (0)	0 (0)	0 (0)	0 (0)	1 (5)	0 (0)
1 (endplate only)	3 (15)	3 (15)	2 (10)	1 (5)	2 (10)	1 (5)
2 (<25% vertebral body)	10 (50)	11 (55)	10 (50)	6 (30)	9 (45)	6 (30)
3 (25%–50% vertebral body)	5 (25)	6 (30)	6 (30)	11 (55)	6 (30)	10 (50)
4 (>50% vertebral body)	2 (10)	0 (0)	2 (10)	2 (10)	2 (10)	3 (15)

Upper and Lower refer to the vertebral endplate and body above (superior) and below (inferior) to the disc associated with Modic change.

Table 2: **Nordic Modic score at baseline.**

than in the placebo group (8/20 vs 3/20). Groups were balanced for LBP NRS and RMDQ23 at baseline. The PP353 group had a shorter duration of back pain, a lower ODI score, fewer hours per month with pain and less leg pain. At 12 months, 37 participants contributed to the analysis, 18 in the PP353 group and 19 in the placebo group.

For the primary objective at 12-months, in the FAS, the PP353 group reported a 3.4-point (–51%) Change from Baseline (CfB) in pain, assessed by LBP NRS, with a statistically significant between treatment group difference of 1.4-points (upper limit of the one-sided 95% CI –0.19; one-sided p = 0.028; Table 3, Fig. 2A). The between group difference was –30% at 12-months and considered clinically meaningful.[41] The PP353 group achieved a clinically-meaningful ≥30% CfB at 3-months onwards. The placebo group did not.

Secondary outcomes confirmed the efficacy of PP353. At 12 months, the PP353 group reported a 9.4-points (–63%) CfB in disability, assessed by RMDQ-23, with a statistically-significant and clinically-meaningful 3.9-point (–38%) between group difference (95% CI –7.69 to –0.07; p = 0.046; Table 4, Fig. 2B). The PP353 group achieved a clinically-meaningful ≥30% CfB from 1 month onwards. Similarly, when assessed by the ODI, at 12 months the PP353 group reported a 16.9 points (–51%) CfB in disability, with a statistically-significant 8.6-point (–46%) between group difference (95% CI –17.3 to –0.0; p = 0.050; Table 5. Fig. 2C).

In the analysis of outcomes based on the PPS, the benefit of PP353 treatment increased for pain and disability assessed by LBP NRS and RMDQ-23, which were statistically different from placebo at 6 and 12 months, and was similar for ODI compared to the FAS

Statistic	LBP NRS				
	PP353	Placebo	Difference PP353—Placebo	95% CI	p-value
Baseline–n	20	20	–	–	–
Mean (SD)	6.7 (1.04)	6.9 (1.52)	–	–	–
1 Month–n	18	20	–	–	–
Mean (SD)	5.2 (1.74)	5.2 (2.38)	–	–	–
LS mean CfB (SE) CfB%	–1.46 (0.365) –21.8%	–1.69 (0.351) –24.5%	0.23	–0.68 to 1.34	0.51
3 Month–n	20	18	–	–	–
Mean (SD)	4.7 (2.38)	5.1 (2.43)	–	–	–
LS mean CfB (SE) CfB%	–2.02 (0.457) –30.1%	–1.75 (0.466) –25.4%	–0.27	–1.59 to 1.05	0.68
6 Month–n	19	19	–	–	–
Mean (SD)	4.0 (2.05)	5.1 (2.42)	–	–	–
LS mean CfB (SE) CfB%	–2.60 (0.45) –38.8%	–1.84 (0.45) –26.7%	–0.85	–2.25 to 0.33	0.14
9 Month–n	18	18	–	–	–
Mean (SD)	4.0 (2.23)	4.5 (2.50)	–	–	–
LS mean CfB (SE) CfB%	–2.67 (0.505) –39.9%	–1.96 (0.501) –28.4%	–0.71	–2.15 to 0.73	0.33
12 Month–n	18	19	–	–	–
Mean (SD)	3.3 (1.89)	4.7 (2.55)	–	–	–
LS mean CfB (SE) CfB%	–3.36 (0.494) –50.1%	–2.00 (0.488) –29.0%	–1.37	–0.19	0.028[a]

LBP NRS Low Back Pain Numerical Ratings Scale Mean (SD) is the observed mean with standard deviation. LS mean CfB (SE) is the baseline covariate adjusted Least Squares mean change from baseline with standard error. [a]The primary endpoint at 12 months used a pre-specified one-sided test of significance.

Table 3: **Low back pain (Full Analysis Set): Low Back Pain Numerical Rating Scale (LBP NRS).**

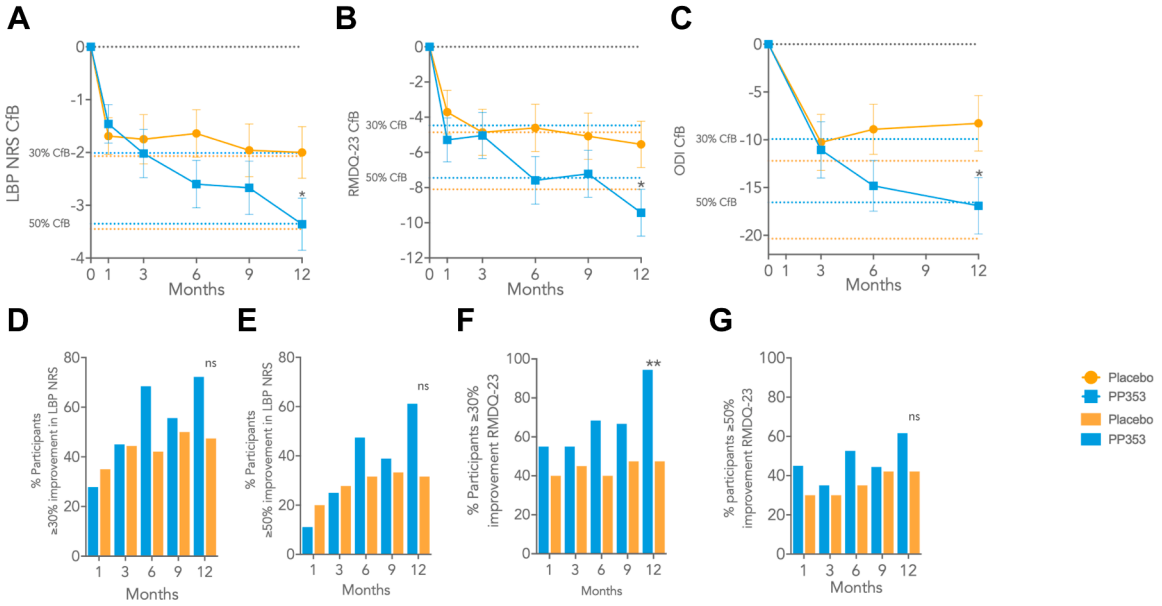

Fig. 2: **Full analysis set mixed model repeated measures least squares mean (SEM) group change from baseline (CfB) in pain**, A) Low Back Pain Numerical Rating Scale (LBP NRS) and B) Roland Morris Disability Questionnaire-23 (RMDQ-23) and C) Oswestry Disability Index (ODI) scores. 30% and 50% reduction from baseline shown, PP353—blue, Placebo—orange. D to G) % of participants improving by ≥ 30% or ≥50% from baseline in LBP NRS or RMDQ23. Figures A–C: significance was determined using a Mixed Model for Repeated Measures. Figures D–G: significance was determined using logistic regression. *p ≤ 0.05, **p ≤ 0.01. ns, Not significant.

(Tables S1–S3, Figure S1). At 12 months, PPS LBP NRS CfB was –3.50 for PP353, a between group difference of –1.77 points (–33%; 95% CI –3.16 to –0.38; p = 0.014) and RMDQ-23 CfB was –9.83 for PP353, a between group difference of –4.55 points, (–43%; 95% CI –8.62 to –0.49; p = 0.029).

Using the FAS, responder analysis showed that in the PP353 group >50% of participants had ≥30%

Statistic	RMDQ-23				
	PP353	Placebo	Difference PP353—Placebo	95% CI	p-value
Baseline–n	20	20	–	–	–
Mean (SD)	14.9 (3.83)	16.2 (3.59)	–	–	–
1 Month–n	20	20	–	–	–
Mean (SD)	9.8 (4.84)	12.3 (6.59)	–	–	–
LS mean CfB (SE) CfB%	–5.29 (1.247) –35.5%	–3.71 (1.243) –22.9%	–1.59	–5.19 to 2.01	0.38
3 Month–n	20	20	–	–	–
Mean (SD)	10.1 (6.76)	11.2 (6.31)	–	–	
LS mean CfB (SE) CfB%	–5.04 (1.311) –33.8%	–4.86 (1.306) –30.0%	–0.19	–3.97 to 3.59	0.92
6 Month–n	19	20	–	–	–
Mean (SD)	7.7 (5.86)	11.4 (7.21)	–	–	
LS mean CfB (SE) CfB%	–7.59 (1.356) –50.9%	–4.61 (1.341) –28.5%	–2.98	–6.87 to 0.91	0.13
9 Month–n	18	19	–	–	–
Mean (SD)	8.4 (5.96)	10.4 (6.91)	–	–	–
LS mean CfB (SE) CfB%	–7.22 (1.332) –48.5%	–5.08 (1.316) –31.4%	–2.13	–5.95 to 1.69	0.27
12 Month–n	18	19	–	–	–
Mean (SD)	6.1 (5.43)	9.9 (7.10)	–	–	–
LS mean CfB (SE) CfB%	–9.43 (1.334) –63.3%	–5.54 (1.314) –34.2%	–3.88	–7.69 to –0.07	0.046

RMDQ-23, Roland Morris Disability Questionnaire-23. Mean (SD) is the observed mean with standard deviation. LS mean CfB (SE) is the baseline covariate adjusted Least Squares mean change from baseline with standard error.

Table 4: **Disability (Full Analysis Set): Roland Morris disability questionnaire-23 (RMDQ-23).**

Statistic	ODI				
	PP353	Placebo	Difference PP353—Placebo	95% CI	p-value
Baseline–n	20	20	–	–	–
Mean (SD)	33.0 (11.34)	40.7 (10.13)	–	–	–
3 Month–n	20	20	–	–	–
Mean (SD)	22.6 (14.98)	29.9 (16.07)	–	–	–
LS mean CfB (SE) CfB%	−11.06 (2.941) −33.5%	−10.27 (2.934) −25.2%	−0.8	−9.4 to 7.8	0.85
6 Month–n	19	20	–	–	–
Mean (SD)	18.7 (11.62)	31.3 (16.71)	–	–	–
LS mean CfB (SE) CfB%	−14.82 (2.654) −44.9%	−8.90 (2.624) −21.9%	−5.9	−13.7 to 1.9	0.13
12 Month–n	18	19	–	–	–
Mean (SD)	16.3 (12.91)	30.3 (17.92)	–	–	–
LS mean CfB (SE) CfB%	−16.91 (2.958) −51.2%	−8.28 (2.910) −20.3%	−8.6	−17.3 to 0.0	0.05

ODI Oswestry Disability Index; ODI was not assessed at months 1 and 9. CI, Confidence interval. Mean (SD) is the observed mean with standard deviation. LS mean CfB (SE) is the baseline covariate adjusted Least Squares mean change from baseline with standard error.

Table 5: **Disability (Full Analysis Set): Oswestry Disability Questionnaire (ODI).**

improvement from 6 months onwards and that >60% had ≥50% improvement at 12 months (Table S4, Fig. 2D and E). The FAS PP353 group also reported greater improvements in disability than placebo with >50% reporting ≥30% improvement from one month onwards which was significant at 12 months, (Odds ratio [PP353 vs Placebo] 22.01, 95% CI 2.39–>90; p = 0.0064), and ≥60% reporting ≥50% improvement at 12 months (Table S4, Fig. 2F and G). In the PPS, the between group difference in response was greater and reached significance for improvement in disability at 6-months (Odds ratio [PP353 vs Placebo] 5.63, 95% CI 1.26–25.21; p = 0.024) and 12-months (Odds ratio [PP353 vs Placebo] 22.40, 95% CI 2.39–>90; p = 0.0065; Table S4, Figure S1D to G).

PP353 reduced the FAS group median number of hours with pain in the previous 28 days from 448 h (IQR 168.0–518.0) at baseline to 67 h (21.0–324.0) at 12 months, compared to placebo baseline 518 h (441.0–630.0) and 448 h (252.0–504.0) at 12 months (Table S5, Fig. 3A). Least-squares mean %CfB hours with pain in the last 28 days was estimated as a post-hoc analysis using MMRM adjusted for baseline (Table S5, Fig. 3B). At 12-months, the FAS PP353 group mean %CfB was −56.7% (SE 9.69) compared with −22.0% (9.56) for placebo (difference −34.7%, 95% CI −62.71 to −6.64; p = 0.017). Responder analyses showed that 61.1% of the PP353 FAS group achieved ≥50% reduction in hours with pain compared to placebo 21.1% at 12 months (Table S4, Fig. 3D). The PPS PP353 group had median 448 h (IQR 168.0–504.0) at baseline and 67 h (280) at 12 months, and the placebo group 532 h (210) at baseline and 448 h (18.5–300.0) at 12 months (Table S5, Figure S2A). For the PPS, the least squares mean %CfB at 12 months for PP353 was −59.8% (SE 9.91) compared with placebo of −18.1% (9.42), (difference −41.7%, 95% CI −69.92 to −13.56; p = 0.005; Table S5, Figure S2B). At 12 months in the PP353 PPS group 75.0% of participants reported ≥30% and 62.5% ≥ 50% change from baseline in hours with pain

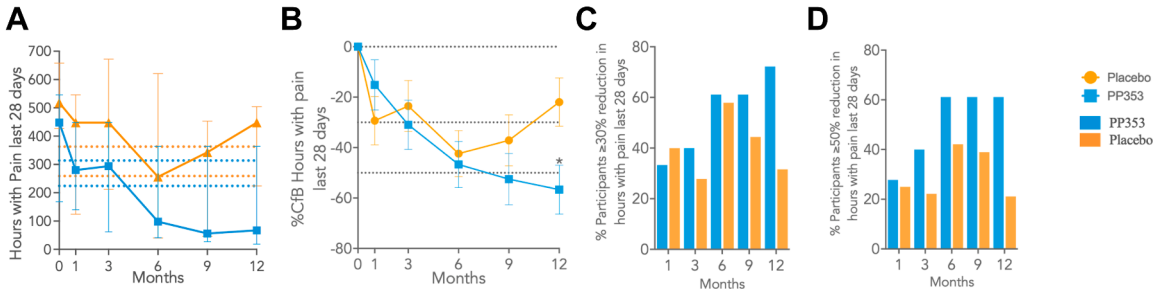

Fig. 3: **Full analysis set time with pain**. A) Group median (IQR) hours with pain in the last 28 days; B) Mean % Change from baseline in hours with pain in last 28 days; C) % Participants responding with ≥30% reduction in hours with pain in the last 28 days: D) % Participants responding with ≥50% reduction in hours with pain in the last 28 days. Figure B: significance was determined using a Mixed Model for Repeated Measures. Figures C & D: significance was determined using logistic regression.*p ≤ 0.05. The significance of results in Figures A, C and D was not tested.

compared with 27.8% ≥ 30% and 16.7% ≥ 50% in the placebo group (Table S4, Figure S2D and E).

Seven days before a visit, the number of participants reporting analgesic use in the FAS was reduced by PP353 from 16/20 (80%) at baseline to 9/18 (50%) at 12-months. The placebo group reported analgesic use in 14/20 participants (70%) at baseline and 11/18 (61%) at 12-months. PP353 substantially reduced the number of participants reporting opioid use from 5/20 (25%) at baseline to 2/18 (11%) at 12-months compared to the number of placebo participants reporting opioid use which was unchanged 6/20 (30%) at baseline and 6/18 (33%) at 12-months.

Post-hoc sensitivity analyses adjusting for individual additional baseline covariates resulted in similar between group efficacy point estimates in each of the models adjusting for sex, disability (ODI), duration of pain and leg pain and the 1-sided 95% confidence intervals were below 0 (Table S6). Adjustment for hours of pain in the 28 days prior to baseline, yielded a point estimate of –0.99 which is similar in magnitude, however the 1-sided confidence interval was above 0 (one-sided 95% CI 0.195).

The pharmacokinetics of intradiscal linezolid was evaluated in 20 participants with extensive sampling for the first 12 (expecting 6 allocated to PP353) and sparse sampling for the remainder. Participants received PP353 (150 mg linezolid), on day 0 and day 4 ± 1. This created 3 groups, with the second dose on day 3, 4 or 5. Plasma linezolid before and after each dose was analysed (Table 6, Fig. 4A–C). Intradiscal administration of PP353 resulted in an average geometric mean linezolid plasma C_{max} of 0.7–0.8 μg/ml at 5–7 h post administration. T_{max} was 300–420 min. The trough concentration before the second dose depended on the day of the second dosing. The pharmacokinetics of the first and second doses were similar. No plasma accumulation after the second dose was observed. The pharmacokinetics of poloxamer 407 was assessed in 12 participants (Table 6; Fig. 3D). Poloxamer 407 was detectable in all participants and at all timepoints. Plasma accumulation after the second dose was noted. Following the second dose, poloxamer half-life was measured in 3 individuals with geometric mean 71.9 h.

Dose/route	Cmax mg/ml	Tmax h	AUC mg h/ml	T1/2 h
150 mg linezolid id First dose (n = 20)	0.84	5.0	25.6	–
150 mg linezolid id Second dose (n = 18)	0.69	7.0	18.9	9.67
432 mg poloxamer 407 id First dose (n = 12)	55.0	7.9	3850	–
432 mg poloxamer 407 id Second dose (n = 11)	77.7	7.9	5790	71.9

Id—intradiscal administration of PP353; Cmax Peak concentration; Tmax Time of Cmax. AUC, Area under the curve to the last quantifiable timepoint. T1/2 halflife. Cmax, AUC and T1/2 are geometric mean values. Tmax is median values.

Table 6: **Pharmacokinetics of intradiscal linezolid and poloxamer 407.**

PP353 was generally safe and well tolerated. Treatment-related Treatment Emergent Adverse Events (TEAEs) were reported by 7 of 21 (33%) PP353 treated participants and by 8 of 20 (40%) placebo participants and were consistent with expectations for an intradiscal procedure (Table 7). One patient in the placebo group reported an unrelated serious TEAE, at 12 months. TEAEs considered potentially related to treatment or procedure were at similar frequency or lower in the PP353 group than in the sham group.

Discussion

Patients with cLBP with MC1 suffer from a serious chronic condition, are often not adequately diagnosed and get inadequate relief from conservative therapies.[9] In some countries, the only approved treatment specifically for cLBP with MC1 is radiofrequency Basivertebral Nerve Ablation (BVNA) which is an invasive procedure that only controls the symptoms.[11]

Based on the hypothesis that a proportion of cLBP with MC1 may be caused by a bacterial infection of the disc, and could therefore be treated with antibiotic therapy, oral antibiotic regimens have been tested in RCTs and have shown positive effects.[12,29,30] However, oral administration provides only modest intradiscal antibiotic exposure, and result in a high and prolonged systemic exposure, significant side-effects and a concomitant risk of poor compliance.[32] The benefit-risk profile of oral antibiotics to treat cLBP with MC1 is suboptimal, especially if deployed in wider clinical practice.[29,30]

To provide a treatment option aimed directly at the cause of cLBP with MC1, linezolid for intradiscal administration (PP353) was developed.[34,35] The linezolid MIC_{90} against *C. acnes* and *Staphylococcus aureus* is approximately 1 μg/ml.[34]

This Phase 1b trial with participants receiving two intradiscal doses of 150 mg of linezolid on day 0 and day 4 ± 1 found that patients with cLBP and MC1 may be readily diagnosed using standard MRI procedures, both the procedure and PP353 were well tolerated with similar rates of TEAEs in placebo and treatment groups and intradiscal administration was well tolerated and straightforward to perform as a day case procedure.

An advantage of intradiscal antibiotic administration is the lower systemic exposure as suggested by the absence of gastro-intestinal side-effects that are commonly associated with prolonged high-dose oral antibiotics.

In this trial, at 12 months, PP353 appears to be a promising and potentially disease-modifying treatment for a subset of patients with chronic low back pain and Modic type 1 changes.

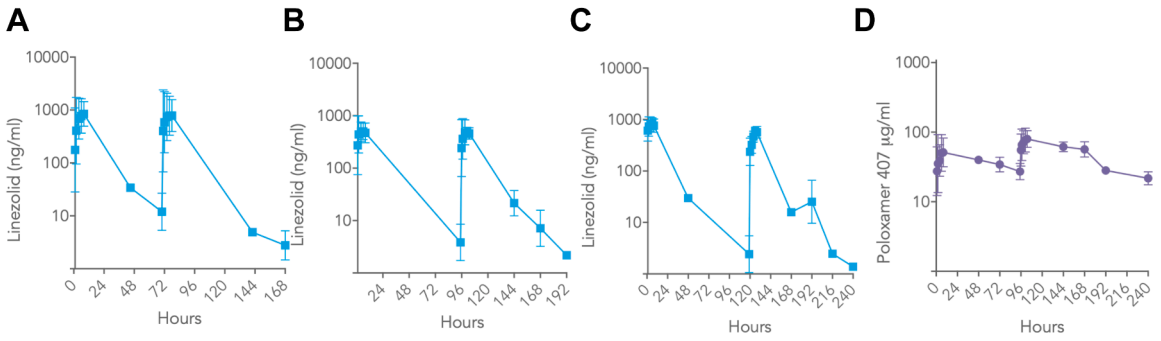

Fig. 4: **Pharmacokinetics of 150 mg intradiscal linezolid**. A) Day 0 and 3; B) Day 0 and 4; C) Day 0 and 5, and 432 mg intradiscal Poloxamer 407 on Day 0 and 4. Geometric mean ± SD.

There was a noticeable improvement in the placebo group at 1 month of about 22% of baseline LBP NRS or RMDQ-23. Placebo effects observed in this study align with those reported in other cLBP trials. An oral antibiotic RCT reported a 14.3% reduction in the placebo group LBP NRS at 3 months.[30] Similar improvements in cLBP with MC1 placebo groups have been reported for standard of care,[44,45] and IV infusion placebo.[46] Invasive sham procedure placebo responses may be greater, for example in BVNA RCTs with placebo response of 37% in the VAS score at 3 months.[47] In this context, the placebo procedure response observed in this trial is unsurprising.

Clinically-meaningful PP353 group mean change from baseline, defined as a 30% reduction, was achieved by 1 month for disability and 3 months for pain. The placebo group did not achieve a clinically-meaningful mean change from baseline for pain and was only achieved at the 12-month timepoint for disability. PP353 group improvements continued to increase at 12 months and may continue over time. Responder analyses showed that for both the LBP NRS pain score and the RMDQ-23 disability score ≥60% of participants reported a ≥50% reduction at 12 months.

Measurement of time with pain during the last 28 days is not a validated clinical endpoint, but it does provide an assessment of how a participant feels during the trial. Treatment with PP353 reduced the duration of pain with 45% of participants reporting clinically-meaningful change from baseline (–30%) at 3 months and nearly 70% of participants experiencing ≥50% reduction in hours with pain at 12 months.

Reduction in pain and disability was not because of increased analgesic use. The PP353 -treated group reported less analgesic and substantially less opioid use at 12 months than at baseline.

Specific sensitivity analysis could not been performed due to sample size. Overall, the primary efficacy result was robust to baseline imbalances, supporting the reliability of the findings. The 1-sided CI for the model including hours with pain in the preceding 28 days exceeded 0 but the estimated treatment difference was of a similar magnitude to the primary analysis. The PP353 group contained two participants with low number of hours with pain which may contribute to baseline imbalance. Future larger studies should reduce baseline differences. The small sample size and post-hoc exploratory nature of the sensitivity analyses mean they should be interpreted cautiously.

The most plausible explanation for our findings is that the antibacterial effect of linezolid in the disc treated the putative bacterial infection and reduced pain and disability. The results suggest that it may be feasible to substitute 300 g of oral antibiotic treatment over 100 days with 0.3 g of intradiscal antibiotic treatment lasting about a week.

Category of TEAE	PP353 (n = 20) n (%) [Number occurrences]	Placebo (n = 20) n (%)[Number occurrences]
Subjects reporting and serious TEAE	0	1 (5.0%) [1]
Subjects reporting a Treatment Related TEAE	7 (35.0%) [13]	8 (40.0%) [13]
Subjects reporting a Treatment Related Serious TEAE	0	0
TEAEs resulting in withdrawal	0	0
Any TEAEs resulting in death	0	0
Treatment or procedure Related Treatment Emergent Adverse Events		
Musculoskeletal and connective tissue disorders	9 (45.0%) [29]	7 (35.0%) [17]
General disorders and administration site conditions	8 (40.0%) [11]	5 (25.0%) [7]
Injection site pain	3 (15.0%) [4]	3 (15.0%) [3]
Injection site bruising	2 (10.0%) [2]	1 (5.0%) [1]
Injection site reaction	2 (10.0%) [3]	0
Procedural pain	0	1 (5.0%) [1]
Injury—poisoning and procedural complications	1 (4.8%)	0
Nervous system disorders	1 (4.8%)	4 (20.0%)

Adverse events were coded according to MedDRA version 26.1 https://www.meddra.org/.

Table 7: **Summary of treatment-emergent and treatment or procedure-related adverse events (Full Analysis Set).**

The linezolid plasma C_{max} observed with intradiscal PP353 is approximately 6% of that observed with a standard administration of 600 mg linezolid.[48] Tmax was delayed from 30 to 80 min observed after IV and oral dosing to 300–420 min after intradiscal dosing, potentially reflecting both the linezolid depot dissolving and the non-vascular compartment of the disc. Continued detectable linezolid concentrations in plasma up to 5 days after administration indicate that linezolid may still be distributing from the disc at day 5. This trial confirms that the two-dose regimen is suitable for use in pivotal studies.

This is the third RCT demonstrating an improvement in pain and disability following antibiotic treatment of cLBP in patients with MC1 at 12 month follow-up (Table 8). The use of a different antibiotic and a different route of administration add to the body of evidence supporting continued investigation of antibiotic treatment for cLBP in patients with MC1 and supports the proposed bacterial infective pathway to cLBP with MC1. The efficacy of PP353 observed in this trial was comparable to BVNA, an approved procedure for patients with Modic changes (Table 8).

There were differences in patient selection across the three RCTs. With a working hypothesis that herniation is a potential initiation step leading to bacterial infection and Modic changes, both Albert et al., and Braten et al., required MRI documented herniation within 2 years of enrolment. As not all herniation events may lead to investigation by MRI or be reported by patients, the current study did not use prior herniation as an enrolment criterion and may be more generalisable to this cLBP with MC1 patient population. Albert et al., included all patients treated surgically but Braten et al., excluded patients with surgery to treat herniation within 12 months and the current study excluded patients with back surgery within 6 months. Albert et al., and the current study included Modic subjects regardless of the size of the Modic lesion but Braten et al., excluded patients with small Modic changes. The effects of these differences in enrolment criteria on the outcomes of the trials are not known.

The participants in these RCTs all presented with painful lumbar levels comprising degenerate, putatively bacterially infected, discs with adjacent Modic changes and may be considered to exhibit discovertebral pain arising from both discogenic and vertebrogenic origin and perceived by both the sinuvertebral and basivertebral nerves.[49] Radio-frequency nerve ablation of either or both nerves to control pain perception is feasible

Study	Statistic	LBP NRS				
		Antibiotic	Placebo	12-month Difference Antibiotic—Placebo	95% CI	p-value
Albert et al.	Baseline–n	90	72			
Oral	Median (IQR)	6.7 (5.3–7.7)	6.3 (4.7–8.0)			
	12 month–n	77	67			
	Median (IQR)	3.7 (1.3–5.8)	6.3 (4.0–7.7)			
	Mann–Whitney test Median (IQR)	−3.0	−0.0	−2.6	–	0.0001
Braten et al.	Baseline–n	58	59			
Oral	Mean (SD)	6.5 (1.1)	6.3 (1.1)			
	12-month	55	56			
	Mean (SD)	4.5 (2.5)	5.2 (2.2)			
	ANCOVA adjusted mean difference	−2.0	−1.1	−0.8	−1.6 to 0.0	0.060
PP353	Baseline–n	20	20			
Intradiscal	Mean (SD)	6.7 (1.04)	6.9 (1.52)			
	12 month–n	18	19			
	Mean (SD)	3.3 (1.89)	4.7 (2.55)			
	MMRM LS mean CfB (SE)	−3.36 (0.494)	−2.00 (0.488)	−1.37	−0.19	0.028
BVNA		BVNA (VAS)	Placebo (VAS)			
Fischgrund et al.	Baseline–n	147	78			
	Mean (SD)	6.73 (1.38)	6.64 (2.34)			
	12 month–n	128	77			
	Mean (SD)	3.96 (2.83)	4.46 (2.78)			
	ANCOVA adjusted mean difference	−2.76 (2.89)	−2.16 (2.69)	−0.6	–	0.038

Albert et al., performed a non-adjusted Mann Whitney test of the difference between groups at 12 months (no adjustment for baseline) and provided group medians and Interquartile Range (IQR). Braten et al., performed a baseline and previous disc surgery adjusted ANCOVA analysis and provided means with Standard Deviation (SD). The PP353 study (FAS results) performed a mixed model repeated measures analysis and provided baseline covariate adjusted Least Squares mean change from baseline with standard error. The primary endpoint at 12 months used a pre-specified one-sided test of significance. Results from the BVNA SMART study (VAS; Per protocol set) are provided for comparison.

Table 8: **Comparison of baseline and 12-month outcomes for Low Back Pain Numerical Rating Scale (LBP NRS) for participants with cLBP with Modic changes type 1 and mixed Modic changes type 1 and 2 across 3 RCTs.**

with basivertebral nerve ablation receiving most attention.[47,50] This study found that intradiscal linezolid provided relief from pain and disability that increased over the duration of the study. Unlike nerve ablation which provides rapid reduction in pain perception, there may be an element of healing once a bacterial infection is effectively treated. There may also be a different response to linezolid in the disc and vertebrae and future studies might explore the effect on discogenic and vertebrogenic pain and investigate whether intradiscal linezolid followed by BVNA leads to additional benefit. PP353 is expected to be used prior to BVNA as it targets the underlying pathology of an infected disc which may drive continued discogenic pain. Observations of reduction in the volume of Modic changes 12 months after antibacterial therapy have been mixed with a report of reduced volume by Albert et al., but not in the Braten et al., study.[51] The expectation that Modic changes may resolve within 12 months after antibacterial therapy assumes that there is a correlation between Modic change volume and pain, that the effect of antibacterial therapy includes reduction in vertebrogenic pain and that sufficient bone remodelling can take place within 12 months to reliably observe change.

There is emerging interest in stem cell based regenerative treatments for degenerate discs in patients with Modic changes.[52] Administration of stem cells into an infected disc may limit benefit and there may be a future role for intradiscal linezolid to treat the infection prior to stem cell administration.

The use of linezolid to treat cLBP may raise concerns that antibiotic resistance may develop. Preliminary estimates suggest that in the USA the number of patients exposed to linezolid may increase by up to 20% per year but the amount of linezolid used would only increase by <0.2% by weight. With intradiscal linezolid administration, systemic exposures may be below concentrations that provide a selective advantage for resistant variants and so resistance development would be minimal. Future studies could assess the effect of intradiscal linezolid on the microbiome and whether linezolid resistance increases.

This trial had limitations. It was a first-in-human Phase 1b trial to assess safety and pharmacokinetics of two doses of intradiscal linezolid that was additionally powered to provide evidence of efficacy to treat participants with cLBP and MC1 in the primary endpoint at 12 months using a single sided test, assuming similar efficacy to oral antibiotics. No adjustments were made for the multiplicity of statistical tests. The presence of a bacterial infection in subject disc tissue was not microbiologically confirmed before enrolment because of the challenges of accessing sufficient sample safely, the damage sampling would cause to already degenerate discs and the challenges of quantitative microbiology. Future studies could assess the sensitivity of *C. acnes* skin and disc isolates to linezolid. This study did not assess whether participants consider the between group effects clinically meaningful. The trial was sham-procedure, placebo-controlled and required an unblinded administration team (pharmacy, injectors and clinical site staff) and a blinded team (investigators, clinical site staff, radiologists and the participant). There was no test of the adequacy of the masking/blinding procedures used in the study. Only one incident of a participant potentially being unblinded to treatment allocation was identified and that participant was removed from the per protocol set. Potential bias in reporting AEs was limited and was monitored by an independent Contract Research Organisation.

This trial provides clinical proof of concept that intradiscal linezolid (PP353) may be safe and effective to treat patients with cLBP and MC1, providing significant and clinically meaningful reductions in pain and disability from both baseline and placebo control. If replicated in larger pivotal studies, PP353 could offer an improvement over current standard of care with an attractive benefit-risk profile compared to oral antibiotics. Further, larger studies, to extend and confirm these findings are recommended.

Contributors

ST, ML, MS, NG, ST, CP, AH, JD, GBa, SA and KO were site Principal Investigators responsible for data acquisition, interpretation, review and approval of the manuscript. DM led the trial conception and design, analysis, interpretation and acted as the Sponsor's Chief Medical Officer. SG and LC contributed to trial design, analysis and interpretation of results. LC provided the first draft of the manuscript. EW was the statistical consultant and contributed to analysis. LC, SG, EW, DM and PR (academic author) verified the data reported. Persica Pharmaceuticals contracted the research organisations at which ML, MS, NG, ST, CP, AH, JD, GBa, SA, KO, EW and DM worked to perform the study. CP is Vice-President of the British Pain Society and Clinical Director of Services HIOW FT. SA was a member of a Project Advisory Board for an EPSRC funded collaborative project with Cardiff and Exeter Universities. All authors edited and approved their sections and approved the final version of the manuscript.

Data sharing statement

Deidentified summary data that underlie the results will be made available for approved use by the trial authors once the trial has been accepted for publication and PP353 has been approved by regulators or the project is terminated from development. Proposals for access should be sent to info@persicapharmaceuticals.com. Trial data will be summarised and published on ClinicalTrials.gov by December 2025. Code availability: Not applicable.

Declaration of interests

MRL is a consultant for Regeneron Inc.; VarmX B.V.; Persica Pharmaceuticals Ltd. GBa has consultant and Teaching agreement with Abbott, Boston Scientific, Globus, Mainstay Medical and Saluda medical; SG and LGC declare a financial interest and salary from Persica Pharmaceuticals Ltd. EW, DM, SK, GS, OR, IF, IR, CB, GBl, VR, RO, CS, HL, MH, HR, MB, SJ, RG, SS, PJC work for research organisations contracted to provide expertise and services and their organisations received payment from Persica Pharmaceuticals Ltd for the work detailed in this manuscript. Other authors declare no financial interests relevant to the manuscript.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2026.103764.

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