2. SYNOPSIS

Name of Sponsor: Mundipharma Research Limited	INDIVIDUAL STUDY TABLE	(For National Authority Use Only)
Name of Finished Product: Lodotra® modified-release tablets	Referring to Part ... of the Dossier	
Name of Active Ingredient: Prednisone	Volume: Page:	
Protocol No.: LOD3501	**EudraCT/IND No.:** 2011-002353-57	

Title of the Study: A randomised, multi-centre, double-blind, active-controlled, parallel group study to assess the efficacy and safety of modified release prednisone (Lodotra® tablets) compared to immediate release prednisone (prednisone IR) in subjects suffering from polymyalgia rheumatica (PMR).

Investigators: Prof. M Cutolo *et al.*

A total of 41 sites in nine countries (Germany [11 sites], Czech Republic [six sites], Spain [six sites], Poland [five sites], Hungary [five sites], United Kingdom [four sites], Denmark [two sites], Romania [one site] and Italy [one site]) enrolled subjects.

A further 24 sites were initiated but did not enrol any subjects.

Publication (Reference): None

Study Dates:	**Study Status:**	**Phase of Development:**
20 March 2013 to 25 March 2014	Terminated early.	Phase 3

Objectives:

Primary:

To show that treatment with Lodotra® modified-release tablets (starting dose of 15 mg daily), administered in the evening, is non-inferior to treatment with prednisone IR (starting dose of 15 mg daily), administered in the morning, with regards to the percentage of complete responders to treatment 4 weeks after randomisation.

Complete response was defined as all three of the following:

1. ≥ 70% improvement in PMR visual analogue scale (VAS)
2. ≥ 70% reduction in the duration of morning stiffness (MST)
3. ≥ 70% reduction in C-reactive protein (CRP) value or CRP value < 2 times upper limit of normal (ULN; ULN is 10 mg/L)

Measures 1 and 2 were assessed relative to baseline (Visit 2) and measure 3 was assessed relative to screening (Visit 1) as blood samples were taken at the Screening Visit. Partial response was defined as two of the three above criteria met. Non-response was defined as one or none of the three criteria met.

Secondary:

1. To demonstrate superiority of Lodotra® tablets (starting dose of 15 mg daily) to prednisone IR (starting dose of 15 mg daily) in the core phase for the following measures:
    - Percentage of complete responders at Week 4;
    - Change from baseline in PMR VAS score over the last 24 hours at Week 4;
    - Change from baseline in duration of morning stiffness at Week 4;
    - Change from baseline (Visit 1, Screening) in CRP at Week 4;
    - Percentage of complete responders at a) Week 1 and b) Week 2.

2. To compare Lodotra® tablets (starting dose of 15 mg daily) and prednisone IR (starting dose of 15 mg daily) in the core phase by means of:
    - Level of response (complete, partial and non-response);
    - PMR VAS;
    - Global pain VAS;
    - Shoulder pain VAS;
    - Fatigue VAS;
    - Duration of morning stiffness;
    - Lab values for CRP;
    - Lab values for erythrocyte sedimentation rate (ESR);
    - Health assessment questionnaire disability index (HAQ-DI);

- Quality of life: Short Form (SF)-36 physical component summary (PCS) and SF-36 mental component summary (MCS); EuroQol (EQ)-5D;
- Interleukin-6 (IL-6) levels.

3. To assess the potential for dose sparing effects between Lodotra® tablets and prednisone IR in the extension phase of the study by means of the following parameters:
    - Percentage of subjects reaching the 5 mg dose level;
    - Total/cumulative dose;
    - Mean daily dose;
    - Level of response (complete, partial and non-response);
    - PMR VAS;
    - Global pain VAS;
    - Shoulder pain VAS;
    - Fatigue VAS;
    - Duration of morning stiffness;
    - Lab values for CRP;
    - Lab values for ESR;
    - Health assessment questionnaire disability index (HAQ-DI);
    - Quality of life: SF-36 PCS and SF-36 MCS; EQ-5D;
    - IL-6 levels;
    - Incidence and number of flares;
    - Incidence and number of adverse events (AEs).

4. To assess safety and tolerability in the core phase of the study and long-term safety from the extension phase by assessing AEs, vital signs (including weight), laboratory data, and electrocardiograms (ECGs).

Methodology: The study consisted of a 1 - 7 day screening phase (depending on the availability of laboratory results), a 4-week double-blind phase and a 48-week open-label extension phase.

Screening Phase (1 - 7 days):

At Visit 1, after written informed consent was obtained, subjects underwent complete evaluation for study eligibility (i.e. all inclusion/exclusion criteria were assessed). Subjects meeting the inclusion criteria and not infringing any of the exclusion criteria could continue in the study. Subjects who provide a separate informed consent had a blood sample taken from them at Visit 1 for genetic analysis.

Double-blind Core Phase (4 weeks):

At Visit 2, subjects who qualified for entry into the double-blind phase of the study were randomised to Lodotra® tablets (starting dose of 15 mg daily) or prednisone IR (starting dose of 15 mg daily) in a 1:1 ratio using an electronic system. Subjects were treated with double-blind study medication for up to 4 weeks. The daily prednisone dose was 15 mg plus respective placebo throughout the double-blind phase.

Throughout the core phase, subjects completed a daily electronic diary recording their PMR VAS, global pain VAS, shoulder pain VAS, fatigue VAS and duration of morning stiffness. The diary was completed in the morning (as soon as morning stiffness allowed completion) and in the evening.

All subjects visited the site 1 week, 2 weeks and 4 weeks after randomisation (Visits 3, 4 and 5) to assess PMR VAS, global pain VAS, shoulder pain VAS, fatigue VAS, duration of morning stiffness and CRP value. For the assessments of PMR VAS, global pain VAS, shoulder pain VAS, fatigue VAS and duration of morning stiffness, the mean value from the 3 days preceding the study visit were taken from the subject's electronic diary. Any other required efficacy and safety measures were assessed and follow-up on any AEs and concomitant therapies were performed. Two questionnaires on quality of life (SF-36 and EQ-5D) and the health assessment questionnaire disability index (HAQ-DI) were completed at Weeks 1 and 4 after randomisation.

Subjects needing prednisone doses of more than 15 mg daily were to be withdrawn from the study and treated adequately.

Subjects were contacted 7 days after discontinuation/the end of the core phase treatment for follow-up of any ongoing AEs, any new AEs that may have occurred, concomitant therapies and subsequent PMR therapy (Safety FU). The Safety FU Visit was conducted as a telephone or clinic visit. Subsequent PMR therapy was only recorded if the subject did not participate in the extension phase of the study.

Open-label Extension Phase (48 weeks):

After the end of the core phase, subjects who fulfilled the re-randomisation criteria were re-randomised (Visit 6) to either Lodotra® tablets (starting dose of 12 mg daily) or prednisone IR (starting dose of 12 mg daily) in a 1:1 ratio using an electronic system. Both groups received open-label study medication.

Subjects who did not fulfil the re-randomisation criteria completed end of study procedures and were followed up for 7 days.

All subjects continuing in the extension phase visited the site 4 weeks after re-randomisation (Visit 7). A subject was downtitrated to a daily dose of 10 mg Lodotra® tablets or prednisone IR, respectively, if they met downtitration criteria defined as demonstrating:

- ≥ 70% improvement in PMR VAS and
- ≥ 70% reduction in the duration of morning stiffness

from baseline (Visit 2).

Subjects who only fulfilled one of the two downtitration criteria remained on a dose of 12 mg daily until the next scheduled visit.

Subjects who did not fulfil any of the downtitration criteria had to be uptitrated again to the 15 mg daily starting dose. If these subjects needed to be uptitrated further (i.e., to a dose greater than 15 mg daily), they were to be discontinued from the study and treated with higher glucocorticoid doses as needed.

Throughout the extension phase of the study, subjects completed a daily electronic diary recording their PMR VAS, global pain VAS, shoulder pain VAS, fatigue VAS and duration of morning stiffness. The diary was completed in the morning (as soon as morning stiffness allowed completion) and in the evening. Subjects visited the site every 4 weeks. At each visit, PMR VAS, global pain VAS, shoulder pain VAS, fatigue VAS and duration of morning stiffness were assessed by using the mean value from the 3 days preceding the study visit, taken from the subject's electronic diary. Any other required efficacy and safety measures were also assessed. At Visits 10, 14 and 18 (completion/early discontinuation), subjects also completed 2 questionnaires on quality of life (SF-36 and EQ-5D) and the HAQ-DI. Furthermore, AEs and concomitant therapies were assessed at each visit.

From Visit 5 onwards, downtitration was to be performed every 4 weeks as long as the above mentioned downtitration criteria were still met. Otherwise, subjects continued to take the current dose of study medication. If the subject's PMR condition worsened after downtitration, the subject was uptitrated to the previous (i.e. last effective) dose.

If the subject's PMR condition worsened, they were to attend an unscheduled visit for uptitration of study medication to the previous dose level. If a sequential uptitration by 2 dose levels was needed, a flare had to be recorded.

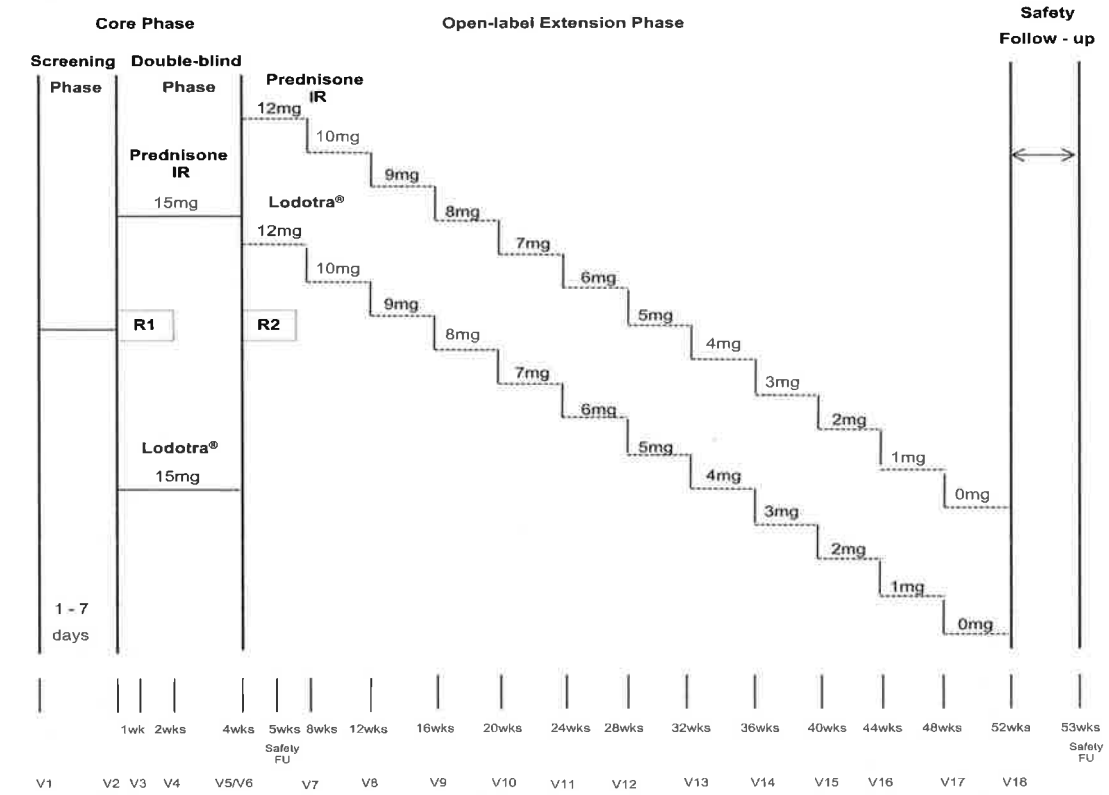
Subjects who had to be uptitrated sequentially by three dose levels or who had to be downtitrated due to intolerability to study medication were to be withdrawn from the study.

Subjects were contacted 7 days after discontinuation/the end of the extension phase treatment for follow-up of any ongoing AEs, any new AEs that may have occurred, concomitant therapies and subsequent PMR therapy (Safety FU). The Safety FU Visit was conducted as a telephone or clinic visit.

This study was prematurely terminated after 11 months of recruitment and 62 subjects had been randomised. Recruitment was stopped on 18 February 2014. Subjects who on that day were in the double-blind core phase of the study were allowed to complete the core phase. Those subjects who were in the open-label extension phase of the study were discontinued at their next regular visit.

The reasons for the early termination were primarily due to recruitment difficulties based on the inclusion criteria and also as a result of the cessation of production of the comparator product Prednisone IR (Decortin® tablets) 1 mg. The high screen failure rate (50%) was primarily due to an insufficiently high CRP value (an elevated value ≥ 2 x ULN was required for study entry, but 77% of screen failures failed to meet this criteria). There were no concerns regarding the safety or efficacy of Lodotra® tablets.

Study Design Graphic:



Number of Subjects: It was planned to randomise approximately 400 subjects (200 subjects per arm) in order to achieve 150 subjects per arm in the Per-Protocol (PP) population at the end of the 4-week double-blind core phase. A total of 62 subjects were randomised to treatment in the double-blind core phase (32 subjects to Lodotra® tablets and 30 subjects to Prednisone IR) and 50 subjects (80.6%) completed the study (27 [84.4%] in the Lodotra® group and 23 [76.7%] in the Prednisone IR group). A total of 27 subjects were re-randomised to treatment in the open-label extension phase (11 subjects to Lodotra® tablets and 16 subjects to Prednisone IR) and all 27 subjects discontinued early due to the premature termination of the study.

Indication and Criteria for Inclusion: The study population comprised males and females aged 50 years or older, newly diagnosed with PMR and previously untreated with glucocorticoids for PMR. All subjects were to present with new onset bilateral shoulder pain or new onset bilateral shoulder and hip girdle pain as well as a morning stiffness lasting at least 45 min on the day before the Screening Visit (changed to > 45 min by protocol amendment 2) and elevated levels of CRP values of ≥ 2 times the ULN.

Test Treatment, Dose, and Mode of Administration (Double-Blind Core Phase): Lodotra® (modified-release prednisone) 5 mg tablets (batch numbers: PN3885, PN3764 and PN3741) and matching placebo for prednisone IR tablets (batch number: PN3722). The starting dose of Lodotra® tablets was 15 mg once daily, administered orally at 22:00 ± 30 minutes with a light meal or snack. Subjects also received prednisone IR placebo starting dose 15 mg daily, which they took in the morning between 05:00 and 09:00. No dose titration was permitted and the doses remained stable throughout the core phase.

Reference Treatment, Dose, and Mode of Administration (Double-Blind Core Phase): Prednisone IR 5 mg tablets (batch number: PN3762) and matching placebo for Lodotra® tablets (batch numbers: PN3742 and PN3899). The starting dose of prednisone IR was 15 mg once daily, administered orally in the morning between 05:00 and 09:00. Subjects randomised to the prednisone IR arm also received Lodotra® placebo 15 mg daily, which they took in the evening at 22:00 ± 30 minutes with a light meal or snack. No dose titration was permitted and the doses remained stable throughout the core phase.

Test Treatment, Dose, and Mode of Administration (Open-Label Extension Phase): Lodotra® 1 mg (batch numbers: PN3884 and PN3763) and 5 mg tablets (batch numbers: PN3885, PN3764 and PN3741). Subjects re-randomised to treatment with Lodotra® tablets at Visit 6 started on a daily dose of 12 mg. Lodotra® tablets were taken in the evening at 22:00 ± 30 minutes with a light meal or snack. During the open-label extension phase, subjects were downtitrated if they met downtitration criteria. The dose levels in the open-label extension phase were 12 mg, 10 mg, 9 mg, 8mg, 7 mg, 6 mg, 5 mg, 4 mg, 3 mg, 2 mg, 1 mg and 0 mg.

Reference Treatment, Dose, and Mode of Administration (Open-Label Extension Phase): Prednisone IR 1 mg (batch numbers: PN3724 and PN3761) and 5 mg tablets (batch number: PN3762). Subjects re-randomised to treatment with prednisone IR at Visit 6 started on a daily dose of 12 mg. The medication was taken in the morning between 05:00 and 09:00. During the open-label extension phase, subjects were downtitrated if they met downtitration criteria. The dose levels in the open-label extension phase were 12 mg, 10 mg, 9 mg, 8mg, 7 mg, 6 mg, 5 mg, 4 mg, 3 mg, 2 mg, 1 mg and 0 mg.

Concomitant Medication Including Rescue: Subjects were not to take any medication for the treatment of PMR, including analgesics, prior to randomisation. Throughout the study, the use of analgesics and co-analgesics (e.g., non-steroidal anti-inflammatory drugs [NSAIDs], anti-convulsants, tumour necrosis factor [TNF]-blockers, steroids [other than those used as study medication], anti-depressants and opioids) was to be avoided. Subjects suffering from chronic osteoarthritis who were using stable doses of NSAIDs and/or antidepressants before Screening could continue with the same stable dose of medication during the study.

Duration of Treatment: Up to 52 weeks (4 weeks treatment in double-blind core phase and 48 weeks treatment in open-label extension phase)

Treatment Schedule: Dose regimens are provided above for each test and reference treatment.

Criteria for Evaluation:

Efficacy Assessments:

The primary efficacy endpoint was the percentage of complete responders at Week 4 of the double-blind core phase. Complete response was defined as all three of the following:

1. ≥ 70% improvement from baseline in PMR visual analogue scale (VAS).
2. ≥ 70% reduction from baseline in the duration of morning stiffness (MST).
3. ≥ 70% reduction from baseline in CRP value or CRP value < 2 times ULN.

Key secondary endpoints for the analysis of the double-blind core phase, i.e. those that were to be formally statistically tested for confirmatory superiority as part of a hierarchical testing strategy to preserve the type I error rate (the significance level, α) are the following:

- The change from baseline in PMR VAS score over the last 24 hours at Week 4;
- The change from baseline in duration of morning stiffness at Week 4;
- The change from baseline (Visit 1, Screening) in CRP at Week 4;
- The percentage of complete responders at Weeks 1 and 2.

Additional secondary endpoints for the analysis of the double-blind core phase that were assessed, and that were considered as exploratory, were the following:

- The percentage of subjects at each level of response at each visit;
- The percentage of subjects with ≥ 70% improvement (response) from baseline in PMR VAS score over the last 24 hours at each visit;
- The percentage of subjects with ≥ 70% reduction (response) from baseline in duration of morning stiffness at each visit;
- The percentage of subjects with ≥ 70% reduction (response) from baseline (Visit 1, screening) in CRP or within 2 times the ULN at each visit;
- The percentage of subjects with ≥ 70% improvement (response) from baseline in global pain VAS score over the last 24 hours at each visit;
- The percentage of subjects with ≥ 70% improvement (response) from baseline in shoulder pain VAS score over the last 24 hours at each visit;
- The percentage of subjects with ≥ 70% improvement (response) from baseline in fatigue VAS score over the last 24 hours at each visit;
- The change from baseline in PMR VAS score over the last 24 hours at Weeks 1 and 2;
- The change from baseline in PMR VAS score at awakening at each visit;
- The change from baseline in duration of morning stiffness at Weeks 1 and 2;
- The change from baseline in global pain VAS score over the last 24 hours at each visit;
- The change from baseline in global pain VAS score at awakening at each visit;
- The change from baseline in shoulder pain VAS score over the last 24 hours at each visit;
- The change from baseline in fatigue VAS score over the last 24 hours at each visit;
- The change from baseline (Visit 1, Screening) in CRP at Weeks 1 and 2;
- The change from baseline (Visit 1, Screening) in ESR at each visit;
- The change from baseline (Visit 1, Screening) in IL-6 levels at Week 4;

- The change from baseline in HAQ-DI score at Weeks 1 and 4;
- The proportion of responders in HAQ-DI at Week 4 (defined as a decrease of ≥ 0.22 points from baseline);
- The change from baseline in SF-36 PCS and MCS domain scores at Weeks 1 and 4;
- The change from baseline in EQ-5D index score at Weeks 1 and 4.

Due to the early termination of the study, no efficacy endpoints were evaluated for the open-label extension phase of the study.

Safety: Safety was assessed by documentation of AEs, clinical laboratory results, vital signs, physical examinations, and electrocardiograms (ECGs) and recorded on the standard Case Report Form (CRF) pages and Serious Adverse Event (SAE) data form.

Statistical Methods:

Analysis Populations:

The enrolled population was defined as all subjects who signed informed consent.

The randomised population was defined as all randomised subjects.

The Safety population (for the double-blind core phase) was defined as all randomised subjects who received at least one dose of double-blind core phase study medication (investigational medicinal product [IMP]).

The Full Analysis population (for the double-blind core phase) was defined as all randomised subjects who received at least one dose of double-blind core phase study medication (IMP).

The Per-Protocol (PP) population was defined as all Full Analysis population subjects without major protocol violations. Major protocol violations were agreed at the Determination of Subject Evaluability (DOSEA) meeting prior to unblinding.

The Safety population (for the open-label extension phase) was defined as all randomised subjects who received at least one dose of open-label extension phase study medication (IMP).

The Full Analysis population (for the open-label extension phase) was defined as all randomised subjects who received at least one dose of open-label extension phase study medication (IMP).

Efficacy Analyses:

The percentage of complete responders at the end of the 4-week double-blind core phase (primary endpoint) was analysed using logistic regression with treatment as factors, and baseline PMR VAS score, baseline duration of morning stiffness (MST), and baseline (Visit 1, Screening) CRP as covariates. The statistical model was used to calculate the difference with respect to the percentage of complete responders for the treatment comparison of Lodotra® tablets vs. Prednisone IR, with associated 95% confidence interval (CI). As such, risk difference estimators based on the logistic regression model were calculated with accompanying standard error for the difference calculated by the delta method. Non-inferiority was to be concluded if the lower limit of the 95% CI was greater than or equal to -15%.

The primary analysis for assessing non-inferiority was performed on the PP population. The analysis conducted using the (double-blind core) Full Analysis population was considered as a sensitivity analysis for assessing non-inferiority. The analyses were conducted using a modified last observation carried forwad (mLOCF) approach to handle missing data and assess the rate of complete responders at the end of the 4-week double-blind treatment phase. Sensitivity analyses were conducted using observed cases.

Changes from baseline in PMR VAS score, CRP levels, global pain VAS, shoulder pain VAS, fatigue VAS, ESR levels, SF-36 PCS and MCS domains were analysed using repeated measures analysis of covariance (ANCOVA) (unstructured covariance), including treatment as a factor and baseline score as a covariate.

The change from baseline in duration of morning stiffness was analysed using the Hodges-Lehmann method for median treatment differences, using last observation carried forward (LOCF) to account for missing data.

The change from baseline in IL-6 levels to Week 4 was analysed using ANCOVA, including treatment as a factor, and baseline IL-6 as a covariate.

The percentage of subjects with ≥70% improvement (response) from baseline in PMR VAS, duration of morning stiffness, global pain VAS, shoulder pain VAS and fatigue VAS was analysed using respective logistic regression models, including factors for treatment, and baseline score as a covariate.

The EQ-5D index score and HAQ-DI score and changes from baseline were summarised descriptively. Additionally, the number and percentage of subjects classified as responders in the HAQ-DI (defined as a decrease of ≥ 0.22 points from baseline) were summarised for each visit.

Interim Analyses: Not applicable.

Safety Analyses: Safety data were summarised descriptively for subjects in the Safety population.

Sample Size Rationale: Assuming a rate of complete responders of 69% in the comparator (Prednisone IR) arm at the end of the 4-week double-blind core phase, an expected treatment difference of 0% (Lodotra® tablets - Prednisone IR) i.e. an identical expected rate of complete responders in the Lodotra® arm of 69%, a non-inferiority bound of -15%, 80% power, and a two-sided alpha of 0.05, this could be achieved with 150 subjects per group in the PP population. In order to achieve 150 subjects per group in the PP population, it was planned to randomise a total of 400 subjects (200 per arm). This was assuming that approximately 25% of randomised subjects would not be part of the PP population.

The trial was terminated after randomisation of 62 subjects. Following the protocol assumption, that 25% of the randomised subjects would be excluded from the PP population, the expected sample size of the primary analysis population would be 46 subjects. Based on this expected sample size for the primary analysis, the actual power would be 19%. Consequently, the trial was no longer powered to demonstrate non-inferiority as planned.

Results:

Efficacy: Non-inferiority of Lodotra® tablets versus Prednisone IR was not proved in the double-blind core phase. The treatment difference (Lodotra® tablets versus Prednisone IR) in the proportion of complete responders at Week 4 in the PP population (primary analysis, mLOCF) was 12.22% (95% CI: -15.82%, 40.25%) in favour of Lodotra® tablets, and the lower limit of the 95% CI was slightly less than the pre-defined threshold for non-inferiority of -15%.

However, the proportion of complete responders at Week 4 was clearly higher in the Lodotra® group (14 out of 26 subjects [53.8%]) compared with the Prednisone IR group (9 out of 22 subjects [40.9%]). The proportion of partial responders at Week 4 was also higher in the Lodotra® group, and more partial responders were observed in the Lodotra® group at earlier time points of Week 1 and Week 4. The overall proportion of responders (i.e., complete responders + partial responders) at Week 4 was 20 out of 26 subjects (76.9%) in the Lodotra® group compared with 12 out of 22 subjects (54.5%) in the Prednisone IR group.

The failure to meet the primary objective can be explained by the small sample size of only 48 subjects in the PP population, which is much lower than the study was powered for (planned sample size of 300 subjects in the PP population) due to the early termination of the study. The CI for the primary endpoint was wide and the lower 95% CI was only just below the -15% cut-off for non-inferiority, while the point estimate was clearly in favour of Lodotra® tablets (12.22%). With a larger sample size (and inherent reduced variability) the lower 95% CI might have exceeded the -15% threshold for non-inferiority.

The sensitivity analysis on the Full Analysis population, which included all 62 randomised subjects, shows a trend in favour of Lodotra® tablets (treatment difference in proportions: 15.56%; 95% CI: -9.16%, 40.28%). The summary statistics for the Full Analysis population (using mLOCF method for imputation of missing data) clearly show a higher proportion of complete responders at Week 4 in the Lodotra® group (17 out of 32 subjects [53.1%]) compared with the Prednisone IR group (10 out of 30 subjects [33.3%]). The overall proportion of responders (i.e., complete responders + partial responders) at Week 4 was also higher in the Lodotra® group (25 out of 32 subjects [78.1.0%]) compared with the Prednisone IR group (14 out of 30 subjects [46.7%]).

The positive trend in the efficacy of Lodotra® tablets versus Prednisone IR as observed in the primary analysis was consistently supported by the secondary efficacy results, with a clear indication of a larger favourable effect with Lodotra® tablets compared with Prednisone IR for all secondary efficacy endpoints, except ESR and CRP (Table S1). For ESR at Week 4, and CRP at Weeks 1, 2 and 4, the mean change from baseline was larger in the Prednisone IR group compared with the Lodotra® group, but the actual mean values were lower (indicating less severe disease) in the Lodotra® group compared with the Prednisone IR group. The improved effect of Lodotra® tablets over Prednisone IR was observed from as early as 1 week after the start of study treatment for most secondary endpoints. The treatment differences at Week 4 were statistically significant (in favour of Lodotra® tablets , $p<0.05$ and upper and lower 95% CI below 0) for PMR VAS, PMR VAS at awakening, global pain VAS, global pain VAS at awakening and shoulder pain VAS scores (Table S2). Elevated levels of the cytokine IL-6 are associated with PMR, and this parameter is considered a sensitive indicator of disease activity. As observed in RA trials, Lodotra® tablets showed good efficacy in reducing IL-6 levels, with a statistically significantly greater decrease in IL-6 levels in the Lodotra® group compared with the Prednisone IR group at Week 4 (estimate of treatment difference: -6.5; 95% CI: -11.84, -1.23; p=0.017), which further supports the observed clinical efficacy results. Generally, the statistically significant results of secondary endpoints should be interpreted with caution due to the type I error inflation of multiple testing. However, a consistent trend in most of the efficacy endpoints was observed in this study, supporting evidence of efficacy of Lodotra® tablets compared to Prednisone IR.

Regarding quality of life results, Lodotra® tablets appeared to have a larger positive effect than Prednisone IR on the mental status of subjects (shown by results for the MCS domain of the SF-36), with a clear trend for a greater favourable effect with Lodotra® tablets compared with Prednisone IR. Results for the EQ-5D and HAQ-DI showed a similar improvement in quality of life for both treatment groups.

Table S1 Secondary Efficacy Results (Double-Blind Core Phase, Full Analysis Population)

Parameter		Lodotra® tablets (N=32)		Prednisone IR (N=30)	
		Baseline	Change from Baseline at Week 4	Baseline	Change from Baseline at Week 4
PMR VAS	Mean (SD)	80.71 (12.884)	-70.37 (20.814)	80.95 (11.700)	-59.77 (24.016)
Response[a]	n (%)	-	25 (78.1)	-	16 (53.3)
PMR VAS at awakening	Mean (SD)	81.73 (17.260)	-70.74 (18.722)	85.92 (9.676)	-63.72 (23.252)
Duration of MST (minutes)	Mean (SD)	529.94 (530.990)	-456.94 (517.912)	615.57 (590.990)	-417.32 (574.652)
Response[a]	n (%)	-	26 (81.3)	-	14 (46.7)
Global pain VAS	Mean (SD)	79.99 (13.142)	-68.70 (21.729)	78.15 (13.958)	-55.47 (25.552)
Response[a]	n (%)		20 (62.5)		14 (46.7)
Global pain VAS at awakening	Mean (SD)	80.59 (18.943)	-69.34 (20.665)	83.36 (13.132)	-60.92 (28.282)
Shoulder pain VAS	Mean (SD)	81.00 (13.308)	-68.38 (21.463)	79.90 (13.011)	-57.71 (25.916)
Response[a]	n (%)	-	21 (65.6)	-	14 (46.7)
Fatigue VAS	Mean (SD)	72.86 (19.309)	-59.40 (27.338)	75.67 (14.313)	-57.60 (23.162)
Response[a]	n (%)	-	19 (59.4)	-	16 (53.3)
CRP (mg/L)	Mean (SD)	50.58 (32.341)	-44.04 (32.238)	69.59 (49.384)	-52.88 (48.333)
Response[a]	n (%)	-	32 (100.0)	-	22 (73.3)
ESR (mm/hr)	Mean (SD)	66.53 (21.618)	-38.77 (24.137)	68.33 (22.842)	-40.12 (23.651)
IL-6 (pg/mL)	Mean (SD)	41.40 (34.967)	-37.41 (41.272)	40.86 (35.183)	-29.84 (32.613)

a: Response is defined as improvement of more than or equal to 70% from baseline.
Decreases from baseline represent a favourable treatment effect.
CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; IL-6 = interleukin-6; MST = morning stiffness; PMR = polymyalgia rheumatica; VAS = visual analogue scale.

Table S2 Secondary Analyses of Covariance (Double-Blind Core Phase, Full Analysis Population)

	Week	Estimate [95% CL][a]	p-value
PMR VAS	1	-9.3 [-22.97, 4.30]	0.176
	2	-17.4 [-31.11, -3.61]	0.014
	4	-12.8 [-22.58, -3.05]	0.011
PMR VAS at awakening	1	-10.9 [-25.45, 3.61]	0.138
	2	-15.8 [-29.20, -2.42]	0.022
	4	-11.6 [-21.33, -1.79]	0.021
Duration of morning stiffness	1	134.5 [18.50, 250.50][b]	0.021
(minutes)	2	114.7 [-21.33, 250.67][b]	0.093
	4	46.9 [-110.00, 203.83][b]	0.592
Global pain VAS	1	-7.5 [-21.10, 6.11]	0.275
	2	-14.5 [-27.44, -1.47]	0.030
	4	-13.6 [-23.93, -3.26]	0.011
Global pain VAS at awakening	1	-9.1 [-23.78, 5.57]	0.219
	2	-13.6 [-26.70, -0.42]	0.043
	4	-12.3 [-23.23, -1.42]	0.028
Shoulder pain VAS	1	-7.4 [-21.55, 6.66]	0.295
	2	-15.8 [-28.99, -2.66]	0.019
	4	-11.1 [-21.30, -0.91]	0.033
Fatigue pain VAS	1	-7.8 [-20.67, 5.07]	0.230
	2	-10.8 [-24.07, 2.44]	0.108
	4	-6.4 [-16.77, 4.04]	0.225
CRP (mg/L)	1	-6.2 [-13.61, 1.22]	0.100
	2	-6.7 [-14.80, 1.30]	0.098
	4	-8.0 [-16.37, 0.37]	0.060
ESR (mm/hr)		Not Estimable	
IL-6 (pg/mL)	4	-6.5 [-11.84, -1.23]	0.017

a: Estimates are Least Square means with Confidence Limits from a repeated measures ANCOVA model, if not stated otherwise.
b: Estimates and CL stem from the Hodges-Lehmann method.
Not Estimable: Convergence criteria not met.
CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; IL-6 = interleukin-6; MST = morning stiffness; PMR = polymyalgia rheumatica; VAS = visual analogue scale.

Safety:

In the study as a whole (double-blind core and open-label extension phases), there were no deaths and the majority of AEs were mild or moderate in severity, with only 2 subjects experiencing a severe AE (both unrelated to study medication). Two subjects experienced SAEs, which were not treatment-related, and 3 subjects discontinued due to AEs.

In the double-blind core phase, approximately twice as many subjects reported AEs in the Lodotra® group (19 subjects [59.4%]) as compared with the Prednisone IR group (9 subjects [30.0%]). However, the AE numbers and incidences were low; the only AEs reported by more than 1 subject in any treatment group were leukocytosis, upper abdominal pain, hyperkalaemia, arthralgia and hypertension (each reported for 2 subjects in the Lodotra® group). AEs were considered to be treatment-related for 8 subjects (25.0%) in the Lodotra® group and 3 subjects (10.0%) in the Prednisone IR group.

In the open-label extension phase, a similar number of subjects in both treatment groups reported AEs (7 subjects [63.6%] in the Lodotra® group and 8 subjects [50.0%] in the Prednisone IR group). The only AEs reported by more than 1 subject in any treatment group were nasopharyngitis and back pain (each reported for 2 subjects [12.5%] in the Prednisone IR group). AEs were considered to be treatment-related for 4 subjects (36.4%) in the Lodotra® group and 1 subject (6.3%) in the Prednisone IR group.

Two subjects experienced SAEs; 1 subject experienced 2 SAEs of pancytopenia (one whilst receiving Lodotra® tablets in the double-blind core phase and one whilst receiving Prednisone IR in the open-label extension phase) and 1 subject experienced temporal arteritis while receiving Prednisone IR in the double-blind core phase. None of the SAEs were considered to be treatment-related by the Investigator.

The AEs observed in both phases of the study were generally consistent with those expected in subjects with PMR taking prednisone or considered explained by underlying conditions.

Three subjects discontinued from the double-blind core phase due to AEs; 1 subject in the Lodotra® group discontinued due to upper abdominal pain, and 2 subjects in the Prednisone IR group discontinued (one due to the SAE of temporal arteritis and one due to a burning sensation).

Out of range values were observed for a few clinical laboratory parameters; notably values above the normal range for cholesterol, glucose and triglycerides in both treatment groups. However, the number of subjects with out of range values for each parameter was similar at baseline and end of study within each treatment group, and there were no notable differences between the treatment groups. Several low haemoglobin and haematocrit values were observed at baseline, or baseline and end of study, for both treatment groups. Several subjects in both treatment groups had high leukocyte and neutrophil counts at end of study. Overall, no clinically notable trend of shifts in one particular direction was identified for any parameter in either treatment group.

There were no clinically important or unexpected changes in mean or individual vital signs values during the study for either treatment group.

One subject (3.3%) in the Prednisone IR group had a clinically significant ECG finding at the end of the double-blind core phase that was not present at baseline (asymptomatic ischemic changes in ST segment).

Conclusions: This randomised, multi-centre, double-blind, active-controlled, parallel group study aimed assess the efficacy and safety of Lodotra® tablets compared to prednisone IR in subjects suffering from PMR. The study population comprised male or female subjects aged 50 years or older, newly diagnosed with PMR and previously untreated with glucocorticoids for PMR. Throughout the study, the use of analgesics and co-analgesics (e.g., NSAIDs, anti-convulsants, TNF-blockers, steroids [other than those used as study medication], anti-depressants and opioids) was to be avoided, except for subjects suffering from chronic osteoarthritis who could continue using stable doses of NSAIDs and/or antidepressants. All subjects were to present with new onset bilateral shoulder pain or new onset bilateral shoulder and hip girdle pain as well as a morning stiffness lasting > 45 min on the day before the Screening Visit and elevated CRP levels ≥ 2 x ULN. The study planned to randomise approximately 400 subjects into the double-blind core phase to achieve 300 evaluable subjects in the PP population.

The study experienced a higher than expected screen failure rate (50%), which was primarily due to subjects failing to meet the requirement for an elevated CRP level ≥ 2 x ULN (77% of screen failures failed to meet this criteria). The study's inclusion/exclusion criteria were based on the 2012 EULAR/ACR Provisional Classification Criteria for PMR and also the 2010 BSR/BHPR guidelines for the management of PMR. From the recruitment pattern observed in this study, it would appear that the PMR patient population is much more heterogeneous than previously understood, and that many subjects presented with clear clinical symptoms of PMR but, unexpectedly, they did not meet the clinical definition as outlined in the guidelines cited above.

Therefore, the study was prematurely terminated after 11 months of recruitment and 62 subjects had been randomised, primarily due to the recruitment difficulties based on the inclusion criteria but also as a result of the unexpected cessation of production of the comparator product Prednisone IR (Decortin® tablets) 1 mg. There were no concerns regarding the safety or efficacy of Lodotra® tablets. Recruitment was stopped on 18 February 2014. Subjects who on that day were in the double-blind core phase of the study were allowed to complete the core phase. Those subjects who were in the open-label extension phase of the study were discontinued at their next regular visit.

However, despite the early termination of the study and the lower than planned sample size (48 subjects in the PP population compared with the anticipated PP population size of 300 subjects), the efficacy results showed a clear trend for a stronger effect of Lodotra® tablets compared with Prednisone IR for all primary and secondary efficacy endpoints. Non-inferiority of Lodotra® tablets versus Prednisone IR could not be proved for the primary endpoint; proportion of complete responders at Week 4 (treatment difference [Lodotra® tablets versus Prednisone IR]: 12.22%; 95% CI: -15.82%, 40.25%. Interestingly, the lower limit of the 95% CI was only marginally below the pre-defined threshold for non-inferiority of only -15%, while the point estimate was clearly in favour of Lodotra® tablets. With the planned larger sample size (and inherent reduced variability) the lower 95% CI might have exceeded the -15% threshold for non-inferiority. The proportion of complete responders at Week 4 was clearly higher in the Lodotra® group (14 subjects [53.8%]) compared with the Prednisone IR group (9 subjects [40.9%]) and furthermore, the sensitivity analysis on the Full Analysis Population supported the trend in favour of Lodotra® tablets (treatment difference in proportions: 15.56%; 95% CI: -9.16%, 40.28%).

The positive trend in the efficacy of Lodotra® tablets versus Prednisone IR as observed in the primary analysis was consistently supported by the secondary efficacy results, with a clear trend for a larger favourable effect with Lodotra® tablets compared with Prednisone IR for all secondary efficacy endpoints. The improved effect of Lodotra® tablets over Prednisone IR was observed from as early as 1 week after the start of study treatment for most secondary efficacy endpoints. Of note, the treatment differences at Week 4 were statistically significant in favour of Lodotra® tablets for PMR VAS, PMR VAS at awakening, global pain VAS, global pain VAS at awakening and shoulder pain VAS scores, and for IL-6. As in RA trials, Lodotra® tablets showed good efficacy in reducing IL-6 levels, with a statistically significantly greater decrease compared with the Prednisone IR group at Week 4 (p=0.017). Generally, the statistically significant results of secondary endpoints should be interpreted with caution due to the type I error inflation of multiple testing. However, a consistent trend in most of the efficacy endpoints was observed in this study, supporting evidence of efficacy of Lodotra® tablets compared to Prednisone IR.

Lodotra® tablets appeared to have a larger positive effect than Prednisone IR on the mental status of subjects (shown by results for the MCS domain of the SF-36), with a clear trend for a larger favourable effect with Lodotra® tablets compared with Prednisone IR.

The incidence of treatment-related AEs was relatively low and those reported were generally consistent with the known safety profiles of Lodotra® tablets and Decortin® tablets. Overall, there were no new or unexpected observations relating to safety in this population of subjects with newly diagnosed PMR and previously untreated with glucocorticoids.

In conclusion, considering the consistently positive and clinically meaningful results for Lodotra® tablets compared with Prednisone IR across all primary and secondary efficacy endpoints observed already at 4 weeks, there is a strong indication of a beneficial clinical effect of Lodotra® tablets over prednisone IR in subjects with PMR.

Date of the Report: 13 February 2015