SUPPLEMENTARY APPENDIX

Inclusion/exclusion criteria

Subjects enrolled in this study were newly diagnosed with PMR. It was planned to randomise approximately 400 subjects to achieve 300 evaluable subjects in the per-protocol population (PPP).

Inclusion Criteria

1. Males or females, 50 years of age or older who provided written informed consent.

2. Females less than one year post-menopausal had to have a negative serum or urine pregnancy test recorded prior to the first dose of study medication, be non-lactating, and willing to use adequate and highly effective methods of contraception throughout the study. A highly effective method of birth control was defined as those which result in a low failure rate (i.e. less than 1% per year) when used consistently and correctly such as sterilisation, implants, injectables, combined oral contraceptives, some intrauterine devices, sexual abstinence or vasectomised partner.

3. Patients newly diagnosed with PMR and previously untreated with glucocorticoids for PMR. The diagnosis of PMR had to be confirmed by all of the following criteria:

   - New onset bilateral shoulder pain or new onset bilateral shoulder and hip girdle pain.
   - PMR VAS score over the last 24 hours before the Screening Visit ≥50 (on a 0-100 scale).
   - Morning stiffness duration of >45 min on the day before the Screening Visit.
   - Acute phase response shown by elevated CRP (≥2 times ULN).

   Subjects enrolled in France had to have been newly diagnosed with PMR within the previous 4 weeks.

4. Patients willing and able to participate in all aspects of the study and comply with the use of study medication.

Exclusion Criteria

1. Females who were pregnant (positive beta-human chorionic gonadotropin test) or lactating.

2. Patients with any contraindication/history of hypersensitivity to predniso(lo)ne or other ingredients.

3. Significant renal impairment (serum creatinine >150 µmol/L).

4. Significant hepatic impairment (alanine aminotransferase, aspartate aminotransferase and gamma-glutamyl transferase >2.5 ULN).

5. Patients suffering from another disease which required glucocorticoid treatment. Topical glucocorticoids, e.g. intra-nasal or inhaled glucocorticoids, were allowed but were to be kept at a stable dose throughout the study.

6. Continued use of systemic glucocorticoids within 4 weeks prior to the Screening Visit.

7. Joint injections with glucocorticoids within 6 weeks prior to the Screening Visit.

8. Patients who required treatment with non-permitted concomitant therapies.

9. Evidence of clinically significant cardiovascular, renal, hepatic, gastrointestinal or psychiatric disease at the time of screening, as determined by medical history, clinical laboratory tests, electrocardiogram results, and physical examination, that would have placed the patient at risk upon exposure to the study medication or that may have confounded the analysis and/or interpretation of the study results.

10. Active alcohol or drug abuse.

11. Patients suffering from giant cell arteritis, late-onset rheumatoid arthritis or other inflammatory rheumatoid diseases. The protocol was amended to exclude patients who had pre-study documented evidence of raised rheumatoid factor (RF) and anti-citrullinated protein antibodies (ACPA) from study entry.

12. Patients suffering from drug-induced myalgia.

13. Patients suffering from fibromyalgia.

14. Patients suffering from systemic lupus erythemathosus.

15. Patients suffering from neurological conditions, e.g. Parkinson's disease.

16. Patients suffering from active cancer.

17. Patients suffering from an active infection. In France, patients who were at risk of infection were also excluded.

18. Patients who participated in a clinical research study involving a new chemical entity or an experimental drug within 30 days prior to the Screening Visit.

The following exclusion criteria were added for France only:

19. Patients suffering from non-controlled diabetes.

20. Patients suffering from non-controlled hypertension.

21. Patients suffering from ophthalmological problems (glaucoma, ulceration, etc.).

22. Patients who had had tuberculosis.

Randomisation and Blinding

Randomisation was performed using an interactive response technology system and used blocking methodology via a country-based randomisation method (stratified for country). The patient and all personnel involved with the conduct and interpretation of the study were blinded to the medication codes.

Matching placebo tablets for MR prednisone and IR prednisone were used to maintain the blind. Patients randomised to IR prednisone took 15mg IR prednisone in the morning between 5am and 9am and took matching placebo for MR prednisone in the evening at 10pm ± 30 minutes. Patients randomised to MR prednisone took matching placebo for IR

prednisone in the morning between 5am and 9am and 15mg MR prednisone in the evening at 10pm ± 30 minutes. Patients were instructed to take the evening dose of MR prednisone/placebo with a light meal or snack.

Quality of Life Assessments

Patients completed health assessment questionnaires (short form 36 [SF-36] version 2, EuroQol five dimensions questionnaire [EQ-5D] and Health Assessment Questionnaire-Disability Index [HAQ-DI]) at study visits at baseline, Week 1 and Week 4.

Study Endpoints

The primary efficacy endpoint was the percentage of complete responders at Week 4. Key secondary endpoints were the change from baseline to Week 4 for PMR VAS score, duration of morning stiffness, and CRP; and the percentage of complete responders at Weeks 1 and 2. Other secondary efficacy endpoints, which were considered exploratory, included the percentage of patients at each level of response; the percentage of patients with ≥70% improvement (response) in each VAS score, duration of morning stiffness and CRP (or CRP <2 x ULN) at Weeks 1 and 4; changes from baseline in each VAS score, duration of morning stiffness, ESR, IL-6, HAQ-DI score, SF-36 domain scores and EQ-5D index score at each visit; and proportion of responders in HAQ-DI (defined as a decrease of ≥0.22 points from baseline) at Week 4.

Statistical Methods

The primary endpoint was analysed using logistic regression with treatment as a factor and baseline PMR VAS score, baseline duration of morning stiffness, and baseline (screening) CRP as covariates. Difference estimators based on the logistic regression model were calculated with accompanying standard error for the difference calculated by the delta method.[3] Non-inferiority was to be concluded if the lower limit of the two-sided 95% confidence interval (CI) was greater than or equal to -15%. The non-inferiority margin was based on clinically important treatment differences, as well as considering ethical and regulatory criteria, cost, and feasibility. It was assumed that the complete response rate with the comparator, IR prednisone, would be 30% higher than for placebo, thus to ensure that MR prednisone preserved at least half of the effect of IR prednisone,[2] the non-inferiority margin was set at -15%. The primary analysis was conducted using a modified last observation carried forward (mLOCF) approach to handle missing data.

For most secondary endpoints, changes from baseline were analysed using repeated measures analysis of covariance, including treatment (and visit, where appropriate) as factors and baseline value as a covariate. Change from baseline in duration of morning stiffness was analysed using the Hodges Lehmann method for median treatment differences, using LOCF. Response endpoints were analysed using logistic regression models, including treatment as a factor, and baseline score as a covariate, using a mLOCF approach. The statistical models were used to calculate the treatment difference/odds ratio, the corresponding 95% CI, and the p-value. The EQ-5D index score, HAQ-DI score and HAQ-DI response rate were summarised descriptively. For EQ-5D, the conversion between the ordinal scores to an index was performed using the UK Time Trade Off preference weights.[3] All secondary efficacy endpoints were analysed using the FAP.

Safety presentations were descriptive and based on the safety population (all randomised patients who received at least one dose of study treatment). Adverse events were coded using MedDRA version 16. Statistical programming and analyses were performed using SAS® version 9.1.3 or higher (SAS Institute, Cary, North Carolina, USA).

Reasons for exclusion of patients from the PPP were: taking excluded concomitant medication (6 patients), violation of inclusion/exclusion criteria (4 patients), <80% compliance with study treatment (3 patients), missing values for primary endpoint (2 patients) and error in treatment assignment (1 patient).

Open-label Extension Phase

A 48-week open-label extension phase followed the 4-week double-blind phase. Patients entering the open-label phase were re-randomised to MR prednisone or IR prednisone (1:1 ratio, starting dose of 12mg daily) to maintain the blind for the double-blind phase. Dose titration was permitted during the open-label phase in accordance with British Society for Rheumatology guidelines for PMR.[4]

A total of 27 patients were randomised into the open-label extension phase; following study termination all were discontinued. The median duration of treatment in the open-label phase was 140 (range: 28 to 306) days for MR prednisone and 112 (range: 21 to 218) days for IR prednisone. Due to the limited data for the open label phase, only adverse events are presented (online supplementary table S3).

Protocol Amendments

There were five amendments to the original protocol (dated 23 August 2012); including one global amendment and four local amendments. All amendments, except protocol amendment 5, were implemented before recruitment of subjects into the study.

Protocol amendment 1 (08 January 2013) was a local amendment (UK only) that amended the inclusion criteria for the extension phase to clarify that subjects with active infection were not eligible for entry into the open-label extension phase of the study.

Protocol amendment 2 (30 January 2013) was a global amendment that reflected the change in the duration of morning stiffness indicating that patients can be classified as having PMR to >45 minutes according to the EULAR/ACR 2012 Provisional Classification Criteria for PMR. The amendment also required the measurement of RF and ACPA. Elevated results for these tests indicated that a subject had underlying rheumatoid arthritis (RA). Underlying RA would have excluded the subject from the PPP.

Protocol amendment 3 (30 January 2013) was a local amendment (France only) that, in response to French Ethics Committee questions, clarified diagnosis time for PMR and added to the inclusion criteria that subjects could not be under legal protection or in the judicial system.

Protocol amendment 4 (01 February 2013) was a local amendment (Germany only) that, in response to German Ethics Committee questions, added to the inclusion criteria that subjects could not be under legal protection or in the judicial system, added that vital signs were to be recorded at each visit, and added that the Declaration of Helsinki Revision 4 (1996) would also be followed.

Protocol amendment 5 (25 July 2013) was a local amendment (France only), which added the following exclusion criteria and also included ophthalmological surveillance in the study in response to French Competent Authority questions:

- Subjects suffering from an active infection or who were at risk of infection;
- Subjects with non-controlled diabetes;
- Subjects with non-controlled hypertension;
- Subjects with ophthalmological problems (glaucoma, ulceration, etc.);

- Subjects with a history of tuberculosis.

Quality of Life Results

For the SF-36 domains, there was a larger improvement from baseline in mental component summary domain score for MR prednisone compared with IR prednisone at Week 1 (mean increases of 19.6 for MR prednisone and 7.6 for IR prednisone) and Week 4 (mean increases of 36.2 for MR prednisone and 15.3 for IR prednisone). There was a similar increase in physical component summary domain scores for both treatment groups at Week 1 (mean increases of 22.3 for MR prednisone and 22.5 for IR prednisone) and Week 4 (mean increases of 43.3 for MR prednisone and 41.8 for IR prednisone).

For the EQ-5D UK time trade-off utility scores, there was an improvement (increase) from baseline in both treatment groups at Weeks 1 and 4 (0.49 [Week 1] and 0.66 [Week 4] for MR prednisone; and 0.40 [Week 1] and 0.57 [Week 4] for IR prednisone).

There was a similar improvement (decrease) in HAQ-DI scores in both treatment groups at Weeks 1 and 4 (-0.26 [Week 1] and -0.34 [Week 4] for MR prednisone; -0.19 [Week 1] and -0.29 [Week 4] for IR prednisone). The proportion of HAQ-DI responders was comparable in both treatment groups at Week 1 (MR prednisone: 37.5%, IR prednisone: 40.0%) and Week 4 (MR prednisone: 50.0%, IR prednisone: 40.0%).

References

1. Ge M, Durham LK, Meyer RD, et al. Covariate-adjusted difference in proportions from clinical trials using logistic regression and weighted risk differences. *Drug Information Journal* 2011:45:481-493.

2. U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER) Guidance for Industry, Non-Inferiority Clinical Trials. 2010 Mar.

3. Dolan P. Modelling valuations for EuroQol health states. *Medical Care* 1997;35(11):1095-1108.

4. Dasgupta B, Borg FA, Hassan N, et al. BSR and BHPR guidelines for the management of polymyalgia rheumatica. *Rheumatology* 2010;49:186-90.

Supplementary Table S1 Demography: Full Analysis Population

Variable	Statistic	Modified Release Prednisone (N=32)	Immediate Release Prednisone (N=30)	Total (N=62)
Age (years)	n	32	30	62
	Mean (SD)	69.7 (7.73)	69.2 (7.27)	69.4 (7.45)
	Median	70.5	69.0	70.0
	Min, Max	52, 84	56, 86	52, 86
Age group [n (%)]	<65	8 (25.0)	8 (26.7)	16 (25.8)
	≥65	24 (75.0)	22 (73.3)	46 (74.2)
Gender [n (%)]	Male	14 (43.8)	7 (23.3)	21 (33.9)
	Female	18 (56.3)	23 (76.7)	41 (66.1)
Race [n (%)]	Caucasian	32 (100.0)	30 (100.0)	62 (100.0)

SD = standard deviation.

Supplementary Table S2 Secondary Efficacy Results – Response Endpoints (Full Analysis Population)

Parameter	Visit	Modified Release Prednisone (N=32)	Immediate Release Prednisone (N=30)	Estimate [95% Confidence Limit][b]	p-value for Treatment Difference
		Response Rate[a] n (%)	Response Rate[a] n (%)		
PMR VAS	Week 1	9 (28.1)	6 (20.0)	1.6 [0.50, 5.34]	0.417
	Week 4	25 (78.1)	15 (50.0)	2.4 [0.65, 8.63]	0.191
Duration of morning stiffness	Week 1	14 (43.8)	5 (16.7)	4.4 [1.31, 15.06]	0.017
	Week 4	25 (78.1)	14 (46.7)	3.1 [0.84, 11.78]	0.090
Global pain VAS	Week 1	9 (28.1)	6 (20.0)	1.6 [0.49, 5.27]	0.434
	Week 4	20 (62.5)	14 (46.7)	1.7 [0.49, 6.00]	0.401
Shoulder pain VAS	Week 1	10 (31.3)	7 (23.3)	1.6 [0.51, 4.90]	0.431
	Week 4	21 (65.6)	14 (46.7)	2.1 [0.58, 7.72]	0.253
Fatigue VAS	Week 1	6 (18.8)	5 (16.7)	1.3 [0.33, 4.74]	0.733
	Week 4	19 (59.4)	16 (53.3)	1.1 [0.32, 3.78]	0.885
C-reactive protein	Week 1	24 (75.0)	21 (70.0)	1.4 [0.41, 4.84]	0.585
	Week 4	31 (96.9)	21 (70.0)	2.0 [0.48, 8.45]	0.338

[a] Response is defined as improvement of ≥70% from baseline.
[b] Estimates are odds ratios with confidence limits from a logistic regression model.

Supplementary Table S3 Number (%) of Patients With Adverse Events (Safety Population)

MedDRA (version 16.0) System Organ Class Preferred Term	Double-Blind Phase		Open-Label Phase	
	Modified Release Prednisone (N=32)	Immediate Release Prednisone (N=30)	Modified Release Prednisone (N=11)	Immediate Release Prednisone (N=16)
Patients with at least one AE	19 (59.4)	9 (30.0)	7 (63.6)	8 (50.0)
Blood and lymphatic system disorders	3 (9.4)	0	1 (9.1)	1 (6.3)
Leukocytosis	2 (6.3)	0	0	0
Lymphopenia	0	0	1 (9.1)	0
Pancytopenia	1 (3.1)	0	0	1 (6.3)
Congenital, familial and genetic disorders	1 (3.1)	0	0	0
Type V hyperlipidaemia	1 (3.1)	0	0	0
Ear and labyrinth disorders	0	1 (3.3)	1 (9.1)	1 (6.3)
Hypoacusis	0	1 (3.3)	1 (9.1)	0
Meniere's disease	0	0	0	1 (6.3)
Vertigo	0	1 (3.3)	0	0
Eye disorders	0	0	0	1 (6.3)
Dry eye	0	0	0	1 (6.3)
Gastrointestinal disorders	5 (15.6)	0	2 (18.2)	0
Abdominal pain	1 (3.1)	0	1 (9.1)	0
Abdominal pain upper	2 (6.3)	0	0	0
Gastric disorder	1 (3.1)	0	0	0
Gastritis	0	0	1 (9.1)	0
Vomiting	1 (3.1)	0	0	0
General disorders and administration site conditions	0	1 (3.3)	0	0
Oedema peripheral	0	1 (3.3)	0	0
Infections and infestations	3 (9.4)	0	1 (9.1)	4 (25.0)
Bronchitis	1 (3.1)	0	0	0
Gastroenteritis viral	0	0	0	1 (6.3)
Gingivitis	1 (3.1)	0	0	0
Nasopharyngitis	0	0	1 (9.1)	2 (12.5)
Rhinitis	0	0	0	1 (6.3)

MedDRA (version 16.0) System Organ Class Preferred Term	Double-Blind Phase Modified Release Prednisone (N=32)	Double-Blind Phase Immediate Release Prednisone (N=30)	Open-Label Phase Modified Release Prednisone (N=11)	Open-Label Phase Immediate Release Prednisone (N=16)
Vaginal infection	1 (3.1)	0	0	0
Injury, poisoning and procedural complications	0	0	1 (9.1)	0
Contusion	0	0	1 (9.1)	0
Post-traumatic pain	0	0	1 (9.1)	0
Investigations	3 (9.4)	2 (6.7)	2 (18.2)	0
Blood pressure systolic increased	0	0	1 (9.1)	0
Blood cholesterol increased	1 (3.1)	0	0	0
Blood glucose increased	1 (3.1)	0	0	0
Blood uric acid increased	1 (3.1)	0	0	0
C-reactive protein increased	0	0	1 (9.1)	0
ECG signs of myocardial ischaemia	0	1 (3.3)	0	0
Electrocardiogram ST segment abnormal	0	1 (3.3)	0	0
Electrocardiogram T wave inversion	0	1 (3.3)	0	0
Hepatic enzyme increased	1 (3.1)	0	0	0
Platelet count decreased	1 (3.1)	0	0	0
Metabolism and nutrition disorders	6 (18.8)	1 (3.3)	2 (18.2)	1 (6.3)
Diabetes mellitus	1 (3.1)	0	1 (9.1)	0
Diabetes mellitus inadequate control	0	1 (3.3)	0	0
Hypercholesterolaemia	1 (3.1)	0	1 (9.1)	0
Hyperglycaemia	1 (3.1)	0	0	1 (6.3)
Hyperkalemia	2 (6.3)	0	0	0
Hypertriglyceridaemia	1 (3.1)	0	0	0
Musculoskeletal and connective tissue disorders	5 (15.6)	3 (10.0)	1 (9.1)	3 (18.8)
Arthralgia	2 (6.3)	0	1 (9.1)	0
Back pain	0	1 (3.3)	0	2 (12.5)
Osteoarthritis	1 (3.1)	0	0	1 (6.3)
Osteopenia	1 (3.1)	0	0	1 (6.3)
Pain in extremity	1 (3.1)	0	0	0
Polymyalgia rheumatica[a]	1 (3.1)	1 (3.3)	0	0
Tendonitis	0	1 (3.3)	0	0
Nervous system disorders	1 (3.1)	2 (6.7)	1 (9.1)	1 (6.3)
Burning sensation	0	1 (3.3)	0	0
Carpal tunnel syndrome	0	0	0	1 (6.3)
Dizziness	0	0	1 (9.1)	0
Headache	0	1 (3.3)	0	0

MedDRA (version 16.0) System Organ Class Preferred Term	Double-Blind Phase Modified Release Prednisone (N=32)	Double-Blind Phase Immediate Release Prednisone (N=30)	Open-Label Phase Modified Release Prednisone (N=11)	Open-Label Phase Immediate Release Prednisone (N=16)
Syncope	1 (3.1)	0	0	0
Psychiatric disorders	2 (6.3)	0	1 (9.1)	1 (6.3)
Insomnia	1 (3.1)	0	1 (9.1)	1 (6.3)
Sleep disorder due to general medical condition, insomnia type	1 (3.1)	0	0	0
Renal and urinary disorders	0	0	1 (9.1)	0
Dysuria	0	0	1 (9.1)	0
Respiratory, thoracic and mediastinal disorders	0	0	1 (9.1)	0
Dyspnoea	0	0	1 (9.1)	0
Skin and subcutaneous tissue disorders	1 (3.1)	0	2 (18.2)	0
Night sweats	0	0	1 (9.1)	0
Rash	0	0	1 (9.1)	0
Swelling face	1 (3.1)	0	0	0
Surgical and medical procedures	1 (3.1)	0	0	0
Tooth extraction	1 (3.1)	0	0	0
Vascular disorders	2 (6.3)	1 (3.3)	0	0
Hypertension	2 (6.3)	0	0	0
Temporal arteritis	0	1 (3.3)	0	0

Note: A patient may have more than one adverse event in any category.
[a] As reported by the Investigator.