**SUPPLEMENTARY INFORMATION**

**Supplementary Methods**

***Protocol modifications***

The following protocol modifications were made before patient recruitment. To permit safety assessment results to be obtained prior to study drug administration, samples for hematology, blood chemistry and urinalysis were obtained, and physical examination, a urine pregnancy test and electrocardiography assessments were performed on the day prior to study drug administration as well as on the day of drug administration (prior to patients receiving the drug). Owing to organizational needs for patients in the treatment group, a time window of ±1 day for visits on day 8 and day 36 and a time window of ±2 days for visits on day 43 and day 57 were allowed. In order to measure peak concentration of the study drug, the first PK blood samples, which were scheduled to be taken 2 hours after study drug administration, had to be collected within ±10 minutes of this time frame. All other PK samples had a time window of ±1 hour. For the untreated reference group, a time window of ±1 day was granted for telephone follow-up visits on days 8, 15 and 29 and a time window of ±2 days on day 43 and day 57. The time interval for bone biomarker collection and sclerostin measurement was prolonged to allow a time window of ±1 hour instead of ±15 minutes. The method of assessing body temperature was changed such that it was no longer limited to oral measurement. Tri-iodothyronine, thyroxine and thyroid-stimulating hormone (TSH) were added to the blood chemistry analysis to monitor thyroid gland function (tri-iodothyronine was only measured if thyroxine was out of normal range; thyroxine was only measured if TSH was out of normal range). Measurement of vitamin D analyte was included in the blood chemistry analysis at screening. BPS804 was administered intravenously; therefore, the need for a meal record for PK analyses was removed.

Additional modifications were made to the eligibility criteria based on information from recently completed chronic preclinical toxicology studies of BPS804 (unpublished data). Specifically, thyroid gland differences noted in a 13-week study of BPS804 in cynomolgus monkeys were not observed following chronic dosing with BPS804 in a 26-week study using the same model. The effects observed in the 13-week study were therefore considered unlikely to be BPS804-related. Therefore, study exclusion criteria based on previous thyroid diseases in the original study protocol were relaxed. Specifically, patients with abnormal thyroid function or those who had undergone thyroidectomy could be included under certain conditions (details are provided in the **Materials and Methods** section). This facilitated recruitment of patients to the study. Further modifications were made to facilitate recruitment, based on experience gained in the first few weeks of screening. For entry criteria, the upper age limit was raised from 45 years to 75 years and seasonal vitamin D3 levels were defined. There was no perceived risk of potential interactions between nutritional substances (e.g. xanthine or alcohol) and the BPS804 antibody; therefore, the dietary restrictions defined in the original study protocol were deleted.

***Study stopping rules***

Dose escalation was to be halted, the trial was to be placed on hold and, on review of study data and discussion with the investigator, the study was to be terminated if any of the following occurred: one or more patients had a severe AE (grade 3 or higher) that was judged to be treatment-related; two or more patients had a similar AE of at least moderate severity that was judged to be treatment-related; the investigator and the sponsor considered that the number and/or severity of AEs justified discontinuation of the study; or the sponsor unilaterally requested it.

**Supplementary Table 1.**

Incidence of adverse events in the BPS804 treatment group and the reference group by preferred term.

|  |  |  |  |
| --- | --- | --- | --- |
| Adverse event, n (%) | BPS804  (*n* = 9) | Reference  (*n* = 5) | Total  (*N* = 14) |
| Total | 9 (100) | 4 (80.0) | 13 (92.9) |
| Headache | 2 (22.2) | 2 (40.0) | 4 (28.6) |
| Influenza | 2 (22.2) | 1 (20.0) | 3 (21.4) |
| Arthralgia | 1 (11.1) | 1 (20.0) | 2 (14.3) |
| Fatigue | 2 (22.2) | 0 (0.0) | 2 (14.3) |
| Abdominal pain upper | 0 (0.0) | 1 (20.0) | 1 (7.1) |
| Ankle fracture | 1 (11.1) | 0 (0.0) | 1 (7.1) |
| Bursitis | 1 (11.1) | 0 (0.0) | 1 (7.1) |
| Cough | 1 (11.1) | 0 (0.0) | 1 (7.1) |
| Diarrhea | 1 (11.1) | 0 (0.0) | 1 (7.1) |
| Excoriation | 1 (11.1) | 0 (0.0) | 1 (7.1) |
| Foot fracture | 1 (11.1) | 0 (0.0) | 1 (7.1) |
| Fungal skin infection | 1 (11.1) | 0 (0.0) | 1 (7.1) |
| Goiter | 0 (0.0) | 1 (20.0) | 1 (7.1) |
| Insomnia | 0 (0.0) | 1 (20.0) | 1 (7.1) |
| Joint dislocation | 1 (11.1) | 0 (0.0) | 1 (7.1) |
| Laryngitis | 1 (11.1) | 0 (0.0) | 1 (7.1) |
| Muscle strain | 1 (11.1) | 0 (0.0) | 1 (7.1) |
| Musculoskeletal pain | 0 (0.0) | 1 (20.0) | 1 (7.1) |
| Myalgia | 1 (11.1) | 0 (0.0) | 1 (7.1) |
| Nausea | 1 (11.1) | 0 (0.0) | 1 (7.1) |
| Oropharyngeal pain | 1 (11.1) | 0 (0.0) | 1 (7.1) |
| Pain | 0 (0.0) | 1 (20.0) | 1 (7.1) |
| Pain in extremity | 0 (0.0) | 1 (20.0) | 1 (7.1) |

**Supplementary Table 1 (continued).**

|  |  |  |  |
| --- | --- | --- | --- |
| Adverse event, n (%) | BPS804  (*n* = 9) | Reference  (*n* = 5) | Total  (*N* = 14) |
| Pharyngitis | 1 (11.1) | 0 (0.0) | 1 (7.1) |
| Presyncope | 1 (11.1) | 0 (0.0) | 1 (7.1) |
| Prostatitis | 0 (0.0) | 1 (20.0) | 1 (7.1) |
| Scapula fracture | 1 (11.1) | 0 (0.0) | 1 (7.1) |
| Sinusitis | 0 (0.0) | 1 (20.0) | 1 (7.1) |
| Temperature intolerance | 1 (11.1) | 0 (0.0) | 1 (7.1) |
| Viral upper respiratory tract infection | 0 (0.0) | 1 (20.0) | 1 (7.1) |
| Vomiting | 1 (11.1) | 0 (0.0) | 1 (7.1) |
| Vulvovaginal candidiasis | 0 (0.0) | 1 (20.0) | 1 (7.1) |