


# Granulocyte–macrophage colony-stimulating factor (GM-CSF) as a therapeutic target in psoriasis: randomized, controlled investigation using namilumab, a specific human anti-GM-CSF monoclonal antibody\*

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**Linked Comment:** Crowley. *Br J Dermatol* 2019; **180**:1286–1287.

## Summary

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### Accepted for publication

6 September 2018

### Funding sources

This study was funded and sponsored by Takeda Pharmaceutical Company

### Conflicts of interest

Statements are listed in the Appendix.

\*Plain language summary available online

DOI 10.1111/bjd.17195

**Background** The relevance of granulocyte–macrophage colony-stimulating factor (GM-CSF) in the management of psoriasis has not been studied previously. GM-CSF is important in the initiation and maintenance of chronic inflammatory processes.

**Objectives** To investigate the clinical use of GM-CSF neutralization by evaluating the efficacy and safety of namilumab (AMG203), a monoclonal antibody GM-CSF inhibitor, in patients with moderate-to-severe plaque psoriasis.

**Methods** A phase II, multicentre, randomized, double-blind, placebo-controlled, parallel-group, dose-finding, proof-of-concept study (NEPTUNE) was conducted. Four doses of namilumab (20, 50, 80 and 150 mg, via subcutaneous injection) were compared with placebo. Assessment of the primary end point – the proportion of patients achieving  $\geq 75\%$  reduction in Psoriasis Area and Severity Index (PASI 75 treatment response) – was performed at week 12. Exploratory investigation at the tissue level was conducted in a subset of the overall study population. The trial was registered with the number NCT02129777.

**Results** In total, 122 patients were enrolled and 106 (86.9%) completed the double-blind treatment; 16 (13.1%) prematurely discontinued study medication. Serum concentration–time profiles were as expected for subcutaneous delivery of an IgG1 monoclonal antibody, and exposure increased proportionally with dose elevation. The number of patients showing PASI 75 treatment response at week 12 was low in all groups; no significant difference was recorded in this end point between placebo and any namilumab group. Similar outcomes were recorded for other clinical study end points. Moreover, no significant treatment-related changes from baseline were observed in laboratory investigations of cell types or subpopulations, or cytokines relevant to inflammatory pathways in psoriasis.

**Conclusions** GM-CSF blockade is not critical for suppression of key inflammatory pathways underlying psoriasis.

**What's already known about this topic?**

- Blockade of granulocyte–macrophage colony-stimulating factor (GM-CSF) signalling is effective in rheumatoid arthritis.
- Potential relevance for psoriasis has been indicated by the presence of GM-CSF in psoriasis-related skin blister fluid and the serum of patients with psoriasis, and also by elevated expression in psoriatic skin lesions.

**What does this study add?**

- This is the first clinical investigation into the efficacy and safety of an anti-GM-CSF antibody in plaque psoriasis.
- This study provides no evidence of benefit for GM-CSF neutralization in the treatment of plaque psoriasis.
- Safety profiles were comparable in the placebo and anti-GM-CSF treatment groups, and no incidences of pulmonary alveolar proteinosis or clinically significant changes in lung function were recorded throughout the short-term duration of study treatment.
- Overall, the findings point to key differences in the role of GM-CSF in the pathogenesis of psoriasis and rheumatoid arthritis.

Psoriasis is a chronic, immune-mediated inflammatory disease associated with significant impairment of physical and psychological quality of life.<sup>1,2</sup> Present understanding of its pathogenesis places importance on interleukin (IL)-23/IL-17 cytokines and T-lymphocyte activation, with the proinflammatory cytokine IL-17 as the key pathogenic driver.<sup>3</sup>

Recent clinical studies have demonstrated the potential for effective control of psoriasis with specific anti-IL-23 therapy.<sup>4,5</sup> Moreover, systemic IL-17 inhibition<sup>6–8</sup> now appears to offer patients the best therapeutic prospect (speed of onset and overall clinical effect). Despite these treatment advances, investigation of agents with new mechanisms of action is still considered crucial for full characterization of relevant inflammatory pathways and future clinical practice.

As a major immune modulator, granulocyte–macrophage colony-stimulating factor (GM-CSF)<sup>9</sup> is of potential relevance in psoriasis. Within the skin, GM-CSF is produced by activated T lymphocytes, myeloid cells, endothelial cells, macrophages, fibroblasts and keratinocytes.<sup>10,11</sup> It is detectable in psoriasis-related skin blister fluid and in the serum of patients with psoriasis.<sup>12</sup> Its expression is elevated in psoriatic lesions.<sup>13</sup> Supporting a key role in pathogenesis, GM-CSF neutralization in a flaky skin mouse model of psoriasis has been shown to inhibit neutrophil migration to the skin with alleviation of psoriasiform features in the skin.<sup>14</sup> Additionally, GM-CSF treatment of neutropenia in patients with psoriasis can trigger maculopapular eruptions and exacerbation of the disease.<sup>15,16</sup> Together, these features have led to the hypothesis that GM-CSF neutralization in patients with psoriasis could offer clinical benefit through inhibition of keratinocyte proliferation,<sup>17,18</sup> inhibition of cellular infiltration of the skin and key

inflammatory cytokines (such as IL-23, IL-12 and IL-17)<sup>19–21</sup> and inhibition of vascularization and angiogenesis.<sup>22</sup>

Namimumab (AMG203) is a human IgG1 monoclonal antibody that potently and specifically neutralizes human and macaque GM-CSF (Takeda: data on file). In the study reported here, the efficacy and safety of namimumab were compared with those of placebo in a 12-week evaluation of treatment for patients with moderate-to-severe plaque psoriasis, providing the basis for a first reported investigation into the relevance of GM-CSF as a therapeutic target for psoriasis.

**Patients and methods****Study population**

This study involved patients with chronic, stable, moderate-to-severe plaque psoriasis. Each patient provided written informed consent for participation. Details of the inclusion and exclusion criteria, and medications restricted during the study, are provided in the Appendix S1 (see Supporting Information) and in the ClinicalTrials.gov registry (NCT02129777).

**Study design and conduct**

This was a phase II, multicentre, randomized, double-blind, placebo-controlled, parallel-group, dose-finding, proof-of-concept study conducted at 17 active sites in Canada, Denmark, Germany, Latvia and Poland. The aim was to compare four dose levels of namimumab (20, 50, 80 and 150 mg) with placebo; patients were randomized to the treatment groups on a

1 : 1 : 1 : 1 : 1 basis. Study medication was administered subcutaneously at baseline and at weeks 2, 6 and 10, and included a loading (double) dose for each group at baseline. Use of concomitant medication was permitted during this study, but only in accordance with restrictions noted in the study protocol (Appendix S1; see Supporting Information). Assessment of the primary end point, using the Psoriasis Area and Severity Index (PASI),<sup>23</sup> was carried out at week 12.

Biopsy sampling was required from a maximum of five patients in each of the study treatment groups (including the placebo group). This was facilitated by participation of these patients in a biopsy substudy, which required additional informed consent. Enrolment of consenting patients was completed consecutively, with treatment blinding maintained through supervision of the process by an individual not involved in any other aspect of the investigation. Biopsies were taken from a single plaque for each participant at baseline, week 2 and week 12; a nonlesional tissue sample was also taken at baseline.

The study protocol was approved by an institutional review board or ethics committee at each participating site (the full trial protocol is available in Appendix S1; see Supporting Information). Study procedures were conducted in accordance with the ethical principles of the Declaration of Helsinki.

### Efficacy and safety evaluations

The primary efficacy end point was the proportion of patients achieving  $\geq 75\%$  reduction in PASI score from baseline to week 12 (PASI 75 treatment response). Clinical responses over this period were also evaluated with secondary end points utilizing PASI and static Physician's Global Assessment (sPGA) scores and Nail Psoriasis Severity Index (NAPSI). Patient-reported outcomes were assessed using an electronic diary, which also included dermatologically relevant and general quality-of-life questionnaires. Exploratory investigations were undertaken on tissue samples from patients providing biopsies and on blood samples obtained from all enrolled patients. In addition, blood samples were used for pharmacokinetic (PK) analysis after dosing with namilumab and to examine systemic pharmacodynamic (PD) interactions with its target GM-CSF. Further details on these assessments are included in Appendix S1 and Table S1 (see Supporting Information).

Safety was evaluated on the basis of adverse events (AEs) and injection-site reactions, physical examinations, clinical laboratory tests, electrocardiograms and vital signs. Exploratory monitoring for signs of pulmonary alveolar proteinosis<sup>24</sup> was conducted throughout the study using pulse oximetry, lung function tests, chest X-ray and the Medical Research Council Breathlessness Scale.<sup>25</sup>

### Statistical aspects

The sample size was based on the primary efficacy end point (PASI 75 treatment response) and determined, using differing assumptions, for comparisons between placebo and

namilumab treatments and between namilumab dose levels. Assuming a placebo response of  $< 10\%$  for this end point, 24 patients per treatment group would provide  $\geq 95\%$  power to detect differences  $\geq 70\%$  between the placebo and namilumab treatments (Fisher exact test and type I error 0.0125, i.e. 0.05 divided by four doses). Similarly, with 24 patients per treatment group,  $\geq 60\%$  power was expected for detecting differences  $\geq 35\%$  between namilumab dose levels (Fisher exact test and type I error 0.05).

Reporting of efficacy was based on the full analysis set of patients – defined as those receiving at least one dose of study medication and providing at least one postbaseline PASI assessment. A supporting sensitivity analysis was also carried out on the primary end point data, examining the incidence of PASI 75 response by clinic visit, with missing responses treated as 'nonresponses'.

## Results

In total, 122 patients were enrolled into this study, of whom 106 (86.9%) completed the double-blind treatment phase between 30 March 2014 (date first patient signed informed consent form) and 23 February 2016 (date of last patient's last clinic visit). Sixteen patients (13.1%) prematurely discontinued study medication (Fig. 1); 11 of the discontinuations were due to lack of efficacy, one involved worsening of psoriasis [reported as a treatment-emergent AE (TEAE)] and one was due to an unplanned pregnancy. Biopsy sampling was performed for 21 patients in total.

### Patient characteristics

The overall study population comprised 69% male and 31% female patients, and the mean age was 40.6 years (Table S2; see Supporting Information). The baseline demographic and disease characteristics, including disease severity, were reasonably balanced across the five treatment groups. Reflective of wide-ranging comorbidities commonly associated with psoriasis,<sup>1</sup> 86 (70.5%) of the patients reported taking medications for skin-related disorders and other conditions before enrolment, with exposure to biologics or other targeted treatments for psoriasis (including etanercept, adalimumab and apremilast) reported for 11 (9.0%) patients. During the course of this study, patients were restricted in the use of treatment agents other than the study medication. However, use of such concomitant medication was begun prior to study baseline by 10 (8.2%) of the enrolled patients and after the baseline clinic visit by 52 (42.6%) patients – treatments required for nonskin conditions in all cases.

### Pharmacokinetic and pharmacodynamic findings

Following initial dosing of namilumab (day 0), serum concentration–time profiles were as expected for subcutaneous administration of an IgG1 monoclonal antibody. Exposure in each of the four namilumab treatment groups increased

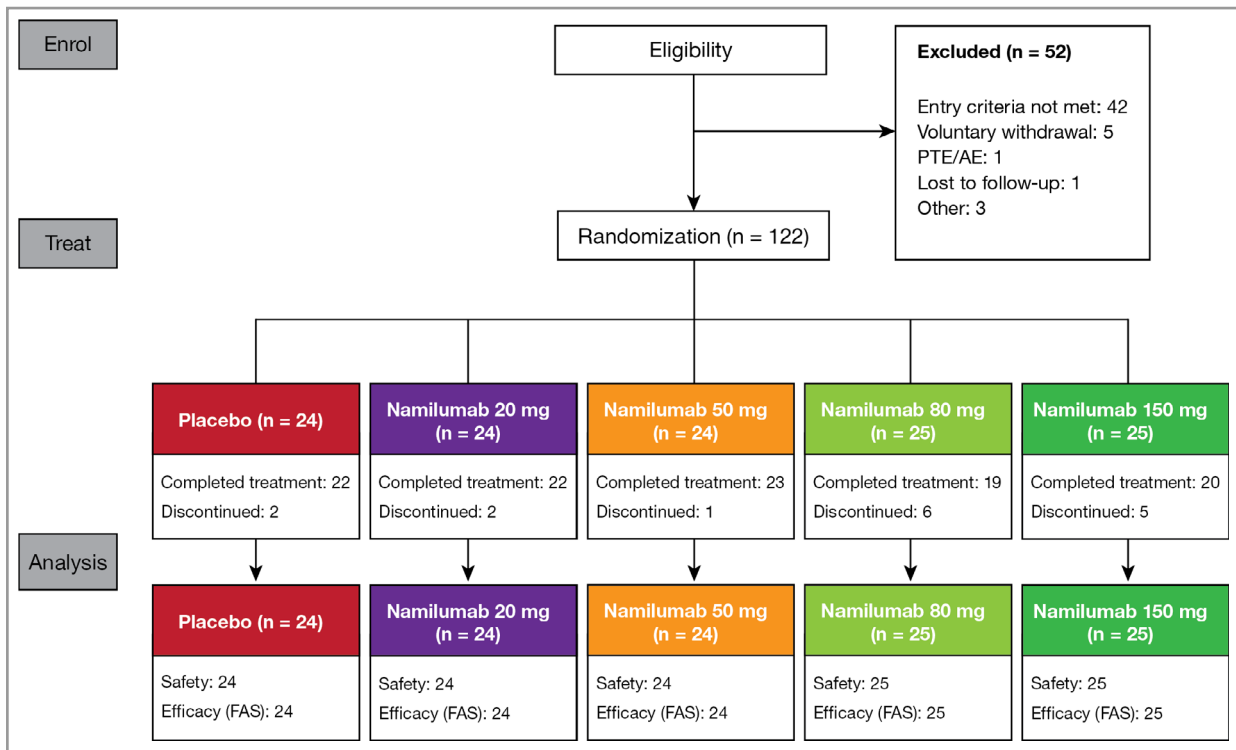


Fig 1. Patient flow diagram. PTE/AE, pretreatment event/adverse event. FAS, full analysis set.

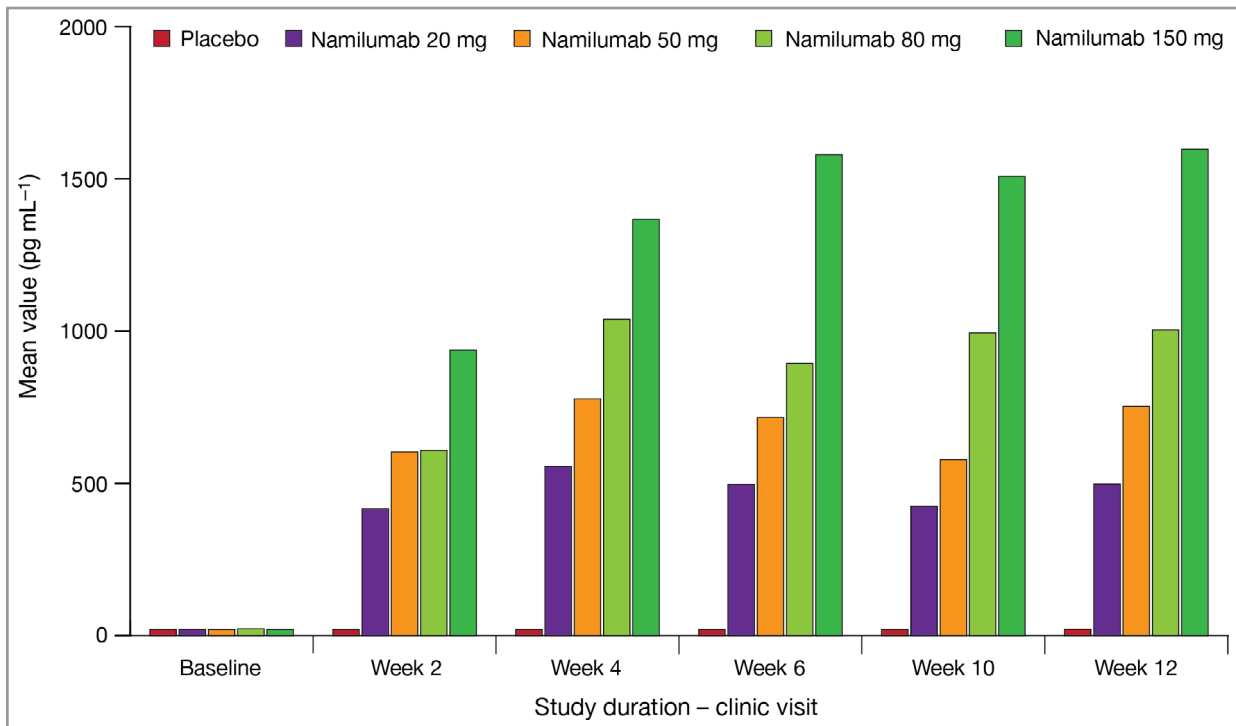


Fig 2. Plasma levels of total granulocyte-macrophage colony-stimulating factor, by treatment group and time.

proportionally with dose elevation (data not shown). In contrast to the placebo group, patients treated with namilumab also showed increased plasma levels of total GM-CSF during the study (Fig. 2).

### Efficacy

At week 12 of this study, PASI 75 responses were recorded for 4.8% of patients – two in the placebo treatment group,

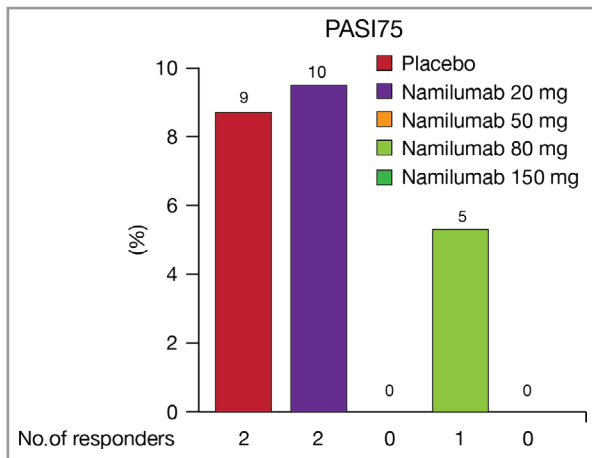


Fig 3. Psoriasis Area and Severity Index (PASI): percentage and number of responders with  $\geq 75\%$  improvement in PASI (PASI 75) in the patient treatment groups at week 12 of the study. Treatment group percentage values were determined for 105 evaluable patients at week 12 (23 in the placebo group and 21, 22, 19 and 20 in the namilumab 20-mg, 50-mg, 80-mg and 150-mg groups, respectively). No statistically significant difference was recorded in comparisons between the namilumab and placebo treatment groups.

two in the 20-mg namilumab group and one in the 80-mg namilumab group (Fig. 3). There was no statistically significant difference between the study treatment groups. Additionally, the mean change in PASI score from baseline to week 12 was similar for each treatment group, with no statistically significant difference observed in comparisons of the placebo cohort with the four namilumab cohorts (Fig. 4a).

Corresponding changes were noted at week 12 for sPGA (Fig. 4b), and no significant trends were evident in data from other clinical end points – including affected body surface area; NAPSI; quality of life as denoted by Dermatology Life Quality Index, EuroQol-5D and Short Form 36 questionnaires; or patient diary assessments of itching, pain and morning stiffness (summary of results shown in Table S3; see Supporting Information).

No statistically significant treatment-related changes from baseline were recorded in laboratory analysis of blood or skin biopsy cell types or subpopulations, or cytokine levels. A primary polyclonal antibody (Bioss Antibodies, Woburn, MA, U.S.A.) confirmed the presence of GM-CSF within psoriatic plaques; in contrast, GM-CSF was not detected in control tissue. Sources of the GM-CSF appeared to be mast cells and neutrophils. Low levels of GM-CSF (colony-stimulating factor 2, CSF2) RNA expression were observed within the plaque tissue samples. RNA analysis also showed significant expression of the GM-CSF receptor  $\alpha$ - and  $\beta$ -subunits, which together comprise the functional heterodimer on receptor-bearing cells.<sup>11</sup>

### Safety

During the course of this study, 50 of 122 patients (41.0%) reported a total of 75 TEAEs, although the incidence was higher in placebo-treated patients (63%) than in the namilumab groups (42%, 33%, 32% and 36% in the 20-mg, 50-mg, 80-mg and 150-mg groups, respectively). Infections and infestations comprised the most common events:

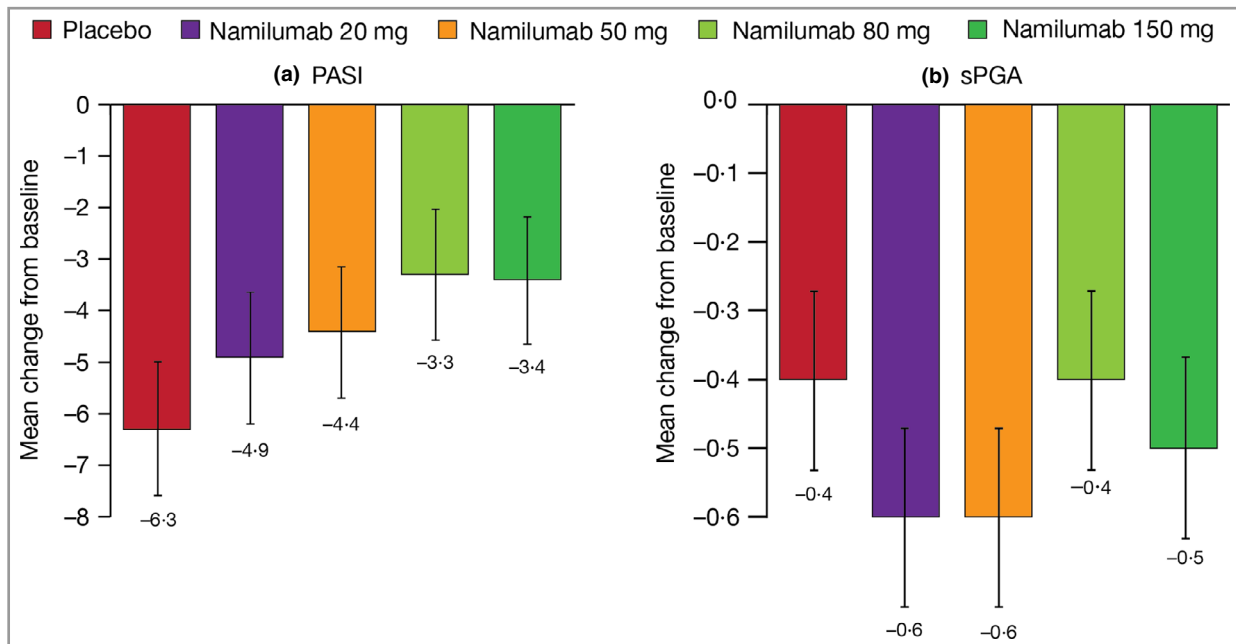


Fig 4. (a) Psoriasis Area and Severity Index (PASI): mean change from baseline to week 12 ( $\pm$  standard error) and (b) static Physician's Global Assessment (sPGA): change from baseline to week 12 for the adjusted mean ( $\pm$  standard error). No statistically significant difference was recorded in comparisons between the namilumab and placebo treatment groups.

nasopharyngitis in eight patients (6.6%) and upper respiratory tract infection in four patients (3.3%) were reported with the greatest frequency. No clinically meaningful trends were evident across the study treatment groups.

TEAEs related to study medication were reported for 13 patients (10.7%): three (13%) in the placebo treatment group compared with five (21%), one (4%), one (4%) and three (12%) in the 20-mg, 50-mg, 80-mg and 150-mg namilumab treatment groups, respectively. Of these events, infections and infestations were the most common, being reported by seven patients (5.7%). These events included single cases of erysipelas and groin abscess in the placebo treatment group; single cases of herpes simplex, herpes zoster and oral herpes in the 20-mg namilumab group; nasopharyngitis in the 80-mg namilumab group; and cystitis in the 150-mg namilumab group. TEAEs were mild in severity for 34 patients (27.9%), moderate for 14 (11.5%) and severe for two (1.6%). The severe TEAEs were both recorded for patients receiving 150 mg namilumab: one involved a case of 'headache' (related to the study medication), which resolved without change of the medication dose, and one involved 'worsening of psoriasis' (not related to study medication), which led to discontinuation from the study.

Two patients (both in the placebo treatment group) experienced serious AEs. One case involved hypertensive crisis for a 51-year-old man; this AE was recorded as not related to study medication and, following hospital treatment, was resolved on the day of occurrence. The second case, also recorded as not related to study medication, involved serum creatinine elevation for a 70-year-old man.

No instances of pulmonary alveolar proteinosis were recorded in this study. Patients showed no clinically significant changes in lung function throughout the (short-term) duration of study treatment.

Namilumab-binding antibodies were detected in blood samples from 10 patients (8.2%) at one or more of the sampling time points (baseline, week 6 and week 12). However, no discernible effect of the binding antibodies was found on PK in these cases. Of the total 18 blood samples positive for binding antibodies, only one sample showed the presence of neutralizing antibodies ( $4\text{-}\mu\text{g mL}^{-1}$  drug tolerance limit recorded in assay validation).

## Discussion

No clinical evidence has so far been made available to support the relevance of GM-CSF as a therapeutic target for psoriasis. This report outlines an investigation into the potential use of a monoclonal antibody GM-CSF inhibitor (namilumab, AMG203) in patients with moderate-to-severe plaque psoriasis. The findings from this study suggest that blockade of GM-CSF pathways is not a viable approach for the management of patients with psoriasis. Notably, no significant changes were detected between baseline and week 12 in exploratory biomarker investigations with blood and skin biopsy tissue. This outcome was striking not only because baseline cytokine levels

for the study patients were comparable with those reported in other published studies,<sup>26,27</sup> but also because of the potentially wide range of lymphoid and myeloid cell subpopulations thought to be affected by GM-CSF neutralization.<sup>11</sup>

Taking account of therapies already available for psoriasis, new agents under development should ideally show fast onset of action and efficacy in terms of PASI 75 response comparable with IL-17 inhibitors.<sup>7,8</sup> These expectations were incorporated into the NEPTUNE study design, by inclusion of a 12-week treatment evaluation period and, furthermore, ensuring adequate power for potential detection of differences  $\geq 70\%$  between namilumab and placebo treatments. Supporting the overall integrity of the study, the PASI 75-level placebo response rate (9%) was consistent with the sample-size assumptions and the range reported for other randomized, controlled psoriasis studies involving biological agents.<sup>28</sup>

Given the low number of patients showing a PASI 75 response in the active-treatment groups, mirrored by lack of namilumab effect at the cellular level, we consider it very unlikely that a study with a larger sample size would demonstrate significant namilumab efficacy in patients with plaque psoriasis. Continued treatment of 60 NEPTUNE study patients for an additional 20 weeks in an open-label treatment regimen with namilumab failed to show an increase in the number of PASI 75 responders. Consequently, any new study conducted with namilumab may well risk unnecessary exposure of the patients to ineffective treatment.

No clinically significant safety signal was detected for namilumab in this study. The overall incidences of TEAEs for namilumab and placebo treatments were comparable with other published figures,<sup>29</sup> and the majority of TEAEs (mild in nature) were not related to the study medication.

Prior to the NEPTUNE study no published data were available to indicate likely levels of anti-GM-CSF treatment responses in patients with psoriasis [such data being accessible only for patients with rheumatoid arthritis (RA)].<sup>11,30</sup> In planning this exploratory phase II investigation with namilumab, a full-analysis-set approach to efficacy evaluation offered the potential to characterize treatment responses free of imputed data and their effects. However, the robustness of the findings from this approach was tested with a sensitivity analysis including imputed missing data for the primary end point. Consistent results were recorded in both analyses.

The same production batch of namilumab antibody was used in the NEPTUNE psoriasis study and in a parallel phase IIb study involving patients with moderate-to-severe RA – the NEXUS study (NCT02379091). Appropriate potency for the batch had been confirmed by *in vitro* assays and stability data. In contrast to the findings outlined here for patients with psoriasis, recent results from the NEXUS study – obtained using a comparable 20–150-mg dose range – have demonstrated high efficacy in patients with RA (publication in preparation). These results are also in line with a previous report on the phase Ib PRIORA study<sup>30</sup> in patients with RA.

Binding of namilumab to its GM-CSF target duly occurred *in vivo* within the blood of NEPTUNE study patients.



Administration of namilumab was found to elevate plasma concentrations of total (free and bound) GM-CSF in proportion to increasing dose. Such elevated levels result from *in vivo* binding of GM-CSF with the antibody. GM-CSF is stabilized by the complexes so formed. Therefore, increased doses of namilumab lead to dose-dependent increases in the amount of GM-CSF detectable within the blood. Finally, GM-CSF clearance occurs at a similar rate to that of the namilumab antibody. This phenomenon has been observed in three prior studies within the namilumab development programme (two studies involving healthy volunteers and one study involving patients with mild-to-moderate RA)<sup>30</sup> and in the binding of other anticytokine antibodies to their respective targets.<sup>31,32</sup>

Subcutaneous doses of namilumab were selected for the NEPTUNE and NEXUS studies using an integrative approach with clinical and nonclinical PK and PD data.<sup>30</sup> Furthermore, similarities between namilumab and anti-tumour necrosis factor (TNF)- $\alpha$  antibodies were used to suggest an efficacious concentration range in the treatment of psoriasis. This range was converted into human doses using a population PK model developed with data from two phase I studies (one involving healthy volunteers and the other a phase Ib study involving patients with RA).<sup>30</sup> Consequently, namilumab doses were selected with the intent to cover low, medium and high efficacious exposures. It is important to emphasize that the highest selected dose level (150 mg) constitutes the 'maximal feasible dose' for subcutaneous injection in a 1-mL volume (i.e. formulation concentration of 150 mg mL<sup>-1</sup>). Additionally, an initial 'loading dose' was included in the NEPTUNE study in order to reach early steady-state exposure, thereby supporting an early onset of action – as seen with TNF antagonists as well as agents targeting the IL-17–IL-23 axis in patients with psoriasis.

Following subcutaneous injection of namilumab, tissue distribution was expected to occur in a similar fashion to that of other IgG monoclonal antibody agents. As estimated from pharmacological modelling,<sup>33</sup> the proportion of a monoclonal antibody found in skin is 15.7% of that in the blood. To our knowledge, the coefficient for monoclonal antibody partitioning between blood and psoriatic lesion (inflamed) skin tissue is not known. However, IgG antibody partitioning into joints affected by RA is reported to be 18–28%.<sup>34</sup> On this basis, namilumab dosing in the psoriasis study was expected to result in the presence of the antibody within skin lesion tissue, and to bring about neutralization of GM-CSF through local target engagement (analogous to interactions clearly demonstrated in the blood). Supporting this view, the quoted partitioning characteristics also apply to anti-TNF and anti-IL-17 antibodies that are now well established as being clinically effective in the treatment of psoriasis. Moreover, the recent demonstration of highly positive clinical efficacy for namilumab in patients with RA (NEXUS study, manuscript in preparation) is consistent with adequate bioavailability and partitioning of this particular antibody into inflamed (synovial) tissues, leading to effective local target engagement.

Evaluation of namilumab treatment in patients with psoriasis was undertaken on the premise that GM-CSF blockade would take effect 'upstream' of other important driver mediators such as IL-23 and IL-17. Blockade of GM-CSF was considered likely to bring about broad suppression of inflammatory processes within the skin, but this has not been borne out by the NEPTUNE study findings.

Differentiation of naive CD4<sup>+</sup> T helper (Th) lymphocytes is recognized as a key feature in the pathogenesis of psoriasis, and the IL-23–Th17 axis is now considered to control T-cell production of the 'driver' pathogenic cytokine IL-17.<sup>35</sup> Recent investigation on human Th cell subsets reveals that expression of IL-17 is promoted by the IL-23–Th17 cell axis, and constrained by the IL-12–Th1 cell axis; in contrast, the opposite trends occur for GM-CSF expression.<sup>36</sup> Interestingly, an investigation into CD4<sup>+</sup> T cells from patients with RA has shown GM-CSF production to be expanded by Th1-promoting, but not Th17-promoting conditions.<sup>37</sup> Such reciprocal regulation for IL-17 and GM-CSF transcription is consistent with the absence of namilumab efficacy in the NEPTUNE study population (with IL-23–Th17 lymphocyte activity leading to predominance of IL-17 over GM-CSF in the tissues of patients with psoriasis), but high namilumab efficacy in the NEXUS study (due to IL-12–Th1 lymphocyte activity and prominence of GM-CSF in patients with RA).

In addition, the inflammatory processes of chronic psoriasis may be sustained through the combined effects of innate immune cell activation, Th17 cell cytokine production and keratinocyte activation and proliferation.<sup>3,35</sup> RNA profiling conducted on biopsy tissue samples from study patients revealed low but notable GM-CSF (CSF2) gene expression. Immunohistochemical analysis on the tissue lesion samples confirmed the presence of GM-CSF (in contrast to nonlesional tissue), with mast cells and neutrophils highlighted as the sources. These cells are capable of producing (or at least releasing) both GM-CSF and IL-17,<sup>11,38,39</sup> and are the predominant IL-17-containing cells (not T lymphocytes) in human skin.<sup>38</sup> Under these circumstances, it is probable that the overall actions of IL-17 (including stimulation of keratinocyte activation and proliferation) would contribute significantly to the perpetuation of psoriasis in skin tissues despite GM-CSF neutralization with namilumab. Such mechanisms provide further rationale for the absence of treatment efficacy in the NEPTUNE psoriasis study.

In retrospect, limitations of the study may be relevant to this outcome – these involve the dose range chosen for namilumab treatment and the study population. Comparable namilumab dose ranges were selected for use in both the NEPTUNE (psoriasis) and NEXUS (RA) studies; moreover, these ranges included the maximum possible dose (150 mg) feasible with the available formulation. While the NEXUS study results confirm potential for the chosen dose range in the treatment of RA, the lack of efficacy in patients with psoriasis may reflect a need for even higher doses (with a different formulation) to achieve any therapeutic impact through GM-CSF neutralization. Nevertheless, in view of these respective findings, the NEPTUNE study is

considered definitive for use of the namilumab anti-GM-CSF monoclonal antibody in the treatment of patients with established psoriasis (the study population). Intriguingly, there remains the possibility that anti-GM-CSF therapy could be effective during early onset of the disease. Even so, given present knowledge, any potential studies in this early setting would require consideration of the risk–benefit profile for monoclonal antibody GM-CSF blockade.

In summary, phase II evaluation of a specific monoclonal antibody GM-CSF inhibitor in the treatment of moderate-to-severe plaque psoriasis has shown no clinical benefit for the study population. These results suggest that, in contrast to RA, GM-CSF blockade is not critical for suppression of key inflammatory pathways underlying established psoriasis.

## Acknowledgments

The authors wish to thank all of the patients and investigators who contributed to this study. In addition to the authors, the overall investigator group comprised I. Hartmane (Skin and Sexually Transmitted Diseases Center, Riga 1 St Hospital, Riga, Latvia), R. Kunynetz (Ultranova Skincare and Probioty Medical Research, Barrie, ON, Canada), C. Lynde (Lynderm Research Inc., Markham, and Department of Medicine, University of Toronto, ON, Canada), J. Narbutt (Center for Dermatology, Dermoklinika, Lodz, Poland), Y. Poulin (Centre de Recherche Dermatologique du Québec Métropolitain, Quebec, QC, Canada), M. Poznanska (Specialised Dermatology Clinic, NZOZ Specderm, Bialystok, Poland), M. Raman (The Centre for Dermatology and Probioty Medical Research, Richmond Hill, ON, Canada), K. Reich (Dermatologikum Hamburg, Hamburg, Germany), L. Rosoph (North Bay Dermatology Centre Inc. and Probioty Medical Research, North Bay, ON, Canada), M. Septe (Ventspils Poliklinika, Ventspils, Latvia), D. Viba (Health Center 4, Riga, Latvia), N. Wasel (Stratica Medical and Probioty Medical Research, Edmonton, AB, Canada), C. Zachariae (Department of Dermatology and Allergy, Herlev and Gentofte Hospital, University of Copenhagen Sygehus, Hellerup, Denmark) and T.M. Falk (Dermatologikum Hamburg, Hamburg, Germany). The authors are also grateful for editorial assistance in formatting the manuscript. This expertise was provided by Caudex (Oxford, U.K.) and funded by Takeda.

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## Appendix

Conflicts of interest. K.A.P. has received consultancy, clinical research and advisory board grants from AbbVie, Akros, Allergan, Amgen, Anacor, Astellas, AstraZeneca, Baxalta, Baxter, Boehringer Ingelheim, Bristol-Myers Squibb, Can-Fite, Celgene, Dermira, Devonian, Dow Pharma, Eli Lilly, Galderma, Genentech, GSK, Janssen, Kyowa HAKKO Kirin, LEO, Medimmune, Meiji Seika Pharma, Merck (MSD), Merck-Serono, Mitsubishi Pharma, Mylan, Novartis, Pfizer, Regeneron, Roche, Sanofi-Aventis/Genzyme, Stiefel, Takeda and UCB. M.G. has received advisory board, principal investigator and consultancy grants from AbbVie, Actelion, Akros, Amgen, Boehringer Ingelheim, Bristol-Myers Squibb, Celgene, Dermira, Eli Lilly, Galderma, GSK, Janssen, LEO, Medimmune, Novartis, Pfizer, Regeneron, Roche, Sanofi-Aventis/Genzyme, UCB and Valeant. R.V. has received grant research support from AbbVie, Amgen, Centocor, Dermira, Galderma, GSK, LEO, Lilly, Takeda, Novartis, Merck, Pfizer and Regeneron; speaker's bureau honoraria from AbbVie, Amgen, Janssen, Galderma, GSK, LEO, Lilly, Novartis, Pfizer, Valeant, Actelion, Celgene, Cipher and Paladin; and consulting fees from AbbVie, Amgen, Janssen, Galderma, GSK, LEO, Lilly, Novartis, Pfizer, Valeant, Actelion, Celgene, Cipher and Paladin. J.C.S. has been a consultant or advisor for AbbVie, Celgene, Dignity Sciences, LEO Pharma, Novartis, Pierre-Fabre and Sandoz; an investigator for AbbVie, Actavis, Actelion, Amgen, GSK, Janssen, Merck, Novartis, Regeneron, Takeda and Trevi; and a speaker for AbbVie, Actavis, Astellas, Janssen, LEO Pharma, Novartis, SunFarm, Sandoz and Eli Lilly. R.J., T.W., B.H. and B.S. were all employees of Takeda during the period in which the study was conducted.

## Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's website:

**Appendix S1** Supplementary methods.

**Table S1** Efficacy: laboratory investigations.

**Table S2** Study population: baseline characteristics.

**Table S3** Efficacy: secondary end points.

**Powerpoint S1** Journal Club Slide Set.