Appendix SI

SUPPLEMENTARY METHODS

Trial design and patients

All 5 trials included adults 18–75 years of age, who were candidates for systemic therapy for stable moderate-to-severe plaque psoriasis. Subjects with known, controlled comorbid conditions and risk factors for diseases such as cardiovascular disease, other than a myocardial infarction (MI), or unstable angina, hypertension, metabolic syndrome, psychiatric illness, or smoking and alcohol abuse could participate. However, exacerbation of inflammatory bowel disease (IBD), including Crohn's disease (CD) and ulcerative colitis, was observed in earlier brodalumab studies, and patients with a known history of CD were therefore excluded from the AMAGINE-1, -2 and -3 clinical trials (15–17, S1).

In the first study (NCT00975637), a phase II randomized, double-blind, placebo-controlled trial, patients (n=198) received brodalumab (70 mg, 140 mg or 210 mg) every 2 weeks (Q2W) or placebo for 12 weeks (20). Patients could then enter its open-label long-term extension (NCT01101100) for 144 weeks where they received brodalumab 140 mg or 210 mg Q2W (13). The Phase III randomized, double-blind, placebo-controlled, 52-week AMAGINE-1 (NCT01708590) (11) trial was designed to assess efficacy, safety, and withdrawal and retreatment with brodalumab. Patients n=661) received brodalumab 140 mg (n=219) or 210 mg (n=222) Q2W or placebo (n=220). A total of 633 patients completed the initial 12-week phase and 558 patients completed the 52-week trial (11). AMAGINE-2 (NCT01708603) and AMAGINE-3 (NCT01708629) were 2 large multicentre, randomized, double-blind, placebo-controlled phase III trials, designed to compare the efficacy of brodalumab therapy with ustekinumab (12). The studies recruited 1,831 and 1,881 patients, respectively, with 1,601 (87%) completing week 52 of AMAGINE-2 and 1,656 (88%) completing week 52 of AMAGINE-3 (12).

Since relatively few patients were exposed to brodalumab 70 mg Q2W (every 2 weeks) and 280 mg every 4 weeks, these data were not included in this analysis.

Adverse events of special interest

Brodalumab disrupts the IL-17 pathway, which is important in host defence against infections pathogens, particularly extracellular bacteria and fungi. Treatment with brodalumab is consequently associated with an increased risk of infection, especially fungal infections. The system organ class for infections and infestations was therefore of special interest, and was further characterized using bacterial and fungal infection high-level group terms, and *Candida* and tinea infection high-level terms.

IBD, including CD, is of special interest, because people with psoriasis are at increased risk of the disease. Furthermore, clinical trials assessing brodalumab efficacy in patients with active CD were terminated early due to safety concerns related to worsening disease in some patients.

Neutropaenia is a recognized risk associated with administration of brodalumab, since it inhibits the action of IL-17A, IL-17F and IL-17A/F, which play a role in the proliferation, maturation and chemotaxis of neutrophils. Clinically relevant neutropaenia was defined as decrease in absolute neutrophil counts grade 3 ($<1.0\times10^9$/l–0.5×10^9/l) and 4 ($<0.5\times10^9$/l).

Higher levels of psychiatric disorders, including suicidal ideation and behaviour (SIB), depression and anxiety, are reported in patients with psoriasis, and there have been reports of suicide events in other psoriasis phase 3 studies (S2). Thus, patients in brodalumab clinical trials identified as being at potential risk of psychiatric disorders and psychiatric events were subsequently monitored using the electronic Columbia-Suicide Severity Rating Scale (eC-SSRS) (S3, S4) and the Patient Health Questionnaire-8 (S5). At the time of introduction of the eC-SSRS, the majority of ustekinumab patients had switched to brodalumab 210 mg. A process for blinded, independent adjudication of SIB events was applied retrospectively to events reported prior to implementation of the eC-SSRS (S6), to ensure all potential SIBs were correctly identified and recorded.

People with psoriasis are at increased risk for cardiovascular comorbidities (28), and a substantial number of the patient population additionally had a history of cardiovascular conditions and/or relevant risk factors, such as hypertension, obesity, smoking, elevated lipid levels or type 2 diabetes mellitus. In the phase 3 AMAGINE-1, -2 and -3 trials, major adverse cardiac events were defined as cardiovascular death, MI or stroke, and were adjudicated by an independent clinical events classification committee.

It is not clear what role, if any, deficiency of IL-17 plays in malignancy; however, in line with safety assessments for all immunomodulatory biologics, malignancies are considered an adverse event (AE) of special interest (AESI). Malignancy-related conditions and malignant or unspecified tumours were medically adjudicated (blinded), and if confirmed, further categorized as either Surveillance, Epidemiology, and End Results malignancies relevant for analysis or not.

Finally, monoclonal antibodies, such as brodalumab, have the potential to cause hypersensitivity reactions, which are important to monitor. All hypersensitivity events occurring within 1 day following administration were assessed.

SUPPLEMENTARY REFERENCES

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