Safety of Brodalumab in Plaque Psoriasis: Integrated Pooled Data from Five Clinical Trials

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Brodalumab is approved for treatment of moderate-to-severe plaque psoriasis. Here, we assess the safety profile of brodalumab using pooled safety data from 5 phase II/III trials of brodalumab 140 mg or 210 mg. In total, 4,464 patients received brodalumab, representing 8,891.6 patient-years of exposure. During the placebo-controlled 12-week induction period, rates of serious adverse events per 100 patient-years were 10.8 and 9.6 (brodalumab 140 mg and 210 mg, respectively) vs 4.3 and 6.5 (ustekinumab and placebo, respectively); infections were the most frequent serious adverse event. Rates of serious adverse events during the comparator-controlled 52-week period were 14.4, 10.2 and 8.3 per 100 patient-years for brodalumab 210 mg, brodalumab 140 mg, and ustekinumab, respectively. Brodalumab was not associated with increased risks of malignancy, major adverse cardiac events, suicidal ideation and behaviour, or fatal events. Overall, brodalumab demonstrated an acceptable safety profile in short- and long-term treatment.

Key words: brodalumab; interleukin-17; psoriasis; safety.

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Psoriasis is a common immune-mediated inflammatory disease that affects 2–3% of the population. Psoriasis, which blocks multiple interleukin-17 family cytokines by binding to the shared A subunit of the interleukin-17 receptor, is an approved treatment for patients with moderate-to-severe plaque psoriasis. This study uses combined data from 5 randomized clinical trials to assess the safety profile of brodalumab. Brodalumab was well tolerated and was not associated with an increased risk of malignancy, major adverse cardiac events, suicidal ideation and behaviour, or fatal adverse events.

MATERIALS AND METHODS

Trial design and patients

Data integration analysis techniques were used to analyse safety data-sets pooled from 5 randomized controlled trials of brodalumab in patients with moderate-to-severe psoriasis. Trial designs (Fig. 1, Appendix SI) have been reported previously (11, 13–16, 20).
Fig. 1. Summary of brodalumab psoriasis. (a) Phase III and (b) phase II trial designs. Q2W: every 2 weeks; Q4W: every 4 weeks; Q8W: every 8 weeks; sPGA: static Physician Global Assessment of psoriasis.

Safety evaluation

Patients were grouped into constant treatment groups, which included all patients exposed to the same planned treatment during the full length of a treatment period. Four time-periods were identified: period 1, the initial double-blind, placebo- and ustekinumab-controlled 12-week induction phase; period 2, the ustekinumab-controlled 52-week period; and periods 3 and 4, which covered the open-label extension trials to the end of treatment (EOT) or last follow-up (Table SI). The only difference between periods 3 and 4 was that the latter included all patients exposed to the same planned treatment during the full length of a treatment period.

During period 1, E/100 PYs for all TEAEs were calculated using the formula E/100 PY = N/100 × 100/EX, where N is the number of events, to account for differences in exposure between the treatment groups.

Only the constant treatment groups were included in the comparative safety analysis. To account for variations in patient experience, the following rules were applied:

• Patients did not contribute to the constant treatment group for a given period if they were re-randomized or switched to another treatment during that period.

• If patients met rescue criteria, they were included in the constant treatment groups until that point and were subsequently reported in the relevant mixed treatment group in the post-rescue exposure period.

• If patients discontinued, they were included in any subsequent period in the applicable constant treatment group.

Data were analysed based on event rate per 100 patient-years (E/100 PY) (95% confidence intervals; 95% CIs), rather than number of events, to account for differences in exposure between the treatment groups.

AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 18.1 and classified by system organ class (SOC), high-level group term (HLGT), and preferred term (PT). A TEAE was an event that occurred or worsened, in intensity or frequency, after initiation of investigational product and prior to the EOT period.

Adverse events of special interest

Periods 1 and 2 were included in the analysis of AEs of special interest (AESIs). Periods 3, 4, and full study period (while on specified treatment) were included in the analysis depending on type and occurrence of AESIs; while the focus was on the constant treatment groups, possibly serious events in the mixed treatment group were also presented. AESIs were: infections, Crohn’s disease, neutropaenia, psychiatric disorders (including suicidal ideation and behaviour), major adverse cardiac events (MACE), malignancies and hypersensitivity within 1 day (Appendix SI).

Withdrawal and rebound

Changes in AEs following withdrawal or interruption of treatment were assessed.

RESULTS

Patients

Overall, 4,464 patients received brodalumab (any dose) during the studies, representing 8,891.6 patient-years of exposure (PYE), of whom 1,600 (35.8%) were exposed to brodalumab for 24–30 months and 110 (2.5%) for >60 months. Median exposure (range) was 2.1 (0–5.7) years. Most patients (4,117; 92.2%) received ≥1 dose of brodalumab 210 mg, representing 6,900.2 PYE. Patient demographics and baseline characteristics were well balanced across treatment groups (Table I).

Overall safety

An overview of the AEs observed for all time-periods for the constant treatment groups is provided in Table II. Placebo-controlled, 12-week induction period (period I). During period 1, E/100 PYs for all TEAEs were 602.7, 589.2, 499.8 and 453.1 E/100 PY for constant brodalumab 210 mg, brodalumab 140 mg, ustekinumab...
Table II. Overview of adverse events for the 4 constant treatment groups

|                      | Placebo (n=881) | Ustekinumab (n=961) | Brodalumab 140 mg Q2W (n=1,490) | Brodalumab 210 mg Q2W (n=1,495) |
|----------------------|----------------|---------------------|---------------------------------|---------------------------------|
| **Period 1**         |                |                     |                                 |                                 |
| All AEs              | n=881, 200.2 E PYE | n=961, 234.8 E PYE | n=1,490, 342.3 E PYE            | n=1,495, 344.4 E PYE            |
| Serious              | 452 (51.3) 907 453.1 | 530 (55.7) 697 499.8 | 850 (57.0) 2,017 589.2          | 879 (58.8) 2,076 602.7          |
| Non-serious          | 449 (51.0) 894 446.7 | 349 (57.0) 691 495.5 | 842 (56.5) 1,980 578.4          | 876 (58.6) 2,043 593.1          |
| Study discontinued   | 2 (0.2) 1.0 2.0 | 3 (0.5) 3.2 | 15 (1.0) 15.4 | 13 (0.9) 16.4 |
| IP discontinued      | 4 (0.5) 2.0 | 7 (1.1) 5.0 | 16 (1.1) 16.7 | 17 (1.1) 22.6 |
| Death                | 0              | 0                  | 0                               | 0                               |
| **Period 2**         |                |                     |                                 |                                 |
| All AEs              | n=612, 432.9 E PYE | n=612, 438.3 E PYE | n=467, 393.3 E PYE              | n=537, 415.8 E PYE              |
| Serious              | 345 (73.9) 1,324 432.3 | 24 (5.1) 30 10.2 | 423 (78.8) 1,771 426.0          | 38 (6.0) 57 14.4 |
| Non-serious          | 486 (79.4) 1,796 414.9 | 15 (3.2) 16 5.5 | 24 (4.5) 28 6.7 | 30 (4.2) 41 11.9 |
| Study discontinued   | 6 (1.0) 6.4 | 16 (3.4) 17 5.8 | 28 (5.2) 37 8.9 | 0 (0.0) 0.3 0.7 |
| IP discontinued      | 13 (2.1) 16 | 2 (0.3) 2.0 | 3 (0.6) 3 0.7 | 0 (0.0) 0.3 0.7 |
| Death                | 0              | 0                  | 0                               | 0                               |
| **Period 3**         |                |                     |                                 |                                 |
| All AEs              | n=667, 529.5 E PYE | n=667, 537.9 E PYE | n=537, 589.7 E PYE              | n=537, 637.4 E PYE              |
| Serious              | 365 (78.2) 1,730 326.7 | 36 (7.9) 32 10.7 | 460 (85.7) 2,775 319.1          | 460 (85.7) 2,816 318.3          |
| Non-serious          | 374 (77.9) 1,678 316.9 | 36 (7.9) 32 10.7 | 454 (84.5) 2,686 308.8          | 454 (84.5) 2,723 307.8          |
| Study discontinued   | 18 (3.9) 19 | 19 (3.9) 19 | 27 (5.0) 31 3.6 | 27 (5.0) 31 3.6 |
| IP discontinued      | 19 (4.1) 20 | 23 (5.0) 27 | 34 (6.3) 44 | 34 (6.3) 44.1 |
| Death                | 0              | 4 (0.7) 4 0.5      | 0                               | 0                               |
| **Period 4**         |                |                     |                                 |                                 |
| All AEs              | n=537, 886.7 E PYE | n=537, 844.6 E PYE | n=537, 884.6 E PYE              | n=537, 884.6 E PYE              |
| Serious              | 368 (78.8) 1,774 322.0 | 36 (8.4) 32 10.7 | 460 (85.7) 2,775 319.1          | 460 (85.7) 2,816 318.3          |
| Non-serious          | 366 (78.4) 1,718 311.8 | 19 (4.1) 20 | 28 (5.2) 32 3.6 | 28 (5.2) 32 3.6 |
| Study discontinued   | 19 (4.1) 20 | 23 (5.0) 27 | 34 (6.3) 44 | 34 (6.3) 44.1 |
| IP discontinued      | 21 (4.5) 24 | 24 (4.4) 24.4 | 36 (6.7) 46 5.2 | 36 (6.7) 46.2 |
| Death                | 0              | 4 (0.7) 4 0.5      | 0                               | 0                               |

aConstant treatment groups included all patients exposed to the same planned treatment during the full length of a treatment period. Four time periods were identified: period 1: the initial double-blind: placebo- and ustekinumab-controlled 12-week induction phase; Period 2: the ustekinumab-controlled 52-week period; and periods 3 and 4, which covered the open-label extension trials up to the end of treatment (EOT) or last follow-up.
AE: adverse event; E: number of events; E/100 PY: event rate per 100 patient-years; IP: investigational product; PY: patient-years of exposure; Q2W: every 2 weeks; TEAE: treatment-emergent adverse event.
(Q2W), respectively, with no apparent dose effects. The rate of AEs leading to study discontinuation in period 3 was slightly higher for patients receiving brodalumab 210 mg compared with brodalumab 140 mg (Table II).

**All treatment exposure: AEs with a fatal outcome.** A total of 18 fatal TEAEs were reported. Most occurred in patients with additional confounding factors relating to prior medical history, concomitant events or the presence of other risk factors. Further details are provided in Appendix SII and Table SVII.

**Adverse events of special interest**

**Table III** provides an overview of TEAEs of special interest for periods 1 and 2.

**Infections.** During period 1, the rate of infections was slightly higher in the brodalumab 210 mg group (157.6 E/100 PY (95% CI 144.7–171.5)) than in the brodalumab 140 mg (124.4 E/100 PY (95% CI: 112.9–136.9)), ustekinumab (133.4 E/100 PY (95% CI 114.9–153.9)) and placebo (135.9 E/100 PY (95% CI 120.2–153.0)) groups. More than 50% of all infection-related events comprised nasopharyngitis, pharyngitis, bronchitis, urinary tract infection, influenza, and sinusitis. Analysis by bacterial HLGT indicated event rates of 10.5 and 7.0 in the brodalumab 210 and 140 mg groups, respectively, compared with 9.0 and 13.6 in the placebo and ustekinumab groups, respectively. Analysis by fungal infection HLGT indicated more fungal events in the brodalumab 210 mg group (11.9 E/100 PY) compared with brodalumab 140 mg (5.0 E/100 PY), ustekinumab (5.0 E/100 PY) or placebo (4.5 E/100 PY). The higher rate was primarily driven by mild-to-moderate skin and mucosal Candida infections (Table SVII).

Serious infectious episodes were relatively infrequent (Table III), but event rates were slightly higher in the brodalumab groups compared with the placebo and ustekinumab groups. One patient treated with brodalumab 210 mg had a serious event of cryptococcal meningitis, which was treated with systemic antifungal therapy and led to study discontinuation. Observations for period 2 were not substantially different from period 1.

In period 2, there was no clear difference in infection rates for brodalumab 210 mg and ustekinumab, but the dose-related differences between brodalumab 140 mg and 210 mg remained. The same ranges of infections by PT and bacterial and fungal infections by HLGT predominated. There was an additional serious coccidioidomycosis infection in the brodalumab 210 mg group that was treated with systemic antifungal therapy; brodalumab 210 mg treatment was resumed following recovery.

There were no reports of tuberculosis.

**Table SVIII** summarizes all serious treatment-emergent infections for the 4 constant treatment groups.

### Table III. Overview of treatment-emergent adverse events (TEAEs) of special interest from baseline to week 52 periods

|                  | Placebo (n = 1495; 344.4 PYE) | Ustekinumab (n = 1490; 342.3 PYE) | Brodalumab 140 mg (n = 1490; 342.3 PYE) | Brodalumab 210 mg (n = 1495; 344.4 PYE) |
|------------------|-------------------------------|----------------------------------|----------------------------------------|----------------------------------------|
| **Period 1**     |                               |                                  |                                        |                                        |
| **Important identified risks** | n = 881; 200.2 PYE | n = 612; 139.5 PYE | n = 1490; 342.3 PYE | n = 1495; 344.4 PYE |
| All infections   | 206 (23.4) 272 135.9          | 155 (25.5) 186 133.4            | 343 (23.0) 426 124.4                   | 421 (28.2) 543 157.6                   |
| Serious          | 1 (0.1) 1 0.5                 | 2 (0.3) 2 1.4                   | 7 (0.5) 7 2.0                         | 7 (0.5) 8 2.3                         |
| Fungal           | 9 (1.0) 9 4.5                 | 6 (1.0) 7 5.0                   | 17 (1.1) 17 5.0                       | 37 (2.5) 41 11.9                       |
| Crohn's disease  | 1 (0.1) 1 0.5                 | 0                               | 0                                      | 0                                      |
| Neutropaenia     | 4 (0.5) 4 2.0                 | 5 (0.8) 8 5.7                   | 11 (0.7) 21 6.1                       | 14 (0.9) 26 7.5                       |
| **Important potential risks** | n = 612; 432.9 PYE | n = 467; 293.3 PYE | n = 467; 293.3 PYE | n = 537; 415.8 PYE |
| Suicidal ideation and behaviour | 0 | 0 | 0 | 0 |
| Adjudicated MACE | 1 (0.1) 1 0.5                 | 0                               | 3 (0.2) 3 0.9                         | 0                                      |
| SEER malignancies | 0 | 1 (0.2) 1 0.7 | 0 | 2 (0.1) 2 0.6 |
| Hypersensitivity | 31 (3.5) 34 17.0              | 22 (3.6) 23 16.5                | 39 (2.6) 42 12.3                      | 27 (1.8) 29 8.4                       |
| **Other events of interest** | n = 612; 432.9 PYE | n = 467; 293.3 PYE | n = 467; 293.3 PYE | n = 537; 415.8 PYE |
| Injection-site reactions | 11 (1.2) 13 6.5 | 12 (2.0) 15 10.8 | 25 (1.7) 47 13.7 | 23 (1.5) 46 13.4 |
| **Period 2**     |                               |                                  |                                        |                                        |
| **Important identified risks** | n = 612; 432.9 PYE | n = 537; 415.8 PYE | n = 537; 415.8 PYE | n = 537; 415.8 PYE |
| All infections   | 304 (49.7) 537 124.1          | 206 (44.1) 318 108.4            | 293 (54.6) 560 134.7                  | 293 (54.6) 560 134.7                  |
| Serious          | 5 (0.8) 5 1.2                 | 5 (1.1) 5 1.7                   | 9 (1.7) 10 2.4                       | 9 (1.7) 10 2.4                       |
| Fungal           | 14 (2.3) 17 3.9               | 15 (3.2) 15 5.1                 | 33 (6.1) 41 9.9                      | 33 (6.1) 41 9.9                      |
| Crohn's disease  | 0 | 0 | 1 | 0 |
| Neutropaenia     | 8 (1.3) 12 2.8                | 3 (0.6) 8 2.7                   | 10 (1.9) 24 5.8                      | 10 (1.9) 24 5.8                      |
| Suicidal ideation and behaviour | 1 (0.2) 1 0.2 | 0 | 2 (0.4) 4 1.0 |
| Adjudicated MACE | 2 (0.3) 2 0.5                 | 3 (0.6) 3 1.0                   | 3 (0.6) 3 1.0                       | 3 (0.6) 3 1.0                       |
| SEER malignancies | 2 (0.3) 2 0.5 | 0 | 2 (0.4) 2 0.5 |
| Hypersensitivity | 39 (6.4) 44 10.2             | 22 (4.7) 26 8.9                 | 21 (3.9) 26 6.3                      | 21 (3.9) 26 6.3                      |
| **Other events of interest** | n = 612; 432.9 PYE | n = 537; 415.8 PYE | n = 537; 415.8 PYE | n = 537; 415.8 PYE |
| Injection-site reactions | 18 (2.9) 22 5.1 | 13 (2.8) 18 6.1 | 9 (1.7) 18 4.3 |

*Constant treatment groups included all patients exposed to the same planned treatment during the full length of a treatment period. Four time periods were identified: period 1, the initial double-blind, placebo- and ustekinumab-controlled 12-week induction phase; Period 2, the ustekinumab-controlled 52-week period; and periods 3 and 4, which covered the open-label extension trials up to the EOT or last follow-up. E: number of events; E/100 PY: event rate per 100 patient-years; EOT: end of treatment; MACE: major adverse cardiac event; PY: patient-years of exposure; SEER: Surveillance: Epidemiology: and End Results; TEAE: treatment-emergent adverse event.*
Inflammatory bowel disease, including Crohn’s disease. During period 1, 1 patient receiving placebo in the constant treatment groups had an AE (IBD) that mapped to the Crohn’s disease Customized MedDRA Query; this query included non-specific AEs, such as enteritis and IBD. One patient treated with brodalumab 210 mg had an event of enteritis that mapped to Crohn’s disease in period 2. An additional event for each of the constant brodalumab 140 mg and brodalumab mixed treatment groups mapped to Crohn’s disease in periods 3 and 4. However, no patients in the constant brodalumab 210 mg group or who received ≥1 dose of brodalumab 210 mg experienced new-onset Crohn’s disease.

Neutropaenia. There were no significant differences in neutropaenia event rates between the active treatment groups in period 1 (Table III). The neutropaenia event rate was lower for period 2, although the pattern was similar across treatment groups.

Most cases of neutropaenia were observed within the first few weeks of treatment, were grades 1–3, transient and reversible. None were associated with serious infections. Psychiatric disorders. In the overall analysis for all treatment exposures, psychiatric AEs were observed with event rates of 6.2, 5.6, 8.8 and 8.4 E/100 PY during treatment with brodalumab 210 mg, brodalumab 140 mg, ustekinumab and placebo, respectively.

Suicidal ideation and behaviour. Two suicide attempts were reported for 1 patient in the brodalumab 210 mg group in period 1 (0.6 E/100 PY), compared with none in the placebo, brodalumab 140 mg or ustekinumab groups. This patient had an additional suicide attempt during period 2 with the event rate increasing to 0.7 E/100 PY. Also in period 2, 1 patient in the constant ustekinumab group attempted suicide (0.2 E/100 PY) and 1 patient in the brodalumab 210 mg had suicidal ideation (0.2 E/100 PY).

Looking at the treatment the patients were receiving at the time of the event, no suicidal ideation and behaviour events were reported when patients were receiving placebo. Non-fatal suicidal behaviour was reported in 1 patient receiving brodalumab 140 mg (0.06 E/100 PY (95% CI 0.00–0.36)). Suicidal ideation was reported in 19 patients receiving brodalumab 210 mg (0.28 E/100 PY (95% CI: 0.01–1.12)). There were 3 suicide events (<0.04 E/100 PY (95% CI 0.01–0.13)) (1 of which was subsequently reclassified as “indeterminate” with respect to intended outcome by an independent adjudication committee) and 10 non-fatal suicidal behaviour events (0.17 E/100 PY (95% CI 0.09–0.30)) in patients receiving brodalumab 210 mg. During the follow-up period, there was 1 suicide event. While on ustekinumab, no patients completed suicide; 1 patient had 2 non-fatal suicidal behaviour events (0.40 E/100 PY (95% CI 0.05–1.45)).

**Fig. 2** shows treatment-emergent suicidal ideation and behaviour events from baseline to EOT. Other psychiatric disorders. During the “while on specified treatment” period, the most frequently observed psychiatric AEs were insomnia, depression and anxiety (Appendix SII).

**Major adverse cardiac events.** In period 1, 4 patients had adjudicated MACE; 3 events (0.9 E/100 PY (95% CI 0.2–2.6)) in the brodalumab 140 mg group and 1 event (0.5 E/100 PY (95% CI: 0.0–2.8)) in the placebo group. In period 2, 8 events were reported in the constant treatment groups, with event rates of 0.7 E/100 PY (95% CI 0.1–2.1) and 1.0 E/100 PY (95% CI 0.2–3.0) in the brodalumab 210 mg and 140 mg groups, and 0.5 E/100 PY (95% CI 0.1–1.7) in the ustekinumab group. No additional MACE were reported in periods 3 and 4 for the constant brodalumab groups.
Including patients who switched treatment, a total of 56 patients had a MACE across all periods. Myocardial infarction was the most common event. Most patients (n = 39) were receiving brodalumab 210 mg when the event occurred (0.6 E/100 PY (95% CI: 0.4–0.8)). All patients for whom a MACE was reported had ≥ 1 (many had ≥ 2) major cardiovascular risk factors and additional confounding comorbidities.

**Malignancy.** In period 1, the event rates for Surveillance, Epidemiology, and End Results–adjudicated malignancies were 0 E/100 PY for brodalumab 140 mg, 0.6 E/100 PY (95% CI 0.1–2.1) for brodalumab 210 mg, 0.7 E/100 PY (95% CI 0.0–4.0) for ustekinumab, and 0 E/100 PY for placebo.

In period 2, malignancy rates were 0 E/100 PY for brodalumab 140 mg, 0.5 E/100 PY (95% CI 0.1–1.7) for brodalumab 210 mg and 0.5 E/100 PY (95% CI 0.1–1.7) for ustekinumab.

To the EOT (period 3), malignancy rates were 0.2 E/100 PY (95% CI 0.0–1.1) and 0.5 E/100 PY (95% CI 0.1–1.2) in the brodalumab 140 mg and 210 mg groups, respectively. In period 4, 1 additional event was reported in each constant brodalumab treatment group. Time-to-first-event analysis did not indicate any differences between constant treatment groups in any periods.

**Hypersensitivity.** In periods 1 and 2, the event rate of hypersensitivity was lowest for brodalumab 210 mg relative to brodalumab 140 mg, ustekinumab and placebo. A higher event rate for brodalumab 140 mg compared with brodalumab 210 mg was also observed for period 3.

**Withdrawal and rebound.** No rebound or specific pattern of AEs was observed that would likely be related to study drug withdrawal or treatment interruption.

### DISCUSSION

This integrated analysis of data pooled from 5 clinical trials of brodalumab within the psoriasis indication assessed TEAEs and 9 AESIs. Overall, brodalumab 210 mg Q2W demonstrated an acceptable safety profile in short- and long-term treatment. There were relatively few differences in the safety profile of brodalumab 210 mg relative to ustekinumab, although increased rates of infections (especially fungal infections) were observed with higher doses of brodalumab, as expected, as a class effect. However, event rates were low, with considerable variability, and relatively few infections were serious. The safety profile of ustekinumab was as expected in this moderate-to-severe psoriasis population.

Together with recently published similar pooled safety analyses for other IL-17-targeting biologics, including secukinumab and ixekizumab (22, 23), this integrated analysis of brodalumab clinical trials provides important context for providers considering optimal treatment for patients with psoriasis. As there are now multiple IL-17 targeting biologics—with 3 distinct mechanisms of action (MOA): anti-IL17A, anti-IL-17RA, anti-IL-17A/F (24, 25) available for the treatment of psoriasis, it will become increasingly important for prescribers to understand specific differences in the efficacy and safety profiles within the class of IL-17-inhibiting drugs. This is particularly relevant in light of potentially class-related safety events, such as *Candida* infections and IBD exacerbation, which may differ between different members of this class, based on their different MOA.

Patients with Crohn’s disease were specifically excluded from the phase III trials because of earlier evidence that brodalumab, as an IL-17 antagonist, may exacerbate pre-existing active disease (26), and active Crohn’s disease is a contraindication in the current label (27). Some AEs due to IBD or enteritis were observed in the study, but no patients treated with brodalumab 210 mg Q2W experienced new-onset Crohn’s disease.

Suicidal ideation and behaviour events have been reported in patients treated with brodalumab (26). In this analysis, there were 4 suicide events during the whole treatment period (3 TEAEs and 1 additional event during the follow-up period), 1 of which was subsequently adjudicated as “indeterminate”. All 4 patients had confounding influences, such as a history of depression or a stressful life situation, and none of the events could conclusively be linked to treatment. As such, no causal link has been established between brodalumab treatment and increased risk of suicidal ideation and behaviour. In further support of this conclusion, in the phase III AMAGINE-1 study, scores for depression and anxiety on the Hospital Anxiety and Depression Scale improved and were significantly lower in subjects treated with brodalumab compared with placebo (Appendix SI) (11).

The event rate for MACE was relatively low, and there was no evidence of an association with brodalumab 210 mg. Instead, observations of MACE suggested that people with psoriasis tend to be at increased risk of cardiovascular comorbidities, since all patients who experienced MACE were characterized by a history of cardiovascular conditions and/or had additional cardiovascular risk factors, such as hypertension, obesity, smoking, elevated lipid levels and type 2 diabetes mellitus. Indeed, recent studies have shown that patients with psoriasis are at greater risk of developing cardiovascular diseases (28).

The event rate of hypersensitivity was lowest for brodalumab 210 mg in all periods. These findings were mainly driven by the PT pruritus, which may be symptomatic of psoriasis rather than of hypersensitivity.

There was no evidence of rebound or a pattern of AEs considered likely be related to study drug withdrawal or treatment interruption.

Reflecting the different trial designs, most patients were exposed to brodalumab 210 mg at some point. This increased the opportunity for events to occur while patients were receiving brodalumab 210 mg, potentially
resulting in higher numbers of events for this treatment group.

This analysis has several limitations. Patients are selected for clinical trials based on protocol-specified criteria and receive close medical follow-up, which may limit comparisons with real-world clinical experience. The original trials were powered to show differences in efficacy and common AEs, but not rare events such as suicide events. Despite this, available evidence does not suggest an association between brodalumab and suicidal ideation and behaviour events. Beyond the 12-week placebo-controlled and 52-week comparator-controlled phases, no comparator was used. This limits understanding of the safety profile of brodalumab relative to comparator drugs over the longer term. It should also be noted that differences between the current analysis and earlier studies of biologics, in terms of timing and design characteristics, also create barriers to comparison of findings. Nonetheless, the data do not suggest that brodalumab treatment was associated with increased risk of serious events, including malignancy, MACE, suicidal ideation and behaviour or fatal AEs, all of which are more likely to manifest over the longer term.

In summary, in this integrated analysis of pooled data based on actual treatment exposure, brodalumab 210 mg Q2W demonstrated an acceptable safety profile during the initial 12-week double-blind induction and comparator-controlled 52-week periods. In the open-label long-term extension period, safety findings remained consistent with the initial 52-week period.

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