ORIGINAL ARTICLE

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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SIGNIFICANCE

Psoriasis is a common immune-mediated inflammatory disease that affects 2–3% of the population. Brodalumab, 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.

Psoriasis is a common immune-mediated inflammatory disease that affects 2–3% of the population. Psoriasis is associated with several comorbidities, such as psoriatic arthritis, cardiovascular diseases, obesity, metabolic syndrome, psychiatric disorders (including depression, anxiety, and suicidal ideation and behaviour), inflammatory bowel disease (IBD), including Crohn's disease and ulcerative colitis, and malignancies (1–3).

Patients with psoriasis are considered candidates for systemic therapy if the body surface area affected exceeds 10%, the disease involves special areas, such as scalp or genitalia, and/or topical therapy has failed (4). Biologics, which have high efficacy in treating moderate-to-severe psoriasis (5–7), target proinflammatory cytokines involved in the pathophysiology of psoriasis, such as interleukin (IL)-17, -23 and/or tumour necrosis factor-alpha (8–10).

Brodalumab is a recombinant fully human monoclonal immunoglobulin G2 antibody that binds with high affinity to the human IL-17 receptor A, blocking IL-17 and inhibiting downstream signalling of multiple proinflammatory cytokines, IL-17A, IL-17F, IL-17A/F heterodimer, IL-17C and IL-17E (IL-25) (8). Consistent with its mechanism of action, brodalumab provides rapid and high levels of skin clearance for ≤5 years in patients with moderate-to-severe psoriasis with consequent improvements in their health-related quality of life (11–13).

Safety results for brodalumab were previously reported based on randomized planned treatment (11–20). To address some of the limitations associated with this approach, including smaller data-sets, variations in treatment doses and regimens (21), and to allay any concerns regarding the safety of brodalumab, the current study reports safety data from a pooled data-set of 5 brodalumab clinical trials within the psoriasis indication and compares patients grouped according to actual treatment received.

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).

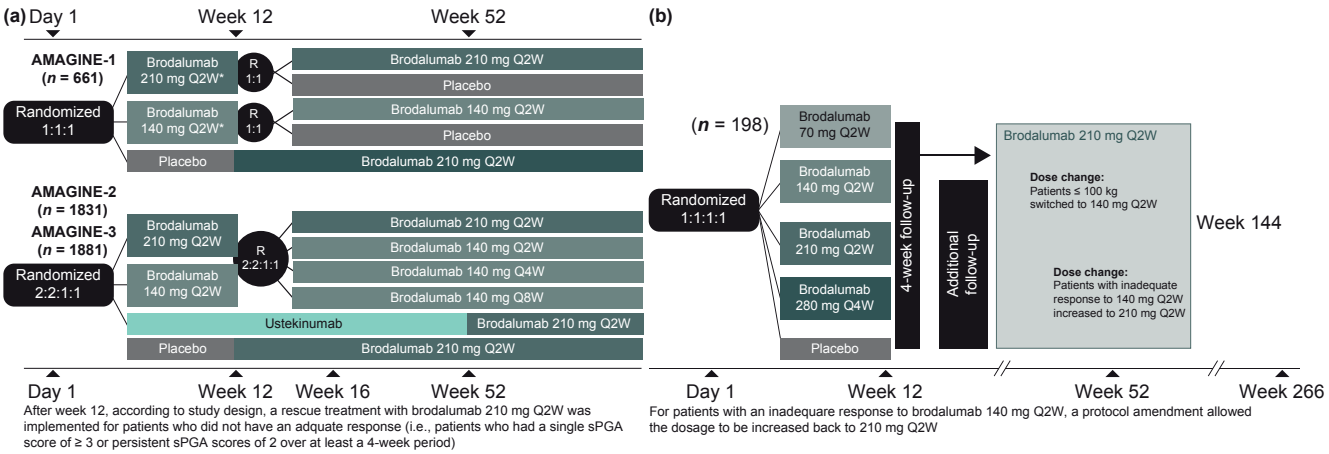

Fig. 1. Summary of brodalumab psoriasis. (a) Phase III and (b) phase II trial designs. Q2W: every 2 weeks; Q4W: every 4 weeks; Q8W: every 8 weeks; sPGA: static Physician Global Assessment of psoriasis.

All studies were conducted in accordance with applicable country and International Conference on Harmonisation Good Clinical Practice regulations/guidelines. The institutional review board at all participating centres approved the study protocols. All patients provided written informed consent. Sites maintained compliance with the Health Insurance Portability and Accountability Act or relevant regional regulations.

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 non-treatment-emergent adverse events (TEAEs) in addition to all AEs presented in the former. Patients who received more than one treatment type were grouped into mixed treatment groups with adverse events (AEs) being allocated to the treatment type at the time of the event (while on specified treatment), regardless of time period or previous treatments.

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 AESI; 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 1). 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 I. Patient characteristics at baseline for the 4 constant treatment groups

			Brodalumab	
	Placebo (*n* = 881)	Ustekinumab (*n* = 612)	140 mg Q2W (*n* = 1,490)	210 mg Q2W (*n* = 1,495)
Age, years, mean (SD)	44.6 (12.9)	45.1 (13.1)	44.8 (13.0)	45.0 (12.9)
Sex, male, *n* (%)	609 (69)	416 (68)	1,036 (70)	1,037 (69)
Race, *n* (%)				
White	801 (91)	550 (90)	1,353 (91)	1,350 (90)
Black	29 (3)	20 (3)	44 (3)	40 (3)
Asian	29 (3)	24 (4)	61 (4)	51 (3)
Other	22 (3)	18 (3)	32 (2)	54 (4)
Weight, kg, mean (SD)	90.0 (22.0)	90.8 (22.8)	90.4 (21.6)	90.7 (23.0)
>100 kg, *n* (%)	242 (27)	172 (28)	426 (29)	428 (29)
Duration of psoriasis, years, mean (SD)	18.5 (12.0)	18.6 (12.2)	18.1 (11.9)	18.6 (12.3)
PASI, mean (SD)	20.1 (8.2)	20.0 (8.4)	20.2 (8.2)	20.2 (8.0)
sPGA, *n* (%)				
1	0	0	0	0
2	0	0	4 (< 1)	2 (< 1)
3	500 (57)	345 (56)	913 (61)	826 (55)
4	332 (38)	234 (38)	501 (34)	583 (39)
5	49 (6)	33 (5)	72 (5)	84 (6)
Psoriatic arthritis, *n* (%)	181 (21)	114 (19)	329 (22)	310 (21)

PASI: Psoriasis Area Severity Index; Q2W: every 2 weeks; SD: standard deviation; sPGA: static Physician Global Assessment of psoriasis.

and placebo, respectively. The most frequently reported TEAEs (≥3%) included nasopharyngitis, upper respiratory tract infection, arthralgia and headache.

The rates of serious AEs (SAEs) (95% CIs) were 10.8 E/100 PY (95% CI 7.6–14.9) and 9.6 E/100 PY (95% CI 6.6–13.5) (brodalumab 140 mg and 210 mg, respectively) compared with 4.3 E/100 PY (95% CI 1.6–9.4) (ustekinumab) and 6.5 E/100 PY (95% CI 3.5–11.1) (placebo) (Table II). The most frequently reported SAE by SOC in the 3 treatment groups was infections: 2.3 E/100 PY (brodalumab 210 mg), 2.0 E/100 PY (brodalumab 140 mg) and 1.4 E/100 PY (ustekinumab) compared with 0.5 E/100 PY (placebo) (Table SII). No Candida infections were reported as SAEs in this study.

Event rates leading to discontinuation were low and similar among the treatment groups (Table II, Tables SIII and SIV).

Comparator-controlled 52-week period (period 2). A similar profile of common AEs was observed for period 2 compared with period 1 (Table SII). The rate for serious TEAEs was slightly higher in the constant brodalumab 210 mg group compared with the constant brodalumab 140 mg and ustekinumab groups, though no pattern or trend was apparent and most SAEs were single events.

There were higher rates of AEs leading to study discontinuation in the brodalumab 210 mg and 140 mg groups compared with ustekinumab (Table II, Tables SV and SVI).

Open-label long-term extension and follow-up (periods 3 and 4). In the periods extending to the EOT, the event rates of SAEs were 10.2 E/100 PY and 9.8 E/100 PY for constant brodalumab 210 mg and 140 mg every 2 weeks

Table II. Overview of adverse events for the 4 constant treatment groups[a]

	Placebo			Ustekinumab			Brodalumab 140 mg Q2W			Brodalumab 210 mg Q2W		
	n (%)	E	E/100 PY	*n* (%)	E	E/100 PY	*n* (%)	E	E/100 PY	*n* (%)	E	E/100 PY
Period 1	*n* = 881; 200.2 PYE			*n* = 612; 139.5 PYE			*n* = 1,490; 342.3 PYE			*n* = 1,495; 344.4 PYE		
All TEAEs	452 (51.3)	907	453.1	350 (57.2)	697	499.8	850 (57.0)	2,017	589.2	879 (58.8)	2,076	602.7
Serious	11 (1.2)	13	6.5	6 (1.0)	6	4.3	28 (1.9)	37	10.8	20 (1.3)	33	9.6
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)	2	1.0	3 (0.5)	3	2.2	15 (1.0)	15	4.4	13 (0.9)	16	4.6
IP discontinued	4 (0.5)	4	2.0	7 (1.1)	7	5.0	16 (1.1)	16	4.7	17 (1.1)	22	6.4
Death	0			0			0			1 (0.1)	1	0.3
Period 2				*n* = 612; 432.9 PYE			*n* = 467; 293.3 PYE			*n* = 537; 415.8 PYE		
All TEAEs				487 (79.6)	1,832	423.2	345 (73.9)	1,324	451.4	429 (79.9)	1,831	440.4
Serious				25 (4.1)	36	8.3	24 (5.1)	30	10.2	41 (7.6)	60	14.4
Non-serious				486 (79.4)	1,796	414.9	344 (73.7)	1,294	441.2	423 (78.8)	1,771	426.0
Study discontinued				6 (1.0)	6	1.4	15 (3.2)	16	5.5	24 (4.5)	28	6.7
IP discontinued				13 (2.1)	16	3.7	16 (3.4)	17	5.8	28 (5.2)	37	8.9
Death				2 (0.3)	2	0.5	0			3 (0.6)	3	0.7
Period 3							*n* = 467; 529.5 PYE			*n* = 537; 869.7 PYE		
All TEAEs							365 (78.2)	1,730	326.7	460 (85.7)	2,775	319.1
Serious							37 (7.9)	52	9.8	63 (11.7)	89	10.2
Non-serious							364 (77.9)	1,678	316.9	454 (84.5)	2,686	308.8
Study discontinued							18 (3.9)	19	3.6	27 (5.0)	31	3.6
IP discontinued							19 (4.1)	20	3.8	34 (6.3)	44	5.1
Death							0			4 (0.7)	4	0.5
Period 4							*n* = 467; 551.0 PYE			*n* = 537; 884.6 PYE		
All TEAEs							368 (78.8)	1,774	322.0	460 (85.7)	2,816	318.3
Serious							39 (8.4)	56	10.2	66 (12.3)	93	10.5
Non-serious							366 (78.4)	1,718	311.8	455 (84.7)	2,723	307.8
Study discontinued							19 (4.1)	20	3.6	28 (5.2)	32	3.6
IP discontinued							21 (4.5)	24	4.4	36 (6.7)	46	5.2
Death							0			4 (0.7)	4	0.5

[a]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 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; PYE: 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 E/100 PY 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[a]

	Placebo			Ustekinumab			Brodalumab 140 mg			Brodalumab 210 mg		
	n (%)	E	E/100 PY	*n* (%)	E	E/100 PY	*n* (%)	E	E/100 PY	*n* (%)	E	E/100 PY
Period 1	*n* = 881; 200.2 PYE			*n* = 612; 139.5 PYE			*n* = 1490; 342.3 PYE			*n* = 1495; 344.4 PYE		
Important identified risks												
All infections	206 (23.4)	272	135.9	156 (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												
Suicidal ideation and behaviour	0			0			0			1 (0.1)	2	0.6
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												
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				*n* = 612; 432.9 PYE			*n* = 467; 293.3 PYE			*n* = 537; 415.8 PYE		
Important identified risks												
All infections				304 (49.7)	537	124.1	206 (44.1)	318	108.4	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
Fungal				14 (2.3)	17	3.9	15 (3.2)	15	5.1	33 (6.1)	41	9.9
Crohn's disease				0			0			1 (0.2)	1	0.2
Neutropaenia				8 (1.3)	12	2.8	3 (0.6)	8	2.7	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	0.7
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
Other events of interest												
Injection-site reactions				18 (2.9)	22	5.1	13 (2.8)	18	6.1	9 (1.7)	18	4.3

[a]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; PYE: 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 0.17–0.43)) and in 1 patient receiving ustekinumab (0.20 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.

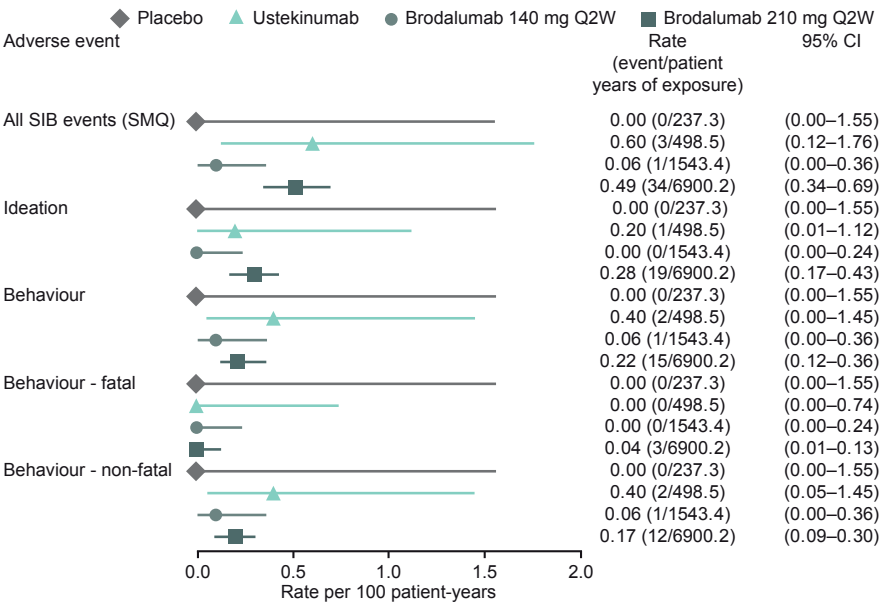

Fig. 2. Forest plot of treatment-emergent suicidal ideation and behaviour events by standardized Medical Dictionary for Regulatory Activities (MedDRA) query and preferred term (PT) from baseline to end of treatment (EOT): safety analysis set. CI: confidence interval; Q2W: every 2 weeks; SIB: suicidal ideation and behaviour.

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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