Neuropsychiatric Adverse Events in Brodalumab Psoriasis Studies

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INTRODUCTION

- Psoriasis has profound psychosocial implications that can affect the ability of patients to socialize with family members, interact with coworkers, and make friends[1]
- Psychiatric comorbidities, such as depression and anxiety, are common in patients with psoriasis[2,3]
- Suicidal ideation has been reported in as many as 17.3% of patients with psoriasis compared with 8.3% of healthy controls[4]
- Brodalumab is a monoclonal antibody that targets interleukin-17 (IL-17) receptor A and is indicated for the treatment of psoriasis[5]
- Brodalumab has demonstrated efficacy in the treatment of plaque psoriasis[5,6]
- Reports of suicide in patients with psoriasis enrolled in clinical trials for brodalumab led to concerns that brodalumab may be linked to psychiatric adverse events (AEs)[6,7]

OBJECTIVE

- To assess psychiatric AEs and improvements in depression and anxiety in patients with psoriasis treated with brodalumab in clinical trials

METHODS

Clinical studies

- Efficacy and safety of brodalumab (140 or 210 mg every 2 weeks [Q2W]) were investigated in one phase 2 trial and in three phase 3, multicenter, randomized trials of patients with moderate-to-severe plaque psoriasis (AMAGINE-1/-2/-3)[5,6]
- In the phase 3 studies, more than 80% of patients were being treated with brodalumab 210 mg Q2W by the end of the week 52 controlled period
- There were no specific exclusion criteria for psychiatric disorders or substance abuse

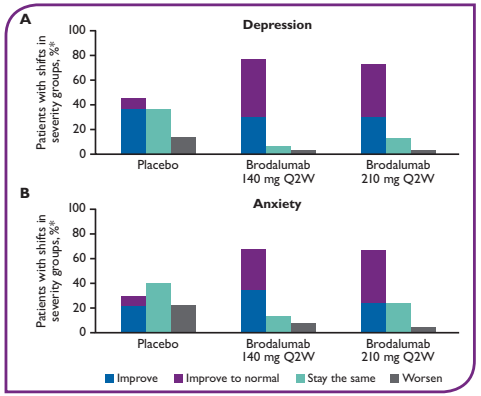
Endpoints

- The hospital anxiety and depression scale (HADS), which determines anxiety and depression on a 21-point scale each, was measured in AMAGINE-1
- The dermatology life quality index (DLQI) assesses the socio-psychological impact of the skin disease[8] on patients' lives and was measured in AMAGINE-1/-2/-3
- Data on psychiatric AEs were pooled for all trials and were summarized as follow-up time–adjusted event rates
  - The follow-up time–adjusted event rate is the total number of events reported during the follow-up observation time divided by total patient-years of observation; this includes gaps and interruptions in exposure and time beyond the exposure period

RESULTS

- Mean HADS anxiety and depression scores significantly improved with brodalumab compared with placebo by 12 weeks (Figure 1)

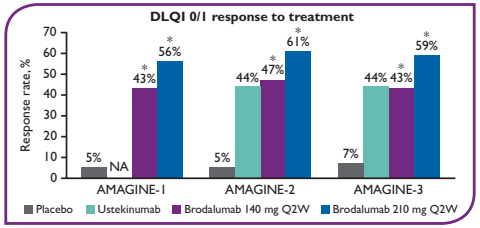
Figure 1. Shifts in HADS severity for **(A)** depression and **(B)** anxiety at week 12 in patients who scored moderate or severe at baseline in the AMAGINE-1 trial.



HADS, hospital anxiety and depression scale; Q2W, every 2 weeks. Shifts in HADS severity at week 12 in patients who scored "moderate" or "severe" at baseline. *Data are shown as observed; percentages do not add up to 100%.

- Mean DLQI significantly improved with brodalumab compared with placebo by 12 weeks (Figure 2)

Figure 2. DLQI 0/1 response rate at week 12 in patients from the AMAGINE-1, -2, and -3 trials.



DLQI, dermatology life quality index. DLQI response = score 0/1. *$P<0.001$ vs placebo.

- Rates of psychiatric adverse events were comparable between treatments at week 52 and did not increase with long-term treatment (Table 1)

Table 1. Incidence of Psychiatric Adverse Events Occurring in ≥0.1% of Patients Treated With Brodalumab During the Initial Placebo-Controlled Study Period[a]

Preferred term, n (%)	Placebo (N=879)	Ustekinumab (N=613)	Brodalumab[b] (N=3066)
Psychiatric disorders SOC	16 (1.8)	12 (2.0)	61 (2.0)
Insomnia	6 (0.7)	4 (0.7)	17 (0.6)
Depression	5 (0.6)	3 (0.5)	14 (0.5)
Anxiety	2 (0.2)	2 (0.3)	13 (0.4)
Libido decreased	0 (0)	0 (0)	5 (0.2)
Depressed mood	1 (0.1)	2 (0.3)	3 (0.1)
Mood swings	0 (0)	0 (0)	3 (0.1)
Stress	1 (0.1)	0 (0)	3 (0.1)

SOC, system organ class. [a]Includes data from the placebo-controlled phase 2 study, AMAGINE-1, AMAGINE-2, and AMAGINE-3. [b]All brodalumab dose groups combined.

- There were 22 suicidal ideations (follow-up time–adjusted rate, 0.24), 6 suicide attempts (0.07), 3 completed suicides (0.03), and 1 additional suicide adjudicated as indeterminate (Table 2)

Table 2. Integrated Analysis of Follow-up Time–Adjusted Patient Incidence Rates of SIB Events Through Week 52 and in Long-term Follow-up

	52-week pool[a]		Long-term pool[b]
	Ustekinumab (N=613; pt-yr = 503.6) n (r) [95% CI]	Brodalumab (N=4019; pt-yr = 3545.7) n (r) [95% CI]	Brodalumab (N=4464; pt-yr = 9161.8) n (r) [95% CI]
Suicidal ideation adverse event	1 (0.20) [0.01, 1.11]	3 (0.08) [0.02, 0.25]	22 (0.24) [0.15, 0.36]
Suicidal behavior adverse event	1 (0.20) [0.01, 1.11]	4 (0.11) [0.03, 0.29]	15 (0.16) [0.09, 0.27]
Completed suicide[c]	0 (0.00) [0.00, 0.73]	2 (0.06) [0.01, 0.20]	4 (0.04) [0.01, 1.11]
Intentional self-injury	0 (0.00) [0.00, 0.73]	1 (0.03) [<0.01, 0.16]	1 (0.01) [0.00, 0.06]
Suicide attempt	1 (0.20) [0.01, 1.11]	1 (0.03) [<0.01, 0.16]	6 (0.07) [0.02, 0.14]
Suicidal behavior	0 (0.00) [0.00, 0.73]	0 (0.00) [0.00, 0.10]	4 (0.04) [0.01, 1.11]
Overall suicidal ideation and behavior	2 (0.40) [0.05, 1.44]	7 (0.20) [0.08, 0.41]	34 (0.37) [0.26, 0.52]

SIB, suicidal ideation and behavior. [a]Cumulative events through the 52-week, controlled treatment period. [b]Includes events in the 52-week treatment period and the uncontrolled open-label extension. [c]Includes fatal event reported as intentional overdose that was adjudicated as indeterminate.

- Two suicidal ideation and behavior (SIB) events (suicide attempts) were reported in 1 patient treated with brodalumab during the 12-week induction phase (0.03%; 1/3066)
- Follow-up time–adjusted rates of SIB were greater in patients with a history of depression compared with those without (1.42 and 0.21 per 100 patient-years, respectively)
- Follow-up time–adjusted rates of SIB were greater in patients with a history of suicidality compared with those without (3.21 and 0.20 per 100 patient-years, respectively)
- Of the 3 completed suicides, all patients were receiving brodalumab 210 mg, had baseline risk factors, and had demonstrated clinical responses (PASI ≥73; Table 3)
  - Time-to-event from first dose ranged from 140 to 845 days. Follow-up time–adjusted SIB rates through week 52 were lower in the brodalumab group compared with the ustekinumab group, with overlapping CIs (0.20 [0.08, 0.41] vs 0.60 [0.12, 1.74])
  - Long-term rates of SIB with brodalumab were slightly higher (0.37 [0.26, 0.52]) compared with those through week 52, with no increase in the completed suicide rate (0.04 [0.01, 0.11] vs 0.06 [0.01, 0.20])

Table 3. Summary of Completed Suicides (Known and Unknown Cause)

Age, y/Sex	Brodalumab dose	Clinical response (PASI score)	Clinical information
59/Male	210 mg	100	• 329 days after first dose of brodalumab • History of financial stressors (lost disability due to brodalumab response and unable to find work)
39/Male	210 mg	73	• 140 days after first dose of brodalumab • Informed investigator he had legal difficulties and was likely to be incarcerated • Family reported he killed himself, means unknown
56/Male	210 mg	100	• 845 days after first dose of brodalumab • Ongoing treatment for depression and anxiety • Described recent stress and isolation due to relocation
Indeterminate case			
56/Male	210 mg	100	• History of depression; on antidepressant and benzodiazepine • 97 days after first dose of brodalumab • Toxic levels of mixed opiates compatible with ingestion of poppy seed tea and methadone; therapeutic level of citalopram, elevated alprazolam, and alcohol • HADS baseline depression and anxiety score decreased from 15 to 2 and 14 to 6, respectively, 2 weeks before the event • Ruled indeterminate by C-CASA adjudication

C-CASA, Columbia classification algorithm of suicide assessment; HADS, hospital anxiety and depression scale; PASI, psoriasis area and severity index.

CONCLUSIONS

- **Mean HADS anxiety and depression scores were reduced from baseline in patients with moderate-to-severe plaque psoriasis receiving brodalumab**
- **A higher patient satisfaction and quality of life was observed with brodalumab compared with placebo, as determined by DLQI response rate**
- **Rates of SIB at week 52 in patients treated with brodalumab were similar to those treated with the active comparator ustekinumab, and SIB rates did not increase with long-term treatment**
- **No pattern emerged between timing of the events and the initiation or withdrawal of brodalumab**
- **Controlled data do not suggest a causal relationship between brodalumab treatment and SIB**

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