BRODALUMAB injection

Food and Drug Administration
Dermatologic and Ophthalmic Drugs Advisory Committee (DODAC)
Meeting Date: July 19, 2016

Errata to
SPONSOR BRIEFING DOCUMENT
AVAILABLE FOR PUBLIC DISCLOSURE

Prepared By:

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Briefing Book Errata description:

The following errata are noted in the Sponsor's briefing book:

1. **Appendix A, Table 1 Subject listing of MACE** was updated to improve readability and to resolve inconsistencies within the listing.

2. The lower bound of the 95% confidence interval for 0 event should be 0 and not NE (not evaluable) using exact method based on the Poisson distribution.

3. To clarify for FDA, a single patient (10312006006) had a suicide attempt which was initially ascribed to brodalumab (ustekinumab to brodalumab 210 mg arm) after 52 weeks and reported as such in the initial BLA submission. After data cleaning and as reported in the 120 day safety update, the SIB event was determined to have occurred on ustekinumab between week 12 and week 52 and prior to starting brodalumab and should be captured in the 52 week data tables as such.

   The interpretation of the results does not change; however, for clarity the following changes are noted to the text and tables presented in the Sponsor's briefing book:

Page 21:

In the psoriasis program in the 12-week period, there was a single patient with 2 suicide attempts and none in placebo or ustekinumab treatment arms. In the 52-Week Pool, the follow-up time-adjusted patient incidence rates of all SIB were 0.~~40~~ 60 and 0.20 per 100 patient years in ustekinumab and brodalumab, respectively. Two completed suicides occurred on brodalumab (0.06 per 100 patient years). In the long-term extension, follow up adjusted rates per 100 patient years of all SIB was 0.37 per 100 patient years (95% CI 0.26, 0.52), attempted suicide/behavior were 0.11 (95% CI: 0.05, 0.20), and completed suicide 0.04 (95% CI 0.01, 0.11) in patients exposed to brodalumab as shown in Table 1-2. The 4 completed suicides were spread across a long period with none occurring in the placebo controlled period, 2 in the 52-week period and 2 more through end of study. Among the 4 suicides, 1 of the events in the 52-week period was adjudicated as indeterminate but Sponsor has included it as a completed suicide. The pooled estimate from a systematic literature review for completed suicides (per 100 patient years) in patients with psoriasis participating in clinical trials and registries irrespective of treatment were consistent with the brodalumab psoriasis rates.

Pages 73-75:

In the 52-week pool, the follow-up time-adjusted patient incidence rate of SIB was 0.20 per 100 patient-years in the all brodalumab group and ~~0.40~~ 0.60 per 100 patient-years in the ustekinumab group. For suicidal behaviors, the patient incidence rate was 0.11 and ~~0.20~~-0.40 per 100 patient years for the brodalumab and the ustekinumab groups, respectively. For suicidal ideations, the patient incidence rate was 0.08 and 0.20 per 100 patient-years, for the brodalumab and the ustekinumab groups, respectively (Table 8-5).

Four patients in the brodalumab treatment group had suicidal behavior events: 1 patient had 3 suicide attempts (2 already reported in 12 week pool), 1 patient with completed suicide, 1 patient with a fatal intentional overdose, later adjudicated as indeterminate and 1 patient with intentional self-injury. There ~~was 1~~were 2 events of suicide attempt in the ustekinumab group.

The 52 week pool shows that patient reports of SIB are few and rates of suicide attempt and ideation are lower in the brodalumab treatment group than ustekinumab. Two completed suicides (includes intentional overdose) occurred in patients receiving brodalumab.

Table 8-5 Exposure- and follow-up time-adjusted patient incidence rates of SIB events through Week 52 – 52 Week Pool - Integrated Safety Analysis Set – Psoriasis Subset [Updated numbers in red]

		Brodalumab		
		Constant Dose		
Event of interest category	Ustekinumab (N = 613) n (r) [95% CI]	140 mg Q2W (N = 280) n (r) [95% CI]	210 mg Q2W (N = 1335) n (r) [95% CI]	All (N = 4019) n (r) [95% CI]
Exposure-Adjusted	**Pt-yr=494.1**	**Pt-yr=215.3**	**Pt-yr=1041.3**	**Pt-yr=3444.6**
Suicidal ideation and behavior	3 (0.61) [0.13, 1.77]	0 (0.00) [0.00, 1.71]	4 (0.38) [0.11, 0.98]	6 (0.17) [0.06, 0.38]
Suicidal behavior adverse event	2 (0.40) [0.049, 1.46]	0 (0.00 [0.00, 1.71]	2 (0.19) [0.02, 0.69]	3 (0.09) [0.02, 0.26]
Completed suicide[a]	0 (0.00) [0.00, 0.75]	0 (0.00) [0.00, 1.71]	1 (0.10) [0.00, 0.54]	1 (0.03) [(0.00, 0.16]
Intentional self-injury	0 (0.00) [0.00, 0.75]	0 (0.00) [0.00, 1.71]	0 (0.00) [0.00, 0.35]	1 (0.03) [0.00, 0.16]
Suicide attempt	2 (0.40) [0.049, 1.46]	0 (0.00) [0.00, 1.71]	1 (0.10) [0.00, 0.54]	1 (0.03) [0.00, 0.16]
Suicidal ideation adverse event	1 (0.20) [0.01, 1.13]	0 (0.00) [0.00, 1.71]	2 (0.19) [0.02, 0.69	3 (0.09) [0.02, 0.26]
Follow-up Time-Adjusted	**Pt-yr=503.4**	**Pt-yr=221.5**	**Pt-yr=1061.4**	**Pt-yr=3547.1**
Suicidal ideation and behavior	3 (0.60) [0.12, 1.74]	0 (0.00) [0.00, 1.67]	5 (0.47) [0.15, 1.1]	7 (0.20) [0.08, 0.41]
Suicidal behavior adverse event	2 (0.40) [0.048, 1.44]	0 (0.00) [0.00, 1.67]	3 (0.28) [0.06, 0.83]	4 (0.11) [0.03, 0.29]
Completed suicide[a]	0 (0.00) [0.00, 0.73]	0 (0.00) [0.00, 1.67]	2 (0.19) [0.02, 0.68]	2 (0.06) [0.01, 0.20]
Intentional self-injury	0 (0.00) [0.00, 0.73]	0 (0.00) [0.00, 1.67]	0 (0.00) [0.00, 1.35]	1 (0.03) [<0.01, 0.16]
Suicide attempt	2 (0.40) [0.048, 1.44]	0 (0.00) [0.00, 1.67]	1 (0.09) [<0.01, 0.53]	1 (0.03) [<0.01, 0.16]
Suicidal ideation adverse event	1 (0.20) [0.01, 1.11]	0 (0.00) [0.00, 1.67]	2 (0.19) [0.02, 0.68]	3 (0.08) [0.02, 0.25]

[a] Includes fatal event reported as intentional overdose.

MedDRA v. 17.1.

N=patients in Studies 20090062/20090403, AMAGINE-1, AMAGINE-2 & AMAGINE-3 with ≥ 1 dose of active investigational product; NE=not evaluable; Pt-yr = Total patient-years of exposure through min (patient's first suicidal ideation and behavior event, Week 52), and are truncated at patients first suicidal ideation and behavior event; n = Number of patients with adverse events; r Exposure- or follow-up time-adjusted patient incidence rate per 100 patient-years (n/pt-yr*100).

Treatment groups are as planned treatment; ustekinumab patients rescued at Week 16, are in "Ustekinumab" until first dose of brodalumab; brodalumab 210 mg Q2W constant dose group includes patients who received 210 mg Q2W at induction and maintenance and patients who received placebo at induction and brodalumab 210 mg Q2W at maintenance. All brodalumab includes all patients who received at least one dose of brodalumab

Multiple occurrences of the same events for patient are counted once.

Exposure- and follow-up time-adjusted rates from the long-term pool are shown below (Table 8-6).

Through the end of the study, 34 patients treated with brodalumab experienced 39 SIB events (Table 8-6). Rates of completed suicide were relatively constant comparing the 52-week pool to the long-term pool: 0.06 vs 0.04 per 100 patient years respectively. Rates of attempts and ideations increased after week 52: 0.03 to 0.11 per 100 patient years and 0.08 to 0.24 per 100 patient years, respectively, suggesting ascertainment bias due to the introduction of the eC-SSRS post week 52 in a significant number of patients.

Table 8-6 Exposure- and Follow-up time-adjusted Patient Incidence Rates (per 100 Patient Years) of SIB in 52-Week Pool and Long-Term Pool – Psoriasis subset [Updated numbers in red]

	52-Week Pool		Long-term Pool
	Ustekinumab N=613	All-brodalumab N=4019	All-brodalumab N=4464
SIB event	n (r) [95% CI]	n (r) [95% CI]	n (r) [95% CI]
Exposure-adjusted	**Pt-yr = 494.1**	**Pt-yr=3444.6**	**Pt-yr = 8647.3**
Suicidal ideation and behaviour	3 (0.61) [0.13, 1.77)]	6 (0.17) [0.06, 0.38]	24 (0.28) [0.18, 0.41]
Suicidal behaviour adverse event	2 (0.40) [0.05, 1.46]	3 (0.09) [0.02, 0.26]	11 (0.13) [0.06, 0.23]
Completed suicide[a]	0 (0.00) [0.00, 0.75]	1 (0.03) [<0.01, 0.16]	1 (0.01) [0, 0.06]
Intentional self-injury	0 (0.00) [0.00, 0.75]	1 (0.03) [<0.01, 0.16]	1 (0.01) [0, 0.06]
Suicide attempt/behaviour[b]	2 (0.40) [0.05, 1.46]	1 (0.03) [<0.01, 0.16]	9 (0.10) [0.05, 0.20]
Suicidal ideation adverse event	1 (0.20) [0.01, 1.13]	3 (0.09) [0.02, 0.26]	16 (0.19) [0.11, 0.30]
Follow-up adjusted	**Pt-yr = 503.4**	**Pt-yr=3547.1**	**Pt-yr = 9161.8**
Suicidal ideation and behaviour	3 (0.60) [0.12,1.74]	7 (0.20) [0.08, 0.41]	34 (0.37) [0.26, 0.52]
Suicidal behaviour adverse event	2 (0.40) [0.048, 1.44]	4 (0.11) [0.03, 0.29]	15 (0.16) [0.09, 0.27]
Completed suicide[a]	0 (0.00) [0.00, 0.73]	2 (0.06) [0.01, 0.20]	4 (0.04) [0.01, 0.11]
Intentional self-injury	0 (0.00) [0.00, 0.73]	1 (0.03) [<0.01, 0.16]	1 (0.01) [0, 0.06]
Suicide attempt/behaviour[b]	2 (0.40) [0.048,1.44]	1 (0.03) [<0.01, 0.16]	10 (0.11) [0.05, 0.20]
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]

[a] Includes fatal event reported as intentional overdose.

[b] Suicide attempt and behavior PTs are combined

CTCAE v. 4.0 or 4.03; MedDRA v. 17.1 (52-week pool), MedDRA v. 18.1 (long-term pool); N=patients in Studies 20090062/20090403, AMAGINE-1, AMAGINE-2, and AMAGINE-3 with ≥ 1 dose of active investigational product.

n=number of patients with SIB events; Multiple Occurrences of the same events for patient are counted once; Pt-yr = total patient-years of exposure through Week 52 (52-Week Pool) and through end of study (Long-Term Pool), and are truncated at patients' first suicidal ideation and behavior event; r=exposure- or follow-up time-adjusted patient incidence rate per 100 patient years (n/pt-yr*100); 95% confidence interval based on exact method assuming Poisson distribution

Summary of SIB events:

- Completed Suicide: Five of 6 were males, 4 were psoriasis patients. All had risk factors, 2 with depression and 4 with significant social stressors. All were receiving brodalumab 210 mg Q2W at the time of event. The time to event from first dose ranged from 97 to 952 days. The time from last known dose evaluation was complicated by lack of retrieval of a number of treatment diaries in. The time to last dose of brodalumab ranged from 7 to 59 days. Two occurred after implementation of the eC-SSRS and recorded scores of 0 prior to the event.
- Attempted suicides: There were 11 suicide attempts on brodalumab, 10 in the psoriasis program and 1 in the rheumatoid arthritis program. Four were associated with suicidal ideation. One patient in the psoriasis program had 3 suicide attempts. In the psoriasis program, the majority had multiple psychiatric risk factors including prior ideation or attempts. The time from first dose of brodalumab to event ranged from 27 to 895 days. The time from last dose was within the dosing interval of 14 days in 8 of 10 patients. One event occurred on brodalumab 140 mg Q2W. Three attempts were detected by eC-SSRS only, including 2 on the first eC-SSRS assessment.
- There were 2 suicide attempts on ustekinumab, 1 with associated suicidal ideation. ~~and~~ There was 1 attempt on placebo in the asthma study.
- Suicidal ideation: There were 24 events of suicidal ideation associated with brodalumab, 22 in the psoriasis program. The majority had multiple risk factors. The time to onset from first dose of brodalumab ranged from 112 to 1945 days. Two of the ideations occurred on patients taking brodalumab 140 mg Q2W. ~~Two~~ One patient~~s~~ taking ustekinumab had an event~~s~~ of suicidal ideation.
- Two patients on placebo in the asthma study had events of suicidal ideation (1 associated with an attempt).

Further details are provided in Appendix A.

VALEANT
Pharmaceuticals North America LLC

BRODALUMAB injection

Food and Drug Administration
Dermatologic and Ophthalmic Drugs Advisory Committee (DODAC)
Meeting Date: July 19, 2016

Errata

Appendix A: Narratives and Case Details for MACE and SIB Events

SPONSOR BRIEFING DOCUMENT

AVAILABLE FOR PUBLIC DISCLOSURE

Prepared By:

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List of Tables

1 MACE Events [Table 1 has been replaced]

Table 1 Subject listing of MACE											
				Baseline risk factors							
Patient ID	**Treatment at Onset**	**A/G/R**	**Study Day of MACE/Day First Broda/Days Since Last Active Dose**	**Overweight/ Obese [a]**	**Glucose Intoler ance/ Diabetes [b]**	**Smoking Status (Former/ Current)**	**Dyslip- idemia [c]**	**HTN [d]**	**Hx of Ischaemic Cerebro- vascular Event**	**Hx of Ischae mic Heart Disease**	**Number of Risk Factors [e]**
MACE: MYOCARDIAL INFARCTION											
24010	Ustekinumab	49/M/W	183/NA/69	Y	N	Y (current)	N	Y	N	N	3
48003	210 mg Q2W	60/M/W	127/85/12	N	Y	Y (current)	Y	Y	N	N	4
08015	210 mg Q2W	65/M/W	413/1/6	Y	N	Y (former)	Y	Y	N	Y	5
09002	140 mg Q2W	64/M/W	159/1/18	Y	Y	Y (former)	N	Y	N	N	4
09044	210 mg Q2W	61/M/W	408/1/2	Y	N	N	N	N	N	Y	2
37005	210 mg Q2W	58/M/W	249/1/10	Y	N	N	N	N	N	N	1
59017	210 mg Q2W	58/M/W	336/1/13	Y	N	Y (former)	N	Y	N	N	3
69004	210 mg Q2W	36/M/O	367/1/13	N	N	Y (current)	Y	Y	N	N	3
81012	210 mg Q2W	56/F/W	174/1/19	Y	Y	N	N	Y	N	Y	4
08028	140 mg Q2W	51/M/W	339/1/2	Y	Y	Y (current)	N	N	N	N	3
13008	210 mg Q2W	58/M/W	242/1/3	Y	N	Y (current)	Y	Y	N	N	4

Table 1 Subject listing of MACE

Patient ID	Treatment at Onset	A/G/R	Study Day of MACE/Day First Broda/Days Since Last Active Dose	Baseline risk factors							
				Overweight/ Obese [a]	Glucose Intoler ance/ Diabetes [b]	Smoking Status (Former/ Current)	Dyslip- idemia [c]	HTN [d]	Hx of Ischaemic Cerebro- vascular Event	Hx of Ischae mic Heart Disease	Number of Risk Factors [e]
31002	210 mg Q2W	56/M/W	313/1/1	Y	N	Y (current)	N	Y	N	Y	4
46012	210 mg Q2W	69/F/W	408/1/3	N	N	N	N	Y	N	N	1
52003	210 mg Q2W	62/M/W	358/1/7	Y	Y	Y (former)	Y	Y	Y	N	6
54010	140 mg Q2W	60/M/W	101/1/15	Y	N	Y (former)	Y	Y	N	N	4
64006	140 mg Q2W	57/M/W	89/1/18	Y	N	Y (former)	N	Y	N	Y	4
29002	140 mg Q2W	45/M/W	38/1/5	N	N	Y (current)	N	N	N	N	1
07023	210 mg Q2W	64/M/W	354/1/3	Y	Y	Y (current)	Y	Y	Y	N	6
12007	210 mg Q2W	38/M/W	212/85/1	Y	N	N	Y	N	N	N	2
18008	210 mg Q2W	57/M/W	124/1/11	Y	N	Y (former)	Y	Y	N	Y	5
19023	210 mg Q2W	63/M/W	228/85/3	N	N	Y (former)	N	N	N	N	1
01007	210 mg Q2W	62/F/W	636/ 85/3	Y	N	N	Y	Y	N	N	3

Table 1 Subject listing of MACE

Patient ID	Treatment at Onset	A/G/R	Study Day of MACE/Day First Broda/Days Since Last Active Dose	Baseline risk factors							
				Overweight/ Obese [a]	Glucose Intoler ance/ Diabetes [b]	Smoking Status (Former/ Current)	Dyslip- idemia [c]	HTN [d]	Hx of Ischaemic Cerebro- vascular Event	Hx of Ischae mic Heart Disease	Number of Risk Factors [e]
17001	210 mg Q2W	55/M/W	719/85/60	N	N	Y (current)	N	N	N	N	1
13009	210 mg Q2W	65/M/W	667/1/2	N	N	Y (former)	N	Y	N	N	2
02011	210 mg Q2W	47/M/W	435/85/14	Y	N	Y (current)	Y	Y	N	N	4
37013	Placebo	57/M/O	2/86/NA	N	N	Y (current)	Y	N	N	N	2
01047	140 mg Q2W	48/M/W	712/1/11	Y	N	N	Y	Y	N	N	3
02004	140 mg Q2W	58/M/W	669/1/3	Y	N	Y (former)	N	N	N	N	2
38012	210 mg Q2W	34/F/W	622/85/17	Y	Y	N	N	N	N	N	2
90012	140 mg Q2W	56/M/W	426/1/1	N	N	N	N	N	N	N	0
92032	210 mg Q2W	36/M/W	446/1/47	N	N	N	N	N	N	N	0
04011	210 mg Q2W	63/M/W	828/1/22	Y	N	Y (former)	N	N	N	N	2
MACE: STROKE											
05002	210 mg Q2W	53/M/W	457/1/8	N	N	Y (current)	Y	Y	N	N	3
03006	210 mg Q2W	50/M/W	151/1/24	N	N	Y (current)	N	Y	N	N	2
13032	210 mg Q2W	64/M/W	323/1/0[f]	Y	N	Y (former)	N	N	N	N	2
12012	140 mg Q2W	66/F/W	28/1/14	N	N	N	N	Y	N	N	1
54004	210 mg Q2W	69/F/W	450/1/1	N	N	N	Y	N	N	N	1

Table 1 Subject listing of MACE

Patient ID	Treatment at Onset	A/G/R	Study Day of MACE/Day First Broda/Days Since Last Active Dose	Baseline risk factors							
				Overweight/ Obese [a]	Glucose Intoler ance/ Diabetes [b]	Smoking Status (Former/ Current)	Dyslip- idemia [c]	HTN [d]	Hx of Ischaemic Cerebro- vascular Event	Hx of Ischae mic Heart Disease	Number of Risk Factors [e]
54006	210 mg Q2W	54/F/W	402/1/9	N	Y	Y (current)	Y	Y	Y	Y	5
07005	210 mg Q2W	72/M/W	243/1/7	Y	Y	Y (current)	Y	Y	N	N	5
10009	210 mg Q2W	66/F/W	729/1/14	Y	Y	N	Y	Y	Y	N	5
03003	210 mg Q2W	46/M/W	711/1/9	N	N	Y (current)	N	N	N	N	1
06002	210 mg Q2W	58/M/W	1005/112/17	N	N	Y (former)	N	N	N	N	1
10035	210 mg Q2W	58/M/W	353/1/2	N	Y	Y (current)	N	Y	N	N	3
83008	210 mg Q2W	58/M/W	728/1/13	Y	Y	N	Y	Y	N	N	4
MACE: CARDIOVASCULAR DEATH											
53011	Ustekinumab	59/M/W	140/NA/28	N	N	N	Y	N	N	Y	2
84031	210 mg Q2W	24/F/W	211/86/14	Y	N	Y (former)	N	N	N	N	2
06003	210 mg Q2W	52/M/W	474/1/39	Y	N	Y (current)	Y	Y	N	N	4
46008	210 mg Q2W	65/M/W	271/1/3	N	Y	Y (current)	N	Y	N	N	3
68006	210 mg Q2W	37/M/W	298/1/87	Y	Y	Y (current)	Y	N	N	N	4
02010	210 mg Q2W	52/MW	556/1/9	N	N	Y (current)	Y	N	N	N	2
09012	210 mg Q2W	70/M/W	267/1/14	Y	N	Y (current)	N	Y	N	N	3
17001	210 mg Q2W	55/M/W	720/85/61	N	N	Y (current)	N	N	N	N	1
42001	210 mg Q2W	74/M/W	198/1/1	Y	Y	Y (former)	N	Y	N	Y	5

Table 1 Subject listing of MACE

Patient ID	Treatment at Onset	A/G/R	Study Day of MACE/Day First Broda/Days Since Last Active Dose	Baseline risk factors							
				Overweight/ Obese [a]	Glucose Intolerance/ Diabetes [b]	Smoking Status (Former/ Current)	Dyslip-idemia [c]	HTN [d]	Hx of Ischaemic Cerebro-vascular Event	Hx of Ischaemic Heart Disease	Number of Risk Factors [e]
05001	210 mg Q2W	56/M/W	594/365/61	Y	N	Y (former)	N	Y	N	N	3
09033	210 mg Q2W	60/M/W	514/1/23	Y	Y	N	N	Y	N	N	3
38015	210 mg Q2W	44/M/W	779/1/91	Y	N	N	Y	Y	N	N	3
04011	210 mg Q2W	63/M/W	828/1/22	Y	N	Y (former)	N	N	N	N	2

[a] Overweight/obese includes patients with BMI > 30 or at least one overweight or obesity-related preferred terms

[b] Glucose intolerance/diabetes includes patients with at least one diabetes-related preferred terms under Metabolism and Nutrition Disorder SOC

[c] Dyslipidemia includes patients with triglycerides > 1.7 mmol/L, cholesterol > 5.2 mmol/L or at least one dyslipidemia-related preferred terms in the Metabolism and Nutrition Disorder SOC

[d] Hypertension includes patients with at least one hypertension-related preferred terms under Vascular Disorder SOC

[e] Risk factors include overweight/obese, glucose intolerance/diabetes, former or current smoker, dyslipidemia, hypertension and at least one relevant medical history (Ischaemic cerebrovascular SMQ or Ischaemic heart disease SMQ)

[f] Subject received brodalumab dose on the day of the MACE event. However, data is not available to determine if dose was received prior to or after the event.

The events of MI with outcome of death in Subjects 17001 and 04011 were counted as 2 separate MACE events in the database (Death and MI) and thus appear twice in this listing.

A = age; BMI = body mass index; F = female; M = male; G = gender; HTN = hypertension; Hx = history; MACE = major adverse cardiac event; Q2W = every 2 weeks; R = race; W = white; O = other.

2 SIB Events Narratives: Completed Suicides

2.1 Psoriasis Studies

- A 56 year-old male with PASI 100 response, history of depression, on anti-depressant and benzodiazepine, found dead at work, 97 days after first dose of brodalumab. Toxicology screen indicated toxic levels of mixed opiates compatible with ingestion of poppy seed tea and methadone, therapeutic level of citalopram, elevated alprazolam, and alcohol. Hospital Anxiety and Depression Scale (HADS) baseline depression and anxiety score decreased from 15 to 2 and 14 to 6, 2 weeks before the event. Ruled intentional by coroner and indeterminate by Columbia-Classification Algorithm for Suicide Assessment (C-CASA) adjudication.
- A 59 year-old male with PASI 100 response and no psychiatric history but financial stressors (lost disability due to brodalumab response and unable to find work), hung himself 329 days after first dose brodalumab.
- A 39 year-old male with PASI 73 response and no psychiatric history informed investigator he had legal difficulties and was likely to be incarcerated. Family reported he killed himself, means unknown, 140 days after first dose brodalumab.
- A 56 year-old male with PASI 100 response and ongoing treatment for depression and anxiety, described recent stress and isolation due to relocation, jumped from roof of building 845 days after first dose brodalumab. Prior electronic Columbia-Suicide Severity Rating Scale (eC-SSRS) and Patient Health Questionnaire-8 (PHQ-8) scores 4 days prior to event were 0.

2.2 Other indications:

- A 42 year-old female without a psychiatric history voiced “overwhelming financial concerns” to her mother and hung herself 118 days after first dose brodalumab.
- A 57 year-old male with psoriatic arthritis with no psychiatric history but significant domestic issues, re-wrote his will and altered finances prior to self-inflicted fatal gunshot wound, 952 days after first dose brodalumab. eC-SSRS and PHQ-8 scores 13 days prior to event were 0.

3 SIB Events Narratives: Treatment Emergent Suicide Attempts

3.1 Psoriasis Studies: Brodalumab Treatment Groups

All subjects were on brodalumab 210 mg except where indicated.

- A 24 year-old female with PASI 75 response and no psychiatric history, death of father 1 year prior cited as stressor, had physical altercation with her roommate, and sat in car in garage with engine running, 706 days after first brodalumab 140 mg every 2 weeks (Q2W). Aborted attempt when roommate called authorities. Not hospitalized and brodalumab discontinued.
- A 61 year-old female with PASI 100 response, history of depression, reported on eC-SSRS that she took unspecified "high" dose of sleeping pills previously on study 647 days after first brodalumab dose. No emergency room (ER) visit or hospitalization reported. Psychiatrist diagnosed depression, no suicidal ideation. Brodalumab was discontinued.
- A 63 year-old male with PASI 94 response, no psychiatric history, developed severe depression 628 days after first brodalumab dose and 45 days later reported suicidal ideation and aborted attempt. eC-SSRS score was 7, PHQ-8 15. Brodalumab was discontinued.
- A 48 year-old male with PASI 100 response, history of depression, alcohol excess, marital stress (restraining order), insomnia, cluster C personality disorder, had 2 adverse events of depression on study (1 serious), had suicidal ideation and wrist laceration 644 days after first dose of brodalumab. eC-SSRS was 0 prior to attempt. Brodalumab discontinued.
- A 45 year-old female with PASI 68.7 response and history of depression, anxiety, intentional cutting, suicide attempt, and domestic stressors, took first eC-SSRS 644 days after first dose of brodalumab, which revealed 6 lifetime attempts (3 aborted) and "attempts" on study without further details. PHQ-8 score was 17. Brodalumab was discontinued.
- A 52 year-old female with PASI 97.5 response and history of suicidal ideation and behavior, took first eC-SSRS 525 days after first dose of brodalumab, and was found positive for suicidal ideation and suicide attempt in previous 3 months on study. Brodalumab was discontinued.

- A 55 year-old male with PASI 100 response and history of depression, anxiety, attention deficit hyperactivity disorder (ADHD), recently denied disability, and in child custody dispute, was found on railroad track with intention of committing suicide, 540 days after first dose of brodalumab. Brodalumab was discontinued.
- A 51 year-old male with PASI 100 response, history of chronic suicidal ideation, depression, anxiety, alcohol abuse, domestic stressors, had 3 suicide attempts. The first occurred 26 days after first dose of brodalumab (pills) and was not reported till the second aborted attempt (carbon monoxide poisoning, 2 pints of vodka and clonazepam) 14 days later. Patient hospitalized in rehab facility. After discharge and 65 days after last event, patient put gun to head at work without firing. Brodalumab was discontinued and patient again admitted to treatment facility.
- A 61 year-old female without psychiatric history and 758 days after first dose of brodalumab had eC-SSRS score of 4 (ideation) then indicated she had made a mistake, retook the test with score of 0. She was referred to a mental health professional and cleared of any suicide risk. Investigator reported the event as a behavior and brodalumab was discontinued.
- A 49 year-old female with a history of depression, developed severe depression on study on ustekinumab and was treated with alprazolam and escitalopram. Patient scored positive for preparatory action on eC-SSRS 168 days after starting brodalumab and brodalumab was discontinued.

3.2 Psoriasis Studies: Ustekinumab Group

- A 48 year-old male with PASI 100 response, history of prior suicidal ideation and attempt, gambling addiction, developed grade 4 depression on ustekinumab, had financial and domestic stressors. One hundred and sixty days after first dose of brodalumab first eC-SSRS indicated lifetime history of suicidal ideation and attempt. Brodalumab was discontinued but investigator indicated the events had occurred on ustekinumab.
- A 22 year-old female with PASI 55.5 response, history of suicidal ideation, multi-substance abuse, and childhood abuse, family, and financial stressors, ingested 50 aspirin tablets after physical altercation with mother and was hospitalized. Event resolved and ustekinumab was continued.

3.3 Rheumatoid Arthritis Study

- A 42 year-old female with a history of insomnia and depression, took an unknown quantity of lorazepam and 3 alcoholic drinks, then notified friend, 70 days after first dose of brodalumab. Went to emergency room and was discharged same day. Brodalumab was discontinued.