Erratum to the FDA Briefing Document

Dermatologic and Ophthalmic Drugs Advisory Committee Meeting
July 19, 2016

BLA 761032, Siliq (brodalumab) injection, 210 mg/1.5 ml for the treatment of adults with chronic moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy

Erratum to the FDA Background Package

1. **General comment:** For the summary tables in PsO trials where incidence or rates were calculated, the Sponsor counted patients in the treatment group to which the patient was assigned during that time period. For example, for the 12 week pool, there were N=879 patients in the placebo group, N=613 patients in the ustekinumab group, and N=3066 patients in the brodalumab group. In the 52 week pool, there were N=613 patients in the ustekinumab group and N=4019 patients in the brodalumab group. In the long term pool, there were N=4464 patients in the all brodalumab group. As per study design, after week 52, all patients received brodalumab (mostly with 210 mg Q2W) throughout the long-term extension period and therefore are included in the N=4464 group. Thus, for the long-term pool, the Sponsor has evaluated safety based on incidence rates in brodalumab patients from the time of first brodalumab dose, based on the pre-specified analysis plan. In contrast, it appears that FDA evaluated safety using analyses that also presented patients who never received brodalumab treatment (i.e., pure ustekinumab and pure placebo patients that discontinued therapy prior to weeks 52 or 12), based on the actual treatment received at the study start.

   Consequently, the FDA incidences/rates differ from the Sponsor's rates for the Week 52 and long-term period, as reflected on page 22, Tables 6 and 7, and pages 39 and 40, Tables 22 and 23."

2. **Page 19:** It should be noted that 1/35 adjudicated SIB events occurred in a subject while they were receiving ustekinumab and before they received brodalumab. This subject was categorized as a brodalumab user, by definition, because they were eventually exposed to brodalumab.

3. **Page 22/Table 7**: A footnote has been added to the table to clarify that 1/35 SIB events occurred while the subject was receiving ustekinumab.

Table 7 SIB incidence and time-adjusted rates in PsO trials from Day 1 to end of follow-up

SIB	Brodalumab n = 3897	Brod after Ustek n = 567	Ustekinumab n = 49	Placebo n = 45
Number (%)	28 (0.72)	7** (1.23)	2 (4.08)	0
Follow-up time	8395.8	778.1	23.1	0
Incidence rate*	0.33	0.9	8.66	0
	Brodalumab + Brodalumab after Ustekinumab n = 4464			
Number (%; 95% CI)	35 ** (0.78; 0.63–1.25)			
Follow-up time	9173.9			
Incidence rate*	0.38 (0.27–0.53)			

*per 100 subject-years

** 1 of the 7 SIBs in the brodalumab after ustekinumab arm, and consequently, 1 of the 35 SIBs in brodalumab users occurred while the subject received ustekinumab.

4. **Page 27/28**: Please note that adverse events in this section and in Table 12 are reported as exposure-adjusted rates and not incidence. The title of Table 12 should be "Exposure-adjusted rates of Psychiatric Adverse Events in the Placebo-controlled Trials."

5. **Page 34**: The table entitled, "Rates of Suicidal Ideation and Behavior with Psoriasis Products" has been revised as follows:

Rates of Suicidal Ideation & Behavior (SIB) with Psoriasis Products

Dataset, indication	N	Exposure Patient - years	Completed suicides, N	Suicide Behaviors/ Attempts N	Suicides/ 100,000 PY	Attempts/ 100,000 PY	Suicides+ Attempts/ 100,000 PY	Suicidal Ideation, N	Ideation/ 100,000 PY
Brodalumab, all (updated from 120d SU)	6,243	10,438	6**	12$	57.5	115.0$	172.5$	24$	229.9$
Brodalumab, Ps trials (from 120d SU)	4,464	9162	4**	11$	43.7	120.1$	163.7$	22$	240.1$
Adalimumab, Ps	1,468	4,069	1**	0	24.6	0	24.6	3	73.7
Apremilast, Ps, PsA, RA‡	2,401	1,483	0†	2	0	134.9	134.9	2	134.9
Etanercept, Ps	1,807	2,773	0	1	0	36.1	36.1	2	72.1
Infliximab, Ps	1,564	1,263	0	3	0	237.5	237.5	0	0
Ixekizumab, Ps	4,209	6,480	0	10	0	154.3	154.3	0	0
Secukinumab Ps, PsA‡	3,928	3,225	0*	1	0	31	31	1	31
Unapproved biologic, Ps	2,520	3,011	2**	0	66.4	0	66.4	1	33.2
Ustekinumab, Ps	3,117	6,791	1	0	14.7	0	14.7	0	0
Pooled w/o brodalumab, apremilast	18,613	27,612	4	14	14.5	50.7	65.2	7	25.4

*There was 1 suicide during screening for a Ps trial , and 1 suicide in an ankylosing spondylitis trial (treatment blinded)
**Includes suicides during post-treatment follow-up †2 suicides occurred on placebo ‡Adjudicated with C-CASA
$Includes events detected with the electronic Columbia Suicide Severity Rating Scale
PY patient-years, Ps psoriasis, PsA psoriatic arthritis, RA rheumatoid arthritis, 120d SU 120 day Safety Update

6. **Page 39/Table 22**: It should be noted that one MACE event (cardiac death) occurred on the exact cut-off date of Week 52. To be consistent with the Sponsor's analysis of MACE events, we re-analyzed the first 52 weeks to include MACE events that occurred on the cut-off date. The updated Table 22 is provided below. At the end of the 12-week induction phase, the majority of placebo subjects and some ustekinumab subjects received brodalumab. During the active-controlled phase, 25 MACE events occurred in the brodalumab arm, and 2 MI events were detected in the ustekinumab arm. The incidence of MACE among subjects exposed to brodalumab was 0.7% (95%CI: 0.46–1.02), and the follow-up time adjusted rates was 0.7 cases per 100 subject-years (95% CI: 0.48–1.10).

Table 22. Number (%) and follow-up time adjusted incidence rates of adjudicated MACE in the active-controlled phase (first 52 weeks) of the three phase 3 PsO trials

MACE	**Brodalumab** **n = 3711**	**Brod after Ustek** **n = 124**	**Ustekinumab** **n = 489**	**Placebo** **n =39**
Number (%)				
MACE	25† (0.7)	0	2 (0.4)	0
CV death	4 (0.1)	0	0	0
MI	16 (0.4)	0	2 (0.4)	0
Stroke	5 (0.1)	0	0	0
Follow-up time	3297.2	75.5	494.8	
Incidence rate*	0.8	0	0.4	0

MACE	**Brodalumab + Brodalumab after Ustekinumab** **n = 3835**
Number (%; 95% CI)	25 (0.7, 0.46–1.02)
Follow-up time	3372.7
Incidence rate* (95% CI)	0.7 (0.48–1.10)

†One subject was originally in the placebo arm and was excluded from this analysis because MACE occurred before the first dose of brodalumab.
*per 100 subject-years

7. **Page 47/Table 29**: The neutropenia SMQ should be 100 events with a rate of 1.8 per 100-subject-years.

8. **Page 71 & 72/Table 16 & 17**: It should be noted that no SIB event occurred in the ustekinumab arm during the 12-week induction phase.