BRODALUMAB injection

Food and Drug Administration
Dermatologic and Ophthalmic Drugs Advisory Committee (DODAC)
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SPONSOR BRIEFING DOCUMENT
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List of Abbreviations and Definitions of Terms

Abbreviation or Term	Definition/Explanation
ADR	Adverse drug reaction
AE	Adverse event
AMQ	Amgen-defined medical queries
ANC	absolute neutrophil count
BLA	Biologic Licensing Application
BQL	below the quantification limit
BSA	body surface area
C-CASA	Columbia-Classification Algorithm for Suicide Assessment
CDC	Center for Disease Control and Prevention
CEC	Cardiovascular Events Committee
CI	confidence interval
CL/F	apparent clearance
CMH	Cochran-Mantel-Haenszel
CNS	central nervous system
CTCAE	Common Terminology Criteria for Adverse Events
CV	cardiovascular
CVD	Cardiovascular disease
CYP450	cytochrome P450
DLQI	Dermatology Life Quality Index
DSU	Day safety update
eC-SSRS	electronic Columbia-Suicide Severity Rating Scale
FDA	Food and Drug Administration
G-CSF	granulocyte colony stimulating factor
HADS	Hospital Anxiety and Depression Scale
HLGT	High-level group term
HLT	high-level term
HR	Hazard ratio
IBSAS	Integrated brodalumab safety analysis set
IgG2	immunoglobulin G2
IL-17	interleukin-17
IL-17RA	interleukin-17 receptor
ISAS	Integrated safety analysis set
ISS	Integrated safety summary
KHK	Kiowa Hakko Kirin
MACE	Major adverse cardiac events
MedDRA	Medical Dictionary for Regulatory Activities
MI	Myocardial infarction
NCI	National Cancer Institute

Abbreviation or Term	Definition/Explanation
NE	not estimable
NRI	Non-responder Imputation
OR	Odds Ratio
PASI	Psoriasis Area and Severity Index
PD	Pharmacodynamics
PHQ-8	Patient Health Questionnaire-8
PK	Pharmacokinetics
PRO	Patient-reported outcome
PSA	Psoriatic arthritis
PSI	Psoriasis Symptom Inventory
PT	Preferred term
Q2W	Every 2 weeks
Q4W	Every 4 weeks
Q8W	Every 8 weeks
QOL	quality of life
RR	risk ratio
SAP	statistical analysis plan
SC	subcutaneous
SD	standard deviation
SEER	Surveillance, Epidemiology, and End Results
SIB	Suicidal Ideation and Behaviour
SMR	Standardized motality rate
SMQ	Standardized MedDRA Queries
SOC	System organ class
sPGA	static Physician's Global Assessment of Psoriasis
TIA	transient ischemic attack
TNF	tumor necrosis factor
UK	United Kingdom
US	United States
Vz/F	volume of distribution

1 Executive Summary

1.1 Brodalumab Product and Indication

Brodalumab is a human interleukin-17 receptor A (IL-17RA) antagonist.

The Sponsor has submitted a Biologic License Application (BLA) for brodalumab injection for the proposed indication: *for the treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy.* The recommended dose is 210 mg of brodalumab administered by subcutaneous (SC) injection at Weeks 0, 1 and 2 followed by 210 mg every 2 weeks (Q2W) thereafter.

1.2 Brodalumab Introduction

The initial IND for brodalumab injection was submitted in 2008 by Amgen. In 2015, the sponsorship of the program was transferred to AstraZeneca, who subsequently transferred the program to Valeant. The BLA contains 21 studies conducted by Amgen and 4 studies conducted exclusively in Japan by Amgen's partner Kiowa Hakko Kirin (KHK). The core Phase 2 and 3 clinical program for brodalumab in psoriasis was comprised of 5 studies, one randomized Phase 2b study with its separate open label extension, and three Phase 3 randomized, placebo-controlled studies (AMAGINE-1, AMAGINE-2, and AMAGINE-3) with open-label, long-term extensions. For all three Phase 3 studies, the primary endpoint compared brodalumab to placebo for PASI 75 and sPGA success at Week 12. For AMAGINE-2, and AMAGINE-3, brodalumab 210 mg Q2W was compared to ustekinumab for PASI 100 as a co-primary endpoint at Week 12. Key secondary endpoints included PASI 100, sPGA 0, PASI 75 at Week 12 and are further detailed in Section 5.1.1. Feedback from the US Food and Drug Administration (FDA) was incorporated in the design of the brodalumab psoriasis program.

Brodalumab met all primary endpoints (PASI 75 vs placebo, sPGA vs placebo, and PASI 100 vs ustekinumab), across all 3 pivotal Phase 3 studies. Approximately twice as many patients who received brodalumab 210 mg Q2W achieved total skin clearance, as measured by PASI 100, compared with ustekinumab at weeks 12 and 52. Total skin clearance is important to patients and results in meaningful improvements to patient quality of life (QOL) (Strober 2016).

Brodalumab's safety profile is consistent with that expected of a biologic agent that targets the IL-17 pathway. Events of Suicidal Ideation and Behavior (SIB) have been observed in the brodalumab program as well as Major Cardiovascular Events (MACE). Although these types of events are not unexpected given the high background comorbidity in the psoriasis population, they are considered important potential risks and will be the focus of the advisory committee.

The Sponsor is proposing pharmacovigilance activities, including follow-up with targeted questionnaires. In addition, the plan for SIB includes labeling in precautions and warnings and a communication and education plan for physicians and patients. Additionally, to augment the understanding of potential risks, a prospective, controlled cohort registry study is planned that will include an appropriate comparator cohort of patients receiving other therapies for moderate to severe plaque psoriasis. This would utilize a large established North American psoriasis registry that currently is expanding its patient population and is managed by an independent organization. The aim is to capture relevant data prospectively, including information on SIB and MACE, to enable comparison among cohorts.

This Briefing Document provides an overview of the brodalumab program (Section 4), focusing on efficacy (Section 4), and general safety including MACE and SIB (Sections 6, 7, and 8, respectively). Conclusions regarding benefit risk and pharmacovigilance recommendations are presented in Section 9.

1.3 Brodalumab's Contribution to Current Psoriasis Treatments

Brodalumab provides an important new therapy for management of psoriasis, because there remains a significant unmet patient need for new agents that can provide novel mechanisms of action, rapid onset of effect, improved, and sustained total skin clearance, greater compliance, and minimization of drug-specific safety concerns.

Psoriasis is a chronic, painful, and frequently life-altering immune-mediated inflammatory skin disease associated with serious comorbidities and substantial impairment of physical and psychological QOL (Griffiths and Barker 2007, de Korte 2004). Most recent estimates in the US using NHANES data suggest that the prevalence of diagnosed psoriasis among adults is around 3.1% (Helmick 2014) or 3.2% (Rachakonda 2014). Of patients with diagnosed psoriasis in the US, about 18% are estimated to have moderate to severe disease (Helmick 2014). More than 75% of patients with moderate to severe plaque psoriasis experience significant itching and greater than 55% report moderate or worse levels of pain (Lebwohl 2014).

Psoriasis patients also experience significant cardiovascular (CV) and psychiatric comorbidities. There is an increased prevalence of traditional CV risk factors, such as diabetes, hypertension, dyslipidemia, tobacco use, and obesity (Neimann 2006). In addition, the prevalence of depression, anxiety, and suicidality, as well as substance abuse is increased (Kimball 2014, Kim 2010, Kurd 2010).

Agents that block tumor necrosis factor (TNF)-α (adalimumab, etanercept, and infliximab) or inhibit IL-12 and IL-23 (ustekinumab) have been associated with high objective response rates in

clinical trials (Gelfand 2012). However approximately 75% of patients in clinical trials or in clinical practice still do not achieve total skin clearance (Menter 2008, Papp 2008, Gelfand 2012). Gniadecki and colleagues reported that the overall efficacy of TNF-α inhibitors diminishes with time, and the major reasons for stopping treatment were loss of efficacy in 21% to 50% of patients (Levin 2014, Yeung 2013, Gniadecki 2011).

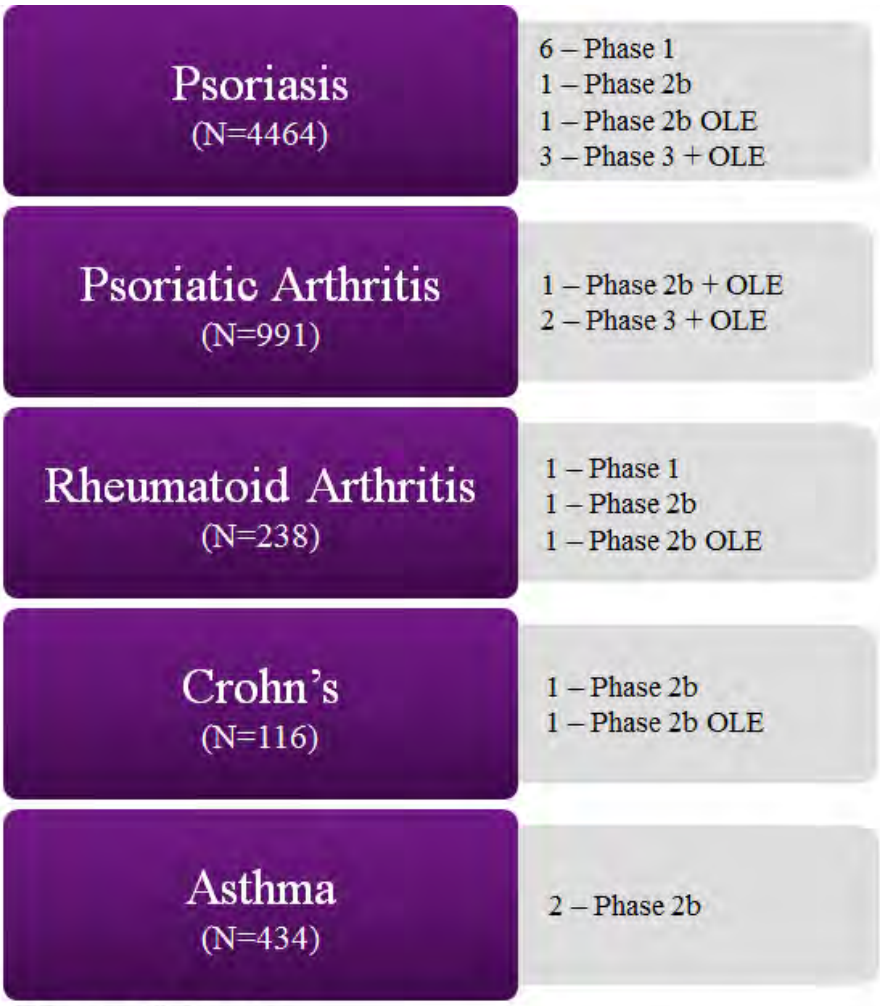
Total skin clearance is an important treatment goal that has both measurable and clinically meaningful benefits, even when compared to small amounts of residual disease. The greatest improvements in patient-reported outcomes are seen in patients achieving total skin clearance. Moreover, clinically important improvements in QOL are associated with the change from almost clear to clear skin (Takeshita 2014, Strober 2016).

1.4 Clinical Program

Brodalumab was robustly investigated, with one of the largest databases accrued for a biologic agent. The overall program is presented in Figure 1–1. Brodalumab safety information was evaluated across multiple indications including psoriasis, psoriatic arthritis, rheumatoid arthritis, asthma, and Crohn's disease. See Sections 6, 7, and 8 for further discussion.

The overall brodalumab safety package includes 6243 brodalumab-treated patients with a total of 9719.7 patient-years of brodalumab exposure and 10452 patient years of follow-up exposure. There were 4464 psoriasis patients exposed to brodalumab, providing an overall exposure of 8655 patient-years and a corresponding follow-up period of 9173.9 patient-years. All brodalumab ongoing studies, including Phase 2 and 3 studies, across all indications, were terminated in mid-2015 due to Amgen's decision (the Sponsor at the time) not to continue development. At that time, all psoriasis studies had moved into the open-label extension periods and the majority of patients had follow-up periods of 1 to 2 years.

Figure 1–1 Studies supporting the indication



OLE = open label extension
4 additional studies across indications were conducted in Japan by KHK

1.5 Efficacy

The Phase 3 program included three studies, AMAGINE-1, AMAGINE-2, and AMAGINE-3. AMAGINE-1 was placebo controlled and included a withdrawal and retreatment evaluation. Patients who were responders at Week 12 were re-randomized to receive placebo or to continue their induction dose in a blinded manner. AMAGINE-2 and AMAGINE-3 were identical in design and included both a placebo and an active control (ustekinumab). Patients originally randomized to receive brodalumab during the induction phase were rerandomized at Week 12 to receive 1 of 4 maintenance regimens of brodalumab. All included open label extensions

(additional detail provided in Section 5.1 and study designs are provided in Figure 5–1 and Figure 5–2).

The inclusion criteria of the 3 Phase 3 clinical studies were similar to other programs for moderate to severe psoriasis with relatively few restrictions. Unlike other recent psoriasis development programs, patients with a history of psychiatric disorders were not specifically excluded.

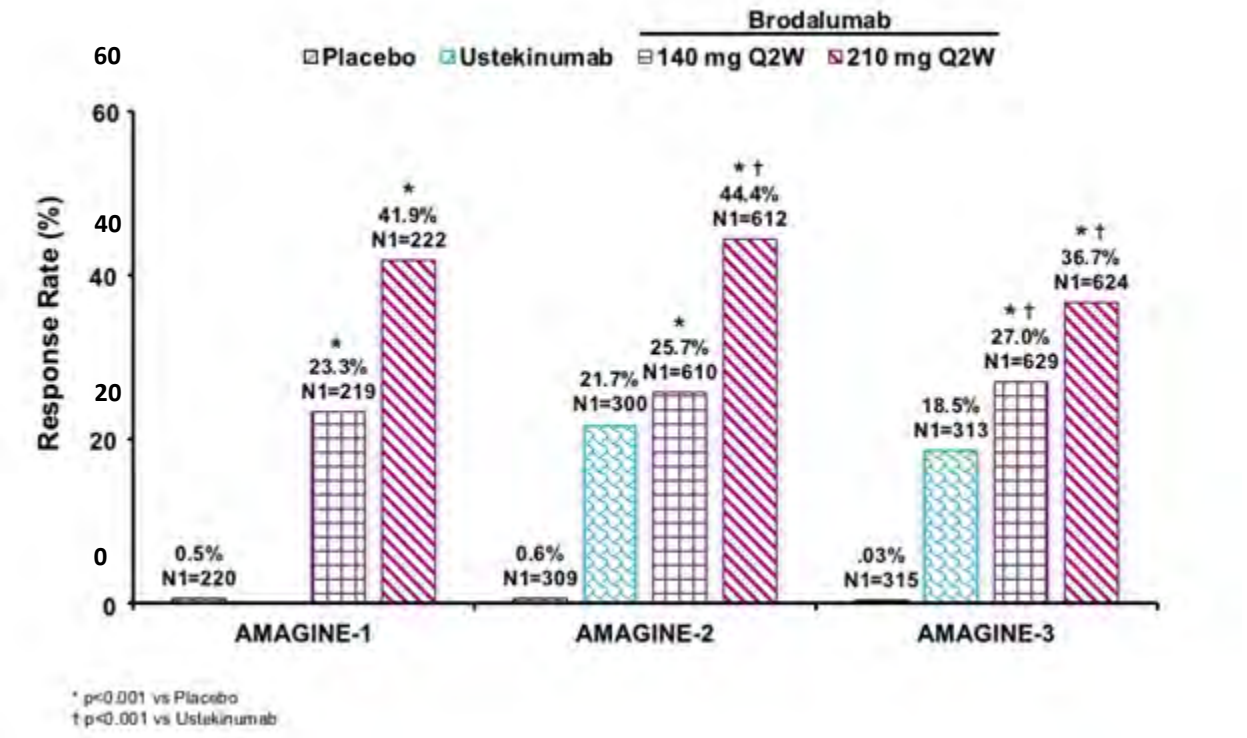
All primary and key secondary endpoints are shown in Table 5–1. The static Physician Global Assessment of Psoriasis (sPGA) success (0 or 1) and the Psoriasis Area and Severity Index 75 (PASI 75) at Week 12 were co-primary efficacy endpoints in all 3 Phase 3 studies for brodalumab and placebo comparisons. PASI 100 was a co-primary endpoint for comparison to ustekinumab for the 210 mg Q2W at Week 12. PASI 100 was chosen as a key endpoint because it represents total skin clearance.

At Week 52, the maintenance endpoint across the three studies was sPGA success (0 or 1) for brodalumab versus placebo in AMAGINE-1, and comparison of the four maintenance regimens for AMAGINE-2 and 3.

Brodalumab 210 mg Q2W demonstrated consistent efficacy; all primary objectives in all 3 Phase 3 studies were met. All key secondary objectives comparing brodalumab 210 mg Q2W and 140 mg Q2W to placebo were also met. Additionally, 210 mg Q2W demonstrated incremental efficacy as compared with the 140 mg Q2W across all efficacy endpoints.

Efficacy results across the 3 studies, as measured by PASI 100 at Week 12, are presented in Figure 1–2. Across AMAGINE-2 and AMAGINE-3, approximately twice as many patients who received 210 mg Q2W achieved total skin clearance compared with ustekinumab.

Figure 1–2 **Summary of PASI 100 at Week 12 by study – AMAGINE-1, AMAGINE-2, and AMAGINE-3 (Full Analysis Set)**



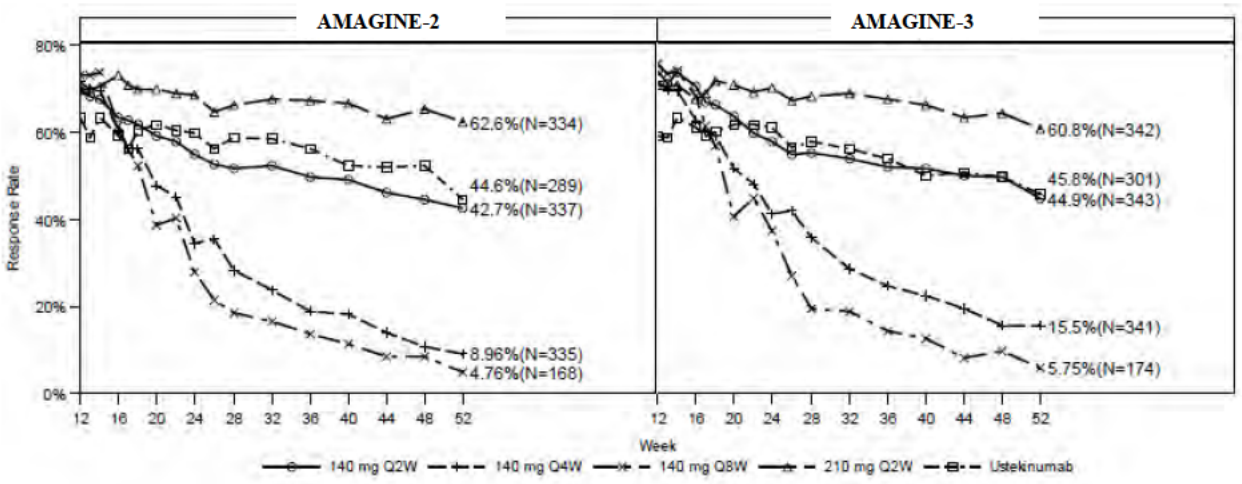
N1=Number of patients randomized and had a valid measurement value at Week 12; PASI 100=100% improvement in the Psoriasis Area and Severity Index; Q2W=every 2 weeks.
Non-responder Imputation (NRI) was used to impute missing data.
Treatment groups are defined as planned treatment for the induction phase.

The onset of action was faster for brodalumab than for ustekinumab. PASI 75 response was apparent as early as Week 2 for the 210 mg Q2W and 140 mg Q2W groups in AMAGINE-2 and AMAGINE-3 versus ustekinumab (see Section 5.2.3.3). A similar trend was observed for sPGA and PASI 100.

For AMAGINE-1, during the withdrawal / retreatment phase 83% of patients on 210 mg Q2W retained their sPGA response. When patients rerandomized to placebo were retreated with 210 mg Q2W, sPGA success (0 or 1) was achieved in 80% of patients after 12 weeks of retreatment.

In both AMAGINE-2 and AMAGINE-3, the percentage of responders in maintenance treatment was higher in the 210 mg Q2W group compared to ustekinumab and 140 Q2W brodalumab maintenance dosing regimens starting at approximately Week 16 and continuing through Week 52 (Figure 1–3).

Figure 1–3 **sPGA success (clear [0] or almost clear [1]) status by Week by study - AMAGINE-2 and AMAGINE-3 (52 Week Analysis Set)**



Q2W=Every 2 weeks; Q4W=Every 4 weeks; Q8W=Every 8 weeks; sPGA=Static Physician's Global Assessment of Psoriasis.

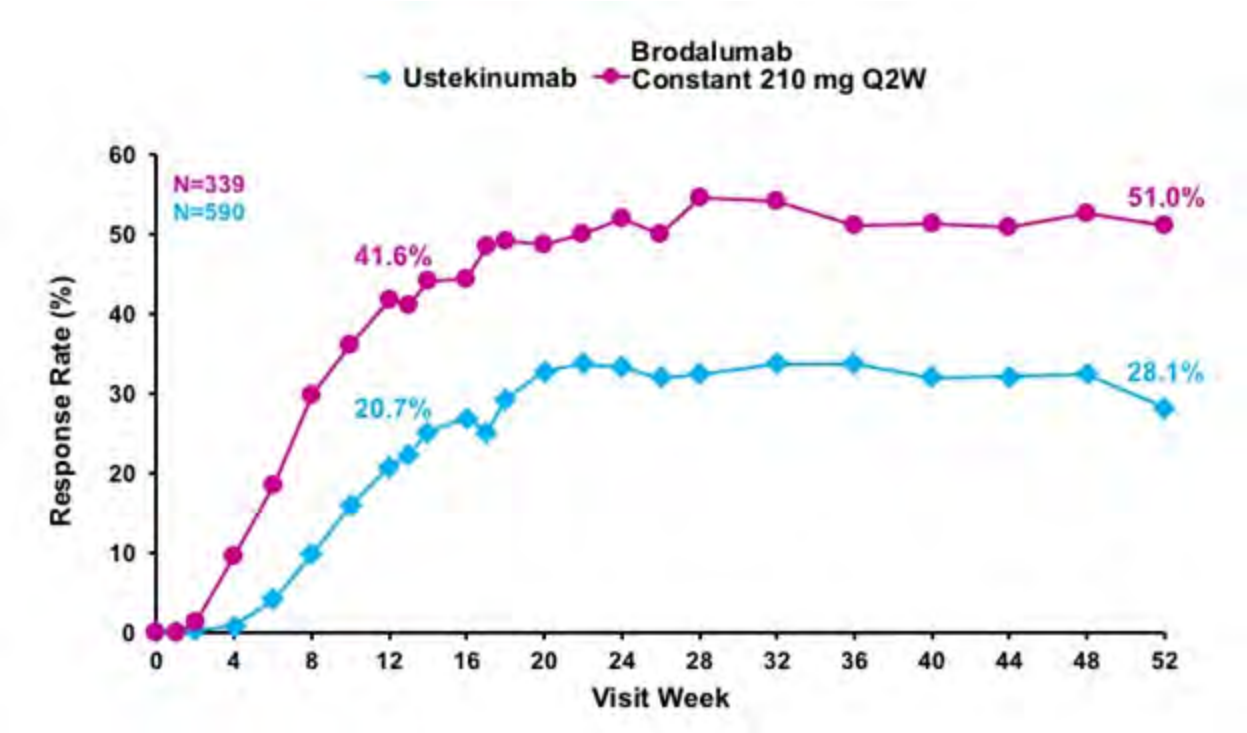
Patients who entered maintenance phase are included.

Patients in all treatment groups with an inadequate response (defined as single sPGA of ≥3 or persistent sPGA values of 2 over at least a 4-week period) at or after Week 16 (and through Week 52) are imputed as non-responders for subsequent weeks up to Week 52

Treatment groups are defined as planned treatment for the maintenance phase.

Integrated results for AMAGINE-2 and AMAGINE-3 are presented below, demonstrating that overall nearly twice as many patients achieved PASI 100 at Week 52 for brodalumab compared to ustekinumab. The percentage of patients originally randomized to brodalumab 210 mg, and who continued the same treatment through 52 weeks achieving PASI 100 was 51.0% compared to patients who remained on ustekinumab over the 52-week period (28.1%) (Figure 1–4). Similar results were observed in the individual studies.

Figure 1–4 **PASI 100 up to Week 52 for brodalumab 210 mg Q2W (constant dose) and ustekinumab (constant dose) - Integrated AMAGINE-2 and AMAGINE-3**



Patients in all treatment groups with an inadequate response (defined as single sPGA of ≥3 or persistent sPGA values of 2 over at least a 4-week period) at or after Week 16 (and through Week 52) are imputed as non-responders for subsequent weeks up to Week 52.

Non-responder Imputation (NRI) is used to impute missing data.

Treatment groups are defined as planned treatment for induction / maintenance phases

Ustekinumab patients were administered ustekinumab in the 12-Week phase, continued on ustekinumab in the maintenance phase.

Brodalumab patients were administered brodalumab 210 mg Q2W in the 12-Week phase, were re-randomized to brodalumab 210 mg Q2W in the maintenance phase.

N=number of patients, presented at: baseline, Week 12, and Week 52

In summary, brodalumab 210 mg Q2W met all primary endpoints against placebo and ustekinumab, across all 3 pivotal Phase 3 studies. It was also consistently better than 140 Q2W. This trend was maintained through the 52 week period. The 210 mg Q2W dose is recommended as both induction and maintenance treatment for patients with moderate to severe psoriasis. Approximately twice as many patients who received brodalumab 210 mg Q2W achieved total skin clearance, as measured by PASI 100, compared with ustekinumab at weeks 12 and 52. Brodalumab 210 Q2W has demonstrated meaningful improvements to psoriasis patients, in achieving total skin clearance, and improvements in patient-reported outcomes and QOL.

1.6 Safety

1.6.1 General Safety Considerations for the Psoriasis Population

Patients suffering from psoriasis are generally afflicted with several comorbidities including those of cardiovascular and psychiatric origin.

Commonly associated comorbidities in psoriasis include cardiovascular (CV) disease (hypertension and increased risk for myocardial infarction, stroke, and CV death), obesity, type 2 diabetes, arthritis, and chronic renal disease (Kimball 2011, Reich 2012). Severe psoriasis is associated with increased risk of MI (Reich 2012), and Gelfand and colleagues have found that severe psoriasis is also associated with increased overall mortality risk (Gelfand 2007).

Psoriasis is also associated with serious psychiatric comorbidities, including depression, anxiety, and suicidality, as well as substance abuse (Kimball 2014, Kim 2010, Kurd 2010). The psychosocial impact of psoriasis can be devastating, with many patients suffering from isolation, stigmatization, shame and embarrassment, and difficulties in sexual relations (Russo 2004, Hrehorow 2012, Armstrong 2012, Gupta and Gupta 1997, Ramsay 1988, Weiss 2002).

1.6.2 Overview of Safety in the Brodalumab Development Program

Brodalumab safety was well-characterized, with a profile consistent with other biologic agents targeting the IL-17 pathway.

The 12-week pool allows direct randomized comparisons of brodalumab with placebo and active comparator (ustekinumab) for the initial 12-week period. The results are generally summarized as patient incidence. Beyond the 12 week period, rates are expressed as exposure adjusted (time from first dose plus 1 dosing interval since last dose). For rare events such as major adverse cardiac events (MACE), suicidal ideation and behavior (SIB) and malignancy, follow up time of observation adjusted (time from first dose plus time till end of observation after last dose) rates are also used.

Overall, in the clinical trial program, brodalumab was well tolerated. In the 12-week placebo controlled pool, there was no imbalance between brodalumab and placebo for adverse events (AE) (57.6% vs 51.3%), serious adverse events (SAE) (1.6% vs 1.7%), adverse events leading to investigational product (IP) discontinuation (1.1% vs 0.9%) and fatal events (<0.1% vs 0) respectively. In the 52-week treatment pool there was no imbalance between brodalumab and ustekinumab (exposure adjusted rates per 100 patient years): AEs 401.3 vs 394.6; SAEs 8.5 vs 8.3; AEs leading to discontinuation of IP (3.4 vs 3.7) and fatal AEs (0.4 vs 0.3).

Common AEs identified in the brodalumab treated patients included nasopharyngitis, upper respiratory tract infection, arthralgia, and headache.

The serious adverse events (SAEs) with the highest exposure-adjusted rates (per 100 patient years) at Week 52 were myocardial infarction (0.3 all-brodalumab group, 0.2 ustekinumab), cellulitis (0.2 all-brodalumab, 0.2 ustekinumab), and cholelithiasis (0.2 all-brodalumab, 0.0 ustekinumab).

Fatal events overall are reported in Section 6.3 and those related to MACE and SIB are discussed in Section 7 and 8, respectively.

There were no increases in the rates of the AE categories between the 52 week and long term pools.

1.6.3 Identified and Potential Risks

Identified risks include worsening of Crohn's disease in patients with active Crohn's disease, infections, and neutropenia (Section 6.7). Potential risks include major adverse cardiovascular events (MACE) (Section 7), suicidal ideation and behavior (SIB) (Section 8), hypersensitivity (Section 6.7), and malignancy (Section 6.7).

1.6.3.1 MACE

Major adverse cardiac events (MACE) were prospectively evaluated in the psoriasis Phase 3 studies (AMAGINE-1, AMAGINE-2, and AMAGINE-3). Events were Cardiovascular Events Committee (CEC)-adjudicated. Most patients for whom a MACE was reported had ≥ 1 major cardiovascular risk factor.

In the 12 week period there were no MACE events in the placebo or ustekinumab arms and 3 (0.1%) in the brodalumab 140 mg Q2W treatment arm (2 myocardial infarctions and 1 stroke). At Week 52, the exposure adjusted rate for brodalumab treated patients was 0.6 per 100 patient years (95% CI: 0.37, 0.94) compared to the rate in ustekinumab treated patients of 0.4 per 100 patient years (95% CI: 0.05, 1.46). The follow-up time adjusted rate for brodalumab treated patients was 0.7 per 100 patient years (95% CI: 0.46, 1.06) compared to the rate in ustekinumab treated patients of 0.4 per 100 patient years (95 %CI: 0.05, 1.41).

In the long term, the exposure adjusted rate for brodalumab treated patients was consistent with that reported at Week 52 (0.5 per 100 patient years (95% CI: 0.36, 0.69)). The exposure-adjusted rate of MACE derived from a systematic literature review of all biologic and systemic therapies for psoriasis and psoriatic arthritis was 0.47 per 100 patient years (95% CI: 0.39, 0.57). The

follow-up time adjusted rate for brodalumab treated patients was 0.6 per 100 patient years (95% CI: 0.48, 0.84).

These rates were based on relatively few MACE events and showed a potentially higher rate of MACE in brodalumab patients, but with overlapping confidence intervals in comparison to ustekinumab.

An evaluation of MACE events was performed which included an assessment of pre-disposing risks related to cardiovascular disease in patients in the program, evaluation of the overall events of cardiovascular disease and adjudicated MACE, comparison of rates of MACE observed with brodalumab to external literature reviews and recent relevant study programs, and assessment of biologic plausibility.

The sponsor concludes that the evidence does not support a causal association of MACE with brodalumab. However, given the seriousness of these events and the high background rate in the patient population the sponsor is considering MACE a potential risk and has proposed pharmacovigilance.

1.6.3.2 Suicidal Ideation and Behavior (SIB)

Patients with psoriasis are at a higher risk of suicidal ideation and behavior (SIB) and have an increased prevalence of psychiatric disorders that are SIB risk factors compared with the general population. Patients with SIB risk factors were not specifically excluded from the brodalumab clinical trials.

Suicidal ideation and behavior was identified as a potential risk in 2014, late in in the brodalumab psoriasis development program, when most patients had completed 52 weeks on study. Screening tools for depression (PHQ-8) and suicidality (eC-SSRS) were implemented but as all psoriasis patients had been enrolled, there is no baseline information available. Per protocol, patients with scores reaching a pre-defined threshold were referred to a mental health professional and/or withdrawn from investigational product.

The Sponsor has evaluated the brodalumab study population for pre-disposing risk factors, and carefully reviewed individual cases, comparison of rates of SIB observed with brodalumab to external literature reviews and recent relevant study programs, and assessment of biologic plausibility.

There were no imbalances in neuropsychiatric events across brodalumab, ustekinumab, and placebo groups in the controlled periods.

Across all indications in the brodalumab program there were 39 patients with suicidal ideation and behavior. Of these, 18 had suicidal behaviors, including 6 completed suicides. There were 24 ideations associated with brodalumab (Table 1–1, see Section 8 for additional information.)

Table 1–1 Follow-up observation time-adjusted patient incidence rates of SIB events from first dose of brodalumab through the 120-day safety update end of study - patients who received ≥1 dose of brodalumab in Phase 2 and Phase 3 Sponsor studies (All Indications)

Event of interest category	Psoriasis Pt-yr =9161.8 (N=4464) n (r)	Asthma (Pt-yr=165) (N=434) n (r)	Crohn's (Pt-yr=33.6) (N=116) n (r)	Psoriatic arthritis (Pt-yr=920.2) (N=991) n (r)	Rheumatoid arthritis (Pt-yr=157.6) (N=238) n (r)	Total (Pt-yr=10438) (N=6243) n (r)
Suicidal ideation and behavior event	**34 (0.37)**	**0 (0.00)**	**0 (0.00)**	**3 (0.33)**	**2 (1.27)**	**39 (0.37)**
Suicidal behavior	15 (0.16)	0 (0.00)	0 (0.00)	1 (0.11)	2 (1.27)	18 (0.17)
Completed suicide[a]	4 (0.04)[b]	0 (0.00)	0 (0.00)	1 (0.11)	1 (0.63)	6 (0.06)[b]
Suicidal ideation	22 (0.24)	0 (0.00)	0 (0.00)	2 (0.22)	0 (0.00)	24 (0.23)

[a] The category "Completed Suicide" includes all fatal events from the Suicidal Behavior events of interest category.
[b] One fatal event reported as suicide was later adjudicated as indeterminate.
MedDRA v. 18.1; N= patients in Studies 20090061/20090402, 20090072/20100008, 20090203, 20101227, AMAGINE-1, AMAGINE-2, AMAGINE-3, 20090406, 20110144, and 20120141 with ≥1 dose of brodalumab.
Patients from site 12002 in the completed phase 2 asthma study were excluded from the analysis.
Pt-yr = Total patient-years of follow-up through min (patients first suicidal ideation and behavior event, end of study); n = number of patients with adverse events; r = follow-up observation time adjusted patient incidence rate per 100 patient-years (n/pt-yr*100). Multiple occurrences of the same events for a patient are counted once.
Total patient-years are truncated at patient's first suicidal ideation and behavior event.

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 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.

Table 1–2 Comparison of Follow Up Observation Time-adjusted Patient Incidence Rates (per 100/patient-years) of SIB Events in Literature to Brodalumab through End of Study – Long Term Pool

	Literature Pooled Estimate[a]			Brodalumab (psoriasis)	
SIB Category	Exposure (Total PY)	n (r)	95% CI	n (r)	95% CI
Attempted suicide/behaviour[b]	10,125	4 (0.040)	0.011, 0.101	10 (0.109)	0.052, 0.201
Completed suicide[c]	28,420	8 (0.028)	0.012, 0.055	4 (0.044)	0.012, 0.112
All SIB	2,740	3 (0.109)	0.023, 0.320	34 (0.371)	0.257, 0.519

[a] E. Delzell and E. Chang. Adverse Event Rates in Psoriasis or Psoriatic Arthritis. Exponent Technical Report. March 19, 2015.

[b] Suicide attempt and behavior PTs are combined

[c] Includes event reported as intentional overdose

The outcome of Brodalumab represents patients from psoriasis studies 20090062/20090403, AMAGINE-2, AMAGINE-3 and AMAGINE-3 with ≥ 1 dose of brodalumab.

Total patient-years (PY) of follow-up through min(patients first suicidal ideation and behavior event, end of study);

n = number of patients with AEs; r = follow-up observation time-adjusted patient incidence rate per 100 patient-years (n/PY*100). Multiple occurrences of the same events for patient are counted once.

Total patient-years are truncated at patients first suicidal ideation and behavior event.

Rates of SIB reported in regulatory review documents from clinical trial programs of recently approved agents for psoriasis include apremilast and anti-IL-17A agents, secukinumab, and ixekizumab as described below:

In the apremilast and the secukinumab psoriasis programs, there was 1 completed suicide each from 52 week data in the apremilast (on placebo) and secukinumab (screening phase) for estimated program rates of 0.052-0.062 per 100 patient-years and 0.034 per 100-patient years of exposure, respectively.

In the overall ixekizumab program, there were 10 suicide attempts in patients treated with ixekizumab, and 1 suicide attempt in a patient treated with placebo, resulting in rates of 0.15 per 100-patient years of exposure and 0.55 per 100-patient years of exposure.

Rates of completed suicide from these development programs are consistent with those seen in the brodalumab program. Rates of attempted suicide in the brodalumab program are similar to those seen in the ixekizumab program, but there is variability across different programs.

The sponsor concludes that the evidence does not support a causal association between brodalumab and SIB. Because these events have been observed in the program and due to the seriousness of these events, the sponsor has proposed language in the Warnings and Precautions section of the proposed labeling, and a risk minimization strategy which includes a communication plan and education tools for physicians and patients.

1.7 Benefit Risk Profile of Brodalumab

The sponsor has concluded that the benefit of skin clearance and the resulting quality of life improvement outweigh the risks observed with brodalumab.

Brodalumab 210 mg Q2W is a highly efficacious novel therapy to treat patients with moderate to severe plaque psoriasis requiring systemic therapy. To further understand adverse events of interest, the Sponsor has proposed pharmacovigilance activities, including targeted questionnaires. In addition, the plan for SIB includes labeling in precautions and warnings and a communication and education plan for physicians and patients. Additionally, to augment the understanding of potential risks, a prospective, controlled cohort registry study is planned that will include an appropriate comparator cohort of patients receiving other therapies for moderate to severe plaque psoriasis. This would utilize a large established North American psoriasis registry that currently is expanding its patient population and is managed by an independent organization. The aim is to capture relevant data prospectively, including information on SIB and MACE, to enable comparison among cohorts.

2 Introduction to the Brodalumab Molecule

Brodalumab is a human anti–IL-17–receptor A (IL-17RA) monoclonal antibody that blocks IL-17–mediated signaling, in contrast to other molecules (secukinumab, ixekizumab) which bind the IL-17A ligand. Blocking the IL-17 receptor on keratinocytes and immune cell types has emerged as a critical target for the treatment of psoriasis and has been shown to reduce inflammation, hyperproliferation, and skin thickening in a number of experimental models (Martin 2013). This cytokine-targeted strategy to block signaling through IL-17RA is a novel mechanism to inhibit the inflammation and clinical symptoms associated with psoriasis.

3 Unmet Medical Need in Psoriasis

Brodalumab provides an important new therapy for management of psoriasis, because there remains a significant unmet patient need for new agents that can provide novel mechanisms of action, rapid onset of effect, improved, and sustained total skin clearance, greater compliance, and minimization of drug-specific safety concerns.

Psoriasis is a chronic, common immune-mediated inflammatory skin disease associated with substantial impairment of physical and psychological quality of life (Griffiths and Barker 2007, de Korte 2004). It has an estimated prevalence of 2% to 3% in the United States (US) (Stern 2004; Koo 1996) and from 0.6% to 8.5% in the European Union (Chandran and Raychaudhuri 2010). For most patients, moderate to severe plaque psoriasis is a chronic, lifelong condition that can be disfiguring. Plaque psoriasis manifests as thickened, well-demarcated, erythematous patches of skin covered with silvery scales. The lesions often arise at predisposed areas (eg, extensor aspects of knees and elbows) but can also be disseminated (generalized) over the body. Other body sites that may be affected by psoriasis include nails and the scalp. The skin lesions are associated with sensory symptoms such as pruritus, pain, and discomfort (Chang 2007; Ljosaa 2010). Other medical comorbidities associated with psoriasis that contribute to the burden on quality of life include obesity, metabolic syndrome, arthritis, cardiovascular disease, depression, and suicidality (Kim 2010, Kurd 2010, Kimball 2011).

The current therapeutic options for moderate to severe plaque psoriasis include phototherapy, topical agents (eg, corticosteroids), conventional systemic therapy (eg, cyclosporine, methotrexate, and oral retinoids), new oral therapies such as apremilast, and biologic therapy (eg, adalimumab, etanercept, infliximab, ustekinumab, secukinumab, and most recently, ixekizumab) (Hsu 2012; Menter 2008). These treatments have varied levels of effectiveness and may be associated with loss of effect, adverse reactions, and dose-limiting toxicities, which can be difficult to manage for this chronic disease.

At the time the brodalumab program was initiated, ustekinumab was the most effective biologic agent available with 18.2% of patients achieving total skin clearance (100% improvement in the Psoriasis Area and Severity Index [PASI 100]) at Week 12 in a large phase 3 study (Papp 2008). Even with these newer agents, many patients still do not achieve optimal efficacy of total skin clearance, with as few as 6% of patients achieving PASI 100 in clinical practice with commonly used biologics and only 39% achieving 90% improvement in PASI (PASI 90) with ustekinumab (Inzinger 2011).

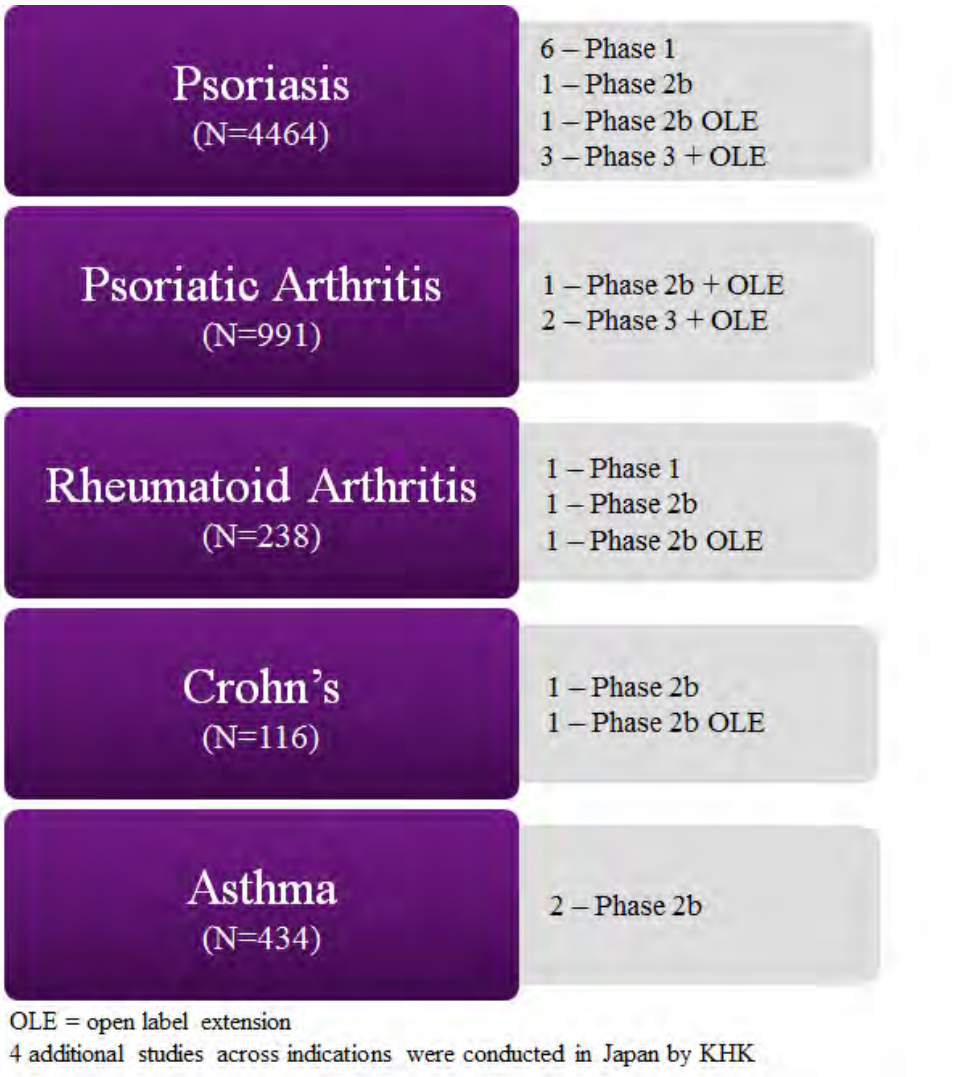
Furthermore, despite the variety of treatment options available, patients are often dissatisfied with current therapeutic approaches, and their compliance with treatment is poor. These patients are looking forward to newer and better agent always as stated by several psoriasis patients in a FDA sponsored workshop in March 2016. Annual treatment discontinuation rates of 15% to 25% for traditional systemic therapies and phototherapy have been reported (Yeung 2013). The most common reasons for discontinuation of these therapies are lack of efficacy, adverse events, and treatment inconvenience. Gniadecki and colleagues reported that the overall efficacy of TNF-alpha inhibitors diminishes with time, and the major reasons for stopping treatment were loss of efficacy in 21% to 50% of patients, followed by adverse events in as many as 37% of patients (infection, skin rash), and treatment inconvenience in 31% of patients receiving phototherapy (Levin 2014; Yeung 2013; Gniadecki 2011).

While newer treatment options provide improved outcomes, there remains a significant unmet patient need for novel agents and mechanisms that can provide a rapid onset of effect, improved and sustained total skin clearance and minimization of drug-specific safety concerns.

4 Clinical Development Program

The BLA contains 21 studies conducted by Amgen and 4 studies conducted exclusively in Japan by Amgen's partner Kiowa Hakko Kirin (KHK) (Figure 4–1).

Figure 4–1 Studies Supporting the Indication



OLE = open label extension
4 additional studies across indications were conducted in Japan by KHK

Feedback from the US Food and Drug Administration (FDA) was incorporated into the brodalumab development program.

The core Phase 2 and 3 clinical program for brodalumab in psoriasis was comprised of 5 studies, 1 Phase 2b study (study 20090062 and open label extension study 20090403), and 3 Phase 3 placebo-controlled studies (AMAGINE-1, AMAGINE-2, and AMAGINE-3) with open-label, long-term extensions. In the brodalumab Phase 2 and 3 psoriasis program, 4464 patients were exposed to brodalumab, providing an overall exposure of 8655.0 patient-years. The majority of all patients had follow-up periods up to 2 years.

All brodalumab ongoing studies, including Phase 2 and 3 studies, across all indications, were terminated in mid-2015 due to Amgen's decision (the Sponsor at the time) not to pursue

development. Sponsorship was assumed by AstraZeneca Pharmaceuticals and was transferred to Valeant Pharmaceuticals in April 2016. The presentations of 52 week controlled data for efficacy and safety were not affected by this termination given that all patients were in the long term phase of the studies.

In addition to the studies that supported the psoriasis indication, relevant safety information is available from completed Phase 2 studies in other indications rheumatoid arthritis, asthma, and Crohn's disease and terminated Phase 2 and 3 studies in psoriatic arthritis.

The overall brodalumab safety package across multiple investigational indications includes 6243 brodalumab-treated patients with a total of 9719.7 patient-years of brodalumab exposure.

5 Efficacy

All primary objectives comparing brodalumab to placebo and ustekinumab in the Phase 3 studies were met. All key secondary objectives comparing brodalumab 210 mg Q2W and 140 mg Q2W to placebo were also met. Additionally patients on 210 mg Q2W dose demonstrated higher efficacy compared with patients on 140 mg Q2W dose.

All 3 studies demonstrated the 210 mg Q2W dose provided consistent efficacy from the results of all primary and key secondary clinical endpoints, as well as Patient Reported Outcome (PRO) endpoints. The response rate for the 210 mg Q2W dose in the pivotal studies was significantly higher for PASI 100 (representing total clearance) than ustekinumab. The response rate for the 210 mg Q2W dose was consistently higher than the response rate for the 140 mg Q2W dose and ustekinumab for PASI 75. Patients reported outcomes were consistent with the efficacy results across all 3 Phase 3 studies.

5.1 Design of the Pivotal Studies in the Psoriasis Program

The efficacy of brodalumab is supported primarily by 3 Phase 3 placebo-controlled studies (AMAGINE-1 AMAGINE-2 and AMAGINE-3) with open-label, long-term extensions. AMAGINE-2 and AMAGINE-3 also had an active control, ustekinumab.

The eligibility criteria were similar across the 3 Phase 3 studies. Patients were between the ages of 18 and 75 years, had stable, moderate to severe plaque psoriasis for at least 6 months before entering the study, had involved body surface area (BSA) $\geq$ 10%, PASI $\geq$ 12, and sPGA $\geq$ 3. Patients with prior psoriasis therapy, including biologic therapy, were allowed to participate in the study. Prior use of ustekinumab was prohibited in AMAGINE-2 and AMAGINE-3 because it was the active comparator in those studies. Patients with a history of Crohn's disease and those

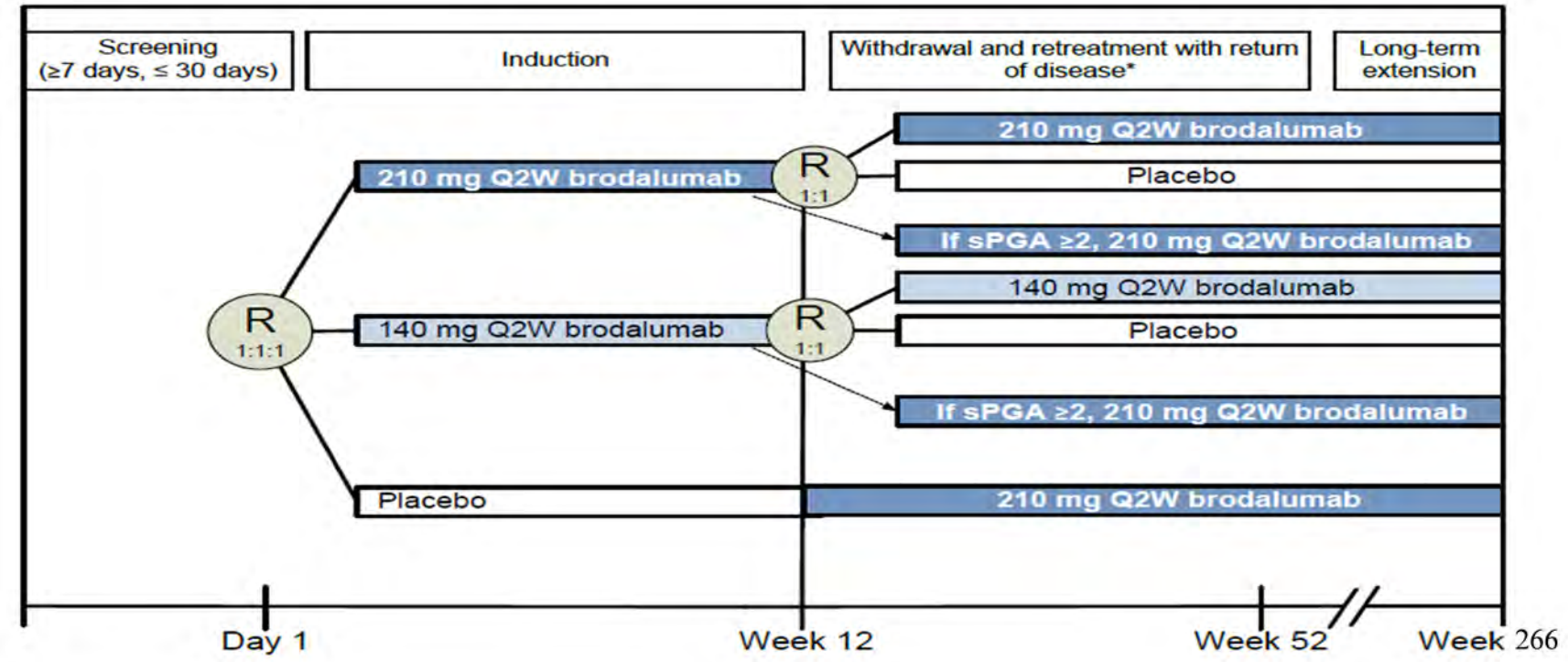
with an active infection or history of infections were excluded from participation in the studies. The Phase 2 study in Crohn's disease resulted in exacerbation and was the reason for the exclusion in the Phase 3 studies. Of note, patients with a history of drug abuse, depression, suicidality or other psychiatric conditions were not specifically excluded, making the study population more representative of the real world.

One Phase 2 dose-ranging study (study 20090062) defined the dose regimens to carry forward to Phase 3 (with an associated long-term extension study 20090403). The results from this study demonstrated the efficacy of 140 mg Q2W and 210 mg Q2W were comparable based on PASI 75, but were differentiated at higher levels of efficacy such as PASI 90 and PASI 100. Therefore, both doses were studied in the three Phase 3 trials (AMAGINE-1, AMAGINE-2, and AMAGINE-3). In addition, this Phase 2 study did not include an evaluation of different doses beyond Week 12 (for maintenance), so a long-term evaluation of different dosing regimens was performed in the Phase 3 program. AMAGINE-1 was conducted at 73 centers across Europe, Canada, and the US Studies. AMAGINE-2 and AMAGINE-3 were conducted at 142 centers across Australia, Canada, Europe, and the US.

Study design and treatment schema for the pivotal Phase 3 studies are presented in Figure 5–1 (AMAGINE-1) and Figure 5–2 (AMAGINE-2 and AMAGINE-3). All 3 phase 3 studies included a placebo-controlled 12-week induction phase comparing 210 mg Q2W and 140 mg Q2W with placebo, a double-blind duration of 52 weeks, and an open-label long-term extension. AMAGINE-2 and AMAGINE-3 included the active comparator ustekinumab.

Because of the randomization and rescue therapy designs of the Phase 3 psoriasis studies, the majority of patients, including those initially randomized to placebo or ustekinumab treatment, ultimately received brodalumab 210 mg. This is an important feature of the brodalumab program and is relevant to the interpretation of the safety data, particularly for rare events, over time.

Figure 5–1 AMAGINE-1 study design and treatment schema



* Patients could qualify for retreatment with their induction dose with a single sPGA of ≥ 3 at or after Week 16. Patients received 3 weekly doses followed by every other week doses upon experiencing return of disease at or after Week 16. If a patient had return of disease through Week 52, he or she received treatment at his or her initially randomized dose (if originally randomized to brodalumab) or 210 mg Q2W (if originally randomized to placebo).

R=randomization; Q2W=every 2 weeks (with an additional loading dose 1 week after initiation of brodalumab); sPGA=static Physician's Global Assessment

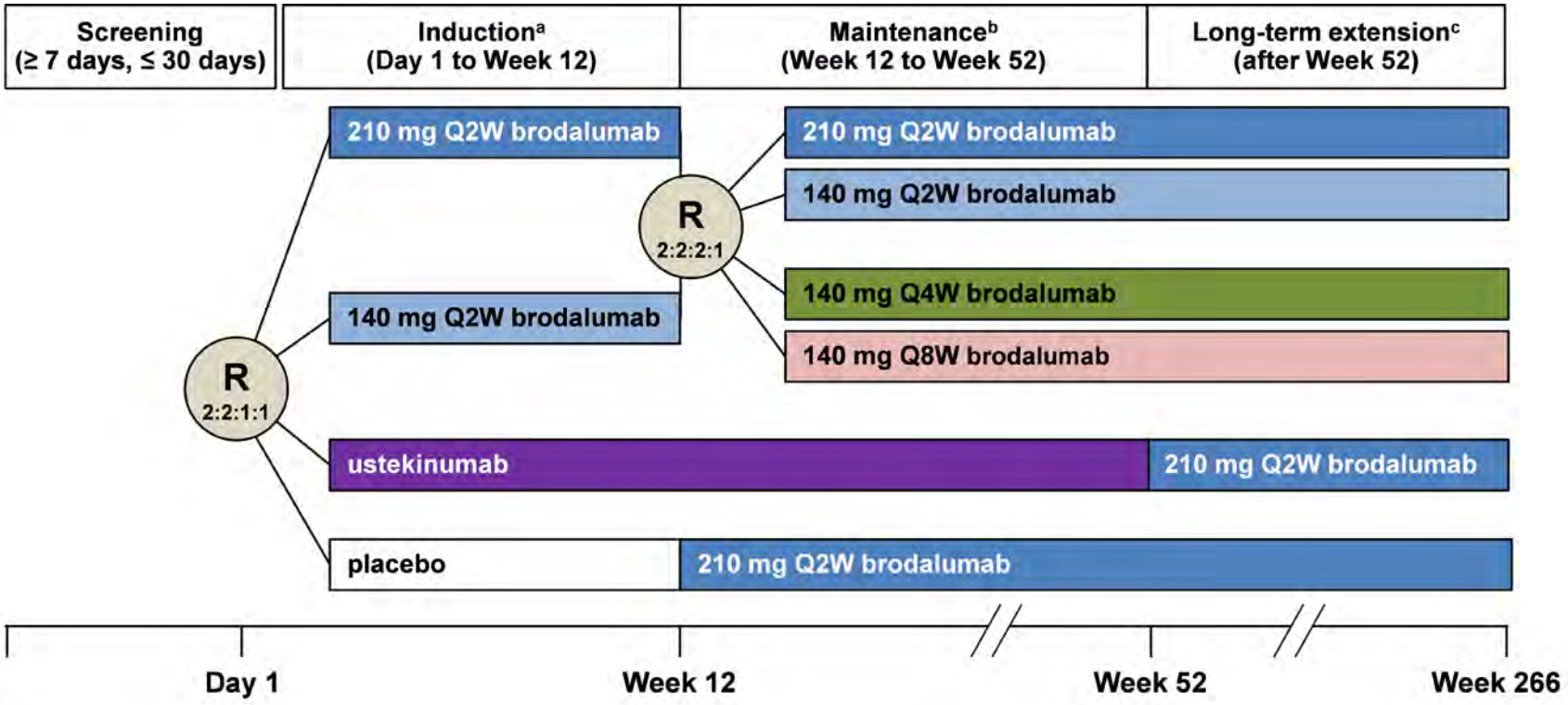
Patients received investigational product subcutaneously at day 1; weeks 1, 2, 4, 6, 8, 10, 12, 13, 14; and every other week thereafter.

Patients who did not attend their Week-12 visit did not receive any further investigational product.

Patients could qualify for rescue treatment after at least 12 weeks of retreatment with inadequate response (defined as persistent sPGAs of 2 over at least a 4-week period or a single sPGA ≥ 3).

After the blind to original and rerandomized treatment assignment had been broken, an analysis to identify the most appropriate maintenance dose(s) of brodalumab was performed. Based upon the results of that analysis, an amendment could be pursued to change the dose and/or frequency in some or all patients.

Figure 5–2 AMAGINE-2 and AMAGINE-2 study design and treatment schema



[a] In the induction phase, patients were randomized in a 2:2:1:1 ratio to receive brodalumab 210 mg Q2W, brodalumab 140 mg Q2W, ustekinumab or placebo.

[b] At the Week 12 visit, patients originally randomized to the brodalumab arms were rerandomized (2:2:2:1) into the maintenance phase to receive brodalumab 210 mg Q2W, 140 mg Q2W, 140 mg Q4W, or 140 mg Q8W. Patients originally randomized to ustekinumab continued to receive ustekinumab and those originally randomized to receive placebo received brodalumab 210 mg Q2W. Patients who did not attend their Week 12 visit did not receive any further investigational product.

[c] At Week 52, patients who were originally randomized to ustekinumab were to begin receiving brodalumab 210 mg Q2W.

R = randomization; Q2W = every 2 weeks (with an additional loading dose 1 week after initiation of brodalumab); Q4W = every 4 weeks; Q8W=every 8 weeks

Patients qualified for rescue treatment at or after Week 16 according to the rules in each study protocol.

Ustekinumab was administered per label: 45 mg if ≤ 100 kg at the baseline visit or 90 mg if > 100 kg at the baseline visit.

5.1.1 Efficacy Endpoints

The primary efficacy endpoints were identical for the placebo-controlled induction phase of all 3 pivotal phase 3 studies and for the ustekinumab-controlled induction phase portion of AMAGINE-2 and AMAGINE-3 (Table 5–1). Key secondary endpoints were similar and are also listed below. A description of PASI and sPGA is provided in Appendix C.

Table 5–1 Summary of endpoints in Phase 3 clinical studies in psoriasis

	AMAGINE-1	AMAGINE-2 and AMAGINE-3
PRIMARY ENDPOINTS[a]		
Placebo comparison		
PASI 75 at week 12	210 mg Q2W vs placebo 140 mg Q2W vs placebo	210 mg Q2W vs placebo 140 mg Q2W vs placebo
sPGA success at week 12 (0/1)	210 mg Q2W vs placebo 140 Q2W vs placebo	210 mg Q2W vs placebo 140 mg Q2W vs placebo
Ustekinumab comparison		
PASI 100 at week 12	NA	210 mg Q2W vs ustekinumab Weight-based: 140 mg Q2W for patients ≤100 kg and 210 mg Q2W for patients >100 kg vs ustekinumab
KEY SECONDARY ENDPOINTS		
PASI 100 at week 12	210 mg Q2W vs placebo 140 mg Q2W vs placebo	210 mg Q2W vs placebo 140 mg Q2W vs placebo 140 mg Q2W vs ustekinumab
sPGA of 0 at week 12	210 mg Q2W vs placebo 140 mg Q2W vs placebo	210 mg Q2W vs placebo 140 mg Q2W vs placebo
PSI responder definition (total score ≤ 8, with no item score > 1) at week 12	210 mg Q2W vs placebo 140 mg Q2W vs placebo	210 mg Q2W vs placebo 140 mg Q2W vs placebo
PASI 75 at week 12	NA	210 mg Q2W vs ustekinumab Weight-based: 140 mg Q2W for patients ≤100 kg and 210 mg Q2W for patients >100 kg vs ustekinumab
MAINTENANCE ENDPOINTS		
sPGA success (0/1) at week 52 (in rerandomized patients)	210 mg Q2W vs placebo 140 mg Q2W vs placebo	210 mg Q2W vs 140 mg Q8W 140 mg Q2W vs 140 mg Q8W 210 mg Q2W vs 140 mg Q4W 140 mg Q2W vs 140 mg Q4W 210 mg Q2W vs 140 mg Q2W

[a] Efficacy endpoints were examined by various subgroups including weight-based comparisons. PASI=Psoriasis Area and Severity Index; PSI=Psoriasis Symptom Inventory; sPGA=static Physician's Global Assessment of Psoriasis; Q2W=every 2 weeks; Q4W=every 4 weeks; Q8W=every 8 weeks

Sequential testing was performed to address multiplicity

For comparisons with placebo, the binary response variables of sPGA success (0 or 1) and PASI 75 at Week 12 were co-primary efficacy endpoints in all 3 phase 3 studies. These co-primary endpoints are the standard measurements for efficacy for moderate to severe plaque psoriasis in global studies. Only once both primary endpoints were met was testing performed on key secondary endpoints.

The binary response of PASI 100 (complete clearance) at Week 12 was a primary endpoint measure for ustekinumab comparisons and a key secondary endpoint measure for placebo comparisons. PASI 100 was chosen as a key endpoint for the Phase 3 studies because it represents total skin clearance, a treatment goal with important clinical benefit to patients. In addition, PASI 100 allows for differentiation between highly effective therapies.

Other efficacy endpoints included PASI 90, time to PASI (75, 90 and 100) response, percentage improvement from baseline in PASI (75, 90 and 100), and Psoriasis Symptom Inventory (PSI), a patient-reported outcome (PRO) measure.

At Week 52, the primary endpoint across all 3 Phase 3 studies was sPGA.

5.2 Results of the Pivotal Studies in Psoriasis

5.2.1 Analytical Methods

All analyses were performed as planned for each of the 3 Phase 3 studies.

Efficacy analyses at Week 12 include all patients as randomized prior to induction. The randomized groups included brodalumab 210 mg Q2W, brodalumab 140 mg Q2W, placebo, and ustekinumab (Studies AMAGINE -2 and AMAGINE-3). As the most conservative approach, patients with missing post baseline data were considered non responders; Non-responder Imputation (NRI). The dichotomous efficacy and PRO endpoints were analyzed using the Cochran-Mantel-Haenszel (CMH) test adjusted by the baseline stratification factors (i.e., baseline total body weight (≤100 kg, >100 kg), prior biologic use, geographic region) and the dichotomized baseline value of the outcome measures.

Efficacy analyses at Week 52 include all patients as re-randomized at Week 12, again using NRI. Additionally, in some analyses where the 210 mg Q2W dose group was compared with other treatment groups, patients in all treatment groups with return of disease (in AMAGINE-1) or with an inadequate response (AMAGINE-2 and AMAGINE-3) were also classified as non-responders for subsequent visits up to Week 52. The dichotomous efficacy and PRO endpoints were analyzed using the Cochran-Mantel-Haenszel (CMH) test adjusted by the dichotomized

Week 12 value of the outcome measures and Week 12 total body weight in all 3 studies, as well as by the baseline stratification factors in AMAGINE-1, and by treatment received in 12-week induction period in AMAGINE-2 and AMAGINE-3.

Within each study, overall Type 1 error rate level was controlled at the 2-sided 0.05 level.

In AMAGINE-1, the co-primary endpoints comparing the brodalumab 210 mg Q2W group with placebo were tested simultaneously, each at the 0.05 alpha level. Only when the hypotheses for both co-primary endpoints at the 210 mg Q2W level were rejected, were the same co-primary hypotheses tested comparing the brodalumab 140 mg Q2W group with placebo. Once all co-primary hypotheses were rejected, the key secondary endpoints were tested sequentially in the pre-specified order.

In AMAGINE-2 and AMAGINE-3, a combination of parallel, sequential, and Bonferroni-based recycling approach was followed for the Week 12 primary and key secondary endpoints. Initially, endpoints were tested in the placebo family at alpha = 0.01 (2-sided) and in the ustekinumab family at alpha = 0.04 (2-sided). Within the placebo and ustekinumab families, the primary endpoints were tested first. Once the null hypotheses for the primary endpoints within a family were rejected, the key secondary endpoints at Week 12 within that family were then tested sequentially in the pre-specified order. If all of the primary and key secondary endpoints within either family were rejected, the fraction of overall alpha (0.01 or 0.04) could be recycled to the testing of the hypotheses in the other family (Burman 2009).

The Week 52 maintenance and rescue phase endpoints were tested sequentially in the pre-specified order, independently of prior testing results.

5.2.2 Key Demographic and Baseline Characteristics

Key demographics and disease characteristics for the 3 Phase 3 studies were generally consistent across the studies. Patient demographics and baseline characteristics were typical of the moderate to severe psoriasis population and were generally well balanced across treatment groups.

Patients were predominantly male (69%) and white (91%) with a mean age of 45 years. Mean baseline body weight was 90.5 kg and 28% of patients had body weight > 100 kg. The baseline PASI score ranged from 9.4 to 72 (median: 17.4) and baseline BSA ranged from 10 to 97 (median: 21). Baseline sPGA score ranged from “3 (moderate)” (58%) to “5 (very severe)” (5%). Median duration of psoriasis was approximately 18 years.

The most common types of prior psoriasis therapy were topical therapy (79.9%) and systemic therapy or phototherapy (73.7%). The most commonly used biologic medications were anti-TNFα biologics (25.6%). In AMAGINE-1, ustekinumab was used as prior therapy by 17.4% of patients.

5.2.3 Induction Phase: Primary and Key Secondary Endpoints at Week 12

All primary endpoints, across all 3 studies, were met. The results are illustrated in Table 5–2 and Table 5–3 for all primary and key secondary end points. Brodalumab was superior to placebo ($p < 0.001$) for both the 210 mg Q2W and 140 mg Q2W doses in all key primary and secondary endpoints of PASI 75, sPGA success, and PASI 100.

Note that in all 3 studies, the number of patients who discontinued from treatment was low (<5%) and they were considered non-responders for all dichotomous efficacy endpoints analyses.

Table 5–2 Summary of primary and key secondary endpoints based on comparisons against placebo – AMAGINE-1, AMAGINE -2 and AMAGINE -3

	Studies	Brodalumab 210 mg N=222 N=612 N=624	Brodalumab 140 mg N=219 N=610 N=629	Placebo N=220 N=309 N=315	Brodalumab 210 mg -Placebo % (95% CI)	p-value	Brodalumab 140 mg -Placebo % (95% CI)	p-value
Co-Primary Endpoint								
PASI 75	AMAGINE-1	83%	60%	3%	81% (75%, 86%)	<0.001	57% (50%, 64%)	<0.001
	AMAGINE-2	86%	67%	8%	79% (74%, 83%)	<0.001	59% (53%, 64%)	<0.001
	AMAGINE-3	85%	69%	6%	80% (75%, 83%)	<0.001	64% (59%, 68%)	<0.001
sPGA success	AMAGINE-1	76%	54%	1%	75% (68%, 80%)	<0.001	52% (45%, 59%)	<0.001
	AMAGINE-2	79%	58%	4%	75% (70%, 79%)	<0.001	53% (48%, 58%)	<0.001
	AMAGINE-3	80%	60%	4%	76% (72%, 80%)	<0.001	57% (52%, 61%)	<0.001
Secondary Endpoints								
PASI 100	AMAGINE-1	42%	23%	0.5%	42% (35%, 49%)	<0.001	24% (18%, 31%)	<0.001
	AMAGINE-2	44%	26%	0.6%	44% (39%, 48%)	<0.001	26% (22%, 30%)	<0.001
	AMAGINE-3	37%	27%	0.3%	37% (32%, 41%)	<0.001	28% (23%, 32%)	<0.001
sPGA 0	AMAGINE-1	42%	23%	0.5%	42% (35%, 49%)	<0.001	23% (17%, 29%)	<0.001
	AMAGINE-2	45%	26%	0.6%	43% (38%, 48%)	<0.001	25% (20%, 29%)	<0.001
	AMAGINE-3	37%	27%	0.3%	36% (32%, 41%)	<0.001	27% (23%, 32%)	<0.001
sPGA success (at Week 52)*	AMAGINE-1	83% (69/83)	70% (40/57)	I-210: 0% (0/84) I-140: 5% (3/59)	83% (74%, 90%)	<0.001	65% (50%, 77%)	<0.001
PSI responder	AMAGINE-1	61%	53%	4%	59% (52%, 66%)	<0.001	50% (43%, 58%)	<0.001
	AMAGINE-2	68%	52%	7%	61% (56%, 66%)	<0.001	45% (40%, 50%)	<0.001
	AMAGINE-3	61%	53%	6%	56% (51%, 61%)	<0.001	47% (41%, 52%)	<0.001

*sPGA success at Week 52 includes patients who received Brodalumab and were sPGA success responders at Week 12 (210 mg Q2W N=167, 140 mg Q2W N=116). These patients were rerandomized to either placebo or their randomized brodalumab dose. I-210 means induction dose was brodalumab 210 mg and I-140 means induction dose was brodalumab 140 mg. Differences, 95% confidence intervals, and nomimal p-values at Week 52 are calculated (without multiplicity adjustment) using Miettinen-Nurminen method adjusting for Week 12 total body weight (≤100 kg, >100 kg), and Week 12 sPGA (0, ≥1)

Differences, 95% confidence intervals, and nomimal p-values at Week 12 are calculated (without multiplicity adjustment) using Miettinen-Nurminen (MN) method adjusting for body weight (≤100 kg, >100 kg), prior biologic use (yes, no), geographic region, and baseline value (≤median, >median) of PASI and PSI; ≥3 for sPGA. Note that MN method yields the same p-values as the pre-specified CMH test.

All statistical tests are 2-sided with a significance level of α=0.05 (AMAGINE-1) and α=0.01 (AMAGINE-2 and AMAGINE-3)

Non-responder imputation (NRI) is used to impute missing data

Table 5–3 Summary of primary and key secondary endpoints (NRI) based on comparisons against ustekinumab – AMAGINE -2 and AMAGINE -3

	Studies	Brodalumab	Ustekinumab N=300 N=313	Brodalumab -Ustekinumab % (95% CI)	p-value
Co-Primary Endpoint					
PASI 100	AMAGINE-2	44%	22%	23% (17%, 29%)	<0.001
(210 mg Q2W)	AMAGINE-3	37%	19%	17% (11%, 23%)	<0.001
PASI 100	AMAGINE-2	34%	22%	12% (6%, 18%)	<0.001
(Weight-Based)	AMAGINE-3	30%	19%	11% (5%, 17%)	<0.001
Secondary Endpoints					
PASI 100	AMAGINE-2	26%	22%	5% (-0.6%, 11.1%)	0.078
(140 mg Q2W)	AMAGINE-3	27%	19%	8% (2%, 13%)	0.007
PASI 75	AMAGINE-2	86%	70%	16% (10%, 22%)	<0.001†
(210 mg Q2W)	AMAGINE-3	85%	69%	16% (10%, 22%)	<0.001
PASI 75	AMAGINE-2	77%	70%	7% (0.8%, 13%)	0.026†
(Weight-based)	AMAGINE-3	77%	69%	8% (2%, 15%)	0.007

† not significant due to sequential testing procedure

Differences, 95% confidence intervals, and nomimal p-values at Week 12 are calculated (without multiplicity adjustment) using Miettinen-Nurminen method adjusting for body weight (≤100 kg, >100 kg), prior biologic use (yes, no), geographic region, and baseline value (≤median, >median) of PASI and PSI; ≥3 for sPGA

Weight-based = subset of randomized patients who at baseline weigh ≤100 kg randomized to 140 mg Q2W or patients who weight >100 kg randomized to 210 mg Q2W (AMAGINE-2 N=612, AMAGINE-3 N=628)

All statistical tests are 2-sided with a significance level of α=0.04 (AMAGINE-2 and AMAGINE-3)

Non-responder imputation (NRI) is used to impute missing data.

Brodalumab was superior to placebo ($p < 0.001$) for both the 210 mg Q2W and 140 mg Q2W doses in all key primary and secondary endpoints of PASI 75, sPGA success, and PASI 100.

5.2.3.1 Primary Endpoint Results

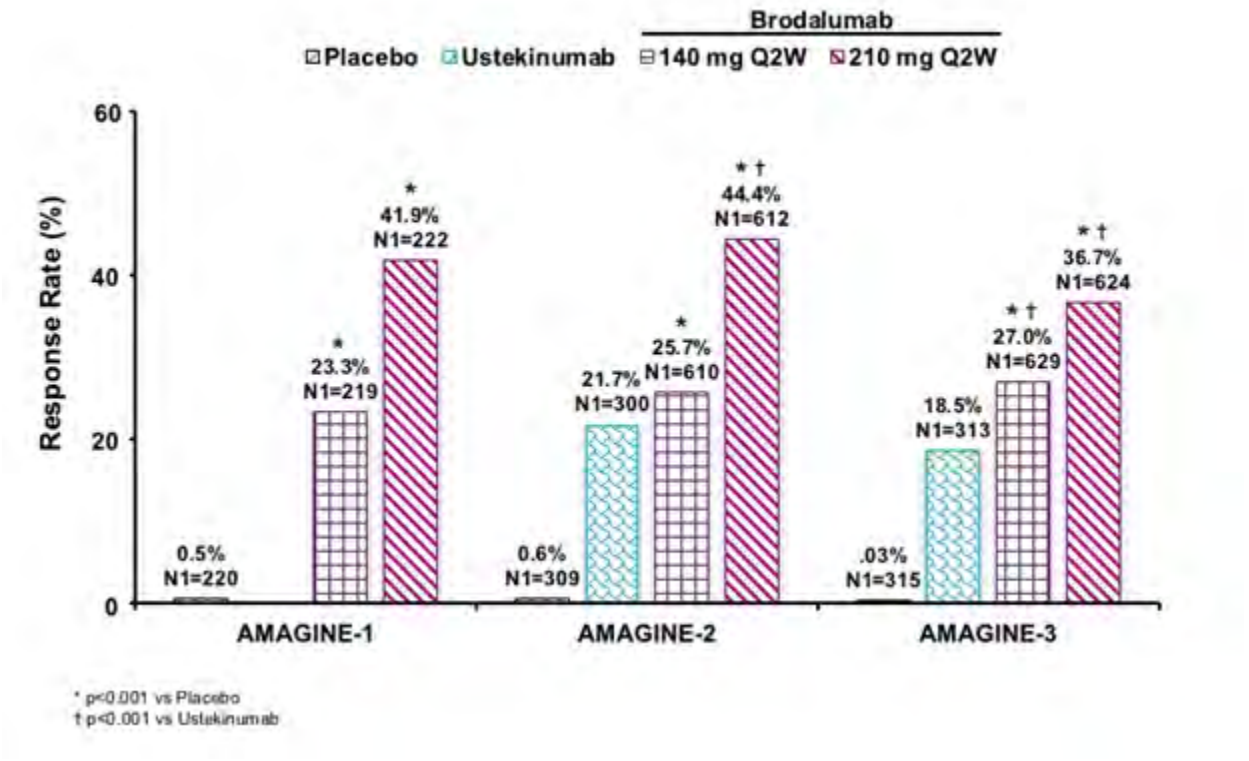
Results from primary endpoints for all three phase 3 studies are summarized in Table 5–2 and Table 5–3. sPGA success (0 or 1) at Week 12 in the 210 mg Q2W (range: 76% to 80%) and the 140 mg Q2W (range: 54% to 60%) groups was higher in comparison with placebo (range: 1% to 4%), ($p < 0.001$). PASI 75 at Week 12 also showed a consistent treatment effect in the brodalumab 210 mg Q2W (range: 83% to 86%) and brodalumab 140 mg Q2W group (range: 60% to 69%) compared with placebo (range: 3% to 8%) ($p < 0.001$).

The ustekinumab comparison (AMAGINE-2 and AMAGINE-3) of PASI 100 at Week 12 indicated a statistically significant difference ($p<0.001$) between ustekinumab and brodalumab 210 mg Q2W. As illustrated below in Figure 5–3, approximately twice as many patients who received brodalumab 210 mg Q2W achieved total skin clearance compared with ustekinumab.

5.2.3.2 Key Secondary Endpoint Results

All key secondary endpoints for AMAGINE -1 and AMAGINE -3 were met. In AMAGINE-2, PASI 100 was achieved in 25.7% of patients in the brodalumab 140 mg Q2W group and 21.7% of patients in the ustekinumab group ($p = 0.078$). As a consequence of the sequential testing scheme, the remaining key ustekinumab comparison secondary endpoints (PASI 75 for brodalumab 210 mg Q2W and the weight-based analysis) were not rejected although the nominal p-values were <0.001 and 0.026 respectively. In AMAGINE-3, PASI 100 was achieved in 27.0% of patients in the brodalumab 140 mg Q2W group and 18.5% in the ustekinumab group ($p = 0.007$).

Figure 5–3 Summary of PASI 100 (NRI) at Week 12 by study – AMAGINE-1, AMAGINE-2, and AMAGINE-3 (Full Analysis Set)

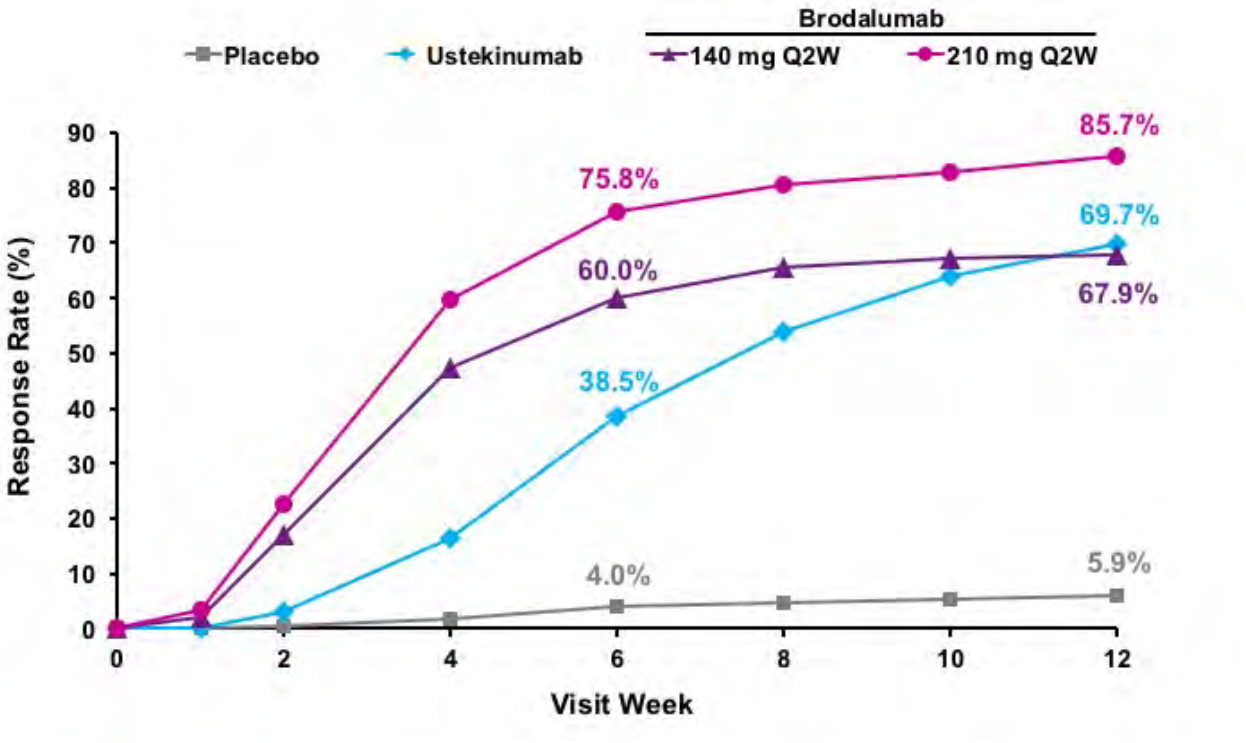


N1=Number of patients randomized and had a valid measurement value at Week 12, after imputation; PASI 100=100% improvement in the Psoriasis Area and Severity Index; Q2W=every 2 weeks
Non-responder Imputation (NRI) was used to impute missing data.
Treatment groups are defined as planned treatment for the induction phase.

5.2.3.3 Onset of Response

PASI 75 response was apparent as early as Week 2 for the brodalumab 210 mg Q2W and brodalumab 140 mg Q2W groups in versus placebo and ustekinumab as shown in Figure 5–4 for AMAGINE-2 and AMAGINE-3. The percentage of PASI 75 responders was consistently higher in the brodalumab 210 mg Q2W group over time throughout the studies. Based on the integrated analysis of AMAGINE-2 and AMAGINE-3 (Figure 5–4), the median (95% CI) time to PASI 75 response was 4.14 (not estimable [NE], NE) weeks for the brodalumab 210 mg Q2W group, 5.86 (4.43, 6.14) weeks for the brodalumab 140 mg Q2W group, 8.14 (8.14, 8.29) weeks for the ustekinumab group and NE for the placebo group. Consistent results were observed for all treatment groups in AMAGINE-1

Figure 5–4 Summary of PASI 75 through Week 12 – AMAGINE-2 and AMAGINE-3



PASI 75=75% improvement in the Psoriasis Area and Severity Index; Q2W=every 2 weeks
Treatment groups are defined as planned treatment for the induction phase.
Non-responder imputation (NRI) was used to impute missing data.

5.2.4 Maintenance Phase: Through Week 52

5.2.4.1 AMAGINE-1

In AMAGINE-1, 75.7% of patients were sPGA success responders at Week 12. Of these responders, 167 patients were rerandomized to either brodalumab 210 mg Q2W (n=83) or placebo (n=84).

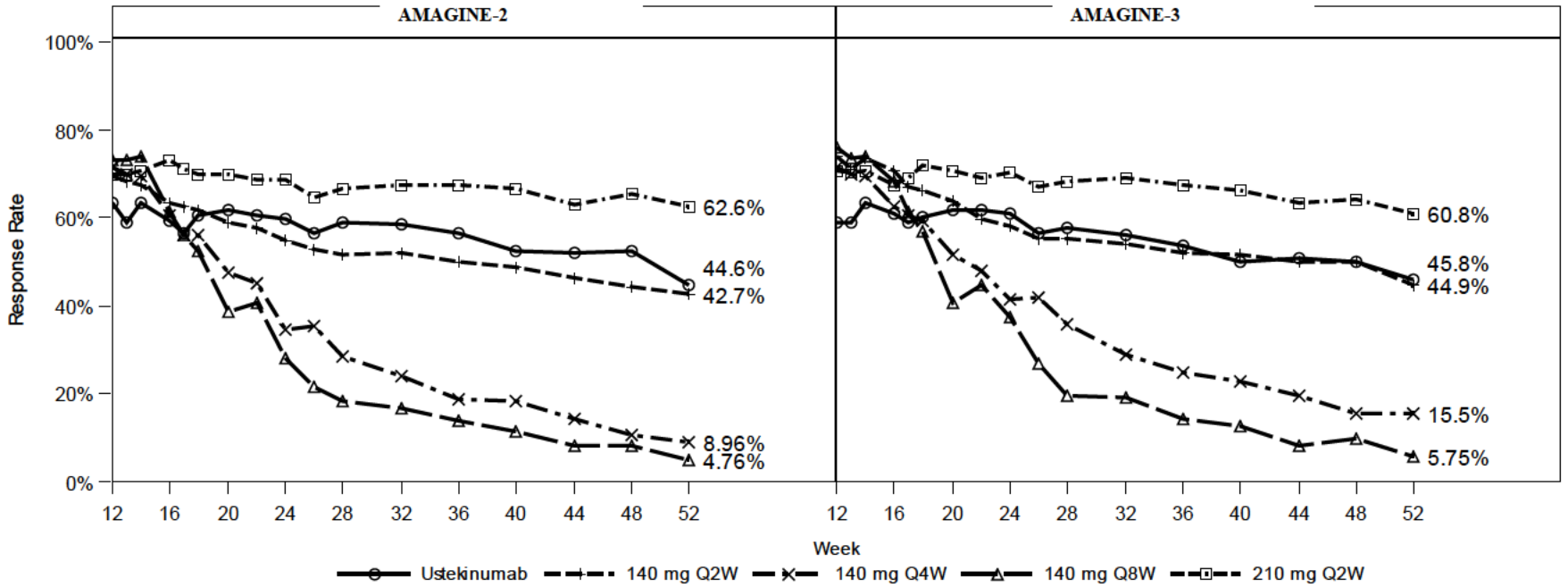
Among patients originally randomized to brodalumab 210 mg Q2W in the induction phase with sPGA success (0 or 1) at Week 12, no patient rerandomized to placebo and withdrawn from brodalumab treatment maintained sPGA success at Week 52, while 83.1% of patients rerandomized to continued treatment with brodalumab 210 mg Q2W maintained sPGA success at Week 52. When patients rerandomized to placebo were retreated with brodalumab 210 mg Q2W, sPGA success (0 or 1) was achieved in 80% of patients after 12 weeks of retreatment.

As seen with sPGA, with continued treatment over 52 weeks, 87% of patients treated with brodalumab 210 mg Q2W demonstrated PASI 75 response at Week 52.

5.2.4.2 AMAGINE-2 and AMAGINE-3

In both AMAGINE-2 and AMAGINE-3, the percentage of responders in maintenance treatment was higher in the brodalumab 210 mg Q2W group compared to the other 3 brodalumab maintenance dosing regimens and ustekinumab starting at approximately Week 16 and continuing through Week 52 (Figure 5–5). All comparisons for the maintenance endpoint at Week 52 were statistically significant ($p<0.001$), with the brodalumab 210 mg Q2W regimen achieving the highest rates of sPGA success at Week 52.

Figure 5–5 **sPGA success (clear [0] or almost clear [1]) status by Week by study - AMAGINE-2 and AMAGINE-3 (52 Week Analysis Set)**



Q2W=Every 2 weeks; Q4W=Every 4 weeks; Q8W=Every 8 weeks; sPGA=Static Physician's Global Assessment of Psoriasis.

Patients who entered maintenance phase are included.

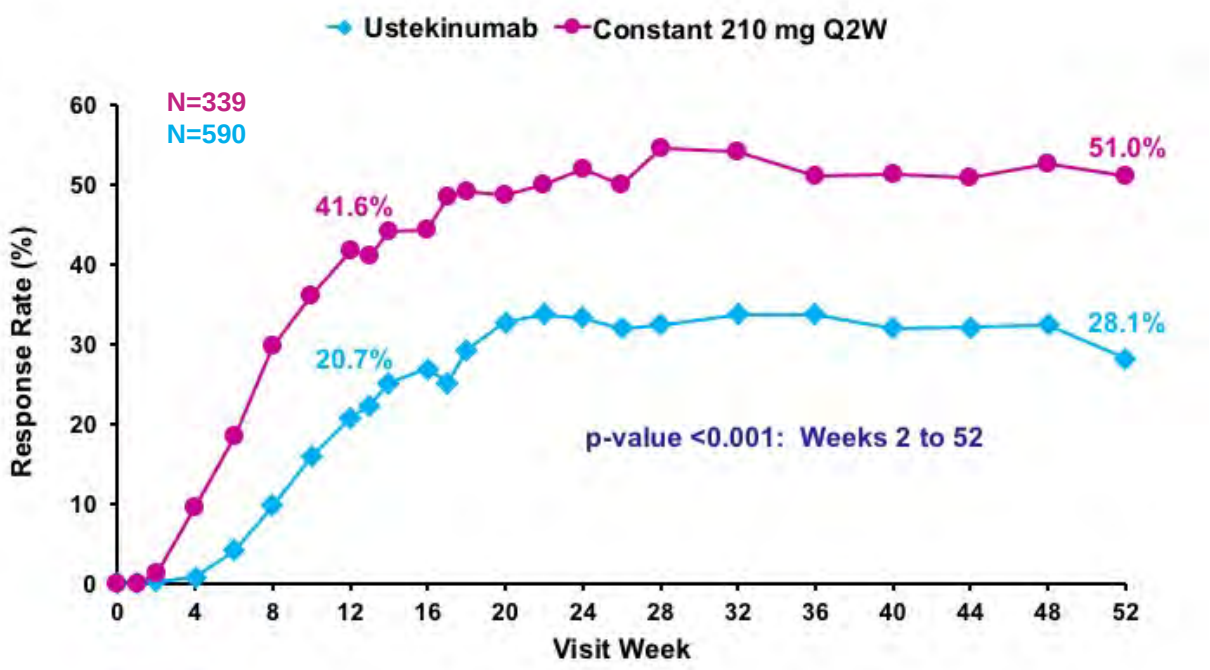
Patients in all treatment groups with an inadequate response (defined as single sPGA of ≥3 or persistent sPGA values of 2 over at least a 4-week period) at or after Week 16 (and through Week 52) are imputed as non-responders for subsequent weeks up to Week 52.

Treatment groups are defined as planned treatment for the maintenance phase.

Non-responder Imputation (NRI) is used to impute missing data.

Integrated results for AMAGINE-2 and AMAGINE-3 are presented below demonstrating that overall nearly twice as many patients achieved PASI 100 at Week 52 for brodalumab compared to ustekinumab. Of patients who were originally randomized to brodalumab 210 mg Q2W and continued the same treatment through 52 weeks, 51.0% achieved PASI 100 response at Week 52 compared to 28.1% of patients who remained on ustekinumab over the 52-week period (Figure 5–6).

Figure 5–6 **PASI 100 up to Week 52 for brodalumab 210 mg Q2W (constant dose) and ustekinumab (constant dose) - Integrated AMAGINE-2 and AMAGINE-3**



Non-responder Imputation (NRI) is used to impute missing data.

Patients in all treatment groups with an inadequate response at or before Week 52 are imputed as non-responders for subsequent visits up to Week 52

Treatment groups are defined as planned treatment for induction / maintenance phases

Ustekinumab patients were administered ustekinumab in the 12-Week phase, continued on ustekinumab in the maintenance phase.

Brodalumab patients were administered brodalumab 210 mg Q2W in the 12-Week phase, were re-randomized to brodalumab 210 mg Q2W in the maintenance phase.

N = number of patients, presented at: baseline, Week 12, and Week 52

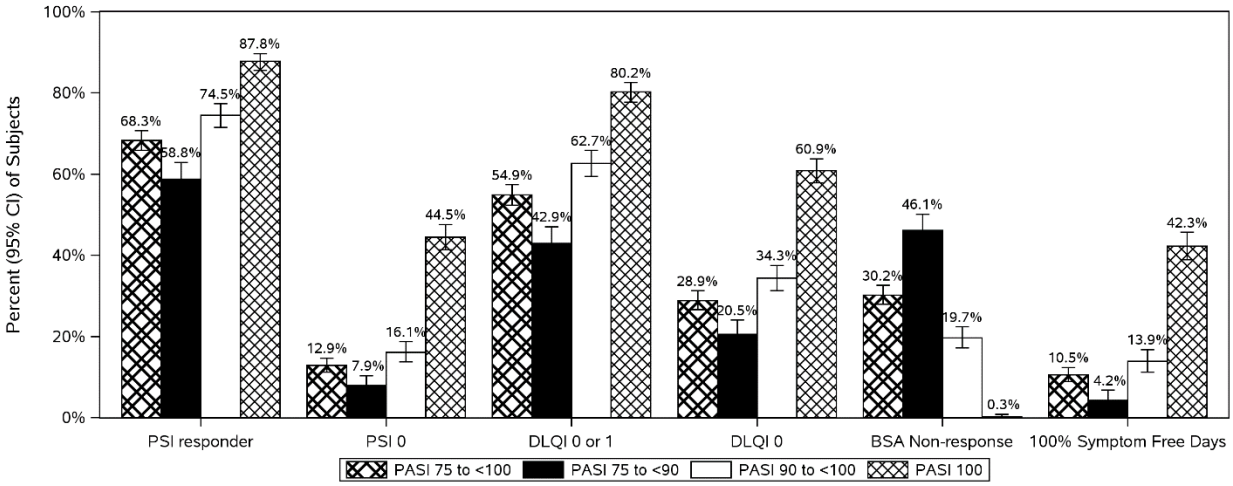
5.2.5 Patient-Reported Outcome Measures

Patients reported outcomes were consistent with the efficacy results across all 3 Phase 3 studies, in that brodalumab 210 mg Q2W dose had better response rates in comparison with both brodalumab 140 mg Q2W and ustekinumab. Patient reported outcomes also provided beneficial supplementary information to interpret clinical meaningfulness of complete clearance.

The results of the analysis comparing efficacy and PRO endpoints, which includes all patients in the brodalumab program regardless of randomized therapy, are summarized in Figure 5–7. Compared with patients who had a treatment response without complete clearance (PASI 75 to < 100 or PASI 90 to < 100), the subgroup with complete clearance (PASI 100) had a significantly higher proportion of patients with favorable PSI and DLQI response.

Thus, PASI 100 results in meaningful improvements in patient-reported signs and symptoms of disease severity, quality of life, and residual disease relative to PASI 75 to <100.

Figure 5–7 Summary of key measures of patient reported outcomes by PASI clearance group at Week 12 (PASI Clearance Integrated Analysis Subset, Induction Phase)



BSA=% Body Surface Area involvement; BSA non-response=BSA ≥ 6%; CI=confidence interval; DLQI=Dermatology Life Quality Index; DLQI total score of 0 or 1= no effect on patient's life; N1=number of patients randomized to ustekinumab or brodalumab who achieved stated level of PASI response and had non-missing endpoint value at Week 12; PASI=Psoriasis Area and Severity Index; PSI responder=Psoriasis Symptom Inventory total score ≤ 8 with no item scores > 1; PSI total score=the weekly average of ≥ 4 daily assessments in the week before the visit; PSI Total Score of 0=signs and symptoms were not at all severe; symptom-free day=reporting a 0 daily total score on the PSI that day
Note: $p < 0.001$ for all comparisons between PASI response without clearance groups and the PASI 100 group; p-value was nominal without multiplicity adjustment and was based on Cochran-Mantel-Haenszel test adjusted by baseline total body weight group (≤ 100 kg, > 100 kg), study, treatment group (brodalumab, ustekinumab), and baseline PSI total score, DLQI total score, or BSA score, as applicable (≤ median, > median)

5.2.6 Efficacy in Key Subgroups

Subgroup analyses of sPGA endpoints by baseline demographics, baseline disease characteristics, and baseline concomitant medication, previous history, and weight were consistent with the overall findings that sPGA responses were greater with brodalumab 210 mg Q2W compared with each of the other brodalumab dose groups.

5.2.7 Persistence of Efficacy

Analysis of the data from the long-term extension phases of both AMAGINE-2 and AMAGINE-3 (patients enrolled in the long-term extension period) shows that patients continue to maintain response through Week 96.

Of the patients with success at Week 52, 417 of 426 patients (97.9%) treated with brodalumab 210 mg Q2W who had completed the Week 96 assessment maintained their sPGA success at

Week 96. Of the patients with success at Week 72, 234 of 244 patients (95.9%) treated with 210 mg Q2W who had completed the Week 96 assessment maintained their sPGA success at Week 96.

Additional supportive long-term data were observed in Phase 2 Study 20090403, during which efficacy endpoints were maintained from weeks 12 through 192. Efficacy of brodalumab was observed for all endpoints, including responses (as observed) of ≥ 90% for PASI 75, ≥ 80% for PASI 90, and ≥ 50% for PASI 100 at Week 192 (N = 132).

5.2.8 Efficacy as a Function of Dose

In the Phase 3 studies (AMAGINE-1, AMAGINE-2, and AMAGINE-3) brodalumab 210 mg Q2W consistently achieved higher rates of response for all evaluated endpoints compared with brodalumab 140 mg Q2W at week 12 and week 52. Relative response rates for brodalumab 210 mg Q2W versus brodalumab 140 mg Q2W were determined and are summarized in Table 5–4.

Table 5–4 Relative response rates of brodalumab 210 mg Q2W versus 140 mg Q2W – AMAGINE-1, AMAGINE -2 and AMAGINE -3

	Response Rate		Relative Response Rate[a]
	Brodalumab 140 mg Q2W (A)	Brodalumab 210 mg Q2W (B)	Brodalumab 210 mg Q2W versus 140 mg Q2W
Week 12 (AMAGINE-1, -2, -3)			
sPGA 0/1	58.2%	78.6%	35%
PASI 75	66.7 %	85.3%	28%
PASI 100	25.9%	40.7%	57%
Week 52 (AMAGINE-2, -3)			
sPGA 0/1	39.2%	64.9%	66%
PASI 75	41.9%	65.5%	57%
PASI 100	28.6%	51.0%	78%

[a] Relative response rate calculated as (B-A)/A*100

The data demonstrated that brodalumab 210 Q2W was clearly differentiated from brodalumab 140 Q2W through 52 weeks. Furthermore, subgroup analyses of sPGA endpoints by baseline demographics, baseline disease characteristics, and baseline concomitant medication, previous history, and weight were consistent with the overall findings that sPGA responses were greater with brodalumab 210 mg Q2W compared with the other brodalumab dose groups. The sponsor proposes the use of the brodalumab 210 mg Q2W dose for induction and maintenance in all patients.

5.3 Conclusions: Efficacy of Brodalumab in Psoriasis

- The primary efficacy endpoints were met in all 3 Phase 3 studies.
- Brodalumab 210 mg Q2W showed superior efficacy to placebo in the key measurements of PASI 75, PASI 100, and sPGA 0/1 in all 3 studies.
- Brodalumab 210 mg Q2W showed superior efficacy to ustekinumab in PASI 100 in 2 studies and in PASI 75 in AMAGINE-3. The differences in PASI 75 observed in AMAGINE-2 was nominally significant and consistent with that observed in AMAGINE-3.
- Brodalumab demonstrated rapid onset of action; improvement in PASI 75 response was observed as early as 2 weeks in patients treated with brodalumab 210 mg Q2W.
- In all three studies, maintenance of effect in sPGA success was observed.
- The proportion of patients who achieved complete clearance (achievement of either PASI 100 or sPGA 0) was significantly higher in brodalumab 210 mg Q2W group compared with the brodalumab 140 mg Q2W.
    - High concordance of sPGA 0 and PASI 100 was observed across the Phase 3 studies.
- The clinical meaningfulness of PASI 100 (complete clearance) as an endpoint was demonstrated by a significant increase in the proportion of patients with PASI 100 whose psoriasis had no impact on their quality of life (Dermatological Life Quality Index 0/1) or psoriasis symptoms (Psoriasis Symptom Inventory 0), compared with patients who achieved PASI 75 to <100 or PASI 90 <100.

6 Safety

6.1 Overall Extent of Exposure

The overall brodalumab safety package across multiple indications includes 6243 brodalumab-treated patients with a total of 9719.7 patient-years of brodalumab exposure and 10452 patient-years of follow-up. For each patient, exposure-time was defined as the time periods when patients are exposed to from first dose of IP up until one dosing interval beyond the last dose, and generally excludes any gaps/interruptions in exposure, and follow-up time was defined as exposure time including any gaps/interruptions in exposure plus follow-up time beyond the exposure period. The majority of all patients had follow-up periods of 1 to 2 years and 102 patients had follow-up for over 5 years.

In the psoriasis studies, 4464 patients had a total of 8655.0 patient-years of brodalumab exposure and the mean duration of exposure to brodalumab was nearly 2 years. Through Week 52, 613 patients received at least one dose of ustekinumab, representing 494.7 patient-years of exposure.

The safety profile of brodalumab in the psoriasis population was analyzed using integrated safety data from the Phase 2 and 3 psoriasis studies, and their open label extensions (unless noted otherwise). Three main data pools were generated based on study treatment period and study design from these studies, and are defined below.

- The 12-week pool allows direct randomized comparisons of brodalumab with placebo and active comparator (ustekinumab) for the initial 12-week induction period. The results are generally summarized as patient incidence (i.e., number and percent) using the following treatment groupings based on initial randomization: Placebo, Ustekinumab, Brodalumab 140 mg Q2W, Brodalumab 210 mg Q2W and All-Brodalumab (including 70 mg Q2W, 140 mg Q2W, 210 mg Q2W and 280 mg Q4W).

- The 52-Week pool provides longer term exposure for brodalumab and ustekinumab groups. Because the study designs included rerandomization at Week 12 and protocol-defined rescue treatment for eligible patients, the 52-week pool was based on the baseline treatment allocation and subsequent rerandomization and rescue treatment (i.e., planned treatment sequence per study design for each patient). The treatment groupings presented are ustekinumab, constant brodalumab 210 mg Q2W (includes patients who received either placebo or brodalumab 210 mg Q2W at induction and brodalumab 210 mg Q2W at maintenance), Constant brodalumab 140 mg Q2W (includes patients who received brodalumab 140 mg Q2W at induction through Week 52 without rescue), and all- brodalumab (includes patients who had at least one dose of brodalumab, and includes patients who received variable doses or patients who crossed over), unless otherwise noted.

Results from the 52-week pool are generally summarized as exposure-adjusted rates, except for rare serious events like death, MACE, SIB, and malignancy which are also summarized as follow-up time-adjusted rates, in order to not exclude certain important events that were reported after the exposure period.

- The long-term pool presents integrated brodalumab safety data for maximum longitudinal exposure. The pool is comprised of all patients who received at least one dose of brodalumab (All-Brodalumab group) and included data from first dose of brodalumab through end of

study. Results from long term pool are generally summarized as follow-up time-adjusted rates or as exposure-adjusted rates.

These safety topics were also investigated and reported using data from the supportive indications.

6.2 Summary of Adverse Events

An overall summary of the incidence of adverse events for the 12-week pool are displayed in Table 6–1. The incidence of adverse events was balanced across all treatment groups at Week 12. The event rates of adverse events at Week 52 and long term pool were balanced (Table 6–2).

Table 6–1 Overall summary of treatment-emergent adverse events during initial double-blind period (12 Week Pool)

			Brodalumab		
	Placebo (Pt-yr =194.9) (N=879)	**Ustekinumab (Pt-yr =139.5) (N=613)**	**140 mg Q2W (Pt-yr =334.0) (N=1491)**	**210 mg Q2W (Pt-yr =335.6) (N=1496)**	**All (Pt-yr =687.6) (N=3066)**
	n (%)	**n (%)**	**n (%)**	**n (%)**	**n (%)**
All treatment-emergent adverse events	451 (51.3)	345 (56.3)	845 (56.7)	870 (58.2)	1765 (57.6)
Serious adverse events	15 (1.7)	6 (1.0)	29 (1.9)	20 (1.3)	49 (1.6)
Leading to discontinuation of investigational product	8 (0.9)	6 (1.0)	16 (1.1)	17 (1.1)	34 (1.1)
Fatal adverse events	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	1 (< 0.1)

N=patients in Studies 20090062 (the Phase 2 study), AMAGINE-1, AMAGINE-2, AMAGINE-3 with ≥1 dose of investigational product; n=number of patients reporting ≥1 occurrence of an adverse event through Week 12; Q2W=every 2 weeks; Q4W=every 4 weeks; Pt-yr=total patient years of exposure through Week 12.

Note: Treatment groups are defined as planned (randomized) treatment. Data for the brodalumab 70 mg Q2W group and the brodalumab 280 mg Q4W group are not shown, on the basis of the very small n's for these groups, but are represented within the all-brodalumab group. Events are coded with CTCAE v. 4.0 or 4.03 (depending on study) and MedDRA v. 17.1.

Table 6–2 Overall summary of exposure- and follow-up adjusted event rates (per 100 patient-years) for treatment-emergent adverse events in 52-week pool and long-term pool – Psoriasis Subset

	52-Week Pool		Long-Term Pool
	Ustekinumab (N=613) n (r)	**All-brodalumab (N=4019) n (r)**	**All-brodalumab (N=4464) n (r)**
Exposure-adjusted	**Pt-yr =494.7**	**Pt-yr =3445.5**	**Pt-yr =8655.0**
All treatment–emergent AEs	1952 (394.6)	13826 (401.3)	25114 (290.2)
Serious adverse events	42 (8.5)	285 (8.3)	639 (7.4)
Leading to discontinuation of investigational product	17 (3.4)	128 (3.7)	238 (2.7)
Fatal adverse events	2 (0.4)	9 (0.3)	9 (0.1)
Follow-up adjusted	**Pt-yr= 504.0**	**Pt-yr= 3547.7**	**Pt-yr=9173.9**
All treatment–emergent AEs	2007 (398.2)	14209 (400.5)	25905 (282.4)
Serious adverse events	45 (8.9)	325 (9.2)	743 (8.1)
Leading to discontinuation of investigational product	17 (3.4)	152 (4.3)	295 (3.2)
Fatal adverse events	2 (0.4)	13 (0.4)	23 (0.3)

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 investigational product.
n=number of adverse events; r=exposure-adjusted event rate per 100 patient-years (n/pt-yr*100); Pt-yr=total patient-years of exposure through Week 52 (52-Week Pool) and through end of study (Long-Term Pool).

6.2.1 Common Adverse Events

Nasopharyngitis (6.8%), upper respiratory tract infection (5.7%), arthralgia (4.7%), and headache (4.3%) were the most common events observed in patients treated with brodalumab 210 mg Q2W occurring at Week 12 in ≥ 2% of patients. These rates were consistently observed as the most common in the Week 52 pool and in the long term follow up pool.

6.3 Deaths

During the controlled treatment period to Week 52, death rates were balanced across all treatment groups, 0.4 per 100 patient years for both ustekinumab and brodalumab.

Through the end of the psoriasis studies, a total of 23 deaths were reported among patients exposed to brodalumab. The largest category was comprised of 13 cardiovascular-related events, including MI (4), sudden death/cardiac arrest (3), cerebrovascular accident (2), and other single events (4). There were a total of 4 completed suicides, including one reported as an intentional overdose, 3 accidental deaths related to motor vehicle accidents and 3 other single unrelated fatal

events. There were 2 deaths, including one due to MI and one due to pancreatic cancer, in the ustekinumab group.

The fatal event rate for brodalumab was 0.3 events per 100 patient years through the end of study.

In addition, in supporting non-psoriasis clinical programs there were 3 fatal events in brodalumab patients, including 2 completed suicides and 1 patient with cardio-pulmonary failure.

Fatal events related to MACE and SIB are discussed in Sections 7 and 8, respectively.

To further evaluate mortality observed in patients treated with brodalumab in the clinical program, a standardized mortality ratio (SMR) was calculated which compares the number of deaths observed in the program with the number that would be expected based on mortality rates in a comparable general population. To calculate the expected number of deaths, age-, sex-, and country-specific mortality rates obtained from national mortality statistics were applied to brodalumab patients in this program through the end of study. Rates for the US were obtained using the CDC Wonder database; rates for Europe were obtained from the EUROSTAT database; rates for other countries (Russia, Canada, Australia, Mexico, and South Korea) were obtained from WHO statistics.

Using data through the end of the study, dividing the observed number of deaths by the expected number of deaths, the SMR was calculated as 0.53 (95% CI 0.33, 0.79). Based on this analysis, there is no indication that brodalumab increases the overall risk of death above what would be expected in a population matched on age, sex, and country.

6.4 Other Serious Adverse Events

For all Serious AEs, there were no imbalances at Week 12 between brodalumab, ustekinumab, or placebo. Serious AEs by preferred term with patient incidence rates ≥0.1% in the all-brodalumab group at Week 12 were cellulitis, appendicitis, gastroenteritis, and acute pancreatitis. The SOCs with the highest exposure-adjusted event rates were Infections and Infestations, Injury, Poisoning, and Procedural Complications, and Cardiac Disorders. Serious AEs at Week 52 were similar between brodalumab and ustekinumab. The preferred terms with the highest exposure-adjusted rates (per 100 patient years) at Week 52 were myocardial infarction (0.3 all-brodalumab group, 0.2 ustekinumab) (Section 7), cellulitis (0.2 all-brodalumab, 0.2 ustekinumab), and cholelithiasis (0.2 all-brodalumab, 0.0 ustekinumab). The rates of these events do not increase in the long term.

6.5 Adverse Events Leading to Discontinuation

The rates of AE's leading to investigational product discontinuation were low and comparable to placebo at 12 weeks and ustekinumab at Week 52, and did not increase over time through the long term period. AE's leading to discontinuation at Week 52 and in the long term were primarily in the SOC of Skin and Subcutaneous Disorders (primarily due to rescue criteria) and Psychiatric Disorders (primarily due to discontinuation criteria related to implementation of the eC-SSRS and PHQ-8).

6.6 Adverse Drug Reactions (ADR)

ADRs were assessed at Week 12, comparing brodalumab incidence versus placebo, and included headache, arthralgia, fatigue, oropharyngeal pain, diarrhea, nausea, myalgia, influenza, injection site reactions, neutropenia, tinea infections, conjunctivitis, and candida infections.

6.7 Identified and Potential Risks

Identified risks, risks with confirmed association with brodalumab, include worsening of Crohn's disease in patients with active Crohn's disease, infections, and neutropenia (Section 6.7). Potential risks, risks with uncertain association with brodalumab and risks that are either typical for immunomodulating drugs used for psoriasis or risks that are associated with administration of foreign proteins, include major adverse cardiovascular events (MACE) (Section 7), SIB (Section 8), hypersensitivity (Section 6.7), and malignancy (Section 6.7).

A summary of the events of Crohn's disease, infections, neutropenia, hypersensitivity, and malignancy is discussed below.

- Worsening of Crohn's disease was initially observed in the early terminated Phase 2 Crohn's disease program. Subsequently, all patients with a known history of Crohn's disease were excluded from all brodalumab clinical studies, including those supporting the psoriasis indication. Across the psoriasis program, there were 2 cases of new onset confirmed Crohn's disease reported. Crohn's disease has been identified as a comorbid condition in psoriasis. The sponsor has proposed Crohn's disease as a contraindication to treatment with brodalumab.

- A higher rate of infections was observed in brodalumab treatment arms and dose response trends were observed for select infection events. At Week 12, the most frequent infections were nasopharyngitis, upper respiratory tract infection, pharyngitis, urinary tract infections, bronchitis, and influenza. Serious infections reported most frequently in

brodalumab treated patients in the 12 week period included cellulitis (0.1%), appendicitis (0.1%), and gastroenteritis (0.1%). These accounted for greater than half of all infections observed; the majority of infections reported were nonserious, mild, and self-limited. A dose-dependent increase in non-serious skin and mucosal fungal infections, primarily candida and tinea, was also observed with brodalumab treatment. Two serious fungal opportunistic infections were observed: one case each of coccidioidomycosis and cryptococcal meningitis.

- Neutropenia was more frequently associated with brodalumab treatment in a dose dependent manner. At Week 12, the Grade 3 laboratory abnormality of neutropenia was reported in 0.2% in brodalumab 140 mg Q2W, 0.5% in brodalumab 210 mg Q2W , 0% in ustekinumab, and 0% in placebo patients. Grade 4 laboratory abnormality of neutropenia was reported in 0.1% for brodalumab 140 mg Q2W, 0% for brodalumab 210 mg Q2W, and 0.2% for ustekinumab patients. Most cases of neutropenia were transient and reversible and no Grade 3 or Grade 4 neutropenic events were associated with serious infections.

- At 12-weeks, the patient incidence rate for hypersensitivity was 1.7% for brodalumab 210 mg Q2W, 1.3% for ustekinumab, and 3.1% for placebo. At 52 weeks, the exposure-adjusted event rate of hypersensitivity events was higher in the all-brodalumab (6.4 per 100 patient years) compared with the ustekinumab (2.2 per 100 patient years) groups. The most frequently observed hypersensitivity event was pruritus. Overall, no clinically meaningful or serious hypersensitivity reactions were observed in patients who received brodalumab, within 1 day of brodalumab administration.

- Exposure-adjusted malignancy event rates, excluding nonmelanoma skin cancer were 0.3 in the all-brodalumab group, and 0.4 in the ustekinumab group at 52 weeks. In the brodalumab long term pool through the end of study, follow-up adjusted event rates did not increase and were 0.4 events per 100 patient-years for adjudicated malignancies.

No additional identified or potential risks arose from analysis of the week 52 and in the long-term pools.

7 Cardiovascular Events including Major Adverse Cardiac Events (MACE)

Major adverse cardiac events (MACE) were prospectively evaluated in the psoriasis Phase 3 studies (AMAGINE-1, AMAGINE-2, and AMAGINE-3). A cardiovascular events committee (CEC) from the Duke Clinical Research Institute was formed to prospectively adjudicate MACE

events in a blinded fashion in order to reduce investigator bias. MACE was defined as CV death, myocardial infarction, or stroke.

At 12 weeks, MACE was reported in 3 brodalumab 140 mg Q2W patients (0.2%) and no patients in the placebo, brodalumab 210 Q2W, or ustekinumab groups experienced CEC-adjudicated MACE.

In the 52-week, active comparator controlled period, the exposure-adjusted MACE event rates were 0.61 per 100 patient years (95% CI: 0.37 to 0.94) in the all-brodalumab group and 0.40 per 100 patient years (95% CI: 0.05 to 1.46) in ustekinumab group. The follow up time-adjusted event rates of MACE were 0.71 per 100 patient years (95% CI: 0.46 to 1.06) in the all-brodalumab group and 0.40 per 100 patient years (95% CI: 0.05 to 1.43) in ustekinumab group. Most patients with a reported MACE had ≥1 major cardiovascular risk factor and additional confounding comorbidities, most with ≥3 risk factors. There was no trend observed across brodalumab doses.

In the long-term group, the exposure-adjusted rate of MACE in brodalumab-exposed patients through the end of study was 0.5 per 100 patient years (95% CI: 0.36 to 0.69). The follow-up time adjusted rate for brodalumab treated patients was 0.6 per 100 patient years (95% CI: 0.48 to 0.84). The exposure adjusted rate of MACE derived from a systematic literature review of all biologic and systemic therapies for psoriasis was 0.45 per 100 patient years (95% CI: 0.36, 0.56).

The MACE findings in the brodalumab program have been assessed. Analyses were conducted which included assessment of pre-disposing risks related to cardiovascular disease in patients in the program, evaluation of the overall events of cardiovascular disease and adjudicated MACE, comparison of rates of MACE observed with brodalumab to external literature reviews and recent relevant study programs, and assessment of biologic plausibility. The cardiovascular findings with brodalumab were also evaluated based on revised Hill criteria described by Howick 2009.

The sponsor concludes that the evidence does not support a causal relationship between brodalumab and MACE. However, given the seriousness of these events and the high background rate in the patient population the sponsor is considering MACE a potential risk.

7.1 Background and Population Risk Factors in Psoriasis Patients

The burden of CV comorbidities is higher in the psoriasis patient population than in the general patient population, which is to be expected given the increased prevalence of traditional CV risk factors, such as diabetes, hypertension, dyslipidemia, tobacco use, and obesity in this patient

population (Neimann 2006). In a recent systematic review and meta-analysis of observational studies analyzing the rate of MACE in psoriasis patients, the authors concluded that severe psoriasis was associated with a significantly increased risk of CV mortality (risk ratio RR=1.39), with an almost 2-fold increase in myocardial infarction (MI), (RR=1.70), and stroke (RR=1.56) as compared to controls (Armstrong 2014). Estimated incidence rates per 100 patient years were 0.31 to 1.62 for CV mortality (Horreau 2013).

7.2 Cardiovascular Risk Factors in the Brodalumab Program

Baseline cardiovascular risk factors were evenly distributed across the treatment groups (Table 7–1). At least one cardiovascular risk factor, aside from male gender, was present at baseline in 83% of brodalumab exposed patients and 3% had a history of ischemic cardiovascular disease. Smoking, obesity and hypertension were the most common baseline risk factors.

Table 7–1 Baseline cardiovascular risk factors, n (%) – Integrated Safety Analysis Set – Psoriasis Subset

	Placebo N=879	Ustekinumab N=613	All Brodalumab N=3066
Overweight/Obese	397 (45%)	285 (47%)	1425 (47%)
BMI > 30	387 (44%)	282 (46%)	1411 (46%)
Overweight/obesity PT	66 (8%)	57 (9%)	264 (9%)
Glucose Intolerance/Diabetes[a]	91 (10%)	77 (13%)	351 (11%)
Smoking status (former/current)	493 (56%)	361 (59%)	1680 (55%)
Dyslipidemia[b]	244 (28%)	111 (18%)	706 (23%)
Hypertension[c]	220 (25%)	189 (31%)	824 (27%)
At least one Relevant Med hx	32 (4%)	24 (4%)	104 (3%)
Ischaemic cerebrovascular SMQ	6 (0.7%)	9 (1.5%)	21 (0.7%)
Ischaemic heart disease SMQ	27 (3%)	16 (3%)	88 (3%)
Risk Factor (0=none to 6)			
0	132 (15%)	109 (18%)	514 (17%)
1	312 (36%)	202 (33%)	1106 (36%)
2	237 (27%)	150 (25%)	741 (24%)
3	124 (14%)	84 (14%)	419 (14%)
≥4	74 (8%)	68 (11%)	286 (9%)
Risk Factor, category			
0	132 (15%)	109 (18%)	514 (17%)
≥1	747 (85%)	504 (82%)	2552 (83%)

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

[b] 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

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

CTCAE v. 4.0 or 4.03; MedDRA v. 18.1;

Includes data from patients in Studies 20090062, AMAGINE-1, AMAGINE-2, and AMAGINE-3 with >= 1 dose of investigational product

7.3 Cardiovascular Events

Cardiovascular events, including MACE, were carefully evaluated in the brodalumab program, across the Phase 2 and 3 psoriasis studies, as they were prospectively identified as adverse events of interest. Overall cardiovascular events were evaluated by grouping all relevant reported adverse event terms for each treatment group by using the two standard MedDRA SMQs of ischemic cerebrovascular disease and ischemic heart disease.

In the 12-week placebo-controlled period (Table 7–2) there were low, single, numbers of events reported and no imbalances noted between placebo, ustekinumab, and 140 and 210 mg

brodalumab Q2W dose groups in either SMQ. There also was no indication of a dose dependency within the brodalumab groups.

In the 52-week controlled period (Table 7–3) exposure and follow-up adjusted event rates of ischemic cerebrovascular disease and ischemic heart disease were balanced between brodalumab and ustekinumab. Exposure adjusted rates of ischemic cerebrovascular disease in brodalumab treated patients was 0.2 per 100 patient years, with 7 total events, and 0.2 per 100 patient years, with 1 event, for the ustekinumab group, respectively. The exposure adjusted rates of ischemic heart disease in the brodalumab treated patients was 1.2 per 100 patient years, 40 total events. In the ustekinumab group, the exposure adjusted rate was 1.0 per 100 patient years, with a total of 5 events.

Table 7–2 Summary of Treatment-Emergent Cardiovascular Adverse Events of Interest During Initial Double-blind Period (12 Week Pool)

			Brodalumab		
	Placebo (N=879)	**Ustekinumab (N=613)**	**140 mg Q2W (N=1491)**	**210 mg Q2W (N=1496)**	**All (N=3066)**
	n (%)	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Ischemic cerebrovascular disease SMQ	0 (0.0)	1 (0.2)	1 (0.1)	1 (0.1)	2 (0.1)
Ischemic heart disease SMQ	1 (0.1)	1 (0.2)	4 (0.3)	0 (0.0)	4 (0.1)

Events are coded with CTCAE v. 4.0 or 4.03 (depending on study) and MedDRA v. 17.1.
n=number of patients reporting ≥1 occurrence of an adverse event through Week 12; SMQ=Standardised MedDRA Queries
Note: Treatment groups are defined as planned (randomized) treatment.

Table 7–3 Summary of event rates (per 100 patient-years) for cardiovascular adverse events of interest - 52-Week Pool and Long-term Pool – Psoriasis Subset

	52-Week Pool		Long-Term Pool
	Ustekinumab (N=613) n (r)	All-brodalumab (N=4019) n (r)	All-brodalumab (N=4464) n (r)
Exposure-adjusted	**Pt-yr = 494.7**	**Pt-yr = 3445.5**	**Pt-yr = 8655.0**
Ischemic cerebrovascular disease SMQ	1 (0.2)	7 (0.2)	21 (0.2)
Ischemic heart disease SMQ	5 (1.0)	40 (1.2)	85 (1.0)
Follow-up time adjusted	**Pt-yr = 504**	**Pt-yr = 3547.7**	**Pt-yr = 9173.9**
Ischemic cerebrovascular disease SMQ	1 (0.2)	11 (0.3)	24 (0.3)
Ischemic heart disease SMQ	6 (1.2)	41 (1.2)	93 (1.0)

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 investigational product.

AE=Adverse event; n=number of adverse events; r=exposure-adjusted event rate per 100 patient-years (n/patient-yr*100); Pt-yr=total patient-years of exposure through Week 52 (52-Week Pool) and through end of study (Long-Term Pool); SMQ=Standardised MedDRA Queries.

Multiple occurrences of the same event for a patient are counted as multiple events.

In the long-term period, the follow-up time adjusted brodalumab rates in both SMQs remained stable, with follow up adjusted rates of 0.3 per 100 patient years for ischemic cerebrovascular disease. The follow up adjusted rate for ischemic heart disease was 1.0 per 100 patient years. Reported cerebrovascular disease and ischemic heart disease adverse events were balanced between brodalumab and ustekinumab, and appear stable over long term treatment.

7.4 Observed MACE Events

From the triggered events, approximately two-thirds of the events were ultimately classified as MACE by the CEC.

Through week 12, 3 patients (0.2%), in the 140 mg Q2W group (2 myocardial infarctions and 1 stroke) and none in placebo, ustekinumab, or brodalumab 210 Q2W, had CEC-adjudicated MACE (Table 7–4).

In the 52-week, active comparator controlled period, the exposure-adjusted MACE event rates were 0.6 per 100 patient years (95% CI: 0.37 to 0.94) in the all-brodalumab group (a total of 20 events) and 0.4 per 100 patient years (95% CI: 0.05 to 1.46) in ustekinumab group (a total of 2 events). The follow up time-adjusted event rates of MACE were 0.7 per 100 patient years (95% CI: 0.46 to 1.06) in the all-brodalumab group (a total of 24 events) and 0.4 per 100 patient years

(95% CI: 0.05 to 1.43) in ustekinumab group (a total of 2 events). There was no trend observed across brodalumab doses.

In the long-term group, the exposure-adjusted rate of MACE in brodalumab-exposed patients through the end of study was 0.5 per 100 patient years (95% CI: 0.36 to 0.69). A total of 40 MACE events were observed in brodalumab treated patients. The follow-up time adjusted rate for brodalumab treated patients was 0.6 per 100 patient years (95% CI: 0.48 to 0.84), with 54 MACE events observed in total (Table 7–5).

Table 7–4 Patient incidence of major adverse cardiac events (MACE) during the initial double-blind period - 12 Week Pool - Psoriasis Phase 3 Studies Only

			Brodalumab		
Type of MACE	**Placebo (N=842) n (%)**	**Ustekinumab (N=613) n (%)**	**140 mg Q2W (N=1452) n (%)**	**210 mg Q2W (N=1456) n (%)**	**All (N=2908) n (%)**
Number of patients reporting MACE	0 (0.0)	0 (0.0)	3 (0.2)	0 (0.0)	3 (0.1)
Cardiovascular death	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Myocardial infarction	0 (0.0)	0 (0.0)	2 (0.1)	0 (0.0)	2 (0.1)
Stroke[a]	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	1 (< 0.1)

[a] Includes stroke and transient ischemic attack.

N=patients in Studies AMAGINE-1, AMAGINE-2, AMAGINE-3 with ≥ 1 dose of investigational product; n=number of patients experiencing ≥1 occurrence of a MACE Event; %=n/N*100.

Major Adverse Cardiac Events (MACE) includes myocardial infarction, stroke, and cardiovascular deaths

Treatment groups are defined as planned (randomized) treatment.

Table 7–5 Exposure- and follow-up adjusted event rates (per 100 patient years) of MACE in 52-Week Pool and Long-Term Pool – Phase 3 Psoriasis subset

	52-Week Pool		Long-term Pool
MACE event	Ustekinumab N=613 n (r) [95% CI]	All-brodalumab N = 3828 n (r) [95% CI]	All-brodalumab N = 4273 n (r) [95% CI]
Exposure-adjusted	**Pt-yr = 494.7**	**Pt-yr = 3294.9**	**Pt-yr = 7870.4**
All MACE Events	2 (0.4) [0.05, 1.46]	20 (0.6) [0.37, 0.94]	40 (0.5) [0.36, 0.69]
CV death	1 (0.2) [0.01, 1.13]	2 (0.1) [0.01, 0.22]	5 (0.1) [0.02, 0.15]
Myocardial infarction	1 (0.2) [0.01, 1.13]	14 (0.4) [0.23, 0.71]	25 (0.3) [0.21, 0.47]
Stroke	0 (0.0) [NE, 0.75]	4 (0.1) [0.03, 0.31]	10 (0.1) [0.06, 0.23]
Follow-up adjusted	**Pt-yr = 504.0**	**Pt-yr = 3378.3**	**Pt-yr = 8365.2**
All MACE Events	2 (0.4) [0.05, 1.43]	24 (0.7) [0.46, 1.06]	54 (0.6) [0.48, 0.84]
CV death	1 (0.2) [0.01, 1.11]	3 (0.1) [0.02, 0.26]	12 (0.1) [0.07, 0.25]
Myocardial infarction	1 (0.2) [0.01, 1.11]	16 (0.5) [0.27, 0.77]	30 (0.4) [0.24, 0.51]
Stroke	0 (0.0) [NE, 0.73]	5 (0.1) [0.05, 0.35]	12 (0.1) [0.07, 0.25]

CTCAE v. 4.0 or 4.03; MedDRA v. 17.1 (52-week pool), MedDRA v. 18.1 (long-term pool);
MACE=major adverse cardiac events; CV=cardiovascular; N=patients in Studies AMAGINE-1, AMAGINE-2 and AMAGINE-3 with ≥1 dose of active investigational product; n=number of MACE events; Pt-yr = total patient-years of exposure through Week 52 (52-Week Pool) and through end of study (Long-Term Pool); r exposure or follow-up adjusted event rate per 100 patient –years (n/pt-yr*100)
Multiple occurrences of the same event for a patient are counted as multiple events.
95% confidence interval based on exact method assuming Poisson distribution

Most patients for whom a new MACE was reported had ≥1 major CV risk factor and additional confounding comorbidities, many had ≥3 risk factors, including family history of CAD, current smoking, obesity, diabetes, dyslipidemia (increased LDL and/or TG count as 1), and hypertension.

Additional case details for MACE events are provided in Appendix A.

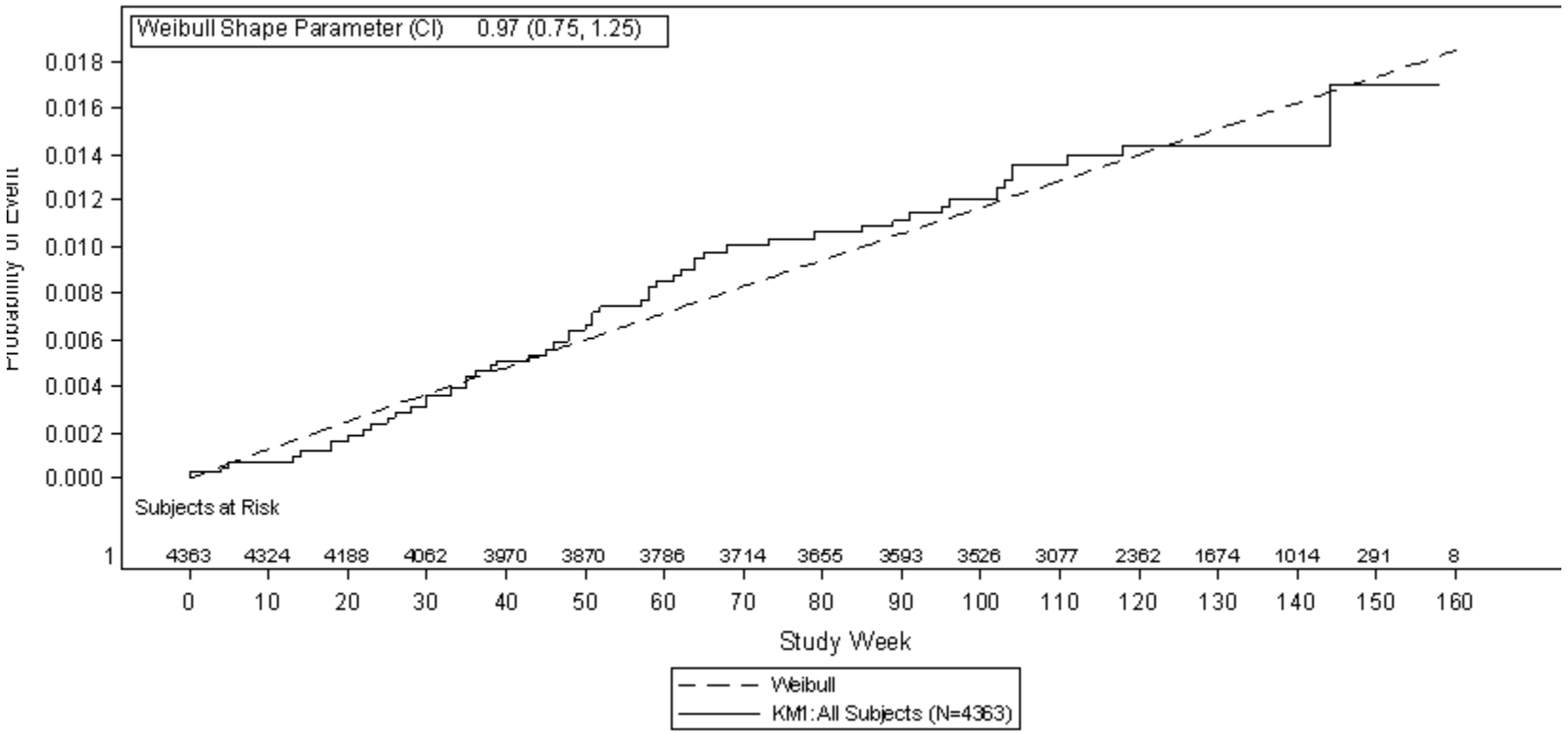
7.5 MACE Rates Over Time

Analyses of time to event for MACE were also performed from study baseline for all patients receiving a dose of investigational product through the end of study to analyze the cumulative probability of the incidence of MACE across the study population. The Weibull model was used to test the constant hazard assumption (an exponential fit with a shape parameter = 1) (Abernethy 1996).

The assumption of constant hazard for the time-to-first adjudicated MACE seemed reasonable, given the estimate for the shape parameter alpha was 0.97 with 95% CI: 0.75 to 1.25, which included the assumed value of 1 (Figure 7–1). This indicates that the rate of adjudicated MACE events remained constant over the full time course. Further, the cumulative probability of patients experiencing MACE through the first year on study (approximately 0.006) and through the second year on study (approximately 0.012) appeared low and showed no notable trends.

Due to the decreased number of patients at risk after the second year and the rareness of the events of MACE, interpretation of these data should be made with caution.

Figure 7–1 **Kaplan Meier plot of time to first adjudicated MACE from study baseline through end of study for all patients - Integrated Safety Analysis Set – Phase 3 Psoriasis Subset**



CTCAE v. 4.0 or 4.03; MedDRA v.18.1;
N=patients in Studies AMAGINE-1, AMAGINE-2, and AMAGINE-3 with ≥ 1 dose of investigational product.
Major Adverse Cardiac Events (MACE) includes myocardial infarction, stroke, and cardiovascular deaths.

7.6 Comparative MACE Rates from External Sources

Limited comparator data are available in the controlled periods of the brodalumab clinical program complicating the evaluation of infrequent events, including MACE. In addition, the long term extensions were uncontrolled. Therefore, external data may help to provide context around these events. Ideally, these data should be derived from a population with similar demographics and risk factors to that studied in the brodalumab program.

A systematic literature review was conducted to obtain information from clinical trials and registries for the incidence rates of specific AEs of interest in adults with psoriasis and/or psoriatic arthritis treated with biological agents and other recently approved agents (Delzell and Chang 2015). These agents included adalimumab, apremilast, certolizumab pegol, etanercept, golimumab, infliximab, ixekizumab, secukinumab, and ustekinumab. Eligible studies included phase 3 and phase 4 clinical trials (including open-label extensions) and patient registries. Data were obtained from published scientific journal articles, the ClinicalTrials.gov website, regulatory agency documents, and drug package inserts. Information was abstracted from PubMed as of August 2014, and from clinicaltrials.gov as of October 2014. Incidence rates were calculated by dividing the number of unique cases across all studies by the total person-time and confidence intervals were calculated using the exact Poisson method.

The pooled estimate of rates of MACE per 100 patient-years in patients with psoriasis or psoriatic arthritis participating in clinical trials or registries, irrespective of treatment was 0.47 per 100 patient years (95% CI 0.39,0.57) and for psoriasis, 0.45 per 100 patient years (95% CI: 0.36, 0.56) (Delzell and Chang 2015). This rate is comparable to the exposure-adjusted rate for brodalumab of 0.5 per 100 patient years (CI: 0.36 to 0.69).

While the rates reported by Delzell and Chang are taken from a somewhat comparable psoriasis population, there are important considerations that must be made when comparing these rates with those observed in the brodalumab program. As with all literature reviews, there are inherent limitations: for example, differing populations, trial design, specific inclusion and exclusion criteria, and concomitant medications, as well as differences in case definitions used and adjudication across different programs. Therefore, comparison of brodalumab program results with the results from the literature review by Delzell and Chang should be interpreted with caution.

Data have been published on the recently approved IL-17A antagonists for psoriasis, eg, secukinumab and ixekizumab. The exposure-adjusted MACE rates for secukinumab have been reported as 0.42 and 0.35 per 100 patient-years for 300 mg and 150 mg doses, respectively (van

de Kerkhof 2016). For ixekizumab, the exposure adjusted rate of MACE was reported as 0.63 (CI 0.46, 0.87) per 100 patient-years (Papp 2016).

In the recent BLA for Ixekizumab, cardiovascular data from psoriasis registries and the literature were tabulated clearly showing the large variation in rates (per 100 patient years) of cardiovascular and cerebrovascular events, ranging from < 0.2 in early psoriasis, ≤ 0.4 in mild psoriasis up to 0.88 in severe psoriasis.

The sponsor concludes that the observations of MACE from the clinical trials of brodalumab in psoriasis are consistent with rates seen with other agents approved for the treatment of this patient group.

7.7 Other CV Safety Assessments

Following a thorough review of the non-clinical findings and collected ECG data, there was no evidence for a direct drug effect of brodalumab on the heart.

7.7.1 Non-Clinical Findings

While the effects of IL-17 pathway inhibition on atherosclerosis and myocardial remodeling are not known, no evidence of an effect has been observed in the brodalumab non-clinical program.

IL-17A positive T cells are present in atherosclerotic plaques in humans and mice; however, their significance is unclear (Butcher and Galkina 2011). This has been investigated in both clinical settings and various animal models with conflicting results. The majority of the data supports a proatherogenic role for the IL-17 pathway, which suggests that inhibition of IL-17RA by administration of brodalumab would be expected to decrease atherogenesis.

7.7.2 QT prolongation and other ECG Abnormalities

There was no evidence of a direct or indirect effect of brodalumab on the QT interval.

Phase 1 data in healthy patients showed no relationship between QT interval measured in triplicate, read centrally, and corrected for heart rate using Fridericia's formula (QTcF) values and serum brodalumab levels over a broad range of brodalumab serum concentrations (<50 to >300,000 ng/mL).

A thorough QT/QTc study was not planned since monoclonal antibodies like brodalumab are unlikely to interact with ion channels resulting in an effect on electrocardiogram (ECG) activity because of their high target specificity.

Routine ECG monitoring (results collected in triplicate with central reading) was conducted in the psoriasis clinical studies and a careful review was performed to monitor for any potential AEs (clinical symptoms including syncope and dizziness) suggestive of QT prolongation. No safety signals were noted based on this review.

7.8 Evaluation of CV/MACE Observations using Bradford Hill Criteria

The cardiovascular findings with brodalumab were also evaluated based on revised Hill criteria described by Howick 2009. The evidence relating to each of the criteria is briefly summarized below in the context of brodalumab and adverse cardiovascular events. The sponsor concludes that the evidence does not support a causal association between MACE and brodalumab.

1. Direct evidence
    a. Direct evidence was based on relatively few MACE events and showed a potentially higher rate of MACE in brodalumab patients, but with overlapping confidence intervals in comparison to ustekinumab. Through Week 12, 3 patients (0.2%), all in the 140 mg Q2W group and none in the other treatment groups, including placebo, ustekinumab, or brodalumab 210 Q2W, had CEC-adjudicated MACE. In the 52-week, active comparator controlled period, the exposure-adjusted MACE event rates were 0.6 per 100 patient years (95% CI: 0.37 to 0.94) in the all-brodalumab group (a total of 20 events) and 0.40 per 100 patient years (95% CI: 0.05 to 1.46) in ustekinumab group (a total of 2 events). The overall long-term MACE rate with brodalumab is within the range seen with other biologics and non-biologics in psoriasis population clinical trials and registries. In the long-term group, the exposure-adjusted rate of MACE in brodalumab-exposed patients through the end of study was 0.5 per 100 patient years (95% CI: 0.36 to 0.69). The follow-up time adjusted rate for brodalumab treated patients was 0.6 per 100 patient years (95% CI: 0.48 to 0.84). The exposure adjusted rate of MACE derived from a systematic literature review of all biologic and systemic therapies for psoriasis was 0.45 per 100 patient years (95% CI: 0.36, 0.56).
    b. Overall mortality is not increased between ustekinumab and brodalumab in the 52-week controlled period.

2. Temporality

    a. There was no temporal pattern or association identified with the observed MACE events in Phase 3 trials. The events occurred throughout the treatment period, as expected with a background population event. Analyses of time to event for MACE were also performed from study baseline for all patients receiving brodalumab through the end of study to analyze the cumulative probability of the incidence of MACE across the study population. Due to the decreased number of patients at risk after the second year and the rareness of the events of MACE, interpretation of these data should be made with caution. However, the cumulative probability of patients experiencing MACE through the second year was low, constant over the time course, and showed no notable trends.

3. Strength of effect

    a. Given that the incidence of MACE is rare, rates in the individual psoriasis clinical programs vary greatly and are likely to represent a range around the true incidence rate.

4. Dose Response

    a. During the 52 week controlled period, there was no trend observed across brodalumab doses. There was no dose trend in MACE events found between the 140 mg and 210 mg brodalumab doses in the Phase 3 studies, although the total patient years of exposure with 140 mg brodalumab is much lower. Through Week 12, 3 patients (0.1%) in the brodalumab 140 mg Q2W group and none in the brodalumab 210 mg Q2W treatment group had CEC-adjudicated MACE (2 myocardial infarctions and 1 stroke).

5. Biological Plausibility

    a. Evidence does not support a link between the mechanism of action and adverse cardiac events. IL-17A positive T cells are present in atherosclerotic plaques in humans and mice; however, their significance is unclear (Butcher and Galkina 2011). The majority of the data supports a pro-atherogenic role for the IL-17 pathway, which suggests that inhibition of IL-17RA by administration of brodalumab would be expected to decrease atherogenesis. The non-clinical testing of brodalumab, including clinical pharmacology testing and animal tissues examined for pathologic findings, has found no evidence of treatment-related adverse cardiovascular effects.

b. In brodalumab clinical trials there was no evidence of adverse effects on metabolic indicators, such as glucose metabolism or lipid levels, or on cardiovascular related parameters such as blood pressure and ECG findings, that might be risk factors for, or associated with adverse cardiovascular effects.

6. Consistency (reproducibility, class effects)

   a. When examining cardiovascular and cerebrovascular adverse events reported from the controlled portions of brodalumab clinical trials there was no indication of an imbalance of events between brodalumab and ustekinumab or placebo. In the 52-week controlled period exposure and follow-up adjusted event rates of ischemic cerebrovascular disease and ischemic heart disease were balanced between brodalumab and ustekinumab. Exposure adjusted rates of ischemic cerebrovascular disease in brodalumab treated patients was 0.2 per 100 patient years, and 0.2 per 100 patient years, for the ustekinumab group, respectively. The exposure adjusted rates of ischemic heart disease in the brodalumab treated patients was 1.2 per 100 patient years. In the ustekinumab group, the exposure adjusted rate was 1.0 per 100 patient years.

   b. The nature of the MACE events observed (predominantly MI) is consistent with what might be expected in the population.

   c. Other molecules that target the IL-17 signaling pathway, such as secukinumab and ixekizumab have not been associated with adverse cardiovascular effects or increased MACE incidence rates. For secukinumab, exposure-adjusted MACE rates have been reported as 0.42 and 0.35 per 100 patient-years for 300 mg and 150 mg respectively (van de Kerkhof 2016). For ixekizumab, the exposure adjusted rate of MACE was reported as 0.63 (95% CI: 0.46, 0.87) per 100 patient-years (Papp 2016).

7. Coherence

   a. The MACE events assessed are non-specific in regards to a potential association with a biologic agent, such as brodalumab, in that they are known to be highly associated with identified cardiovascular risk factors, such as hypertension, dyslipidemia, and previous history of atherosclerotic cardiovascular disease. These risk factors are known to be prevalent in the studied psoriasis patients.

b. Other biological and immune modulatory treatments of psoriasis have been identified as having a potential cardiovascular safety signal from their clinical trial programs. However, cumulative evidence from longer-term trial and post-market registry experience has not confirmed a causal association for any of these agents. For example, a similar situation arose during the review of ustekinumab. The rate of MACE observed across the clinical program was 0.6 (95% CI: 0.28 to 1.16). At the time of approval, postmarketing commitments included evaluation of cardiovascular events through 2 patient registries and 5-year open label extensions for 2 Phase 3 ongoing trials. Following these evaluations, the rate of MACE observed and reported in literature is 0.32 per 100 patient-years (95% CI not reported) (Papp 2015).

In summary, other than the numerical imbalance across limited numbers of events observed in the controlled 52-week period for brodalumab versus ustekinumab, evidence does not support a causal association of brodalumab and CV events, including MACE.

8 Suicidal Ideation and Behavior

Suicidal ideation and behavior was identified as a potential risk in 2014, late in in the brodalumab psoriasis development program, when most patients had completed 52 weeks on study. Screening tools for depression (PHQ-8) and suicidality (eC-SSRS) were implemented but as all psoriasis patients had been enrolled, there is no baseline information available. Per protocol, patients with scores reaching a pre-defined threshold were referred to a mental health professional and/or withdrawn from investigational product.

Across all indications in the brodalumab program there were 39 patients with suicidal ideation and behavior. Of these, 18 had suicidal behaviors, including 6 completed suicides. There were 24 ideations associated with brodalumab (Table 8–1).

Table 8–1 Follow-up observation time-adjusted patient incidence rates of SIB events from first dose of brodalumab through the end of study in patients who received ≥1 dose of brodalumab - Phase 2 and Phase 3 Sponsor Studies (All Indications)

Event of interest category	Psoriasis Pt-yr =9161.8 (N=4464) n (r)	Asthma (Pt-yr=165) (N=434) n (r)	Crohn 's (Pt-yr=33.6) (N=116) n (r)	Psoriatic arthritis (Pt-yr=920.2) (N=991) n (r)	Rheumatoid arthritis (Pt-yr=157.6) (N=238) n (r)	Total (Pt-yr=10438) (N=6243) n (r)
Suicidal ideation and behaviour event	34 (0.37)	0 (0.00)	0 (0.00)	3 (0.33)	2 (1.27)	39 (0.37)
Suicidal behaviour	15 (0.16)	0 (0.00)	0 (0.00)	1 (0.11)	2 (1.27)	18 (0.17)
Completed suicide[a]	4 (0.04)[b]	0 (0.00)	0 (0.00)	1 (0.11)	1 (0.63)	6 (0.06)[b]
Suicidal ideation	22 (0.24)	0 (0.00)	0 (0.00)	2 (0.22)	0 (0.00)	24 (0.23)

[a] The category "Completed Suicide" includes all fatal events from the Suicidal Behavior events of interest category.

[b] Includes event reported as intentional overdose

MedDRA v. 18.1.

N= patients in Studies 20090061/20090402, 20090072/20100008, 20090203, 20101227, AMAGINE-1, AMAGINE-2, AMAGINE-3, 20090406, 20110144, and 20120141 with ≥1 dose of brodalumab.

Patients from site 12002 in the completed phase 2 asthma study were excluded from the analysis.

Pt-yr = Total patient-years of follow-up through min(patients first suicidal ideation and behavior event, end of study); n=number of patients with adverse events; r=follow-up observation time adjusted patient incidence rate per 100 patient-years (n/pt-yr*100). Multiple occurrences of the same events for a patient are counted once.

Total patient-years are truncated at patient's first suicidal ideation and behavior event.

For the purposes of this review, CDC nomenclature was used for the spectrum of suicidal ideation and behavior: suicidal ideation; suicidal behavior (intent to die must be present) including preparatory acts, attempts (including aborted and interrupted); and completed suicide.

8.1 SIB Analysis Methods

Three main data pools were generated based on study treatment period and study design to evaluation SIB events in the brodalumab psoriasis population from the Phase 2 and 3 psoriasis studies.

The 12-week pool refers to data from the initial double-blind, 12 week period and includes placebo and ustekinumab comparator groups

The 52-week pool includes data from the active comparator ustekinumab. Of note, only AMAGINE-2 and AMAGINE-3 included ustekinumab, but all Phase 2 and Phase 3 studies were included in this pool. These data are analyzed and presented as exposure- and follow-up time adjusted patient-incidence rates.

The Long Term pool includes cumulative data from the first dose of brodalumab through the end of study. Note that a comparator group was not available for the assessment of safety with long-term brodalumab exposure. These data are presented as exposure- and follow-up time adjusted patient-incidence rates.

8.2 Suicidal Behavior Risk Factors

8.2.1 General Population

People who contemplate, attempt, and/or die from suicide usually have 1 or more psychopathologies (Gvion and Apter 2011). Approximately 90% of completed suicide cases have psychiatric disorders, particularly major depression, substance use disorders, certain personality disorders, and schizophrenia (Arsenault-Lapierre 2004, Cavanagh 2003), with mood disorders the most commonly associated with suicidal behavior (Groholt and Ekeberg 2009, Renaud 2008, Yoshimasu 2008). A lifetime history of depression more than doubles the odds of a suicide attempt (O'Connor 2013) and a history of suicide attempt is strongly associated with increased risk of suicide (Yoshimasu 2008). In addition, precipitating circumstances for completed suicide include intimate partner problem or disclosed suicidal intent (30%), physical health problems (22.5%) and job or financial problems (12.5%) (CDC 2015).

It is generally acknowledged that suicide is under reported (Reynders 2011, Phillips and Ruth 1993, Warshauer and Monk 1978). According to the Centers for Disease Control and Prevention (CDC 2015), rates of suicidal ideation and behaviors vary by age and gender. While the overall suicide rate for the general population is 0.013 per 100 person-years, for males aged 45-64 it is 0.03 per 100 person-years. Males commit suicide more frequently than females (4:1), females attempt suicide more frequently than males and rates of ideation are equal between men and women (CDC 2015).

8.2.2 Psoriasis Population

Patients with psoriasis are at increased risk for depression and suicidal ideation and behavior. Exclusion criteria for the last 4 agents approved for moderate to severe plaque psoriasis (ustekinumab, aprelmilast, secukinumab, and ixekizumab) all had specific exclusion language for significant psychiatric disorders, some excluded substance abuse and ixekizumab had a specific screening tool for suicidality. In contrast to other psoriasis development programs, patients with depression and suicidality were not specifically excluded from brodalumab clinical trials.

There is an increased risk of depression in patient with psoriasis. In the Nurses' Health Study the risk of depression in women with psoriasis was increased (RR of 1.29 (95% CI: 1.10, 1.52) and 1.52 (95% CI: 1.06, 2.19) for those with concomitant psoriatic arthritis (Dommasch 2015). In a multi-national cross-sectional study, patients with psoriasis were more likely to have clinical depression compared to those without skin disease Odds Ratio (OR) 3.02, (95% CI: 1.86, 4.90) and anxiety, OR 2.91, (95% CI: 2.01, 4.21) (Dalgard 2015). Patients with worse psoriasis had worse depression scores (Gupta 1993). In an analysis of UK General Practice Research Database, age and sex adjusted hazard ratios (HR) for incident depression in patients with mild psoriasis was 1.38 (95% CI: 1.35, 1.40) and severe depression was 1.72 (95% CI: 1.57, 1.88). Men had an even greater risk of developing depression (Kurd 2010). Data from NHANES indicate a 2 fold increase in depression in people with psoriasis (Cohen 2016).

In a recent multi-national cross-sectional study the overall prevalence of reported suicidal ideation was 17.3% in patients with psoriasis and 67.6% attributed it to their psoriasis. Compared to healthy controls, patients with psoriasis reported more suicidal ideation, adjusted Odds Ratio (OR) 1.94, (95% CI: 1.33, 2.82) (Dalgard 2015). In a US study of 217 patients with psoriasis active suicidal ideation was reported in 5.5%, and 9.7% of patients reported a wish to be dead (Gupta 1993). There was almost a 3-fold higher rate of active suicidal ideation in patients with more severe psoriasis (hospitalized for psoriasis) compared with non-hospitalized patients (7.2% vs 2.5%) (Gupta and Gupta 1998).

In a UK-based study in psoriasis patients there was an increased risk of hospitalization for self-harm, RR: 1.6 (95% CI: 1.5, 1.7) (Singhal 2014). In another UK database study, the adjusted HR for suicidality was 1.44 (95% CI: 1.32, 1.57) for patients with mild psoriasis compared with controls, and the HR was 1.51 (95% CI: 0.92, 2.49) for patients with severe psoriasis (Kurd 2010). In a Danish population database study, severe psoriasis was associated with a significant increase in the rates of self-harm and attempts (incidence rate ratio [IRR] 1.69 95% CI: 1.00-2.84) but not completed suicide (Egeberg 2016).

8.2.3 Prevalence of Psychiatric Disorder in the Brodalumab Psoriasis Program

Expected rates of SIB events vary with age and gender. In the brodalumab psoriasis program, the mean age was 44.8 years and 69% of patients were male.

Baseline medical history obtained at screening did not have specific data capture for psychiatric disorders.

The prevalence of psychiatric disorders in the patients in the psoriasis program obtained by medical history is presented in Table 8–2. Overall 17.5% had a psychiatric disorder; approximately 10% of patients had depression and 1.1% prior suicidal ideation, attempts, or behavior. Additional baseline history obtained from lifetime eCSSRS, baseline medical history search with depression SMQ and suicide self-injury SMQ, and baseline antidepressant use resulted in updated baseline medical history of depression in 14.1% (n = 602) and SIB in 2.8% (n = 119) of brodalumab patients.

Table 8–2 Baseline medical history of interest – 12-Week Pool - Integrated Safety Analysis Set - Psoriasis Subset

			Brodalumab		
	Placebo (N=879) n (%)	**Ustekinumab (N=613) n (%)**	**140 mg Q2W (N=1491) n (%)**	**210 mg Q2W (N=1496) n (%)**	**All (N=3066) n (%)**
Any medical or surgical history	**710 (80.8)**	**526 (85.8)**	**1228 (82.4)**	**1251 (83.6)**	**2556 (83.4)**
Psychiatric disorders	**150 (17.1)**	**121 (19.7)**	**240 (16.1)**	**284 (19.0)**	**538 (17.5)**
Depression	77 (8.8)	68 (11.1)	146 (9.8)	152 (10.2)	306 (10.0)
Anxiety	60 (6.8)	32 (5.2)	69 (4.6)	94 (6.3)	168 (5.5)
Insomnia	28 (3.2)	27 (4.4)	47 (3.2)	52 (3.5)	104 (3.4)
Attention deficit/hyperactivity disorder	11 (1.3)	4 (0.7)	12 (0.8)	16 (1.1)	28 (0.9)
Suicidal ideation	10 (1.1)	10 (1.6)	9 (0.6)	14 (0.9)	23 (0.8)
Bipolar disorder	9 (1.0)	6 (1.0)	7 (0.5)	8 (0.5)	16 (0.5)
Suicide attempt	3 (0.3)	3 (0.5)	2 (0.1)	7 (0.5)	9 (0.3)
Panic attack	1 (0.1)	2 (0.3)	5 (0.3)	5 (0.3)	10 (0.3)
Alcoholism	1 (0.1)	1 (0.2)	5 (0.3)	5 (0.3)	10 (0.3)
Suicidal behavior	1 (0.1)	1 (0.2)	2 (0.1)	1 (0.1)	3 (0.1)
Depressed mood	1 (0.1)	0 (0.0)	1 (0.1)	0 (0.0)	1 (0.0)
Major depression	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.1)	1 (0.0)

Coded using MedDRA version 17.1; % = n/N *100.

Includes data from patients in Studies 20090062, AMAGINE-1, AMAGINE-2, and AMAGINE-3 who had at least 1 dose of investigational product.

Note: The subcategories within each category are not mutually exclusive. Patients are only included once within each subcategory. Treatment groups are defined as planned (randomized) treatment during the double-blind placebo-controlled phase.

The Hospital Anxiety and Depression Scale (HADS) was used in AMAGINE-1 as a predefined endpoint, and was implemented at study start. Baseline prevalence of anxiety and depression are

indicated by the subscales. A baseline HADS score 8-10 would indicate mild, 11-14 moderate and 15-21 severe anxiety or depression.

The prevalence of depression and anxiety at baseline, as measured by HADS, in patients in AMAGINE-1 is presented below in Table 8–3. At baseline, 36% had anxiety, 16% could be categorized as moderate to severe. For depression, 26.6% had depression at baseline, 12.4% could be categorized as moderate to severe. The prevalence of baseline anxiety and depression as determined by HADS in AMAGINE-1, is higher than the self-reported rates from medical history.

Table 8–3 Anxiety and depression at baseline by HADS subscores – AMAGINE-1

Category Score	Placebo N = 220 (%) n (%)	Brodalumab N = 441 (%) n (%)	All[a] N = 661 (%) n (%)
Anxiety			
Mild 8-10	51 (23.2)	81 (18.4)	132 (20.0)
Moderate 11-14	24 (10.9)	54 (12.2)	78 (11.8)
Severe 15-21	3 (1.4)	25 (5.7)	28 (4.2)
Any Anxiety	78 (35.5)	160 (36.3)	238 (36.0)
Depression			
Mild 8-10	35 (15.9)	59 (13.4)	94 (14.2)
Moderate 11-14	16 (7.3)	50 (11.3)	66 (10.0)
Severe 15-21	6 (2.7)	10 (2.3)	16 (2.4)
Any Depression	57 (25.9)	119 (26.9)	176 (26.6)

[a] Includes placebo and all brodalumab groups
HADS=hospital anxiety and depression scale; N = total number of patients in AMAGINE-1; n = number of patients.

8.3 Observed Incidence of SIB

Narratives for completed suicides and suicide attempts from all indications in the brodalumab development program are provided in Appendix A.

8.3.1 Psoriasis Data

Through Week 12, 2 events of suicide attempt were reported in 1 patient in the 210 mg Q2W group (0.07%). No other suicidal behavior and ideation events were reported in the placebo or ustekinumab groups (Table 8–4). Of note, the attempted suicides included 2 of 3 events by a single patient with a history of suicidal ideation, depression, anxiety, and alcohol abuse; the third event occurred later in the 52-week treatment period.

Table 8–4 Patient incidence of SIB events during the initial double- blind period (12 Week Pool) - Integrated Safety Analysis Set – Psoriasis Subset

	Placebo (N = 879) n (%)	Ustekinumab (N = 613) n (%)	Brodalumab 140 mg Q2W (N = 1491) n (%)	Brodalumab 210 mg Q2W (N = 1496) n (%)	All (N = 3066) n (%)
Suicidal behavior adverse event	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.07)	1 (0.03)
Suicide attempt	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.07)	1 (0.03)
Completed suicide	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Suicidal ideation adverse event	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

CTCAE v. 4.0 or 4.03; MedDRA v. 17.1.

N=patients in Studies 20090062, AMAGINE-1, AMAGINE-2, AMAGINE-3 with ≥ 1 dose of investigational product; n=number of patients reporting ≥1 occurrence of an AE through Week 12; %=n/N *100

Treatment groups are defined as planned (randomized) treatment.

Data for the brodalumab 70 mg Q2W group and the brodalumab 280 mg Q4W group are not shown, on the basis of the very small n's for these groups, but are represented within the all-brodalumab group.

The exposure adjusted rates for the 52-Week pool are shown in Table 8–5 below. A number of events are not captured in the exposure-adjusted rates, so the ongoing discussion of SIB will use the follow-up adjusted rates.

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 per 100 patient-years in the ustekinumab group. For suicidal behaviors, the patient incidence rate was 0.11 and 0.20 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 event 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

		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=494.3**	**Pt-yr=215.3**	**Pt-yr=1041.1**	**Pt-yr=3444.4**
Suicidal ideation and behavior	2 (0.40) [0.05, 1. 46]	0 (0.00) [NE, 1.71]	4 (0.38) [0.11, 0.98]	6 (0.17) [0.06, 0.38]
Suicidal behavior adverse event	1 (0.20) [0.01, 1.13]	0 (0.00 [NE, 1.71]	2 (0.19) [0.02, 0.69]	3 (0.09) [0.02, 0.26]
Completed suicide[a]	0 (0.00) [NE, 0.75]	0 (0.00) (NE, 1.71]	1 (0.10) [0.00, 0.54]	1 (0.03) [(0.00, 0.16]
Intentional self-injury	0 (0.00) [NE, 0.75]	0 (0.00) (NE, 1.71]	0 (0.00) [NE, 0.35]	1 (0.03) [0.00, 0.16]
Suicide attempt	1 (0.20) [0.01, 1.13]	0 (0.00) (NE, 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) (NE, 1.71]	2 (0.19) [0.02, 0.69	3 (0.09) [0.02, 0.26]
Follow-up Time-Adjusted	**Pt-yr=503.6**	**Pt-yr=221.1**	**Pt-yr=1060.7**	**Pt-yr=3545.7**
Suicidal ideation and behavior	2 (0.40) [0.05, 1.44]	0 (0.00) [NE, 1.67]	5 (0.47) [0.15, 1.1]	7 (0.20) [0.08, 0.41]
Suicidal behavior adverse event	1 (0.20) [0.01, 1.11]	0 (0.00) [NE, 1.67]	3 (0.28) [0.06, 0.83]	4 (0.11) [0.03, 0.29]
Completed suicide[a]	0 (0.00) [NE, 0.73]	0 (0.00) [NE, 1.67]	2 (0.19) [<0.01, 0.53]	2 (0.06) [<0.01, 0.16]
Intentional self-injury	0 (0.00) [NE, 0.73]	0 (0.00) [NE, 1.67]	0 (0.00) [NE, 1.35]	1 (0.03) [<0.01, 0.16]
Suicide attempt	1 (0.20) [0.01, 1.11]	0 (0.00) [NE, 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) [NE, 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

	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 = 494.3**	**Pt-yr=3444.4**	**Pt-yr = 8647.3**
Suicidal ideation and behaviour	2 (0.40) [0.05, 1.46]	6 (0.17) [0.06, 0.38]	24 (0.28) [0.18, 0.41]
Suicidal behaviour adverse event	1 (0.20) [0.01, 1.13]	3 (0.09) [0.02, 0.26]	11 (0.13) [0.06, 0.23]
Completed suicide[a]	0 (0.00) [NE, 0.75]	1 (0.03) [<0.01, 0.16]	1 (0.01) [0, 0.06]
Intentional self-injury	0 (0.00) [NE, 0.75]	1 (0.03) [<0.01, 0.16]	1 (0.01) [0, 0.06]
Suicide attempt/behaviour[b]	1 (0.20) [0.01, 1.13]	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 = 503.6**	**Pt-yr=3545.7**	**Pt-yr = 9161.8**
Suicidal ideation and behaviour	2 (0.40) [0.05, 1.44]	7 (0.20) [0.08, 0.41]	34 (0.37) [0.26, 0.52]
Suicidal behaviour 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[a]	0 (0.00) [NE, 0.73]	2 (0.06) [<0.01, 0.16]	4 (0.04) [0.01, 0.11]
Intentional self-injury	0 (0.00) [NE, 0.73]	1 (0.03) [<0.01, 0.16]	1 (0.01) [0, 0.06]
Suicide attempt/behaviour[b]	1 (0.20) [0.01, 1.11]	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

NE=not evaluable

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 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 patients taking ustekinumab had events 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.

8.3.2 Effect of Brodalumab Withdrawal on SIB Events

In AMAGINE-1, per protocol, 143 patients on brodalumab were re-randomized to placebo and treatment efficacy was lost in 6 to 8 weeks. In AMAGINE-2 and 3, 1015 patients on brodalumab Q2W patients were re-randomized to 140 mg Q4W or Q8W with loss of efficacy over 4 to 8 weeks. No events of SIB were observed with either scenario. At study termination, 3237 patients were discontinued from brodalumab. Two events of suicidal ideation occurred.

8.3.3 Retrospective C-CASA Review

Consistent with industry guidance, C-CASA adjudication was performed on events from all completed and ongoing studies reported prior to implementation of the eC-SSRS, in an attempt to ensure all potential SIB events were captured. This was a blinded adjudication and methodology and results are presented in this section.

The Columbia - Classification Algorithm for Suicide Assessment (C-CASA) is a classification system that uses definitions of suicidality derived from empirical findings regarding the phenomenology of suicidality and identified predictive and risk factors (Posner 2007).

Standard methodology was used including string text search using root terms (eg, accident-", "attempt", "burn", "cut", "drown", "gas", "gun", "hang", "hung", "immolat", "injur-", "jump", "monoxide, etc), and review of all accidental injuries, accidents, all serious adverse events and all deaths (Posner 2007). Adverse events from a total of 1217 patients (1036 in psoriasis studies) met the search criteria and were adjudicated by a blinded external group. Of these, 16 patients across all indications were adjudicated as having at least 1 suicidal event.

Four completed suicides were adjudicated. One of these 4 events, which was reported as an intentional overdose and initially categorized as a completed suicide, was adjudicated as indeterminate. Despite this change in classification, this event has been included as a completed suicide in all analyses. There were no new events adjudicated as completed suicides.

Of the 6 preferred term-categorized suicidal attempt events, 2 remained as suicidal attempts and 4 were downgraded to preparatory action towards imminent behavior (2), suicidal ideation (1), or indeterminate (1).

Of the 4 preferred terms not previously characterized as SIB, 1 was a carbon monoxide poisoning already captured as an attempt in a patient with other attempts; 1 was a cognitive dysfunction upgraded to suicidal ideation in a patient who already had an event of suicidal ideation; and two were serious depressions upgraded to suicide attempt (1) and suicidal ideation (1).

Overall, C-CASA adjudication resulted in some re-catagorization of events, but did not result in a substantive change in the rates of SIB events.

8.3.4 Brodalumab Exposure and SIB Events

To explore possible impact of higher dose on the occurrence of SIB in the patient population, the trough exposures in patients that experienced SIB events and all others were compared for

AMAGINE-1, AMAGINE-2, and AMAGINE-3. Overall the observed concentrations in patients reporting SIB were within the range of all other patients.

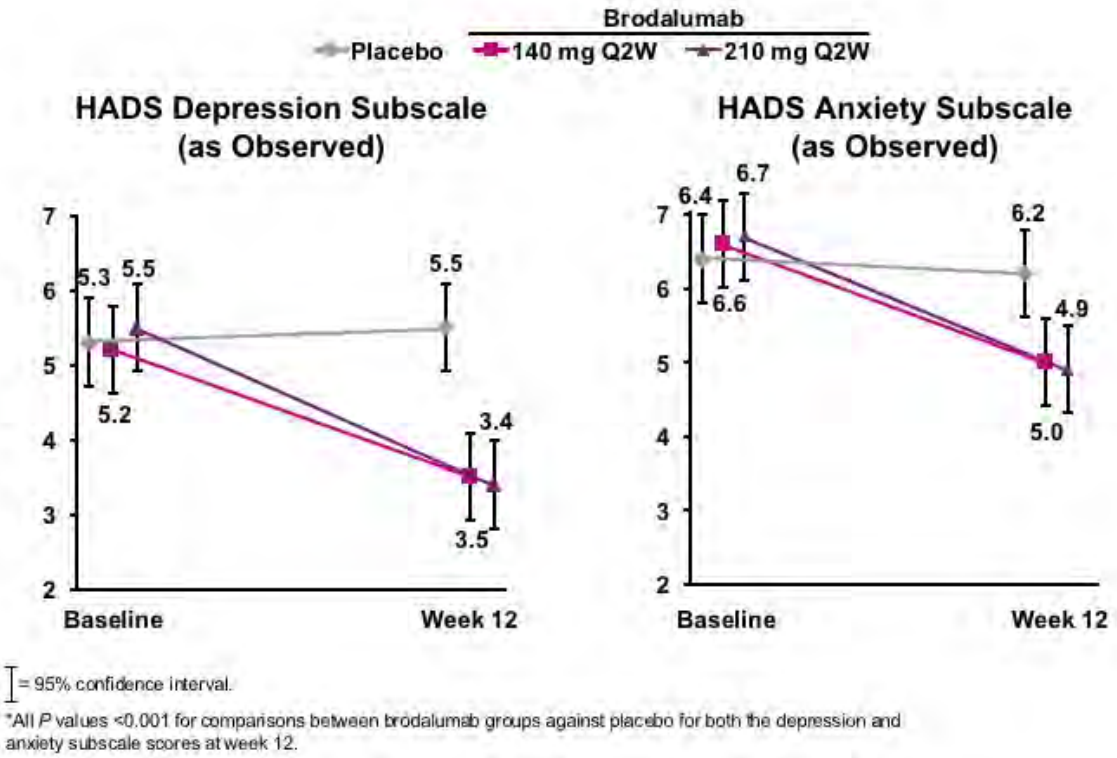
8.4 Neuropsychiatric Adverse Events

An increased frequency of neuropsychiatric AEs, including depression and/or anxiety, which are known to be associated with SIB and might be anticipated to precede suicidal events, was not observed with brodalumab use in the psoriasis program. This was investigated using the HADS data from AMAGINE-1, nervous systems disorders SOC, the depression SMQ, and the psychiatric disorders system organ class (SOC).

8.4.1 Evaluation of Anxiety and Depression in AMAGINE-1 (HADS)

A significantly greater improvement in mean HADS scores was demonstrated from baseline in the HADS depression score and anxiety score in the 210 mg Q2W and 140 mg Q2W groups compared with patients receiving placebo at Week 12 and no dose effect was observed (Figure 8–1).

Figure 8–1 AMAGINE-1 hospital anxiety and depression scale (HADS) changes from baseline to Week 12



= 95% confidence interval.

*All *P* values <0.001 for comparisons between brodalumab groups against placebo for both the depression and anxiety subscale scores at week 12.

8.4.2 Nervous System Disorders

To assess for a potential central nervous system effect, patient incidence for nervous system disorders in the initial 12-week period is presented in Table 8-7. The follow up adjusted event rates for the 52-week pool and the long-term pools are presented in Table 8–8. No imbalance was seen between brodalumab and placebo or between ustekinumab and brodalumab in the 52-week data. Through the end of study, the follow up adjusted rates per 100 patient years of nervous system disorders did not increase in the long term pool compared to the 52 week pool for brodalumab (15.8 and 23.5, respectively) indicating no evidence of increasing rates of nervous system disorders over time, with increasing patient-years of exposure to brodalumab.

Table 8-7 Patient incidence of AEs in the nervous system disorders SOC during the initial double- blind period (12 Week Pool) – Integrated Safety Analysis Set – Psoriasis Subset

System Organ Class	Placebo (N = 879) n (%)	Ustekinumab (N = 613) n (%)	Brodalumab 140 mg Q2W (N = 1491) n (%)	Brodalumab 210 mg Q2W (N = 1496) n (%)	Brodalumab All (N = 3066) n (%)
Nervous system disorders	1 (0.1)	0 (0.0)	3 (0.2)	4 (0.3)	7 (0.2)

MedDRA v. 17.1 ; N = patients in Studies 20090062, AMAGINE-1, AMAGINE-2, and AMAGINE-3 with ≥ 1 dose of investigational product

n = number of patients reporting ≥1 occurrence of an AE through week 12; % = n/N * 100

Treatment groups are defined as planned (randomized) treatment.

Table 8–8 Follow-up observation time-adjusted rates of nervous system disorder AEs through Week 52 and end of study – Psoriasis Subset

	52-Week Pool		Long-Term Pool
	Ustekinumab (Pt-yr=504.0) N =613 n (r)	All-brodalumab (Pt-yr=3547.7) N =4019 n (r)	All-brodalumab (Pt-yr=9173.9) N =4464 n (r)
Nervous System disorders SOC	121 (24.0)	833 (23.5)	1402 (15.3)

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 investigational product.

n=number of adverse events; r=follow-up observation time-adjusted event rate per 100 patient-years (n/pt-yr*100), where pt-yr is the total patient-years of follow-up through Week 52 and end of study. Multiple occurrences of the same events for a patient are counted as multiple events.

8.4.3 Psychiatric Disorders

At Week 12, the patient incidence rates of treatment-emergent adverse events mapping to the depression SMQ were similar between 210 mg Q2W (0.7%), 140 mg Q2W (0.9%), ustekinumab (1.0%), and placebo (1.0%) groups (Table 8–9). The patient incidence rates of treatment-emergent AEs in the psychiatric SOC were also similar between 210 mg Q2W (2.1%), 140 mg Q2W (2.0%), ustekinumab (2.0%), and placebo (1.8%).

Table 8–9 Patient incidence of treatment-emergent Depression SMQ and Psychiatric SOC during the initial double-blind period – Week 12 - Integrated Safety Analysis Set – Psoriasis Subset

Event of Interest Category System Organ Class Preferred Term	Placebo (N = 879) n (%)	Ustekinumab (N = 613) n (%)	Brodalumab 140 mg Q2W (N = 1491) n (%)	Brodalumab 210 mg Q2W (N = 1496) n (%)	Brodalumab All (N = 3066) n (%)
Depression SMQ	9 (1.0)	6 (1.0)	13 (0.9)	11 (0.7)	24 (0.8)
Psychiatric SOC	16 (1.8)	12 (2.0)	30 (2.0)	31 (2.1)	61 (2.0)

MedDRA v. 17.1 ; N = patients in Studies 20090062, AMAGINE-1, AMAGINE-2, and AMAGINE-3 with ≥ 1 dose of investigational product

n = number of patients reporting ≥1 occurrence of an AE through Week 12; % = n/N * 100

Treatment groups are defined as planned (randomized) treatment.

Through Week 52, overall follow up adjusted event rate (per 100 patient-years) for depression was higher in the ustekinumab group (4.2) than in the all-brodalumab group (2.6) (Table 8–10). For psychiatric SOC, the exposure-adjusted event rate (per 100 patient-years) was 9.3 in the ustekinumab group and 7.6 in the all-brodalumab group.

Through end of study, the follow up time-adjusted rate was 2.4 per 100 patient-years for the depression SMQ in the all brodalumab group and 6.2 per 100 patient-years for the psychiatric SOC. These rates are consistent with those observed in the 52-week pool indicating no evidence of increasing rates of depression over time and with increasing patient-years of exposure to brodalumab.

Table 8–10 Follow-up time-adjusted event rates of treatment emergent AEs in the Depression SMQ and the Psychiatric Disorders SOC through Week 52 and end of study - Psoriasis Subset

	Ustekinumab (Pt-yr=504) (N=613) n (r)	All Brodalumab (Pt-yr=3548) (N=4019) n (r)	Long-term Pool End of Study All Brodalumab (Pt-yr=9174) (N=4464) n (r)
Depression SMQ	21 (4.2)	92 (2.6)	221 (2.4)
Psychiatric disorders SOC	47 (9.3)	269 (7.6)	571 (6.2)

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 investigational product

n=number of AEs; r=follow-up observation time adjusted event rate per 100 patient-years (n/pt-yr*100). Multiple occurrences of the same event for a patient are counted as multiple events.

8.5 External Comparisons

8.5.1 Comparison of SIB Observations in the Brodalumab Program With Rates in External Psoriasis/Psoriatic Arthritis Clinical Studies and Registries

There are limited comparator data available in the brodalumab clinical program due to short placebo controlled period, smaller exposure for placebo and ustekinumab and late occurrence of events, complicating any evaluation of rare events observed in the trial, including SIB events.

Absent available controlled data, external data may help to provide context around rare events observed in a clinical trial program. Ideally, these rates should be derived from a population most similar to that in the clinical program, (eg, with similar demographics and risk factors for the event(s) of interest). To this end, the Sponsor conducted a comprehensive review of multiple data sources through late 2014 as described below to obtain information from clinical trials and registry patient populations for the incidence rates of specific AEs of interest in adults with psoriasis and/or psoriatic arthritis treated with biological agents and other recently approved agents (Delzell and Chang 2015 further described in Section 7.6). As a non-serious adverse event, suicidal ideation was often not mentioned in these publications, so rates were not derived for it.

The rate for completed suicides in psoriasis patients in the brodalumab program (0.04 per 100 patient-years, 95% CI: 0.01, 0.11) is consistent with the rate observed in the analysis of published clinical trials and/or registries for psoriasis (0.03 per 100 patient-years, 95% CI 0.01,

0.06) (Table 8–11). The rates of suicide attempts per 100 patient years for brodalumab psoriasis program are 0.109 (95% CI 0.052-0.201) compared to the external pooled estimate of 0.04 (95% CI 0.01 to 0.10). The rates for all SIB are higher (0.37 per 100 patient years, 95% CI: 0.26 to 0.52) for brodalumab compared to the literature review (0.11) with (95% CI: 0.02 to 0.32), but the latter did not capture suicidal ideations.

While the rates reported by Delzell and Chang are the best available estimates of rates in a somewhat comparable psoriasis population, there are important considerations that must be made when comparing these rates with those observed in the brodalumab program. The external rate includes a variety of trials and registries with differing populations, trial design, and specific inclusion and exclusion criteria. Differences in demographics, geography, concomitant medications, and other variables likely exist across studies and all may contribute to differences in observed rates. Differences in case definitions may be used, and there may be differences in adjudication across different programs. Therefore, the results from the literature review by Delzell and Chang should be interpreted with caution in light of several limitations as described in detail in their report.

Table 8–11 Comparison of follow up observation time-adjusted patient incidence rates (per 100/patient-years) of SIB events in literature to brodalumab through end of study – Long-Term Pool

	Literature Pooled Estimate[a]			Brodalumab (psoriasis)	
SIB Category	Exposure (Total PY)	n (r)	95% CI	n (r)	95% CI
Attempted suicide	10,125	4 (0.040)	0.011, 0.101	10 (0.109)[b]	0.052, 0.201
Completed suicide	28,420	8 (0.028)	0.012, 0.055	4 (0.044)[c]	0.012, 0.112
All SIB	2,740	3 (0.109)	0.023, 0.320	34 (0.371)	0.257, 0.519

[a] E. Delzell and E. Chang. Adverse Event Rates in Psoriasis. Exponent Technical Report. March 19, 2015.
[b] Attempted suicide includes suicide attempt and suicide behavior preferred terms combined
[c] Includes event reported as intentional overdose

CTCAE v. 4.0 or 4.03; MedDRA v. 17.1 (52-week pool), MedDRA v. 18.1 (long-term pool).
The outcome of Brodalumab represents patients from psoriasis studies 20090062/20090403, AMAGINE-1, AMAGINE-2, and AMAGINE-3 with ≥ 1 dose of brodalumab.

Total patient-years (PY) of follow-up through min (patients first suicidal ideation and behavior event, end of study); n=number of patients with AEs; r=follow-up observation time-adjusted patient incidence rate per 100 patient-years (n/pt-yr*100). Multiple occurrences of the same events for patient are counted once. Total patient-years are truncated at patients first suicidal ideation and behavior event.

8.5.2 Comparison of SIB Rates from Recent Regulatory Materials

The more recently approved psoriasis therapeutic agents were not adequately represented in the comprehensive literature review because of its 2014 publication cutoff date. An assessment of more recently approved biologic psoriasis agents, apremilast, secukinumab and ixekizumab, was conducted to examine incidence rates of SIB observed in these programs to determine additional population rates. Note that the Sponsor calculated 95% confidence intervals using exact method assuming Poisson distribution, based on available data.

There was 1 completed suicide in the 52 week data from the apremilast program (on placebo). Using a range of conservatively estimated exposures, the completed suicide rate was 0.052-0.062 per 100 patient-years (95% CI (0.002, 0.345) to (0.001, 0.288). (Apremilast Medical Review, FDA, 2014; USPI 2015)

In the secukinumab 52 week program there was 1 completed suicide (in the screening period) for an estimated rate of 0.034 per 100-patient years of exposure (95% CI: 0.001 to 0.190) (Secukinumab Advisory Committee Briefing Book, 2014).

In the overall ixekizumab program, there were 10 suicide attempts in patients treated with ixekizumab, and 1 suicide attempt in a patient treated with placebo: attempted suicide rates were 0.15 per 100-patient years of exposure (95% CI: 0.072 to 0.276), and 0.55 per 100-patient years of exposure (95% CI: 0.014 to 3.064), respectively (Ixekizumab Summary Review, FDA, 2016).

8.5.3 Suicide in the General Population

Rates of completed and attempted suicide vary by age and gender. While the overall suicide rate in the general population is 0.013 per 100 person years, for males aged 45-64 years it is 0.03 per 100 person years, in comparison to the rate of 0.04 per 100 patient years seen in the brodalumab psoriasis program (CDC 2015).

8.5.4 Conclusions on external SIB data and comparison to brodalumab SIB incidence rates

Patients with psoriasis have a high burden of psychiatric comorbidity, specifically depression and anxiety. Further, psoriasis is associated with an increased risk of suicidality, and the risk may be even higher in those with more severe psoriasis (ie, those eligible for treatment with brodalumab or other biologic agents.) Suicide rates are high in the largest patient demographic enrolled in the brodalumab program (white males age 45 to 54 years).

While the rates from the literature and regulatory document review are the best available estimates of SIB rates in a somewhat comparable psoriasis population, there are important considerations that must be made when comparing these rates with those observed in the brodalumab program. First, the external rate includes a variety of trials and registries with differing populations and specific inclusion and exclusion criteria. For example, the brodalumab program did not exclude patients with pre-existing psychological comorbidity; however, such exclusion criteria were included in other biologic psoriasis programs (eg, secukinumab and ixekizumab). This difference could potentially have led to different baseline levels of risk for SIB. Further, the eC-SSRS was implemented during the conduct of the brodalumab program and thereby provided a measure for better identifying suicidal ideation; rates of these events could be expected to be lower in studies which did not include an assessment for these events above the standard adverse event reporting measures. Finally, differences in demographics, geography, concomitant medications (including treatment for anxiety and/or depression), and other variables likely exist across studies and all may contribute to differences in observed rates.

Although comparison of clinical trial data with external data should be made with caution because of the limitations discussed above, the rate of completed suicide in psoriasis patients in the long-term brodalumab program in 100 patient-years of 0.044 (95% CI: 0.012, 0.112) is consistent with the estimated completed suicide rates in:

1. published clinical trials and/or registries for psoriasis 0.028 (95% CI 0.012, 0.055),
2. apremilast 0.052-0.062 (95% CI (0.002, 0.345) to (0.001, 0.288),
3. secukinumab 0.034 (95% CI: 0.001 to 0.190),
4. that seen in the age and gender adjusted general population (0.03/100 patient-years).

While rates of attempted suicide were higher in the brodalumab program compared to the published literature, they are consistent with those observed in the ixekizumab program.

Higher rates of suicidal ideation may be due to the introduction of the eCSSRS screening tool late in the brodalumab program.

The incidence of suicide is rare and rates in individual psoriasis clinical programs vary greatly and are likely to represent a range around the true incidence rate.

8.6 Review of SIB from the discontinued Psoriatic Arthritis (PSA) Phase 3 program

An evaluation of SIB was conducted from the discontinued psoriatic arthritis (PSA) Phase 3 program, which included two Phase 3 studies, Study 20090406 and Study 20110144 to assess the impact of eC-SSRS and PHQ-8 when included at screening, as it was for 79% of patients enrolled after the amendment. Both of these studies were terminated (announced June 2015) with the change of sponsorship of the program (Section 4).

An integrated analysis of SIB through Week 16 of the Phase 3 psoriatic arthritis studies is shown in (Table 8–12). Although placebo control was included in the protocol for up to 24 weeks in the studies, patients meeting inadequate response criteria could be rescued at Week 16 and placebo patients switched to brodalumab. Therefore, these controlled summaries used the 16-week period prior to the confounding introduced by treatment switching.

Table 8–12 Patient incidence of SIB events in psoriatic arthritis by category and preferred terms in the initial double-blind period through Week 16 – Phase 3 Psoriatic Arthritis Subset

	Psoriatic arthritis	
Event of interest Category Preferred Term	Placebo (N=320) n (%)	Brodalumab (N=639) n (%)
Suicidal behavior adverse event	0 (0.0)	0 (0.0)
Suicidal behavior	0 (0.0)	0 (0.0)
Suicide attempt	0 (0.0)	0 (0.0)
Suicidal ideation adverse event	0 (0.0)	1 (0.2)
Suicidal ideation	0 (0.0)	1 (0.2)

CTCAE v. 4.0 or 4.03; MedDRA v. 17.1.
N=patients in Studies 20090406, and 20110144 with ≥ 1 dose of investigational product.
n=number of patients reporting ≥1 occurrence of an adverse event through Week 16; %=n/N*100
Treatment groups are defined as planned (randomized) treatment.

Through Week 16 of the controlled treatment period in these studies, 1 patient receiving brodalumab 140 mg had an AE in the SIB category. The event was a nonserious event of suicidal ideation (grade 1) that occurred 8 days after initiation of brodalumab treatment and 2 days after the last active dose of study drug. This patient had a treatment emergent positive eC-SSRS. This patient had a medical history of depression and SIB. The patient continued receiving brodalumab for 11 months with no further events of SIB or depression. Patient incidence was 0.2% in the all-brodalumab group compared to 0 in the placebo group.

In these studies, there were no additional SIB events observed in the total of 959 patients, many of whom completed a year of treatment before the studies were discontinued.

As was the case in the psoriasis studies, there was no increase in neuropsychiatric events in patients treated with brodalumab compared to placebo (Table 8–13).

Table 8–13 Patient incidence of Nervous System SOC, Depression SMQ and Psychiatric Disorders SOC during the double-blind period through Week 16 - Phase 3 PsA Subset

		Brodalumab		
Neuropsychiatric AE	**Placebo (N=320) n (%)**	**140 mg Q2W (N=318) n (%)**	**210 mg Q2W (N=321) n (%)**	**All (N=639) n (%)**
Nervous system disorders	1 (0.3)	1 (0.3)	0 (0)	1 (0.2)
Depression SMQ	5 (1.6)	4 (1.3)	1 (0.3)	5 (0.8)
Psychiatric disorders	13 (4.1)	10 (3.1)	4 (1.2)	14 (2.2)

CTCAE v. 4.0 or 4.03; MedDRA v. 17.1.
N=patients in Studies 20090406 & 20110144 with ≥ 1 dose of investigational product.
n=number of patients reporting ≥ 1 occurrence of an adverse event through Week 16; %=n/N*100
Treatment groups are defined as planned (randomized) treatment.

The patient incidence rate of positive eC-SSRS for any SIB was generally balanced across the placebo and brodalumab treatment groups among all patients and in the subgroup of patients with no prior history of suicidality. The percentage of patients with scores positive for any SIB event were 4.1% and 3.9% in the placebo and all-brodalumab groups, respectively. There were very few patients in these trials with a known prior history of suicidality due to study exclusions.

Patient incidences within each category of PHQ-8 total scores were balanced across the treatment groups. The majority of patients in both the placebo and all-brodalumab group showed none to minimal depression through 16 weeks of treatment (67.3% and 70.8%, respectively). Patient incidences of depression SMQ through 16 weeks of treatment were 1.6% and 0.8% for the placebo and all-brodalumab groups, respectively.

Overall, these results do not indicate any increase in neuropsychiatric events or positive eC-SSRS or PHQ-8 findings. The limited data are most suggestive of the effectivenes of screening tools at eliminating at risk patients from the trial and do not suggest a drug effect in patients treated with brodalumab during the 16-week controlled treatment period of the Phase 3 psoriatic arthritis studies.

8.7 Biologic Plausibility

A biologic linkage between brodalumab and SIB events appears unlikely. A review of available nonclinical and clinical, PK, and PD data from the brodalumab development program and from published literature was performed and is summarized in Appendix B.

8.7.1 Serum IL-17A Results

In AMAGINE-1, the effect of brodalumab on serum IL-17A levels was evaluated in patients who were continuously treated with brodalumab after Week 12. Serum IL-17A levels were measured at baseline, Week 12, Week 24, and Week 48.

A dose-dependent increase in serum IL-17A was observed that is attributed to blockade of the receptor-mediated clearance of IL-17A. In patients who received a constant 210 mg Q4W dose of brodalumab through the treatment period, median IL-17A levels increased by 3-fold, relative to baseline. The median increase was similar on Week 12, 24, and 48.

For the 210 mg Q2W dose, the post-treatment IL-17A levels remained within the range of baseline IL-17A levels for the majority (>75%) of patients.

8.8 Conclusions regarding SIB findings

The SIB observations with brodalumab were also evaluated based on revised Hill criteria described by Howick 2009. The evidence relating to each of the criteria is briefly summarized below in the context of brodalumab and SIB. The sponsor concludes that there is no clear association of SIB with brodalumab.

1. Direct evidence
    a. The most relevant direct evidence is from the controlled treatment period of a randomized, controlled trial. There was a single subject with 2 events in the 12-week placebo controlled period. SIB event rates were comparable between ustekinumab and brodalumab during the 52-week controlled period of the Phase 2/3 psoriasis studies.
    b. In 16-week controlled psoriatic arthritis Phase 3 studies, a single event of suicidal ideation occurred in a patient receiving brodalumab 140 mg Q2W, and there was no imbalance in the occurrence of neuropsychiatric events between placebo and brodalumab.

2. Temporality

    a. There was no change in the rates of completed suicides over time (across the 12- and 52-week controlled and the long-term extension treatment periods). There was an observed increase in reporting of suicidal ideation and suicide attempts over the time course, particularly after 52 weeks, coinciding with the fact that most patients had already completed the 52-week treatment period and were participating in the long-term extension treatment period before implementation of the eC-SSRS in the program. It is likely that use of this questionnaire resulted in increased capture of events of suicidal ideation and suicide attempts among patients receiving long-term brodalumab treatment.

    b. Based on the timing of SIB events relative to the brodalumab dosing interval and on an evaluation of events in patients initially randomized to brodalumab who were re-randomized to placebo, or were re-randomized to brodalumab 140 mg Q4W and Q8W dosing, with loss of efficacy or were discontinued from brodalumab due to study termination, there was no evidence for a withdrawal-emergent increase in SIB rates.

3. Strength of effect

    a. Given that the incidence of suicide is so rare, rates in other psoriasis clinical programs which were evaluated varied greatly and reflect a range of SIB rates around the true incidence rate.

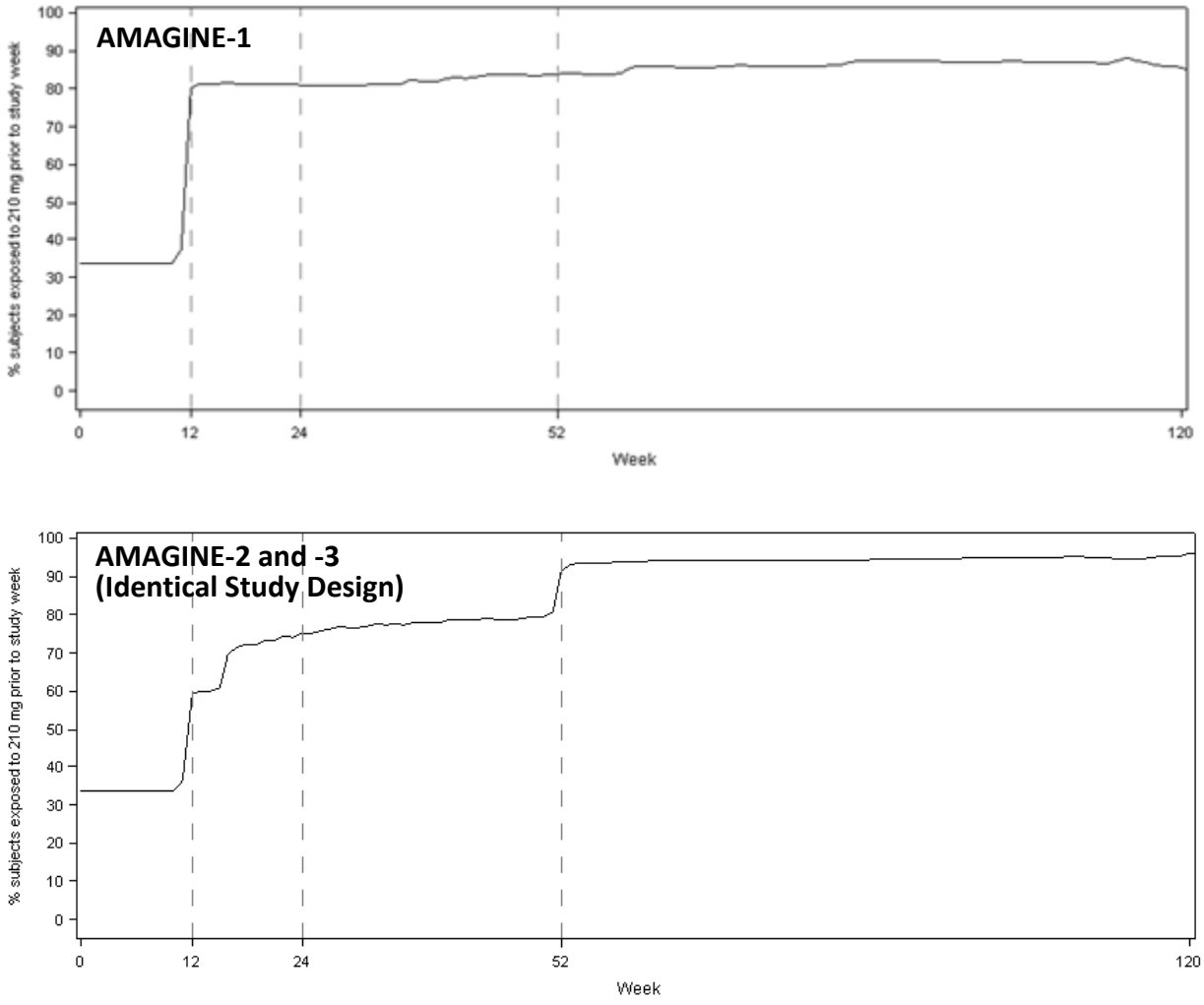
4. Dose response

    a. Based on the design and randomization of the studies, dose response could only be looked at credibly in the induction period (first 12 weeks), as there was equal randomization between 140 mg and 210 mg. During this period, there was only one patient with events of SIB, thus comparison cannot be made. When reviewing other neuropsychiatric events and HADS data, no clear dose-dependent patterns emerged. Therefore, based on the limited data to date out to 12 weeks, there is no evidence of a dose effect for SIB events.

b. By nature of the study designs of the Phase 2/3 psoriasis studies, most patients were exposed to the 210 mg Q2W dose of brodalumab at some point. The cumulative percentage plot below (Figure 8-2) presents the cumulative proportion of patients who have ever received 210 mg dose during or prior to a given study week among those who were on study at the given study week. As an example, in AMAGINE-1 at week 12, about 80% of patients received 210 mg dose during or prior to week 12, and cumulatively at week 52, about 84% received 210 mg dose during or prior to week 52.

   Given the cumulative exposure for patients receiving the 210 mg Q2W dose by study design and the late occurrence of most of the SIB events, the probability that a patient would have been on the 210 mg Q2W dose at the time of any given adverse event (AE) is high.

Figure 8-2 Proportion of patients exposed to brodalumab 210 mg Q2W by study –Phase 3 Psoriasis Subset



Y-axis is the cumulative proportion of patients who have ever received 210 mg dose during or prior to a given study week among those who were on study at the given study week.

5. Biological plausibility

    a. A biologically plausible mechanism by which brodalumab treatment could impact SIB has not been identified based on evaluation of clinical and nonclinical data from the program and exhaustive review of the literature.

        i. Peripheral action of brodalumab has no known direct or indirect effect or identified theoretical impact on psychiatric conditions or SIB.

ii. No evidence of a plausible direct or indirect mechanistic link between IL-17R inhibition and psychiatric conditions or SIB.

iii. No evidence of brodalumab-related effects on the CNS in nonclinical data.

iv. No evidence of a drug-drug or disease-drug-drug interaction that could contribute to SIB or CNS effects.

v. Increased IL-17A levels are generally not associated with depression, although there are conflicting reports. The increase in IL-17A levels associated with brodalumab treatment peak at 12 weeks, while the majority of SIB events occurred later. Potential active transport of IL-17 across the BBB would be inhibited by brodalumab.

vi. Extremely low levels of brodalumab are anticipated to cross the BBB and IL-17 is not expected to cross the BBB.

vii. The observed brodalumab plasma concentrations in patients with SIB were similar to all other patients in the individual trials.

viii. No intrinsic PK differences between patients experiencing SIB and the overall population were noted.

ix. There was a wide range in the timing of the occurrences of SIB events after the first dose of brodalumab (range 26 to 1945 days).

6. Biological gradient

   a. There is no clear evidence of a relationship between brodalumab exposure and SIB events.

   b. At the highest 210 mg Q2W dose of brodalumab, the median 3-fold increase remained within the range of baseline IL-17A levels for the majority of patients.

7. Consistency (reproducibility, class effects)

   a. An assessment of rates of treatment-emergent psychiatric and nervous system disorders was performed, as these are known to be associated with SIB and might be anticipated to precede suicidal events. The rates of nervous system, depression, and psychiatric disorders were similar between the all-brodalumab treatment group and comparators at Week 12 and 52 and did not increase in the long term.

   b. A review of US labeling of drugs linked to suicidality found that these drugs were linked to increased rates of other mood/psychotic disorders over placebo.

c. The results from assessment of HADS in AMAGINE-1 suggest an improvement in anxiety and depression scores after treatment with brodalumab compared to placebo, likely through improvement of their skin disease.

d. Other anti-IL-17 agents have not reported a causal association with SIB.

e. Comparison of clinical trial data with external data should be made with caution, however, the rate of completed suicide in psoriasis patients in the brodalumab program is similar to the rate observed in an analysis of published clinical trials and/or registries for psoriasis, the apremilast and secukinumab psoriasis programs, and close to that seen in the age and gender matched general population. Rates of suicidal attempts observed with brodalumab were consistent with another contemporary therapeutic agent, ixekizumab. Increased rates of suicidal ideation and attempts and their timing are suggestive of ascertainment bias due to the introduction of a screening tool late in the psoriasis program.

8. Coherence

a. SIB event rates observed in the brodalumab program are consistent with rates observed in psoriasis patients enrolled in the external clinical trials and/or registries. Overall, the brodalumab patient population appears to be representative of a patient population with moderate to severe psoriasis, which is at high background risk of depression and suicidality.

b. The brodalumab clinical studies were designed such that inclusion criteria were typical to define moderate to severe psoriasis with relatively few restrictions, ensuring that the population was reflective of the proposed target population of moderate to severe plaque psoriasis. There were no specific exclusion criteria based on the presence or history of psychiatric disorders or substance abuse, and psychiatric medical history was based on patient self-reporting, possibly leading to under-reporting. HADS analysis from AMAGINE-1 and additional lifetime history of SIB events obtained after implementation of the eC-SSRS made it apparent that baseline prevalence of depression and suicidality was higher than that observed in initially reported baseline medical histories. By HADS scores, 27% of patients had baseline depression including 13.6% with moderate to severe depression in AMAGINE-1. The eC-SSRS lifetime reporting raised the prevalence of baseline medical history of past or ongoing suicidal ideation and behavior to 2.8%.

The sponsor concludes there is no clear causal association between brodalumab and SIB. However, the sponsor takes the important potential risk of SIB seriously, and has specified SIB

accordingly in the proposed label and proposed post-approval measures. In addition, the sponsor has proposed a risk minimization strategy including a communication plan and educational tools.

9 Summary of Benefits and Risks

9.1 Benefits Associated with Brodalumab Treatment

Total skin clearance is an important treatment goal that has both measurable and clinically meaningful benefits, even when compared to small amounts of residual disease. Clearance of psoriasis has been shown to reduce the negative impact that active psoriasis has on a patient's QOL. Clinically important improvements in QOL have been observed in patients who achieve clear compared to those achieving almost clear to clear skin (Takeshita 2014).

The short-term efficacy of brodalumab in psoriasis was demonstrated in 3 Phase 3 studies in comparison with placebo, as well as in 2 of the 3 Phase 3 with an active control, ustekinumab, an IL-12 and IL-23 antagonist currently marketed for psoriasis treatment. Benefit was demonstrated at Week 12 with the brodalumab 210 mg Q2W dose. Improved efficacy response rates for all primary and secondary endpoints compared with placebo ($p<0.001$) were observed. In AMAGINE-2 and AMAGINE-3, brodalumab 210 mg Q2W was superior to ustekinumab based on the primary endpoint of PASI 100 ($p<0.001$). At Week 12, approximately twice as many patients treated with brodalumab 210 mg Q2W achieved the clinically meaningful outcome of total skin clearance when compared to patients on ustekinumab.

The efficacy of the brodalumab 210 Q2W dose was also demonstrated in the longer term. The efficacy response of the brodalumab 210 mg Q2W dose group was regained at week 52 in AMAGINE-1, with the majority of patients regaining response after 12 weeks of retreatment. In AMAGINE-2 and AMAGINE-3 greater efficacy, as measured by sPGA success, was maintained for the brodalumab 210 mg Q2W dose throughout the 52-week period compared with brodalumab 140 mg Q2W and ustekinumab. Greater than 50% on brodalumab 210 mg Q2W were completely clear of their disease (PASI 100) within a year of initiating treatment.

The efficacy of the brodalumab 210 mg dose over the 140 mg Q2W dose was consistent across the study population, which included systemic treatment-naïve patients, as well as patients previously exposed to systemic therapies, including use of, or failure with, prior biologic therapies. The benefits of the 210 mg Q2W dose over the 140 mg Q2W dose were also demonstrated across all subgroups evaluated, including age, sex, race, region, and in weight-based comparisons.

Across all studies, the response to the brodalumab 210 mg Q2W dose was rapid. In AMAGINE-2 and AMAGINE-3, brodalumab 210 mg Q2W showed rapid onset of action based on PASI 75, PASI 90, and PASI 100, with improvement apparent by Week 2. Total skin clearance was observed in the majority of brodalumab-treated patients sooner than in patients treated with ustekinumab.

Results of the PRO measures demonstrate that brodalumab 210 mg Q2W provides meaningful benefit to patients. The results of the PSI demonstrated improvement in patient-reported signs and symptoms of psoriasis in brodalumab-treated patients compared with placebo at Week 12. Similarly, DLQI responder rates at Week 12 were consistently higher in the brodalumab 210 mg Q2W group than in the 140 mg Q2W, placebo, or ustekinumab treatment groups.

Analysis of PRO results by PASI clearance in the brodalumab program showed that patients who achieved total skin clearance showed greater improvement in QOL than patients who were almost clear of their psoriasis. Moreover, patients who were not clear still had significant residual disease, which had a meaningful impact on their QOL and symptoms of psoriasis, including pain and itch.

In summary, brodalumab 210 mg Q2W met all primary endpoints, across all three pivotal Phase 3 studies, demonstrating short and longer term efficacy in the treatment of psoriasis. Approximately twice as many patients who received brodalumab 210 mg Q2W achieved total skin clearance, as measured by PASI 100, compared with ustekinumab at weeks 12 and 52. Greater than 50% on brodalumab 210 mg Q2W were completely clear of their disease (PASI 100) within a year of initiating treatment. Brodalumab 210 Q2W has demonstrated meaningful improvements to psoriasis patients, in achieving total skin clearance, and improvements in patient reported outcomes and QOL.

The recommended dose of brodalumab is 210 mg subcutaneous at weeks 0, 1 and 2 weeks then every 2 weeks thereafter for patients with moderate to severe plaque psoriasis.

9.2 Risks Associated With Brodalumab Treatment

Brodalumab safety was well-characterized, with a profile consistent with other biologic agents targeting the IL-17 pathway for the treatment of moderate-to-severe psoriasis.

Across all indications, 6243 patients received brodalumab, representing 9719.7 patient-years of exposure and 10452 patient-years of follow-up. The majority of all patients had follow-up periods of 1 to 2 years and 102 patients had follow-up for over 5 years.

The most common AEs with brodalumab were nasopharyngitis, upper respiratory tract infection, arthralgia, and headache. ADRs identified include headache, arthralgia, fatigue, oropharyngeal pain, diarrhea, nausea, myalgia, influenza, injection site reactions, neutropenia, and tinea infections, conjunctivitis, and candida infections.

Based on the comprehensive review of the safety data, worsening of Crohn's disease in patients with active Crohn's disease, infections, and neutropenia have been specified as identified risks and SIB, MACE, hypersensitivity and malignancy as potential risks.

The MACE findings in the brodalumab program have been assessed. Analyses were conducted which included assessment of pre-disposing risks related to cardiovascular disease in patients in the program, evaluation of the overall events of cardiovascular disease and adjudicated MACE, comparison of rates of MACE observed with brodalumab to external literature reviews and recent relevant study programs, and assessment of biologic plausibility. The sponsor concludes that the evidence does not support a causal association between MACE and brodalumab.

A thorough review of the observations of SIB related to brodalumab has been performed, including evaluation of the brodalumab study population for pre-disposing risk factors, careful review of individual cases, comparison of rates of SIB observed with brodalumab to external literature reviews and recent relevant study programs, and assessment of biologic plausibility. The sponsor concludes that the evidence does not support a causal association between brodalumab and SIB.

The Sponsor has proposed pharmacovigilance activities, including targeted questionnaires. In addition, the plan for SIB includes labeling in precautions and warnings and a communication and education plan for physicians and patients. Additionally, to augment the understanding of potential risks, a prospective, controlled cohort registry study is planned that will include an appropriate comparator cohort of patients receiving other therapies for moderate to severe plaque psoriasis. This would utilize a large established North American psoriasis registry that currently is expanding its patient population and is managed by an independent organization. The aim is to capture relevant data prospectively, including information on SIB and MACE, to enable comparison among cohorts.

9.3 Integrated Benefit-to-Risk Assessment

Integrated benefit and risk plots were created to characterize the benefits and risks of brodalumab treatment quantitatively. Based on this assessment the incremental benefit of total skin clearance and the resulting quality of life improvement outweigh the risks observed with brodalumab in the short and longer term treatment periods.

In the integrated benefit and risk analyses, the endpoints sPGA success, PASI 75, PASI 100, PSI responder, and DLQI 0/1 were used to assess benefit. For the assessment of risk, the following were evaluated: serious infections, fungal infections (non-serious skin and mucosal), neutropenia grade ≥3, SIB, adjudicated MACE, and malignancy. The integrated benefit-risk assessment included data from the 12- and 52-week controlled treatment periods, for which comparator data are available (in other words, AMAGINE-2 and AMAGINE-3). No additional risks have been identified in the long term, uncontrolled extensions of the pivotal brodalumab studies.

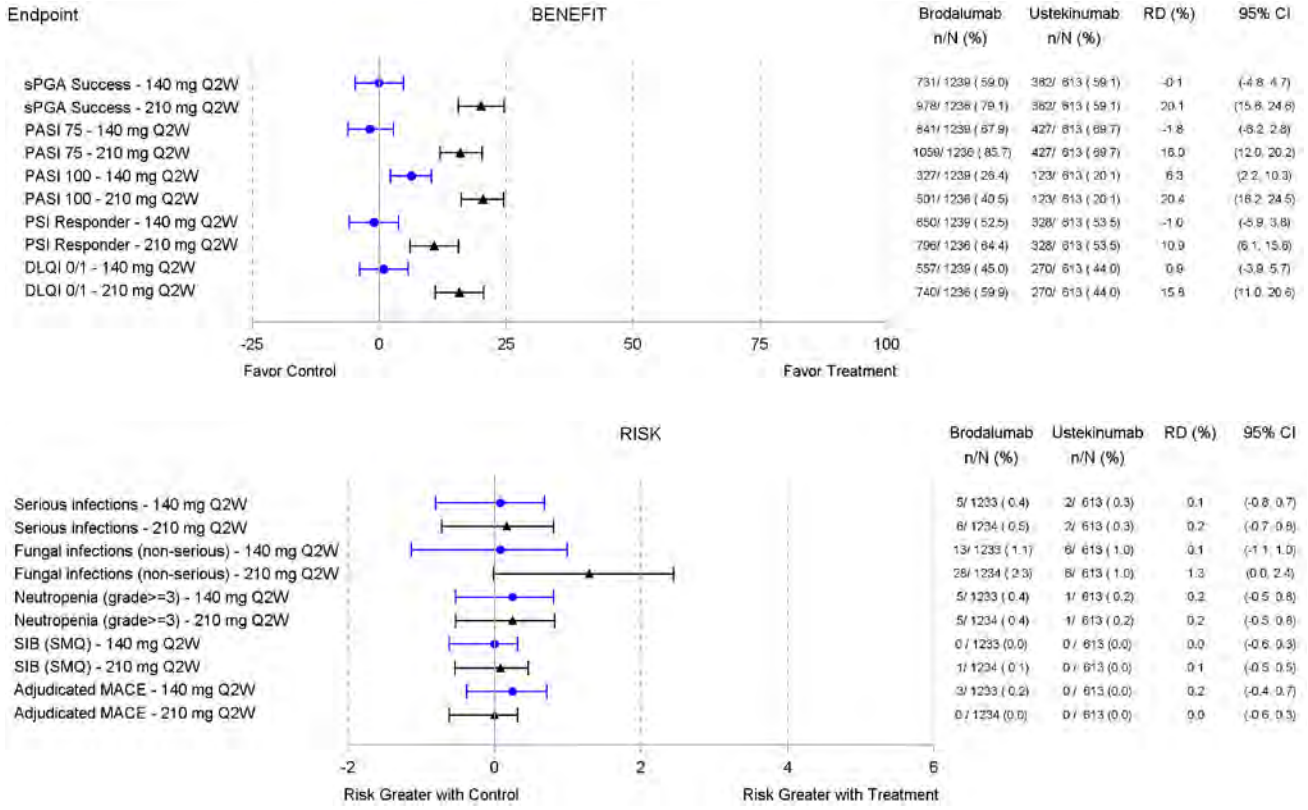
At 12 weeks of treatment, brodalumab 210 mg Q2W showed meaningful benefit compared to ustekinumab in treating psoriasis, across all key efficacy outcomes (Figure 9–1, upper panel). The improved efficacy with brodalumab 210 mg Q2W versus 140 mg Q2W was achieved with a safety profile that was comparable across identified risks, with the exception of an increased incidence of non-serious fungal infection (Figure 9–1, lower panel). There was no difference in the risks for serious infections, SIB, and malignancy between brodalumab and ustekinumab. The benefit-risk balance for the brodalumab 210 mg Q2W over 12 weeks of treatment is considered acceptable.

Over the controlled 52-week treatment period, in AMAGINE-2 and AMAGINE-3, the benefit of the brodalumab 210 mg dose continued to be superior to ustekinumab across all endpoints selected (Figure 9–2, upper panel) when comparing patients who received constant doses over 52 weeks. When evaluating the safety profiles of the two treatments during the 52-week period, no significant risk differences were seen across the various safety parameters, although the confidence intervals are wide (Figure 9–2, lower panel). The results show overall similarity between brodalumab 210 Q2W and ustekinumab.

To further characterize the safety of 210 mg Q2W, all patients who received brodalumab 210 mg Q2W from Week 12 to Week 52 (N=932) were added to the analysis (total N=1271), as this was the most comparable evaluation of the safety of brodalumab 210 mg Q2W through Week 52 (Figure 9–3). The results show overall similarity between brodalumab 210 mg Q2W and ustekinumab with risk differences close to zero for all events of interest, and 95% CIs encompassing the null, with the exception of non-serious fungal infections.

Following this benefit risk assessment, the sponsor concludes that brodalumab has a favorable benefit risk profile, and offers a beneficial contribution to addressing the unmet needs in the management of psoriasis.

Figure 9–1 Benefit-risk summary plot at Week 12 (brodalumab versus ustekinumab [control])

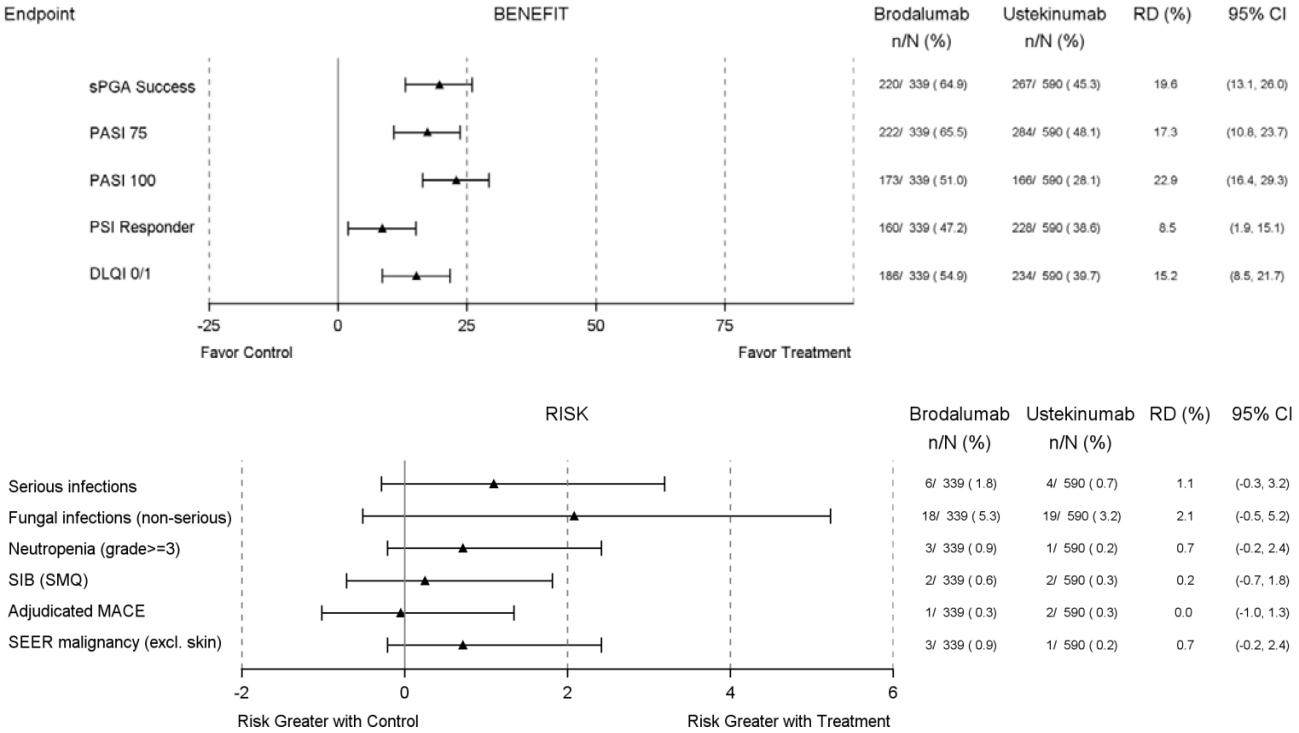


MedDRA v. 17.1; AMAGINE-2 and AMAGINE-3 for efficacy and safety analysis. NRI used to impute missing data for the efficacy endpoints at Week 12. Induction Phase Ustekinumab Comparison Analysis Set for efficacy analysis; Integrated Safety Analysis Set - Psoriasis Subset for safety analysis. Miettinen & Nurminen's approach was used for estimating the RD and CIs. The analysis was stratified by study, using Cochran's weighting scheme. Treatment groups are defined as planned treatment for the induction phase.

Note that the scales are based on size of N and vary between figures.

CI Confidence interval; NE Not estimable; n Number of patients with benefit or risk; N Number of patients who had a valid measurement value at the specified week, after imputation; RD Risk difference; %=n/N * 100.

Figure 9–2 Benefit-risk summary plot at Week 52 (brodalumab 210 mg Q2W versus ustekinumab [control] – constant dosing arms)

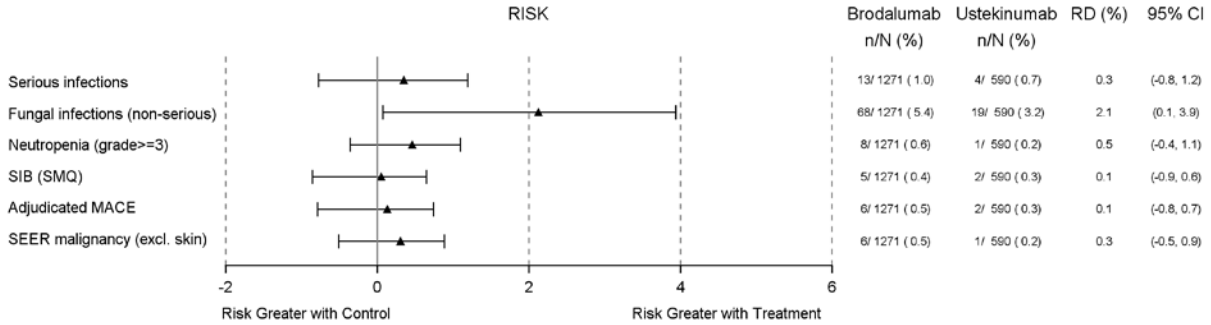


MedDRA v. 17.1; AMAGINE-2 and AMAGINE-3 for efficacy and safety analysis. For efficacy endpoints, patients in all treatment groups with an inadequate response (defined as the case of a single sPGA of=3 or persistent sPGA values of 2 over at least a 4-wk period) at or after wk 16 (and through wk 52) are imputed as non-responders for subsequent visits up to wk 52. Wk 1 to 52 Analysis Set – Constant Arms for efficacy analysis; Integrated Safety Analysis Set - Psoriasis Subset for safety analysis. Miettinen & Nurminen's approach was used for estimating the risk difference (RD) and CIs. The analysis was stratified by study, using Cochran's weighting scheme. Treatment groups are defined as planned treatment for the induction phase.

Note that the scales are based on size of N and vary between figures.

CI=confidence interval; NE=not estimable; n=number of patients with benefit or risk; N=number of patients who had a valid measurement value at the specified week, after imputation; %=n/N*100

Figure 9–3 **Risk summary plot at Week 52 (brodalumab 210 mg Q2W [maintenance dose] versus ustekinumab [constant dose] [control])**



MedDRA v. 17.1; Includes patients in AMAGINE-2 and AMAGINE-3. Integrated Safety Analysis Set - Psoriasis Subset for safety analysis. Miettinen & Nurminen's approach was used for estimating the risk difference (RD) and CIs. The analysis was stratified by study, using Cochran's weighting scheme. Brodalumab 210 mg Q2W (maintenance dose) includes: placebo > brodalumab 210 mg Q2W; brodalumab 140 mg Q2W > brodalumab 210 mg Q2W; brodalumab 210 mg Q2W > brodalumab 210 mg Q2W. Treatment groups are defined as planned treatment for the induction/maintenance phases.

Note that the scales are based on size of N and vary between figures.

CI Confidence interval; NE Not estimable; n Number of patients with benefit or risk; N Number of patients who had a valid measurement value at the specified week, after imputation; %=n/N * 100.

10 Conclusion

The Sponsor is proposing pharmacovigilance activities, including follow-up with targeted questionnaires. In addition, the plan for SIB includes labeling in precautions and warnings and a communication and education plan for physicians and patients. Additionally, to augment the understanding of potential risks, a prospective, controlled cohort registry study is planned that will include an appropriate comparator cohort of patients receiving other therapies for moderate to severe plaque psoriasis. This would utilize a large established North American psoriasis registry that currently is expanding its patient population and is managed by an independent organization. The aim is to capture relevant data prospectively, including information on SIB and MACE, to enable comparison among cohorts.

The sponsor has concluded that the benefit of skin clearance and the resulting quality of life improvement outweigh the risks observed with brodalumab.

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BRODALUMAB injection,

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

Appendix A: Narratives and Case Details for MACE and SIB Events
SPONSOR BRIEFING DOCUMENT
AVAILABLE FOR PUBLIC DISCLOSURE

Prepared By:

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U.S. Agent for Valeant Pharmaceuticals Luxembourg S.a.r.l

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1 MACE Events

Table 1 Subject listing of MACE

				Baseline Risk factors								
					Glucose tolerance			Lipids				
Treatment at time of event	A/G/R	MACE event	Study day/ TTO active/ TTO last	BMI >30	Gluc. >5.6 mmol/L	T2DM	Current /former smoker	Trigl.[a] >1.7 mmol/ L	Chol. >5.2 mmol/ L	HTN	Additional relevant medical history	No. of risk factors
MACE: MYOCARDIAL INFARCTION												
Ustekinumab	49/M/W	MI	178/-/-	34.2	6.661	-	✓	-	-	✓	Right bundle branch block; stress	4
210 mg Q2W	60/M/W	Acute MI	124/42/12	-	15.598	✓	✓	-	5.534	✓	-	4
210 mg Q2W	65/M/W	MI	423/423/ -	36	5.718	-	✓	✓	-	✓	Ischemic heart disease; coronary artery bypass	5
140 mg Q2W	64/M/W	MI	167/167/ -	33.6	5.773	✓	✓		-	✓	Arrhythmia	4
210 mg Q2W	61/M/W	MI	400/400/2	33.1		-		-	-	✓	MI, ACS	3
210 mg Q2W	58/M/W	CAD	-/244/9	30.5	7.938	-		-	-	✓	Anxiety	2
210 mg Q2W	58/M/W	Acute MI	331/331/-	48.4	6.550	-	✓	-	-	✓	-	4
210 mg Q2W	36/M/O	MI	349/349/-	-	6.162	-	✓	✓	-	✓	Arrhythmia, MI Angina pectoris, CAD Family history (coronary artery bypass)	5
210 mg Q2W	56/F/W	AV Block	150/150/21	43.1	15.487	✓		✓	-	✓	Angina pectoris CHF, MI, CAD	5
210 mg Q2W	51/M/W	MI	331/331/-	31.6	5.384	-	✓	-	-	✓	Glucose intolerance impaired	4
210 mg Q2W	58/M/W	MI	244/244/-	34.6	7.716	-	✓	✓	-	✓	Family History (CAD, non-STEMI)	6

Table 1 Subject listing of MACE

				Baseline Risk factors								
					Glucose tolerance			Lipids				
Treatment at time of event	**A/G/R**	**MACE event**	**Study day/ TTO active/ TTO last**	**BMI >30**	**Gluc. >5.6 mmol/L**	**T2DM**	**Current /former smoker**	**Trigl.[a] >1.7 mmol/ L**	**Chol. >5.2 mmol/ L**	**HTN**	**Additional relevant medical history**	**No. of risk factors**
210 mg Q2W	56/M/W	MI	308/308/1	30.1	4.663	-	✓	-	-	✓	MI; family Hx (Cardiac disease)	5
210 mg Q2W	69/F/W	MI	401/401/-	-	4.496	-	-	-	-	✓	Stress	3
210 mg Q2W	62/M/W	MI	352/352/7	33.1	6.606	✓	✓	✓	-	✓	Cardiac catheterization Alcohol abuse	5
140 mg Q2W	60/M/W	Acute MI	98/98/-	36.7	5.607	-	✓	✓	-	✓	Anxiety	5
140 mg Q2W	57/M/W	Angina Unstable	86/86/17	42.1	5.995	-	✓	-	-	✓	Arrhythmia AF, CABG	5
140 mg Q2W	45/M/W	MI	36/36/5	-	-	-	✓	-	-	✓	-	2
210 mg Q2W	64/M/W	MI	348/348/3	34.6	12.379	-	✓	2.337	3.62	✓	T1DM	5
210 mg Q2W	38/M/W	MI	209/124/1	31.1	6.661	-	-	5.780	7.163		Family history (Father dx with CAD at 40)	4
210 mg Q2W	57/M/W	Acute MI	123/123/-	35.4	12.934	-	✓	3.726	4.241	✓	CAD, stent placement	6
210 mg Q2W	63/M/W	MI	253/171/-	-	-	-	✓	-	-	✓	-	3
Overall 210 mg Q2W	62/F/W	MI	636/ 85/3	49.2	7.216	-	-	1.434	7.499	✓	-	3
Overall 210 mg Q2W	55/M/W	MI	719/85/60	-	6.217	-	✓	1.084	5.017	-	Blood cholesterol increased, depression	2
Overall variable dosing	65/M/W	MI	667/1/2	-	5.218	-	✓ (former)	-	-	✓	COPD	1
Overall variable dosing	47/M/W	Acute MI	435/85/14	42.9	6.273	-	✓	✓	-	✓	Hyper-cholesterolemia	4

Table 1 Subject listing of MACE

				Baseline Risk factors								
					Glucose tolerance			Lipids				
Treatment at time of event	**A/G/R**	**MACE event**	**Study day/ TTO active/ TTO last**	**BMI >30**	**Gluc. >5.6 mmol/L**	**T2DM**	**Current /former smoker**	**Trigl.[a] >1.7 mmol/ L**	**Chol. >5.2 mmol/ L**	**HTN**	**Additional relevant medical history**	**No. of risk factors**
Overall 210 mg Q2W (Placebo at time of event)	57/M/O	Non-cardiac chest pain	2/86/NA	-	5.273	-	✓	✓	-	-	Hyperlipidemia	2
Overall variable dosing	48/M/W	Pulmonary oedema	712/1/11	35.0	5.995	-	-	✓	-	✓	Pulmonary embolism, lung disorder, myocarditis, hyper-cholesterolemia	3
Overall variable dosing	58/M/W	MI	669/1/3	30.1	5.495	-	✓ (former)	-	-	-	-	1
Overall 210 mg Q2W	34/F/W	Acute MI	622/85/17	39.0	6.495	✓	-	-	-	-	Obesity	2
Overall variable dosing	56/M/W	MI	426/1/1	-	5.44	-	-	-	-	-	-	0
Overall variable dosing	36/M/W	MI	446/1/47	-	5.718	-	-	-	-	-	-	0
Overall variable dosing	63/M/W	MI	828/1/22	30.8	5.218	-	✓ (former)	-	-	-	Per investigator report, (b) (6) ECG (2.5 months prior to MI) showed evidence of hx of inferior MI	1
MACE: STROKE												
210 mg Q2W	47/M/W	Subarachnoid hemorrhage	277/277/11	31.9	6.106	-	-	1.8	-	-	-	3
210 mg Q2W	53/M/W	Ischaemic stroke	512/512/ -	-	6.106	-	✓	✓	-	✓	-	4

Table 1 Subject listing of MACE

				Baseline Risk factors								
					Glucose tolerance			Lipids				
Treatment at time of event	**A/G/R**	**MACE event**	**Study day/ TTO active/ TTO last**	**BMI >30**	**Gluc. >5.6 mmol/L**	**T2DM**	**Current /former smoker**	**Trigl.[a] >1.7 mmol/ L**	**Chol. >5.2 mmol/ L**	**HTN**	**Additional relevant medical history**	**No. of risk factors**
210 mg Q2W	50/M/W	Cerebrovascular accident	147/147/23	-	6.883	-	✓	✓	-	✓	Alcoholic	4
210 mg Q2W	64/M/W	Stroke	318/318/-	30.8	-	-	✓	-	-	✓	-	2
140 mg Q2W	66/F/W	Cerebrovascular accident	26/26/13	-	-	-	-	-	-	✓	-	1
210 mg Q2W	69/F/W	Ischaemic Stroke	444/444/1	-	-	-	-	✓	-	-	Cardiomyopathy	1
210 mg Q2W	54/F/W	Hemorrhage intracranial	395/395/8	-	11.435	✓	✓	✓	-	✓	CAD, Cardiac murmur, Carotid artery occlusion, TIA, Cerebral artery bypass, Coronary arterial stent insertion	6
210 mg Q2W	72/M/W	Cerebrovascular accident, Carotid artery stenosis	282/282/-	32	6.106	-	✓	✓	-	✓	Alcohol use, Factor V Leiden, Hyperglycemia Family history (stroke, MI, T2DM)	6
Overall variable dosing	66/F/W	Cerebro-vascular accident	729/1/14	31.3	12.545	✓	-	✓	-	✓	Hyperlipidemia, transient ischemic attack, edema, obesity	4
Overall variable dosing	46/M/W	Ischaemic stroke	711/1/9	-	5.718	-	✓	-	-	-	No medical hx available	1
210 mg Q2W after ustekinumab	58/M/W	Ischaemic stroke	1005/112/17	-	5.218	-	✓ (former)	-	-	✓	Hypertension Taking ACE inhibitor	1

Table 1 Subject listing of MACE

				Baseline Risk factors								
					Glucose tolerance			Lipids				
Treatment at time of event	**A/G/R**	**MACE event**	**Study day/ TTO active/ TTO last**	**BMI >30**	**Gluc. >5.6 mmol/L**	**T2DM**	**Current /former smoker**	**Trigl.[a] >1.7 mmol/ L**	**Chol. >5.2 mmol/ L**	**HTN**	**Additional relevant medical history**	**No. of risk factors**
Overall variable dosing	58/M/W	Ischaemic stroke	353/1/2	-	9.77	✓	✓	-	-	✓	-	3
Overall variable dosing	58/M/W	TIA	728/1/13	33.3	6.384	✓	-	✓	-	✓	Obesity, hyperlipidemia	4
MACE: CARDIOVASCULAR DEATH												
Ustekinumab	59/M/W	Death	129/- /-	-	9.159	-		✓			MI, CHF	3
210 mg Q2W	24/F/W	Death	221/124/14	42.5	6.384	-	✓	-	-	-	Multiple drugs that could lead to QT prolongation; alcohol use; Suicidal ideation; Depression; Anxiety	4
210 mg Q2W	52/M/W	Cardiopulmonary failure	451/451/40	32.5	5.884	-	✓	✓	-	✓	-	4
210 mg Q2W	65/M/W	Cardiac arrest	264/264/3	-	5.607	✓	✓	-	-	✓	Stress	3
210 mg Q2W	37/M/W	Atrial Fibrillation	291/291/85	79.5	5.995	✓	✓	✓	-	-	-	3
Overall 210 mg Q2W	52/MW	Cardiac arrest	556/1/9	-	5.995	-	✓	1.366	5.793	-	Hyper-cholesterolemia	2
Overall variable dosing	70/M/W	Cerebro-vascular accident	267/1/14	33.8	6.273	-	✓	1.208	4.913	✓	Arrhythmia, sleep apnea	3
Overall 210 mg Q2W	55/M/W	MI	719/85/60	-	6.217	-	✓	1.084	5.017	-	Blood chol. Increased, depression	2

Table 1 Subject listing of MACE

				Baseline Risk factors								
					Glucose tolerance			Lipids				
Treatment at time of event	**A/G/R**	**MACE event**	**Study day/ TTO active/ TTO last**	**BMI >30**	**Gluc. >5.6 mmol/L**	**T2DM**	**Current /former smoker**	**Trigl.[a] >1.7 mmol/ L**	**Chol. >5.2 mmol/ L**	**HTN**	**Additional relevant medical history**	**No. of risk factors**
Overall 210 mg Q2W	74/M/W	Sudden death	198/1/1	40.1	6.939	✓	✓ (former)	1.411	2.741	✓	Blood chol. increased, coronary artery bypass	4
210 mg Q2W after ustekinumab	56/M/W	Pulmonary embolism	594/365/61	43.1	5.273	-	✓ (former)	-	-	√	COPD, Rt ventricular failure, sleep apnea, obesity, asthma, depression	2
Overall variable dosing	60/M/W	MI	514/1/23	30.5	12.212	✓	-	-	-	✓	Diabetic retinopathy	3
Overall variable dosing	44/M/W	Acute MI	779/1/91	34.8	5.392	-	-	✓	-	✓	Hyper-cholesterolemia	3
Overall variable dosing	63/M/W	MI	828/1/22	30.8	5.218	-	✓ (former)	-	-	-	Per investigator report, (b) (6) ECG (2.5 months prior to MI) showed evidence of hx of inferior MI	1

[a] A checkmark is given for subjects for whom baseline triglyceride levels were not available, but a medical history of hyperlipidemia, high cholesterol, or hypercholesterolemia was reported.

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

A = age; ACS = acute coronary syndrome; AF = atrial fibrillation; AV = atrioventricular; BMI = body mass index; CABG = coronary artery bypass graft; CAD = coronary artery disease; CHF = congestive heart failure; chol. = cholesterol; dx = diagnosis; F = female; G = gender; gluc. = glucose; HTN = hypertension; Hx = history; M = male; MACE = major adverse cardiac event; MI = myocardial infarction; No. = number; non-STEMI = non-ST segment elevated myocardial infarction; O = other; Q2W = every 2 weeks; R = race; T1DM = type 1 diabetes mellitus; T2DM = type 2 diabetes mellitus; TIA = transient ischemic attack; trigl. = triglycerides; TTO = time to onset; W = white.

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.

BRODALUMAB injection

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

Appendix B: Investigations of Biologic Plausibility of Causal Relationship Between Brodalumab and SIB

SPONSOR BRIEFING DOCUMENT

AVAILABLE FOR PUBLIC DISCLOSURE

Prepared By:

Valeant Pharmaceuticals North America,

U.S. Agent for Valeant Pharmaceuticals Luxembourg S.a.r.l

Table of Contents

1 Nonclinical investigations of potential neurobehavioral and central nervous system effects

Evaluation of potential brodalumab-related neurobehavioral effects and effects on the central nervous system (CNS) was accomplished through standard endpoints included in the 1-, 3-, and 6-month Good Laboratory Practice (GLP) toxicity studies conducted in the cynomolgus monkey. Weekly subcutaneous doses up to 350 mg/kg were used in the 1- and 3-month studies, and up to 90 mg/kg in the 6-month study. The no-observable-adverse-effect level (NOAEL) exposures ranged from 47- to 111-fold higher than in patients who received brodalumab 210 mg every 2 weeks (Q2W).

There were no brodalumab-related neurobehavioral effects or effects on the CNS as assessed clinically and through anatomic pathology endpoints. In the 1-month study in cynomolgus monkeys (5/sex/group), 1 low dose (25 mg/kg) male had clonic convulsions lasting <1 minute during the dosing phase physical exam (day 24) that was attributed to the use of ketamine as an anesthetic. In the 6-month study in cynomolgus monkeys (4-6/sex/group), 1 high dose (90 mg/kg) male was noted with circling on day 1 only after 1 dose. The veterinary exam on day 2 was normal; this event was considered to be unrelated to administration of brodalumab and may have represented locomotor stereopathy with trigger (increased room activity during dosing and clinical observations). No other instances of CNS related signs were noted throughout the remainder of either of these studies.

Additionally, behaviors in animals (including nonhuman primates and rodents) that have been associated with depression include fluctuations in body weight, food consumption, locomotor activity, and responsiveness to stimuli (Dzirasa and Covington 2012, Willard and Shively 2012). Willard and Shively 2012 describe an increase in heart rate (also noted in depressed humans) and a 17% reduction in body weight in behaviorally depressed monkeys compared with non-depressed animals. There were no clinical observations or effects on body weight, food consumption, or heart rate in the repeated-dose toxicity studies that supported a brodalumab-related change in any of these endpoints.

2 Evaluation of Literature of Neuropsychiatric Effects of IL-17

2.1 Expression of IL-17 and IL-17R in the CNS

Comprehensive analyses of the expression of interleukin-17 (IL-17) family members and receptors in the CNS have not been published, but relevant data can be found in several published databases. Data from NextBio, Allen Brain Atlas, Protein Atlas databases are not in absolute concordance, but agree that the mRNAs for IL-17A, C and F and IL-25 (IL-17E) are

detectable at low to medium levels (compared to other tissues) across many regions of the human brain. Compared to immune cells, such as T helper 17 (Th17) cells, the detected levels are very low. IL-17RA is also widely expressed at low levels across many regions of the human brain. Highest mRNA expression of IL-17RA in the brain occurs in the caudate, putamen and nucleus accumbens regions of the brain. Compared to human neutrophils, these levels are low.

Among the CNS-resident cells, neuroglial cells, particularly astrocytes, but also microglia, and oligodendrocytes, express IL-17R and respond to IL-17 by producing chemokines/cytokines and boosting local inflammation (Liu 2014). In the mouse, functional IL-17R can also be detected on cultured astrocytes and microglia from untreated control animals (Sarma 2009). By immunohistochemistry, IL-25 is mainly expressed by the vascular tissues in the brain (Sonobe 2009).

2.2 Conditions of elevated IL-17 in the CNS: inflammation associated with multiple sclerosis, ischemia, or brain infection

While the levels of IL-17 and IL-17R appear to be low in the healthy brain, the expression can be increased under conditions of local inflammation, for example in the neuroinflammatory disease multiple sclerosis (MS), in which immune cells enter the CNS to mount an immune response against myelin-associated antigens resulting in foci of inflammation, demyelination, and tissue damage. The standard mouse model of this disease, experimental allergic encephalitis (EAE) suggests a key role for IL-17 producing T cells in this pathology. Mice lacking the IL-17 or IL-17R are not susceptible to EAE induction, and inhibition of the IL-17 axis attenuates inflammation (Komiyama 2006). Astrocytes have been shown to constitutively express IL-17R, allowing a direct effect of IL-17 on astrocytes (Kebir 2007). Adding further validity to these findings was a recent report by Kang and coworkers (Kang 2010), who identified astrocytes as a major target cell population that were stimulated by IL-17A during EAE (Kang 2010). IL-17 has been shown in previous reports to be up-regulated in the areas around the blood vessels in the brains of MS (Potula 2004) with concomitant astrogliosis detected in MS patients (Matusevicius 1999, Tzartos 2008).

In EAE, and presumably in MS, IL-17 is predominantly produced by immigrating CD4+ αβ Th17 cells and possibly γδ T cells (Shichita 2009). Some IL-17 is produced by human astrocytes and oligodendrocytes in MS lesions (Tzartos 2008).

The expression of IL-17R also increases after induction of other types of brain damage, such as ischemic injury (stroke) or infection. Animal models and human studies implicate IL-17 and related cytokines, eg, IL-23 and IL-21, as mediators of CNS tissue damage in the delayed phase of the inflammatory cascade (Starkweather 2014

Starkweather AR1, Sherwood P, Lyon DE, Bovbjerg DH, Broaddus WC, Elswick RK Jr, Sturgill J. Depressive symptoms and cytokine levels in Serum and Tumor Tissue in patients with an Astrocytoma: a pilot study. BMC Res Notes. 2014;7:423.

Swardfager 2013). IL-17 secreting T cells are potentially important mediators of brain pathology post-stroke in mice (Shichita 2009, Starkweather 2014

Starkweather AR1, Sherwood P, Lyon DE, Bovbjerg DH, Broaddus WC, Elswick RK Jr, Sturgill J. Depressive symptoms and cytokine levels in Serum and Tumor Tissue in patients with an Astrocytoma: a pilot study. BMC Res Notes. 2014;7:423.

Swardfager 2013). Indeed, post-mortem studies of stroke victims show the presence of a significantly greater number of IL-17 expressing cells also in human ischemic brain tissue (Li 2005, Wang 2009).

In vitro, IL-17 can worsen neuronal injury induced by oxygen-glucose deprivation in a dose-dependent manner (Wang 2009) and IL-17 knockout mice showed a significant reduction of infarct volume 4 days post-ischemia (Shichita 2009). Ischemia upregulates IL-17R on astrocytes, microglia, and neurons (Wang 2009). On these cells, IL-17R signals both through glycogen synthase kinase 3β (GSK3β), (Hetman 2000, Pap and Cooper 2002), as well as through NF-κB pathways involved in microglial activation, inducing the expression of pro-inflammatory cytokines. Collectively, these processes perpetuate neuroinflammation, compromise the blood-brain barrier (BBB), exacerbate neuronal, glial and oligodendral injury and impair neuronal resilience and viability.

Taken together these studies show that the IL-17 axis is active under conditions of CNS injury and that it acts together with other cytokines and mediators in a pro-inflammatory capacity. These studies do not illuminate whether the low levels of IL-17R and possibly present low levels of IL-17 in healthy brains play any physiologic role in the brain in the absence of ischemic, infectious, or direct autoimmune attack on the CNS. If so, such mechanisms would be unaffected by brodalumab, which does not appreciably penetrate the BBB.

2.3 Studies relating IL-17 to depression and other psychiatric conditions

Patients with psoriasis are more likely to show signs of depression when compared to the general population (Dowlatshahi 2014, Tyring 2006, Langley 2010). As such, decreasing inflammation in patients with autoimmune disorders may also decrease clinical signs of depression. Administration of ustekinumab, an IL-12/IL-23 inhibitor that decreases differentiation of IL-17 producing Th17 cells, to patients with moderate to severe psoriasis resulted in significant improvement in indicators of anxiety and depression as measured by the Hospital Anxiety and Depression Scale (HADS) (Langley 2010). Administration of the anti-TNFα antibody etanercept to patients with psoriasis resulted in improvements in symptoms of depression (Tyring 2006). If these observations are related to direct or indirect effects of cytokines in the CNS, inhibition of IL-17RA signaling by brodalumab would also be expected to improve signs of depression.

A number of papers report work done to correlate IL-17 and other cytokines with various forms of depression and other psychiatric conditions. Findings of these studies have been discordant, however, and no causal relationship has been established between the changes in serum levels of proinflammatory cytokines and suicidal behavior or suicidal ideation (Chen 2011, Serafini 2013, Haroon 2012, Lindqvist 2009, Liu 2012). Most studies measured IL-17 in the serum of patients and healthy controls, while assessments of IL-17 in the central nervous system were carried out only in specific disease conditions which often are accompanied by depression, such as ischemic disease (stroke) or malignancies (astrocytoma). In these latter studies, the confounding effects of tissue damage-induced inflammation make possible causal relationships impossible to discern. There are also a few papers reporting the effects of IL-17 axis perturbance in mouse models of depressive-like behaviors.

Kim 2013 measured IL-23 and IL-17 levels in patients with major depressive disorders and found no differences and no effects of anti-depressive medication. Similarly, when Hestad 2016 compared cytokine levels in both the serum and cerebrospinal fluid of patients with depression and patients with diffuse neurological symptoms (eg, fatigue) but no diagnosis of depression, they found no difference in IL-17A levels between groups, nor any correlation between IL-17A levels in serum and cerebrospinal fluid. In contrast, Chen 2011 found that patients with major depressive illness had a significant increase in peripheral Th17 cell number, and a decrease in T-reg cell number, resulting in an imbalance of Th17/Treg ratio compared to healthy controls. They also found a higher level of mRNA for cells, in peripheral blood lymphocytes by RT-PCR, and serum concentration of IL-17 by ELISA in patients. The authors conclude that Th17 cells may be involved in the autoimmunity often associated with major depressive disorder. In contrast, Rybka 2012 reported a decrease in circulating IL-17A with depression in a cohort of patients with chronic obstructive pulmonary disease and depression.

Pallavi and co-workers reported that serum levels of IL-17 were indistinguishable in 77 adolescents (13 to 18 years of age) with depression compared to 54 healthy controls (Pallavi 2015), while IL-2 and IL-6 levels were statistically significantly higher in these patients. Medication did not influence IL-17 levels. Similarly, a study of 38 medical students with moderate to severe depression found that the levels of IL-17 in their sera were the same as in 43 healthy controls (Momeni 2014).

The effects of three anti-depressive medications, citalopram, escitalopram and mirtazapine, on the levels of cytokines in the serum of patients were measured by Munzer and co-workers (Munzer 2013). Changes in IL-17 levels varied depending upon medication. The authors found that citalopram increased production of IL-1β, IL-6, TNFα and IL-22, while mirtazapine increased IL-1β, TNFα and IL-22, and escitalopram decreased IL-17 levels. Compared to escitalopram, citalopram led to higher levels of IL-1β, IL-6, IL-17 and IL-22; and mirtazapine to higher levels of IL-1β, IL-17, IL-22 and TNFα. Mirtazapine and citalopram increased IL-22 production. The authors concluded that differing profiles of cytokine production may relate to differences in therapeutic effects, risk of relapse, and side effects.

There are no animal models of suicidal ideation or behavior, but in a mouse model of depression-like behaviors that included 'learned helplessness', 'chronic restraint stress', and 'novelty-suppressed feeding', adoptively transferred Th17 cells increased symptom measures, while RORγt knock-out mice (deficient in Th17 differentiation) or administration of a small molecule RORγt inhibitor or blocking anti-IL17A antibodies rendered the mice resistant to induction of these behaviors (Beurel 2013). These authors propose that inhibition of the IL-17 axis may provide therapeutic benefit to patients with depression. Another study (Tallerova 2011) did not find any effects of anti-depressives on IL-17 levels in a mouse model of depression-like syndrome.

Taken together, the available data do not point to a consistent or clear role for IL-17 signaling in promoting depression or depression-like behaviors in either humans or relevant animal models. Brodalumab would not be expected to increase depression, and in alleviating comorbidities associated with depression, might reduce it.

2.4 Studies relating IL-17 to other CNS diseases with concomitant depression

Ischemia and associated tissue damage are well known to cause inflammation. A study (Swardfager 2014) of 47 stroke patients (age 71.8 ± 14.4 years, 36% female), 19 of which had depressive symptoms (Center for Epidemiological Studies Depression [CES-D] ≥16), reported elevated levels of many cytokines, including IL-17, IL-23, IL-10, and interferon [IFN]γ, as well

as markers of oxidative stress. However, there were no differences in IL-17 concentration between patients who had depressive symptoms versus those who did not. All markers of inflammation, including IL-17, were associated with poorer cognitive status in patients with depressive symptoms.

While all the above papers examined peripheral levels of cytokines, the study published by Starkweather 2014 also measured IL-17 in surgically removed astrocytoma tissue from 22 patients and compared the data to the pre-operative presence of depression in these patients. Their data suggest that IL-8 levels in serum and IL-17 levels in the tumor were negatively associated with pre-operative depression. Liu 2012 reported that serum levels of TNFα, IL-6 and IL-17 were significantly higher in 18 rheumatoid arthritis patients than those of 18 healthy patients ($p<0.001$, $p=0.012$ and $p=0.016$, respectively) and that elevated IL-17 was positively correlated with the severity of anxiety, but not depression, even after adjustment for DAS-28 (disease activity score in 28 joints) and pain.

2.5 Genome-wide association studies of suicide or suicidal ideation: no connections with IL-17 axis

While over 90% of suicide attempters or victims have a psychiatric diagnosis, particularly major depression and bipolar disorder (Beautrais 1996, Qin 2011), twin, family, and adoption studies have recognized a genetic component to suicidal behavior, which is independent of other psychiatric disorders (Schulsinger 1979, Beurel 2013

Beurel E, Harrington LE, Jope RS. Inflammatory T helper 17 cells promote depression-like behavior in mice. Biol Psychiatry. 2013;73:622-30.

Brent 1996, Roy and Segal 2001).

Candidate gene and genome-wide association studies on suicidal behavior have yielded either inconsistent or negative results (Perlis 2010, Schosser 2011, Willour 2012, Galfalvy 2013). Other genetic studies have focused on treatment emergent or treatment worsening suicidal ideation in patients taking antidepressant drugs (Laje 2009, Perroud 2012). A recent meta-analysis of these genome-wide association studies (GWAS) found several loci that link suicidality with depressive illnesses (Mullins 2014). None of these loci are related to IL-17 biology.

2.6 Potential effects of brodalumab on IL-17 signaling in the brain

Based on published data on the distribution of immunoglobulin G2 (IgG) after parenteral administration in rodents, a low fraction of brodalumab may cross the BBB by passive diffusion,

although central concentrations and activity are expected to be very low; partitioning to cerebrospinal fluid is approximately 0.1% of serum concentration (St-Amour 2013, Watts and Dennis 2013, Yu 2011). Thus, brodalumab would not be expected to inhibit IL-17RA signaling in the CNS more than perhaps briefly after dosing when serum concentrations of brodalumab are at their highest.

Clinical data from patients with psoriasis (single-dose Phase 1 Study 20110184) and preliminary data from patients with psoriatic arthritis (long-term Phase 2 Study 20101227) indicate that brodalumab treatment results in a 2- to 6-fold elevation of mean serum IL-17A levels dependent on study phase and dosage. The kinetics of this increase is suggestive of decreased receptor-mediated clearance of cytokine. Indeed, genetic deletion of IL-17RA in mice can result in elevated circulating and/or tissue levels of IL-17A (Smith 2008, Freches 2013, Vidlak and Kielian 2012), and similar data have been observed for other antibodies that bind cytokine receptors, such as the interleukin-6 (IL-6) receptor antibody tocilizumab, which can induce an approximately 2- to 20-fold increase in IL-6 levels depending on the disease state (Nishimoto 2008). Blocking IL-17R in the periphery could theoretically allow for elevation of peripheral IL-17 levels sufficient to increase CNS levels of IL-17. This possibility must be considered in evaluating a plausible hypothesis for a detrimental effect of brodalumab on suicidal ideation and behavior (SIB).

The plausibility of this hypothesis rests on IL-17's ability to cross the blood-brain barrier (BBB). While there have been no specific reports that address IL-17's interaction with the BBB, there are 3 routes by which molecules pass into the CNS: passive diffusion, active transport, or BBB disruption. IL-17 is a 32 kDa protein making significant passive diffusion of peripheral IL-17 into the CNS unlikely (Banks 2009). Alternatively, IL-17 could be actively transported into the CNS as has been described for a variety of proinflammatory cytokines in rodent studies. For example, transporters across the BBB have been described for TNFα, IL-1α and IL-6. The mechanism is not completely understood but typically requires binding of the cytokine to its appropriate receptor on the luminal surface of the brain microvascular endothelium. While IL-17R has been detected on the surface of human BBB endothelial cells (Kebir 2007), it is not known whether IL-17 can be actively transported across the BBB by this type of mechanism. Regardless, such a mechanism would be blocked by brodalumab. Moreover, active transport into the CNS is often minimal; only 0.02% to 0.18% of IFNα in plasma is able to reach the brain (Fioravanti 2012) in the presence of an active transport mechanism.

Finally IL-17 entry into the CNS could be facilitated by disruption of the BBB allowing local influx of pro-inflammatory cells and inflammatory mediators. There is evidence that elevated IL-17 can reduce BBB integrity in both murine and human systems. In murine systems, IL-17A

increases production of ROS in brain endothelial cells, leading to the activation of the endothelial contractile machinery followed by loss and disorganization of tight-junction proteins, leading to loss of BBB integrity (Huppert 2010). To the best of our knowledge, all such pro-inflammatory effects of IL- 17 are mediated by the IL-17R, which will be blocked in brodalumab-treated psoriasis patients. None of the predicted effects of BBB abrogation (neuroinflammation) were observed in the studies.

3 Pharmacokinetic and pharmacodynamic effects of brodalumab

3.1 Potential drug-drug or disease-drug-drug interaction with antidepressants

The possibility that the events of SIB could be related to drug exposure, a drug-drug interaction with antidepressants in patients receiving treatment was considered. Brodalumab is unlikely to be a perpetrator or victim of drug-drug interactions. As a monoclonal antibody targeting a receptor, brodalumab is eliminated by receptor-mediated clearance and by high capacity reticuloendothelial clearance. Catabolism of monoclonal antibodies occurs within the lysosomes following internalization by IL-17RA, pinocytosis, or phagocytosis. Because of the high target specificity of monoclonal antibodies and high molecular weight and hydrophilicity, brodalumab is not expected to interact directly with xenobiotic drug metabolizing enzymes.

Although no role for IL-17A and IL-17RA in the regulation of CYP450 enzymes has been reported, a theoretical potential exists for a disease-drug-drug interaction with brodalumab. The formation of CYP450 enzymes can be altered by increased levels of other inflammatory cytokines (eg, IL-1, IL-6, IL-10, TNFα, IFNγ) during chronic inflammation. IL-17A is upregulated in the serum of psoriasis patients relative to healthy volunteers. Therefore, the effect of brodalumab on CYP3A4/3A5 activity was evaluated in a disease-drug-drug interaction study. In patients with moderate to severe plaque psoriasis, a single dose of brodalumab subcutaneous (SC) increased the exposure of midazolam, a selective substrate of CYP3A4/3A5, by approximately 24%, which is not suggestive of a clinically significant interaction.

Because of the low risk for pharmacokinetic (PK) drug interactions, brodalumab is not expected to increase the clearance and decrease the efficacy of concomitantly administered antidepressant medications. Most selective serotonin reuptake inhibitor (SSRI) and serotonin-norephinephrine reuptake inhibitor (SNRI) antidepressants (eg, citalopram, venlafaxine, desvenlafaxine, escitalopram, fluoxetine, sertraline, paroxetine, milnacipran) are eliminated through multiple pathways, making them less susceptible to drug-drug interactions related to inhibition or induction of single metabolic pathways, even by strong inhibitors and inducers. Based on the disease-drug-drug interaction study of brodalumab, antidepressants with major elimination

pathways by CYP3A4/3A5 (eg, trazodone, vilazodone, buspirone, mianserin) will not be susceptible to PK drug interactions with brodalumab.

In conclusion, there is no evidence that a drug-drug or disease-drug interaction in patients taking antidepressants has the potential to play a causal role in the observed SIB events.

3.2 Pharmacodynamic effects and SIB events: IL-17 levels

The effect of brodalumab on serum IL-17A levels in Study 20120102 was evaluated in patients who were continuously treated with brodalumab after Week 12. Serum IL-17A levels were measured at baseline, Week 12, Week 24, and Week 48.

A dose-dependent increase in serum IL-17A was observed that is attributed to dose-dependent blockade of the receptor-mediated clearance of IL-17A. In patients who received a constant 140 mg Q2W or 210 mg every 4 weeks (Q4W) dose of brodalumab through the treatment period, median IL-17A levels increased by 2-fold and 3-fold, respectively, relative to baseline. The median increase was similar on Week 12, 24, and 48.

At the top dose of 210 mg Q2W, the post-treatment IL-17A levels remained within the range of baseline IL-17A levels for the majority (>75%) of patients. Given the generally modest elevation of IL-17A relative to the baseline range for the psoriasis population and the expected low partitioning of IL-17A across the BBB, the increased levels of IL-17A in serum are not expected to exert effects within the CNS.

3.3 Brodalumab exposure and SIB events

To explore possible impact of higher exposure on the occurrence of SIB in the patient population, the trough exposures in patients that showed SIB and all others were compared for AMAGINE-1, AMAGINE-2, AMAGINE-3. Overall the observed concentrations in patients reporting SIB were similar to those in all other patients, indicating the lack of any intrinsic PK differences between these groups of patients in any of the 3 trials. The wide range in the timing of the occurrences of SIB events after a dose (range 1 to 128 days after previous dose) also precludes the existence of a pharmacokinetic/pharmacodynamic (PK/PD) relationship.

The results of this analysis indicate a lack of evidence of a relationship between drug exposure and SIB events.

4 Conclusions on biologic plausibility

In summary, a biological linkage between brodalumab treatment and suicidal ideation appears unlikely as there is no evidence of direct effects of brodalumab on the CNS, either as observed

from the nonclinical program or from PK data, no conclusive evidence establishing a direct link between IL-17 and psychiatric disorders, and none of the typical inflammatory effects that IL-17 can have on the CNS were observed in our trials.

PK/PD investigations indicate that there is no evidence that a drug-drug or disease-drug interaction in patients taking antidepressants has the potential to play a causal role in the observed SIB events. Moreover, there is no evidence of a relationship between brodalumab exposure levels with SIB.

Also supporting the lack of a plausible association between brodalumab and SIB are the findings summarized in the briefing document that there is no evidence of an increased risk of neuropsychiatric effects with brodalumab, based on incidence rates for Psychiatric Disorders system organ class (SOC), Depression standardized MedDRA query (SMQ), or the Nervous System Disorders SOC. Because suicidal behavior is typically a manifestation of an underlying neuropsychiatric disorder, the absence of neuropsychiatric AEs that would typically precede suicidal behavior is notable.

Taken all together, the available data do not provide evidence of a mechanism of action or biologic plausibility for a causal association between brodalumab and SIB.

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BRODALUMAB injection,

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

Appendix C: PASI and sPGA Assessments
SPONSOR BRIEFING DOCUMENT
AVAILABLE FOR PUBLIC DISCLOSURE

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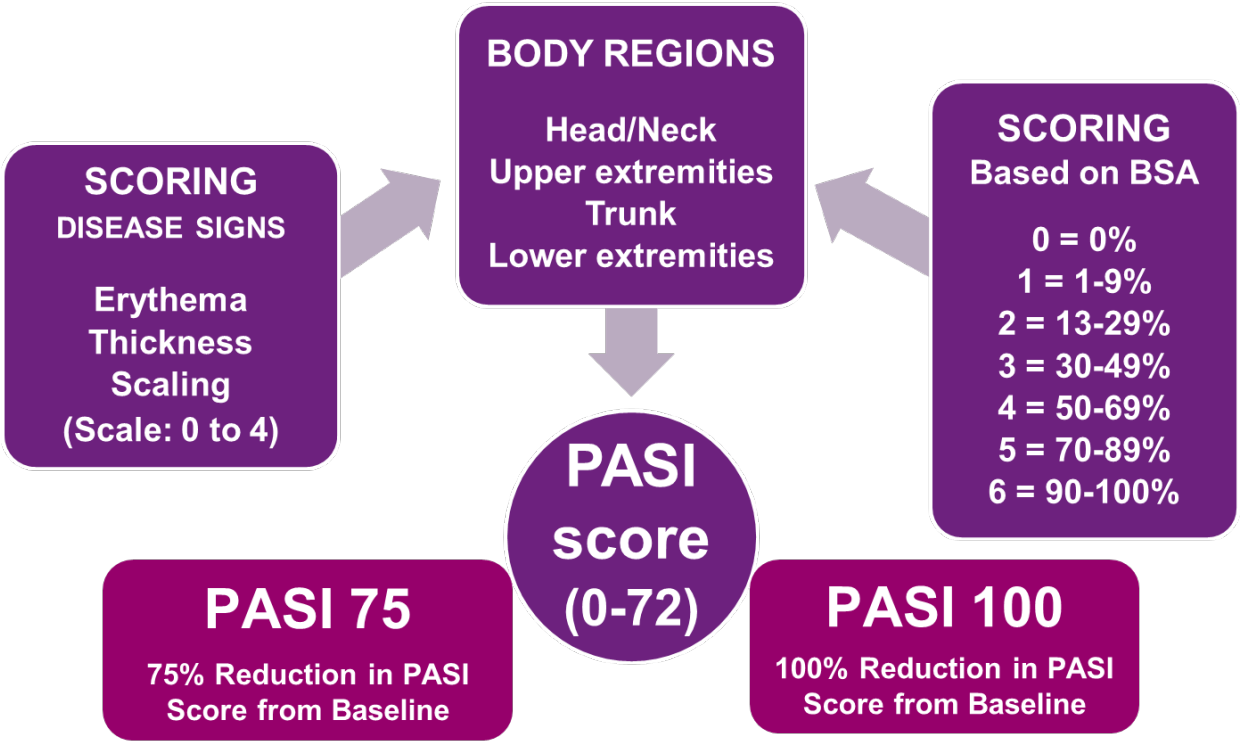
PASI:

The Psoriasis Area Severity Index (PASI) is a tool used in clinical studies to evaluate the severity and extent of psoriasis. The PASI score is a composite of the intensity of disease signs and the extent of body surface area involvement in each of the body regions and ranges from 0 to 72.



The assessor scores psoriasis disease signs (scale: 0 to 4) and area of involvement (scale: 0 to 6) for each of 4 body areas: head and neck, upper extremities, trunk, and lower extremities.

The scores for psoriasis disease signs for each body region are summed to provide a total severity score for each body region.

Area of involvement and total severity scores for each body region are combined in a following weighted manner to arrive at a Psoriasis Area and Severity Index (PASI) score:

PASI = 0.1 * (Head and Neck Involvement) * (Head and Neck Severity) +
0.2 * (Upper Extremities Involvement) * (Upper Extremities Severity) +
0.3 * (Trunk Involvement) * (Trunk Severity) +

0.4 * (Lower Extremities Involvement) * (Lower Extremities Severity)

The most common representation of PASI is PASI 75 which represents a 75% reduction in the PASI score from baseline. PASI 100 corresponds to a PASI score of 0 which translates to complete clearance of psoriasis in all affected areas and is the highest level of clearance achievable for a patient.

sPGA:

The Static Physician's Global Assessment (sPGA) assesses the severity of psoriasis at any given time on a 6-point scale ranging from 0 (clear) to 5 (very severe).

Patients in the brodalumab psoriasis development program were enrolled in the studies with a baseline score of ≥3 and sPGA success was defined as achieving a score of either 0 or 1.

A description of each score in the scale is provided in Table below.

Score	Category	Category Description
0	Clear	Plaque elevation = 0 (no elevation over normal skin) Scaling = 0 (no scale) Erythema = 0 (no evidence of erythema; hyperpigmentation may be present)
1	Minimal	Plaque elevation = ± (possible but difficult to ascertain whether there is a slight elevation above normal skin) Scaling = ± (surface dryness with some white coloration) Erythema = (faint erythema)
2	Mild	Plaque elevation = slight (slight but definite elevation, typically edges are indistinct or sloped) Scaling = fine (fine scale partially or mostly covering lesions) Erythema = (light red coloration)
3	Moderate	Plaque elevation = moderate (moderate elevation with rough or sloped edges) Scaling = coarser (coarse scale covering most of all of lesions) Erythema = moderate (definite red coloration)
4	Severe	Plaque elevation = marked (marked elevation typically with hard or sharp edges) Scaling = coarse (coarse, non-tenacious scale predominates covering most or all of the lesions) Erythema = severe (very bright red coloration)
5	Very severe	Plaque elevation = very marked (very marked elevation typically with hard sharp edges) Scaling = very coarse (coarse, thick tenacious scale over most of all the lesions; rough surface) Erythema = very severe (extreme red coloration; dusky to deep red coloration)