Brodalumab, a Human Anti–interleukin-17 Receptor A Monoclonal Antibody, Shows Low Immunogenicity in Patients With Moderate-to-Severe Psoriasis

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INTRODUCTION

- Brodalumab is a human anti–interleukin (IL)-17 receptor A monoclonal antibody, which is delivered via subcutaneous injection, that demonstrated high efficacy in the treatment of moderate-to-severe psoriasis[1–4]
- Biologic therapies, such as brodalumab, have the potential to elicit an immune response in humans, which may result in the production of anti-drug antibodies (ADAs)[5]
- ADAs may change the pharmacokinetic and/or pharmacodynamic profile of a drug and thereby compromise its efficacy and/or safety profile[6]
  - ADAs have been associated with hypersensitivity and immune reactions,[7,8] which may be preceded by localized inflammation at an injection site[9,10]
  - Neutralizing antibodies can prevent the drug from binding to the target receptor[11]
- This analysis was performed to evaluate immunogenicity and rates of hypersensitivity and injection-site reactions related to brodalumab

METHODS

Study design

- Immunogenicity data from a 12-week Phase II study (NCT00975637),[1] its open-label extension (NCT01101100; cut-off date: 16 June 2014),[2] and three 52-week Phase III studies (AMAGINE-1,[3] -2 and -3[4]) were included
- All studies were placebo controlled for the first 12 weeks, and AMAGINE-2 and -3 also included ustekinumab as a comparator up to week 52
  - Treatment changes were incorporated into the design of each study; therefore, patients had exposure to different therapies and experienced different durations of treatment with those therapies
  - Brodalumab was administered at doses of 70, 140 or 210 mg every 2 weeks (Q2W), with an additional initial dose at week 1, or at a dose of 280 mg every 4 weeks (Q4W)

Immunogenicity assessments

- In the Phase II study, serum samples were tested at baseline and weeks 4 and 16
- In the Phase II open-label extension, serum samples were tested at the open-label extension baseline and weeks 4, 12, 24, 36, 48 and every 24 weeks thereafter (to a maximum of week 336 or end of treatment)
- In the Phase III studies, serum samples were tested at baseline and weeks 0, 4, 12, 24, 48 and 52
- Samples were treated with 300 mM acetic acid to enable antibody complex dissociation prior to analysis and thus increase the probability that anti-brodalumab antibodies would be detected
- A highly sensitive (15 ng/mL) electrochemiluminescent bridging immunoassay with a drug tolerance threshold of 100.0 µg/mL, defined by a positive-control antibody, was used to detect brodalumab-specific ADAs in samples
- Samples with a positive immunoassay result were tested for brodalumab-specific neutralizing ADAs with a validated cell-based assay that used IL-8 cytokine measurement as a surrogate endpoint
  - Assay sensitivity was 0.5 µg/mL, with a lower limit of reliable detection of 2.5 µg/mL and a drug tolerance of 0.78–1.25 µg/mL
  - Confirmatory assays were conducted on positive samples by incubating the sample in the absence of IL-17 and brodalumab

Statistical analysis

- This analysis included all patients who received at least one dose of brodalumab in any of the studies
- ADAs were considered to be transient if the result of the patients' final on-study test was negative
- Descriptive statistics were used to summarize positive and negative antibody responses in each treatment group

RESULTS

Patients

- Immunogenicity was assessed in a total of 4461 patients across all studies
  - 564 patients were treated with ustekinumab before they received brodalumab 210 mg

Anti-drug antibodies

- Steady-state brodalumab serum concentrations were below the drug tolerance threshold in all samples for the immunoassay used to detect ADAs
- 122 patients (2.7%) tested positive for ADAs at any time after receiving brodalumab (Table 1)
  - 15 patients also tested positive for ADAs at baseline
  - ADAs were transient in 58 patients (1.4%)
- No patients had neutralizing ADAs, including those who received brodalumab 210 mg after ustekinumab (Table 1)

Effect of anti-drug antibodies

Pharmacokinetics

- Because anti-brodalumab antibody incidence was <3% of the patient population, anti-brodalumab antibody status was not evaluated in a population pharmacokinetic model; however, based on tabulated pharmacokinetic data (data not shown), no trends were observed to suggest reduction in pharmacokinetics due to the presence of binding ADAs

Table 1. Total Antibody Incidence

	Brodalumab 140 mg Q2W* (N=279)	Brodalumab 210 mg Q2W† (N=1291)	Variable brodalumab dosing‡ (N=2327)	Brodalumab 210 mg after ustekinumab§ (N=564)	All (N=4461)
Patients with a positive ADA result prior to the first dose of brodalumab					
	N=255	**N=1257**	**N=2231**	**N=562**	**N=4305**
Binding	0	4 (0.3)	4 (0.2)	7 (1.2)	15 (0.3)
Neutralizing	0	0	0	0	0
Patients with an on-study positive ADA result					
	N=277	**N=1287**	**N=2325**	**N=564**	**N=4453**
Binding	6 (2.2)	24 (1.9)	78 (3.4)	14 (2.5)	122 (2.7)
Neutralizing	0	0	0	0	0
Patients with a positive ADA result after the first active brodalumab dose who had a negative or no result before the first active brodalumab dose					
	N=274	**N=1281**	**N=2316**	**N=375**	**N=4246**
Binding	6 (2.2)0	20 (1.6)	74 (3.2)	7 (1.9)	107 (2.5)
Transient	*3 (1.1)*	*8 (0.6)*	*44 (1.9)*	*3 (0.8)*	*58 (1.4)*
Neutralizing	0	0	0	0	0
Transient	*0*	*0*	*0*	*0*	*0*

All data are n (%) unless otherwise stated. Treatment groups are as treated after the first dose of brodalumab. *≥75% of doses were 140 mg. †≥75% of doses were 210 mg. ‡All other brodalumab-treated patients without ustekinumab exposure. §Includes three patients not randomized to ustekinumab who inadvertently received a dose of ustekinumab.

Efficacy

- There was no clear initial indication that patients with ADAs developed tolerance to brodalumab with loss of therapeutic effect, based on Static Physician's Global Assessment (sPGA) responses. Among patients with binding ADAs:
  - 3/5 (60%) patients treated with brodalumab 210 mg Q2W and 9/14 (64%) patients treated with brodalumab 140 mg Q2W achieved sPGA success (score of 0 or 1) at week 12
  - 7/14 (50%) patients in the brodalumab 210 mg Q2W group, 1/12 (8.3%) in the 140 mg Q8W group, 0/8 in the 140 mg Q4W group, and 5/21 (24%) in the 140 mg Q2W group achieved sPGA success at week 52

Hypersensitivity and injection-site reactions

- No meaningful differences were observed in the incidence of hypersensitivity or injection-site reactions for brodalumab compared with placebo or ustekinumab within the 12 weeks of the Phase II study or the 12-week induction phases of the Phase III studies (Table 2)
  - The most frequent (≥0.3% in any group) hypersensitivity reaction was pruritus
  - The most frequent injection-site reactions were injection-site pain, erythema, bruising, and generalized injection-site reaction
- There were no reports of serious hypersensitivity or injection-site reactions in the first 12 weeks of the study, including hypersensitivity within 1 day of treatment administration

Table 2. Incidence of Hypersensitivity and Injection-Site Reactions Up to Week 12

	Placebo (N=879)	Ustekinumab (N=613)	Brodalumab 140 mg Q2W (N=1491)	Brodalumab 210 mg Q2W (N=1496)	All brodalumab doses* (N=3066)
Hypersensitivity AEs†	27 (3.1)	8 (1.3)	39 (2.6)	26 (1.7)	66 (2.2)
Pruritus	14 (1.6)	5 (0.8)	18 (1.2)	10 (0.7)	28 (0.9)
Injection-site reaction‡	11 (1.3)	12 (2.0)	25 (1.7)	23 (1.5)	56 (1.8)
Injection-site pain	3 (0.3)	4 (0.7)	7 (0.5)	9 (0.6)	20 (0.7)
Injection-site erythema	3 (0.3)	3 (0.5)	6 (0.4)	5 (0.3)	16 (0.5)
Injection-site bruising	2 (0.2)	1 (0.2)	4 (0.3)	4 (0.3)	9 (0.3)
Injection-site reaction	0 (0.0)	1 (0.2)	5 (0.3)	1 (0.1)	4 (0.1)

All data are n (%). *70 mg Q2W (N=38), 140 mg Q2W (N=1491), 210 mg Q2W (N=1496), 280 mg Q4W (N=41). †Standardized Medical Dictionary for Regulatory Activities (MedDRA) query. ‡Amgen-defined medical query.

CONCLUSIONS

- **The overall incidence of brodalumab-specific immunogenicity in patients with moderate-to-severe psoriasis was low, and ADAs were transient in almost half the patients in whom they were detected**
- **Brodalumab-neutralizing ADAs were not detected in any patients, including those who received brodalumab 210 mg after ustekinumab**
- **There was no association between ADAs and reduction of response to brodalumab or increased incidence of hypersensitivity or injection-site reactions**

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