ORIGINAL ARTICLE

A Phase 2 Trial of Guselkumab versus Adalimumab for Plaque Psoriasis

Kenneth B. Gordon, M.D., Kristina Callis Duffin, M.D., Robert Bissonnette, M.D., Jörg C. Prinz, M.D., Yasmine Wasfi, M.D., Ph.D., Shu Li, Ph.D., Yaung-Kaung Shen, Ph.D., Philippe Szapary, M.D., M.S.C.E., Bruce Randazzo, M.D., Ph.D., and Kristian Reich, M.D., Ph.D.

ABSTRACT

BACKGROUND

Little is known about the effect of specific anti–interleukin-23 therapy, as compared with established anti–tumor necrosis factor therapies, for the treatment of moderate-to-severe plaque psoriasis.

METHODS

In a 52-week, phase 2, dose-ranging, randomized, double-blind, placebo-controlled, active-comparator trial, we compared guselkumab (CNTO 1959), an anti–interleukin-23 monoclonal antibody, with adalimumab in patients with moderate-to-severe plaque psoriasis. A total of 293 patients were randomly assigned to receive guselkumab (5 mg at weeks 0 and 4 and every 12 weeks thereafter, 15 mg every 8 weeks, 50 mg at weeks 0 and 4 and every 12 weeks thereafter, 100 mg every 8 weeks, or 200 mg at weeks 0 and 4 and every 12 weeks thereafter) through week 40, placebo, or adalimumab (standard dosage for psoriasis). At week 16, patients in the placebo group crossed over to receive guselkumab at a dose of 100 mg every 8 weeks. The primary end point was the proportion of patients with a Physician's Global Assessment (PGA) score of 0 (indicating cleared psoriasis) or 1 (indicating minimal psoriasis) at week 16.

RESULTS

At week 16, the proportion of patients with a PGA score of 0 or 1 was significantly higher in each guselkumab group than in the placebo group: 34% in the 5-mg group, 61% in the 15-mg group, 79% in the 50-mg group, 86% in the 100-mg group, and 83% in the 200-mg group, as compared with 7% in the placebo group ($P \leq 0.002$ for all comparisons). Moreover, the proportion was significantly higher in the 50-mg, 100-mg, and 200-mg guselkumab groups than in the adalimumab group (58%) ($P<0.05$ for all comparisons). At week 16, the proportion of patients with at least a 75% improvement in Psoriasis Area and Severity Index scores was significantly higher in each guselkumab group than in the placebo group ($P<0.001$ for all comparisons). At week 40, the proportion of patients with a PGA score of 0 or 1 remained significantly higher in the 50-mg, 100-mg, and 200-mg guselkumab groups than in the adalimumab group (71%, 77%, and 81%, respectively, vs. 49%) ($P<0.05$ for all comparisons). Between week 0 and week 16, infections were observed in 20% of the patients in the guselkumab groups, 12% in the adalimumab group, and 14% in the placebo group.

CONCLUSIONS

The results of this phase 2 trial suggest that guselkumab may be an effective therapy for plaque psoriasis and that control of psoriasis can be achieved with specific anti–interleukin-23 therapy. (Funded by Janssen Research and Development; X-PLORE ClinicalTrials.gov number, NCT01483599.)

From the Department of Dermatology, Feinberg School of Medicine, Northwestern University, Chicago (K.B.G.); the Department of Dermatology, University of Utah School of Medicine, Salt Lake City (K.C.D.); Innovaderm Research, Montreal (R.B.); the Department of Dermatology, Ludwig-Maximilians-Universität München, Munich (J.C.P.), and the Dermatologikum Hamburg, Hamburg (K.R.) — both in Germany; and Janssen Research and Development, Spring House (Y.W., S.L., Y.-K.S., P.S., B.R.), and the Department of Dermatology, University of Pennsylvania, Philadelphia (B.R.) — both in Pennsylvania. Address reprint requests to Dr. Reich at Dermatologikum Hamburg, Stephansplatz 5, Hamburg 20354, Germany, or at kreich@dermatologikum.de.

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Psoriasis is a chronic skin disease that is characterized by the infiltration of inflammatory cells into the skin and excessive keratinocyte proliferation, which result in raised, well-demarcated erythematous lesions[1]; the disease has a substantial effect on quality of life.[2,3] The pathogenesis of psoriasis involves environmental factors and immune dysregulation in persons with a genetic predisposition.[4] The proinflammatory interleukin-12–mediated type 1 helper T (Th1) cell and interleukin-23–mediated type 17 helper T (Th17) cell signaling pathways[5,6] are up-regulated in psoriatic lesions; antibodies that inhibit both interleukin-12 and interleukin-23[7,8] and those that inhibit interleukin-17[9-13] inhibit the expression of molecular and clinical disease characteristics associated with psoriasis. Interleukin-12 induces the development of Th1 cells,[14] whereas interleukin-23 is required for terminal differentiation of Th17 cells[15] and maintenance of the Th17 phenotype.[16] Th17 cells produce interleukin-17 and interleukin-22, both of which have proinflammatory effects in skin that are relevant to the pathogenesis of psoriasis.[17]

Guselkumab (CNTO 1959, Janssen Research and Development) is a fully human IgG1 lambda monoclonal antibody that inhibits interleukin-23–specific intracellular and downstream signaling. A phase 1 study showed that a single dose of guselkumab resulted in significant clinical responses in patients with moderate-to-severe plaque psoriasis.[18] This phase 2, dose-ranging, 52-week study included an active-comparator group that received adalimumab, an anti–tumor necrosis factor α (TNF-α) therapy that is widely used for the treatment of moderate-to-severe plaque psoriasis.

METHODS

PATIENTS

We conducted this multicenter, phase 2, randomized, double-blind, placebo-controlled, active-comparator trial (X-PLORE) at 31 sites in North America and 12 sites in Europe from October 2011 through August 2013. Patients were 18 years of age or older and had had moderate-to-severe plaque psoriasis for 6 months or longer. Moderate-to-severe plaque psoriasis was defined as disease involvement of 10% or more of the total body-surface area at baseline, a score of 3 or higher on the Physician's Global Assessment (PGA; on which scores range from 0 to 5, with 0 indicating cleared psoriasis, 1 minimal psoriasis, 2 mild psoriasis, 3 moderate psoriasis, 4 marked psoriasis, and 5 severe psoriasis), and a score of 12 or higher on the Psoriasis Area and Severity Index (PASI; on which scores range from 0 to 72, with higher scores indicating more severe disease). Patients could have received previous systemic treatment or phototherapy but were excluded if they had been previously exposed to adalimumab or guselkumab.

STUDY DESIGN

The study consisted of a screening phase (weeks −4 to 0), a treatment phase (weeks 0 to 40), and a follow-up phase through 1 year (weeks 40 to 52) (Fig. S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org). At baseline, 293 patients were randomly assigned to receive subcutaneously administered placebo (42 patients), one of five guselkumab regimens (5 mg at weeks 0 and 4 and every 12 weeks thereafter [41 patients], 15 mg every 8 weeks [41 patients], 50 mg at weeks 0 and 4 and every 12 weeks thereafter [42 patients], 100 mg every 8 weeks [42 patients], or 200 mg at weeks 0 and 4 and every 12 weeks thereafter [42 patients]), or adalimumab (80 mg at week 0 and 40 mg at week 1 and every other week thereafter through week 39 [43 patients]). At week 16, patients in the placebo group crossed over to receive guselkumab at a dose of 100 mg every 8 weeks. Adalimumab was not administered in a blinded, placebo-controlled manner; however, to ensure objectivity, all efficacy assessments were performed by an evaluator at each study site who was unaware of the study-group assignments.

STUDY OVERSIGHT

This study was sponsored by Janssen Research and Development. Janssen supplied the study agents and collected and analyzed the data. All the authors had full access to the data and vouch for the completeness and accuracy of the data and analyses and the fidelity of this report to the study protocol (available at NEJM.org). All the authors collaborated on writing the manuscript, with the assistance of professional medical writers employed by Janssen, and made the decision to submit the manuscript for publication.

EFFICACY AND SAFETY ANALYSES

Efficacy assessments were performed with the use of the PGA, the PASI, and the Dermatology Life Quality Index (DLQI; on which scores range from 0 to 30, with higher scores indicating a more negative effect on quality of life). Safety assessments included documentation of adverse events, injection-site and allergic reactions, and concomitant medications.

The primary end point was the proportion of patients with a PGA score of 0 or 1 at week 16 in each guselkumab group, as compared with the proportion in the placebo group. Major prespecified secondary end points were the proportion of patients with at least a 75% improvement from baseline in the PASI score at week 16 and the change in the DLQI score from baseline to week 16. An additional prespecified secondary end point was the difference (with 95% confidence intervals) between the proportion of patients with a PGA score of 0 or 1 at weeks 16 and 40 in each guselkumab group and the proportion in the adalimumab group.

STATISTICAL ANALYSIS

Multiplicity adjustment was performed only for the five pairwise comparisons of the primary end point between guselkumab, sequentially from the highest dose (200 mg) to the lowest dose (5 mg), and placebo (each at a two-sided alpha significance level of 0.05).[19] If a given comparison in the test sequence was not significant, the remaining subsequent comparisons were not considered to be significant.

The primary end point and other key binary end points associated with PGA and PASI scores at week 16 were analyzed on an intention-to-treat basis. Patients in whom the study drug was discontinued because of unsatisfactory therapeutic effect or an adverse event of worsened psoriasis or patients who used a therapy after baseline that was prohibited in the protocol because it could improve psoriasis were considered in the analysis of binary end points (e.g., at least 75% improvement in PASI score) as not having had a response and were assigned a score of zero in the analysis of continuous end points (e.g., change in DLQI score) from that point onward. Patients with missing PGA or PASI scores at week 16 were categorized as not having had a response.

Efficacy was analyzed according to treatment group. Analyses of the placebo group after week 16 included only patients who had crossed over to receive guselkumab. Data were compared with the use of the Cochran–Mantel–Haenszel chi-square test for binary variables and analysis of covariance with the van der Waerden normal scores for continuous variables. Differences in response rates between the guselkumab groups and adalimumab group and the corresponding 95% confidence intervals were calculated, with stratification according to baseline weight (≤90 kg vs. >90 kg), at weeks 16 and 40. Safety analyses included patients who underwent randomization and received at least one dose of a study drug. Adverse events were summarized in two time periods: week 0 to week 16 and week 16 to week 52. The visit at week 16 (for the adalimumab group) or the injection at week 16 (for the other treatment groups) marked the beginning of the second time period.

RESULTS

PATIENT CHARACTERISTICS

Of the 394 patients who were screened, 293 were randomly assigned to receive guselkumab (208 patients), adalimumab (43 patients), or placebo (42 patients) (Fig. S1B in the Supplementary Appendix). One patient in the 200-mg guselkumab group underwent randomization but was not treated and therefore was not included in the safety analysis. A total of 39 of 42 patients in the placebo group crossed over to receive guselkumab at week 16, in accordance with the protocol. The study agent was discontinued in 15% of the patients in the guselkumab groups and in 26% of the patients in the adalimumab group.

Although some variability was observed, baseline demographic and disease characteristics were generally similar among the treatment groups (Table 1, and Table S1 in the Supplementary Appendix). A total of 91% of the patients were white and 71% were men; the median age was 45 years, the mean baseline weight was 91.3 kg (weight ≤90 kg, 51%; weight >90 kg, 49%), the mean duration of psoriasis was approximately 19 years, and the median baseline PASI score was 18.2. In addition, 44% of the patients had a baseline PGA score of 4 or 5, and 70% had received previous treatment with conventional systemic therapies or biologic agents (Table 1).

Table 1. Patient Characteristics.*

Characteristic	Placebo Group (N=42)	Guselkumab Groups (N=208)	Adalimumab Group (N=43)
Median age — yr	46.5	44.0	50.0
Male sex — no. (%)	28 (67)	149 (72)	30 (70)
White race — no. (%)†	39 (93)	189 (91)	39 (91)
Weight — kg	93.6±22.62	90.7±22.34	91.6±19.88
Duration of psoriasis — yr	18.0±13.30	18.5±12.17	19.3±12.79
Involvement of body-surface area — %	27.5±19.26	24.6±14.48	26.8±16.80
PASI score‡	21.8±9.98	20.9±8.05	20.2±7.58
PGA score — no. (%)§			
3	22 (52)	116 (56)	24 (56)
4	19 (45)	81 (39)	14 (33)
5	1 (2)	11 (5)	4 (9)
Psoriatic arthritis — no. (%)	12 (29)	52 (25)	11 (26)
Scalp psoriasis — no. (%)	41 (98)	192 (92)	39 (91)
Previous treatment — no. (%)			
Conventional systemic therapy¶	21 (50)	109 (52)	17 (40)
Biologic agent‖	15 (36)	85 (41)	26 (60)
Conventional systemic therapy or biologic agent¶‖	27 (64)	148 (71)	30 (70)
Topical agent	41 (98)	200 (96)	42 (98)
Phototherapy**	21 (50)	109 (52)	24 (56)
Psoralen plus ultraviolet A therapy	9 (21)	49 (24)	12 (28)

* Plus–minus values are means ±SD.
† Race was self-reported.
‡ On the Psoriasis Area and Severity Index (PASI), scores range from 0 to 72, with higher scores indicating more severe disease.
§ On the Physician's Global Assessment (PGA), scores range from 0 to 5, with 0 indicating cleared psoriasis, 1 minimal psoriasis, 2 mild psoriasis, 3 moderate psoriasis, 4 marked psoriasis, and 5 severe psoriasis.
¶ Conventional systemic therapies included psoralen plus ultraviolet A therapy, methotrexate, acitretin, and cyclosporine.
‖ Biologic agents included ustekinumab, etanercept, infliximab, efalizumab, alefacept, and briakinumab.
** Phototherapy included ultraviolet B therapy and psoralen plus ultraviolet A therapy.

EFFICACY

Weeks 0 to 16

At week 16, the proportion of patients with a PGA score of 0 or 1 (primary end point) was significantly higher in each guselkumab group than in the placebo group: 34% in the 5-mg group, 61% in the 15-mg group, 79% in the 50-mg group, 86% in the 100-mg group, and 83% in the 200-mg group, as compared with 7% in the placebo group ($P=0.002$ for the comparison of the 5-mg group; $P<0.001$ for all other comparisons) (Table 2 and Fig. 1A). Among the guselkumab groups, a dose response was observed among the four lowest-dose groups, whereas results were similar in the 100-mg and 200-mg groups (Table 2).

In addition, the proportion of patients with at least a 75% improvement from baseline in the PASI score, at least a 90% improvement, and a 100% improvement was significantly higher in each guselkumab group than in the placebo group at week 16 ($P<0.001$) (Table 2 and Fig. 1B, and Fig. S2 in the Supplementary Appendix). Clinical responses of a PGA score of 0 or 1 and at least a 75% improvement in PASI score were observed as early as week 4 after the initiation of guselkumab (Fig. 1). The decrease in DLQI score (indicating improvement in quality of life) from baseline to week 16 was significantly greater in the guselkumab groups than in the placebo group ($P\leq0.008$) (Table 2).

Table 2. Efficacy Outcomes at Week 16.*

Outcome	Placebo Group (N=42)	5-mg Guselkumab Group (N=41)	15-mg Guselkumab Group (N=41)	50-mg Guselkumab Group (N=42)	100-mg Guselkumab Group (N=42)	200-mg Guselkumab Group (N=42)	Adalimumab Group (N=43)
PGA score of 0 or 1 — no. (%)	3 (7)	14 (34)†	25 (61)‡	33 (79)‡	36 (86)‡	35 (83)‡	25 (58)‡
PGA score of 0 — no. (%)	0	6 (15)§	8 (20)†	11 (26)‡	19 (45)‡	15 (36)‡	13 (30)‡
≥75% Improvement from baseline in PASI score — no. (%)	2 (5)	18 (44)‡	31 (76)	34 (81)‡	33 (79)‡	34 (81)‡	30 (70)‡
≥90% Improvement from baseline in PASI score — no. (%)	1 (2)	14 (34)‡	14 (34)‡	19 (45)‡	26 (62)‡	24 (57)‡	19 (44)‡
100% Improvement from baseline in PASI score — no. (%)	0	4 (10)‡	5 (12)‡	8 (19)‡	14 (33)‡	12 (29)‡	11 (26)‡
Change in DLQI score from baseline¶	−2.3±6.80	−6.2±5.24†	−10.3±5.49‡	−11.1±7.38‡	−10.8±7.34‡	−11.4±6.83‡	−10.1±9.00‡
DLQI score of 0 or 1 — no./total no. (%)¶‖	3/42 (7)	10/38 (26)§	14/41 (34)†	17/40 (42)‡	25/40 (62)‡	26/37 (70)‡	19/39 (49)‡

* Plus–minus values are means ±SD. The 5-mg, 50-mg, and 200-mg guselkumab groups received doses at weeks 0 and 4 and every 12 weeks thereafter, and the 15-mg and 100-mg guselkumab groups received doses every 8 weeks.
† P<0.01 for the comparison with placebo.
‡ P<0.001 for the comparison with placebo.
§ P<0.05 for the comparison with placebo.
¶ On the Dermatology Life Quality Index (DLQI), scores range from 0 to 30, with higher scores indicating a more negative effect on quality of life.
‖ Included are data from patients who underwent randomization and had a baseline DLQI score greater than 1.

Weeks 16 to 40

The proportion of patients with a PGA score of 0 or 1 continued to increase over time, reaching the maximum response at week 20 in most guselkumab groups (Fig. 1A). Responses were generally maintained from week 24 to week 40, at which time 77% of patients in the 100-mg guselkumab group and 81% of patients in the 200-mg guselkumab group had a PGA score of 0 or 1. Between week 16 and week 40, a substantial proportion of patients in the guselkumab groups had a PGA score of 0 and a 100% improvement from baseline in the PASI score (Fig. S2 in the Supplementary Appendix). After week 16, PGA scores among patients in the placebo group who had crossed over to receive guselkumab were similar to the scores among patients in the 100-mg guselkumab group. Some variations in PGA scores were observed over time among guselkumab groups. A modest loss of efficacy near the end of each dosing interval occurred more consistently among the patients who received guselkumab every 12 weeks than among those who received guselkumab every 8 weeks. The pattern of PASI scores was generally similar to that observed for PGA scores, with maximum responses achieved by approximately week 20 and maintained through week 40 (Fig. 1, and Fig. S2 in the Supplementary Appendix).

COMPARISON OF GUSELKUMAB WITH ADALIMUMAB

At week 16, the proportion of patients with a PGA score of 0 or 1 was higher in all guselkumab groups, except for the 5-mg group, than in the adalimumab group (Table 2 and Fig. 1A). The differences in proportions between the 50-mg, 100-mg, and 200-mg guselkumab groups and the adalimumab group were significant: 20 percentage points (95% confidence interval [CI], 2 to 39), 28 percentage points (95% CI, 10 to 46), and 25 percentage points (95% CI, 7 to 44), respectively. At week 40, the proportion of patients with a PGA score of 0 or 1 was significantly higher in the 50-mg, 100-mg, and 200-mg guselkumab groups than in the adalimumab group: 71%, 77%, and 81%, respectively, versus 49%. The differences in proportions between the 50-mg, 100-mg, and 200-mg guselkumab groups and the adalimumab group were 23 percentage points (95% CI, 2 to 44), 29 percentage points (95% CI, 9 to 49), and 33 percentage points (95% CI, 13 to 53), respectively. Moreover, P values for post hoc analyses of pairwise comparisons (performed with the use of the Cochran–Mantel–Haenszel chi-square test and stratified according to baseline weight [≤90 kg vs. >90 kg]) between the 50-mg, 100-mg, and 200-mg guselkumab groups and the adalimumab group were significant at week 16 (P=0.05, P=0.005, and P=0.01, respec-

tively) and at week 40 (P=0.04, P=0.01, and P=0.003, respectively).

SAFETY

Weeks 0 to 16

During the placebo-controlled period, the proportion of patients with one or more adverse events was similar among the treatment groups (52% in the placebo group, 50% in the guselkumab groups, and 56% in the adalimumab group) (Table 3). Among the guselkumab groups, there was no evidence of a relationship between the dose and the rate of adverse events (Table S2 in the Supplementary Appendix). The rates of adverse events of infection were 14% in the placebo group, 20% in the guselkumab groups, and 12% in the adalimumab group.

The proportion of patients in whom the study agent was discontinued because of an adverse event, serious adverse event, or serious infection was low through week 16. All serious adverse events that occurred through week 16 were single events. A serious infection occurred in two patients in the 50-mg guselkumab group (appendicitis in one patient and lung abscess in one patient). The proportion of adalimumab injections associated with an injection-site reaction was higher than the proportion of placebo or guselkumab injections associated with an injection-site reaction (6% vs. 1% and 1%, respectively).

Weeks 16 to 52

Between week 16 and week 52, the proportion of patients in whom the study agent was discontinued because of an adverse event was low and similar among the groups (Table 3, and Table S2 in the Supplementary Appendix). The proportion of patients with one or more adverse events through week 52 was somewhat higher in the adalimumab group than in the guselkumab groups (61% vs. 49%). Among the guselkumab groups, there was no evidence of a relationship between the dose and the rate of adverse events. As in the period between week 0 and week 16, the most commonly reported adverse event during the period between week 16 and week 52 was infection, which was reported in approximately 30% of the patients. No additional serious infections were reported in patients in the guselkumab groups during this period, but a serious case of pneumonia was reported in a patient in the adalimumab group. No cases of tuberculosis or opportunistic infections were reported during the study.

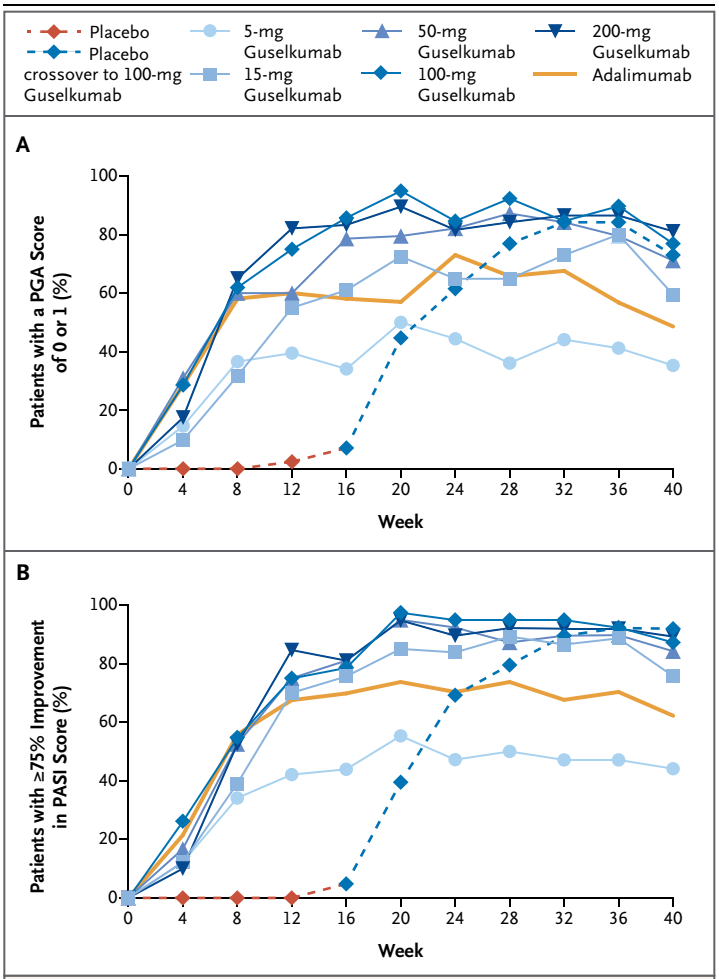

Figure 1. Efficacy Outcomes.

Panel A shows the proportion of patients with a score on the Physician's Global Assessment (PGA) of 0 (indicating cleared psoriasis) or 1 (indicating minimal psoriasis). Panel B shows the proportion of patients with at least a 75% improvement from baseline in the Psoriasis Area and Severity Index (PASI) score. The 5-mg, 50-mg, and 200-mg guselkumab groups received doses at weeks 0 and 4 and every 12 weeks thereafter, and the 15-mg and 100-mg guselkumab groups received doses every 8 weeks. At week 16, patients in the placebo group crossed over to receive guselkumab at a dose of 100 mg every 8 weeks.

One case of cancer (grade 3 cervical intraepithelial neoplasia) was reported during the study in a patient who was receiving guselkumab (Table S2 in the Supplementary Appendix). Between week 16 and week 52, major adverse cardiovascular events were observed in three patients who were receiving guselkumab (one in the 5-mg group and two in the 100-mg group), including one death from a myocardial infarction (Table 3, and Table S2 in the Supplementary Appendix).

By week 52, antibodies to guselkumab had developed in 6% of the patients who had been

Table 3. Safety Outcomes from Weeks 0 to 16 and Weeks 16 to 52.

Outcome	Placebo Group (N=42)	Guselkumab Groups (N=207)	Adalimumab Group (N=43)
		number (percent)	
Weeks 0–16*			
Patients in whom study agent was discontinued because of ≥1 adverse events	3 (7)	5 (2)	3 (7)
Patients with ≥1 adverse events	22 (52)	103 (50)	24 (56)
Patients with ≥1 serious adverse events	1 (2)	3 (1)	1 (2)
Patients with ≥1 infections	6 (14)	41 (20)	5 (12)
Patients with ≥1 serious infections	0	2 (1)	0
Patients with ≥1 infections requiring treatment	3 (7)	14 (7)	2 (5)
		Guselkumab Groups (N=235)	**Adalimumab Group (N=38)**
Weeks 16–52†			
Patients in whom study agent was discontinued because of ≥1 adverse events		3 (1)	1 (3)
Patients with ≥1 adverse events		115 (49)	23 (61)
Patients with ≥1 serious adverse events		4 (2)	1 (3)
Patients with ≥1 infections		70 (30)	14 (37)
Patients with ≥1 serious infections		0	1 (3)
Patients with ≥1 infections requiring treatment		21 (9)	6 (16)
Patients with ≥1 cancers		1 (<1)	0
Patients with ≥1 major adverse cardiovascular events‡		3 (1)	0

* Data for weeks 0 to 16 included patients who received at least one dose of a study drug. One patient in the 200-mg guselkumab group underwent randomization but was not treated and therefore was not included in the safety analysis.
† Data for weeks 16 to 52 included patients who received at least one dose of a study drug at or after week 16. Data for the guselkumab groups included patients who were originally assigned to receive guselkumab, as well as patients originally assigned to the placebo group who crossed over at week 16, per protocol, to receive guselkumab at a dose of 100 mg every 8 weeks. Eleven patients in the guselkumab groups and five patients in the adalimumab group did not receive the study agent at or after week 16; therefore, these patients were not included in the safety analyses from weeks 16 to 52.
‡ Major adverse cardiovascular events were defined as myocardial infarction, stroke, or cardiovascular death.

treated with guselkumab (15 of 240 patients with serum samples that could be evaluated); the antibodies generally had low titers (≤1:320) and were non-neutralizing. No anaphylactic or serum sickness–like reactions associated with the administration of the study agent occurred through week 52.

DISCUSSION

This study provides several insights into the pathogenesis of and therapeutic options for psoriasis. Benefits observed with the use of TNF antagonists in the treatment of psoriasis have shown that proinflammatory cytokines are effective targets for psoriasis therapy. A better understanding of the pathogenesis of psoriasis now allows selective cytokine targeting that is specific to psoriasis, an approach that may translate into effective treatments for psoriasis that have less effect on normal immune function than do current treatments.

One example of a drug that selectively targets cytokines is ustekinumab, a monoclonal antibody that modulates proinflammatory Th1 and Th17 pathways through the inhibition of both interleukin-12 and interleukin-23; it has proved to be a safe and effective treatment for both psoriasis and psoriatic arthritis.[7,8,20-25] Interleukin-23 is a heterodimeric cytokine that is composed of p19 and p40 subunits. Interleukin-12 is also a heterodimeric cytokine that is composed of the same p40 subunit as interleukin-23 and a unique p35 subunit. In contrast to ustekinumab, which targets p40 and therefore antagonizes the activity of both interleukin-12 and interleukin-23, guselkumab antagonizes the activity of only interleukin-23, through its p19 subunit. Thus, results from the clinical trials of guselkumab provide further insight into the relative importance of

the Th17 pathway, as compared with the Th1 pathway, in the pathogenesis of psoriasis.

Recently reported results from a small (24 participants) proof-of-concept study showed that selective antagonism of interleukin-23 with guselkumab resulted in clinical improvement of psoriasis, characterized by reductions in epidermal thickness, T-cell and dendritic-cell infiltration, expression of genes associated with psoriasis, and serum interleukin-17A levels.[18] The results of this study validate the use of interleukin-23 as a therapeutic target by showing that therapy involving selective antagonism of this single cytokine in patients with moderate-to-severe psoriasis is highly efficacious, as compared with adalimumab therapy. In addition, these data suggest that activation of the proinflammatory Th1 pathway by interleukin-12 may not be as critical to psoriasis immunopathogenesis as had been previously thought.[26] Interleukin-23 has an essential role in the terminal differentiation of Th17 cells[15] and maintenance of the Th17 phenotype.[16] Th17 cells are believed to be a chief source of interleukin-17A in vivo, but a critical role of interleukin-23 in the regulation of interleukin-17A production by neutrophils has also been recently shown.[27] Because neutrophils are found at higher densities in psoriatic lesional skin than are Th17 cells and because the release of interleukin-17A by neutrophils in human psoriatic lesions has been described in the literature,[28] one can hypothesize that the effects of interleukin-23 inhibition by guselkumab that were shown in this clinical trial could involve modulation of neutrophils in addition to Th17 cells.

This phase 2 study evaluated the use of guselkumab at a broad range of doses and two different dosing intervals for up to 40 weeks of continuous treatment. The onset of guselkumab activity was rapid; efficacy was evident at the earliest assessment (week 4). Several of the guselkumab regimens were associated with considerably better response rates than those associated with adalimumab, a biologic agent that is commonly used to treat psoriasis. The efficacy of guselkumab continued to increase beyond week 16 (primary end-point assessment) and was maintained through week 40. Moreover, the majority of patients in the 100-mg guselkumab group had completely cleared psoriasis, as indicated by a PGA score of 0 (in 62% of patients) and a 100% improvement from baseline in PASI score (in 54% of patients) after 40 weeks of continuous treatment. Total clearance of psoriasis is correlated with improvements in patient-reported health-related quality of life.[29]

At week 16, which was the end of the placebo-controlled period, the rates of adverse events, serious adverse events, and infections were similar among the placebo, guselkumab, and adalimumab groups. Between week 0 and week 16, infections were reported in 14% of the patients in the placebo group, in 20% of those in the guselkumab groups, and in 12% of those in the adalimumab group; between week 16 and week 52, infections were reported in 30% of the patients in the guselkumab groups and in 37% of those in the adalimumab group. Between week 16 and week 52, major adverse cardiovascular events were reported in three patients receiving treatment with guselkumab.

The inclusion of groups receiving various regimens of guselkumab, the inclusion of an active-comparator group, and the 40-week duration of continuous treatment provide substantial information about the emerging benefit–risk profile of guselkumab. However, this study has some limitations that are typical of phase 2, dose-ranging studies. The relatively small overall sample size and the multiple treatment groups resulted in some imbalances among groups with respect to certain baseline patient characteristics (e.g., previous treatments for psoriasis) (Table 1, and Table S1 in the Supplementary Appendix); these imbalances may have influenced the results. Furthermore, some elements of the study design limited the ability to assess uncommon adverse events or adverse events that might have developed during long-term treatment: there was a relatively small amount of total exposure to guselkumab, and there were more patients receiving guselkumab than other treatments (i.e., the study included seven groups with an equal number of patients in each group, yielding a 5:2 ratio of guselkumab to adalimumab or placebo during the placebo-controlled period and a 6:1 ratio of guselkumab to adalimumab after the placebo-controlled period). It is also difficult to interpret the significance of the rates of rare adverse events, such as the three reported major adverse cardiovascular events. Another potential issue was the use of a blinded efficacy evaluator at each site instead of the administration of adalimumab in a blinded manner. However, the efficacy outcomes for adalimumab in this phase 2 trial were similar to those reported in a large

pivotal, placebo-controlled, phase 3 study of adalimumab.[30]

In the current era, in which treatment options for psoriasis are expanding, head-to-head comparisons of new therapies with established products are important for allowing evidence-based treatment decisions. Guselkumab has more robust efficacy than does adalimumab and has a mechanism of action that is more specifically targeted to psoriasis than does ustekinumab. Larger and longer-term phase 3 trials (ClinicalTrials.gov numbers, NCT02207231, NCT02207244, and NCT02203032) are under way to examine the safety and comparative efficacy of guselkumab for the treatment of moderate-to-severe psoriasis.

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