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REVIEW

Guselkumab for the treatment of psoriasis – evidence to date

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Abstract

Psoriasis is a chronic, immune-mediated, inflammatory, and debilitating skin disease with significant impact on patients' quality of life. Its pathogenesis is complex and not yet fully understood. However, the IL-23/IL-17 axis is currently considered the main pathogenic pathway in psoriasis. Guselkumab is a fully human immunoglobulin G1 λ (IgG1λ) monoclonal antibody (mAb) that binds to the p19 subunit of IL-23. It is the first of its class, already approved by the US Food and Drug Administration (FDA), as well as the European Medicines Agency (EMA) for the treatment of adult patients with moderate-to-severe plaque psoriasis who are candidates for either systemic therapy or phototherapy. Several clinical trials have demonstrated potential benefits of guselkumab over other already approved immunomodulators in terms of safety and efficacy. The results of the head-to-head trial ECLIPSE were recently released and are addressed in this review. They contribute to the increasing confidence in guselkumab, demonstrating great potential for long-term treatment of psoriasis. However, further long-term data and additional comparative studies will be essential for positioning guselkumab in the therapeutic armamentarium for psoriasis.

Keywords: antibodies, biological products, interleukin-23, monoclonal, psoriasis.

Citation

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Introduction

Psoriasis is a chronic, immune-mediated, inflammatory skin disease that affects over 125 million people worldwide,[1–3] with significant impact on patients' quality of life.[4] Due to its systemic nature, psoriasis is associated with several medical comorbidities, including cardiovascular disease, inflammatory bowel disease, and psychiatric diseases.[5–9]

Psoriasis pathogenesis is complex and not yet fully understood. Even though, disease knowledge has significantly evolved in past years leading to the development of increasingly specific and efficacious targeted therapies.[10–13]

During the initiation phase of the psoriatic skin lesions, an increment of the production of TNF occurs and, as a result, activation of dermal dendritic cells.[14,15] These cells are responsible for the increased production of IL-23 and the subsequent activation of distinct subgroups of IL-17 producing cells (T17) (helper T cells [Th17]; cytotoxic T cells [Tc17]; innate lymphoid cells [ILC3]; and γδ T cells).[14,16–18] As IL-23 levels rise, secreted mainly from inflammatory dermal dendritic cells, T17 cells increase in number and produce large amounts of IL-17, specifically isoforms IL-17A and F, which drive the upregulation of many psoriasis-related genes.[14,19] The clonal expansion of T17 cells and subsequent increased levels of IL-17 feedforward an inflammatory response and lead to keratinocyte hyperproliferation.[14,15,20,21] Other types of cells, such as dermal macrophages and epidermal keratinocytes, were also associated with the increased production of IL-23 and may contribute to psoriatic lesions' installation and maintenance.[14,22] The discovery of the IL-23/IL-17 axis, widely considered the most critical pathogenic pathway on the development of psoriasis, and the development of drugs targeting this pathway shifted the paradigm of the management of this condition.[15,20,23]

The development of IL-17 inhibitors showed that the blockade of the pathway of this cytokine was associated with high levels of efficacy and rapid onset of action in moderate-to-severe psoriasis, but also better clinical responses than either TNF-α inhibitors or ustekinumab, a nonselective IL-23 inhibitor.[24–31] However, several side effects such as neutropenia, candidiasis, and exacerbations of Crohn's disease have been associated with these agents,[24–31] reinforcing the need for new therapeutic solutions. More recently, selective IL-23 inhibitors such as guselkumab, tildrakizumab, and risankizumab have emerged, showing a very effective, durable, and safe profile[32–40]

This article intends to review the current literature on guselkumab in the management of psoriasis.

Guselkumab pharmacology

Guselkumab® (Janssen Biotech, Inc., Horsham, PA, USA) is a fully human immunoglobulin G1 λ (IgG1λ) monoclonal antibody (mAb) that binds to the p19 subunit of IL-23. It is first of its class to be approved by the US Food and Drug Administration (FDA)[41] as well as the European Medicines Agency (EMA)[42,43] for the treatment of adult patients with moderate-to-severe plaque psoriasis who are candidates for either systemic therapy or phototherapy. In light of its clinical efficacy in plaque psoriasis, guselkumab has also been or is currently being evaluated for the treatment of other diseases, namely generalized pustular psoriasis (GPP), erythrodermic psoriasis (EP), psoriatic arthritis, rheumatoid arthritis, and Crohn's disease.

Pharmacodynamic properties

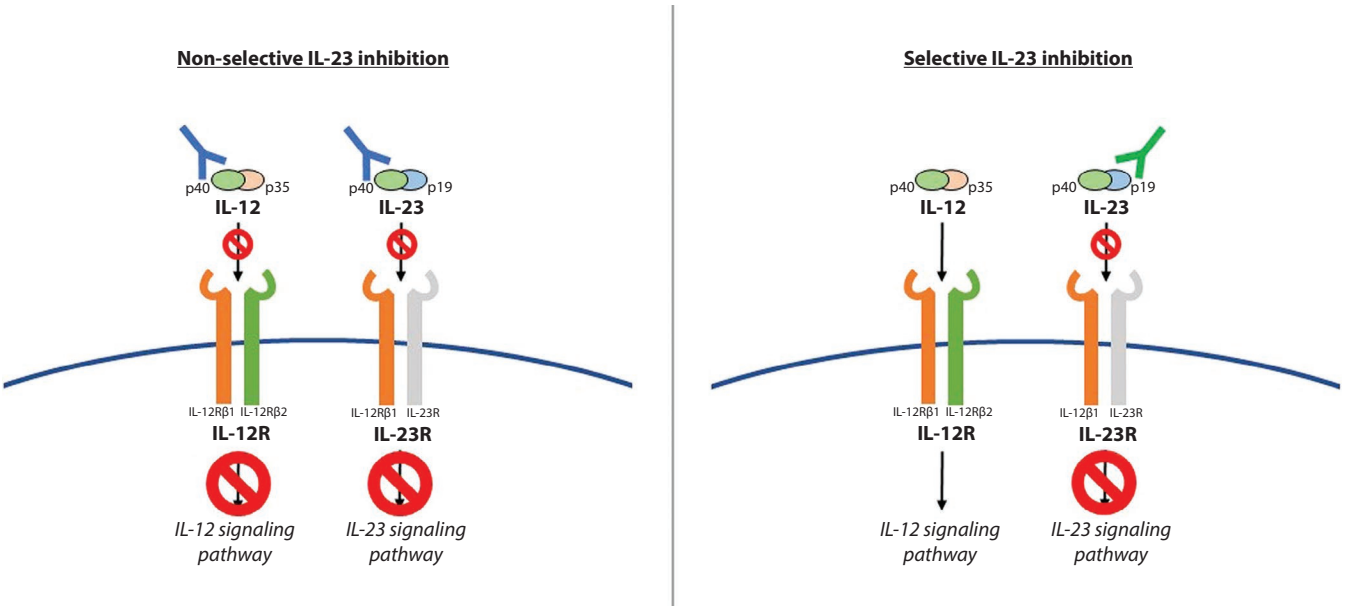
Guselkumab binds with both high affinity and high specificity to IL-23,[43] preventing the interaction of the cytokine with its receptor on the surface of the cell. This action is responsible for blocking the initiation of the IL-23 pathway and the subsequent release of other proinflammatory cytokines (Figure 1).

In patients with moderate-to-severe plaque psoriasis, the biopsy of skin samples from body regions affected with the disease, compared to nonlesional regions, before and after a single dose of guselkumab, showed that the drug is responsible for a significant ($p<0.05$) reduction in inflammatory dendritic cell and T-cell counts, and epidermal thickness at week 12 compared to baseline.[32] Significant reductions in IL-17A serum levels since week 1 were observed when compared to baseline values (*versus* no change in placebo recipients) in patients considered as responders to guselkumab (with ≥50% improvement in the Psoriasis Area and Severity Index score [PASI 50] measured at week 12), with a response that was dose-dependent.[32] Guselkumab has also shown a substantial impact in both the reduction of mRNA expression of IL-17F and IL-22, as well as in increased levels of INF-γ, produced by T-helper 1 (Th1) cells, thus proposing that the drug's clinical performance relies primarily in the inhibition of the IL-23/Th17 pathway, allowing the IL-12/Th1 axis to remain intact[32] (Figure 1).

Pharmacokinetic properties

Zhuang and colleagues[37] conducted a first-in-human, phase I, randomized trial to assess the pharmacokinetics, immunogenicity, safety, and tolerability of guselkumab following a single intravenous (IV; 0.03–10 mg/kg) or subcutaneous (SC; 10–300 mg) administration in healthy subjects and patients with moderate-to-severe psoriasis. The pharmacokinetic profile of guselkumab was generally comparable between healthy subjects and patients with psoriasis. Investigators also noted that there was a

Figure 1. The IL-12 and IL-23 heterodimers are each composed of a common p40 subunit and a unique p35 and p19 subunit, respectively. The nonselective IL-23 inhibitors, such as ustekinumab, bind to the p40 subunit on IL-12 and IL-23, thereby inhibiting both signalling pathways. The selective IL-23 inhibitors, as guselkumab, bind to the p19 subunit on IL-23 and inhibit only the IL-23-mediated signalling pathway, allowing the IL-12 axis to remain intact.



dose-dependent increase in the mean maximum serum concentration and area under the zero-to-infinity serum concentration–time curve.[37]

Yao and colleagues[44] established a population pharmacokinetics model using the information from three clinical trials involving guselkumab: the phase II X-PLORE (NCT01483599) and two phase III trials, namely VOYAGE 1 (NCT02207231) and VOYAGE 2 (NCT02207244). The final model showed an apparent clearance and apparent volume of distribution of 0.516 L/day, and 13.5 L, respectively. Mean half-life time values were consistent between both healthy subjects (12–19 days) and patients with psoriasis (15–17 days). The model-derived elimination half-life of the drug allowed for the conclusion that steady-state serum guselkumab concentrations occurred between weeks 12 and 14.[44] However, Smolen and colleagues[45] reported that the median serum levels of guselkumab would only reach the steady state by week 20, which is the information provided by EMA about the product.[43]

Therapeutic efficacy of guselkumab in psoriasis

Large, randomized, multinational, phase III trials (VOYAGE 1, VOYAGE 2, NAVIGATE [NCT02203032], and ECLIPSE [NCT03090100]) assessed the clinical efficacy of subcutaneous guselkumab in the treatment of moderate-to-severe plaque psoriasis in adults. Results from other trials support this data and will not be discussed further.[33,46]

Patients enrolled in the previously reported phase III clinical trials were individuals with ≥18 years of agewith moderate-to-severe plaque psoriasis for at least 6 months and had to be eligible for systemic therapy or phototherapy. Patients in VOYAGE trials and NAVIGATE had an initial Investigator Global Assessment (IGA) score of 3 or more, a minimum affected body surface area (BSA) of ≥10%, and a PASI score of 12 or more. These studies excluded patients with history or symptoms of active tuberculosis, other types of psoriasis (guttate, erythrodermic, or pustular), or who had been exposed to guselkumab or the active comparator (adalimumab in VOYAGE trials; ustekinumab in NAVIGATE; and secukinumab in ECLIPSE).[34–36,38]

VOYAGE trials

VOYAGE 1 was a phase III randomized, double-blind trial, which evaluated the effectiveness of guselkumab compared to placebo and adalimumab.[34] For study design, see Table 1. The proportion of patients with an IGA score of 0/1 (cleared/minimal disease) and the proportion of patients with an at least PASI 90 response, both at week 16, were used to evaluate the clinical efficacy of guselkumab compared to placebo (as coprimary endpoints). To assess the efficacy of guselkumab compared to that of adalimumab, investigators used as major secondary endpoints the proportion of patients achieving an IGA score of 0/1, PASI 75, and PASI 90 responses at weeks 16, 24, and 48, respectively. A fixed sequence method of analyses was used to control the overall type 1 error rate.

At week 16, comparing to the placebo group, a significantly higher proportion of patients receiving guselkumab had achieved an IGA score of 0/1 (85.1 *versus* 6.9%) and PASI 90 (73.3 *versus* 2.9%) response. In addition, a significantly higher proportion of patients achieving IGA 0, PASI 75, and PASI 100 was observed in guselkumab group *versus* the placebo group (Table 2).[34] When compared to adalimumab at week 16, guselkumab was statistically superior, as observed by the percentage of patients achieving an IGA score of 0/1 (85.1 *versus* 65.9%), PASI 75 (91.2 *versus* 73.1%), and PASI 90 (73.3 *versus* 49.7%) responses. These responses maintained significance throughout week 24 (IGA 0/1 [84.2 *versus* 61.7%], PASI 75 [91.2 *versus* 72.2%], and PASI 90 [80.2 *versus* 53.0%]) and week 48 (IGA 0/1 [80.5 *versus* 55.4%], PASI 75 [87.8 *versus* 62.6%], and PASI 90 [76.3 *versus* 47.9%]). Similarly, the proportion of patients who achieved a PASI 100 response in the guselkumab group was significantly higher than in the adalimumab group at every checkpoint (weeks 16 [37.4 *versus* 17.1%], 24 [44.4 *versus* 24.9%], and 48 [47.4 *versus* 23.4%]). With the initiation of guselkumab at week 16, patients in the placebo crossover group achieved similar responses to those receiving guselkumab since week 0.[34] Guselkumab was proven superior to both the placebo and/or adalimumab in the attainment of the coprimary endpoints and all major secondary endpoints (all $p<0.001$) in this clinical trial.[34] For a more detailed analysis of the results, see Table 2.

Regional psoriasis was also evaluated and analysed in this trial. For this purpose, investigators used scores such as scalp-specific IGA (ss-IGA), Nail Psoriasis Severity Index (NAPSI), fingernail Physician's Global Assessment (PGA) (f-PGA), and PGA of the hands and/or feet (hf-PGA). A significantly greater proportion of patients treated with guselkumab reached an ss-IGA score of 0/1 compared with placebo at week 16 (83.4 *versus* 14.5%; $p<0.001$). Using the same score, guselkumab also showed significantly higher efficacy than adalimumab at weeks 24 (84.5% in guselkumab group *versus* 69.2% in adalimumab group) and 48 (78.3% in guselkumab group *versus* 60.5% in adalimumab group) (both $p<0.001$).[34] Compared to placebo at week 16, the guselkumab group had a higher mean per cent improvement in the NAPSI score and a greater proportion of patients achieving an f-PGA score of 0/1. Compared to adalimumab, the results in the f-PGA score were similar at week 24 but significant differences were observed at week 48 in patients treated with guselkumab ($p=0.038$).[34] There were no differences between guselkumab and adalimumab groups concerning the NAPSI score, measured at weeks 24 and 48.[34] A higher percentage of patients receiving guselkumab, comparing to those receiving placebo, achieved the hf-PGA score of 0/1 at week 16 (73.3 *versus* 14.0%; $p<0.001$). Regarding to the same score, guselkumab-treated patients also had better responses when compared to adalimumab-treated patients at week 24 (78.9 *versus* 56.8%; $p<0.001$) and week 48 (75.6 *versus* 62.1%; $p<0.045$).[34]

Table 1. Study design for each phase III trials.

Clinical trial	Number of patients	Study design
VOYAGE 1	837	Patients were randomized in a 1:2:2 ratio for one of three scenarios: (1) Placebo (weeks 0, 4, and 12), followed by guselkumab (100 mg; weeks 16, 20, and every 8 weeks through week 44) (n=174); (2) Guselkumab (100 mg; weeks 0, 4, and every 8 weeks through week 44) (n=329); (3) Adalimumab (80 mg at week 0, 40 mg at week 1, and 40 mg every 2 weeks through week 47) (n=334).
VOYAGE 2	992	Patients were randomized in a 2:1:1 ratio to: (1) Guselkumab (100 mg; weeks 0, 4, 12, and 20) (n=496); (2) Placebo (weeks 0, 4, and 12), and then receive guselkumab (100 mg; weeks 16 and 20) (n=248) – placebo–guselkumab crossover group; (3) Adalimumab (80 mg at week 0, then 40 mg at week 1, and every 2 weeks through week 23) (n=248) At week 28, the patients treated with guselkumab with PASI 90, considered as responders, were rerandomized in a 1:1 ratio to guselkumab or placebo, with guselkumab after loss of response (loss of 50% or more of week-28 PASI response). Placebo–guselkumab crossover responders and adalimumab responders received placebo, then guselkumab after loss of response. Nonresponders received guselkumab. Patients received either placebo or guselkumab through week 72.
NAVIGATE	871	Patients received open-label ustekinumab (45 mg for patients ≤100 kg, 90 mg for patients >100 kg) at weeks 0 and 4. At week 16, 268 patients with an inadequate response to ustekinumab, considered as an IGA score of 2 or more, were randomized (double-blind) to: (1) Guselkumab (100 mg; weeks 16, 20, and every 8 weeks thereafter through week 44) (n=135); (2) Continue ustekinumab (week 16 and every 12 weeks after that through week 40) (n=133).
ECLIPSE	1048	Participants received one injection of active guselkumab and one injection of placebo when guselkumab was scheduled to be administered (weeks 0, 4, 12, and every 8 weeks thereafter through week 44) or two injections of placebo when no guselkumab was scheduled to be administered (weeks 1, 2, 3, 8, 16, 24, 32, and 40). Placebo injections were administered to maintain the blind. On the other hand, participants received two injections of secukinumab subcutaneously at weeks 0, 1, 2, 3, 4, and every 4 weeks thereafter through week 44.

Health-related quality of life (HRQoL) was also evaluated with patient-reported outcomes using the Psoriasis Symptoms and Signs Diary (PSSD) and the Dermatology Life Quality Index (DLQI). Mean changes in the PSSD score from baseline for guselkumab-treated patients were higher than placebo at week 16 and higher than adalimumab at weeks 24 and 48 ($p<0.001$ for all three). It was possible to observe a significantly higher improvement from baseline DLQI in the group of patients who received guselkumab compared with placebo (–11.2±7.2 *versus* –0.6±6.4; $p<0.001$), with a concomitant higher proportion of patients achieving the DLQI score of 0/1 (56.3 *versus* 4.2%; $p<0.001$) at week 16. The investigators noted that guselkumab also outperformed adalimumab concerning both improvements from the baseline DLQI score (week 24 [–11.6±7.6 *versus* –9.5±7.9; $p<0.001$] and week 48 [–11.8±7.9 *versus* –9.2±8.3; $p<0.001$]) and achievement of the DLQI score of 0/1 (week 24 [60.9 *versus* 39.5%; $p<0.001$] and week 48 [62.5 *versus* 38.9%; $p<0.001$]).[34]

Still in VOYAGE 1, an open-label extension period began where patients who were having guselkumab as treatment agreed to continue to receive the drug every 8 weeks, whereas patients in the adalimumab group accepted to change to guselkumab at week 52 and every 8 weeks thereafter, after taking their last dose of adalimumab at week 47. At week 100, the proportion of patients who achieved an IGA score of 0/1, the IGA score of 0, PASI 75, PASI 90, and PASI 100 responses were 82.4, 53.8, 94.8, 82.1, and 49.0%, respectively. Placebo–guselkumab crossover and adalimumab–guselkumab crossover groups achieved similar results at week 100. It was concluded that efficacy was maintained through 2 years amongst patients who had continued treatment with guselkumab, and patients who changed from adalimumab to guselkumab after 1 year had improved efficacy at 2 years.[47]

In VOYAGE 2 trial, investigators assessed the efficacy and safety of guselkumab in moderate-to-severe psoriasis *versus* both

Table 2. Summary of key results from clinical trials with guselkumab.

Clinical trial	Proportion of patients achieving				
	PASI 75	**PASI 90**	**PASI 100**	**IGA 0/1**	**DLQI 0/1**
VOYAGE 1	**At wk 16:** Gus 91.2%; ADA 73.1%; PL 5.7%	**At wk 16:** GUS 73.3%; ADA 49.7%; PL 2.9%	**At wk 16:** GUS 37.4%; ADA 17.1%; PL 0.6%	**At wk 16:** GUS 85.1%; ADA 65.9%; PL 6.9%	**At wk 16:** GUS 56.3%; ADA 38.6%; PL 4.2%
	At wk 24: GUS 91.2%; ADA 72.2%	**At wk 24:** GUS 80.2%; ADA 53.0%	**At wk 24:** GUS 44.4%; ADA 24.9%	**At wk 24:** GUS 84.2%; ADA 61.7%	**At wk 24:** GUS 60.9%; ADA 39.5%
	At wk 48: GUS 87.8%; ADA 62.6%	**At wk 48:** GUS 76.3%; ADA 47.9%	**At wk 48:** GUS 47.4%; ADA 23.4%	**At wk 48:** GUS 80.5%; ADA 55.4%	**At wk 48:** GUS 62.5%; ADA 38.9%
	(all p<0.001)	*(all p<0.001)*	*(all p<0.001)*	*(all p<0.001)*	*(all p<0.001)*
VOYAGE 2	**At wk 16:** GUS 86.3%; ADA 68.5%; PL 8.1%	**At wk 16:** GUS 70.0%; ADA 46.8%; PL 2.4%	**At wk 16:** GUS 34.1%; ADA 20.6%; PL 0.8%	**At wk 16:** GUS 84.1%; ADA 67.7%; PL 8.5%	**At wk 16:** GUS 51.7%; ADA 39.0%; PL 3.3%
	At wk 24: GUS 89.1%; ADA 71.0%	**At wk 24:** GUS 75.2%; ADA 54.8%	**At wk 24:** GUS 44.2%; ADA 26.6%	**At wk 24:** GUS 83.5%; ADA 64.9%	**At wk 24:** GUS 57.6%; ADA 41.1%
	(all p<0.001)	*(all p<0.001)*	*(all p<0.001)*	*(all p<0.001)*	*(all p<0.001)*
NAVIGATE	**NR**	**At wk 28:** GUS 48.1%; UST 22.6%	**At wk 28:** **NR**	**At wk 28:** GUS 31.1%; UST 14.3%	**At wk 28:** **NR**
		(p<0.001)		*(p=0.001)*	
		At wk 52: GUS 51.1%; UST 24.1%	**At wk 52:** GUS 20.0%; UST 7.5%	**At wk 52:** GUS 36.3%; UST 17.3%	**At wk 52:** GUS 38.8%; UST 19.0%
		(p<0.001)	*(p=0.003)*	*(p<0.001)*	
ECLIPSE	**At wk 12:** GUS: 89.3%; SEC 91.6%	**At wk 12:** GUS 69.1%; SEC 76.1%	**At wk 12:** **NR**	**At wk 12:** **NR**	**NR**
	At wk 48: **NR**	**At wk 48:** GUS 84.5%; SEC 70.0%	**At wk 48:** GUS 58.2%; SEC 48.4%	**At wk 48:** GUS 85.0%; SEC 74.9%	
		(p<0.001)			

Nonresponder imputation was used to assess binary endpoint missing data. All comparisons were made with guselkumab, and *p*-value represents the significance value of this comparison.
ADA, adalimuma; GUS, guselkumab; NR, not reported; PL, placebo; SEC, secukinumab; UST, ustekinumab; wk, week(s).

placebo and adalimumab, including in the study one arm with discontinuation of guselkumab and another with switching adalimumab nonresponders to guselkumab[35] (Table 1).

At week 16, comparing to the placebo group, a higher number of patients receiving guselkumab achieved an IGA score of 0/1 (84.1 *versus* 8.5%) and PASI 90 (70.0 *versus* 2.4%) response (coprimary endpoints) (both $p<0.001$). Guselkumab was also superior to adalimumab at weeks 16 and 24, as measured by the proportion of patients achieving an IGA score of 0/1 (week 16 [84.1 *versus* 67.7%] and week 24 [83.5 *versus* 64.9%]), PASI 75 (week 16 [86.3 *versus* 68.5%] and week 24 [89.1 *versus* 71.0%]), PASI 90 (week 16 [70.0 *versus* 46.8%] and week 24 [75.2 *versus* 54.8%]), and PASI 100 (week 16 [34.1 *versus* 20.6%] and week 24 [44.2 *versus* 26.6%]) responses (all $p<0.001$). From weeks 28 to 48, a higher persistence of response (PASI≥90) was observed in the guselkumab maintenance group *versus* the withdrawal group (88.6 *versus* 36.8%; $p<0.001$). For withdrawal patients, the median time to loss of PASI 90 response was 15.2 weeks.[35] Regarding the group of patients considered as nonresponders to adalimumab who switched to guselkumab, 66.1% achieved PASI 90 at week 48, and 28.6% achieved PASI 100. Guselkumab

improved patient-reported outcomes (DLQI and PSSD), similar to what was already demonstrated in VOYAGE 1.[35] For a more detailed analysis of the results, consult Table 2. The efficacy of guselkumab *versus* both placebo and adalimumab was confirmed in VOYAGE 2 trial, because the results were similar to those observed in VOYAGE 1.[35]

Gordon and colleagues[48] evaluated the consistency of guselkumab's efficacy across several subpopulations of patients with psoriasis (defined by baseline demographics, disease characteristics, and previous exposure to treatments) using pooled information from VOYAGE 1 and VOYAGE 2 trials. Guselkumab provided significant benefit across almost all subpopulations, showing a more consistent response amongst lighter and heavier patients when comparing to adalimumab.[48]

NAVIGATE

NAVIGATE was a phase III, randomized, double-blind trial that assessed the clinical efficacy of guselkumab in patients with moderate-to-severe psoriasis who had a poor response to ustekinumab.[36] For study design, consult Table 1. Amongst the initial 871 patients, 585 (67%) with an IGA score of 0/1 at week 16 continued to receive open-label ustekinumab.[36] The investigators defined the number of visits in which randomized patients achieved an IGA score of 0/1 and at least a two-grade improvement in the IGA score (comparing to the IGA score at week 16) from week 28 through week 40 as the primary endpoint.[36]

The number of visits in which randomized patients achieved IGA of 0/1 was significantly higher in the group of patients receiving guselkumab *versus* the group receiving ustekinumab (1.5±1.6 *versus* 0.7±1.3; $p \leq 0.001$).[36] Langley and colleagues[36] also observed that a higher proportion of patients treated with guselkumab achieved an IGA score of 0/1 with an at least two-grade improvement at weeks 28 (31.1 *versus* 14.3%; $p=0.001$) and 52 (36.3 *versus* 17.3%; $p<0.001$). Investigators also noted that a greater proportion of patients treated with guselkumab, comparing to those receiving ustekinumab, achieved PASI 90 (51.1 *versus* 24.1%) and PASI 100 (20.0 *versus* 7.5%) responses (both $p<0.005$), as well as the DLQI score of 0/1 (38.8 *versus* 19.0%) at week 52.[36] For a more detailed analysis of the results, see Table 2. This clinical trial gave us the opportunity to conclude that patients treated with ustekinumab who had a poor response at week 16 derived significant benefit from switching to guselkumab.[36]

ECLIPSE

A phase III randomized, double-blind, head-to-head trial called ECLIPSE was designed to assess guselkumab's efficacy and safety compared to secukinumab in patients with moderate-to-severe plaque psoriasis. For study design, consult Table 1.

The study demonstrated that guselkumab was superior to secukinumab for the primary endpoint assessed at week 48; that is, achievement of at least PASI 90 response (84.5% with guselkumab *versus* 70.0% with secukinumab; $p<0.001$).[38] For a more detailed analysis of the results, see Table 2.

ECLIPSE incorporated six secondary endpoints evaluated at weeks 12 and 48. Investigators used a fixed statistical sequence procedure to control for multiple comparisons. At both weeks 12 and 48, 84.6% of patients receiving guselkumab achieved a PASI 75 response (*versus* 80.2% in the secukinumab group), demonstrating that guselkumab was not inferior to secukinumab in the first major secondary endpoint ($p<0.001$). However, it failed to demonstrate superiority and, with this in mind, *p*-values for all the subsequent major secondary endpoints were considered nominal.[38]

Another three major secondary endpoints were evaluated at week 48. Compared to secukinumab, a higher proportion of patients in guselkumab group achieved an IGA score of 0/1 (85.0 *versus* 74.9%), IGA of 0 (62.2 *versus* 50.4%), and PASI 100 (58.2 *versus* 48.4%) response.[38]

The remaining major secondary endpoints were assessed at week 12. Moreover, 89.3% of patients receiving guselkumab achieved a PASI 75 response, against 91.6% of patients receiving secukinumab. The proportion of patients achieving a PASI 90 response was 69.1% for guselkumab and 76.1% for secukinumab.[38]

Safety and tolerability of guselkumab

Guselkumab was generally well tolerated in adults with moderate-to-severe plaque psoriasis in all pivotal trials.[34–36,38] Data from other phase I, II, and III trials support this information[32,33,46] and will not be discussed further.

In VOYAGE 1, investigators reported comparable adverse events (AEs) amongst patients in the different treatment groups. Nasopharyngitis and upper respiratory tract infection were the most common adverse events reported.[34] In addition to the fact that serious AEs and AEs leading to the discontinuation of the agent were uncommon, these events occurred in similar proportions for each treatment group throughout the study. Overall infections and infections requiring antibiotic treatment occurred at comparable rates across all treatment groups through week 48.[34] By week 16, two major adverse cardiac events (MACEs) occurred, one in each of the guselkumab and adalimumab groups, and one patient receiving guselkumab developed a basal cell carcinoma. Between weeks 16 and 48, four cases of serious infections were reported: two in the group of patients receiving guselkumab (one thigh abscess and one cellulitis with postoperative wound infection) and two in the group of patients receiving adalimumab (one abdominal abscess and one fatal staphylococcal pneumonia). Two malignancies (breast and prostate cancers), both in the guselkumab group, and two basal cell carcinomas, one in each of the guselkumab and adalimumab groups, were observed up to week 48. No additional MACEs were reported after week 16. There were no differences between groups in the incidence

of neutropenia and candidiasis, which was low in all treatment groups. There were no differences between groups regarding the incidence of laboratory abnormalities, which was also low. No Crohn's disease-related events were reported.[34]

VOYAGE 2 corroborated the safety data observed in VOYAGE 1 regarding the comparable proportion of patients with one or more AE, AEs leading to discontinuation, and serious AEs in placebo and guselkumab groups through week 16.[35] The most commonly reported events during placebo-controlled period (weeks 0–16) were nasopharyngitis, headache, and upper respiratory tract infection. That was the same pattern of AEs that were observed during the active-comparator period (weeks 0–28). No malignancies or nonmelanoma skin cancers (NMSCs) were reported through week 16. One MACE, specifically a myocardial infarction, occurred in the group of patients receiving the active-comparator adalimumab during placebo-controlled period. A higher proportion of patients treated with adalimumab had Injection site reactions (ISR) (6.9 *versus* 2.6%).[35] Concerning to the active-comparator period, three serious infections were observed in each of the active treatment groups (guselkumab group: bronchitis, erysipelas, and soft tissue infection; adalimumab group: two cases of tuberculosis and one injection-site abscess). One malignancy (prostate cancer) and two NMSCs (one squamous cell carcinoma in the group of patients receiving guselkumab and one basal cell carcinoma in the placebo–guselkumab crossover group) were also reported. One patient in each of guselkumab- and adalimumab-treated groups developed a MACE through week 28.[35] From weeks 28 to 48, one serious infection was reported in the maintenance group (appendicitis). During this randomized withdrawal and retreatment period (weeks 28–48), one case of MACE was reported in the placebo–guselkumab crossover group. One additional basal cell carcinoma and one squamous cell carcinoma were noted in the same placebo–guselkumab group through week 48. Similar to what was observed in VOYAGE 1 results, the incidence of laboratory abnormalities was low and comparable between groups.[35]

No new signs that would endanger the safety of the drug were identified during the long-term treatment (through 100 weeks) with open-label extension with guselkumab in VOYAGE 1 and VOYAGE 2.[49]

NAVIGATE brought no new safety data regarding patients who switched from ustekinumab to guselkumab without a washout period. Moreover, 64.0% of patients randomized to guselkumab had one or more AEs (*versus* 56.0% in ustekinumab group). Serious AEs were reported in 7% of patients treated with guselkumab (*versus* 5% with ustekinumab), and 2% of each group discontinued treatment due to an AE.[36]

In the ECLIPSE trial, the safety profiles observed for both drugs (guselkumab and secukinumab) were consistent with the information already presented in the respective registration trials. Similar percentage of patients reported at least one AE (77.9% with guselkumab *versus* 81.6% with secukinumab). Serious AEs were reported in 6.2% of patients receiving guselkumab (*versus* 7.2% of patients receiving secukinumab). Investigators documented six serious infections in guselkumab-treated patients (*versus* five in the secukinumab group).[38]

Immunogenicity

Zhuang and colleagues[37] reported that 1 out of 20 (5.0%) patients in the second part of the phase I trial (which included patients with psoriasis) had positive antibodies to guselkumab. The incidence of antibodies to guselkumab reported in X-PLORE was 6.0%.[33] However, they were nonneutralizing and had low titres.[33] VOYAGE 1, VOYAGE 2, and NAVIGATE reported rates of antibody development of 5.3% through week 44, 6.6% through week 48, and 9.0% through week 60, respectively. No association between antibody incidence and reduced efficacy was noted.[34–36]

Other indications

A phase III, single-arm, open-label, multicentre trial conducted in Japan with 21 patients demonstrated the clinical benefit of using guselkumab in the treatment of other types of psoriasis, such as GPP and EP.[50] Its efficacy was verified throughout the study period (52 weeks), and the safety profile of guselkumab was consistent with data already published in psoriasis. Sano and colleagues[50] concluded that there would be a favourable risk–benefit profile for treating both GPP and EP patients with the selective IL-23 inhibitor. Nevertheless, further studies are required to confirm this effectiveness.

In a phase II randomized, double-blind, placebo-controlled trial, guselkumab demonstrated significant improvement in joints' symptoms, physical function, enthesitis, dactylitis, and quality of life in patients with psoriatic arthritis.[51] Two phase III trials are now underway to ascertain the efficacy and safety of guselkumab in patients who suffer from this pathological condition, either biologic-naive (NCT03158285) or previously treated with TNF-α inhibitors (NCT03162796).

Smolen and colleagues[45] conducted a phase II trial that evaluated the safety and efficacy of guselkumab in patients suffering from active rheumatoid arthritis despite concomitant treatment with methotrexate. No statistically significant differences in the percentage of patients who achieved an American College of Rheumatology (ACR)-20 response between those who received guselkumab and the control group were found.[45]

To date, no published studies demonstrate the impact of guselkumab in the treatment of Crohn's disease. However, ustekinumab, as a nonselective IL-23 inhibitor, has been shown to be effective treating this disease.[52,53] Currently, a clinical trial is ongoing (GALAXI [NCT03466411]), and is recruiting patients and pretends to evaluate the efficacy and safety of guselkumab in participants with Crohn's disease.

Discussion

As previously mentioned, the discovery of the IL-23/IL-17 axis has led to a substantial increase in our knowledge of the

pathogenic immune events present in psoriasis and to shift the paradigm of the management of this condition. IL-17 inhibitors were approved previously than IL-23 selective inhibitors for the treatment of moderate-to-severe psoriasis. However, several complications have been associated with these agents, raising the need for different therapeutic solutions.

Although the inhibition of IL-23 alone rather the coinhibition of both IL-23 and IL-12 presents as a novel mechanism of action, the favourable safety profile of guselkumab has not come as a surprise, because long-term data were available for ustekinumab.[53,54] However, allowing the IL-12/Th1 axis to remain intact, as is the case with guselkumab, may be a net-positive effect because the cytokines involved in this pathway contribute vitally to the hosts' defence through their ability to stimulate both innate and adaptive immune effector cells against intracellular microbial infection and malignant cells.[55–57] These cytokines also allow the initiation of a protective transcriptional program in keratinocytes that will limit skin inflammation mediated by T17 cells.[15,58] Treatment with an IL-23p19 inhibitor led to long-term responses in some patients with just a single dose[32] or after a withdrawal after 28 weeks of contact with the drug (in VOYAGE 2, 36.8% of patients rerandomized to placebo sustained PASI 90 at week 48).[35] This clinical response can be explained in part by the impact of IL-12 in promoting transdifferentiation of Th17 cells into regulatory T cell or Th1 populations.[15,59]

Although IL-23 and IL-39 (another proinflammatory cytokine likely expressed in psoriatic skin) share the p19 subunit, whether guselkumab can bind to or inhibit human IL-39 is unknown, and further studies are required to explore the individual role of this cytokine.[20]

Several reviews have been published regarding the role of guselkumab in the treatment of psoriasis.[60–63] However, recent divulgation of the results of ECLIPSE reinforces the role of the selective IL-23 inhibitor concerning other already approved immunomodulators, such as the active-comparator secukinumab used in trial.[38] Even though secukinumab achieved a slightly faster onset of response, detailed analysis with the response-over-time curves showed that maximum response rates with guselkumab are achieved later – after 6 months – and are maintained over time through 1 year, translating into superiority for the primary endpoint of the study (PASI 90 response).[38] The superiority of guselkumab in comparison to secukinumab is also apparent in the less frequent dosing regimen of the selective IL-23 inhibitor (guselkumab: initially at weeks 0 and 4, but then every 8 weeks *versus* secukinumab: administered weekly for 4 weeks followed by every 4 weeks as a maintenance dosing). From the patients' point of view, characteristics such as less frequent drug administration or the option of self-administration contribute to better adherence and thus better clinical outcomes.

Conclusion

Guselkumab is a monoclonal antibody that selectively targets IL-23, and it is the first in its class to be approved to treat moderate-to-severe plaque psoriasis. Its efficacy and safety profiles were reinforced by recent studies such as ECLIPSE, demonstrating great potential for long-term treatment of psoriasis. Long-term data and additional comparative studies will be essential for positioning guselkumab in the therapeutic armamentarium for psoriasis.

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