Guselkumab is superior to fumaric acid esters in patients with moderate-to-severe plaque psoriasis who are naive to systemic treatment: results from a randomized, active-comparator-controlled phase IIIb trial (POLARIS)

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Summary

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Background Guselkumab, a fully human interleukin-23 antibody, is approved for systemic treatment of patients with moderate-to-severe plaque psoriasis.

Objectives To compare the efficacy and safety of guselkumab with those of fumaric acid esters (FAE) in patients with moderate-to-severe plaque psoriasis who are naive to systemic treatment.

Methods Eligible patients were randomized to this multicentre, randomized, open-label, assessor-blinded, active-comparator-controlled phase IIIb study to receive guselkumab 100 mg by subcutaneous injection or oral FAE according to local label guidelines.

Results Through week 24, 56 of 60 patients completed guselkumab treatment and 36 of 59 completed FAE treatment. The primary endpoint (proportion of patients with ≥ 90% improvement from their baseline Psoriasis Area and Severity Index; PASI 90 response) was achieved by significantly more patients receiving guselkumab than FAE at week 24 (82% vs. 14%, P < 0·001). Analysis of the major secondary endpoints confirmed a statistically significant difference between the treatments with regards to PASI 75 response (90% vs. 27%, P < 0·001) and Dermatology Life Quality Index score of 0 or 1 (no effect at all on the patient's quality of life; 62% vs. 17%, P < 0·001). More patients in the guselkumab group achieved completely clear skin (PASI 100 response) than in the FAE group (32% vs. 3%, P < 0·001). The incidence of adverse events was lower with guselkumab than with FAE (73% vs. 98%). Overall, 28% of patients on FAE discontinued due to an adverse event, compared with none receiving guselkumab. No new safety findings were observed for guselkumab.

Conclusions Guselkumab demonstrated superiority over FAE in systemic-treatment-naive patients with moderate-to-severe plaque psoriasis through 24 weeks.

What's already known about this topic?

- Guselkumab is approved as treatment for patients with moderate-to-severe plaque psoriasis who are candidates for systemic therapy.

- Guselkumab is a monoclonal antibody that specifically targets the p19 subunit of the immune-regulatory cytokine interleukin-23, a key driver of immune response in psoriasis.
- Fumaric acid esters (FAE) are among the most commonly prescribed first-line systemic therapies for plaque psoriasis in Germany and they are increasingly being used in other countries.

What does this study add?

- In patients with psoriasis who are naive to systemic treatment, guselkumab was superior to FAE in achieving $\geq$ 75%, $\geq$ 90% and 100% improvement in Psoriasis Area and Severity Index, and Dermatology Life Quality Index scores of 0 or 1 at week 24.
- Guselkumab showed a favourable safety profile, and fewer patients discontinued treatment due to adverse events compared with FAE-treated patients.
- The results support the use of guselkumab in systemic-treatment-naive patients with moderate-to-severe plaque psoriasis.

Psoriasis is a chronic, immune-mediated inflammatory skin disease, affecting approximately 2% of the population.[1] It often negatively impacts the physical and emotional wellbeing of affected patients, as well as their quality of life.[2]

Fumaric acid esters (FAE) are among the systemic compounds recommended by the European S3-Guidelines for the management of moderate-to-severe plaque psoriasis.[3] In Germany, a fixed mixture of dimethylfumarate (DMF) and monoethylfumarate (MEF) is one of the most commonly prescribed first-line systemic therapies.[4] In 2017, DMF monotherapy (LAS41008) received approval in all European Union member states plus Iceland, Norway and Switzerland based on the results of the phase III BRIDGE study, in which DMF was noninferior to the DMF/MEF mixture.[5]

Biologic compounds that interfere with T-cell function or inhibit cytokines such as tumour necrosis factor, interleukin (IL)-12/23 or IL-17A have also emerged as treatments for moderate-to-severe psoriasis.[6] Guselkumab (CNTO 1959) is the first approved monoclonal antibody that inhibits IL-23 signalling. Blockade of IL-23 leads to rapid and sustained reduction of IL-23-dependent effector cytokines, including IL-17A, IL-17F and IL-22, which correlates with clinical improvement in psoriasis.[7] Guselkumab received approval from the U.S. Food and Drug Administration and European Medicines Agency as a first-line psoriasis therapy based on the results from three global phases III studies (VOYAGE 1,[8] VOYAGE 2[9] and NAVIGATE),[10] which included more than 2000 patients. These studies demonstrated high efficacy and a favourable safety profile for guselkumab. However, guselkumab has not yet been compared with a conventional systemic compound, and long-term randomized controlled trials comparing FAE with other systemic psoriasis therapies are rare.

For objective assessment of first-line therapies such as guselkumab and FAE, a direct comparison of these treatments is important. The objectives of the POLARIS trial were to compare the efficacy, safety and tolerability; and improvements in health-related quality of life and other patient-reported outcomes (PROs) of guselkumab vs. FAE. The study was designed in accordance with the scientific guidance of the national health technology assessment agency in Germany.

Patients and methods

Patients

Adult, systemic-treatment-naive patients with a diagnosis of moderate-to-severe plaque psoriasis for $\geq$ 6 months, an absolute Psoriasis Area and Severity Index (PASI) score > 10 or affected body surface area (BSA) > 10%, and a Dermatology Life Quality Index (DLQI) score > 10 at baseline were eligible for study participation. Patients might have previously received phototherapy, including psoralen with ultraviolet A, narrowband ultraviolet B or balneophototherapy. Key exclusion criteria were any previous systemic treatment for psoriasis, known contraindications to guselkumab or FAE, and ongoing use of a prohibited concomitant medication. Data were collected at hospitals and dermatological practices from patients recruited by referral or self-selection. The study protocol was approved by the relevant institutional review boards and independent ethics committees, and written informed consent was provided by all patients.

Study design and treatments

This multicentre, randomized, open-label, assessor-blinded, active-comparator-controlled phase IIIb study was initiated in December 2016 at 27 German sites, and the last week-24 visit was in September 2017. Eligible patients were randomized

1 : 1 to receive guselkumab 100 mg by subcutaneous injection administered by study personnel at weeks 0 and 4, then every 8 weeks; or to receive FAE tablets (Fumaderm® initial or Fumaderm®; Biogen Idec, Cambridge, MA, U.S.A.), intended for self-administration according to the local label (individual dosing with a maximum of three × two tablets per day; Table S1; see Supporting Information). POLARIS was conducted in accordance with the Declaration of Helsinki and was registered at ClinicalTrials.gov (NCT02951533). The study was amended twice (study parts II and III). In this report, the results of study part I (active treatment up to week 24) are described (Fig. 1).

Assessments

Efficacy evaluations were reported first by patients (using PROs) and then by a blinded assessor. PRO assessments were conducted before any tests, procedures or other consultations for that visit.

Efficacy measures evaluated by the assessor included PASI,[11] the affected BSA,[12] Investigator's Global Assessment (IGA)[13] and the scalp-specific IGA (ss-IGA). PROs included the DLQI,[14] the 7-day version of the Psoriasis Symptom and Sign Diary (PSSD; higher scores indicate more severe disease)[15] and the Short Form Health Survey version 2 (SF-36v2).[16] The data were analysed with QualityMetric Health Outcomes Scoring Software 5·0 (QualityMetric, Lincoln, RI, U.S.A.).

Safety was monitored by collecting information on adverse events (AEs; defined as events with onset during or worsening since treatment), clinical laboratory values, tuberculosis, physical examination, bodyweight, vital signs and concomitant medication. The Medical Dictionary for Regulatory Activities (MedDRA) version 19·1 was used for coding of AEs, and prior and concomitant medications. The study objectives and corresponding endpoints are listed in Table 1.

Randomization and blinding

Patients were randomized 1 : 1 based on a computer-generated randomization schedule that was prepared before the start of the study. The randomization was balanced using randomly permuted blocks of four. The interactive web-based electronic case report forms assigned a unique treatment code, which dictated the treatment assignment at the baseline visit for each patient. The blinded efficacy assessors were not involved in any other study procedure and did not have access to the allocation data.

Statistical analysis

Statistical analysis was carried out using the software system SAS 9·4 (SAS Institute Inc., Cary, NC, U.S.A.). The analyses were conducted to assess the primary and major secondary endpoints with a significance level of a two-sided type 1 error
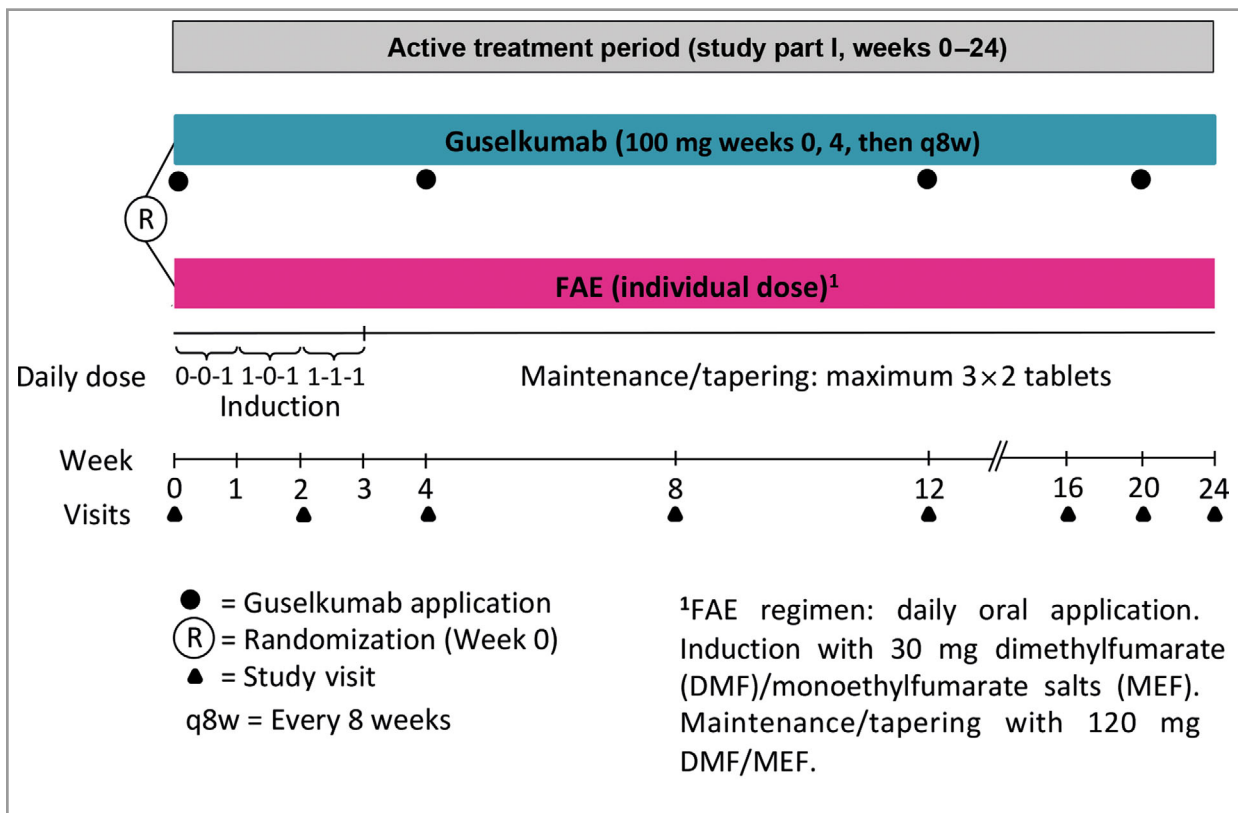

Fig 1. POLARIS study scheme, overview of study part I. FAE, fumaric acid esters.

Table 1 Objectives and endpoints of POLARIS study part I (weeks 0–24)

Primary objectives
- To compare the efficacy of guselkumab with that of fumaric acid esters in systemic-treatment-naive patients with moderate-to-severe plaque-type psoriasis
- To assess the safety and tolerability of guselkumab in systemic-treatment-naive patients with moderate-to-severe plaque-type psoriasis

Secondary objective
- To compare improvement of health-related quality of life and other patient-reported outcomes when systemic-treatment-naive patients with moderate-to-severe plaque-type psoriasis are treated with guselkumab compared with fumaric acid esters

Primary endpoint[a]
- Proportion of patients achieving PASI 90 response at week 24

Major secondary endpoints[a]
- Proportion of patients achieving PASI 75 response at week 24
- Proportion of patients achieving a DLQI score of 0 or 1 at week 24

Other secondary endpoints
- Proportion of patients achieving PASI 100 response at week 24
- Proportion of patients achieving an absolute PASI score ≤ 1 at week 24
- Proportion of patients achieving an absolute PASI score ≤ 3 at week 24
- Change from baseline in BSA of psoriatic involvement at week 24
- Proportion of patients achieving an IGA score of 0 at week 24
- Proportion of patients achieving an ss-IGA score of 0 at week 24[b]
- Change from baseline in DLQI score at week 24
- Change from baseline in the signs and symptoms aggregate scores of the PSSD at week 24
- Change from baseline in the individual scale scores for itch, pain and scaling of PSSD components at week 24
- Change from baseline in the Physical and Mental Component Summary scores of SF-36 at week 24
- Summary of safety and tolerability data using descriptive statistics

BSA, body surface area (size of palm = 1%); DLQI score of 0 or 1, Dermatology Life Quality Index showing almost no effect on patient's quality of life because of skin problems; IGA score of 0, Investigator's Global Assessment score of 0 (clear); PASI 75/90/100 response, $\geq 75\%/\geq 90\%/100\%$ improvement from baseline in Psoriasis Area and Severity Index; PSSD, Psoriasis Symptoms and Signs Diary; ss-IGA score of 0, scalp-specific IGA score of 0 (absence of disease); SF-36v2, Short Form (36) Health Survey version 2. [a]To control the overall type 1 error rate, primary and major secondary endpoints were tested using a fixed sequence method, where the first major secondary endpoint was tested only if the primary endpoint was positive, and the second major secondary endpoint was tested only if the primary secondary endpoint was positive. [b]In randomized patients with scalp psoriasis and an ss-IGA score ≥ 2 at baseline.

rate alpha of 5%. For the efficacy analyses, all randomized patients were analysed according to their group allocation regardless of actual treatment ('intent-to-treat' principle). For the safety analyses, all randomized patients who received at least one dose of study treatment were analysed according to the treatment they actually received.

Baseline data were compared using Fisher's exact tests and two-sample t-tests. For binary endpoints (PASI $\geq 75\%$, $\geq 90\%$, 100% response; absolute PASI score ≤ 1 or ≤ 3; DLQI score 0 or 1; IGA score 0; and ss-IGA score 0) χ^2-tests and Fisher's exact tests were used for comparison. Continuous response parameters (affected BSA, DLQI score, PSSD scores and SF-36v2 scores) were compared using an ANCOVA model. Relative risk, 95% confidence intervals, least square mean differences and P-values were derived from these models.

For binary endpoints, all patients with missing data were considered nonresponders (nonresponder imputation analysis). For continuous endpoints, the last available observation after baseline was carried forward (last observation carried forward analysis). Two sensitivity analyses were conducted: one applying multiple imputation to replace missing values and one analysing only patients who completed 24 weeks in the trial (observed case analysis).

The study was powered to show that guselkumab is superior to FAE as assessed by the proportion of patients achieving a PASI 90 response, a PASI 75 response and a DLQI score of 0 or 1 at week 24. To control the overall type 1 error rate, the primary and major secondary endpoints were tested in a fixed sequence as a priori ordered hypotheses. Based on guselkumab phase II results and unpublished data from the German Pso-Best Registry,[17] a sample size of 57 patients per treatment group was predicted to provide $\geq 90\%$ power to demonstrate superiority of guselkumab over FAE at a 5% significance level (two-sided) for these measures. The respective PASI 90, PASI 75 and DLQI responder rates at week 24 were assumed to be 60%, 80% and 60% for guselkumab and 25%, 45% and 30% for FAE.

Results

Patients

Sixty patients were randomly assigned to receive guselkumab and 59 patients to receive FAE. All randomized patients were included in the efficacy analyses (n = 119). One patient assigned to FAE did not receive any study medication and was
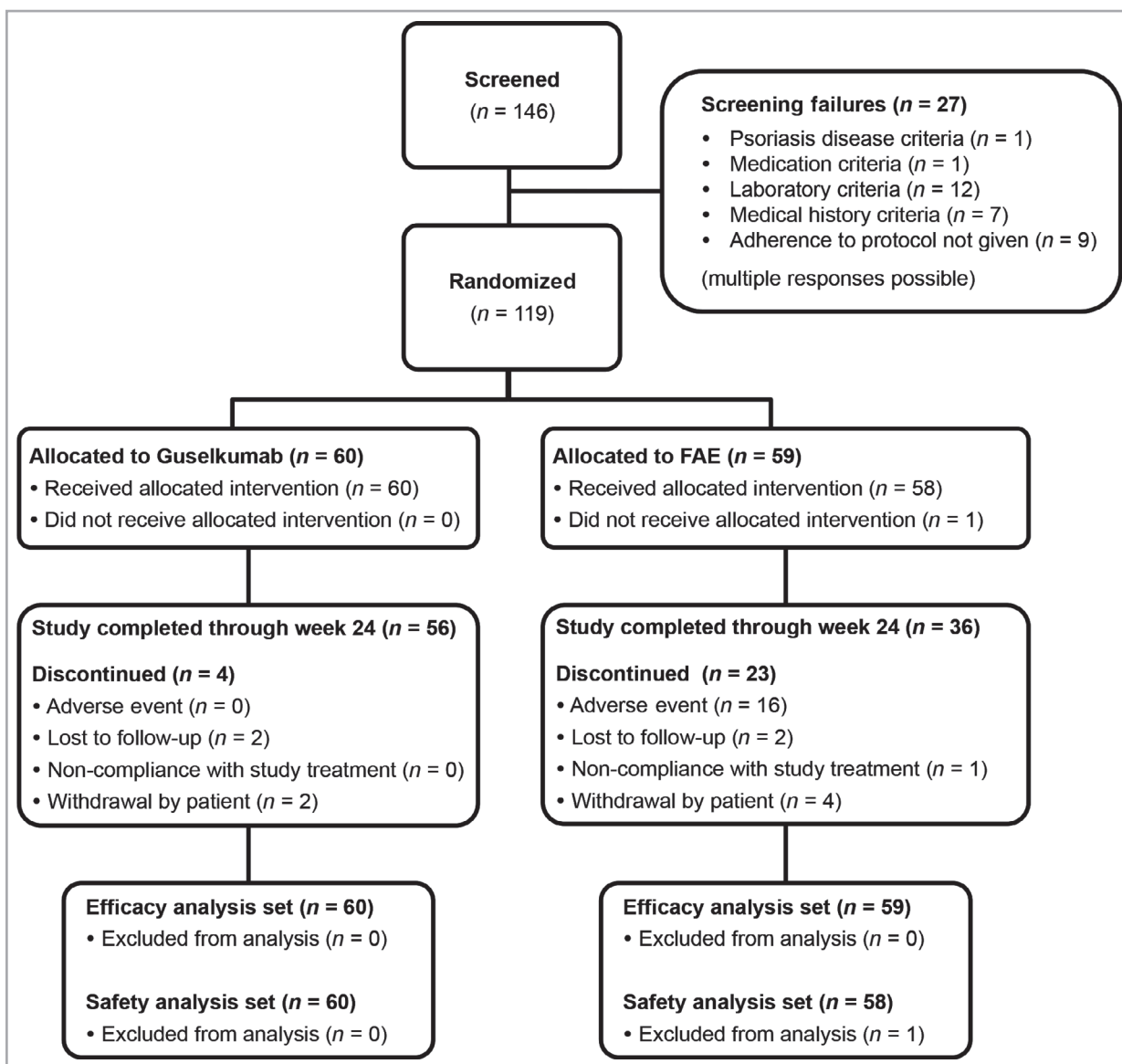
Fig 2. Patient disposition through week 24. FAE, fumaric acid esters.

excluded from the safety analyses (n = 118). Study week 24 was completed by 56 patients receiving guselkumab and by 36 receiving FAE (Fig. 2).

The baseline demographics of the two treatment groups were generally comparable, but patients in the FAE group were older, had slightly more severe disease characteristics and had longer duration of disease (Table 2; Table S2; see Supporting Information). The majority of patients (90%) had scalp involvement with an ss-IGA score ≥ 2 at baseline. Three of the 60 patients (5%) assigned to guselkumab and four of the 59 patients (7%) assigned to FAE had a history of psoriatic arthritis.

Among the 60 patients randomized to guselkumab treatment, 56 (93%) received all four scheduled doses through to week 24. Thirty-six of 59 patients (61%) in the FAE group completed the study treatment through week 24, with a

median final dose of 4·5 tablets per day (Table S1; see Supporting Information).

Efficacy

Guselkumab was superior to FAE with respect to the primary and all major secondary endpoints of the study (Table 3). At week 24, 82% of patients on guselkumab and 14% of patients on FAE achieved a PASI 90 response (P < 0·001). A PASI 75 response was achieved by 90% of guselkumab patients vs. 27% of FAE patients (P < 0·001). A DLQI score of 0 or 1, indicating no impact on quality of life due to skin problems, was achieved by 62% of guselkumab patients vs. 17% of FAE patients (P < 0·001). Superiority of guselkumab was confirmed by different sensitivity analyses and the per protocol endpoint analyses (Table S3; see Supporting Information).

Table 2 Demographics and baseline disease characteristics

Characteristics	Guselkumab	FAE
Randomized patients, n	60	59
Male, n (%)	40 (67)	42 (71)
White, n (%)	57 (95)	57 (97)
Age (years), mean ± SD	39·0 ± 14·0	45·8 ± 13·7
Body mass index (kg m^{-2}), mean ± SD	28·1 ± 5·0	29·6 ± 6·2
Time since first diagnosis (years), mean ± SD	14·8 ± 11·7	17·2 ± 13·9
PASI score, mean ± SD (possible range 0–72)	16·7 ± 6·4	18·3 ± 7·4
IGA score (%), n: clear (0), minimal (1), mild (2), moderate (3), severe (4)	0, 0, 10, 73, 17	0, 2, 12, 71, 15
DLQI score, mean ± SD (possible range 0–30)	17·3 ± 4·4	18·9 ± 5·1
BSA involvement (%), mean ± SD	21·4 ± 10·5	22·3 ± 10·1
ss-IGA score, mean ± SD (possible range 0–4)	2·8 ± 1·0	2·7 ± 0·9
ss-IGA score ≥ 2, n (%)	54 (90)	53 (90)
PSSD (possible range 0–100)		
Sign score, mean ± SD	69·8 ± 15·0	75·7 ± 13·0
Symptom score, mean ± SD	59·6 ± 20·0	65·3 ± 19·7
SF-36v2 (possible range 0–100)		
PCS score, mean ± SD	49·0 ± 7·2	48·8 ± 7·5
MCS score, mean ± SD	44·7 ± 10·3	39·8 ± 12·2
Psoriatic arthritis, n (%)	3 (5)	4 (7)
Previous phototherapy, n (%)	28 (47)	35 (59)
Ultraviolet B, n (%)	16 (27)	28 (47)
Topical PUVA, n (%)	11 (18)	9 (15)
Oral PUVA, n (%)	1 (2)	1 (2)
Other, n (%)	4 (7)	6 (10)

DLQI, Dermatology Life Quality Index; FAE, fumaric acid esters; IGA, Investigator's Global Assessment; MCS, Mental Component Summary; PASI, Psoriasis Area and Severity Index; PCS, Physical Component Summary; PSSD, Psoriasis Symptom and Sign Diary; PUVA, psoralen plus ultraviolet A; SF-36v2, Short Form (36) Health Survey version 2; ss-IGA, scalp-specific IGA.

Higher efficacy of guselkumab than FAE was also observed for PASI 100 response (32% vs. 3%, P < 0·001) and response rates based on achieving an absolute PASI score of ≤ 1 (67% vs. 10%, P < 0·001) or ≤ 3 (90% vs. 24%, P < 0·001). Overall, patients receiving guselkumab achieved higher PASI and DLQI response rates than patients receiving FAE at each assessed point in time throughout 24 weeks of treatment (Fig. 3). In addition, guselkumab demonstrated a faster onset of efficacy, with patients first achieving a PASI 90 response sooner than with FAE (4 weeks vs. 12 weeks).

The mean BSA affected with psoriasis at baseline was 21·4% in the guselkumab group and 22·3% in the FAE group. At week 24, the mean changes in BSA were −18·5% and −9·2%, respectively (P < 0·001). The proportion of patients with an IGA score of 0 (clear) at week 24 was also higher in the guselkumab group than in the FAE group (52% vs. 7%, P < 0·001).

Among patients with scalp involvement and an ss-IGA score ≥ 2 at baseline, the results were favourable for guselkumab vs. FAE, with 48% vs. 13% (P < 0·001) of patients achieving an ss-IGA score of 0 (clear) at week 24 (Table 3). The mean baseline DLQI score was 17·3 for the guselkumab group and 18·9 for the FAE group. At week 24, the mean changes in DLQI score were −15·2 and −9·4, respectively, indicating more improved quality of life related to skin problems for patients treated with guselkumab (P < 0·001).

Changes from baseline in PSSD symptom and sign scores were also higher (i.e. improved) for patients treated with guselkumab than with FAE (symptom score: −52·0 vs. −34·0, P < 0·001; sign score: −59·8 vs. −39·7, P < 0·001). The same pattern was also observed for improvements in the individual scores for itch, pain and scaling (all P < 0·001).

For SF-36v2 assessments, improvement in the Physical Component Summary was more pronounced for the guselkumab group, with a change from baseline of 8·0, compared with the FAE group with a change of 2·3 (P < 0·001). However, no significant difference for change in the SF-36v2 Mental Component Summary was seen at week 24 (P = 0·29).

Safety

Through week 24, the incidence of AEs was lower in the guselkumab group (73% of patients, 147 events) than in the FAE group (98% of patients, 309 events), with 30·6% and 1·4% of events, respectively, classified as moderate and severe for guselkumab vs. 43·7% and 5·5% for FAE. The most commonly reported AEs mapped to MedDRA terms under 'infections and infestations' (50%) in the guselkumab group and 'gastrointestinal disorders' (81%) in the FAE group (Table 4).

AEs leading to dose modification or temporary interruption were documented for 2% of guselkumab patients and 84% of FAE patients. Study medication was permanently stopped due

Table 3 Efficacy results

Response to measures	Guselkumab, n = 60	FAE, n = 59		
Binary endpoints[a]	n (%), 95% CI of %	n (%), 95% CI of %	RR	P-value[a]
PASI 100	19 (32), 19·9–43·4	2 (3), 0·0–8·0	9·34	< 0·001
PASI 90[b]	49 (82), 71·9–91·5	8 (14), 4·8–22·3	6·02	< 0·001
PASI 75[c]	54 (90), 82·4–97·6	16 (27), 15·8–38·5	3·32	< 0·001
PASI ≤ 1	40 (67), 54·7–78·6	6 (10), 2·5–17·9	6·56	< 0·001
PASI ≤ 3	54 (90), 82·4–97·6	14 (24), 12·9–34·6	3·79	< 0·001
DLQI 0/1[c]	37 (62), 49·4–74·0	10 (17), 7·4–26·5	3·64	< 0·001
IGA 0	31 (52), 39·0–64·3	4 (7), 0·4–13·2	7·62	< 0·001
ss-IGA 0[d]	26 (48), 34·8–61·5	7 (13), 4·1–22·3	3·65	0·001 (χ^2), < 0·001 (Fisher)
Continous endpoints, change from baseline[e]	% or score, mean ± SD	% or score, mean ± SD	LSMD	P-value[a]
Physician-reported outcome				
Body surface area (%)	−18·5 ± 10·4	−9·2 ± 11·2	−9·72	< 0·001
Patient-reported outcomes				
DLQI score	−15·2 ± 5·1	−9·4 ± 7·2	−6·86	< 0·001
PSSD sign score	−59·8 ± 18·3	−39·7 ± 26·7	−23·87	< 0·001
PSSD symptom score	−52·0 ± 22·0	−34·0 ± 25·4	−21·93	< 0·001
PSSD itch score	−5·85 ± 2·83	−3·90 ± 2·86	−2·40	< 0·001
PSSD pain score	−5·07 ± 2·86	−2·93 ± 3·12	−2·25	< 0·001
PSSD scaling score	−6·48 ± 2·25	−4·43 ± 3·02	−2·69	< 0·001
SF-36v2 PCS	8·0 ± 6·9	2·3 ± 8·2	5·81	< 0·001
SF-36v2 MCS	5·8 ± 10·6	6·5 ± 9·3	1·70	0·29

DLQI, Dermatology Life Quality Index; FAE, fumaric acid esters; IGA, Investigator's Global Assessment; LSMD, least squares mean difference; MCS, Mental Component Summary; PASI, Psoriasis Area and Severity Index; PCS, Physical Component Summary; PSSD, Psoriasis Symptom and Sign Diary; RR, relative risk; SF-36v2, Short Form (36) Health Survey version 2; ss-IGA, scalp-specific IGA. [a]Nonresponder imputation analyses: χ^2 P-value according to Wald and Fisher's exact test resulted in the same P-values unless indicated otherwise. [b]Primary endpoint. [c]Major secondary endpoints. [d]Among patients with scalp psoriasis and ss-IGA score ≥ 2 at baseline. [e]Last observation carried forward analyses: ANCOVA P-value.

to an AE for 28% of FAE patients and for none of the patients receiving guselkumab. Only one patient receiving guselkumab experienced an injection-site reaction, which was of mild intensity.

Infections occurred in 50% of guselkumab patients and in 45% of FAE patients. Given that the cumulative duration of treatment differed between the guselkumab and FAE groups (1394·0 vs. 1095·7 weeks), the rate of AEs related to infection per patient per treatment-week was calculated. Through week 24, the rate was 0·035 infections per treatment-week in the guselkumab group vs. 0·041 in the FAE group (P = 0·45). The most common infection was nasopharyngitis in both groups (33% vs. 26%). Infections requiring treatment occurred in 13% of guselkumab patients and 7% of FAE patients. No cases of active tuberculosis or serious infection were observed.

Serious AEs were documented in three of 60 guselkumab patients (thymus enlargement, inguinal hernia and hydronephrosis) and in two of 58 FAE patients (sarcoidosis and lipoma). All SAEs were assessed as being not related to study medication. No cases of nonmelanoma skin cancers, other skin cancers, non-skin-related malignancies, major adverse cardiovascular events or deaths were reported through week 24.

Rates of abnormal laboratory results or vital signs were low, except for lymphopenia, which was observed in 26% of FAE patients and no guselkumab patients. Among FAE patients

with lymphopenia, cases were considered severe in 7%, moderate in 53% and mild in 40% of patients.

Discussion

POLARIS is the first randomized controlled trial comparing guselkumab with FAE in patients with moderate-to-severe plaque psoriasis naive to systemic treatment. The comparison of guselkumab with a conventional systemic agent was recommended by the Joint Federal Committee (Gemeinsamer Bundesausschuss) in Germany. FAE were considered appropriate as a comparator, as they are one of the most commonly prescribed first-line systemic therapies for patients with psoriasis in Germany.

The baseline characteristics of the patients indicated a high disease burden, with a mean time since initial diagnosis of 15·9 years, a mean baseline PASI score of 17·4 and a mean baseline DLQI score of 18·1. These characteristics were comparable with those of other randomized controlled trials for plaque psoriasis.[5,18]

Superiority of guselkumab over FAE in achieving a PASI 90 response was demonstrated after 24 weeks, when 82% of guselkumab patients and 14% of FAE patients achieved a PASI 90 response, the new treatment goal specified by European Medicines Agency.[19] Notably, guselkumab demonstrated rapid and clinically meaningful onset of efficacy, with some patients achieving a PASI 90 response as early as 4 weeks, compared
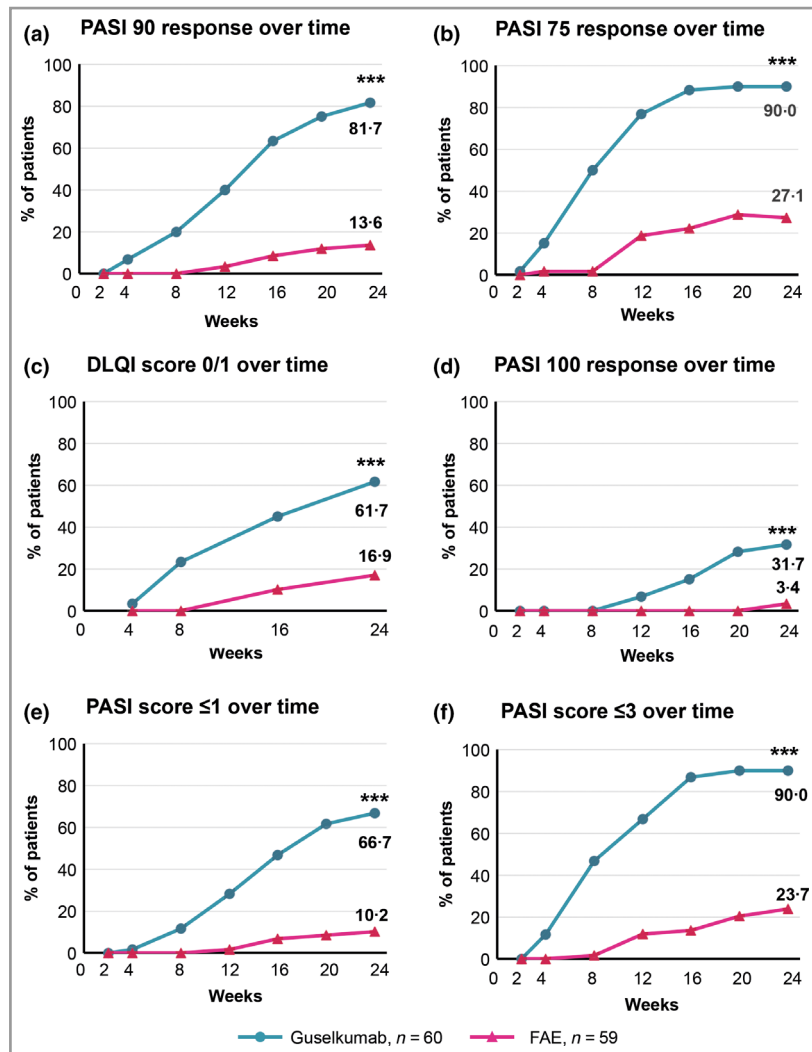
Fig 3. (a, b, d–f) Psoriasis Area and Severity Index (PASI) and (c) Dermatology Life Quality Index (DLQI): treatment responses through week 24. PASI was assessed at weeks 2, 4, 8, 12, 16, 20 and 24. DLQI was assessed at weeks 4, 8, 16 and 24. In nonresponder imputation, patients with missing values were considered nonresponders. FAE, fumaric acid esters mixture. ***$P < 0.001$.

with 12 weeks in the FAE group. These findings are consistent with observations from other studies demonstrating superior efficacy for other biologics (e.g. secukinumab)[18] over FAE.

Despite a wide range of therapeutic options, scalp psoriasis remains difficult to treat. Given the high prevalence of scalp involvement among patients with moderate-to-severe plaque psoriasis, response of scalp disease is an important consideration when starting a first-line systemic therapy for psoriasis. In this study, guselkumab showed significantly higher efficacy than FAE in treating scalp psoriasis.

Significantly better DLQI, PSSD sign and symptom scores, and SF-36v2 physical component ratings were observed, indicating that guselkumab had a substantially greater impact on improving quality of life than FAE.

The superior efficacy of guselkumab likely reflects its specific inhibition of IL-23, and the central role of the IL-23–T helper (Th)17 axis in the pathogenesis of psoriasis.[20–23] FAE

also target Th17 cells, but probably have a broader mechanism of action including Th1 cells and other immune and nonimmune factors.[24–27]

Differences in mechanism of action may also account for the differences in safety observations between guselkumab and FAE. The incidence of AEs through week 24 was lower for the guselkumab group than for the FAE group. In addition, 28% of patients receiving FAE discontinued the study due to an AE, as opposed to none receiving guselkumab. Low rates of discontinuation due to safety for guselkumab were also seen in the VOYAGE 1[8] (2·7% through week 48), VOYAGE 2[9] (2·2% through week 48) and NAVIGATE[10] (2·2% through week 60) studies, indicating that guselkumab is well tolerated. AEs leading to discontinuation for FAE were mostly related to gastrointestinal disorders (13·8%) or lymphopenia (10·3%), as expected based on the known safety and tolerability profile of FAE.[28] There were few serious AEs in either group, none of

Table 4 Key safety events by Medical Dictionary for Regulatory Activities 19·1, primary system organ class and preferred term

	Fuselkumab	FAE
Patients randomized	60 (100)	58 (100)
Patients with at least one AE,[a] number of events	44 (73), 147	57 (98), 309
AEs related to study medication[b]	22 (37)	54 (93)
AEs leading to dose modification	1 (2)	49 (84)
AEs leading to permanent stop of study medication	0	16 (28)
Most common AEs[c]		
Nasopharyngitis	20 (33)	15 (26)
Diarrhoea	5 (8)	34 (59)
Abdominal pain (upper and lower)	1 (27)	24 (41)
Flushing	0	18 (31)
Lymphopenia	0	15 (26)
Severe	0	1 (2)
Moderate	0	8 (14)
Mild	0	6 (10)
Patients with at least one SAE	3 (5)	2 (3)
SAEs related to study medication	0	0
SAEs leading to permanent stop of study medication	0	1 (2)
SAEs leading to death	0	0
Infections	30 (50)	26 (45)
Infections requiring treatment	8 (13)	4 (7)
Serious infections	0	0
Active tuberculosis	0	0
Infections per treatment period		
Weeks 0–24: total treatment duration (weeks)	1394·0	1095·7
Weeks 0–24: rate per patient per week	0·0352	0·0411
Injection-site reactions	1 (2)	NA
Malignancies	0	0
Nonmelanoma skin cancer	0	0
Other skin cancers	0	0
Major adverse cardiovascular events	0	0

The data are presented as n (%). AE, adverse event (starting in treatment phase or worsened after baseline); FAE, fumaric acid esters; NA, not applicable; SAE, serious adverse event. [a]Adverse events include nonserious and serious AEs. [b]Possible, probable or very likely. [c]Multiple responses possible.

which was related to the study medication. No cases of non-melanoma skin cancers, other skin cancers, non-skin-related malignancies, major adverse cardiovascular events or death occurred through week 24.

Guselkumab and FAE both modulate the immune system and may thus increase the risk for infections. Through week 24, the infection AE rate per patient per treatment-week was slightly lower for the guselkumab group than for the FAE group (0·035 vs. 0·041, P = 0·45), with nasopharyngitis being the most common infection in both groups. Overall, no patients receiving FAE and one receiving guselkumab experienced an intertriginous *Candida* infection. The AE of candidiasis for guselkumab was considered moderate in severity and not related to study medication. No cases of serious infections or active tuberculosis were observed.

The incidences of abnormal laboratory values, except for lymphopenia, and abnormal vital signs were generally low and occurred in similar proportions of patients across both groups. Physical examination and evaluation of bodyweight in treated patients revealed no clinically meaningful changes in post-treatment values in either group. Overall, no new or unexpected safety findings were observed for guselkumab.

Through week 24, 7% of patients receiving guselkumab and 39% of patients receiving FAE discontinued the study prematurely. The high discontinuation rate observed for the FAE group is comparable with that in previous FAE studies.[29,30] To account for dropouts and not to endanger the statistical power of the study, sensitivity analyses using different methods for imputing missing data were performed, which confirmed the findings of the primary analysis and the superiority of guselkumab (Table S3; see Supporting Information).

A limitation of this trial is its open-label design. A blinded assessor performed the efficacy assessments to ensure objectivity and to decrease bias. In addition, individualized dosing of FAE was allowed to optimize the benefit-to-risk ratio, while dose optimization for guselkumab was not performed.

The POLARIS study demonstrated superior clinical efficacy, improvement in quality of life, and better safety and tolerability for guselkumab compared with FAE treatment through week 24. The findings for guselkumab were consistent with those from the pivotal trials,[8–10] thus further supporting the conclusions derived from this study. Based on the results of POLARIS, the Joint Federal Committee Germany certified guselkumab as providing a considerable additional benefit for

patients with moderate-to-severe plaque psoriasis naive to systemic treatment.[31]

Acknowledgments

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Appendix

Conflicts of interest. D.T. has received honoraria as an investigator or consultant for and/or received speakers' honoraria and/or research grants from AbbVie, Almirall, Amgen, Boehringer Ingelheim, Celgene, Dignity, Dr Reddy, Galapagos, GSK, Janssen, LEO, Lilly, Morphosis, MSD, Novartis, Pfizer, Regeneron/Sanofi, Sandoz-Hexal and UCB. A.P. has received honoraria as an investigator for, and/or received speakers' honoraria from, and/or received grants from, and/or been an advisor for AbbVie, Almirall-Hermal, Amgen, Biogen Idec, Boehringer Ingelheim, Celgene, GSK, Eli Lilly, Galderma, Hexal, Janssen, LEO Pharma, Medac, Merck Serono, Mitsubishi, MSD, Novartis, Pfizer, Tigercat Pharma, Regeneron, Roche, Sandoz Biopharmaceuticals, Schering-Plough and UCB Pharma. M. Sebastian has received honoraria as an investigator for, received grants from, and been an advisor or consultant for AbbVie, Boehringer Ingelheim, Celgene, Dr Reddy, GSK, MSD, Mundipharma, Novartis, UCB Pharma, Janssen, Almirall, LEO Pharma, Galderma, Lilly and Regeneron. C.T. has received honoraria as an investigator for, and/or received speakers' honoraria and/or grants from, and/or been an advisor for Janssen, Almirall, Allergopharma, AbbVie, LEO and UCB. M. Sticherling has received honoraria as an investigator and/or speaker for, has received grants from, and/or has participated in clinical studies for AbbVie, Actelion, Almirall, Amgen, Celgene, Galderma, GSK, Janssen, LEO, Lilly, MSD, Mundipharma, Novartis, Pfizer, Sandoz, Sanofi and UCB Pharma. S.G. has been an advisor for, and/or received speakers' honoraria from, and/or received grants from, and/or participated in clinical trials for Abbott/AbbVie, Almirall-Hermal, Amgen, Baxalta, Bayer Health Care, Biogen Idec, Bioskin, Boehringer Ingelheim, Celgene, Centocor, Dermira, Eli Lilly, Foamix, Forward Pharma, Galderma, Hexal AG, Isotechnika, Janssen, LEO Pharma, Medac, Merck Serono, Mitsubishi Tanabe, MSD, Novartis, Pfizer, Polichem SA, Regeneron Pharmaceuticals, Sandoz Biopharmaceuticals, Sanofi-Aventis, Schering-Plough, Sienna Biopharmaceuticals, Takeda, Teva, UCB Pharma, VBL Therapeutics and Wyeth Pharma. S.W., S.K., C.R., H.B. and A.M. are employees of Janssen-Cilag GmbH, Germany. K.E. has received honoraria as an investigator for, and/or received speakers' honoraria from, and/or received grants from, and/or been an advisor for Janssen, AbbVie, Celgene, Hexal, LEO, Lilly, Novartis and Sanofi.

Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's website:

Table S1 Uptitration scheme of Fumaderm® initial or Fumaderm® and fumaric acid ester doses throughout the study.

Table S2 Baseline comparison tests.

Table S3 Sensitivity and per protocol analyses of the primary and major secondary endpoints.

Powerpoint S1 Journal Club Slide Set.