Guselkumab (TREMFYA) in Ulcerative Colitis

National Drug Mini-Monograph

February 2025

VA Pharmacy Benefits Management Services and National Formulary Committee

The purpose of VA PBM Services drug monographs is to provide a focused drug review for making formulary decisions. The Product Information or other resources should be consulted for detailed and most current drug information.

Abbreviations: 2L, second-line; AC, active-controlled; ADA, adalimumab; BIO, biologic; CO, crossover; DB, double-blind; DD, double-dummy / placebo; GOL, golimumab; GRADE, Grading of Recommendations, Assessment, Development, and Evaluation; IFX, infliximab; IMM, immunomodulator; INT, intolerance; IR, inadequate response; LOR, loss of response; MC, multicenter; MIA, medical inadvisability; MN, multinational; PC, placebo-controlled; PNR, primary nonresponse; Q, GRADE quality of evidence; RCT, randomized clinical trial; S1PRM, sphingosine 1-phosphate receptor modulator; SNR, secondary nonresponse; UST, ustekinumab; VEDO, vedolizumab

FDA APPROVAL INFORMATION	
Description / MOA	Human monoclonal IgG1λ antibody that selectively binds to the interleukin 23 (IL-23) p19 subunit
Indication Under Review[1]	Treatment of adults with moderately to severely active ulcerative colitis (UC)
Dosage Regimen	Induction: 200 mg IV infusion over at least one hour at Weeks 0, 4, and 8 Maintenance: Either 100 mg SC at Week 16 then every 8 weeks, or 200 mg SC at Week 12 then every 4 weeks
Dosage Forms Under Review	IV Infusion: 200 mg/20 mL (10 mg/mL) solution in a single-dose vial SC Injection: 100 mg/mL in a single-dose One-Press patient-controlled injector or single-dose prefilled syringe, and 200 mg/2 mL in a single-dose prefilled pen or single-dose prefilled syringe

EFFICACY CONSIDERATIONS	
Active-controlled Trial	**Guselkumab plus golimumab combination therapy versus guselkumab or golimumab monotherapy in patients with ulcerative colitis (VEGA): a randomised, double-blind, controlled, phase 2, proof-of-concept trial[2]**
Design	Phase 2 MN DB DD active-controlled, proof-of-concept RCT *Primary endpoint*: Week-12 clinical response, defined as ≥ 30% decrease from baseline in full Mayo score and ≥ 3-point absolute reduction with either a decrease of ≥ 1 point in rectal bleeding score (RBS) or RBS of 0 or 1. *Major secondary endpoint*: Week-12 clinical remission, defined as a full Mayo score of ≤ 2 with no subscore > 1.
Population	Adults aged ≥ 18 to 65 years, moderately to severely active UC (Mayo score 6–12) with centrally-read endoscopy subscore of ≥ 2. Inadequate response or intolerance to oral or IV corticosteroids or immunosuppressants. No prior TNFi, IL-12/23i, or IL-23p19i. Prior vedolizumab or tofacitinib was allowed. *Allowed Co-medications*: Stable doses of oral aminosalicylates and corticosteroids (prednisone or equivalent ≤ 20 mg/d). 54% (116/214) men; mean age 38.4 years; 97% White.
Interventions	*Combination Induction Therapy Followed by Monotherapy (CMBN)*: Golimumab (GOL) 200 mg SC at Week 0, 100 mg SC at Weeks 2, 6, and 10 plus guselkumab (GUS) 200 mg IV at Weeks 0, 4, and 8, then guselkumab monotherapy 100 mg SC every 8 weeks for 32 weeks *GOL Monotherapy*: 200 mg SC at Week 0 then 100 mg at Week 2 then every 4 weeks for 34 weeks *GUS Monotherapy*: 200 mg IV at Weeks 0, 4, and 8, then 100 mg SC every 8 weeks for 32 weeks

Results

Efficacy and Safety Results

Outcome	Time Point (Wks)	CMBN N = 71	GOL N = 72	GUS N = 71	Diff, CMBN–GOL (80% CI)	Diff, CMBN–GUS (80% CI)	Calc Diff, GUS–GOL (95% CI)	Q
CR, n (%)	12	26 (37)	16 (22)	15 (21)	14.5 (4.9, 24.0)*	15.5 (6.0, 25.0)**	13.5 (–1.6, 28.7)	L[α]
CR, n (%)	38	31 (44)	16 (22)	22 (31)	21.5 (11.9, 31.2)	12.7 (2.7, 22.7)	8.7 (–5.7, 23.2)	L[α]
HR + EN, n (%)	38	17 (24)	4 (6)	9 (13)	18.5 (11.3, 25.6)	11.3 (3.3, 19.2)	7.1 (–2.3, 16.5)	M[β]
Infections†	50	10 (14)	16 (22)	10 (14)	–8	0	–8	
SAE, n (%)†	50	4 (6)	4 (6)	4 (6)	0	0	0	
DAE, n (%)	50	7 (10)	4 (6)	1 (1)	4	9	–5	
≥ 1 AE, n (%)†	50	45 (63)	55 (76)	46 (65)	–13	–2	–11	

CR, clinical remission; EN, endoscopic normalization; HR, histologic remission

* Nominal p = 0.0578; ** Nominal p = 0.0412

† Opportunistic infections occurred in 2 CMBN patients (3%) and serious infections occurred in 2 patients (3%) in each treatment group. Colon adenocarcinoma was reported in 1 GUS patient. Most common AEs were UC, upper respiratory tract infection, headache, anemia, nasopharyngitis, neutropenia, and pyrexia. After the final dose of study drug, 2 patients died (1 on CMBN and 1 on GUS).

[α] Downgraded for indirectness (clinical remission is a surrogate for clinical remission with endoscopic and histologic remission), and imprecision (use of 80% CI; wide margins; optimal information size not met)

[β] Downgraded for imprecision (use of 80% CI; wide margins; optimal information size not met)

Onset of Effect, Symptomatic Remission: Apparent numerical differences (CMBN > GOL > GUS) observed as early as 2 weeks

Duration of Adequate Therapeutic Trial, Symptomatic Remission: 12 weeks

Authors' Conclusions

Results suggest that CMBN therapy may be more effective than either GOL or GUS monotherapy. Larger RCTs are needed to confirm the results.

Published RCT

Guselkumab in Patients With Moderately to Severely Active Ulcerative Colitis: QUASAR Phase 2b Induction Study[3] (aka UC3)

Design

MN DB PC Dose-controlled Induction RCT; part of QUASAR series of RCTs (phase 2b induction, phase 3 induction, and phase 3 randomized withdrawal maintenance)

Primary analysis excluded patients with modified Mayo score (mMS) of 4.

Primary Efficacy Endpoint: Week-12 clinical response

Population

Adults ≥ 18 years, moderately to severely active UC for ≥ 3 months, Mayo rectal bleeding score (RBS) ≥ 1 and Mayo endoscopy subscore (ES) ≥ 2; inadequate response and/or intolerance to corticosteroids, immunosuppressants, and/or advanced therapy, including ≥ 1 TNFi, integrin-receptor antagonist (vedolizumab), and/or JAKi (tofacitinib). No prior IL-12i and/or IL-23i.

Excluded UC limited to the rectum only or to < 30 cm of colon, extensive colonic resection, presence of stoma.

Interventions

At Weeks 0, 4, and 8:

- Guselkumab 200 mg IV
- Guselkumab 400 mg IV
- Placebo

Allowed Co-medications: Stable doses of immunosuppressants, oral 5-aminosalicylic acid (5ASA), and corticosteroids (prednisone or equivalent ≤ 20 mg/d).

Results

Efficacy Results

Outcome	Time Point (Wks)	PBO N = 105	GUS200 N = 101	GUS400 N = 107	Diff, GUS200–PBO (95% CI)	Diff, GUS400–PBO (95% CI)	Q
CR, n (%)	12	10 (10)	26 (26)	27 (25)	16.3 (6.3, 26.3)	15.7 (6.0, 25.4)	L[α]
EN, n (%)	12	7 (7)	18 (18)	15 (14)	11.3 (2.6, 20.0)	7.3 (–0.5, 15.2)	L[α]

[α] Downgraded for indirectness (endpoint is a surrogate for clinical remission with endoscopic and histologic remission), and imprecision (use of 80% CI; wide margins; optimal information size not met)

Onset of Effect, Symptomatic Response: Week 4

Authors' Conclusions

GUS 200 mg and 400 mg are superior to placebo at Week 12. Both doses were comparable in efficacy and safety. Phase 3 RCTs are needed.

Unpublished RCTs

UC1 and UC2 ((QUASAR)[1,4,5]

Design

UC1: 12-week induction RCT (3:2). *Primary Endpoint*: Week-12 mMS clinical remission.

UC2: 44-week rerandomized maintenance RCT

Population

UC1: Moderately to severely active UC (mMS 5–9 and endoscopic score of 2 or 3). Inadequate response, loss of response, or intolerance to corticosteroids, immunomodulators, biologic (TNFi, vedolizumab) and/or JAKis.

UC2: Achieved mMS clinical response after Week 12 following IV induction in the UC1 or UC3 RCT

Intervention and Comparator

UC1: GUS 200 mg IV at Weeks 0, 4, and 8 vs PBO.

Allowed Co-medications: Stable doses of oral 5ASAs, immunomodulators, and/or oral corticosteroids (prednisone or equivalent ≤ 20 mg/d).

UC2: GUS 100 mg SC every 8 weeks or GUS 200 mg every 4 weeks vs PBO

Results

Clinical Remission at Week 12

Population	PBO	GUS 200 mg IV at Wks 0, 4, 8	RR (95% CI)	AAE, (95% CI)	Q
Total, n (%)	22/280 (8)	97/421 (23)	2.9 (1.89, 4.54)	150 (100, 200)	ID
Prior BIO and/or JAKi failure, n (%)	5/136 (4)	27/208 (13)	3.5 (1.39, 8.94)	90 (40, 150)	
No prior BIO or JAKi failure, n (%)	17/144 (12)	68/213 (32)	2.7 (1.66, 4.40)	200 (120, 280)	

Maintenance of Clinical Remission at Week 44 in Week-12 Clinical-Remission Achievers

Population	PBO	GUS 100 mg SC Q8W	GUS 200 mg SC Q4W	RR (95% CI), GUS100/PBO	RR (95% CI), GUS200/PBO	RR (95% CI), GUS200Q4 / GUS 100Q8	AAE (95% CI), GUS100Q8–PBO	AAE (95% CI), GUS200Q4–PBO	ARD (95% CI), GUS200–GUS100	Q
Total, n (%)	20/59 (34)	40/66 (61)	50/69 (72)	1.8 (1.19, 2.68)	2.1 (1.45, 3.14)		26 (9, 43)	38 (23, 54)		ID
Prior BIO and/or JAKi failure, n (%)	4/15 (27)	12/20 (60)	10/18 (56)	2.2 (0.90, 5.60)	2.1 (0.82, 5.31)		33 (2, 64)	29 (–3, 61)		
No prior BIO or JAKi failure, n (%)	16/44 (36)	28/46 (61)	40/51 (78)	1.7 (1.06, 2.64)	2.2 (1.42, 3.27)		24 (4, 44)	42 (24, 60)		

AAE, anticipated absolute effect per 1000; ID, inadequate data; RR, relative risk

* Calculated

[α] Downgraded for indirectness (endpoint is a surrogate for clinical remission with endoscopic and histologic remission), and imprecision (use of 80% CI; wide margins; optimal information size not met)

Authors' Conclusions

Not available. Data from prescribing information.

SAFETY CONSIDERATIONS

Overall

The safety profile of GUS in UC was consistent with those seen for its other approved indications (plaque psoriasis and psoriatic arthritis).

THERAPEUTIC OPTIONS FOR UC

DRUG	VANF	CFU / Other Clinical Guidance	RCT Place in Therapy	FDA Place in Therapy	2020 AGA Guideline Place in Therapy (2020)[6]	2019 ACG Guideline Place in Therapy (2019)[7]
IL-23is						
Guselkumab	NonF	TBD	**As early as 2L** IR or INT to CS IMM and/or advanced tx, which could include PNR, SNR / LOR, or INT to ≥1 TNFi, VEDO, and/or JAKi (TOFA) VEGA: GUS + GOL vs GUS vs GOL	No prerequisite therapy specified	Not mentioned; FDA-approved for UC in 9/2024	
Risankizumab-rzaa	NonF	TBD	**As early as 2L** IR or INT to 5ASA CS IMM BIO JAKi and/or S1P. 52% failed ≥1 BIO, JAKi, or S1P.	No prerequisite therapy specified	Not mentioned; FDA-approved for UC in 6/2024	
Mirikizumab-mrkz	NonF	**Either**: TNFI MIA and vedolizumab MIA, INT, or IR Or after IFX / TNFI **And ALL of**: JAKi + S1P + UST	**As early as 2L** IR LOR or INT to ≥1 of: CS IMM BIO JAKi	No prerequisite therapy specified	Not mentioned; FDA-approved in 2023	
S1PRMs						
Etrasimod	TBD	TBD	**As early as 2L** IR, LOR, or INT to ≥1 of conventional txs (oral 5ASA, CS, or TP), TNFi; ITGi / VEDO, UST, or JAKi (TOFA)	No prior treatments specified	Not mentioned (FDA-approved in 2023)	
Ozanimod	NonF	None / 3L*	**As early as 2L** IR to 5ASA and/or CS; ± prior TNFi	No prior treatments specified	Not mentioned (FDA-approved in 2021)	
TNFis						
Infliximab / Biosimilar	PA-F,* -abda biosimilar is the preferred infliximab product	—	**As early as 2L** IR to CS or CS + IMM (AZP or 6MP) [ACT 1] or IR to CS or CS + IMM + 5ASA [ACT 2]	IR to conventional therapy Also for mucosal healing and eliminating GC use	*Induction, Biologic-naïve*: Suggested over adalimumab	*Induction*: Recommended (in combination with a thiopurine) *Maintenance*: Recommended
Golimumab	NonF	—	**As early as 2L** IR or INT to ≥1 of conventional txs (oral 5ASAs, oral CS, AZP, and/or 6MP) or were CS dependent.	GC dependence and an IR or INT to oral 5ASAs, oral GCs, AZP, or 6MP	*Induction*: Recommended over no treatment; no active-comparator recommendations.	*Induction*: Recommended *Maintenance*: Recommended
Adalimumab / Biosimilar	PA-F,* -hwwd biosimilar is the	—	**As early as 2L**	No prerequisite therapy specified	*Induction, Biologic-naïve*: Alternative to infliximab (e.g.,	*Induction*: Recommended

DRUG	VANF	CFU / Other Clinical Guidance	RCT Place in Therapy	FDA Place in Therapy	2020 AGA Guideline Place in Therapy (2020)[6]	2019 ACG Guideline Place in Therapy (2019)[7]
	preferred adalimumab product		IR to CS and/or IMM (AZP or 6MP) IR to CS and/or IMM; included TNFi-exposed		hypersensitivity) or vedolizumab	*Maintenance*: Recommended
Intregrin Receptor Antagonist						
Vedolizumab inj for IV use	PA-F	After TNFi or infliximab / BSM therapy	**As early as 2L** IR or INT to ≥1 CS, IMM, or TNFi PNR, LOR, or INT to TNFi; previous TNFi use DC'd b/o reasons other than safety; or TNFi-naïve but failing current tx (e.g., CS, 5ASA, or IMM)	No prerequisite therapy specified	*Induction, Biologic-naïve*: Suggested over adalimumab	*Induction*: Recommended including in patients who previously failed TNFi therapy *Maintenance*: Recommended
Vedolizumab inj for SC use	PA-F	Clinical response after Wk 6 following IV induction doses at Wks 0 and 2 or is receiving IV doses to maintain clinical remission		*Maintenance*: May start SC injections Q2W at Wk 6 after IV induction doses at Wks 0 and 2 or switch to SC injections Q2W in place of next scheduled Q8W maintenance IV infusion	FDA-approved in 2023	
IL-12/23i						
Ustekinumab / Biosimilar	NonF	TNFI MIA and vedolizumab MIA, INT, or IR Or after TNFI	**2L** IR or INT to TNFi, VEDO, or conventional (i.e., nonBIO) tx	No prerequisite therapy specified	*Induction, Infliximab-exposed (particularly for PNR)*: Suggested over vedolizumab or adalimumab	Not mentioned; FDA-approved in 2019
JAKis						
Tofacitinib	NonF	TNFI MIA and vedolizumab MIA, INT, or IR Or after TNFI	**As early as 2L** Failure or INT to ≥1 of: CS IMM IFX or ADA	IR or INT to ≥ 1 TNFi	*Biologic-naïve*: Use in clinical or registry study; no recommendation‡ *Induction, Infliximab-exposed (particularly for PNR)*: Suggested over vedolizumab or adalimumab	*Induction*: Recommended at dosage of 10 mg orally twice daily for 8 wks, including in patients who previously failed TNFi therapy *Maintenance*: Recommended
Upadacitinib	NonF	Same as for tofacitinib	**As early as 2L** IR, LOR, or INT to ≥1 5ASA CS IMM or BIO (IFX, ADA, GOL, VEDO, or UST)	IR or INT to ≥ 1 TNFi	Not mentioned; FDA-approved in 2022	

POTENTIAL PLACE IN THERAPY	
Proposed Place in Therapy in VHA	1. Guselkumab is the first IL-23i to be evaluated in combination with a TNFi (golimumab) and compared with a TNFi as monotherapy. The results from this early-phase RCT suggest that induction with a combination of guselkumab and golimumab followed by guselkumab monotherapy maintenance therapy is better than either agent alone in achieving clinical remission (low-quality evidence; small–moderate effects) and in achieving a composite of histologic remission and endoscopic normalization (moderate-quality evidence; small–moderate effects). Guselkumab was comparable to golimumab. Larger RCTs are needed to confirm these results. Additional trials are needed to evaluate combination therapy using other TNFis such as infliximab and adalimumab. 2. Use of combination guselkumab plus a TNFi may be considered on a case-by-case basis. Golimumab is currently the costliest TNFi. The safety and efficacy of using other TNFis in combination with guselkumab have not been evaluated in UC. 3. There are no RCTs comparing the IL-23is approved for UC with each other. 4. Guselkumab monotherapy may be used for the induction and maintenance therapy of moderately to severely active UC in patients who have had medical inadvisability, inadequate response, intolerance, or loss of response to a TNFi, and two of the following (one of which should be risankizumab): vedolizumab, tofacitinib, upadacitinib, etrasimod, ozanimod, or risankizumab.

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