USZ Universitäts Spital Zürich

New therapies in IBD

Gerhard Rogler, Department of Gastroenterology and Hepatology

UniversitätsSpital Zürich

Dislcosures

Consulting to Abbvie, Arena, Astra Zeneca, Augurix, BMS, Boehringer, Calypso, Celgene, Eli Lilly, FALK, Ferring, Fisher, Genentech, Gilead, Janssen, MSD, Novartis, Pfizer, Phadia, Pierre Fabre, Roche, UCB, Takeda, Tillots, Vifor, Vital Solutions and Zeller;

Speaker's honoraria from Abbvie, Astra Zeneca, BMS, Eli Lilly, FALK, Janssen, MSD, Pfizer, Phadia, Pierre Fabre, Takeda, Tillots, UCB, Vifor and Zeller;

Educational grants and research grants from Abbvie, Ardeypharm, Augurix, Calypso, FALK, Flamentera, MSD, Novartis, Pfizer, Roche, Takeda, Tillots, UCB and Zeller.

Founder und Head of Scientific Advisory Board: PharmaBiome


Very high rates of *M tuberculosis infection*
• An important consideration in diagnosing IBD in SSA
• Differentiating Intestinal tuberculosis from Crohn's disease is challenging
• Many overlapping clinical, endoscopic, radiographic, histological features
• A definitive diagnosis of ITB requires one of the following on tissue biopsy:
➢Caseating granulomas
➢Presence of acid-fast bacilli
➢Positive tissue GeneXpert MTB rifampicin (RIF) assay/TB PCR
➢A positive TB culture
• These findings are present in fewer than 30% of cases of ITB
©ECCO'23 Congress - Speaker: Gil Watermeyer, South Africa
Gillian Watermeyer
Very high rates of *M tuberculosis infection*
• An important consideration in diagnosing IBD in SSA
• Differentiating Intestinal tuberculosis from Crohn's disease is challenging
• Many overlapping clinical, endoscopic, radiographic, histological features
• A definitive diagnosis of ITB requires one of the following on tissue biopsy:
➢Caseating granulomas
➢Presence of acid-fast bacilli
➢Positive tissue GeneXpert MTB rifampicin (RIF) assay/TB PCR
➢A positive TB culture
• These findings are present in fewer than 30% of cases of ITB

Parasitic Colitis

oni, and S stercoralis
ymptoms that closely resemble IBD

ent bouts of diarrhoea (often bloody)
loss of appetite and loss of weight

rarity of IBD
cases are mistakenly labelled as infectious entero-colitis

patients to receive multiple courses of metronidazole
rther work up

neyer, South Africa

Gill Watermeyer

Parasitic Colitis

E histolytica, S mansoni, and S stercoralis
Can all present with symptoms that closely resemble IBD

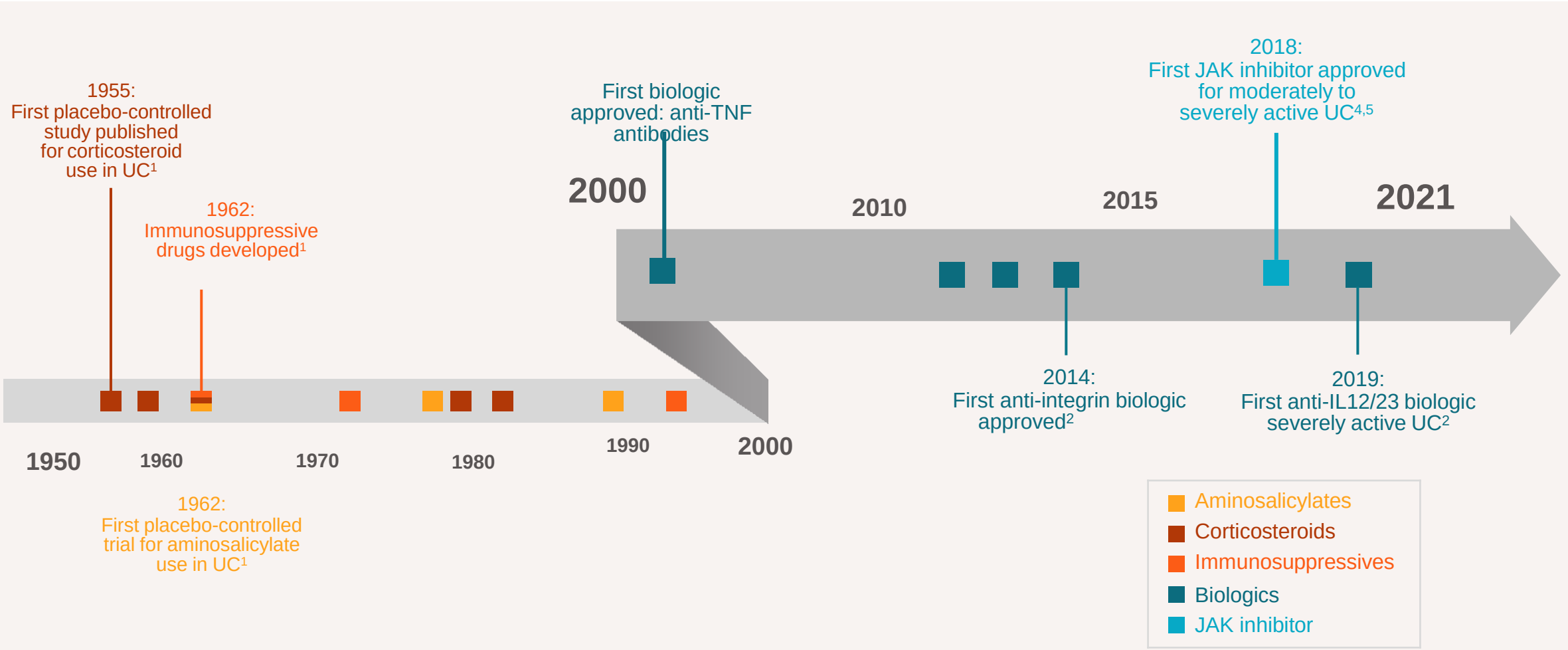
- Chronic or intermittent bouts of diarrhoea (often bloody)
- Abdominal cramps, loss of appetite and loss of weight
- Anaemia

- Given the perceived rarity of IBD
- It is likely that many cases are mistakenly labelled as infectious entero-colitis

- Common practice for patients to receive multiple courses of metronidazole
- Before referral for further work up

©ECCO'23 Congress - Speaker: Gill Watermeyer, South Africa

IBD treatment options are evolving[1,2]



1. Mudireddy PR et al. In: Lichtenstein GR, ed. Medical Therapy of Ulcerative Colitis. Springer; 2014:1-14. **2.** D'Amico F et al. Exp Opin Drug Saf. 2020;19:807-816. Long-term safety of approved biologics for ulcerative colitis **3.** Remicade [package insert]. Horsham PA: Janssen Biotech, Inc; 2013. **4.** Fernández-Clotet A et al. Curr Pharm Des. 2019;25:32-40. JAK Inhibition: The Most Promising Agents in the IBD Pipeline?. **5.** Xeljanz [package insert]. New York, NY: Pfizer Inc; 2018. Inc; 2020.

S1P binding to the $S1P_1$ receptor on the lymphocyte surface regulates egress of most lymphocytes from lymphoid tissues[1,2]

1 Lymphocytes migrate into the lymphoid tissues[1,2,b]

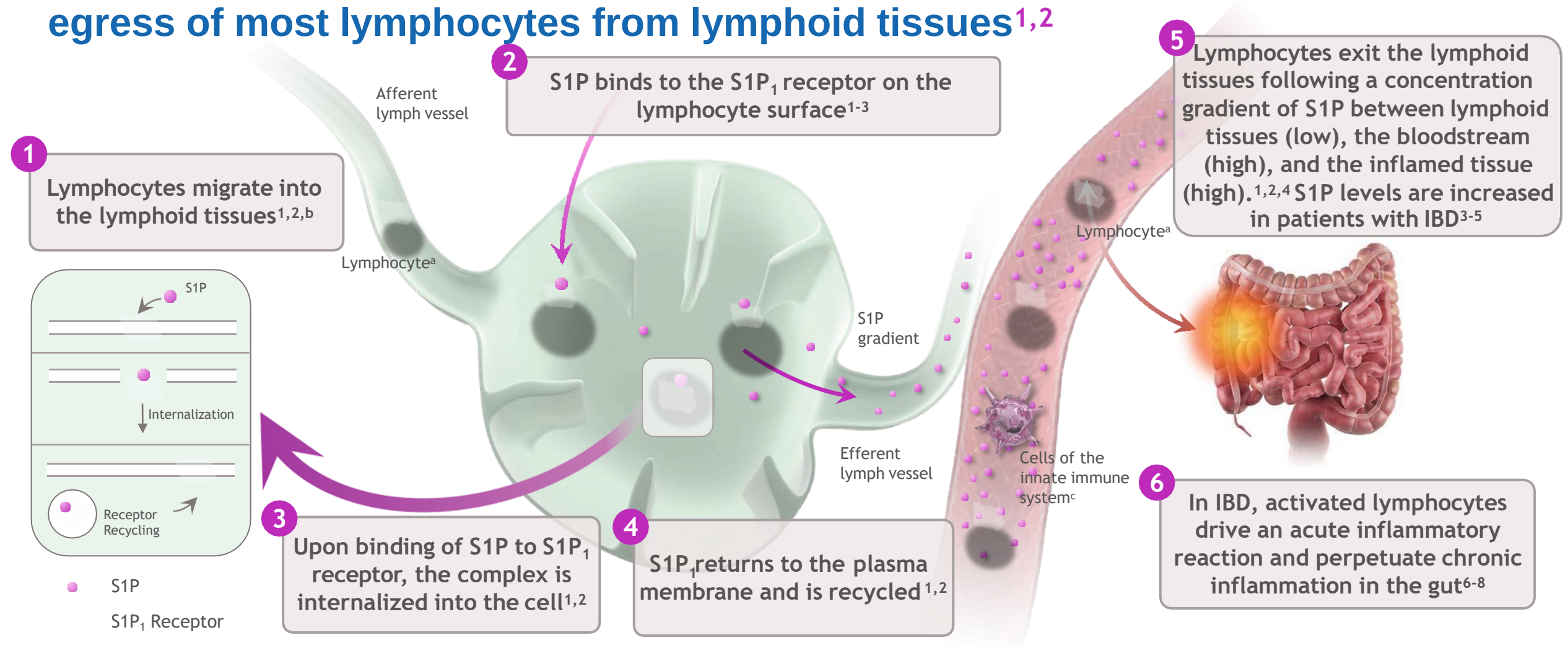
2 S1P binds to the $S1P_1$ receptor on the lymphocyte surface[1-3]

3 Upon binding of S1P to $S1P_1$ receptor, the complex is internalized into the cell[1,2]

4 $S1P_1$ returns to the plasma membrane and is recycled[1,2]

5 Lymphocytes exit the lymphoid tissues following a concentration gradient of S1P between lymphoid tissues (low), the bloodstream (high), and the inflamed tissue (high).[1,2,4] S1P levels are increased in patients with IBD[3-5]

6 In IBD, activated lymphocytes drive an acute inflammatory reaction and perpetuate chronic inflammation in the gut[6-8]

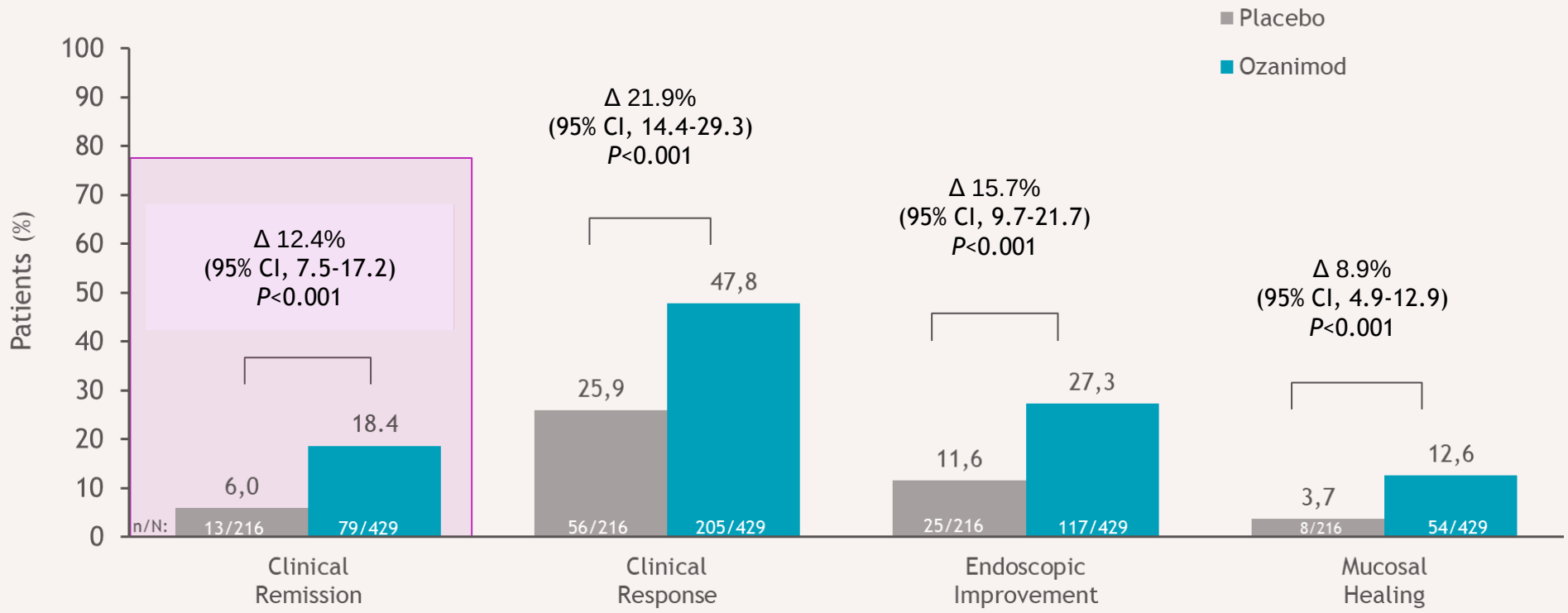


[a]Including T cells and B cells. [b]Controlled by various signals e.g. chemokine receptor 7. [c]Innate immune cells, include macrophages, monocytes, and natural killer cells, among others. IBD, inflammatory bowel disease; S1P, sphingosine 1-phosphate; $S1P_1$, sphingosine 1-phosphate receptor subtype 1.

1. Aoki M et al. *Mediators Inflamm.* 2016;2016:8606878. Sphingosine-1-Phosphate Signaling in Immune Cells and Inflammation: Roles and Therapeutic Potential. 2. Schwab SR, Cyster JG et al. *Nature Immunol.* 2007;8(12):1295-1301. Finding a way out: lymphocyte egress from lymphoid organs. 3. Karuppuchamy T et al. *Mucosal Immunol* 2017;10:162-171. Sphingosine-1-phosphate receptor-1 (S1P 1) is expressed by lymphocytes, dendritic cells, and endothelium and modulated during inflammatory bowel disease. 4. Danese S et al. *J Crohns Colitis.* 2018;12(2):S678-S686. Targeting S1P in Inflammatory Bowel Disease: New Avenues for Modulating Intestinal Leukocyte Migration. 5. Suh JH, Saba JD. *Transl Cancer Res.* 2015;4:469-83. Sphingosine-1-phosphate in inflammatory bowel disease and colitis-associated colon cancer: the fat's in the fire. 6. Neurath MF. *Nat Rev Immunol.* 2014;14:329-42. Cytokines in inflammatory bowel disease. 7. Guan Q. *J Immunol Res.* 2019;2019: 7247238. A Comprehensive Review and Update on the Pathogenesis of Inflammatory Bowel Disease 8. Souza HSP, Fiocci C. *Nat Rev Gastroenterol Hepatol.* 2016;13:13–27. Immunopathogenesis of IBD: current state of the art.

USZ Universitäts Spital Zürich

True North results: efficacy — induction period



Endpoint	Definition
Clinical Remission	3-component Mayo score: RBS=0, SFS=0-1 (+ decrease ≥1 point), MES=0-1
Clinical Response	Decrease in 9-point Mayo score of ≥2 points and ≥35%, and a decrease in RBS of ≥1 or an absolute RBS=0 or 1
Endoscopic Improvement	MES ≤ 1
Histologic Remission	Geboes score < 2 (no eosinophils, no neutrophils in lamina propria, no neutrophils in the epithelium, no erosion, no ulceration)

Reproduced with permission from *N Engl J Med*.

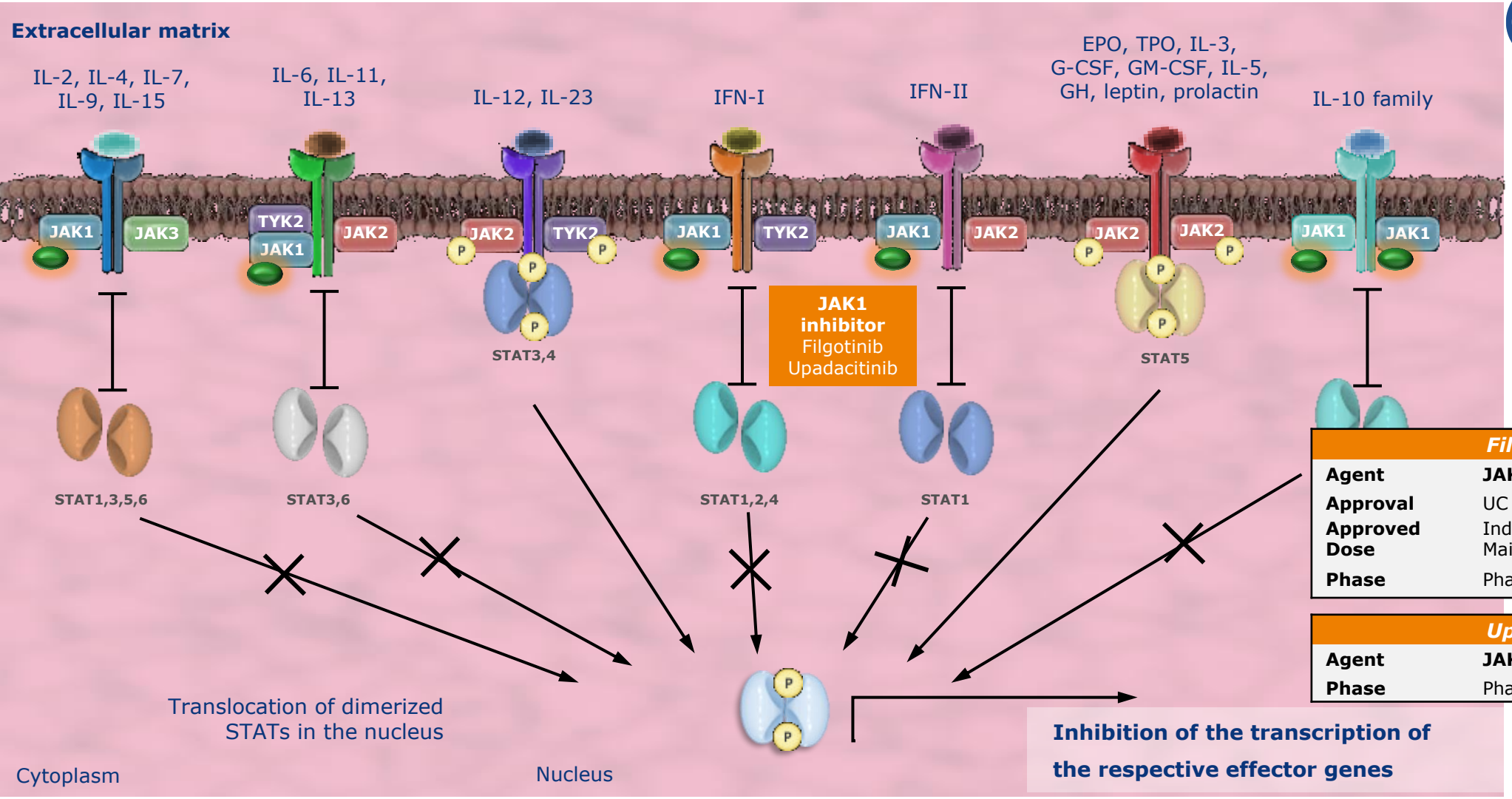
Purple box indicates primary endpoint.

Sandborn WJ et al. *N Engl J Med*. 2021;385:1280-1291. Ozanimod as Induction and Maintenance Therapy for Ulcerative Colitis.

Personal Opinion:

- S1P1 agonists are mainly effective in UC
- Potency comparable to adalimumab or ustekinumab
- Problem: You need an ECG and an opthalmology exam before starting the drug

JAK/STAT inhibitors in IBD



Reduced tanscription of pro-inflammatory mediators

Filgotinib (Galapagos)	
Agent	**JAK1 inhibitor**, *small molecule*
Approval	UC
Approved Dose	Induction: oral (200 mg/day) Maintenance: oral (200 mg/day)
Phase	Phase 3: oral (CD)

Upadacitinib (AbbVie)	
Agent	**JAK1 inhibitor**, *small molecule*
Phase	Phase 3: oral (CD, UC)

USZ Universitäts Spital Zürich

Vetter M. & Neurath MF. Therap Adv Gastroenterol 2017;10:773-790.
Seif F. et al. Cell Commun Signal 2017;15:23.
Danese S. et al. Gut. 2019 Oct;68(10):1893-1899.

PRAC Warning EMA, Nov 11th 2022

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

11 November 2022
EMA/860610/2022

EMA confirms measures to minimise risk of serious side effects with Janus kinase inhibitors for chronic inflammatory disorders

EMA's human medicines committee (CHMP) has endorsed the measures recommended by the **Pharmacovigilance Risk Assessment Committee** (PRAC) to minimise the risk of serious side effects with Janus kinase (JAK) inhibitors used to treat several chronic inflammatory disorders. These side effects include cardiovascular conditions, blood clots, cancer and serious infections.

These medicines should be used in the following patients **only if no suitable treatment alternatives** are available: **those aged 65 years or above, those at increased risk of major cardiovascular problems (such as heart attack or stroke), those who smoke or have done so for a long time in the past and those at increased risk of cancer.**

JAK inhibitors should be used with caution in patients with risk factors for blood clots in the lungs and in deep veins (venous thromboembolism, VTE) other than those listed above. Further, the doses should be reduced in patient groups who are at risk of VTE, cancer or major cardiovascular problems, where possible.

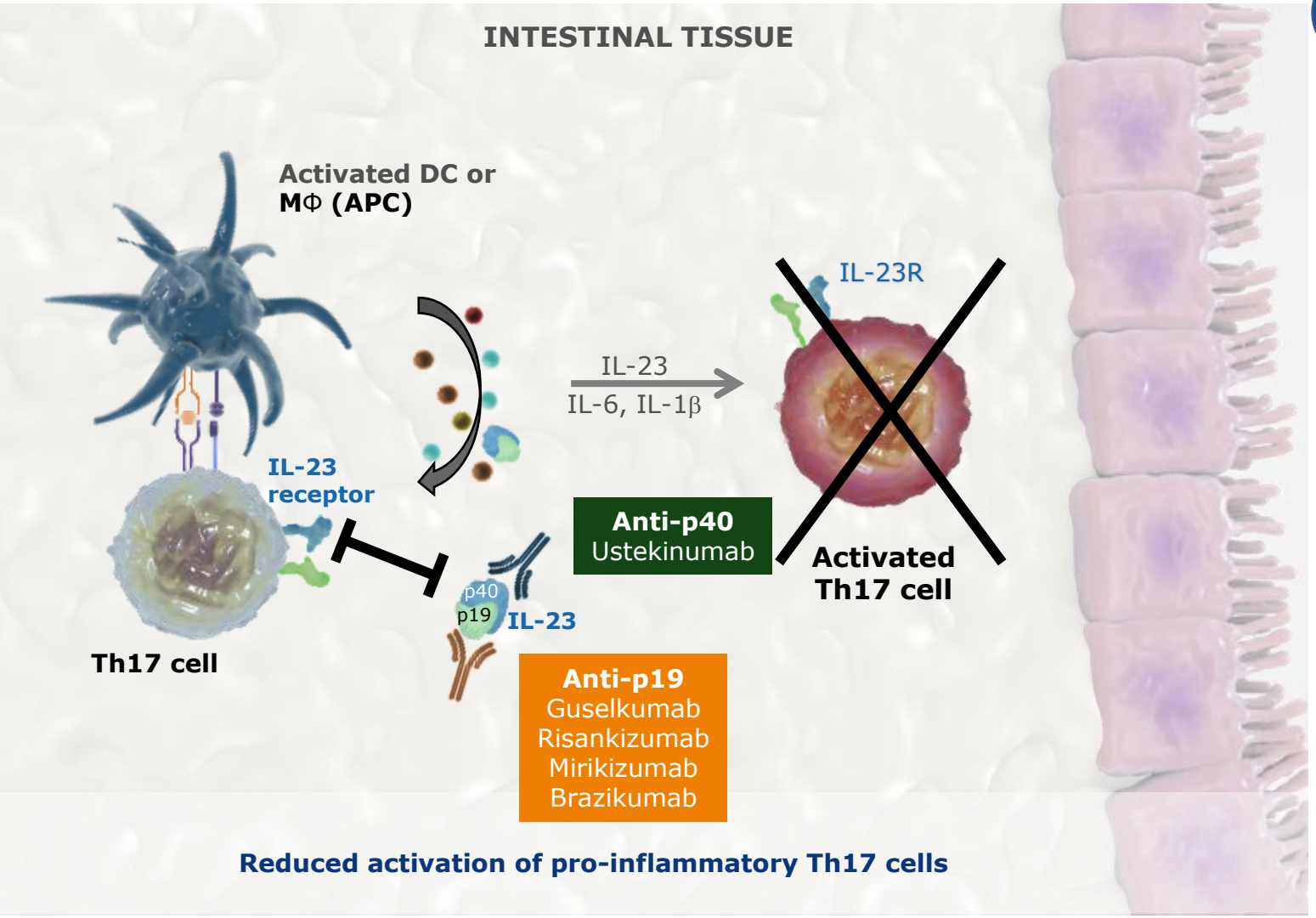
USZ Universitäts Spital Zürich

Ytterberg SR, et al. Cardiovascular and cancer risk with tofacitinib in rheumatoid arthritis. New Engl J Med 2022;386(4):316-326. doi: 10.1056/NEJMoa2109927.

Personal Opinion:

- Upadacitinib works both in UC and in CD and shows really encouraging activity
- It is the first drug to work even after multiple failed therapies
- Tofacitinib and Filgotinib failed in CD trials and are/will be only approved for UC
- There is a PRAC warning but the risk in IBD has never been documented so far

Anti IL-23 therapies



Blocking of the IL-23 pathway reduces T-cell activation ans mainly interferes with adaptive immunity

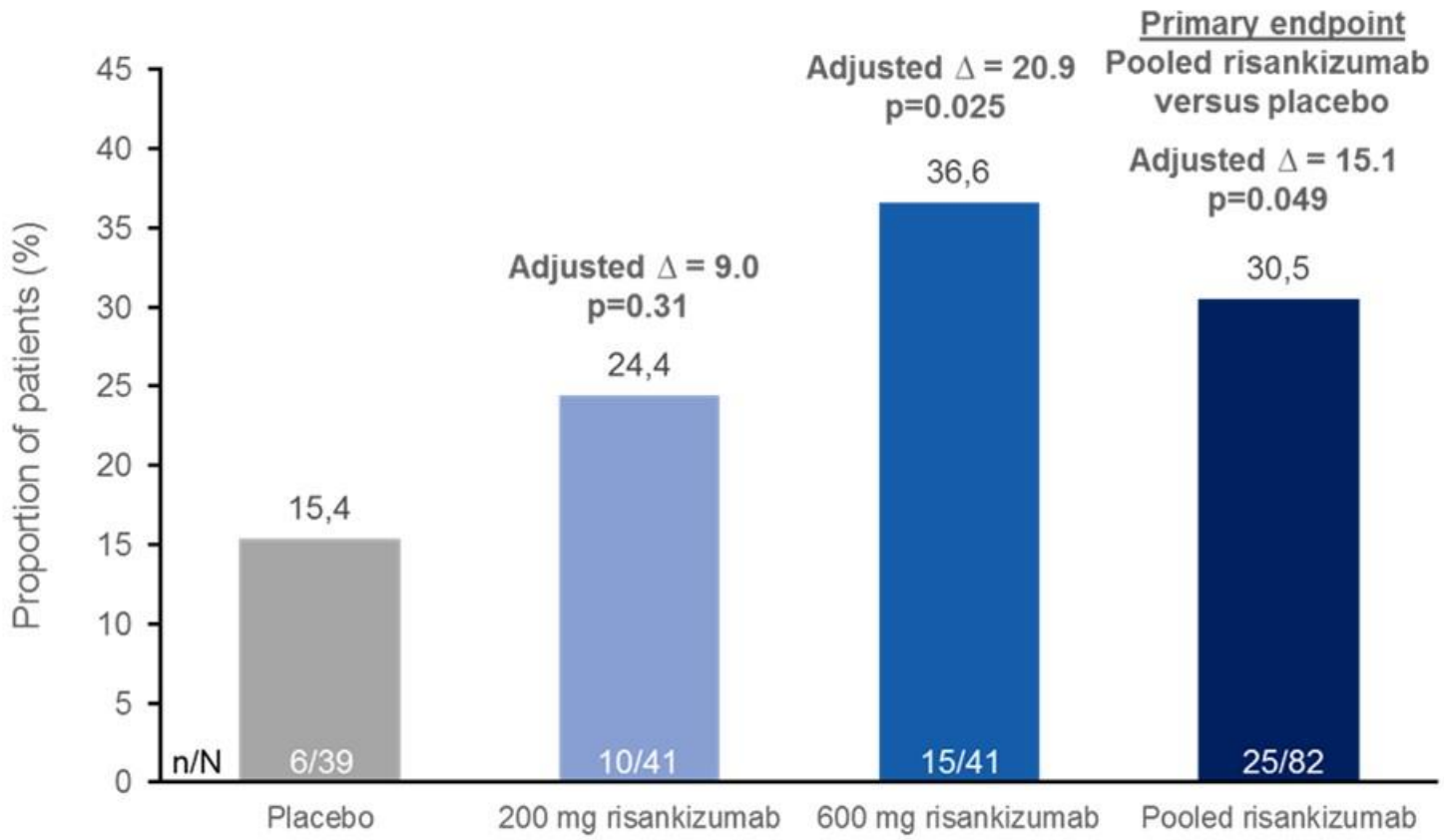
Ustekinumab (Janssen)	
Agent	Human **Anti-p40 AB***
Approval	CD, UC
Approved Dose	Induction: i.v. (~6 mg/kg) Maintenance: s.c. (90 mg, q12w/q8w)
Guselkumab (Janssen)	
Agent	Human **Anti-p19 AB**
Phase	Phase 2/3: Induction: i.v.; Maintenance: s.c. (CD) Phase 3: Induction: i.v.; Maintenance: s.c. (CD) Phase 3: Induction: s.c.; Maintenance: s.c. (CD) Phase 2/3: Induction: i.v.; Maintenance: n.a. (UC)
Risankizumab (Abbvie)	
Agent	Humanized **Anti-p19 AB**
Phase	Phase 3: Induction: i.v.; Maintenance: s.c. (CD/UC)
Mirikizumab (Eli Lilly)	
Agent	Humanized **Anti-p19 AB**
Phase	Phase 3: Induction: i.v.; Maintenance: s.c. (UC) Phase 3: Induction: i.v.; Maintenance: s.c. (CD)
Brazikumab (AstraZeneca)	
Agent	Human **Anti-p19 AB**
Phase	Phase 2: Induction: i.v.; Maintenance: s.c. (UC) Phase 3: Induction: i.v.; Maintenance: s.c. (CD)

Neurath MF. Nat Rev Immunol 2014;14:329-342.

Neurath MF. Nat Rev Gastroenterol Hepatol 2017;14:269-278.

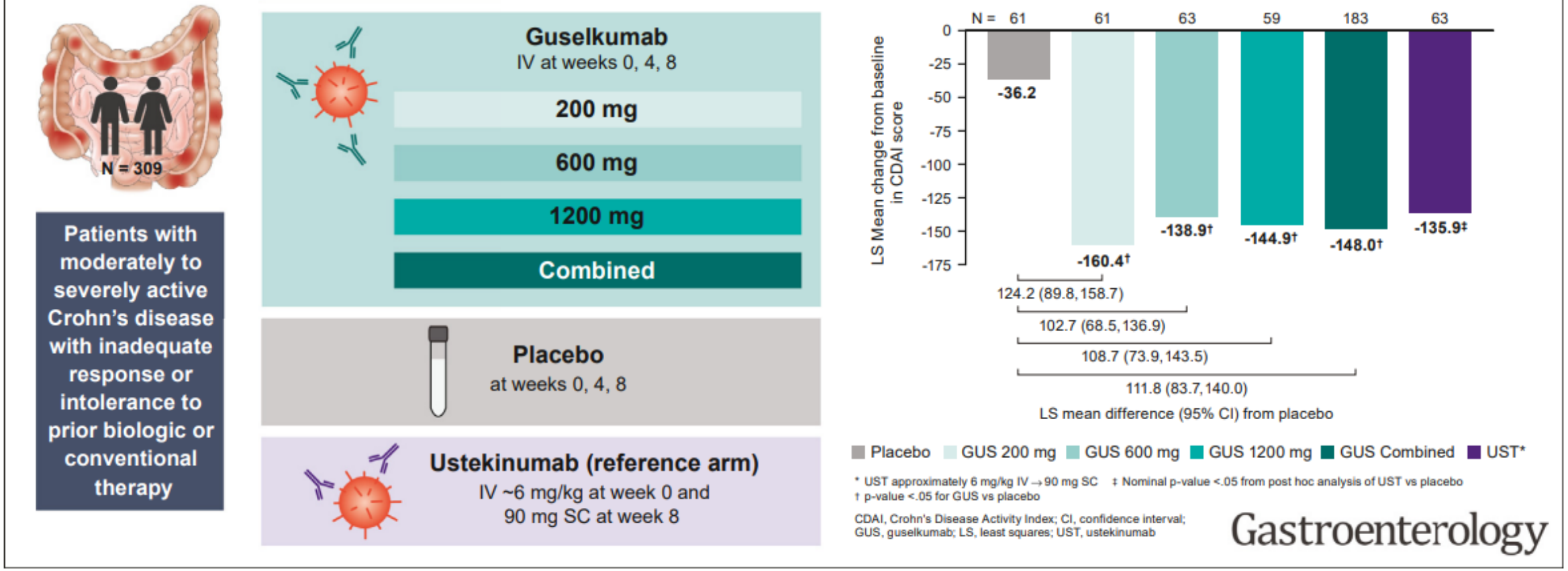
Anti-IL23 therapies:
Rizankizumab for Crohn's disease (Advance/Motivate)

- **Clinical remission (CDAI <150) at week 12**



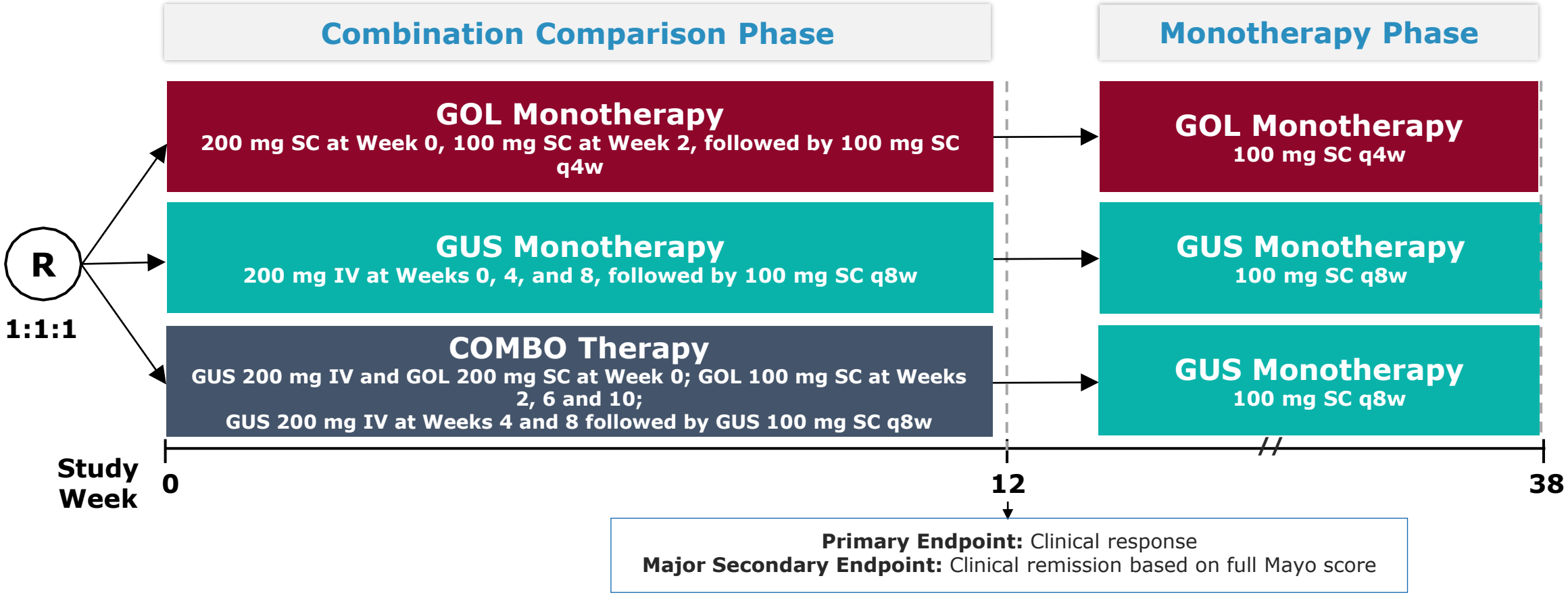
Feagan BG, *Lancet* 2017

Anti-IL23 therapies
Guselkumab for Crohn's disease: Induction Results From the Phase 2 GALAXI-1 Study



Sandborn WJ, *Gastroenterology 2022*

The VEGA combination trial



Patient Population

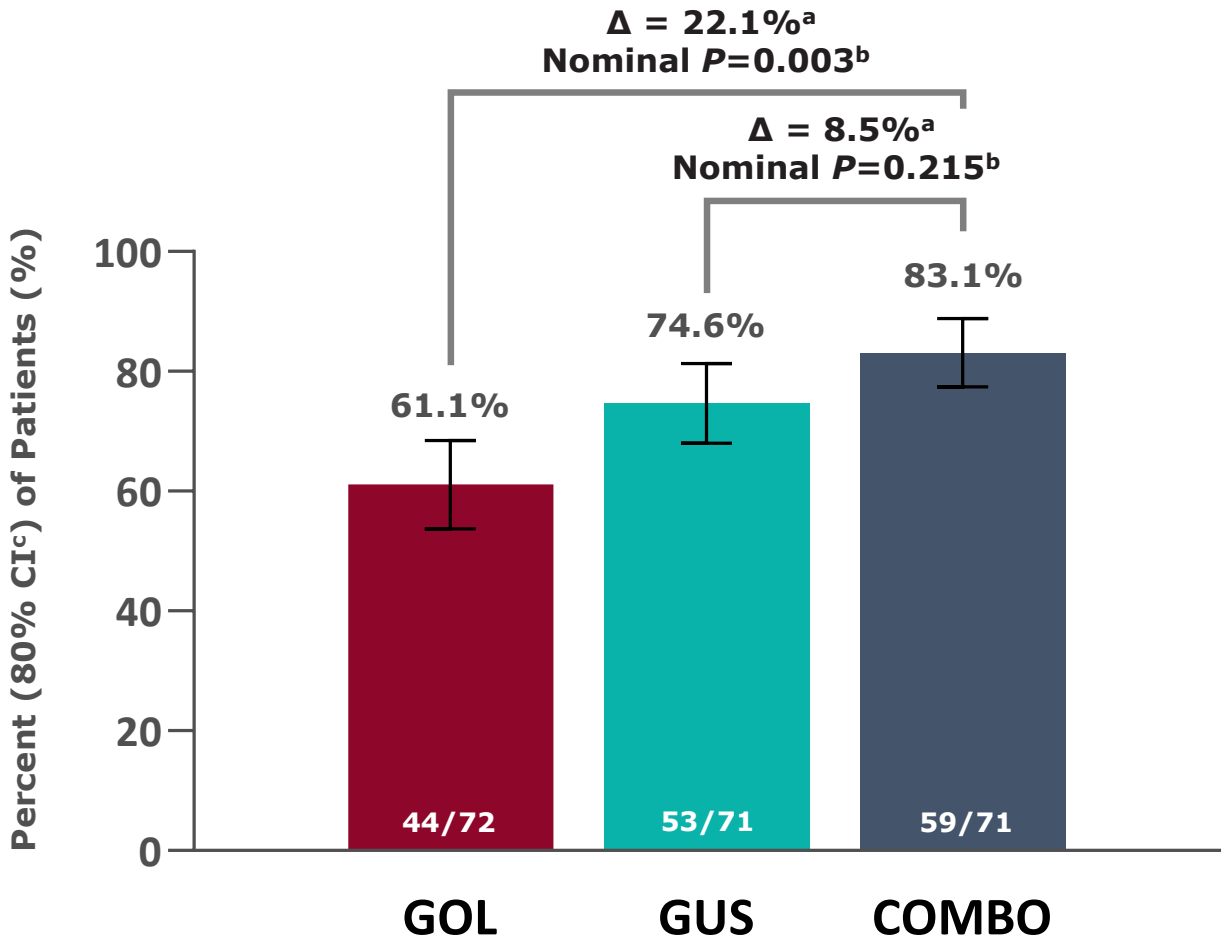
- Moderately-to-severely active UC (Mayo score 6-12, inclusive, and an endoscopy subscore ≥2 by central review)
- Naïve to anti-TNFα antagonists and have had an inadequate response or intolerant to conventional therapy (immunosuppressants [AZA, 6-MP] and/or corticosteroids)
- Immunosuppressants must have been discontinued prior to randomization
- Corticosteroids up to a dose of prednisone (or equivalent) of 20 mg/day permitted with mandatory tapering beginning at Week 6.

USZ Universitäts Spital Zürich

Sands B.E., et al. OP36. 17th Congress of ECCO; February 16-19, 2022; Virtual.

Primary Endpoint: Clinical Response at Week 12

Decrease from Baseline in the Mayo Score ≥30% and ≥3 Points with Either a Decrease in Rectal Bleeding Subscore ≥1 or a Rectal Bleeding Subscore of 0 or 1



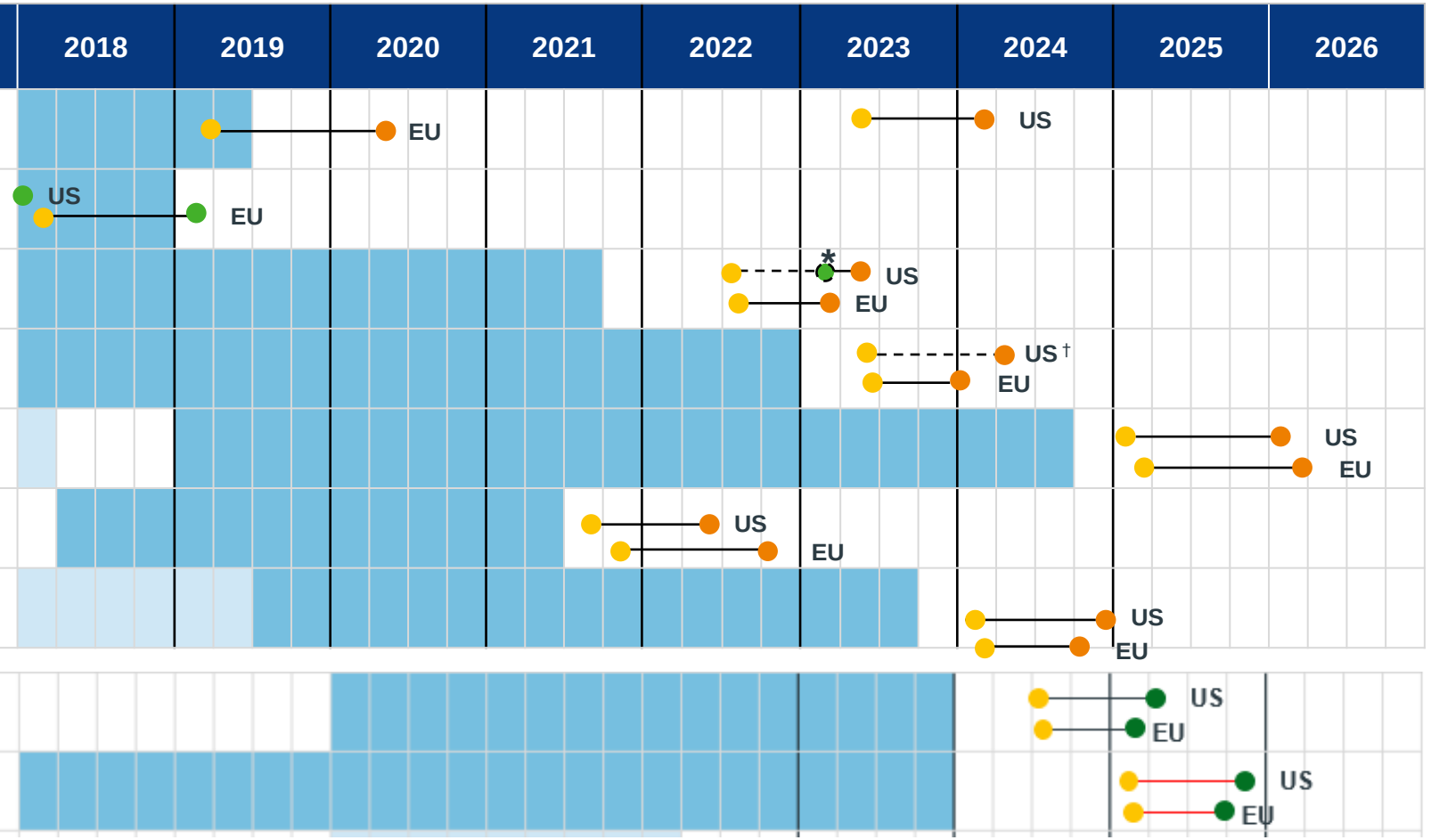
Sands B.E., et al. OP36. 17th Congress of ECCO; February 16-19, 2022; Virtual.

Personal Opinion:

- Anti-p19 AB are a safe and efficient option to treat IBD
- In CD there seems to be no big advantage over ustekinumab (anti p40)
- In UC the new anti-p19 may be better than Ustekinumab
- Due to their safety they may be used for combination approaches (once they become cheaper)

Crohn's Disease–Pipeline

Product	MoA	Indication (RoA)	Current Phase
Entyvio SC (Takeda)	α4β7 integrin antagonist	CD (SC)	Approved (EU)
Ustekinumab (Janssen)	IL-12/IL-23 inhibitor	CD (IV/SC)	Approved
Upadacitinib (AbbVie)	JAK1 inhibitor	CD (oral)	Approved (US & EU)
Filgotinib (GLPG)	JAK1 inhibitor	CD (oral)	Failed in CD
Guselkumab (Janssen)	IL-23 inhibitor	CD (IV/SC)	IIb/III
Risankizumab (AbbVie)	IL-23 inhibitor	CD (IV/SC)	Approved (US; EU)
Mirikizumab (Eli Lilly)	IL-23 inhibitor	CD (IV/SC)	III
Etrasimod (Pfizer)	S1P1/4/5 agonist	CD (SC)	II/III
Ozanimod (BMS)	S1P1/S1P5 agonist	CD (oral)	III



USZ Universitäts Spital Zürich

Key Ph. II Ph. III **Regulatory** Submission Approval
Expedited Approval Date CRL

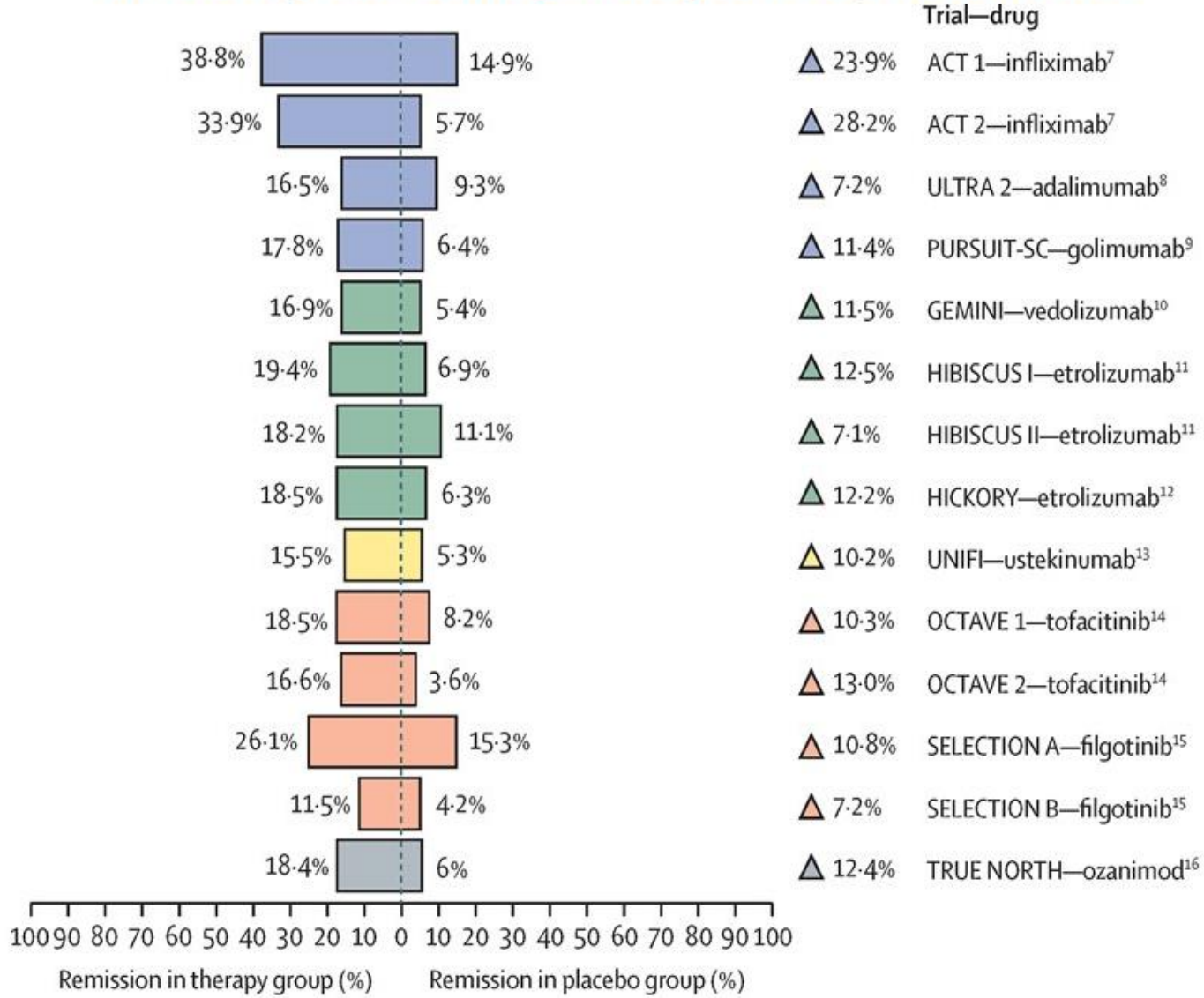
Ulcerative Colitis Pipeline

Product	MoA	Indication (RoA)	Current Phase	2018	2019	2020	2021	2022	2023	2024	2025	2026
Entyvio SC (Takeda)	α4β7 integrin antagonist	UC (SC)	Approved (EU)			✖ EU				US		
Ustekinumab (Janssen)	IL-12/IL-23 inhibitor	UC (IV/SC)	Approved (US, EU)		US	EU						
Upadacitinib (AbbVie)	JAK1 inhibitor	UC (oral)	Approved (US, EU)					US	EU			
Filgotinib (GLPG)	JAK1 inhibitor	UC (oral)	Approved (EU)				EU			US †		
Ozanimod (BMS)	S1P1/5 agonist	UC (oral)	Approved (EU &US)				US ††	EU				
Guselkumab (Janssen)	IL-23 inhibitor	UC (IV/SC)	II/III							US	EU	
Risankizumab (AbbVie)	IL-23 inhibitor	UC (IV/SC)	Filed (US & EU)							* US EU		
Mirikizumab (Eli Lilly)	IL-23 inhibitor	UC (IV/SC)	Filed (US & EU)					**	US	EU		

USZ Universitäts Spital Zürich

Key Ph. II Ph. III **Regulatory** Submission Approval
Expedited Approval Date CRL

The therapeutic ceiling in drug development in U.C.



USZ Universitäts Spital Zürich

Alsoud D, Lancet Gastroenterol Hepatol 2021

- messages: How will the pipeline translate into clinical practice?

- Recent studies have demonstrated the promise of new drugs with distinct modes of action for the treatment of ulcerative colitis (UC) and Crohn's disease (CD).
- These include agents targeting leukocyte trafficking, therapies directed against IL-12/23 and Janus kinases (JAK)
- New S1P1, anti-IL23 AB and new JAK inhibitors are soon to come
- Their role in IBD treatment algorithms has still to be determined
- Combinations therapies will provide improved efficacy for IBD therapy but they have to be carefully explored
- Patient preferences and pricing may play a more important role for the choice of IBD treatment in the future

A final remark:

New treatment options and new treatment targets may not necessarily be better

Mucosal Healing

Window of opportunity

Treat to target

Histological healing

Disease clearance

STARDUST: Treat to target versus standard of care for patients with Crohn's disease treated with Ustekinumab (STARDUST): an open-label, multicentre, randomized phase 3b trial

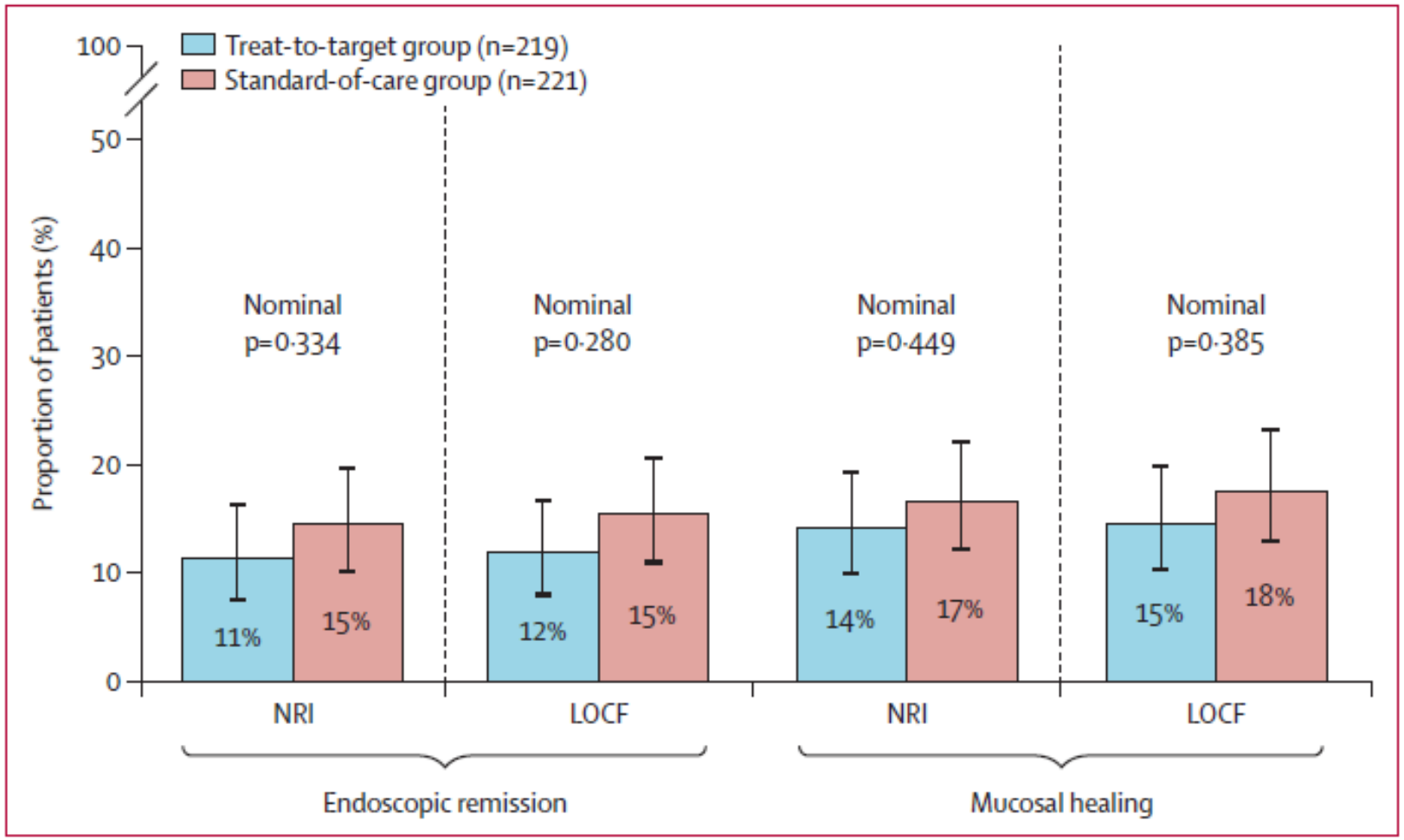


Figure 4: Endoscopic remission and mucosal healing at week 48

«*Timely escalation of ustekinumab therapy for patients with Crohn's disease, based on early endoscopic response, clinical symptoms, and biomarkers,* ***did not result in significantly better endoscopic outcomes at week 48 than symptom-driven decisions alone.***»

USZ Universitäts Spital Zürich

Danese S, Vermeire S, D'Haens G, Panés J, Dignass A, Magro F, Nazar M, Le Bars M, Lahaye M, Ni L, Bravata I, Lavie F, Daperno M, Lukáš M, Armuzzi A, Löwenberg M, Gaya DR, Peyrin-Biroulet L; STARDUST study group. Treat to target versus standard of care for patients with Crohn's disease treated with ustekinumab (STARDUST): an open-label, multicentre, randomised phase 3b trial. Lancet Gastroenterol Hepatol. 2022 Apr;7(4):294-306.