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IBD patiëntenavond november 2022

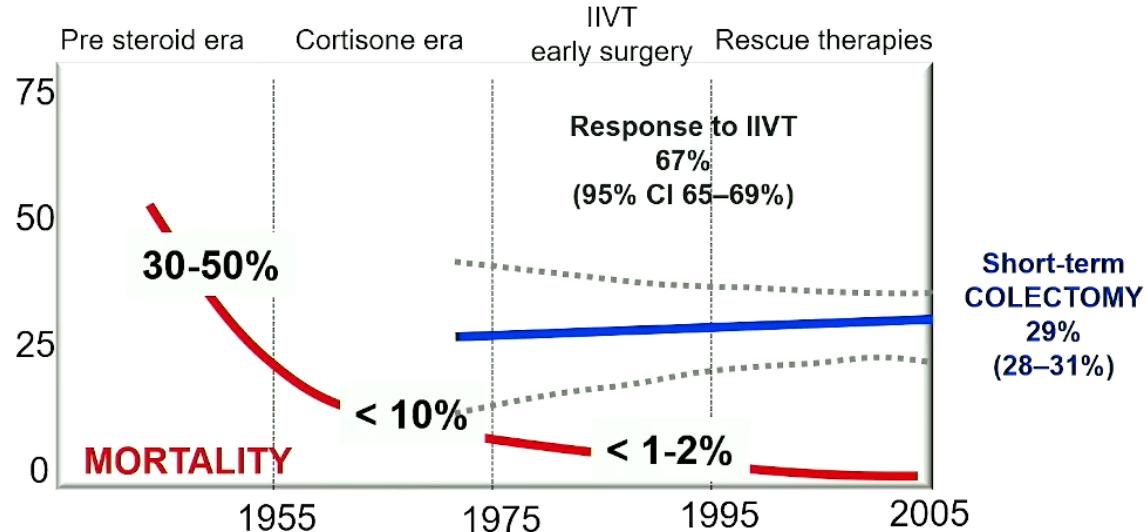
JAK: a tablet a day keeps colitis away

Michiel Schils

ueg week

Postgraduate Teaching Programme

ASUC: mortality & colectomy rates in the pre-biologic era

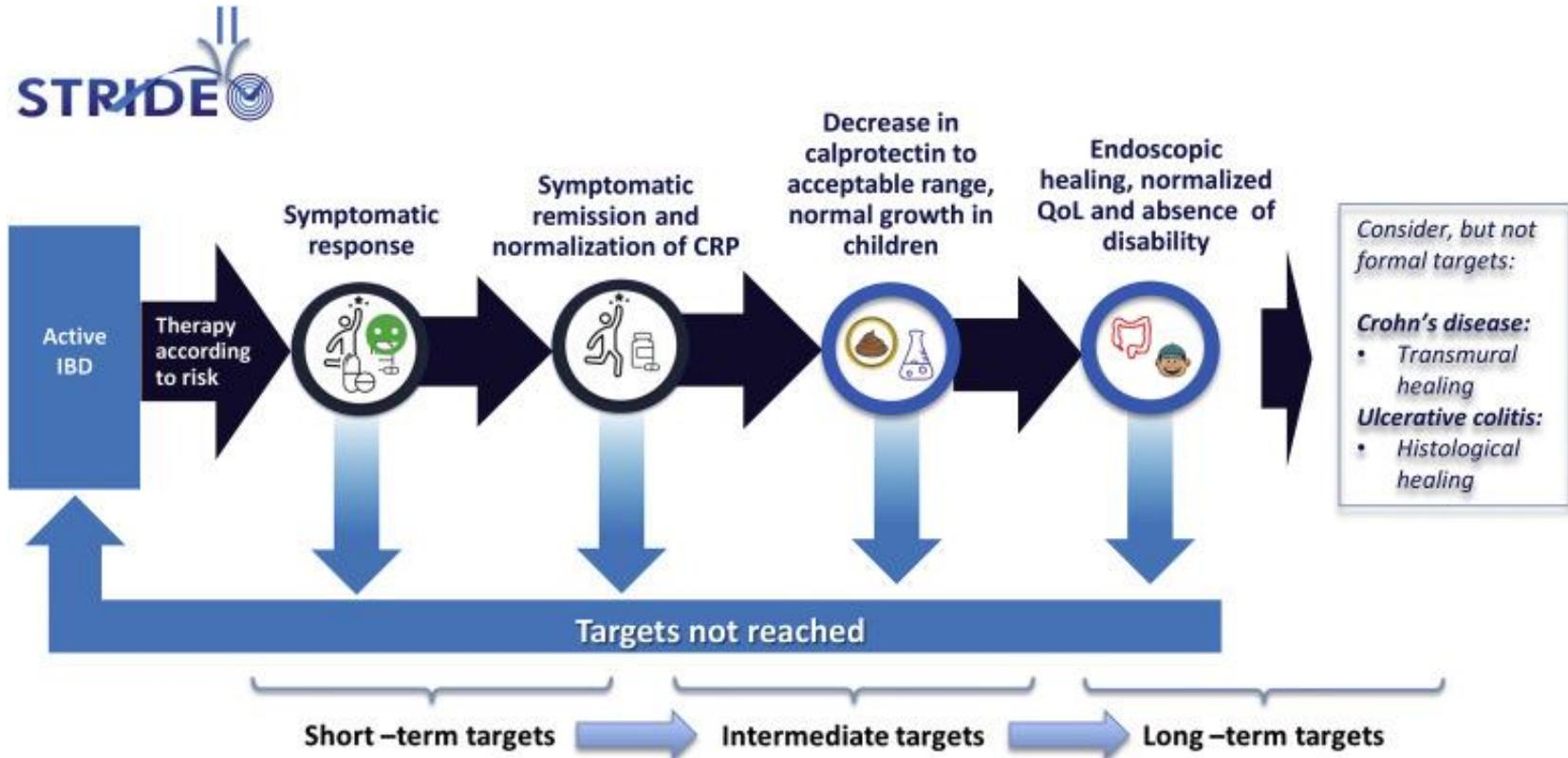


Evolutie behandelingsprincipes – doelstellingen

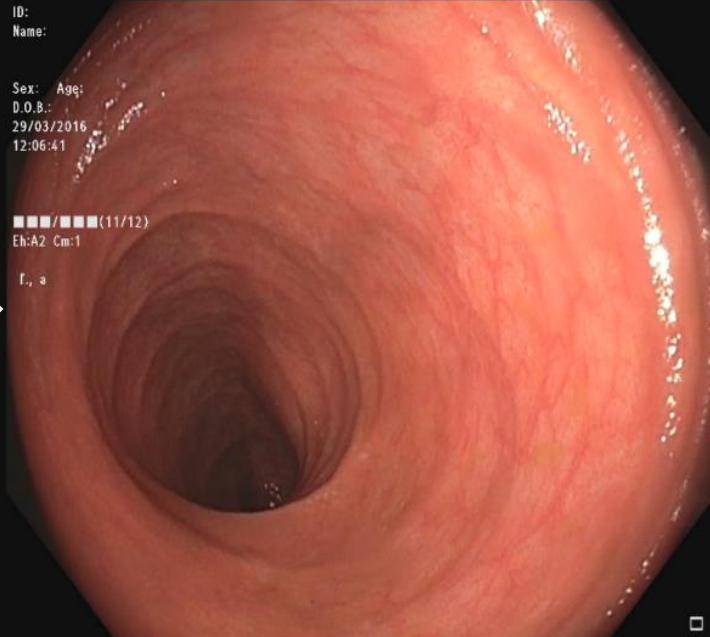
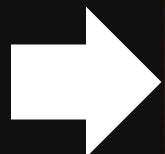
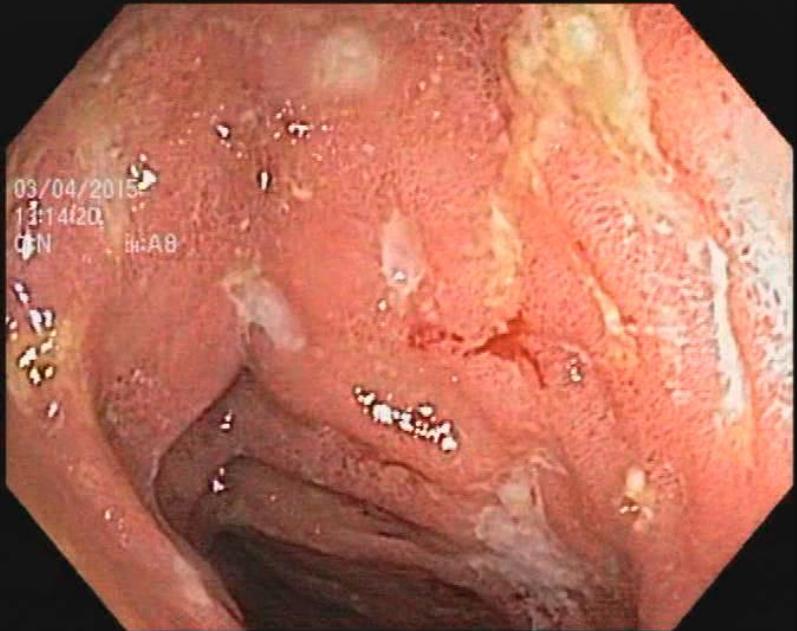


- ▶ Vroeger: opvang van symptomen = “klinische remissie”
- ▶ Voortschrijdend inzicht:
 - “biochemische remissie”
 - “endoscopische remissie” = mucosale heling
- ▶ Target-strategie: “treat to target”
- ▶ Belang:
 - labo-analyses : inflammatoire parameters, bloedbeeld, ijzerstatus
 - Fecal Calprotectine
 - Trough levels
 - Endoscopische controles +/- MR-enterografie
 - Multidisciplinaire stafvergaderingen

Treat to Target



Endoscopische Remissie



Niet allemaal rooskleurig



UC: Systematic review of long-term outcomes in 17 longitudinal, population-based global cohorts^{‡2}

At 10-year follow-up:

70–80% cumulative risk
of relapse



39–66% cumulative risk
of hospitalisation



10–15% cumulative risk
of colectomy

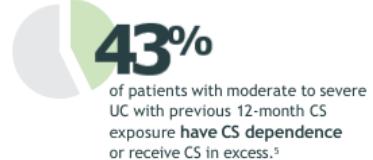


Despite treatment advances, the UC journey can be challenging and complex³⁻¹⁵

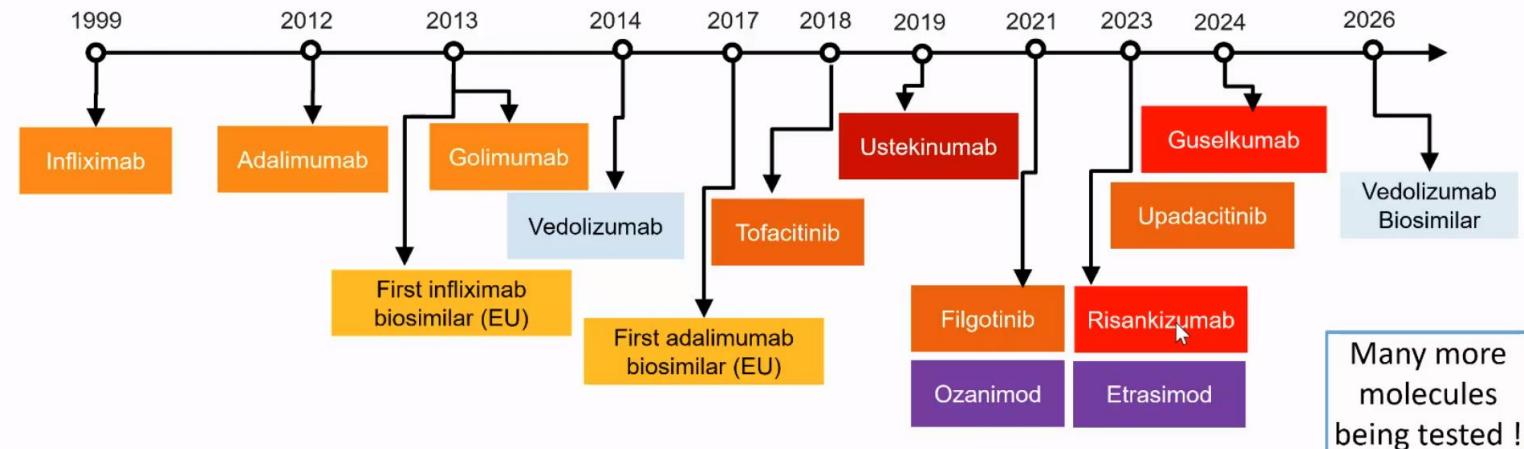
SUB-OPTIMAL ACHIEVEMENT OF REMISSION³⁻⁴



CORTICOSTEROID DEPENDENCE AND INTOLERANCE⁵⁻⁶



Welcome to the Multiverse!



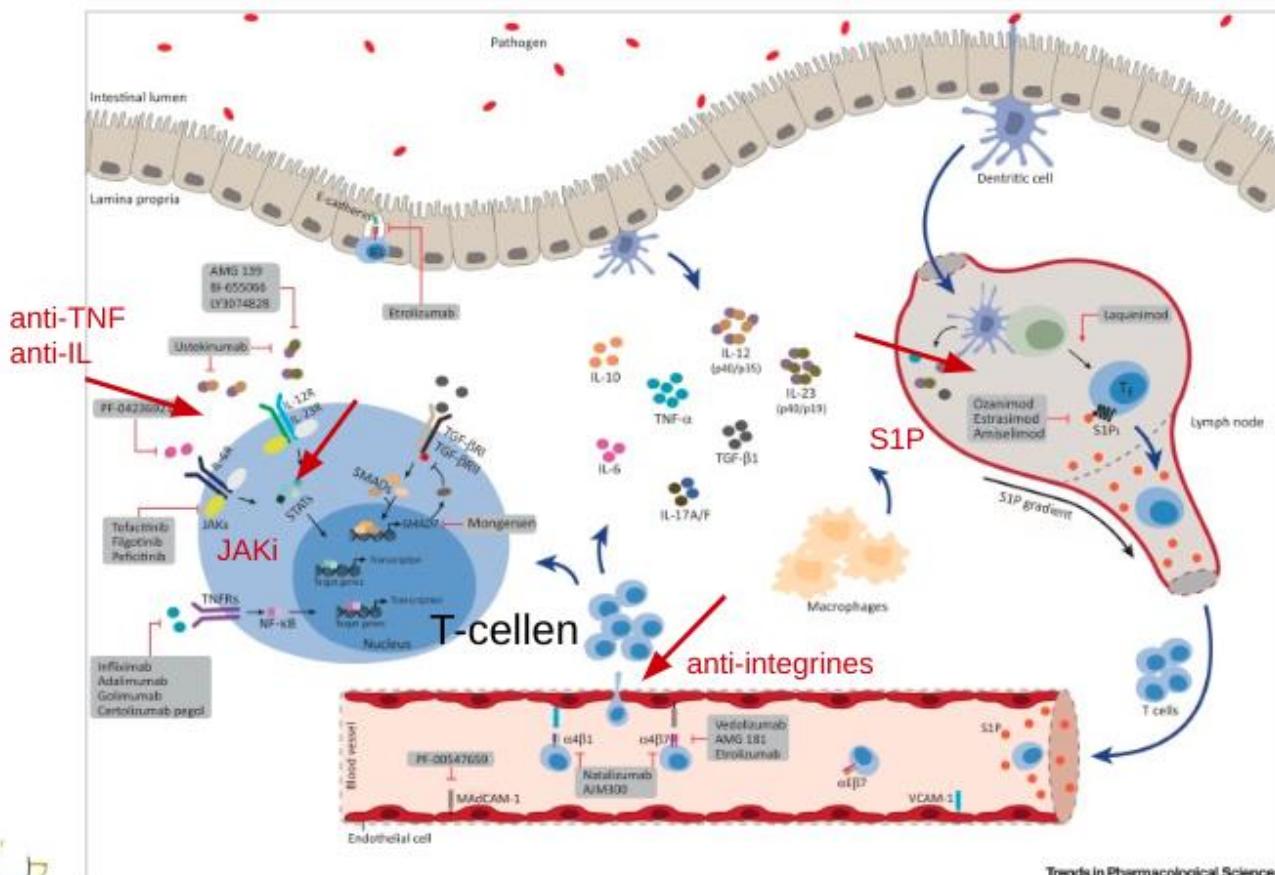
Anti-TNFs

Anti-integrin

IL12/23

JAKi

Verminder de inflammatie



Doel:

- blokkeren van extra-cellulaire signalen en hun onderliggende processen,
- interfereren met intra-cellulaire signaaltransductie
- verstoren van leukocyten trafficking naar de intestinale mucosa.

Hoe kiezen?

► Comorbiditeiten

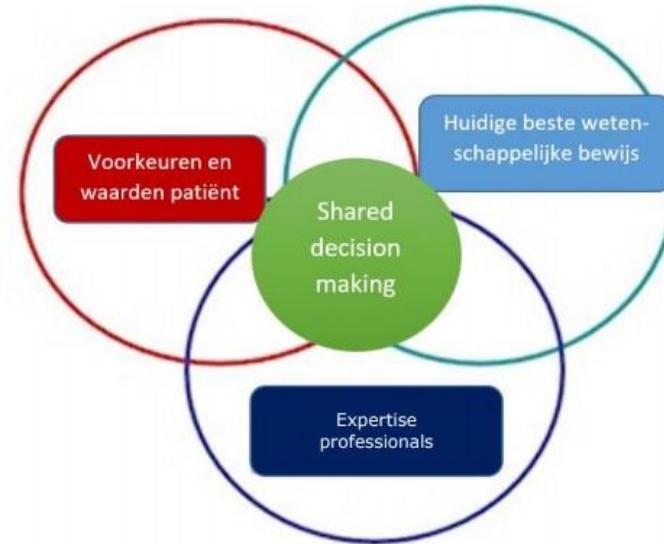
► Leeftijd

► Zwangerschapswens

► SC vs IV vs PO

► Nevenwerkingen profiel

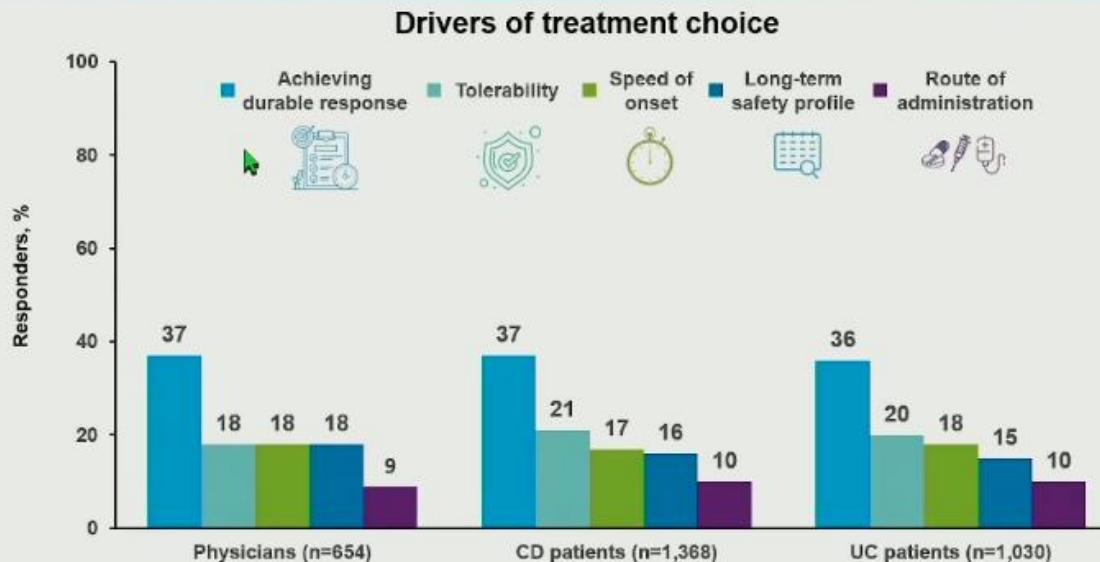
► Respons rate



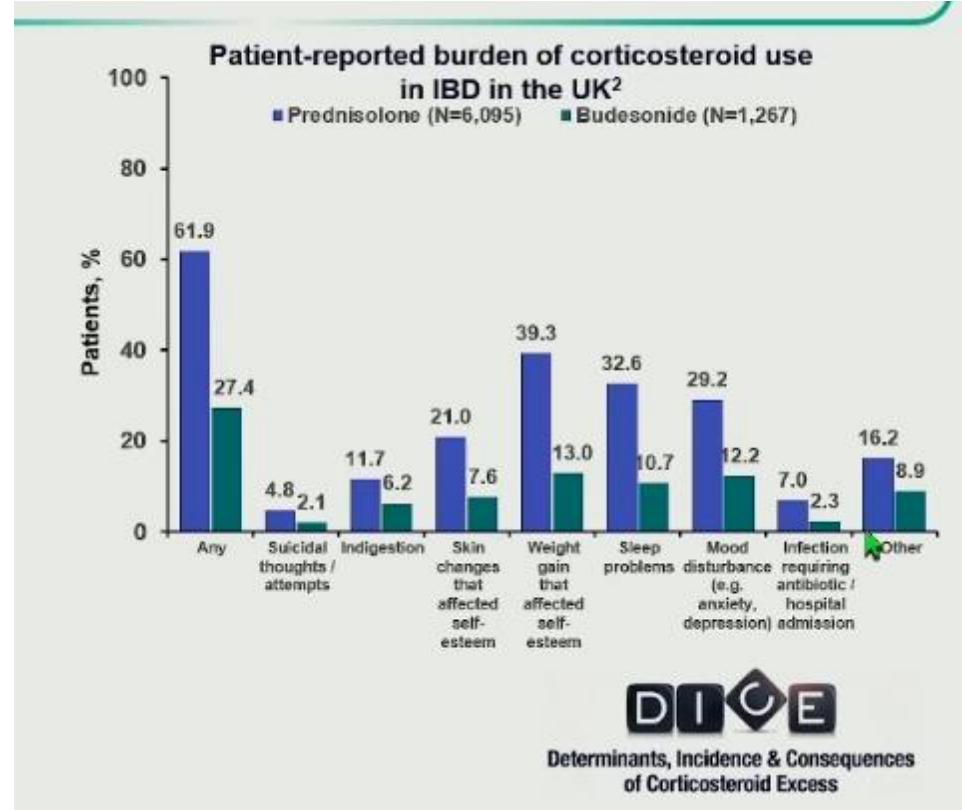
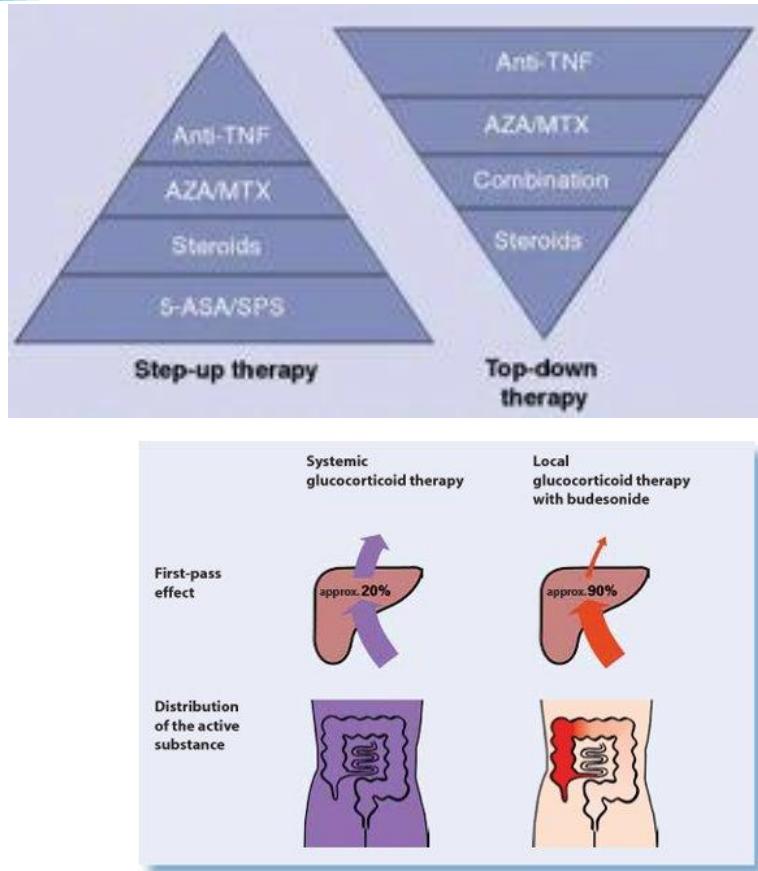
Shared decision making

Wat verkiest de patiënt?

Achieving immediate targets is rated highly by patients with IBD and clinicians, while those aware of long-term goals have higher aspirations



Cortisine, BAH!



Keuzes Maken

Drug-related factors

 Indication	 Efficacy	 Mucosal healing	 Safety profile
 Rapidity of onset	 Corticosteroid use	 Cost	

Patient-related factors

 Age and gender	 Comorbidities (including EIM)	 Pregnancy
 Current and prior therapies	 Surgery	 Convenience/mode of administration

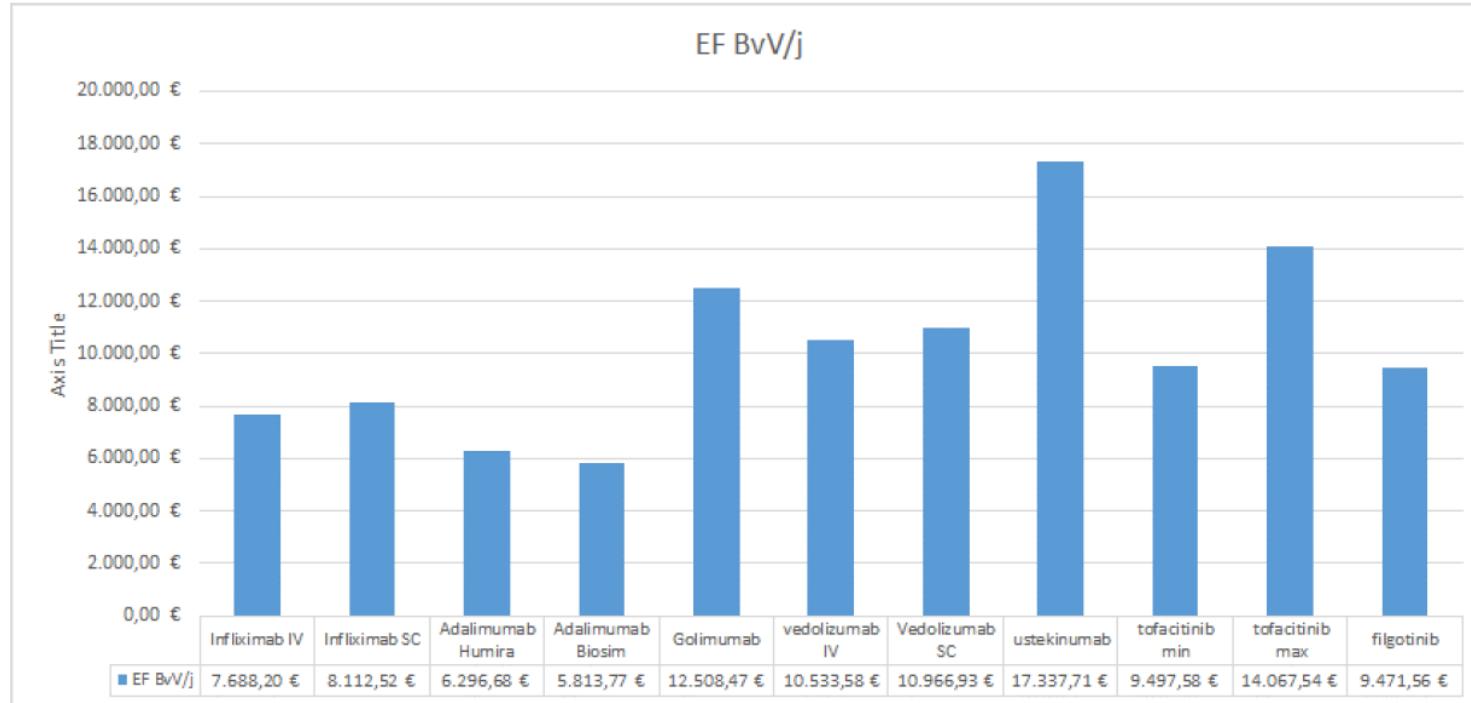


Precision medicine may guide
the future of treatment



Kostprijs van een jaar therapie

Versie finale: 08.02.2022



Multiple therapies available and more coming

1950s
First use
of corticosteroids¹

1980s
First use
of MTX³

2005
Approval of
anti-TNF
for UC⁵

2013
Start of the
biosimilar era⁶

2014
Vedolizumab⁷

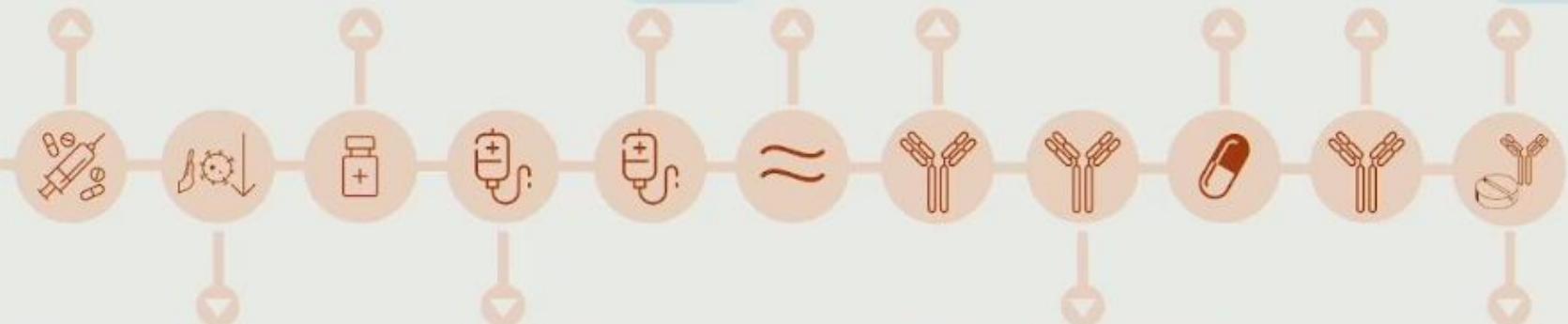
2018

Tofacitinib⁹

2019

Ustekinumab¹⁰

2021–2022
Ozanimod¹¹
Filgotinib¹²
Upadacitinib¹³



IBD
UC
CD

We worden strenger en strenger



Early intervention

- Recognise excess oral corticosteroid exposure
- Risk stratify to avoid delaying effective therapy



Monitoring

- Use all available tools, including FC, CRP PROs, oral corticosteroid monitoring and imaging



Treat-to-target – endoscopic healing

- Adapt therapy to the target
- Consider immediate, intermediate and the best endoscopic and QoL outcome

Mucosal endpoints in UC clinical trials have evolved to become more stringent over time



CRP, C-reactive protein; FC, faecal calprotectin; PRO, patient-reported outcome; QoL, quality of life.

JANUS Kinase

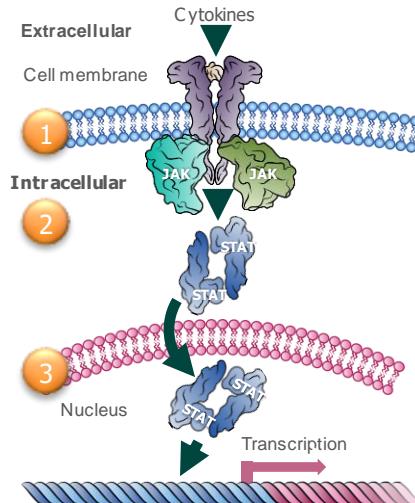


In de Romeinse mythologie was Janus de god van het begin en het einde, van het openen en het sluiten.

Janus werd voornamelijk afgebeeld als een man met twee gezichten (**Janus Bifrons**) of als een tweeling (**Janus Gemini**). Zijn twee gezichten represideerden oorspronkelijk de zon en de maan.



JAK-STAT pathways mediate the signalling of several immunoregulatory molecules^{1,2}



JAKs are intracellular proteins that associate with cytokine receptors to enable the signalling of several molecules, e.g. cytokines and growth factors^{1,2}

- 1 JAK proteins are activated when molecules bind to the receptor^{1,2}
- 2 In turn, JAK proteins activate STAT proteins, which then dimerise and migrate to the nucleus^{1,2}
- 3 STAT proteins regulate the expression of genes that facilitate numerous physiological processes, e.g. immune cell activity and intestinal homoeostasis¹⁻⁵

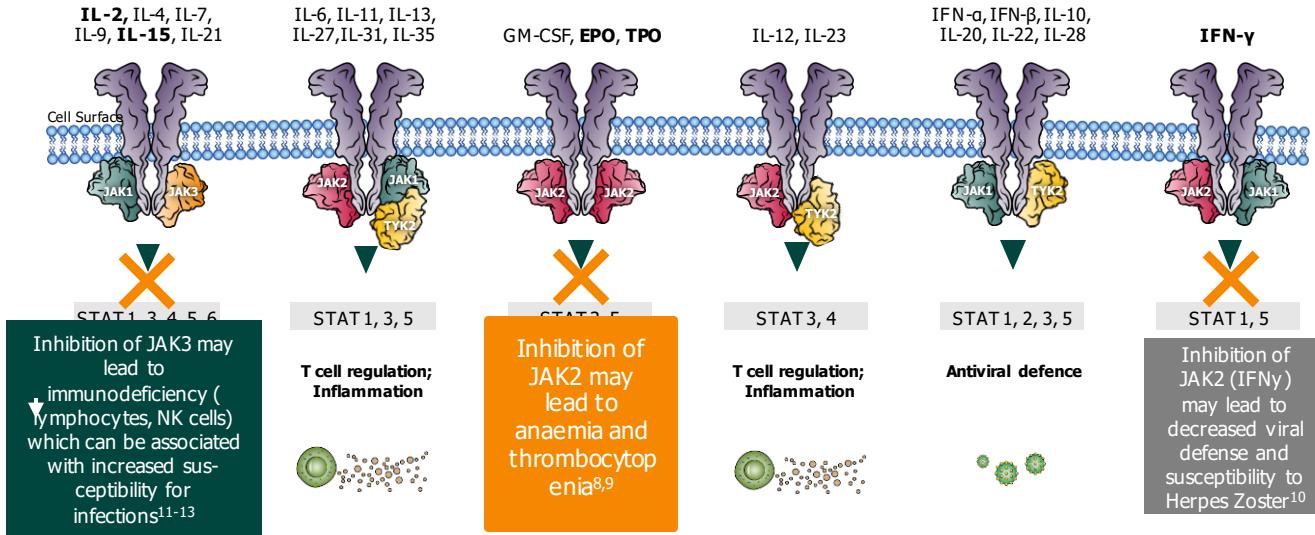
TYK: tyrosine kinase

1. O'Shea JJ, et al. *Annu Rev Med* 2015; 66:311–328. 2. Clark JD, et al. *J Med Chem* 2014; 57:5023–5038.

3. Schwartz DM, et al. *Nat Rev Drug Discov* 2017; 16:843–862. 4. Salas A, et al. *Nat Rev Gastroenterol Hepatol* 2020; 17:323–337. 5. Danese S, et al. *Gut* 2019; 10:1893–1899.



Why does preferential JAK1 inhibition matter?



EPO: erythropoietin; TPO: thrombopoietin

* Please note, cytokines and physiological processes listed here are examples of the unique JAK roles and do not provide an exhaustive list

Figure adapted from: 1. Schwartz DM, et al. *Nat Rev Drug Discov* 2017; 16:843–862. 2. Clark JD, et al. *J Med Chem* 2014; 57:5023–5038. 3. Waggoner SN, et al. *Curr Opin Virol* 2016; 16:15–23.

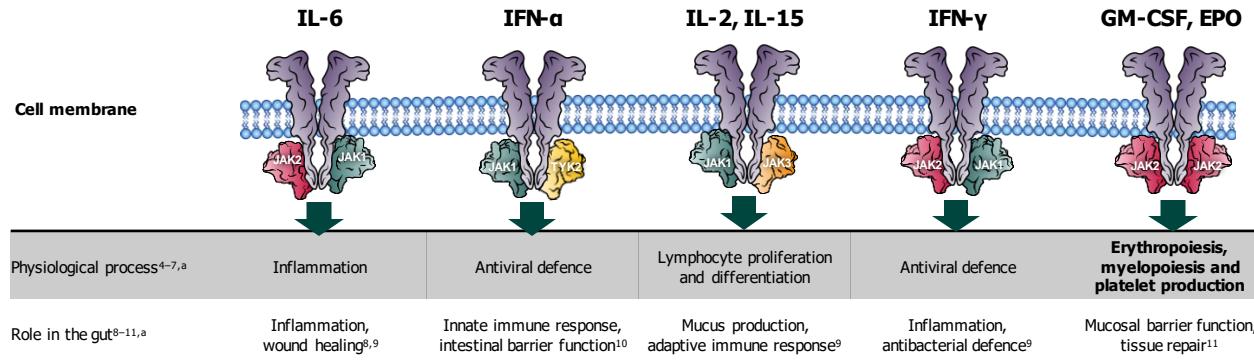
4. Tato CM, et al. *J Immunol* 2004; 173:1514–1517. 5. Winkthrop KL. *Nat Rev Rheumatol* 2017; 13:234–243. 6. Akada H, et al. *Stem cells* 2014; 32:1878–1889. 7. Choy EH. *Rheumatology (Oxford)* 2019; 58:953–962. 8. Akada H, et al. *Stem Cells* 2014; 32:1878–1889. 9. Vainchenker W. *Leukemia* 2013; 27:1219–1223. 10. Sen N, et al. *Journal of Virology*; 2018;92(21).

11. Robinette ML, et al. *Nature* 2018; 11:50–60. 12. O’Shea JJ. *Ann Rheum Dis* 2004; 63(Suppl II):ii67–ii71. 13. Schwartz DM, et al. *Nat Rev Rheumatol* 2016; 12:25–36.

BNL-RA-FIL-202011-00001



Filgotinib reduces signalling of several proinflammatory cytokines while preserving the activity of others^{1–3}



Preferential inhibition of JAK1 may preserve the activity of some JAK signalling pathways and physiological processes^{12,13}

^a Processes listed here are examples and do not provide an exhaustive list

EPO: erythropoietin

See slide notes for references

FI



Filgotinib is an orally administered small molecule that preferentially inhibits JAK1

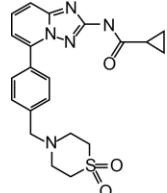
Filgotinib is an orally administered small molecule^{1,2}
No immunogenicity expected



Filgotinib is metabolised in a non-CYP450-dependent manner
Filgotinib metabolism is independent of liver and kidney function



Preferentially inhibits JAK1^{4,5}
In biochemical assays, filgotinib has a >5-fold higher potency for JAK1 over other JAKs



Filgotinib

Demonstrated efficacy in CD and UC^{6–8,a}
Early and sustained responses were observed in patients with CD^b and UC^c



Acceptable safety profile^{6–11,a}
In clinical trials, low rates of HZ, VTE and serious infections were observed in patients with RA and UC



Filgotinib inhibits multiple cytokines¹
Filgotinib targets intracellular signalling pathways used by several cytokines

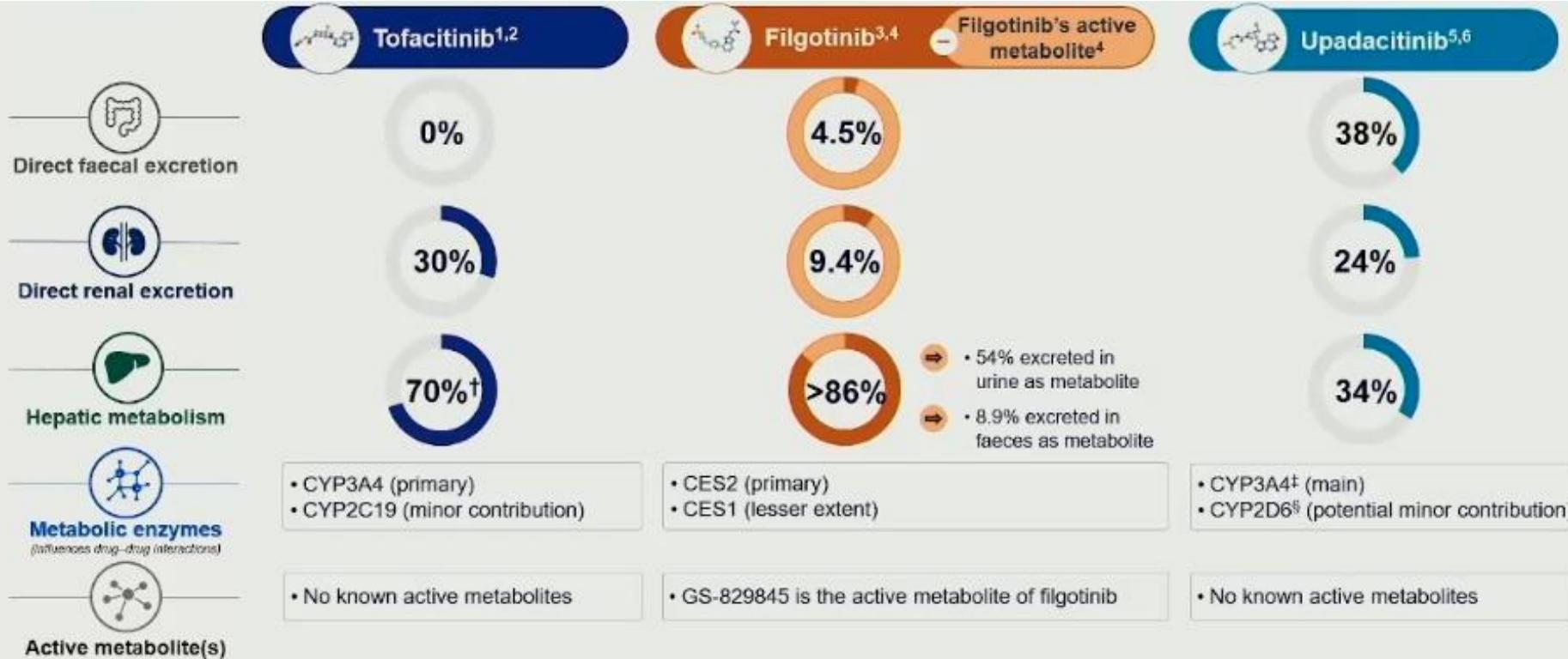


^b Phase 2 FITZROY trial; ^c Phase 3 SELECTION trial CYP450: cytochrome P450; HZ: herpes zoster; VTE: venous thromboembolism

See slide notes for references

FILGOTINIB IS NOT APPROVED FOR USE IN CD OR UC

De JAK remmers

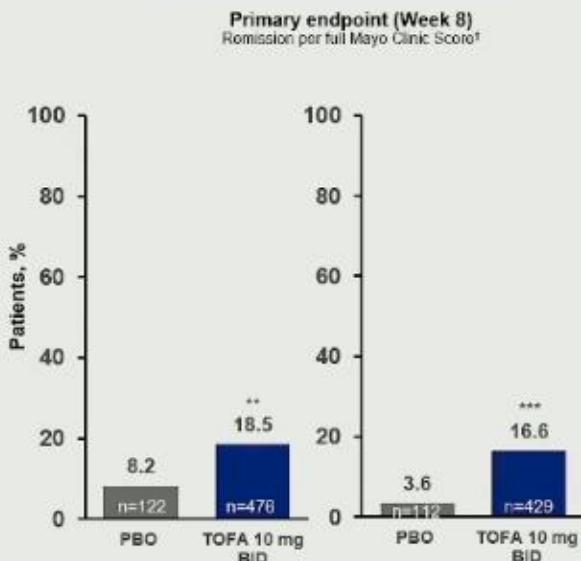


De JAK remmers

		Tofacitinib ¹	Filgotinib ²	Upadacitinib ³
Renal impairment†	Mild	No dose adjustment required in patients with CrCl 50–80 mL/min	No dose adjustment required in patients with CrCl ≥60 mL/min	No dose adjustment required
	Moderate	No dose adjustment required in patients with CrCl 30–49 mL/min	100 mg QD in patients with CrCl 15–<60 mL/min	No dose adjustment required
	Severe	Dose should be reduced to 5 mg QD in patients with CrCl <30 mL/min, including patients undergoing haemodialysis	Not recommended in patients with CrCl <15 mL/min	Use with caution in patients with eGFR 15–<30 mL/min/1.73 m ² . Induction: 30 mg QD; maintenance: 15 mg QD Not studied in end-stage renal disease and therefore not recommended
Hepatic impairment†	Mild	No dose adjustment required	No dose adjustment required	No dose adjustment required
	Moderate	Dose should be reduced to 5 mg QD	No dose adjustment required	No dose adjustment required
	Severe	Contraindicated	Not recommended for use	Contraindicated

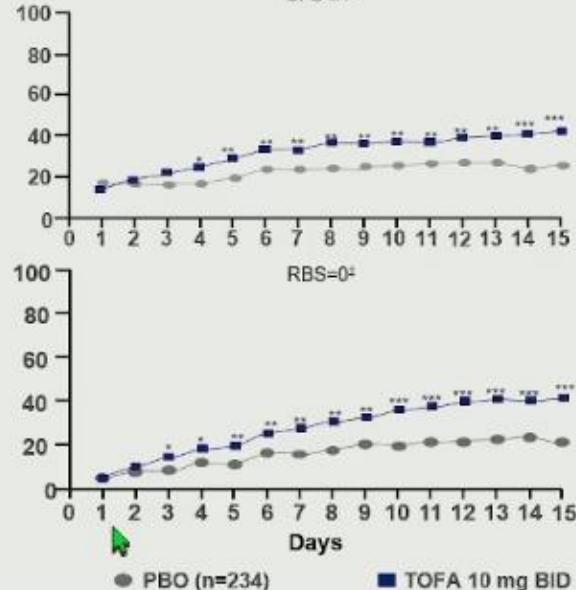
Tofacitinib

OCTAVE 1¹ OCTAVE 2¹



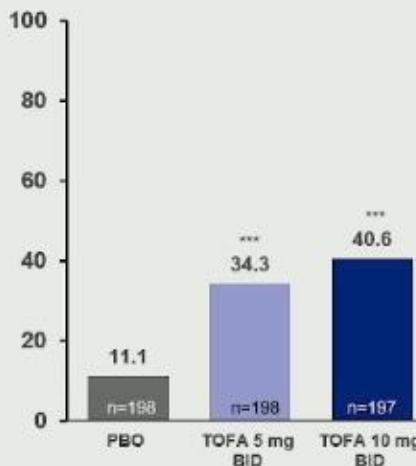
OCTAVE 1 and OCTAVE 2²

Early response symptomatic outcomes over 2 weeks
SFS ≤1[‡]

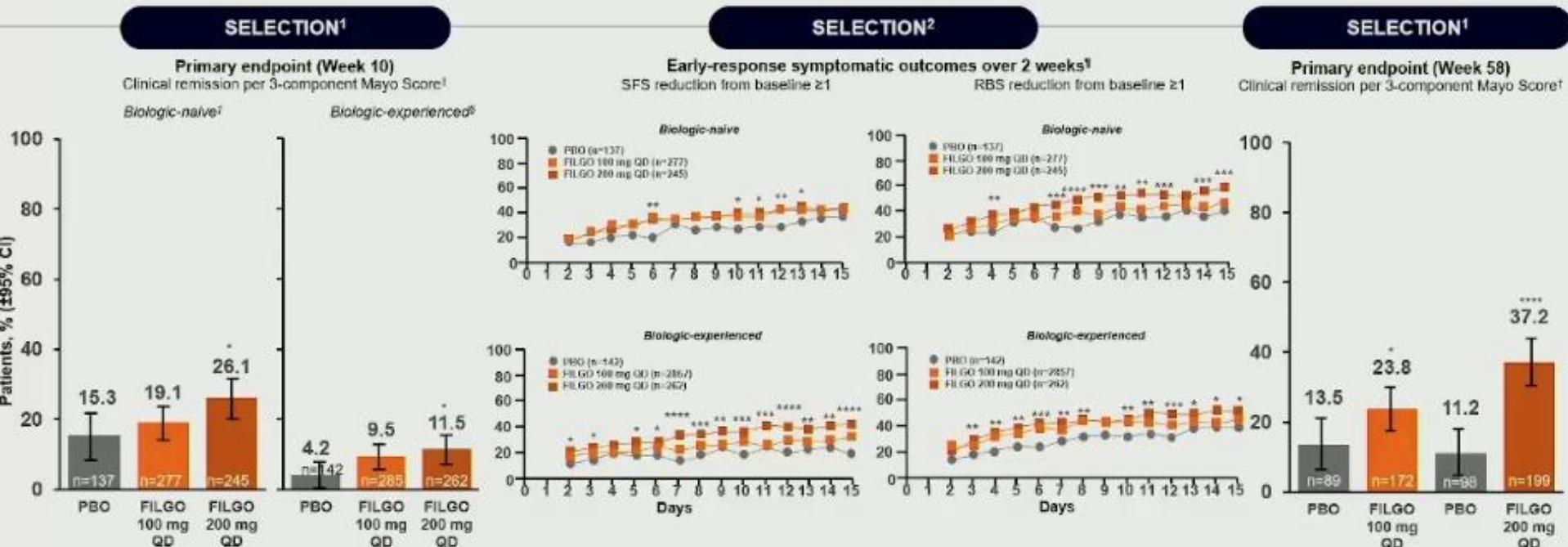


OCTAVE SUSTAIN¹

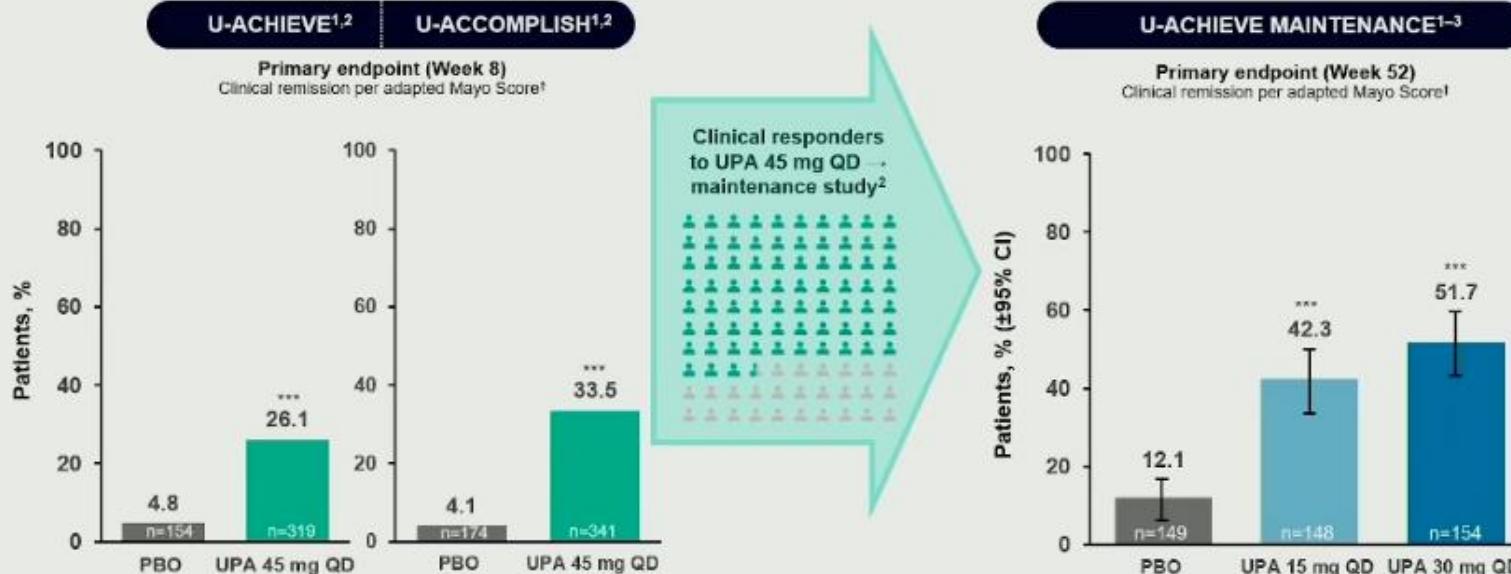
Primary endpoint (Week 52)
Remission per full Mayo Clinic Score[†]



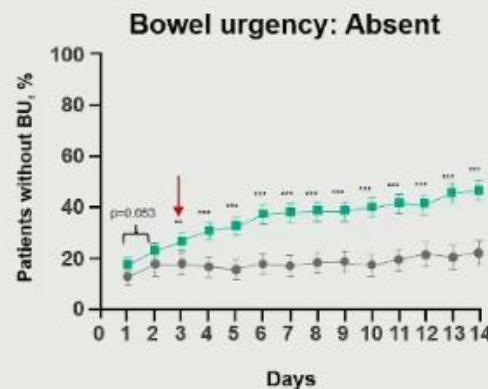
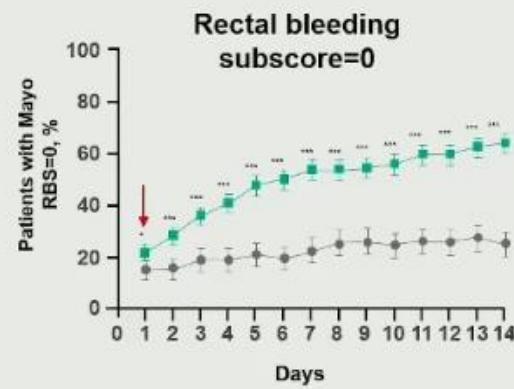
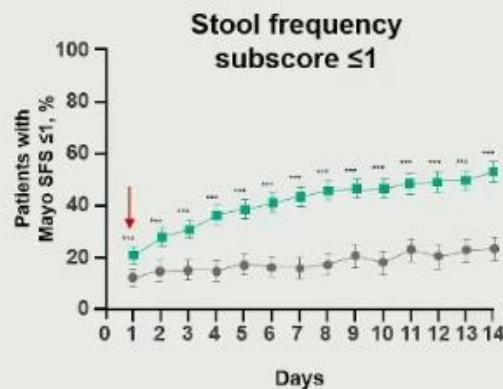
Filgotinib



Upadacitinib



UPA 45 mg QD provides patients with significant relief from abdominal symptoms within Week 1

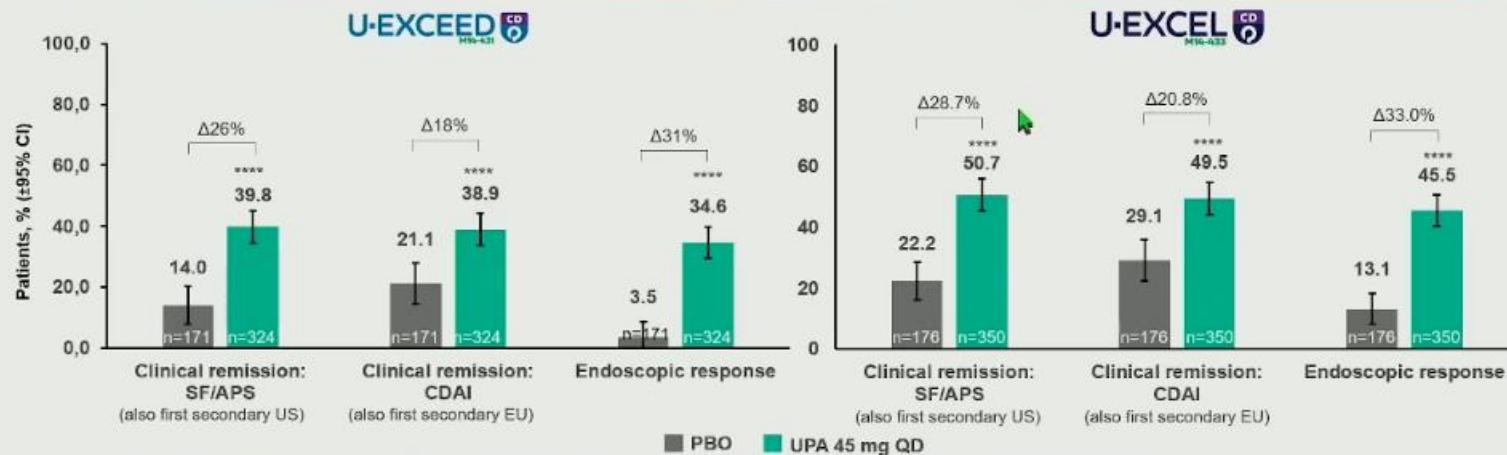


● PBO ■ UPA 45 mg QD

In de toekomst ook voor Crohn?



The co-primary endpoints for US and EU at Week 12 were both met^{1,2}



Clinical remission (SF/APS): Average daily SF ≤2.8 and not worse than baseline AND average daily APS ≤1 and not worse than baseline.^{1,2}

Clinical remission (CDAI): CDAI <150.^{1,2}

Endoscopic response: Decrease in SES-CD >50% from baseline (or for subjects with isolated ileal disease and a baseline SES-CD of 4, at least a 2-point reduction from baseline), scored by central reader.^{1,2}



Data from compounds in the JAK inhibitor class show **symptomatic response within 1 week in UC**, some as early as Day 1¹⁻³



Sustained reduction in clinical and mucosal inflammation can be achieved with JAK inhibitors



Significant levels of mucosal healing in UC have been achieved at 1 year using UPA vs PBO⁴



Considering the efficacy and safety profiles of therapies can aid selection of appropriate and individualised treatments for patients

Warnings & Precautions - all JAK inhibitors

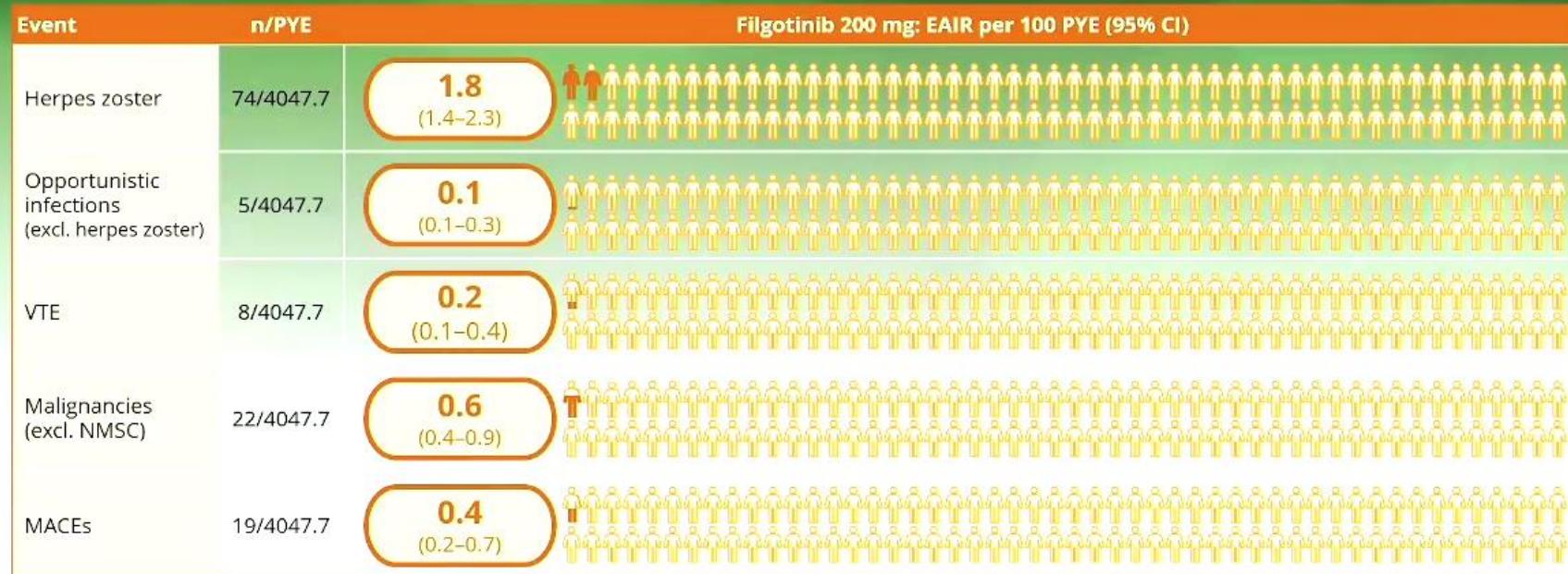
- More **precautionary approach** is recommended for JAKi use in **selected patient population**:
 - those aged 65 years or above
 - those at increased risk of major cardiovascular problems (such as heart attack or stroke)
 - those who smoke or have done so for a long time in the past
 - those at increased risk of cancer
- > In these patients JAK inhibitors should only be used if no suitable treatment alternatives are available
- Recommendation using JAK inhibitors 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.

AEs of Special Interest in the Overall + Phase 3b/4 Cohort (≤ 7.8 years)



[†]All events, including those occurring >28 days after the last dose of study drug, were excluded. [‡]Defined as any infection AE that requires hospitalization or parenteral antimicrobials, or meets other criteria that require the infection to be classified as a serious AE. [§]Excludes tuberculosis and HZ with two adjacent dermatomes. [¶]GI perforation excludes preferred terms of pilonidal cyst, perirectal abscess, rectal abscess, anal abscess, perineal abscess, and any preferred terms containing the word fistula. AE, adverse event; BID, twice daily; CI, confidence interval; GI, gastrointestinal; HZ, herpes zoster; IR, incidence rate; MACE, major adverse cardiovascular event; N, number of patients in the treatment group; n, number of unique patients with a particular AE; NMSC, nonmelanoma skin cancer; PD, predominant dose; PY, patient-years.
Sandborn WJ, et al. J Crohn's Colitis. 2022; doi: 10.1093/ecco-jcc/jac141.

Filgotinib 200 mg: demonstrated safety profile with >4000 patient-years of exposure in RA



Data were integrated from seven trials (NCT01668641, NCT01894516, NCT02889796, NCT02873936, NCT02886728, NCT02065700 and NCT03025308). Results are from placebo-controlled trials through Week 12 and long-term, as-treated (all available data for patients receiving ≥1 dose filgotinib 200 mg daily) datasets. CI, confidence interval; EAIR, exposure-adjusted incidence rate; MACE, major adverse cardiovascular event; NMSC, non-melanoma skin cancer; PI, Prescribing Information; PYE, patient-years of exposure; RA, rheumatoid arthritis; VTE, venous thromboembolism.

Winthrop KL, et al. *Ann Rheum Dis* 2022;81:184–192.

Filgotinib 200 mg: demonstrated safety profile with >4000 patient-years of exposure in RA

Event	n/PYE	Filgotinib 200 mg: EAIR per 100 PYE (95% CI)
 Filgotinib and male fertility - spermatogenesis		
Two specific Phase 2 clinical trials (MANTA and MANTA RAY, n=240) were conducted to assess testicular safety in men with inflammatory arthritis diseases and inflammatory bowel disease.		
Main results		
Primary Endpoint (pooled)		
Proportion of patients with $\geq 50\%$ decrease in sperm concentration (M/mL) at week 13, n (%)	Filgotinib 200mg n=120	Placebo n=120
	8 (6.7%)	10 (8.3%)

Conclusion : Overall, the clinical data from these studies at weeks 13 and 26 do not suggest any filgotinib-related effects on testicular function.

Data were integrated from seven trials (NCT01668641, NCT01894516, NCT02889796, NCT02873936, NCT02886728, NCT02065700 and NCT03025308). Results are from placebo-controlled trials through Week 12 and long-term, as-treated (all available data for patients receiving ≥ 1 dose filgotinib 200 mg daily) datasets. CI, confidence interval; EAIR, exposure-adjusted incidence rate; MACE, major adverse cardiovascular event; NMSC, non-melanoma skin cancer; PI, Prescribing Information; PYE, patient-years of exposure; RA, rheumatoid arthritis; VTE, venous thromboembolism.
Winthrop KL, et al. Ann Rheum Dis 2022;81:184-192.

JAK voor wie?



Patients aiming to withdraw steroids

Patients in need of rapid relief of symptoms

Patients receiving AZA who have residual symptoms

Patients aiming for improved health-related QoL

Patients aiming for long-term disease control

Busy patients with minimal time for appointments

Patients who prefer simple regimens/monotherapy

Expanding treatment options provide opportunities to explore patient preferences and make patient-centric choices

Redenen om in tweede lijn aan JAKi te denken



Treatment impact

Fast relief

Reduces bloody diarrhoea

Reduces non bowel-related pain

Reduces abdominal pain

Reduces bowel urgency

Consistent relief/durability

Prevents UC flare



Level of risk

Tolerability

Long-term safety profile

Avoids aesthetic side effects



Quality of life

Reduces fatigue

Improves sexual/social life

Improves psychological wellbeing

Trust that it will work



Treatment burden

Convenient to take

Route of administration

Flexible dosing

Cost