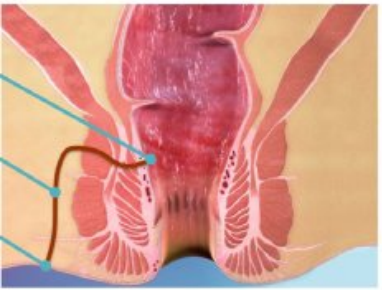

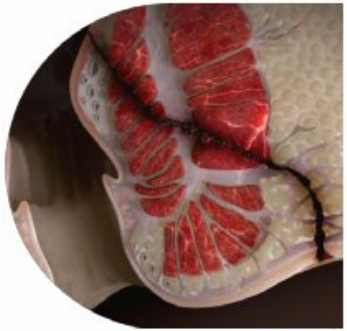

Crohn's fistula: New kids on the block

– Gastroenterologist's options -

PD Dr. med. Pascal Juillerat, M.Sc. (epidemiology)

Leitender Arzt Lindenhofspital & Leitung Crohn und Colitis Kantonsspital Freiburg
Intesto Gastroenterologische Praxis & Crohn-Colitis-Zentrum Bern & Freiburg

www.intesto.ch, juilleratp@intesto.ch

THE UNUSUAL FISTULA:
43. Schweizerische Koloproktologie-Tagung
43ème Journée Suisse de Coloproctologie

27. Januar 2024, Kursaal Bern

Disclosure of potential conflicts of interest

- **P. Juillerat** has received research support from: Vifor Pharma; and has been a consultant and/or advisory board member and/or speaker for: AbbVie, Amgen, Arena Pharmaceuticals, Bristol Myers Squibb, Eli Lilly and Company, Ferring Pharmaceuticals, Gilead Sciences, Janssen, Merck Sharp & Dohme, Pfizer, Pierre Fabre, Roche, Sandoz, Takeda, Tillotts Pharma AG, and UCB Pharma.

OUTLINE

- A short history of FISTULA treatment
- Recent concept in fistulizing Crohn's disease
- New Therapies and Recommendations
- What to do in practice ?

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IBD therapies over time for IBD

1950s
Steroide

1970s
Thiopurines

1990s
Methotrexate

2000s
Anti-TNFs

2015
Anti-Integrines

2016

2017
Ustekinumab

2019
Tofacitinib

2019

Biosimilars

2022
Ozanimod

2023
Risankizumab

USTE

TOFA

OZA

RISA

2024 **:**
JAK -1- inhibitors
Add. IL-23 inhib.
S1P modulators

1998 IFX 2006

2007 ADA 2012

Mulder DJ, et al. J Crohns Colitis. 2014;8:341-8; Park SC, et al. Gut Liver. 2015;9:18-27.

IBD therapies over time for FISTULIZING CROHN'S DISEASE

1950s
Steroide

1970s
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Antibiotics

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1998

2000s
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BASED on evidence

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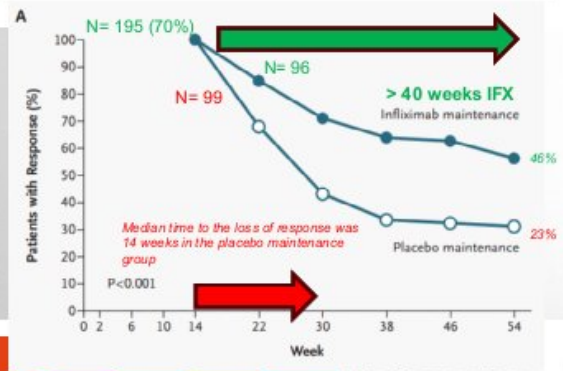
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Infliximab Maintenance Therapy for Fistulizing Crohn's Disease

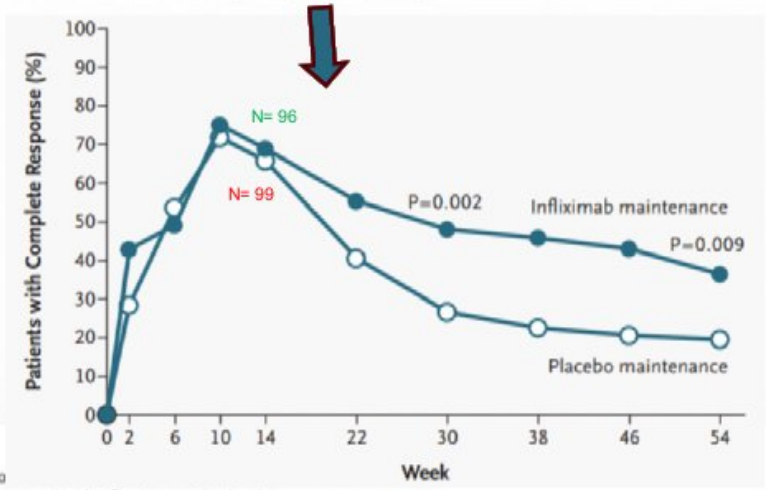
Bruce E. Sands, M.D., Frank H. Anderson, M.D., Charles N. Bernstein, M.D., William Y. Chey, M.D., D.Sc., Brian G. Feagan, M.D., Richard N. Fedorak, M.D., Michael A. Kamm, M.D., Joshua R. Korzenik, M.D., Bret A. Lashner, M.D., Jane E. Onken, M.D., Daniel Rachmilewitz, M.D., Paul Rutgeerts, M.D., Ph.D., Gary Wild, M.D., Ph.D., Douglas C. Wolf, M.D., Paul A. Marsters, M.S., Suzanne B. Travers, M.D., Marion A. Blank, Ph.D., and Sander J. van Deventer, M.D., Ph.D.

ABSTRACT



Only 1 RCT …

- **306 adults** with **CD** with ≥ 1 draining abdominal or perianal **fistulas**
- 282 received IFX (no PBO)
- **195 pts responded (70%) ; 95 (49%) with complete response !**



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ABSTRACT

What we already learned !

– Cross – over response:

PBO → IFX : **61% success !**

IFX 5mg/KG → 10 mg/Kg: **57% success !**

- *Combination Therapy (with AZA and CST), to **prevent** the development of antibodies against infliximab. (4% vs. 13% CST vs. 11% AZA vs. 24% IFX monotherapy)*
- *Antibodies to IFX , lead to 2-3x more Infusion reactions. No change in efficacy.*

Reactions only in 4% (70 of 1728)

Table 2. Incidence of Infusion Reactions According to Infliximab Antibody Status up to Week 54.*

Variable	Antibody Status			All Patients
	Positive†	Negative‡	Inconclusive§	
No. of patients with appropriate samples who could be evaluated (%)¶	44 (17)	80 (31)	134 (52)	258 (100)
Infusion reaction				
No. of patients/total no. (%)	13/44 (30)	13/80 (16)	15/134 (11)	41/258 (16)
No. of infusions/total no. (%)	20/226 (9)	16/332 (5)	24/971 (2)	60/1529 (4)

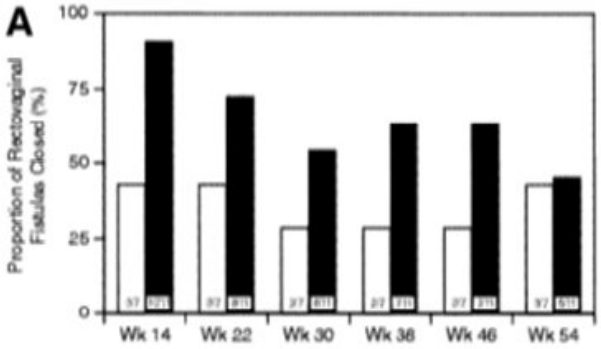
Long-term Treatment of Rectovaginal Fistulas in Crohn's Disease: Response to Infliximab in the ACCENT II Study

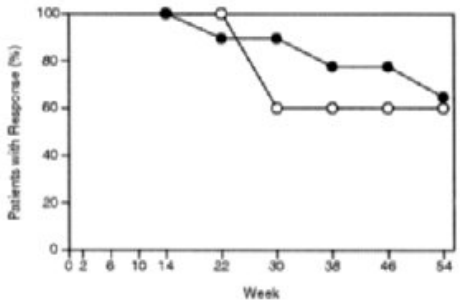
…even Recto-vaginal!

BRUCE E. SANDS,* MARION A. BLANK,† KAM PATEL,† and SANDER J. VAN DEVENTER§
*Gastrointestinal Unit and Center for the Study of Inflammatory Bowel Diseases, Massachusetts General Hospital and Harvard Medic School, Boston, Massachusetts; †Centocor, Inc., Malvern, Pennsylvania; and §Academic Medical Center, Amsterdam, The Netherland

Table 3. Duration of Closure for Draining Rectovaginal Fistulas at Baseline (Excluding Visits After Crossover): All Patients Randomized as Responders

	Placebo maintenance	5 mg/kg Infliximab maintenance
Number of patients randomized	99	96
Number of patients with rectovaginal fistulas	6	10
Average weeks of follow-up	47.6	53.3
Cumulative duration of closure (*weeks*)		
Number of rectovaginal fistulas evaluated	7	11
Mean ± SD	25.1 ± 22.7	44.8 ± 12.7
Median	33.3	46.1
IQ range	(0.0, 46.3)	(40.9, 53.1)
Range	(0.0, 47.6)	(10.1, 54.0)





Treatment Algorithm

10 years ago …

A global consensus on the classification, diagnosis and multidisciplinary treatment of perianal fistulising Crohn's disease

Krisztina B Gecse,[1,2] Willem Bemelman,[3] Michael A Kamm,[4] Jaap Stoker,[5] Reena Khanna,[6,7] Siew C Ng,[8] Julián Panés,[9] Gert van Assche,[10] Zhanju Liu,[11] Ailsa Hart,[12,13] Barrett G Levesque,[14,15] Geert D'Haens,[1,2] for the World Gastroenterology Organization, International Organisation for Inflammatory Bowel Diseases IOIBD, European Society of Coloproctology and Robarts Clinical Trials

Gecse KB, Bemelman W, Kamm MA, et al. Gut 2014;63: 1381–1392.

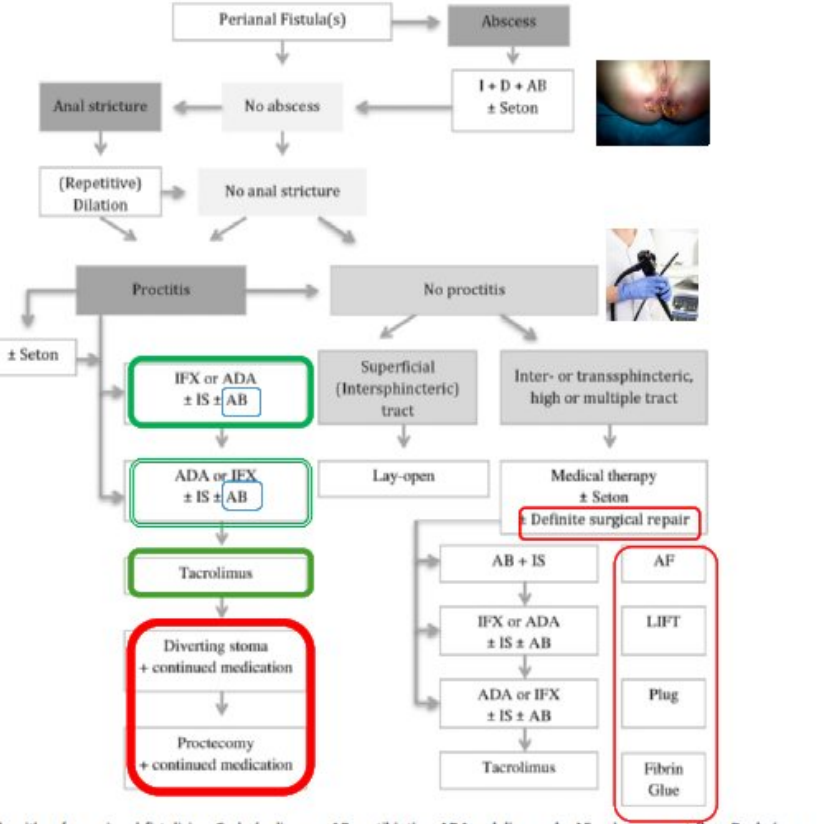


Figure 5 Treatment algorithm for perianal fistulising Crohn's disease. AB, antibiotics; ADA, adalimumab; AF, advancement flap; D, drainage; I, incision; IFX, infliximab; IS, immunosuppressants; LIFT, ligation of the intersphincteric fistula tract.

Intest

OUTLINE

- A short history of FISTULA treatment
- Recent concept in fistulizing Crohn's disease
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- What to do in practice ?

THE LANCET
Gastroenterology & Hepatology

Volume 7, Issue 6, June 2022, Pages 576-584

Viewpoint

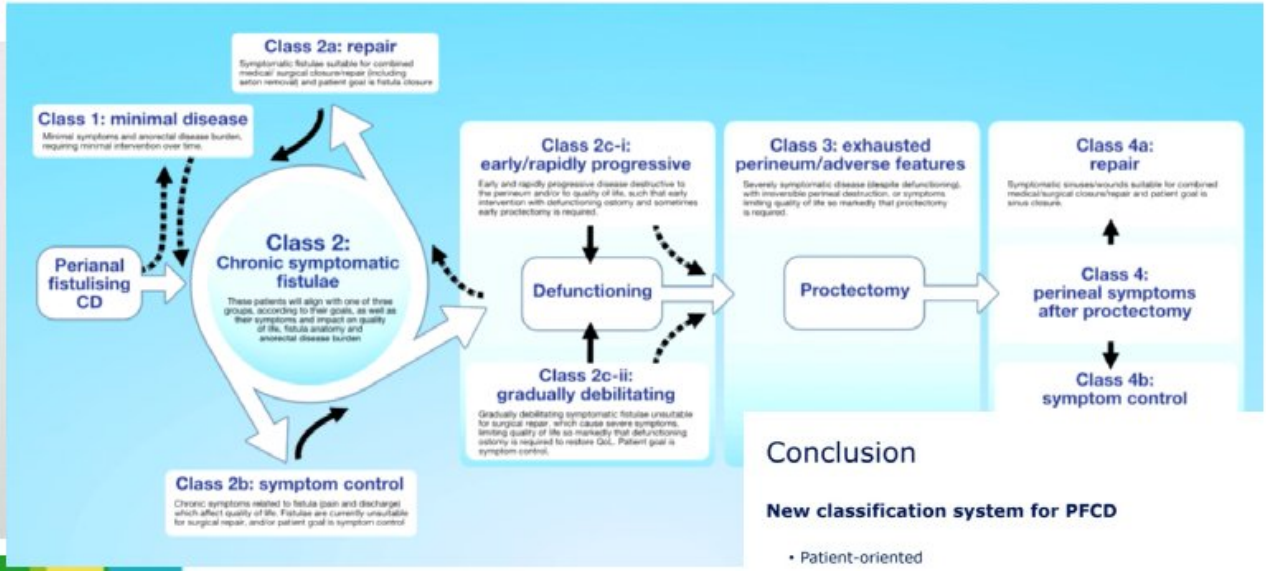
Classifying perianal fistulising Crohn's disease: an expert consensus to guide decision-making in daily practice and clinical trials

Methodology

- Modified nominal group expert consensus process
- Participants:
  - Gastroenterologists
  - Radiologists
  - Surgeons
  - Patient representative

Results

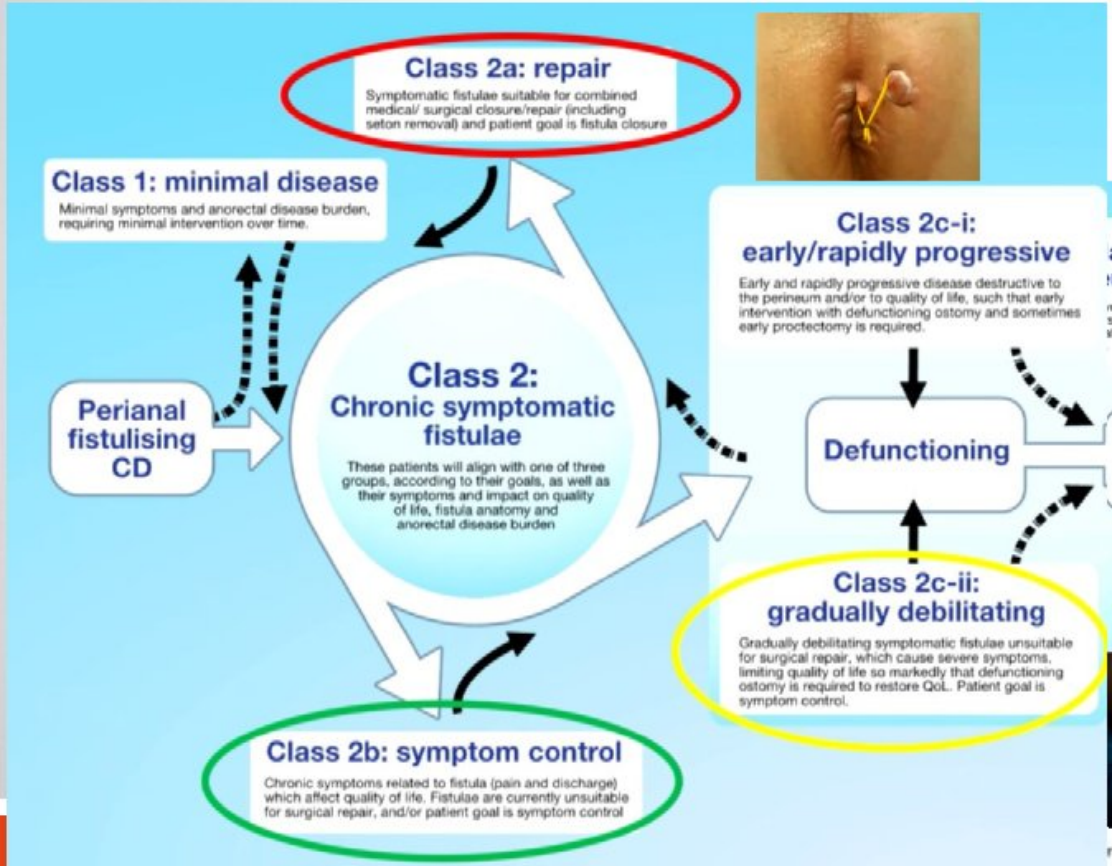
- Identification of **4 groups** of patients with PFCD
- Flexible system – patients cycle over time
- **Key elements:**
  - Stratification by disease severity/outcome
  - Synchronization of patient and clinician goals
  - Proactive, combined medical + surgical approach
  - On '**treat to patient goal**' basis



Conclusion

New classification system for PFCD

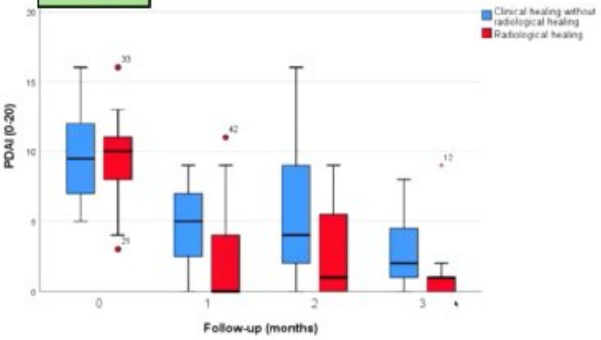
- Patient-oriented
- Paired treatment suggestions and clinical trial suitability


Class 2a: repair
Symptomatic fistulae suitable for combined medical/ surgical closure/repair (including seton removal) and patient goal is fistula closure
Class 1: minimal disease
Minimal symptoms and anorectal disease burden, requiring minimal intervention over time.
Perianal fistulising CD
Class 2: Chronic symptomatic fistulae
These patients will align with one of three groups, according to their goals, as well as their symptoms and impact on quality of life, fistula anatomy and anorectal disease burden
Class 2b: symptom control
Chronic symptoms related to fistula (pain and discharge) which affect quality of life. Fistulae are currently unsuitable for surgical repair, and/or patient goal is symptom control
Class 2c-i: early/rapidly progressive
Early and rapidly progressive disease destructive to the perineum and/or to quality of life, such that early intervention with defunctioning ostomy and sometimes early proctectomy is required.
Defunctioning
Class 2c-ii: gradually debilitating
Gradually debilitating symptomatic fistulae unsuitable for surgical repair, which cause severe symptoms, limiting quality of life so markedly that defunctioning ostomy is required to restore QoL. Patient goal is symptom control.
Proctectomy
ass 3: exhausted
um/adverse features
mptomatic disease (despite defunctioning), sible perineal destruction, or symptoms ality of life so markedly that proctectomy
Symptomatic sin
medical/surgical
sinus closure.
perin
after
sym
Chronic sympton
affect quality of l
surgical repair. O

RADIOLOGICAL CLOSURE OF FISTULA

- Radiological closure is better than clinical closure
- Medical therapy ***only*** is not able to achieve radiological closure in the large majority
- Combination with surgery is warranted to achieve radiologic closure

MRI



Meima et al. Submitted

What is the risk of clinical closure only?

- Recurrent abscess
- Reopening when trough levels are too low
- Stoppage of biologicals not possible
- Additional tracts might develop

Conclusions

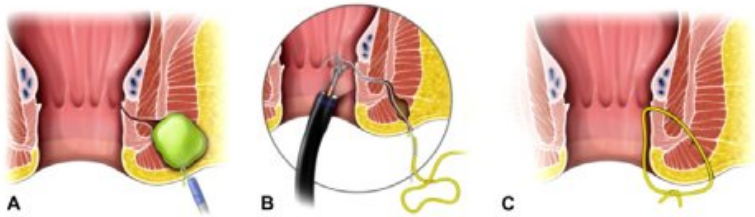
- Failure or success of surgery largely depends on the referring gastroenterologist and the quality of the multidisciplinary team
- Surgery is always an alternative:
  - There are surgeries as alternative for maintenance therapy (**consultation surgeon & shared decision making**)
  - There are surgeries as damage control of failing medical therapy (**no choice!**)

Prof. W.A. Bemelman MD PhD

Intesto Gastro Centre

Endoscopical Management

Endoscopic abscess drainage and seton placement in perianal fistulas in CD:

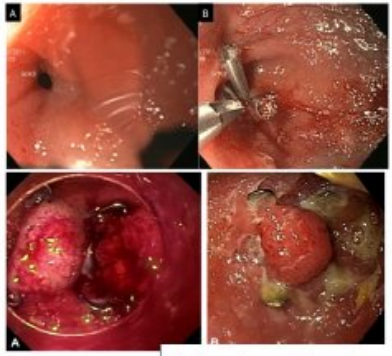


Position statement on endoscopic fistulotomy.

- Endoscopic fistulotomy may be attempted in patients with primary or secondary short, superficial fistulas. (EL-4; GR-C)

- Ileum-cecum
- **Perianal**
- Pouch-pouch

Endoscopic therapy in perianal CD: internal opening closure (clips)



Simple clipping

"Over-the-scope" clipping

Position statement on endoscopic fistula closure.

- Endoscopic closure of a primary fistula opening from CD with clips is not recommended. (EL-4; GR-D)
- Endoscopic clipping may be attempted in anastomotic leak–associated fistula. (EL-4; GR-C)

©ECCO'22 V

Disadvantages of Endoscopic therapy in Perianal CD:

- Inability to excise inflammatory granular tissue from fistula tracks
- Positioning of the patient for better assessment of the perianal region
- Need for local anesthesia in drainage and seton placement
- Lack of prompt alternatives if fistula track cannot be identified due to intrinsic limitations

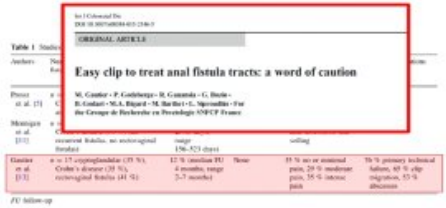
©ECCO'21 Copenhagen Congr

Shen B. Gastrointest Endoscopy, 2017

Internal opening closure in CD perianal fistulas

intest Endoscopy, 201

artesy of Bo Shen (USA



Easy clip to treat anal fistula tracts: a word of caution

Gastroenterologische Praxis & Crohn
Centre Fribourgeois de Gastroentérologie

©ECCO'22 Virtual Congress - Speaker: Paulo G. Kotze

OUTLINE

- A short history of FISTULA treatment
- Recent concept in fistulizing Crohn's disease
- New Therapies and Recommendations
- What to do in practice ?

NKOTB - WHAT ABOUT ?

Officially accepted

- Vedolizumab (Entyvio®) IV or IV → SC.
- Ustekinumab (Stelara®) IV → SC.
- Risankizumab (Skyrizi®) IV → SC.
- Darvadstrocel (Alofisel®) Local injection / surgical suture.

«Off Label» (a glimpse into the future)

- JAK- 1 Inhibitors : Upadacitinib (Rinvoq®) / Filgotinib (Jyseleca®)

Study Design

ENTERPRISE

Phase 4, randomized, double-blind, multicenter study to evaluate the efficacy and safety of two vedolizumab IV dosing regimens in patients with perianal fistulizing CD

Enrollment and study population

N = 52 patients were screened:

- 18–80 years — moderately to severely active CD
- 1–3 — draining perianal fistulae
- inadequate response, loss of response, or intolerance to conventional therapy or anti-TNF

- If a seton was placed as part of the standard of care, it had to be removed by week 14.
- Enrolment was closed after randomizing 34 participants because of challenges in recruitment, not because of safety concerns. Thus, all analyses are descriptive.

Schwartz DA, et al. *Clin Gastroenterol Hepatol*. 2021;S1542-3565(21)01042-9. doi: 10.1016/j.cgh.2021.09.028.

Baseline demographics and disease characteristics

ENTERPRISE

10/28 patients had complex fistula

	VDZ (N=14)	VDZ + week 10 (N=14)	VDZ POOLED (N=28)
Median age (min, max), years	31.5 (23, 44)	36.0 (21, 59)	34.0 (21, 59)
Male, n (%)[a]	8 (57.1)	9 (64.3)	17 (60.7)
Median (min, max) duration of CD, years[b]	11.2 (0.7, 37.6)	6.1 (0.5, 25.4)	8.5 (0.5, 37.6)
Mean (SD) baseline[b] CDAI	281.9 (73.1)	302.8 (90.9)	292.3 (81.6)
Previous anti-TNF treatment, n (%)[a]	11 (78.6)	11(78.6)	22 (78.6)
Concomitant treatment at baseline,[c] n (%)[a] Corticosteroids Immunosuppressants	 3 (21.4) 4 (28.6)	 2 (14.3) 3 (21.4)	 5 (17.9) 7 (25.0)
Number of draining fistulas at baseline,[c] n (%) 1 2	 5 (35.7) 9 (64.3)	 12 (85.7) 2 (14.3)	 17 (60.7) 11 (39.3)
Median (min, max) duration of fistulizing disease, years	4.6 (0.5, 20.7)	1.8 (0.1, 15.8)	3.0 (0.1, 20.7)
Mean (SD) baseline[d] PDAI	8.1 (2.2)	7.5 (3.1)	7.8 (2.7)
Seton placement[e] at baseline,[b] n (%)[a]	13 (92.9)	13 (92.9)	26 (92.9)

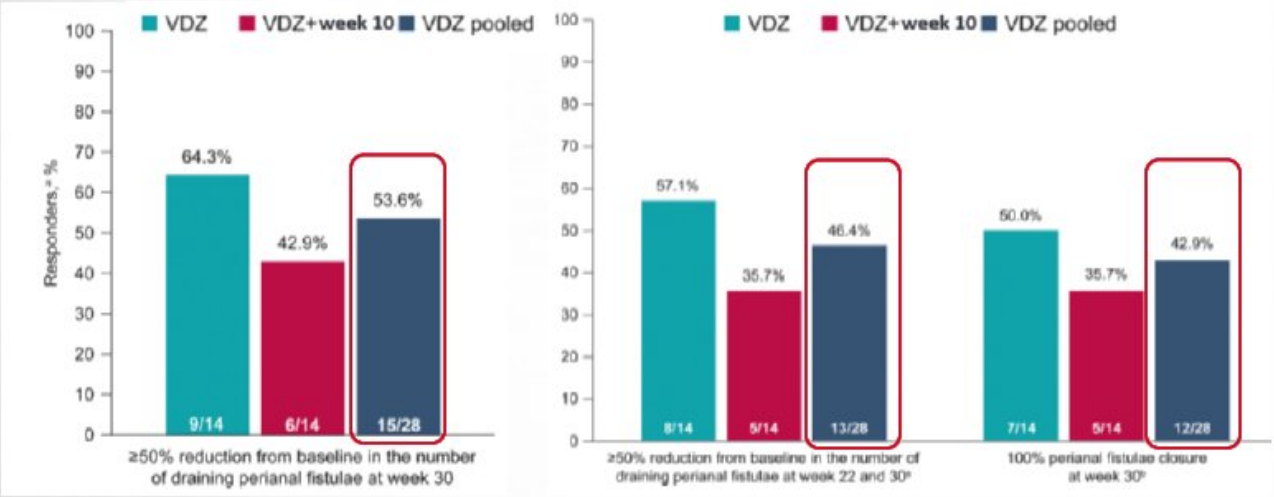
Schwartz DA, et al. *Clin Gastroenterol Hepatol*. 2021;S1542-3565(21)01042-9. doi: 10.1016/j.cgh.2021.09.028.

Intesto

Gastroenterologische Praxis & Crohn-Colitis-Zentrum Bern
Centre Fribourgeois de Gastroentérologie

More than half of all vedolizumab patients achieved ≥50% decrease from baseline in the number of draining fistulas at Week 30

ENTERPRISE



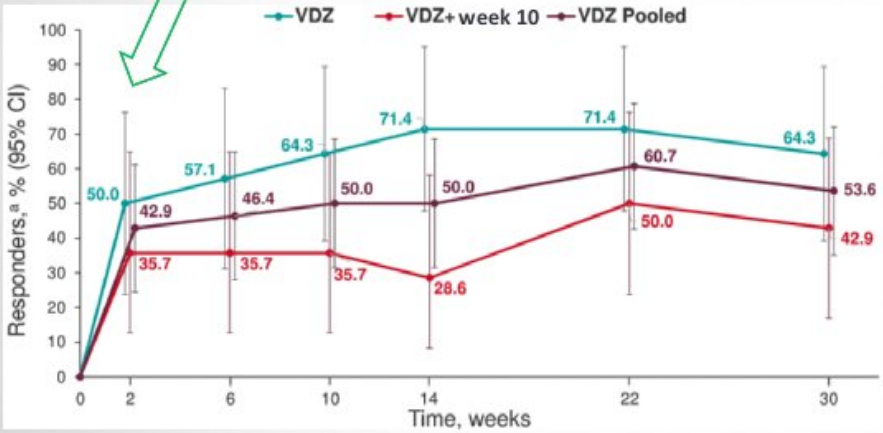
Schwartz DA, et al. *Clin Gastroenterol Hepatol*. 2021;S1542-3565(21)01042-9. doi: 10.1016/j.cgh.2021.09.028.

Intesto

Gastroenterologische Praxis & Crohn-Colitis-Zentrum Bern
Centre Fribourgeois de Gastroentérologie

Vedolizumab was associated with rapid improvement in fistula response

ENTERPRISE



> Half of all vedolizumab patients (53.6%) achieved > 50% decrease from baseline in the number of draining fistulas at week 30

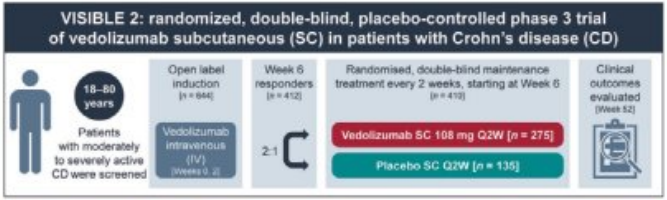
clinically relevant reductions in the number of draining fistulas were seen **as early as Week 2** and maintained through week 30 regardless of the dosing regimen

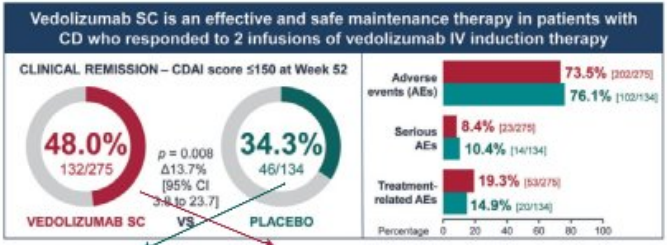
Schwartz DA, et al. *Clin Gastroenterol Hepatol*. 2021;S1542-3565(21)01042-9. doi: 10.1016/j.cgh.2021.09.028.

Vedolizumab SC – **VISIBLE 2 Study**

- History of fistulizing disease, n [%] : 34 [25.4] 53 [19.3]
- Draining fistula at baseline, n [%] 12 [9.0] 14 [5.1]

Vermeire, S., G. D'Haens, F. Baert, S. Danese, T. Kobayashi, E.V. Loftus, Jr, S. Bhatia, C. Agboton, M. Rosario, C. Chen, W. Zhang, K. Kisfalvi and W.J. Sandborn, 2021. Efficacy and safety of subcutaneous vedolizumab in patients with moderately to severely active crohn's disease: Results from the visible 2 randomised trial. Journal of Crohn's and Colitis, 16(1): 27-38.





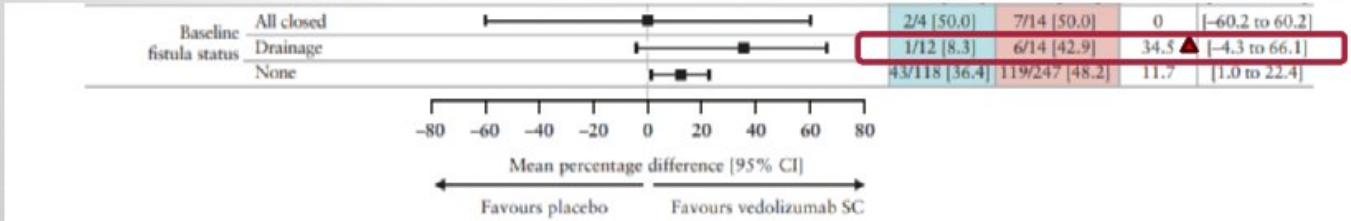
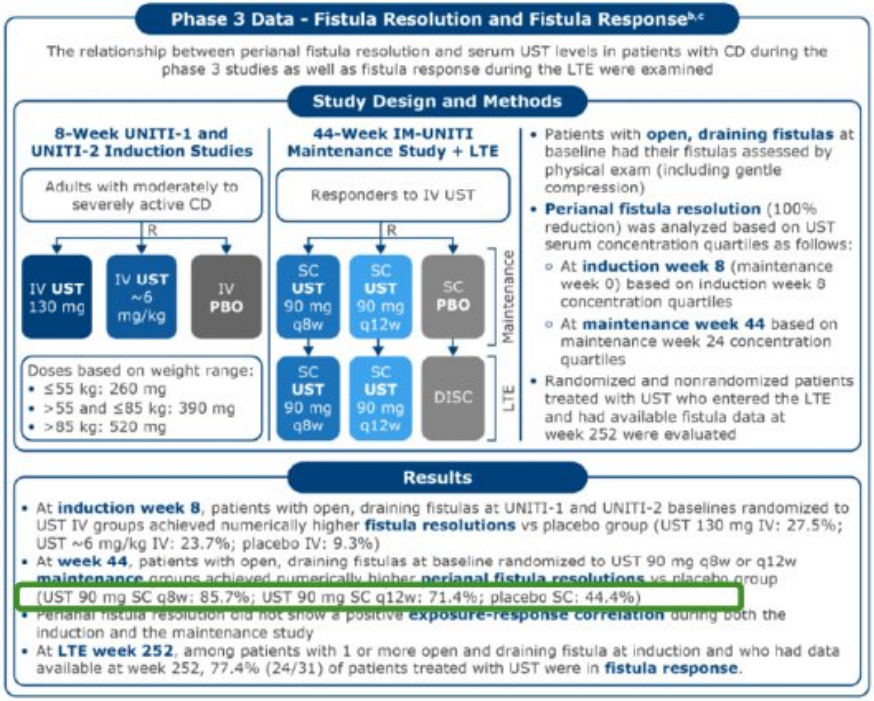


Figure 2. Clinical remission at Week 52 by subgroups based on key patient and disease characteristics [full analysis set]. Anti-TNF, anti-tumour necrosis factor; CI, confidence interval; CRP, C-reactive protein; CS, corticosteroids; IMM, immunomodulator; SC, subcutaneous.

Ustekinumab – S

Table 3 Efficacy data of ustekinumab for Crohn's disease in registration trials and po

Study	Design	Patients
Registration trials		
Sandborn *et al.* (CERTIFI)[51]	RCT (phase 2b) *Induction:* IV UST 1 mg/kg vs 3 mg/kg vs 6 mg/kg vs placebo *Maintenance:* SC UST 90 mg at week 8 and 16	CD: 526
N=15 Perianal CD		
Feagan *et al.* (UNITI-1, UNITI-2, and IM-UNITI)[43]	RCT (phase 3) Induction UNITI-1 (patients failing anti-TNF therapy) IV UST 130 mg vs 6 mg/kg vs placebo UNITI-2 (patients failing conventional therapy) IV UST 130 mg vs 6 mg/kg vs placebo Maintenance (IM-UNITI) SC UST 90 mg Q8W vs Q12W vs placebo	CD: 741 CD: 628 CD: 397



While up to 43% of patients in UNITI-1 and 30% of patients in UNITI-2 trials had perianal disease,
→ the efficacy of ustekinumab in patients with perianal CD was not specifically addressed.

Limited real-world data have reported favorable efficacy, with a clinical improvement rate of 61–100%.
It is possible that this cohort of patients may benefit from a higher ustekinumab trough level, but more data will be required.

12:30 - 13:30

★ *P495: Perianal fistula closure in patients receiving ustekinumab: Results from the SEAVUE and STARDUST trials*

L. Peyrin-Biroulet[1], R. Panaccione[2], C. Gasink[3], T. Hoops[3], J.L. Izanec[3], T. Ma[4], M. Nazar[5], I. Bravata[6], M. Lahaye[7], P.M. Irving[8], E.V. Loftus[9], S. Danese[10], B.E. Sands[11].

[1]Nancy University Hospital, Gastroenterology, Vandœuvre-lès-Nancy, France.

P495

PERIANAL FISTULA CLOSURE IN PATIENTS RECEIVING USTEKINUMAB: RESULTS FROM THE SEAVUE AND STARDUST TRIALS

L. Peyrin-Biroulet,[1] R. Panaccione,[2] C. Gasink,[3] T. Hoops,[4] J.L. Izanec,[3] T. Ma,[3] M. Nazar,[5] I. Bravatà,[6] M. Lahaye,[7] P.M. Irving,[8,9] E.V. Loftus, Jr.,[10] S. Danese,[11] B.E. Sands[12]

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BACKGROUND/OBJECTIVE

- Perianal fistulas are common in patients with Crohn's disease (CD) and cause significant quality of life impairment
- Ustekinumab (UST), an IL12/23(p40) antagonist, is approved for the treatment of moderate to severe CD
- In previous Phase 2 and 3 studies, ustekinumab has demonstrated some efficacy in fistula resolution with no clear dose-response relationship[1]
- Additional studies are required to evaluate the role of ustekinumab in perianal fistula treatment
- **We evaluated the outcomes of patients with fistulas in two recent studies of ustekinumab, SEAVUE and STARDUST, which both featured one year of continuous treatment**

CONCLUSIONS

- **Half (50%) of the ustekinumab treated patients from SEAVUE and STARDUST were in fistula resolution after ~1 year of maintenance therapy**
- **No relationship was observed between fistula resolution and ustekinumab or adalimumab serum drug concentrations**
- **The SEAVUE and STARDUST studies provide additional data for the utility of ustekinumab in achieving fistula resolution**

12:30 - 13:30

P495: Perianal fistula closure in patients receiving ustekinumab: Results from the SEAVUE and STARDUST trials

L. Peyrin-Biroulet[1], R. Panaccione[2], C. Gasink[3], T. Hoops[3], J.L. Izanec[3], T. Ma[4], M. Nazar[5], I. Bravata[6], M. Lahaye[7], P.M. Irving[8], E.V. Loftus[9], S. Danese[10], B.E. Sands[11].

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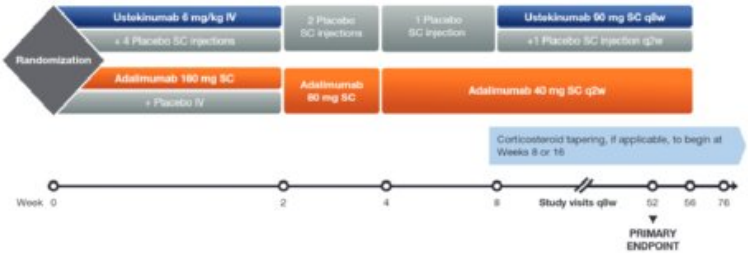
METHODS

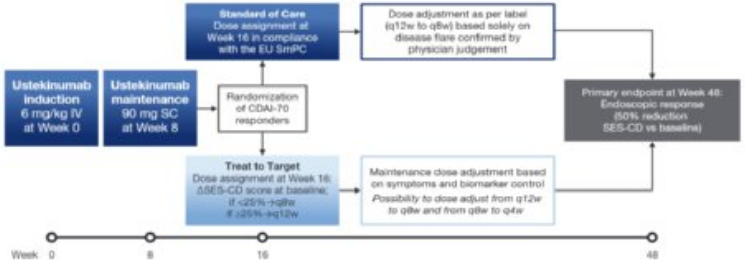
SEAVUE[2]

- Biologic-naive patients
- Randomized and blinded treatment with ustekinumab or adalimumab
- Perianal fistulas were evaluated at baseline and week 52
- Perianal fistula resolution was defined as **closure of all fistulas**
- Patients with missing data at week 52 were considered to not have fistula resolution
- Patients who had a prohibited CD-related surgery, discontinued for lack of efficacy or an adverse event of worsening CD, or had prohibited concomitant medication changes before week 52 were considered not to be in fistula resolution



STARDUST[1]

- Biologic-naive patients or those who previously failed one biologic
- Open-label ustekinumab induction and maintenance treatment
  - At week 16, patients who had responded to induction treatment were randomized to standard of care or treat-to-target maintenance treatment regimens per the figure below
- Perianal fistulas were evaluated at baseline and week 48
- Perianal fistula resolution was defined as **closure of all fistulas**
- Patients with missing data at week 48 were considered to not have fistula resolution



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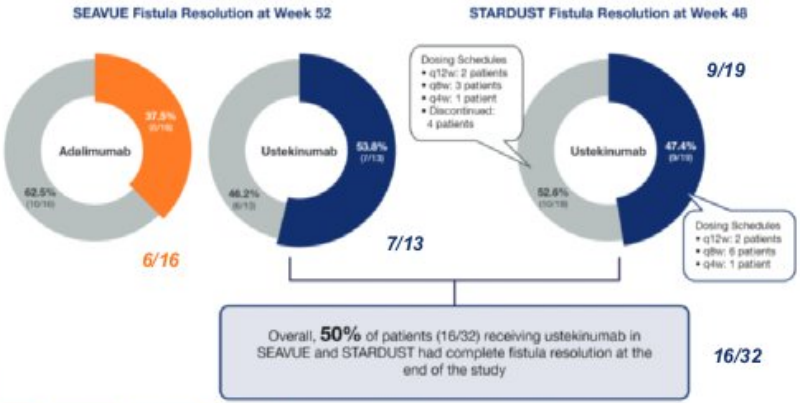
Patients with open and draining fistulas at baseline: **N= 48**

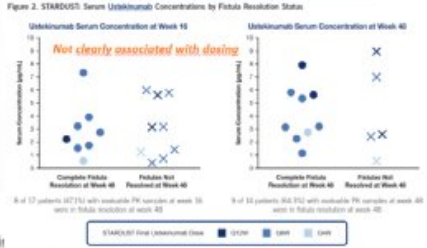
- SEAVUE: 13 of 191 patients (6.8%) randomized to ustekinumab and 16 of 195 patients (8.2%) randomized to adalimumab
- STARDUST: 19 of 440 patients (4.3%) randomized to maintenance treatment (standard of care or treat-to-target)
- In both SEAVUE and STARDUST the median fistula number was 1

Figure 1. Perianal Fistula Resolution at Week 48 and 52



numericaly higher rate of fistula resolution compared to adalimumab, however small groups

No dose response (according to PK)



RISANKIZUMAB - GETAID multicenter cohort study

- **Methods :** From May 2021 to May 2022, all patients with refractory luminal CD treated with risankizumab in 22 French GETAID centers were retrospectively included.
  - **Population :** All patients (**N= 100**) were **exposed to at least 3 biologics**

Effectiveness of Risankizumab in Fistulizing Crohn's disease at week 12

- **Among the 25 patients with active perianal CD at week 0:**
  - **12/25 (48%)** achieve **response** according to physician judgement
  - **7/25 (28%)** achieve **remission** according to physician judgement

Risankizumab was administered intravenously at a dose of 600 mg at week 0, 4 and 8.

Fumery M, et al. Effectiveness and safety of risankizumab induction therapy for 100 patients with Crohn's disease: A GETAID multicenter cohort study. Aliment Pharmacol Ther. 2023 Feb;57(4):426-434.

Darvadstrocel – Landmark study : **ADMIRE -CD**

European countries and Israel from July 6, 2012, to July 27, 2015. N= 212 patients

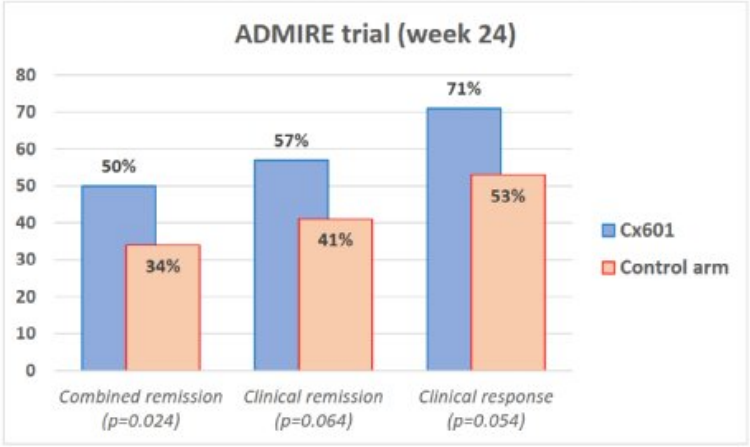


Figure 2. ADMIRE randomized trial results of efficacy at week 24.

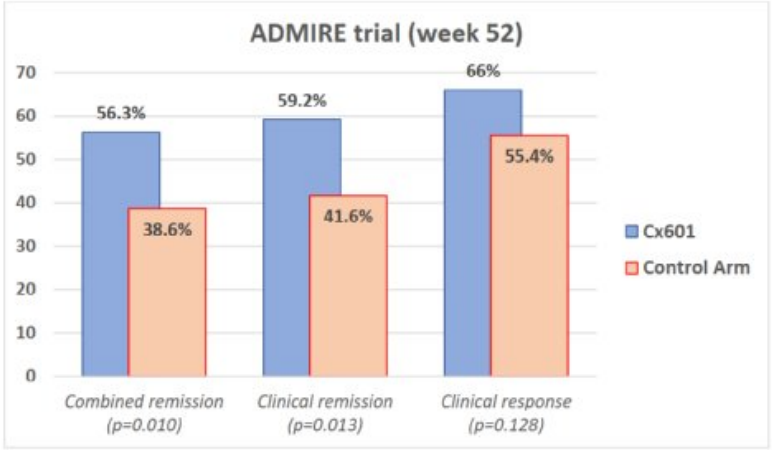
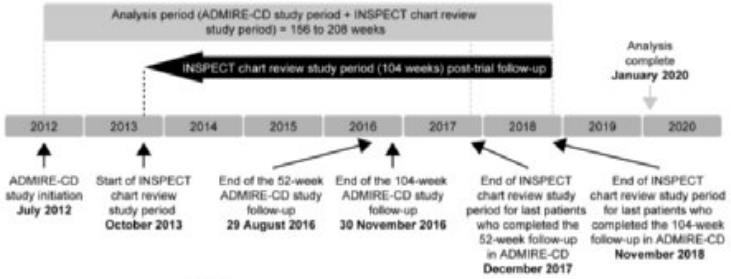
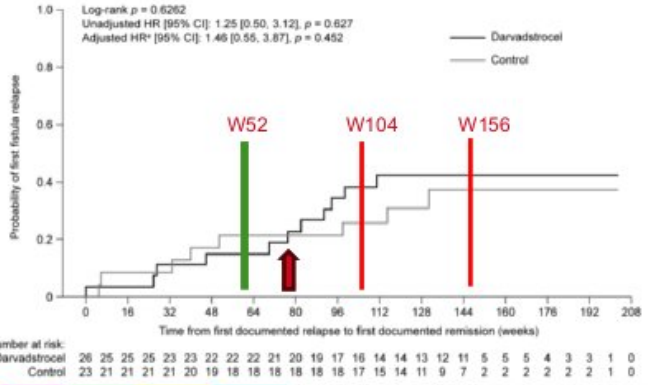


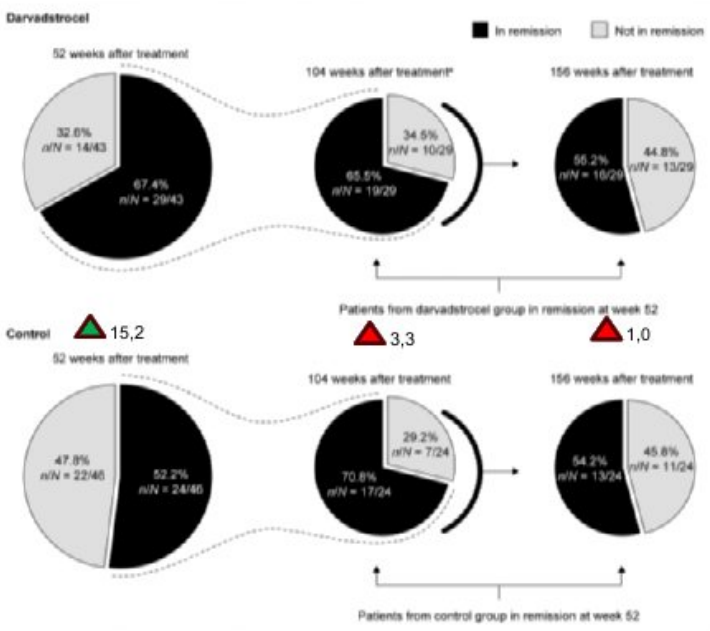
Figure 3. Long-term extension efficacy results of the ADMIRE randomized trial at week 52.

Panés, J., et al., 2016. Expanded allogeneic adipose-derived mesenchymal stem cells (cx601) for complex perianal fistulas in crohn's disease: A phase 3 randomised, double-blind controlled trial. **The Lancet, 388(10051): 1281-1290.**

Darvadstrocel – Follow up study : **INSPECT**







Panes et al. Inflammatory Bowel Diseases, 2022, **28**, 1737–1745

Darvadstrocel – Phase III study : **ADMIRE-CD II**

European countries, **US and canadian centers** and Israel from July 6, 2012, to July 27, 2015. N= 554 participants

Takeda ABOUT SCIENCE OUR IMPACT NEWSROOM INVESTORS CAREERS SEARCH... GLOBAL | EN

Takeda Announces Topline Results of Phase 3 ADMIRE-CD II Trial of Alofisel® (darvadstrocel) in Complex Crohn's Perianal Fistulas

October 17, 2023 Share

OSAKA, Japan, October 18, 2023, and CAMBRIDGE, Massachusetts, October 17, 2023 – Takeda (TSE:4502/NYSE: TAK) today announced that the Phase 3 ADMIRE-CD II study, assessing the efficacy and safety of Alofisel® (darvadstrocel) for the treatment of complex Crohn's Perianal Fistulas (CPF), did not meet its primary endpoint of combined remission at 24 weeks, based on topline data. The safety profile for darvadstrocel was consistent with prior studies and there were no new safety signals identified.

"While we are disappointed with this outcome, we recognize that medical research for difficult-to-treat conditions such as complex CPF remains challenging," said Chinwe Ukomadu, head of the GI & Inflammation Therapeutic Area Unit at Takeda. "We believe there are valuable lessons to learn from ADMIRE-CD II and are grateful to the patients and investigators who made this important research possible."

Full results of the study will be presented at a future medical meeting or published in a peer-reviewed journal.

Efficacy and Safety of Upadacitinib for the Treatment of Fistulas and Fissures in Patients With Crohn's Disease

Jean-Frederic Colombel,[1] Peter Irving,[2] Florian Rieder,[3] Remo Panaccione,[4] David Schwartz,[5] Ryohei Hayashi,[6] Xuan Zhu,[7] Ana P. Lacerda,[8] Elena Dubcenco,[8] Elena Marced,[8] Patrick Hecht,[8] Tian Feng,[8] Sofie Berg,[8] Walter Reinisch[9]

[1]Department of Gastroenterology, Icahn School of Medicine at Mount Sinai, New York, NY, USA; [2]IBD Centre, Guy's and St Thomas' NHS Foundation Trust, London, UK; [3]Department of Gastroenterology, Hepatology & Nutrition, Digestive Diseases and Surgery Institute, Cleveland Clinic, Cleveland, OH, USA; [4]Inflammatory Bowel Disease Unit, University of Calgary, Calgary, AB, Canada; 5Department of Gastroenterology and Hepatology, Vanderbilt University Medical Center, Nashville, TN, USA; [6]Department of Endoscopy, Hiroshima University Hospital, Hiroshima, Japan; [7]Departments of Gastroenterology and Hepatology, First Affiliated Hospital of Nanchang University, Nanchang, Jiangxi, China; [8]AbbVie Inc., North Chicago, IL, USA; [9]Department of Internal Medicine, Medical University of Vienna, Vienna, Austria

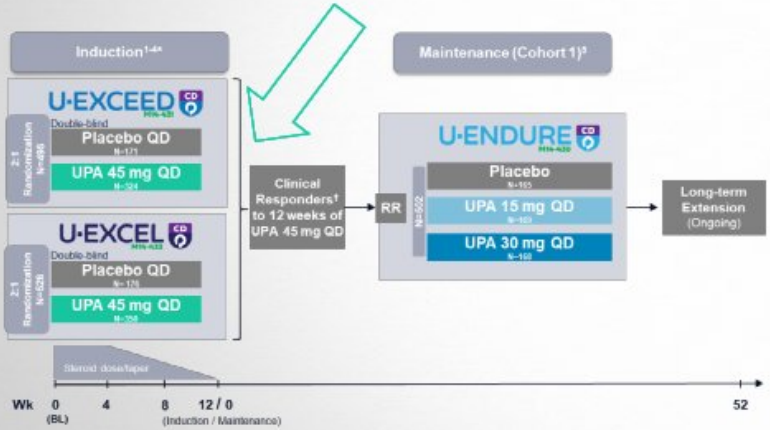
Upadacitinib is not approved for IBD by Swissmedic

Intesto

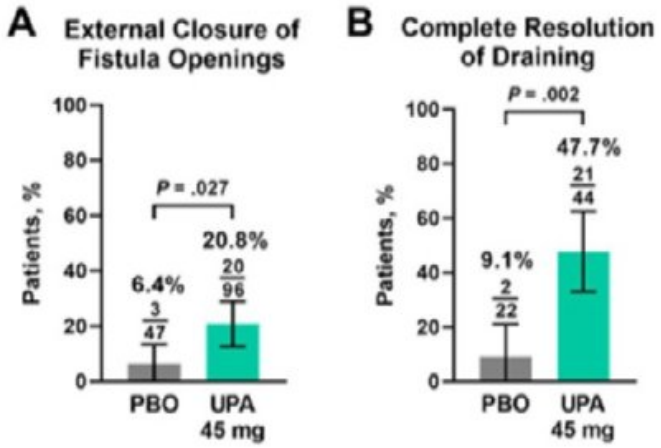
18th Congress of the European Crohn's and Colitis Organisation (ECCO) 2023, Copenhagen, Denmark

JAK-Inhibitors : **Upadacitinib**

Upadacitinib Phase 3 CD Clinical Program



At week 12



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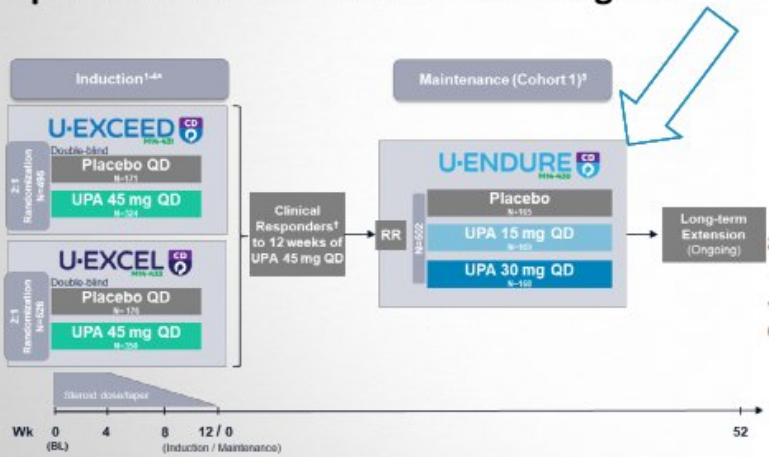
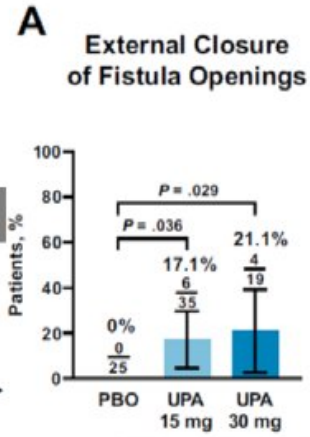
Colombel J-F. et al. Efficacy and Safety of Upadacitinib for the Treatment of Fistulas and Fissures in Patients With Crohn's Disease; Mar 2023 ECCO

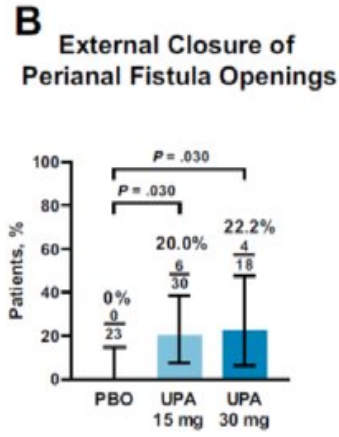
JAK-Inhibitors : **Upadacitinib**

Upadacitinib Phase 3 CD Clinical Program



At week 52





Upadacitinib is not approved for IBD by Swissmedic

Colombel J-F. et al. Efficacy and Safety of Upadacitinib for the Treatment of Fistulas and Fissures in Patients With Crohn's Disease; Mar 2023 ECCO

JAK-Inhibitors : **Filgotinib**

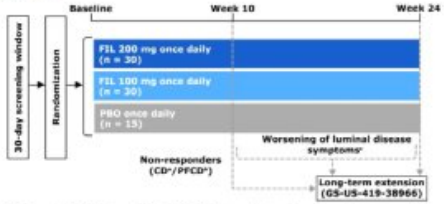
Efficacy and safety of filgotinib for the treatment of perianal fistulizing Crohn's disease: results from the phase 2 DIVERGENCE 2 study

Presenting author: Walter Reinisch[1]

Co-authors: Jean-Frederic Colombel[2], Geert R D'Haens[3], Jordi Rimola[4], Angela de Haas-Amatsaleh[5], Matt McKevitt[6], Xuehan Ren[6], Adrian Serone[6], David A Schwartz[7] and Krisztina B Gecse[3]

DIVERGENCE 2 study design

- Adults (18–75 years) with PFCD, defined as 1–3 perianal external openings (EOs) with drainage (spontaneous or on compression) at day 1 and for ≥ 4 weeks before screening. Noncutting perianal seton(s) were removed ≥ 14 days prior to day 1
- Documented diagnosis of CD for at least 3 months (CDAI score ≤ 300 at screening)
- Prior treatment failure



Methods

Efficacy assessments:

- **The primary endpoint** was combined fistula response at week 24
  - Reduction ≥ 1 from baseline in the number of draining EOs, as determined by investigator assessment, and no fluid collections > 1 cm on centrally read pelvic MRI
- **A key secondary endpoint** was combined fistula remission at week 24
  - Closure of all draining EOs present at baseline and no fluid collections > 1 cm
- **Additional secondary endpoints** included:
  - Time to clinical fistula response

Safety assessments included adverse events, physical examinations, vital signs, clinical laboratory evaluations and electrocardiogram.

A total of approximately 75 patients were planned to be randomized. The study was not powered for statistical comparisons

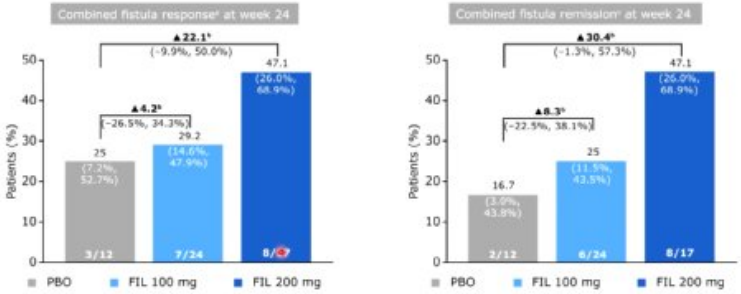
AE, adverse event; CDAI, Crohn's disease Activity Index; EO, external opening

*CD non-responder: baseline CDAI score ≥ 220 without a ≥ 70-point CDAI reduction from baseline at any point up to week 10, or baseline CDAI score < 220 with an increase in CDAI of ≥ 100 points from baseline, with CDAI ≥ 220 at week 10; †PFCD non-responder: PDAI 'Discharge' subscore > 1 and ≥ 1-point increase from baseline, at weeks 6 and 10, or PDAI 'Pain/restriction of activities' subscore > 1, and a ≥ 1-point increase from baseline, at weeks 6 and 10; ‡ Worsening of luminal disease symptoms: ≥ 100-point increase in CDAI score from the week 10 value and CDAI score ≥ 220 points at two consecutive visits

CD, Crohn's disease; CDAI, Crohn's disease Activity Index; FIL, filgotinib; PBO, placebo; PDAI, Perianal Disease Activity Index; PFCD, perianal fistulizing Crohn's disease

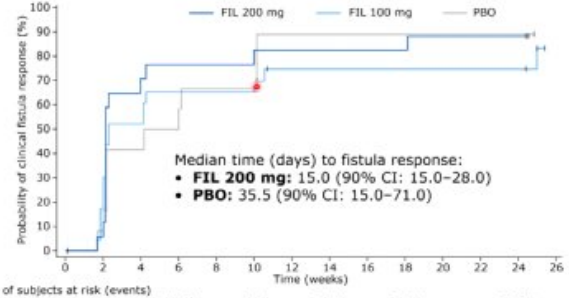
Folgotinib is not approved for IBD by Swissmedic

Results: combined fistula response and remission at week 24



[a]Combined fistula response was defined as the reduction of ≥ 1 from baseline in the number of draining EOs and the absence of fluid collections > 1 cm on MRI
[b]Risk difference in proportions (90% CI): non-responder imputation
[c]Combined fistula remission was defined as perianal fistula closure of all EOs that were draining at baseline and absence of fluid collections > 1 cm on MRI
CI, confidence interval; EO, external opening; FIL, filgotinib; MRI, magnetic resonance imaging; PBO, placebo

time to clinical fistula closure



CI, confidence interval; FIL, filgotinib; PBO, placebo

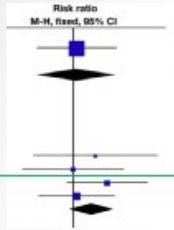
Folgotinib is not approved for IBD by Swissmedic

OUTLINE

- A short history of FISTULA treatment
- Recent concept in fistulizing Crohn's disease
- New Therapies and Recommendations
- What to do in practice ?

Treatment Algorithm: 10 years LATER …

INDUCTION OF
FISTULA REMISSION



ATB : **1.20** [0.17, 8.38]

AZA : **2.47** [0.85, 7.21]

Anti-TNF: **2.06** [1 .40, 3.04] → **3.57** [1.38, 9.25]

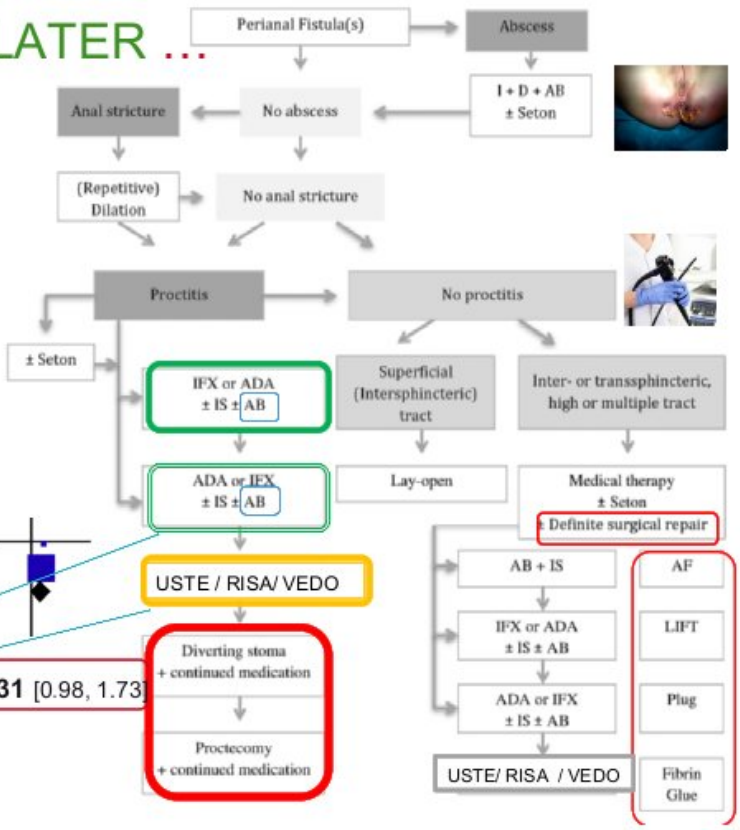
USTE : **1.77** [0.93, 3.37]

VEDO : **2.54** [0.63, 10.29]

RISA : ?

JAK – inhibitors ?

STEM Cells : **1.31** [0.98, 1.73]



Intest

Lee MJ, *et al*. Efficacy of Medical Therapies for Fistulizing Crohn's Disease: Systematic Review and Meta-analysis. Clin Gastroenterol Hepatol. 2018 Dec;16(12):1879-1892. doi: 10.1016/j.cgh.2018.01.030. Epub 2018 Jan 31. PMID: 29374617.

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