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GastroHighlights
9. Dezember 2023
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IBD

Gerhard Rogler, Klinik für Gastroenterologie und Hepatologie
UniversitätsSpital Zürich

Interessenskonflikte

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.

Co-Founder and Head of Scientific Advisory Board: PharmaBiome

….und es stimmt doch…..

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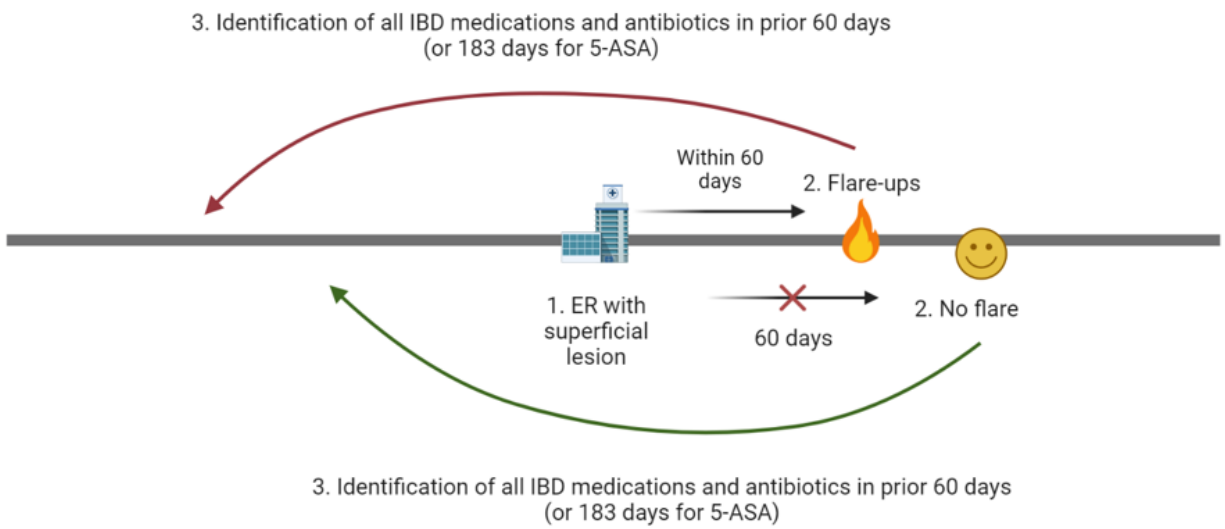
Specific antibiotics increases the risk of flare-ups in patients with inflammatory bowel disease – results from a Danish nationwide population-based nested case-control study.

Bobby Lo[1,2], Luc Biederman[3], Gerhard Rogler[3], Barbara Dora[3], Andrea Kreienbühl[3], Ida Vind[1,2,4], Flemming Bendtsen[1,2,4], Johan Burisch[1,2]

Figure 1 – How the cohorts were assembled.



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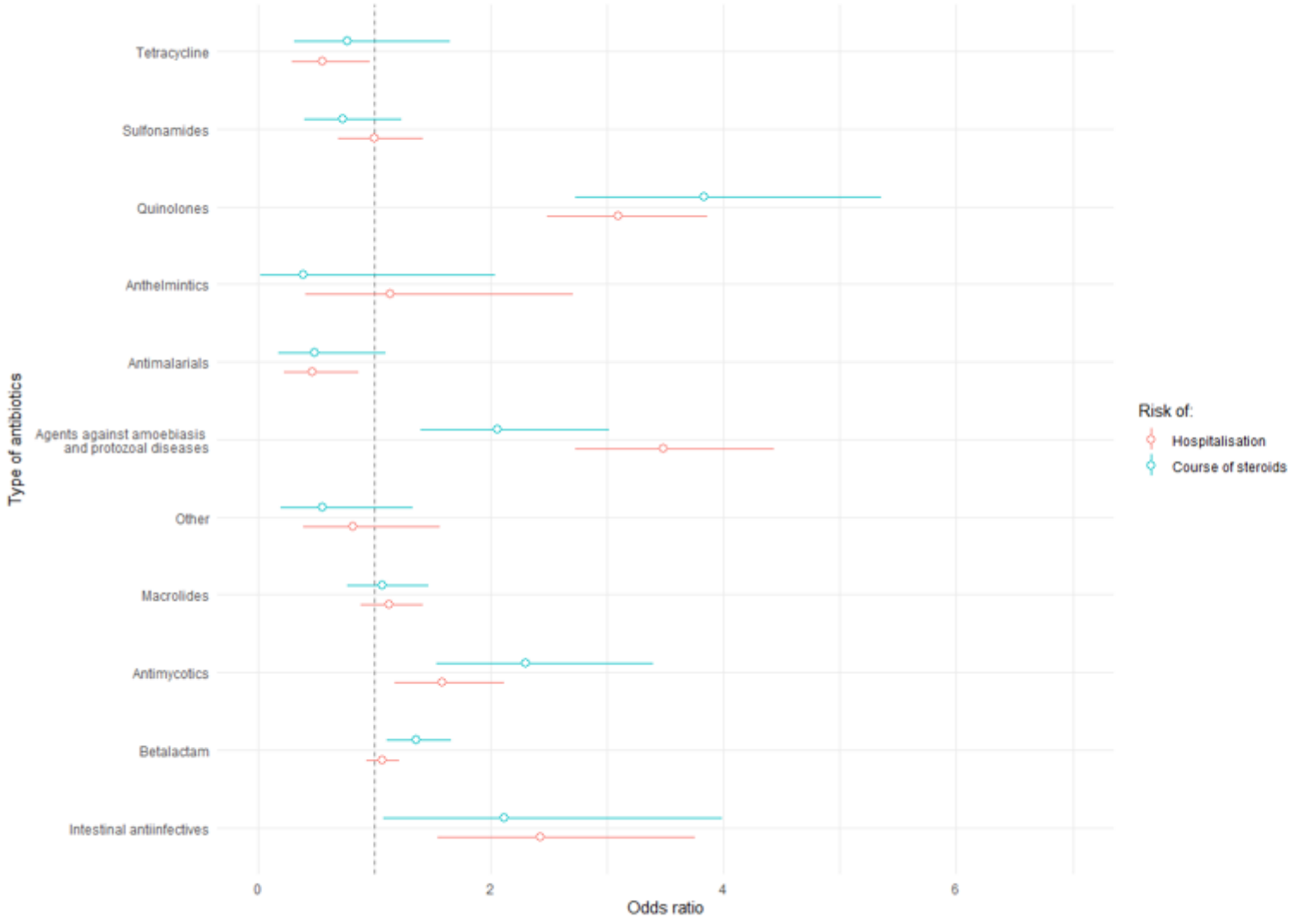
Risiko von Schüben bei IBD

Figure 2 – Odds ratios of antibiotics for the risk of flare-ups defined as either an inflammatory bowel disease-related hospitalisation or course of steroids.



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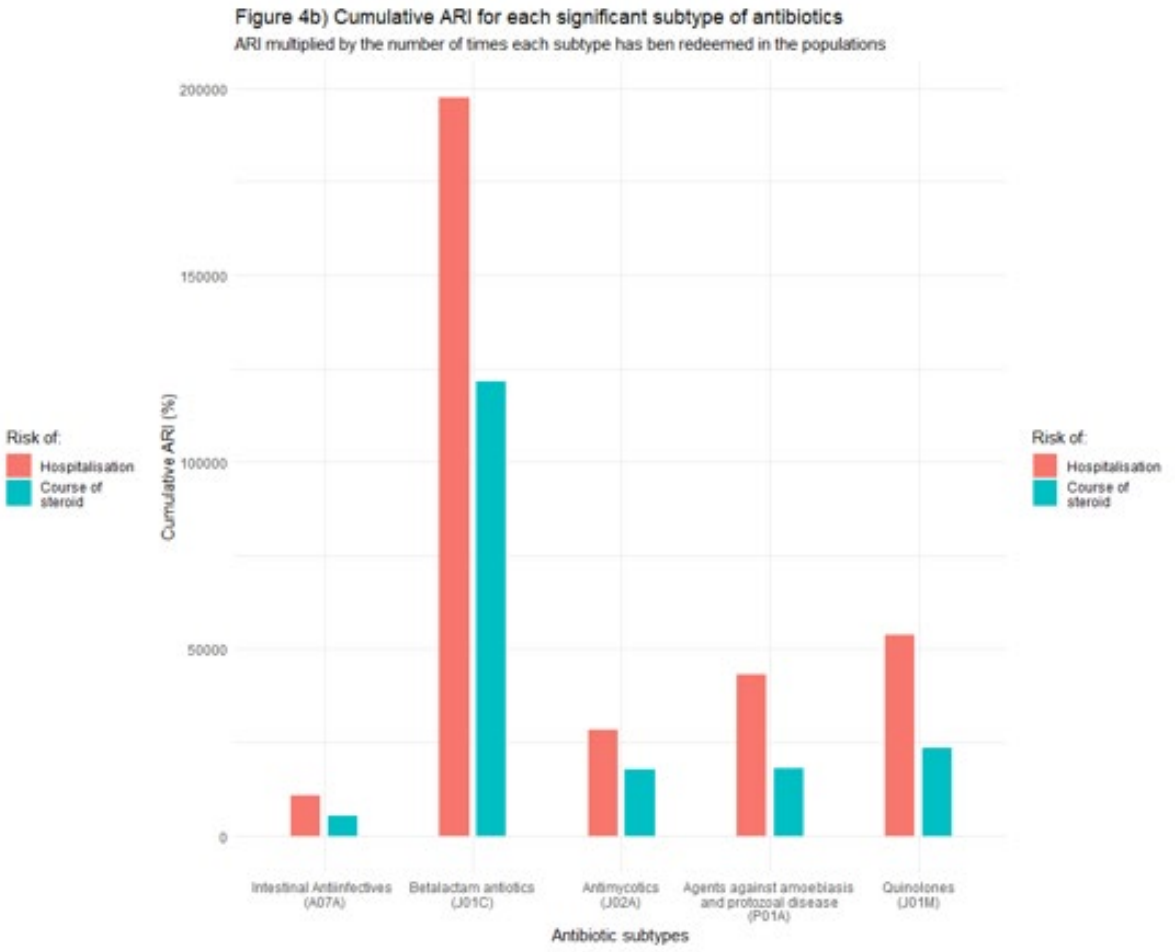
Risiko von Schüben bei IBD



"We found distinctive antibiotics to be significantly associated with an increased risk of IBD flare-ups. Our findings are corroborated by our GBDT machine learning models. Healthcare providers should be aware about the deleterious potential of specific antibiotic groups in patients with IBD only using these agents in a restrictive manner or preferentially consider alternative antibiotic groups."

Neue Daten zu JAK Hemmern

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9. Dezember 2023
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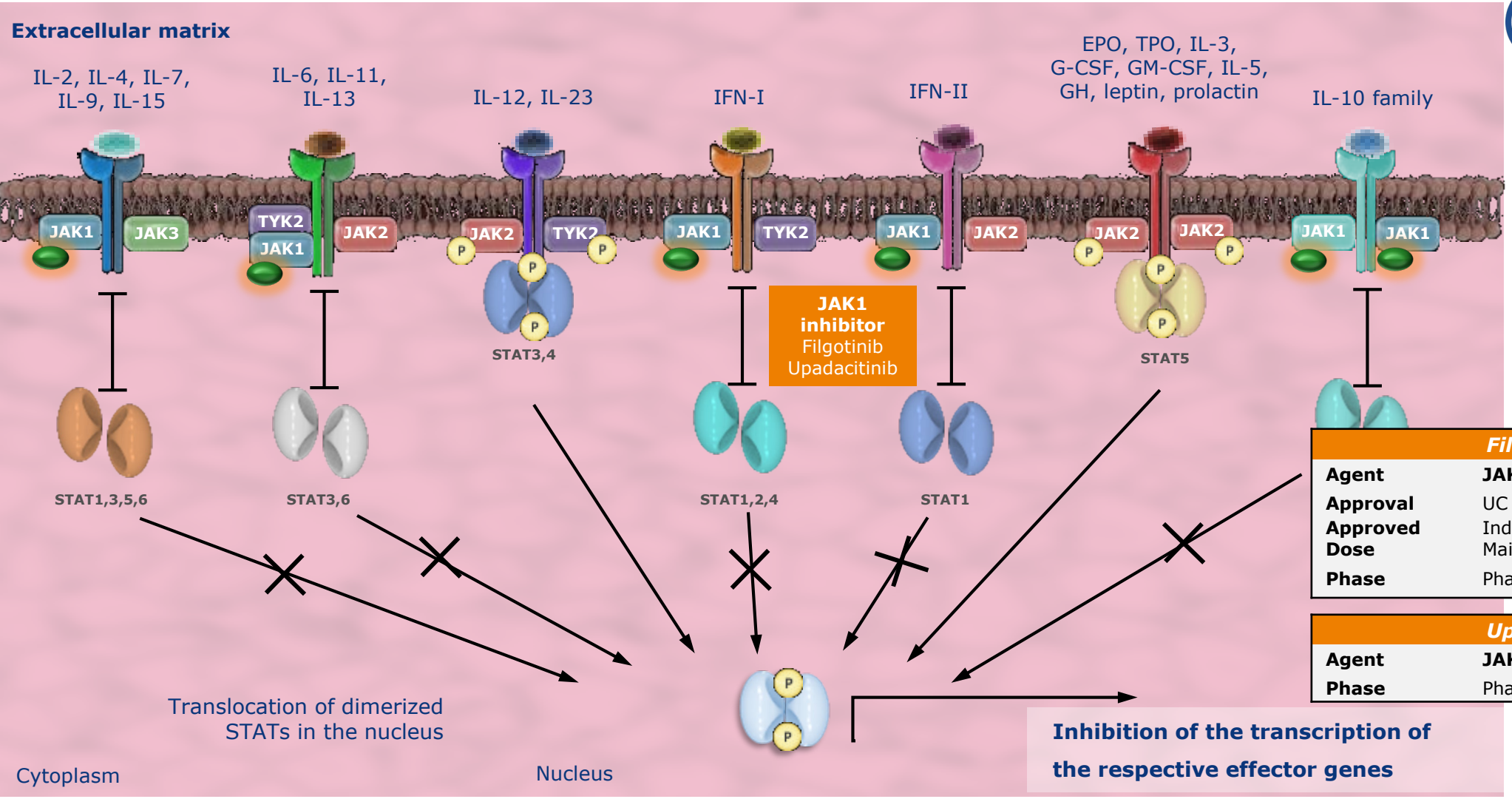
Der JAK/STAT Signalweg als Therapietarget bei IBD



Reduzierte Transkription von entzündungsfördernden Signal- und Effektorgenen durch Blockierung der JAK-Kinase-Aktivität

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)

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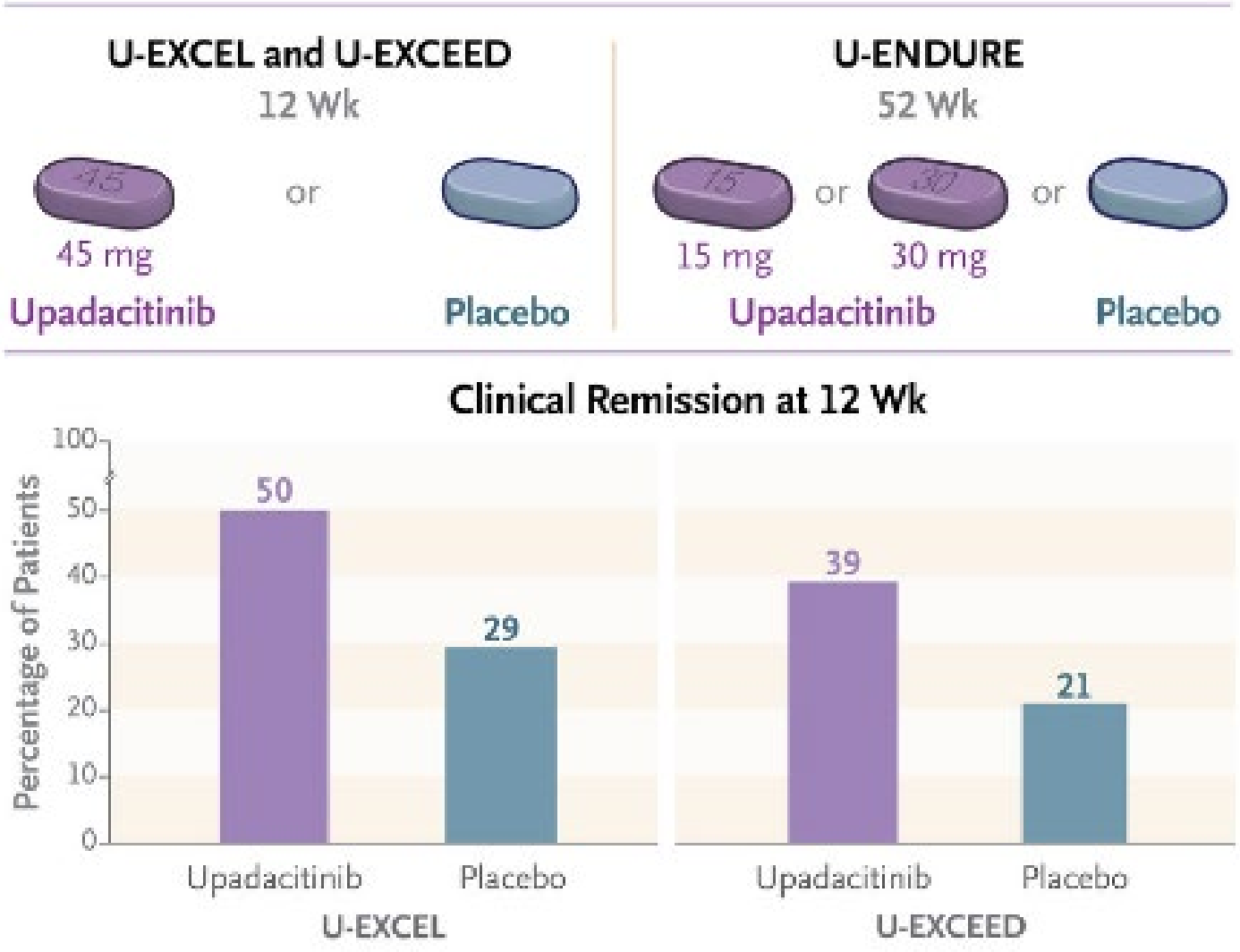
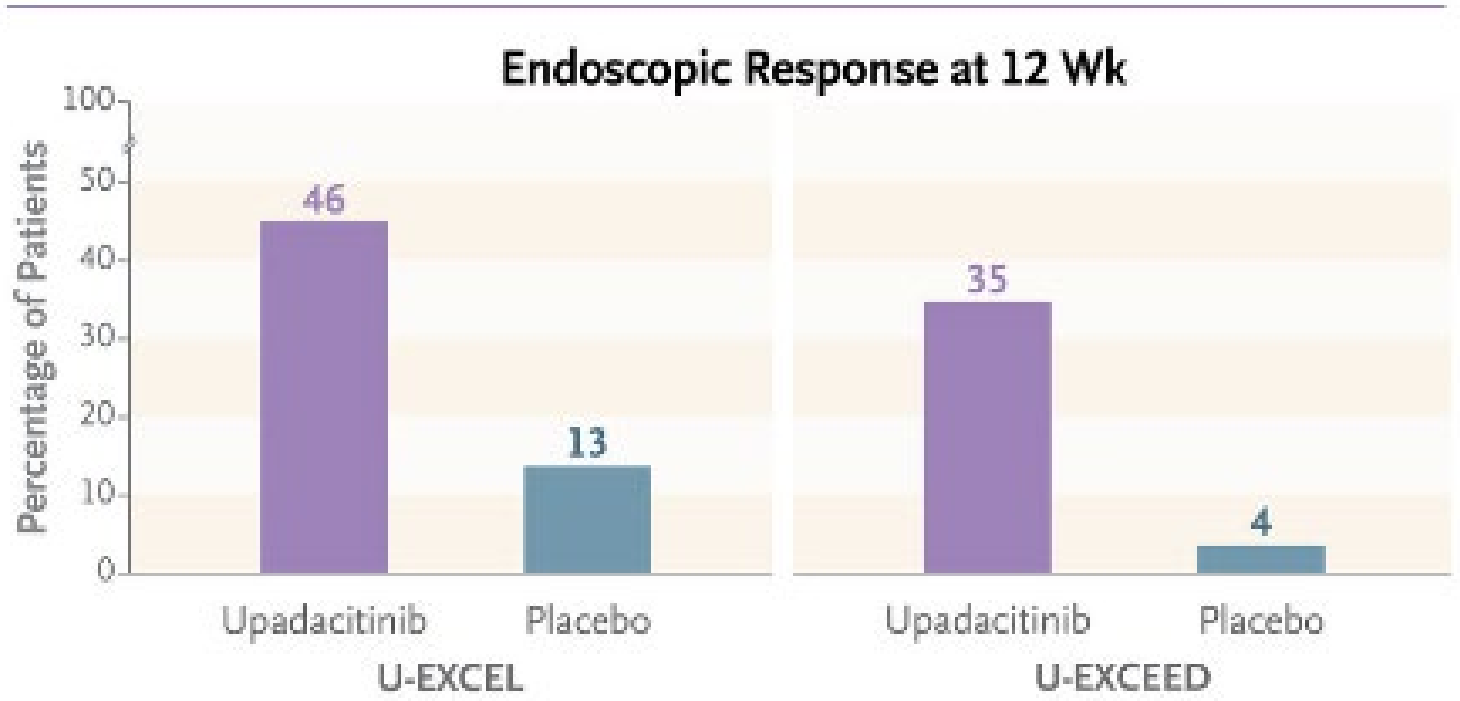
Abreu MT. JAK1 Inhibition to Treat Crohn's Disease. N Engl J Med. 2023 May 25;388(21):2005-2009
Seif F. et al. Cell Commun Signal 2017;15:23.
Danese S. et al. Gut. 2019 Oct;68(10):1893-1899.

Upadacitinib Induktion und Remissionserhaltung bei M. Crohn



Loftus EV Jr, Panés J, Lacerda AP, Peyrin-Biroulet L, D'Haens G, Panaccione R, Reinisch W, Louis E, Chen M, Nakase H, Begun J, Boland BS, Phillips C, Mohamed MF, Liu J, Geng Z, Feng T, Dubcenco E, Colombel JF. Upadacitinib Induction and Maintenance Therapy for Crohn's Disease. N Engl J Med. 2023 May 25;388(21):1966-1980.

Upadacitinib Induktion und Remissionserhaltung bei M. Crohn



Upadacitinib induction and maintenance treatment was superior to placebo in patients with moderate-to-severe Crohn's disease.

Loftus EV Jr, Panés J, Lacerda AP, Peyrin-Biroulet L, D'Haens G, Panaccione R, Reinisch W, Louis E, Chen M, Nakase H, Begun J, Boland BS, Phillips C, Mohamed MF, Liu J, Geng Z, Feng T, Dubcenco E, Colombel JF. Upadacitinib Induction and Maintenance Therapy for Crohn's Disease. N Engl J Med. 2023 May 25;388(21):1966-1980.

Upadacitinib Induktion und Remissionserhaltung bei M. Crohn

Table 4. Overview of Adverse Events in the Induction Trials.*

Adverse Event	U-EXCEL Induction Trial (12 wk)		U-EXCEED Induction Trial (12 wk)	
	Placebo (N=176)	Upadacitinib, 45 mg (N=350)	Placebo (N=171)	Upadacitinib, 45 mg (N=324)
	number of patients (percent)			
Any adverse event	103 (58.5)	219 (62.6)	112 (65.5)	221 (68.2)
Severe adverse event	15 (8.5)	31 (8.9)	20 (11.7)	28 (8.6)
Serious adverse event	12 (6.8)	24 (6.9)	17 (9.9)	30 (9.3)
Adverse event possibly related to trial agent	38 (21.6)	109 (31.1)	39 (22.8)	112 (34.6)
Adverse event leading to discontinuation of trial agent	10 (5.7)	15 (4.3)	7 (4.1)	18 (5.6)
Adverse event related to Covid-19	1 (0.6)	3 (0.9)	0	2 (0.6)
Death from any cause†	0	0	0	1 (0.3)
Adverse events of special interest				
Serious infection	3 (1.7)	4 (1.1)	3 (1.8)	9 (2.8)
Opportunistic infection, excluding tuberculosis and herpes zoster infection‡	0	0	0	2 (0.6)
Herpes zoster infection	0	10 (2.9)	0	5 (1.5)
Tuberculosis	0	0	0	0
Anemia§	8 (4.5)	28 (8.0)	11 (6.4)	22 (6.8)
Lymphopenia	6 (3.4)	5 (1.4)	2 (1.2)	6 (1.9)
Neutropenia	1 (0.6)	9 (2.6)	0	4 (1.2)
Creatine kinase elevation	0	12 (3.4)	4 (2.3)	9 (2.8)
Hepatic disorder	4 (2.3)	10 (2.9)	6 (3.5)	8 (2.5)
Renal disorder	0	0	0	2 (0.6)
Adjudicated cardiovascular events¶	1 (0.6)	0	0	0
Adjudicated thrombotic events¶	0	0	0	0
Adjudicated gastrointestinal perforation¶‖	0	0	0	1 (0.3)
Cancer of any type	0	0	0	0

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Cancer of any type	0	0	0	0

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Upadacitinib Induktion und Remissionserhaltung bei M. Crohn

Table 5. Overview of Exposure-Adjusted Adverse Events in the Maintenance Trial.*

Adverse Event	Placebo (N=223)	Upadacitinib, 15 mg (N=221)	Upadacitinib, 30 mg (N=229)
	no. of events (events per 100 person-yr)†		
Any adverse event	502 (469.2)	518 (349.5)	539 (323.7)
Severe adverse event	38 (35.5)	37 (25.0)	31 (18.6)
Serious adverse event	40 (37.4)	37 (25.0)	35 (21.0)
Adverse event possibly related to trial agent	135 (126.2)	135 (91.1)	139 (83.5)
Adverse event leading to discontinuation of trial agent	8 (7.5)	19 (12.8)	14 (8.4)
Adverse event related to Covid-19	11 (10.3)	12 (8.1)	18 (10.8)
Death from any cause	0	0	0
Adverse events of special interest			
Serious infection	9 (8.4)	9 (6.1)	13 (7.8)
Opportunistic infection, excluding tuberculosis and herpes zoster infection‡	0	1 (0.7)	1 (0.6)
Herpes zoster infection	5 (4.7)	6 (4.0)	12 (7.2)
Tuberculosis	0	0	0
Anemia§	13 (12.2)	15 (10.1)	11 (6.6)
Lymphopenia	10 (9.3)	4 (2.7)	10 (6.0)
Neutropenia	1 (0.9)	3 (2.0)	5 (3.0)
Creatine kinase elevation	3 (2.8)	5 (3.4)	8 (4.8)
Hepatic disorder	3 (2.8)	11 (7.4)	17 (10.2)
Renal disorder	2 (1.9)	0	0
Adjudicated cardiovascular events¶	0	0	0
Adjudicated thrombotic events¶	0	0	1 (0.6)
Adjudicated gastrointestinal perforation¶	1 (0.9)	1 (0.7)	1 (0.6)
Cancer of any type	0	1 (0.7)	2 (1.2)
Excluding NMSC	0	1 (0.7)	2 (1.2)

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Herpes zoster infection	5 (4.7)	6 (4.0)	12 (7.2)
Tuberculosis	0	0	0
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Adjudicated cardiovascular events¶	0	0	0
Adjudicated thrombotic events¶	0	0	1 (0.6)
Adjudicated gastrointestinal perforation¶	1 (0.9)	1 (0.7)	1 (0.6)
Cancer of any type	0	1 (0.7)	2 (1.2)
Excluding NMSC	0	1 (0.7)	2 (1.2)

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Frühe Operation bei M. Crohn: Es gibt immer bessere Daten

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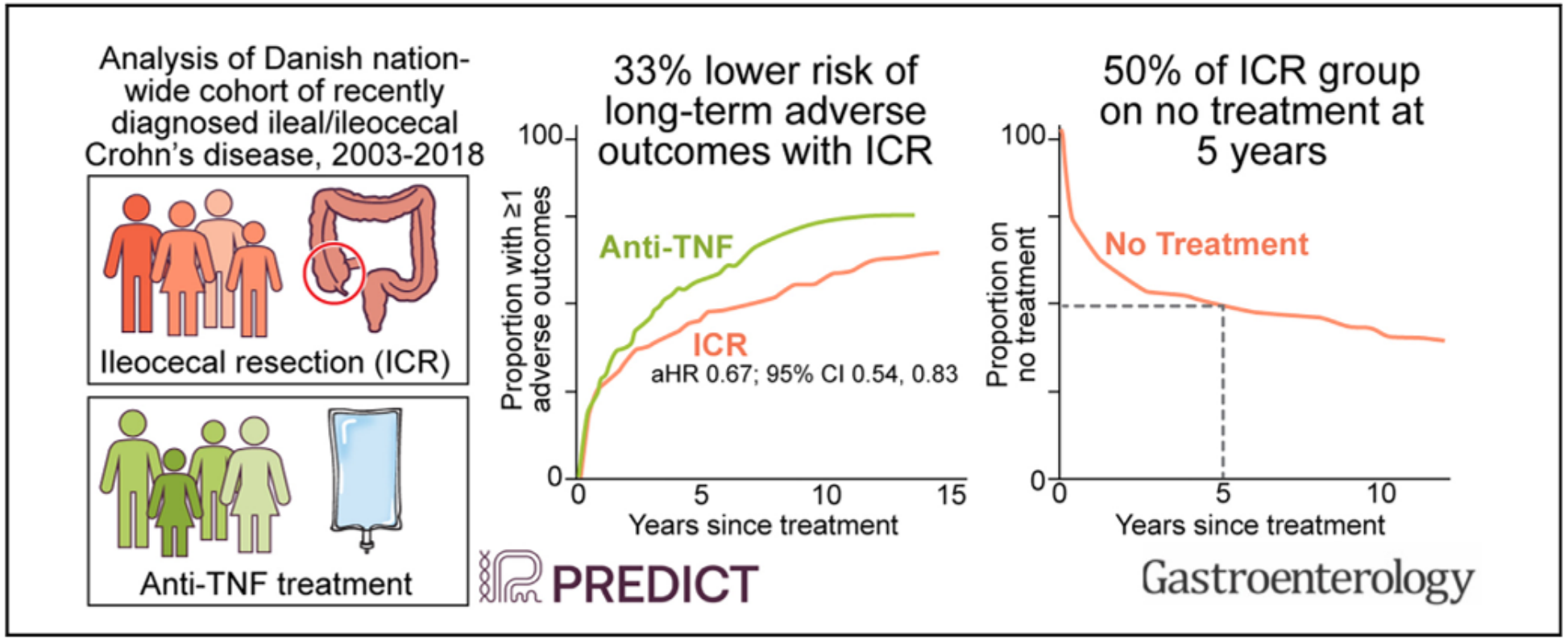
Early Ileocecal Resection for Crohn's Disease Is Associated With Improved Long-term Outcomes Compared With Anti-Tumor Necrosis Factor Therapy: A Population-Based Cohort Study



«These data suggest that ICR may have a role as first-line therapy in CD management and chal lenge the current paradigm of reserving surgery for complicated CD refractory or intolerant to medications. .»

Agrawal M, Ebert AC, Poulsen G, Ungaro RC, Faye AS, Jess T, Colombel JF, Allin KH. Early Ileocecal Resection for Crohn's Disease Is Associated With Improved Long-term Outcomes Compared With Anti-Tumor Necrosis Factor Therapy: A Population-Based Cohort Study. Gastroenterology. 2023 Oct;165(4):976-985

Early Ileocecal Resection for Crohn's Disease Is Associated With Improved Long-term Outcomes Compared With Anti-Tumor Necrosis Factor Therapy: A Population-Based Cohort Study

Aber: «The primary outcome was a composite of ≥1of the following: CD-related hospitalization, systemic corticosteroid exposure, CD-related surgery, and perianal CD."

							ICR vs Anti-TNF					
	ICR			Anti-TNF			Model 1[a]			Model 2[b]		
Outcome	Events	PY	IR	Events	PY	IR	aHR	95% CI		aHR	95% CI	
Primary outcome												
Composite outcome[c]	273	2474	110	318	1575	202	0.72	0.60	0.86	0.67	0.54	0.83
Secondary outcomes												
CD-related hospitalization	190	3039	63	215	1964	109	0.84	0.68	1.04	0.79	0.61	1.01
Systemic corticosteroids	162	3415	47	193	2155	90	0.61	0.49	0.77	0.71	0.54	0.92
CD-related surgery	82	3932	21	123	2397	51	0.49	0.36	0.67	0.56	0.39	0.80
Perianal CD	30	4229	7	40	2682	15	0.62	0.37	1.04	0.70	0.38	1.30

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Metaanalysen und Alexander Ford…

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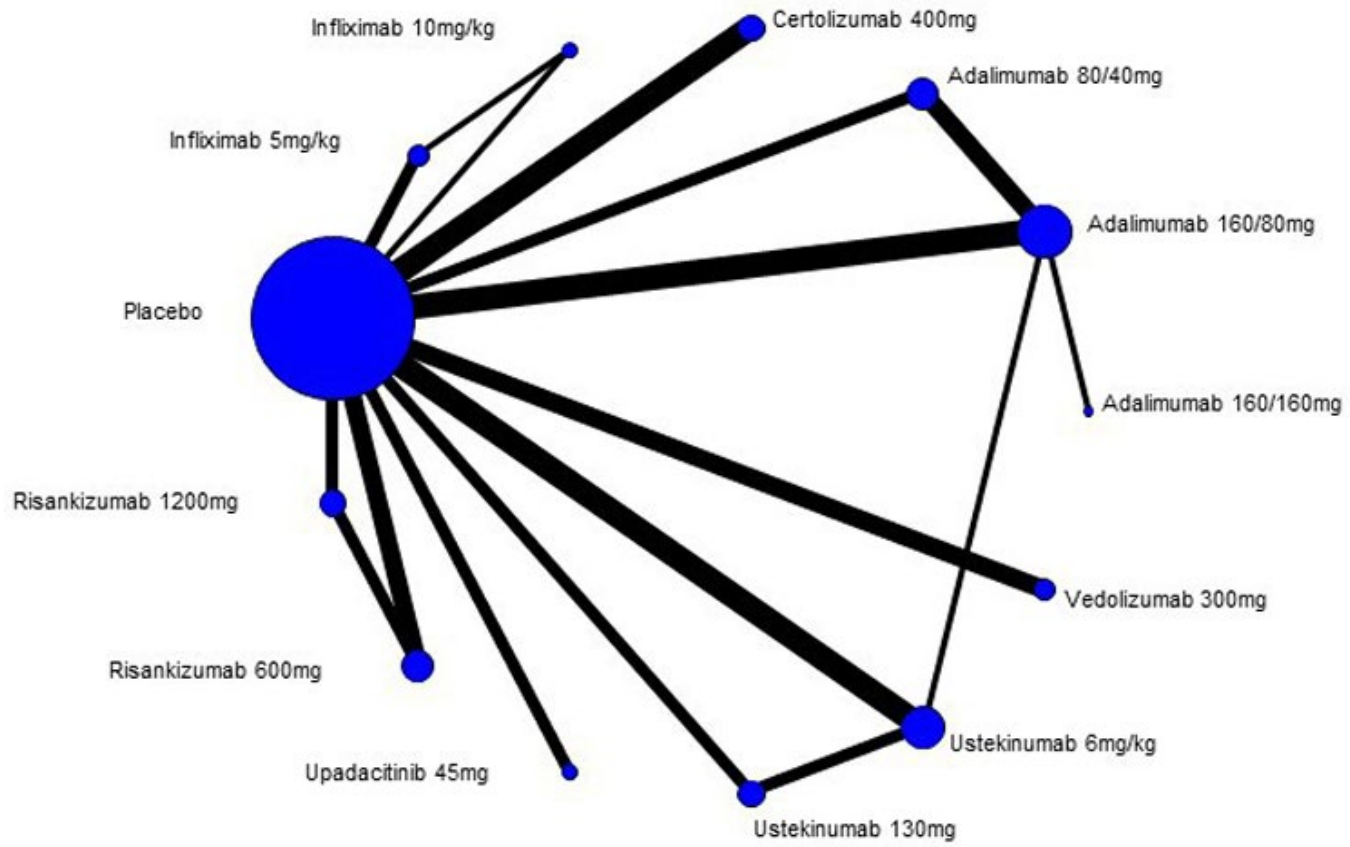
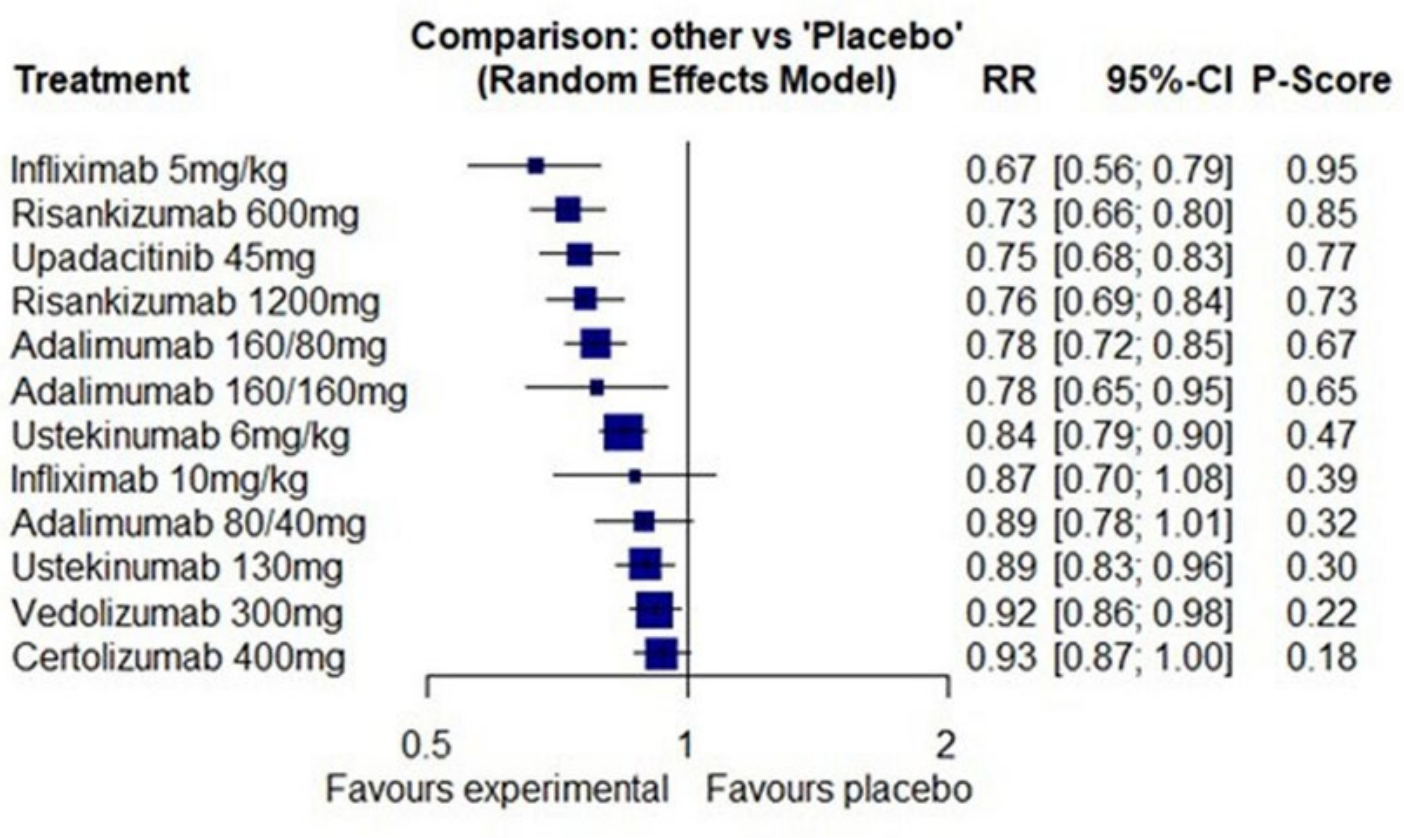
Efficacy of biological therapies and small molecules in induction and maintenance of remission in luminal Crohn's disease: systematic review and network meta- analysis



Network plot

Barberio B, Gracie DJ, Black CJ, Ford AC. Efficacy of biological therapies and small molecules in induction and maintenance of remission in luminal Crohn's disease: systematic review and network meta-analysis. Gut. 2023 Feb;72(2):264-274

Efficacy of biological therapies and small molecules in induction and maintenance of remission in luminal Crohn's disease: systematic review and network meta- analysis



Remissionsinduktion:
Alle Patienten

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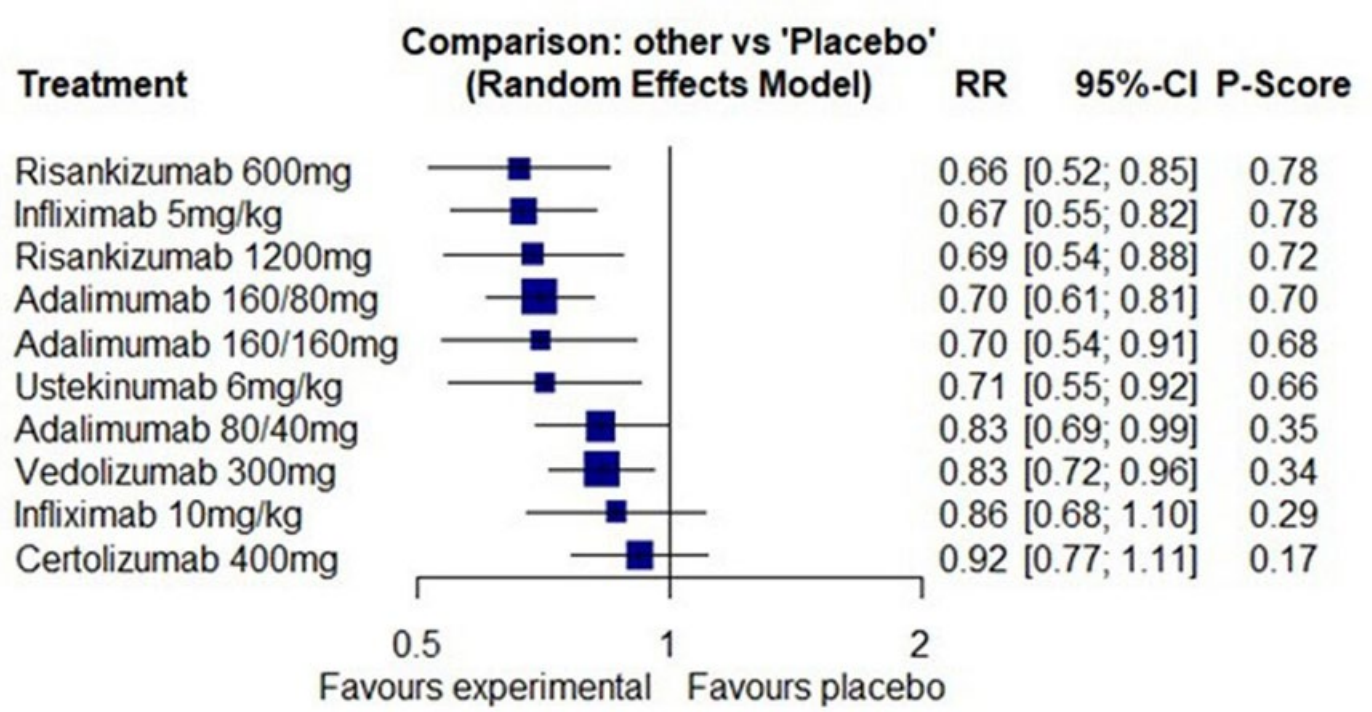

Remissionsinduktion: «Biologika-naive Patienten»

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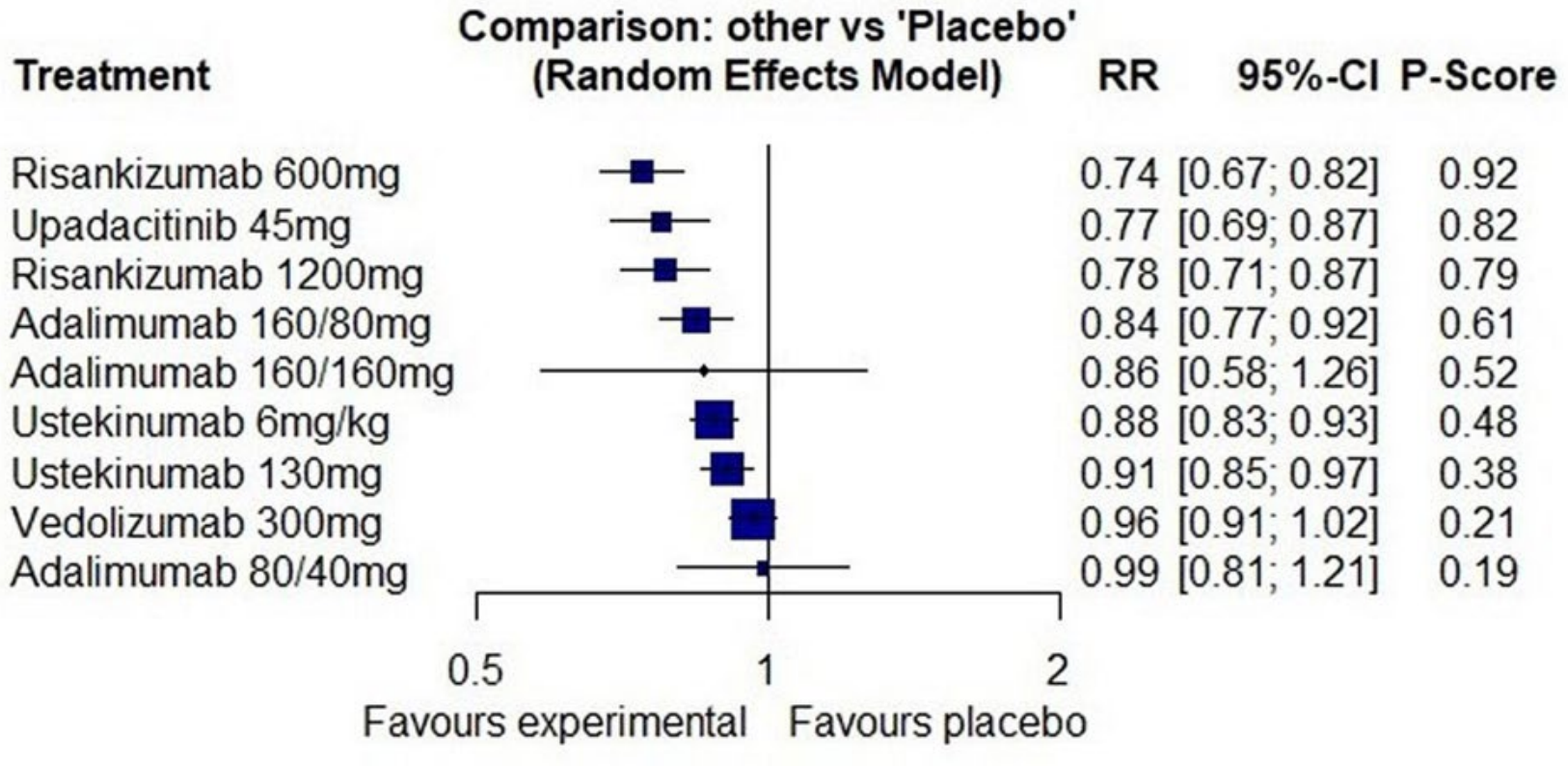

Remissionsinduktion: «Patienten mit Biologika-Vortherapie»

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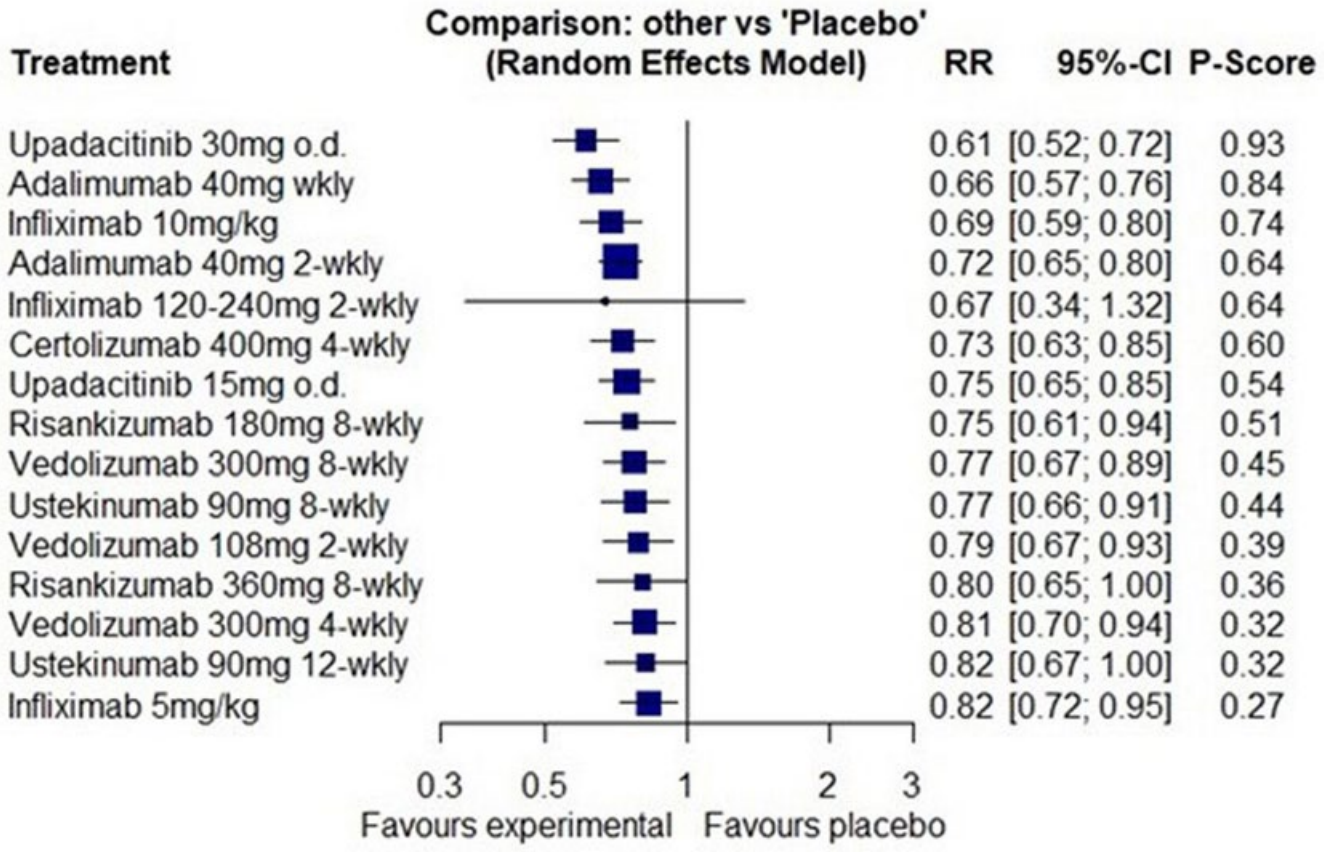

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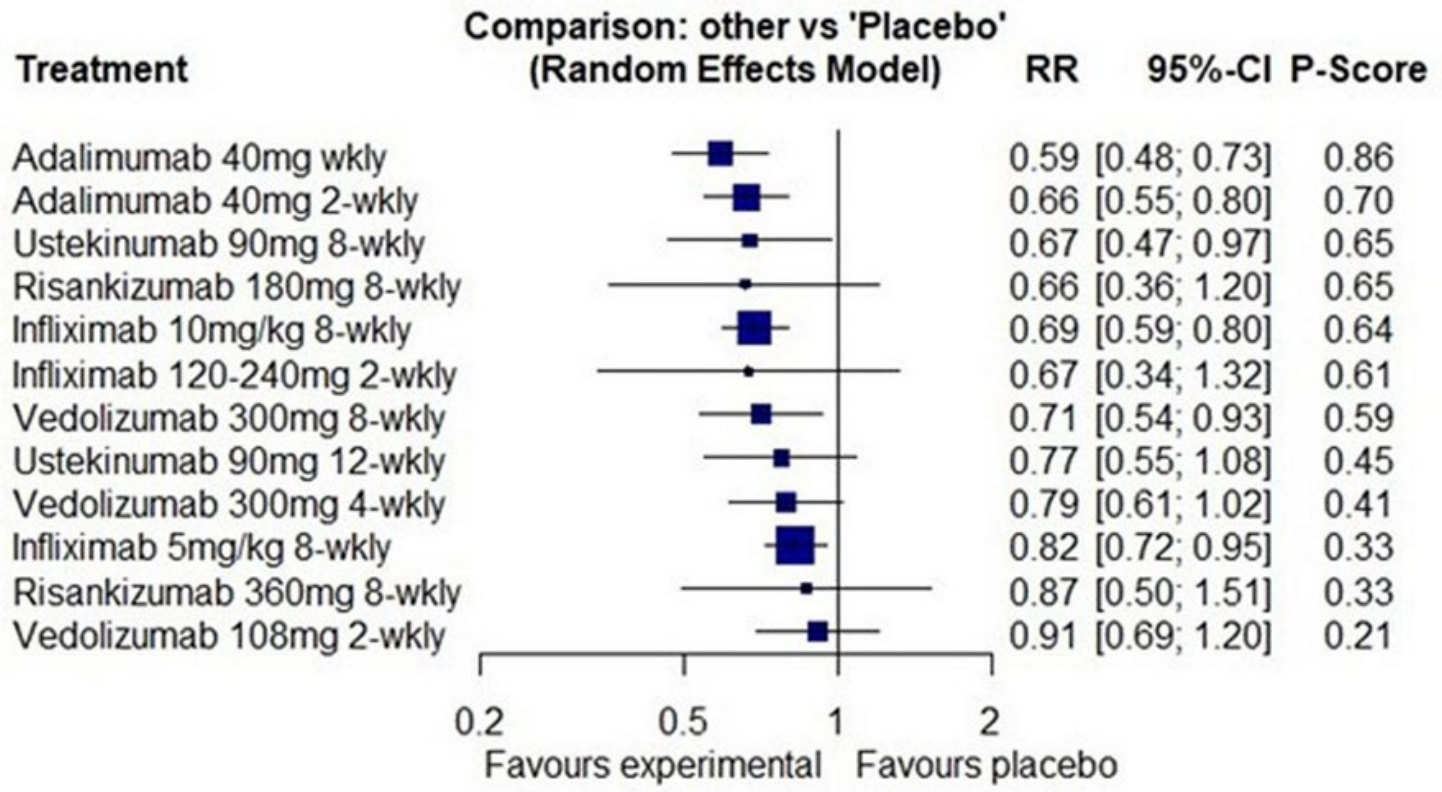

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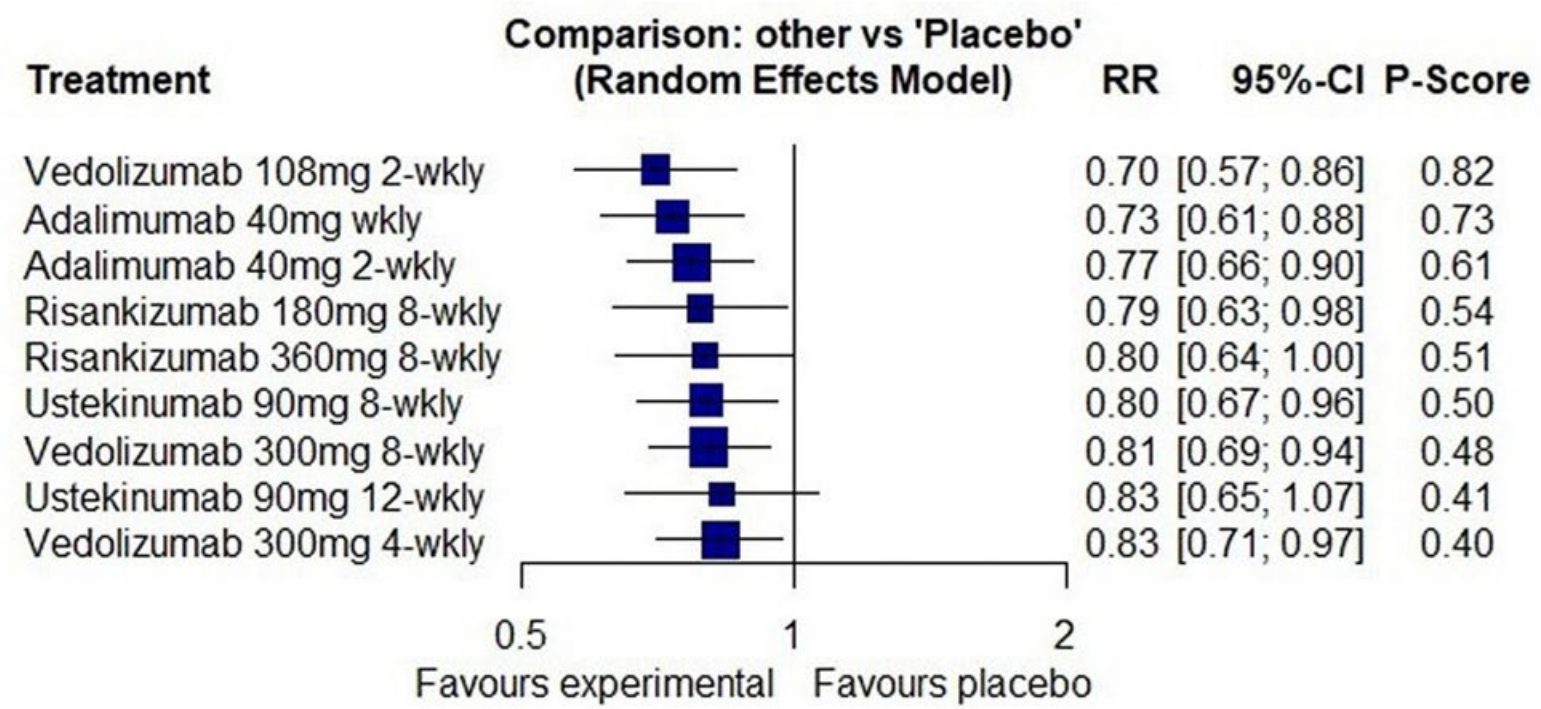

Remissionsinduktion: «Patienten mit Biologika-Vortherapie»

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Barberio B, Gracie DJ, Black CJ, Ford AC. Efficacy of biological therapies and small molecules in induction and maintenance of remission in luminal Crohn's disease: systematic review and network meta-analysis. Gut. 2023 Feb;72(2):264-274

Head to Head

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GastroHighlights
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Risankizumab Versus Ustekinumab for Patients With Moderate to Severe Crohn's Disease: Results From the Phase 3b SEQUENCE Study

- Risankizumab (RZB) und Ustekinumab (UST) sind humanisierte monoklonale Antikörper, die für die Behandlung von mittelschwerem bis schwerem Morbus Crohn (CD) zugelassen sind.

- Beide Wirkstoffe blockieren Interleukin (IL)-23, ein Zytokin, das entscheidend an der Pathogenese mehrerer chronischer immunvermittelter Erkrankungen beteiligt ist

- IL-23 ist ein Heterodimer, das aus p19- und p40-Untereinheiten besteht

- Risankizumab bindet an die IL-23 p19-Untereinheit
- Ustekinumab bindet an die p40-Untereinheit und hemmt so sowohl IL-23 als auch IL-12

- Die SEQUENCE-Studie verglich direkt die Wirksamkeit und Sicherheit von RZB im Vergleich zu UST über einen Zeitraum von 48 Wochen bei Patienten mit mittelschwerem bis schwerem m. Crohn, bei denen zuvor ≥ 1 Anti-TNF-Therapie versagt hatte

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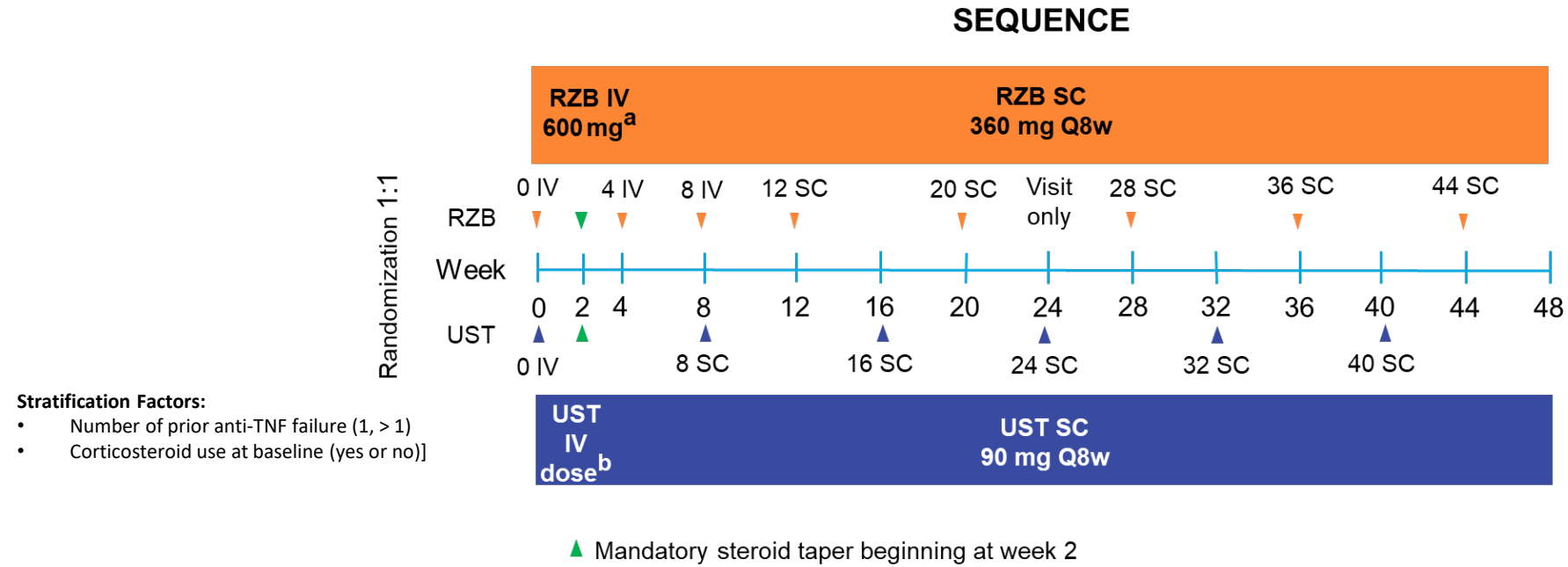
Laurent Peyrin-Biroulet, J. Casey Chapman, Jean-Frederic Colombel, Flavio Caprioli, Geert D'Haens, Marc Ferrante, Stefan Schreiber, Raja Atreya, Silvio Danese, James O. Lindsay, Peter Bossuyt, Britta Siegmund, Peter Irving, Remo Panaccione, Ezequiel Neimark, Kori Wallace, Toni Anschutz, Kristina Kligys, W Rachel Duan, Valerie Pivorunas, Xiu Huang, Sofie Berg, Lei Shu, Marla Dubinsky; United European Gastroenterology Week (UEGW 2023), October 14 – 17, 2023, Copenhagen, Denmark

Risankizumab Versus Ustekinumab for Patients With Moderate to Severe Crohn's Disease: Results From the Phase 3b SEQUENCE Study



Stratification Factors:

- Number of prior anti-TNF failure (1, > 1)
- Corticosteroid use at baseline (yes or no)]

Key Eligibility Criteria

Moderate to severe CD

- CDAI 220 - 450
- Average daily SF ≥ 4 and/or average daily APS ≥ 2
- SES-CD, excluding the narrowing component, ≥ 6 (≥ 4 for isolated ileal disease), as scored by the site Investigator and confirmed by a central reader

Prior failure of ≥ 1 anti-TNF therapies

- Prior biologic therapy that could potentially influence the therapeutic impact on CD was exclusionary, including vedolizumab

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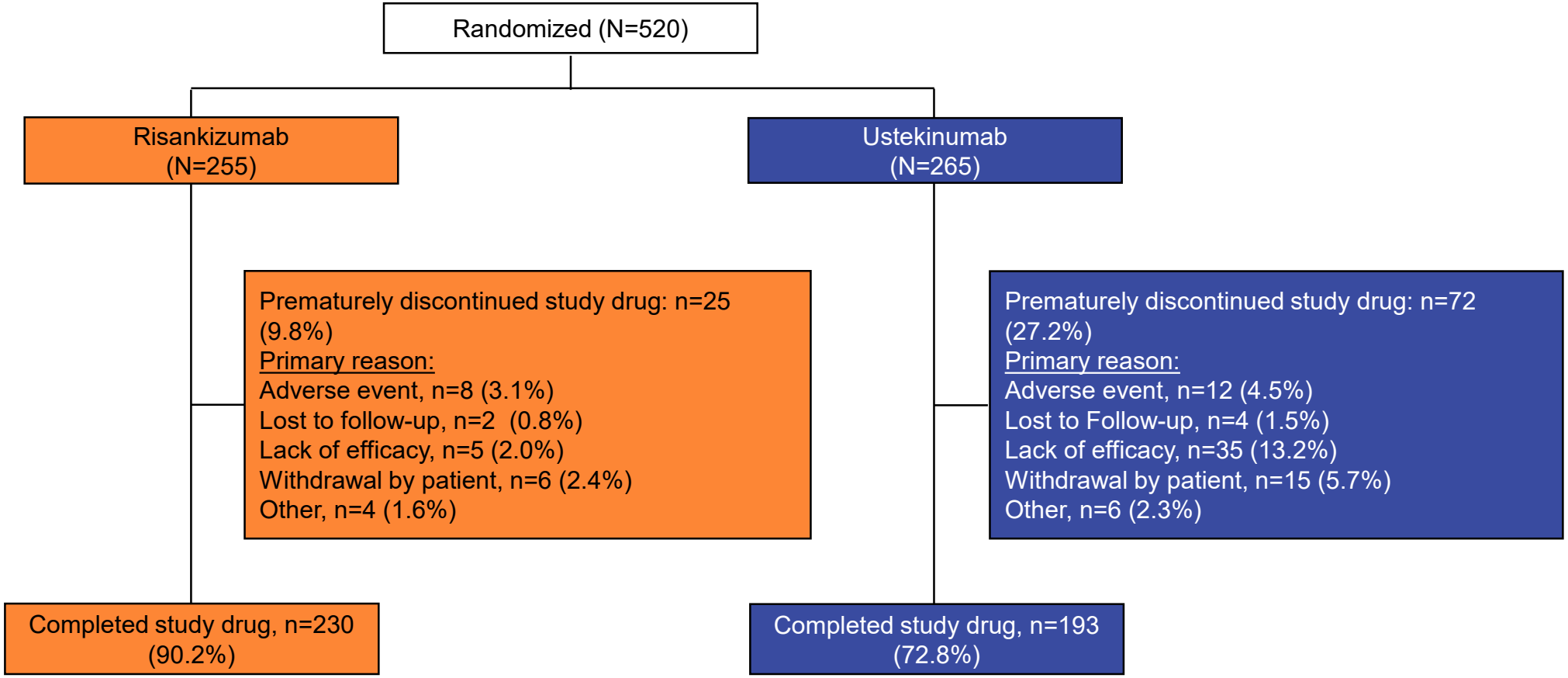

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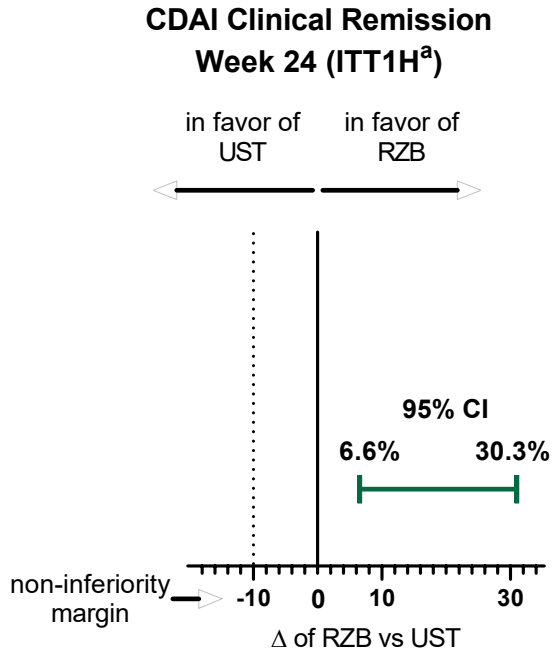

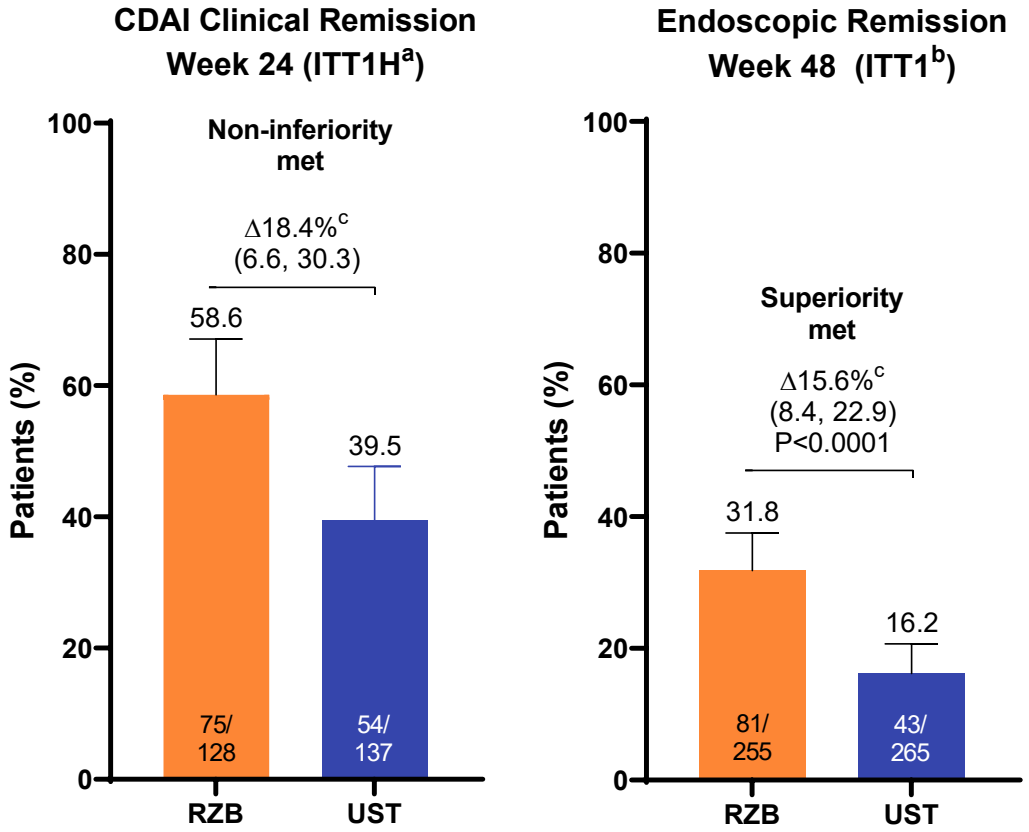

CDAI clinical remission: CDAI < 150
Endoscopic remission: SES-CD ≤ 4 and at least a 2-point reduction versus BL and no subscore > 1 in any individual variable, as scored by a central reviewer

Nominal *P* <0.01 from a post hoc analysis testing for superiority

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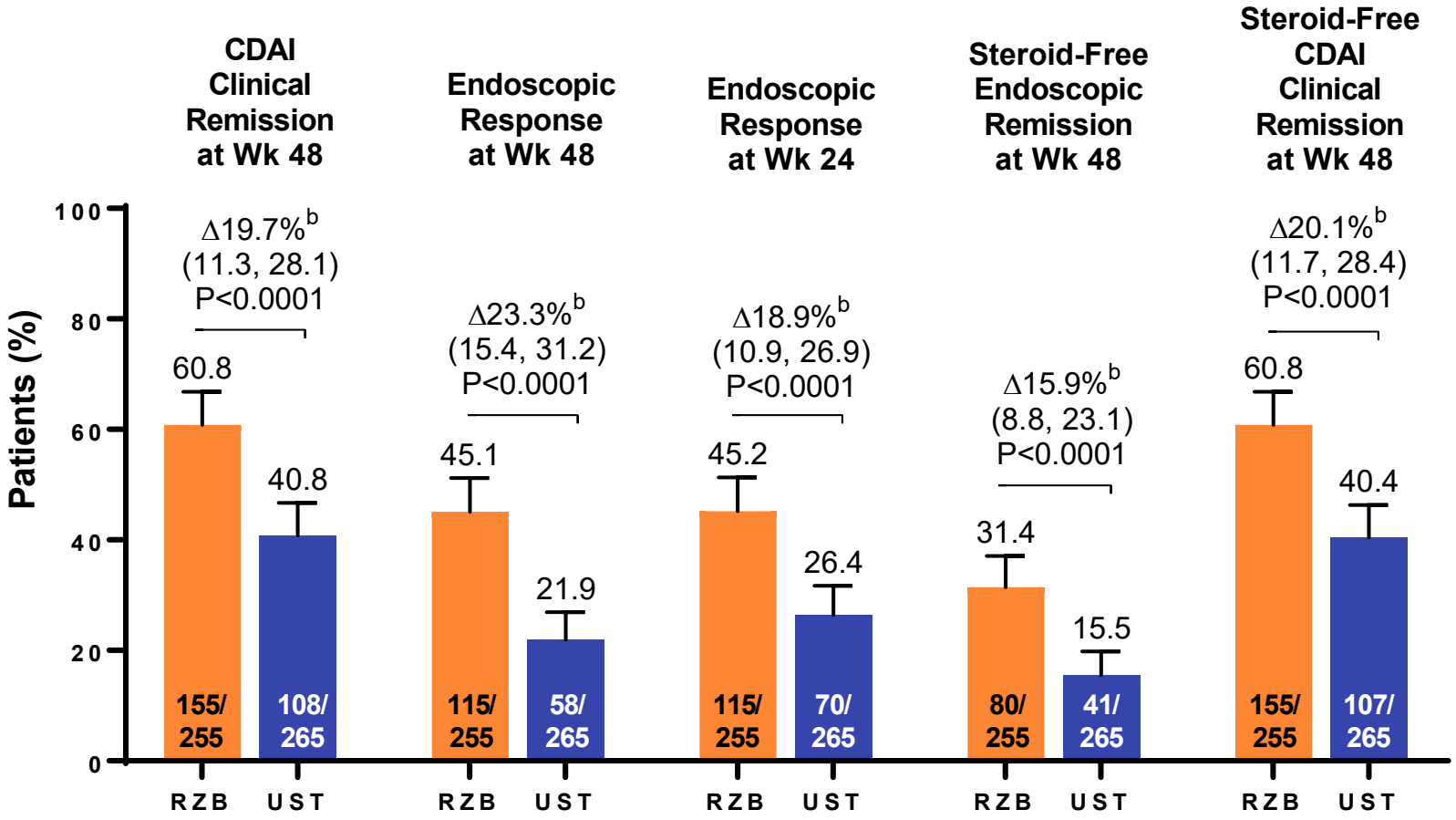

CDAI clinical remission: CDAI < 150
Endoscopic response: Decrease in SES-CD > 50% from BL (or for subjects with isolated ileal disease and a baseline SES-CD of 4, at least a 2-point reduction from baseline), as scored by central reviewer.
Endoscopic remission: SES-CD ≤ 4 and at least a 2-pt reduction versus BL and no subscore > 1 in any individual variable, as scored by a central reviewer
Steroid-free: Patient not receiving steroids at the corresponding visit

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AESI	Risankizumab		Ustekinumab	
	N=262 n (%)	PYs=257.6 Events (E/100PYs)	N=265 n (%)	PYs=269.9 Events (E/100PYs)
Adjudicated MACE / Extended MACE[b]	0	0	1 (0.4)[c]	1 (0.4)[c]
Serious infections	8 (3.1)	10 (3.9)	11 (4.2)	14 (5.2)
Active tuberculosis	0	0	0	0
Opportunistic infections excluding TB & herpes zoster	1 (0.4)[d]	1 (0.4)[d]	0	0
Herpes zoster	1 (0.4)	1 (0.4)	1 (0.4)	1 (0.4)
Malignant tumors	1 (0.4)[e]	1 (0.4)[e]	1 (0.4)[f]	1 (0.4)[f]
Non-melanoma skin cancer (NMSC)	1 (0.4)[e]	1 (0.4)[e]	0	0
Malignancies excluding NMSC	0	0	1 (0.4)[f]	1 (0.4)[f]
Hypersensitivity	28 (10.7)	37 (14.4)	24 (9.1)	32 (11.9)
Serious hypersensitivity	0	0	0	0
Adjudicated anaphylactic reaction	0	0	0	0
Hepatic events	18 (6.9)	26 (10.1)	14 (5.3)	23 (8.5)
Injection site reactions	5 (1.9)	5 (1.9)	6 (2.3)	8 (3.0)

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Anti-IL23 bei Colitis ulcerosa

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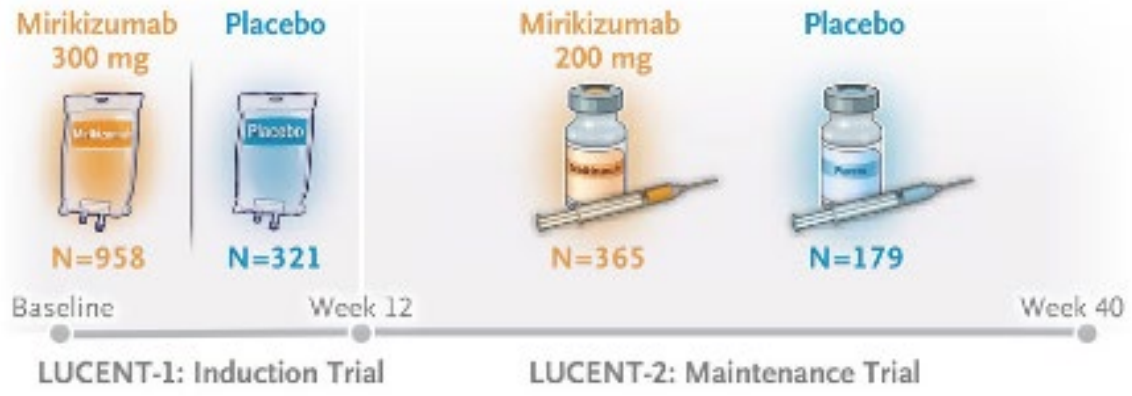
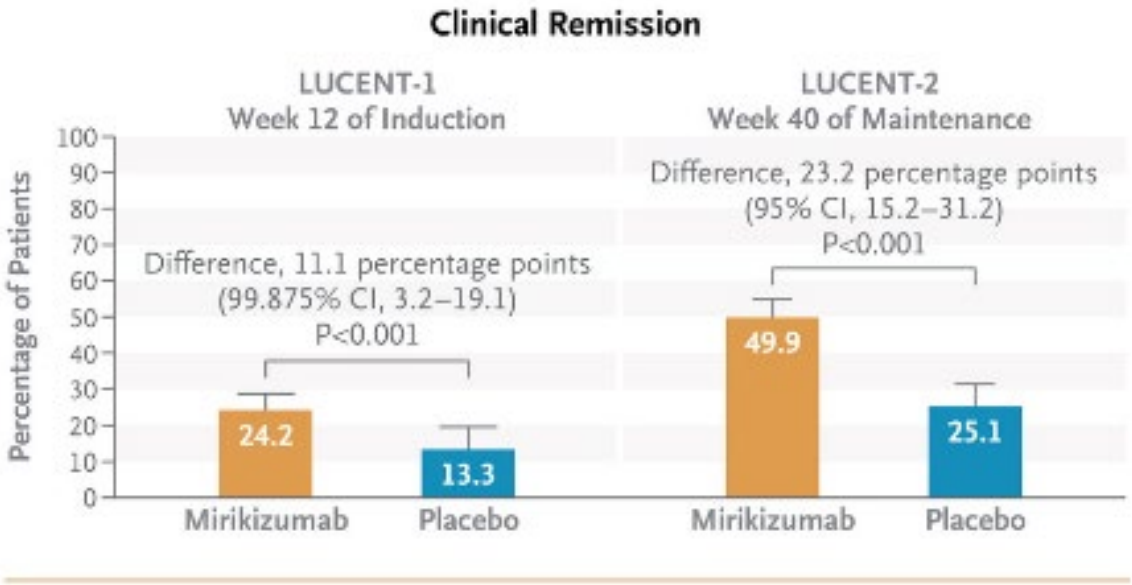
Mirikizumab Induktion und Remissionserhaltung bei Colitis ulcerosa





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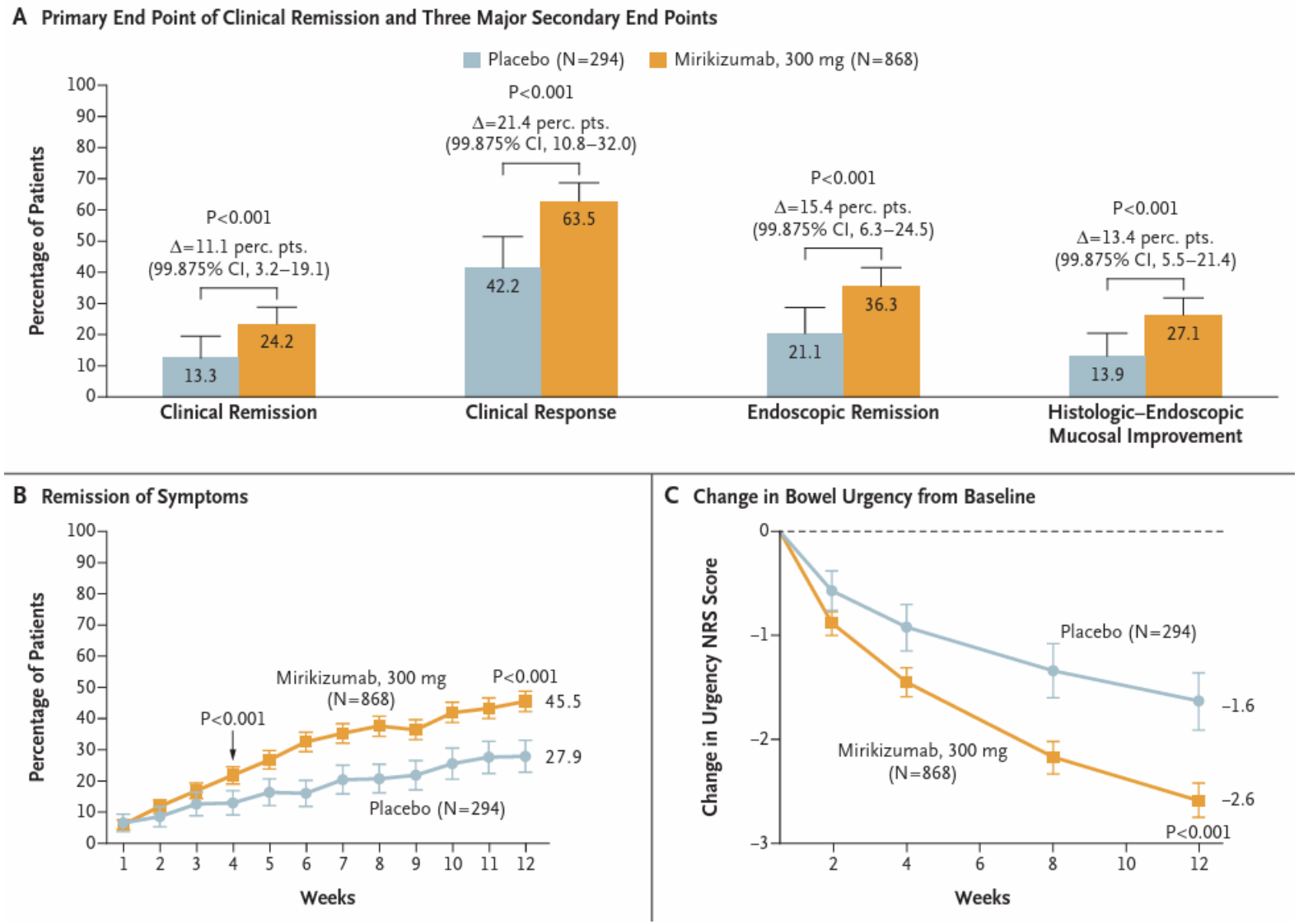
Mirikizumab Induktion und Remissionserhaltung bei Colitis ulcerosa



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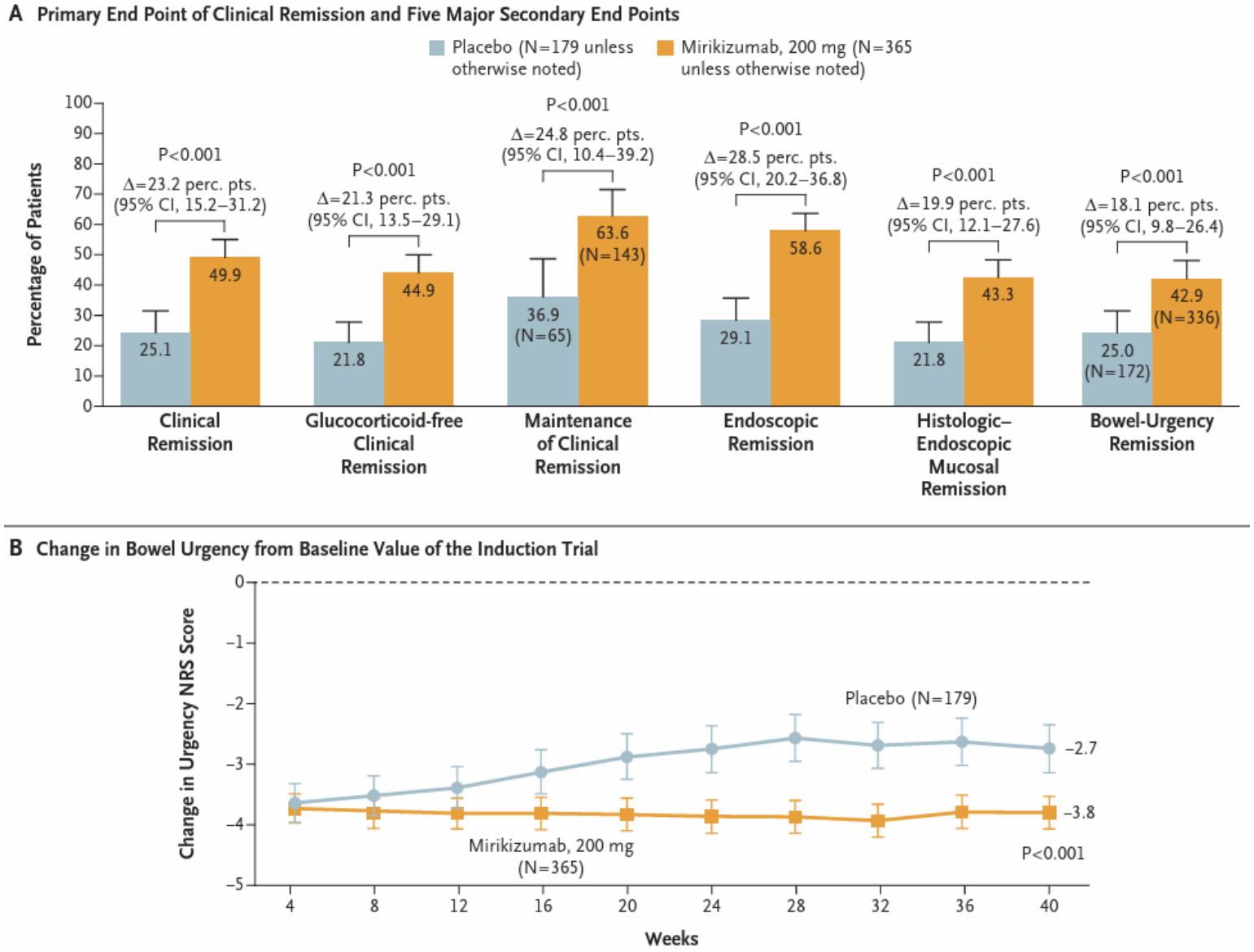

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Mirikizumab Induktion und Remissionserhaltung bei Colitis ulcerosa

Safety Outcomes

	Mirikizumab	Placebo
	no. of patients	
Opportunistic infections	15	1
Herpes zoster	6	1
Candidiasis	4	0
Cytomegalovirus disease	4	0
Intestinal tuberculosis	1	0
Cancers	8	0
Colon adenocarcinoma	3	0
Nonmelanoma skin cancer	1	0
Gastric cancer	1	0
Squamous-cell carcinoma	2	0
Rectal cancer	1	0
Kaposi's sarcoma	1	0

Mirikizumab data shown are for the induction and maintenance trials; placebo data are for the induction trial only.

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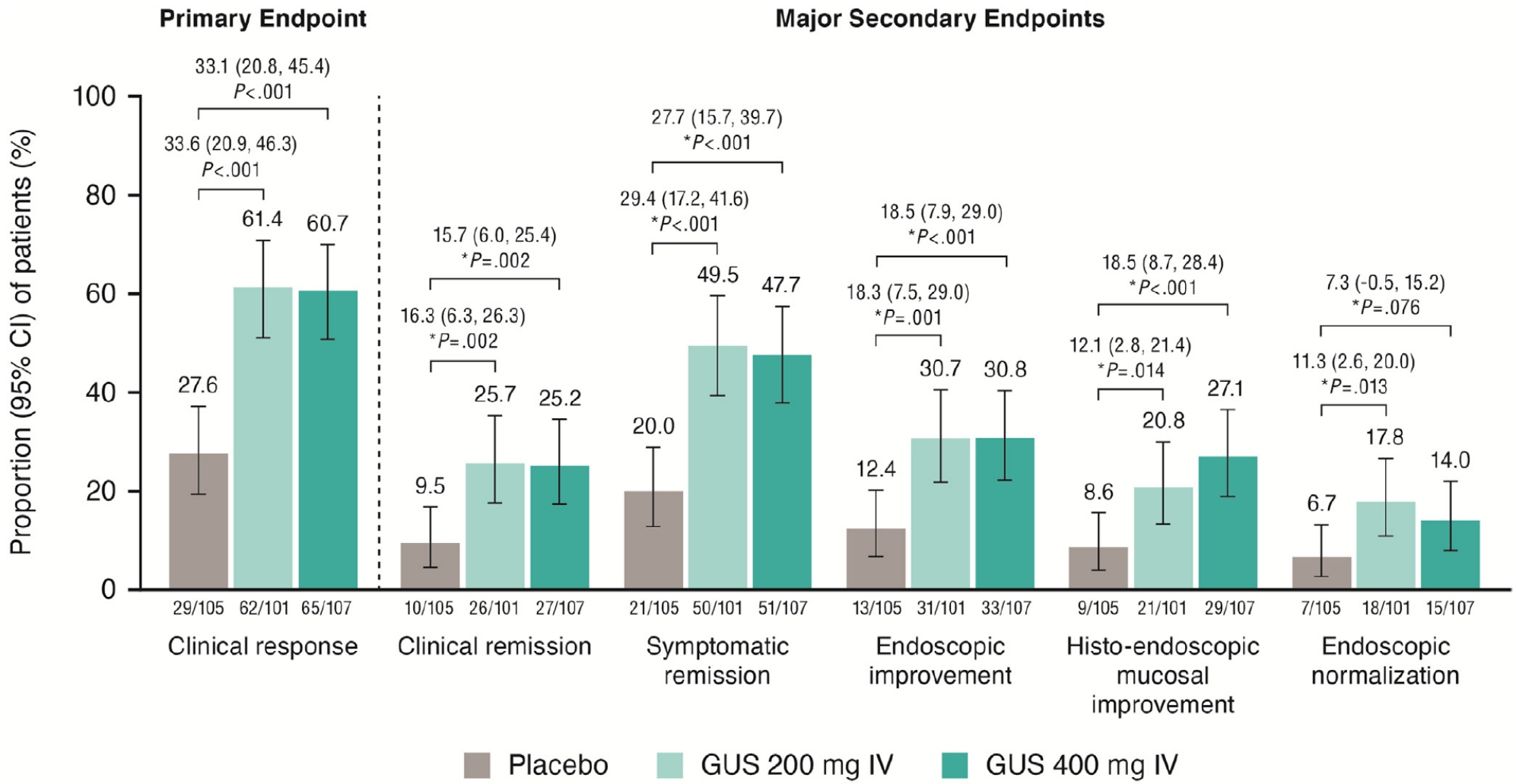
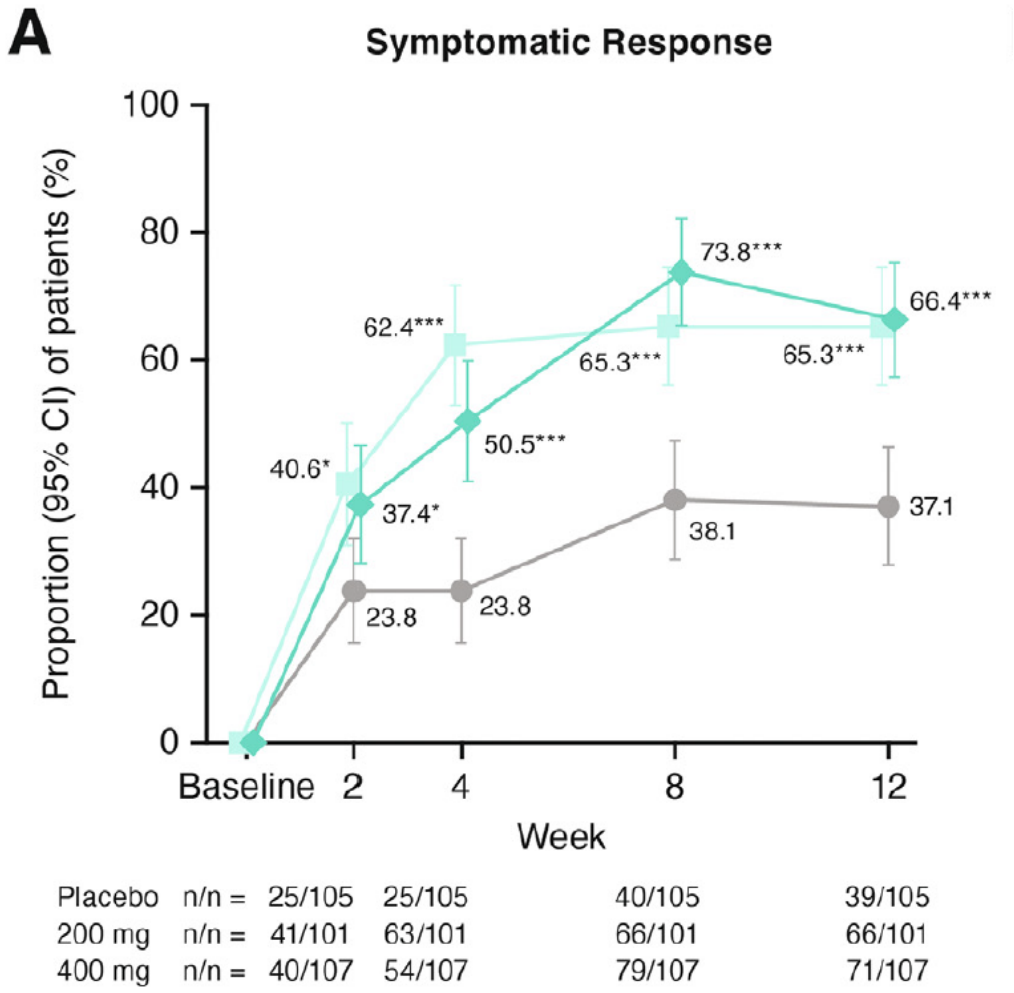
Guselkumab zur Induktion und Remissionserhaltung bei Colitis ulcerosa



Peyrin-Biroulet L, Allegretti JR, Rubin DT, Bressler B, Germinaro M, Huang KG, Shipitofsky N, Zhang H, Wilson R, Han C, Feagan BG, Sandborn WJ, Panés J, Hisamatsu T, Lichtenstein GR, Sands BE, Dignass A; QUASAR Study Group. Guselkumab in Patients With Moderately to Severely Active Ulcerative Colitis: QUASAR Phase 2b Induction Study. Gastroenterology. 2023 Sep 1:S0016-5085(23)04963-

Guselkumab zur Induktion und Remissionserhaltung bei Colitis ulcerosa



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S1P1 bei Colitis ulcerosa

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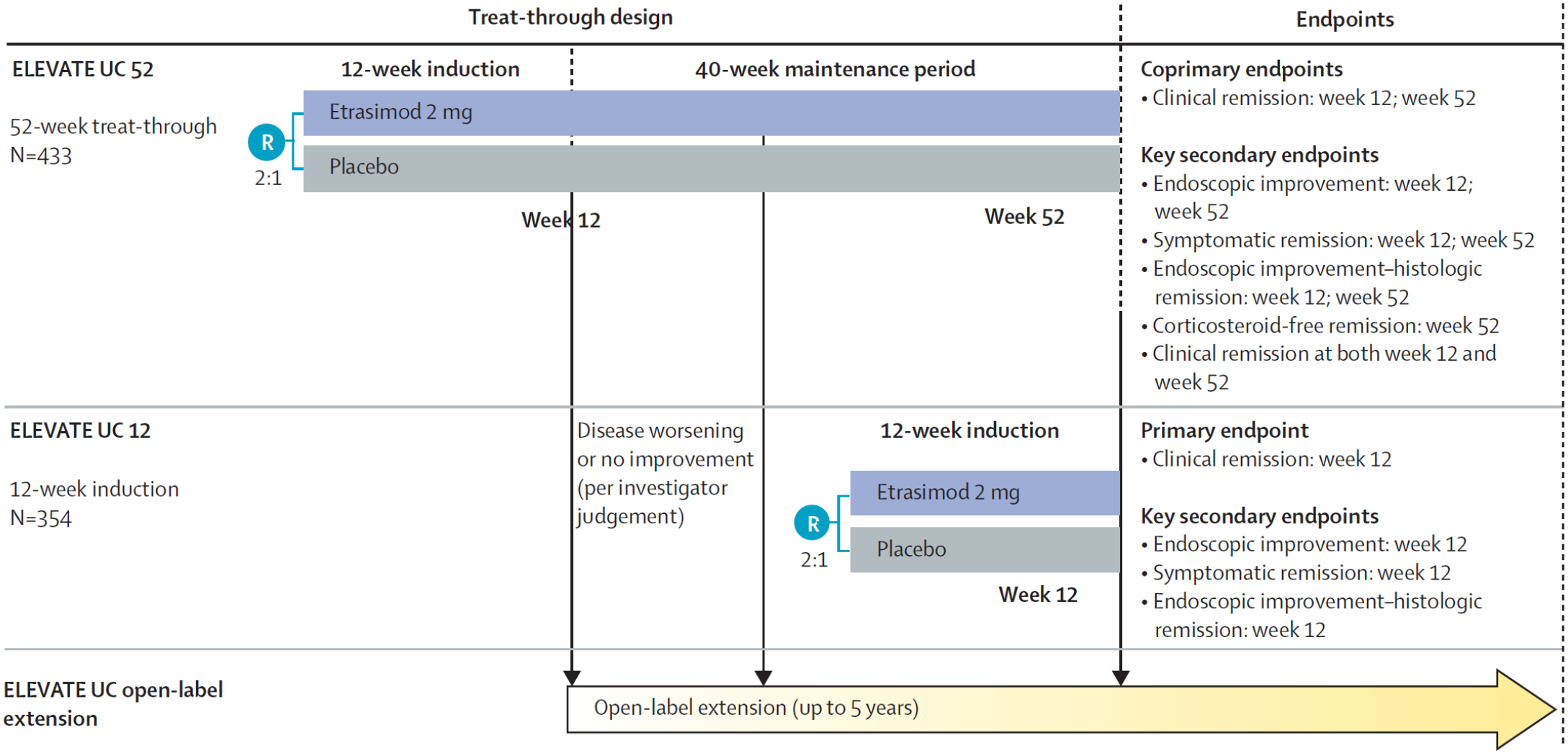
Etrasimod zur Induktion und Remissionserhaltung bei Colitis ulcerosa



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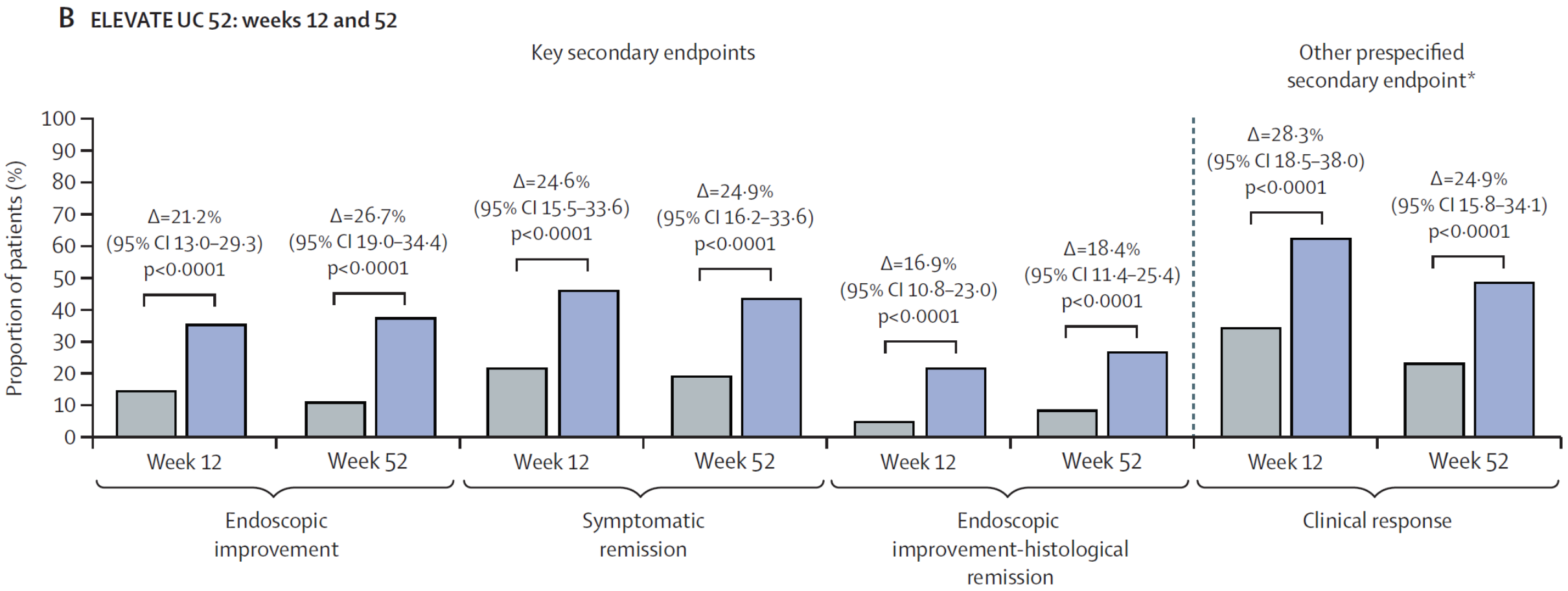
Etrasimod zur Induktion und Remissionserhaltung bei Colitis ulcerosa



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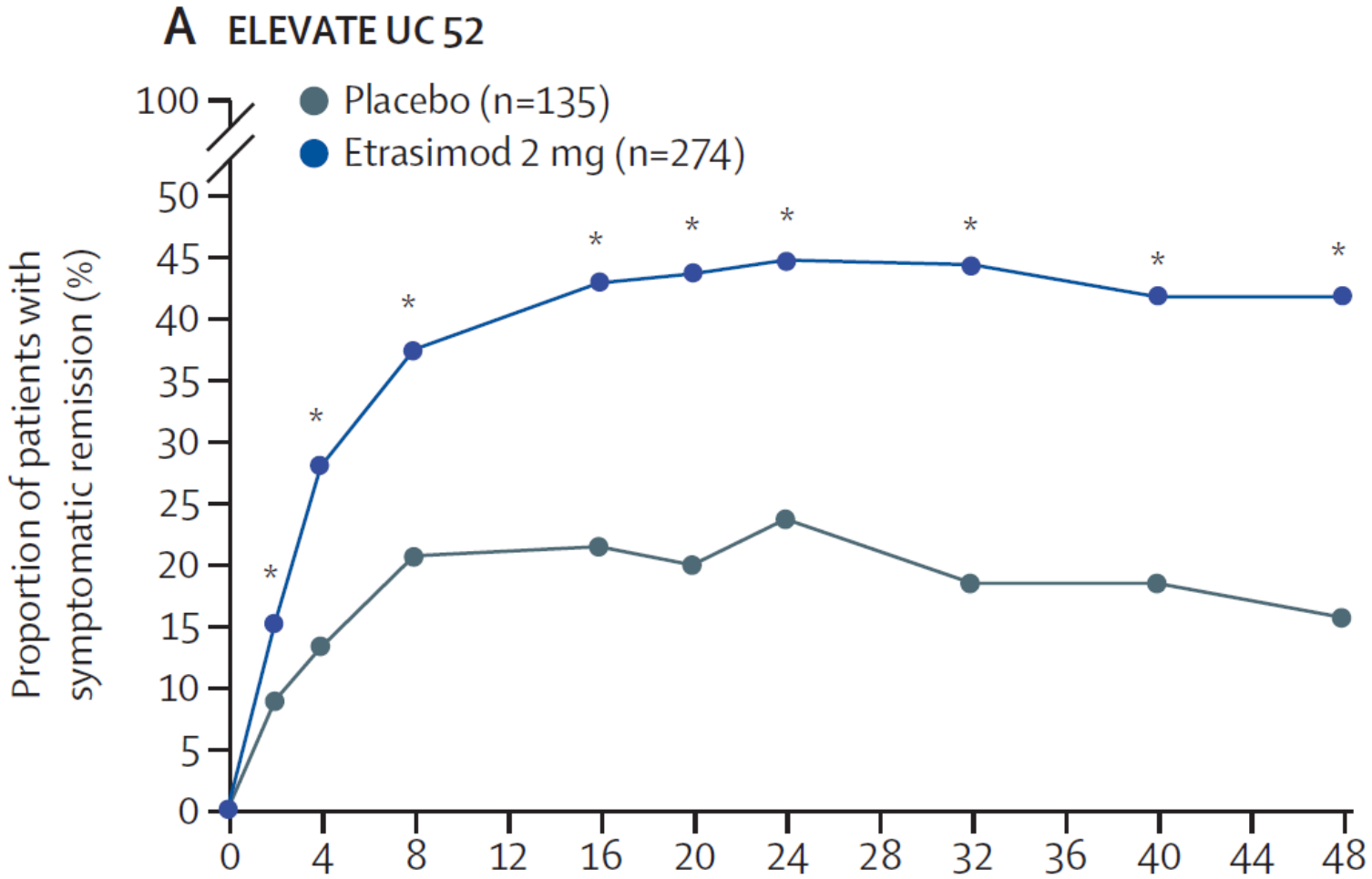

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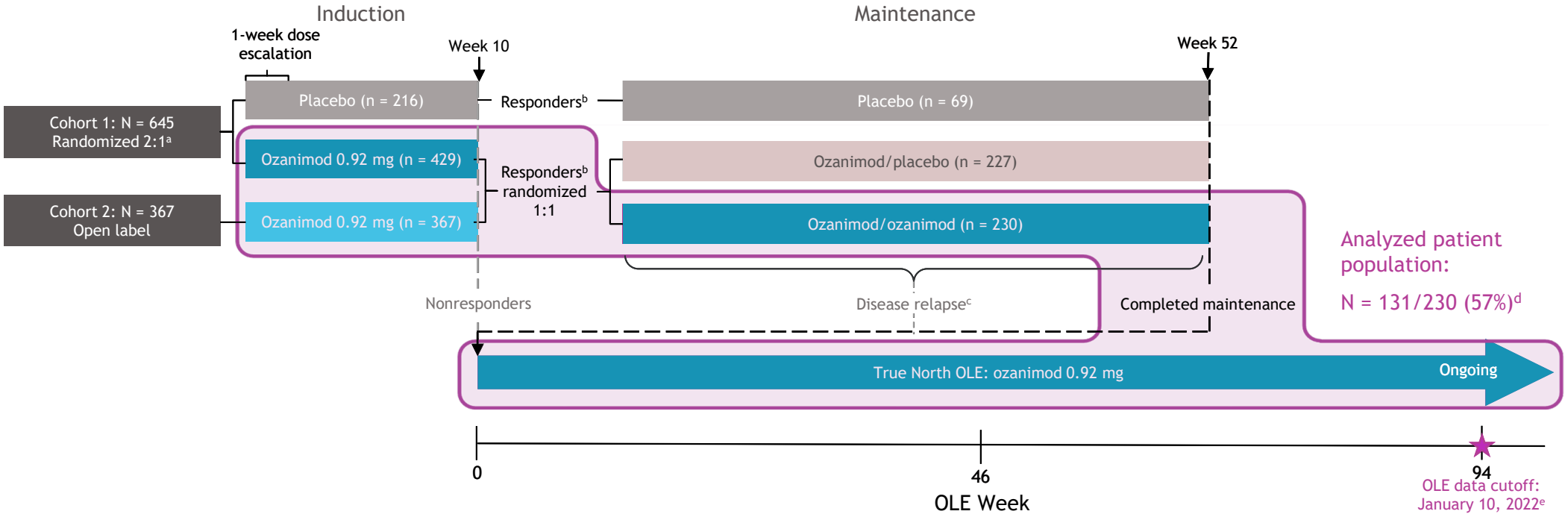
Ozanimod zur Remissionserhaltung bei Colitis ulcerosa

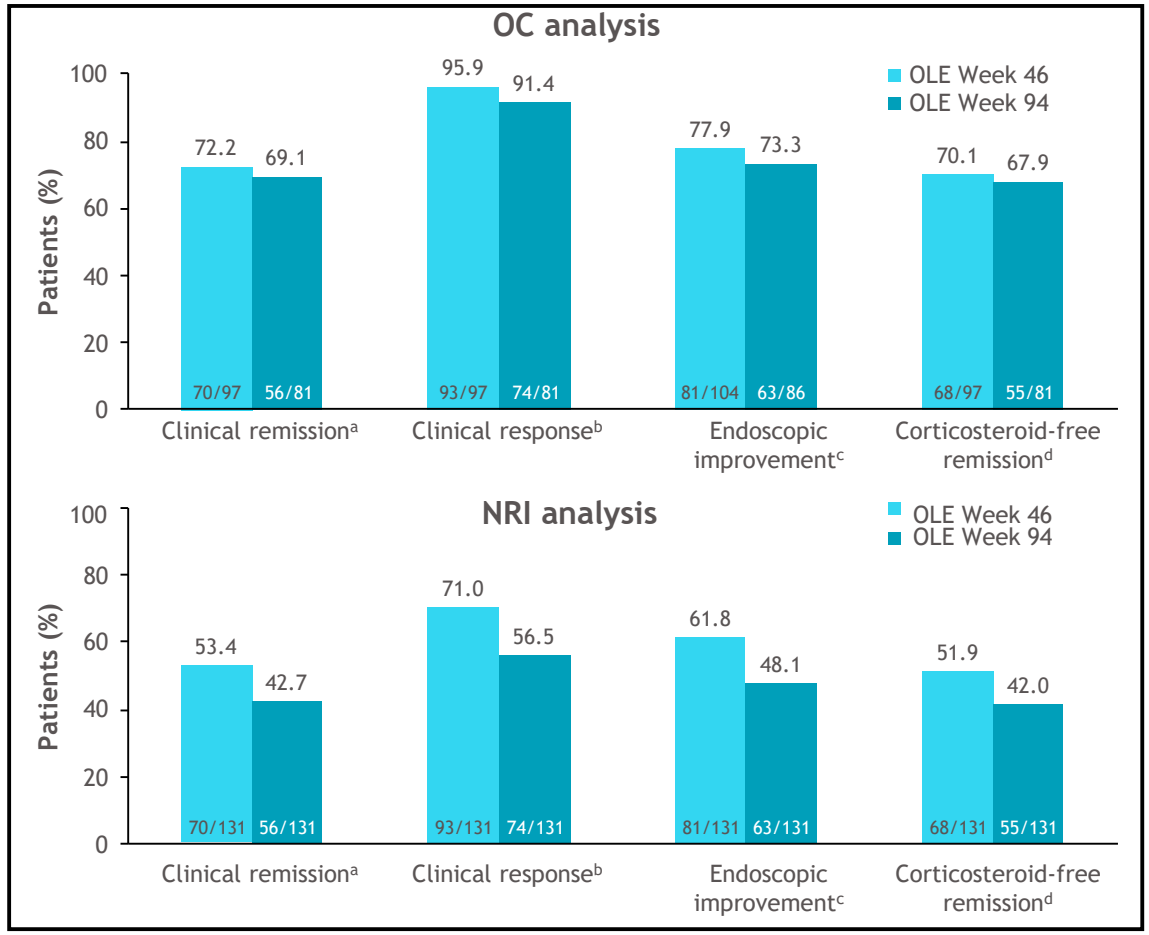
Efficacy and safety of 3 years of continuous ozanimod treatment: an interim analysis of the True North open-label extension study

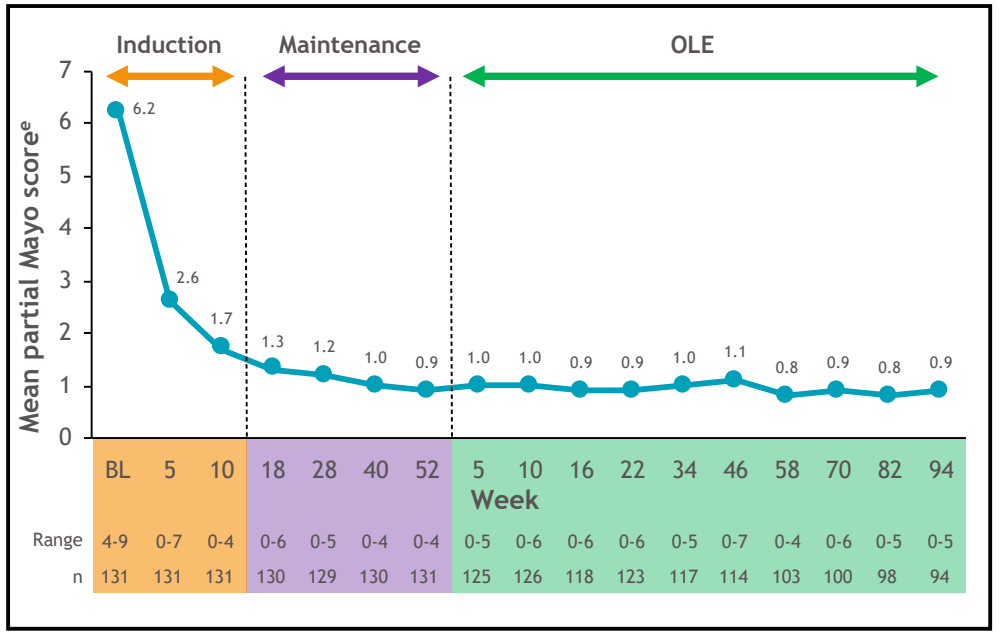
Objective: To evaluate the long-term efficacy and safety of ozanimod in patients with UC with approximately 3 years of continuous ozanimod treatment in an interim analysis of the ongoing True North OLE study



Silvio Danese, Maria T. Abreu, Douglas C. Wolf, James B. Canavan, Anjali Jain, Hsiuanlin Wu, AnnKatrin Petersen, Lorna Charles, Remo Panaccione, Anita Afzali; Oral Presentation DOP37; Presented at ECCO 2023; March 1-4, 2023; Copenhagen, Denmark

Ozanimod zur Remissionserhaltung bei Colitis ulcerosa





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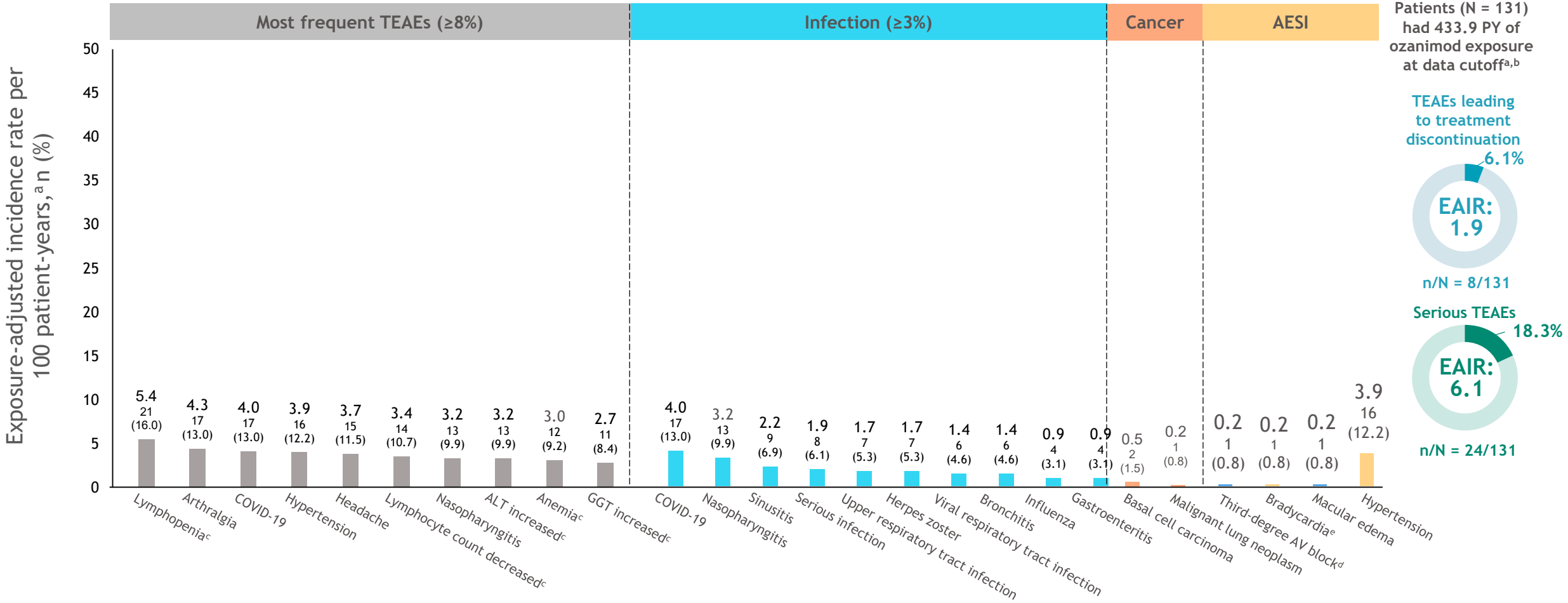
Safety in True North and subsequent OLE under continuous ozanimod exposure



Patients (N = 131) had 433.9 PY of ozanimod exposure at data cutoff[a,b]

TEAEs leading to treatment discontinuation

n/N = 8/131

Serious TEAEs

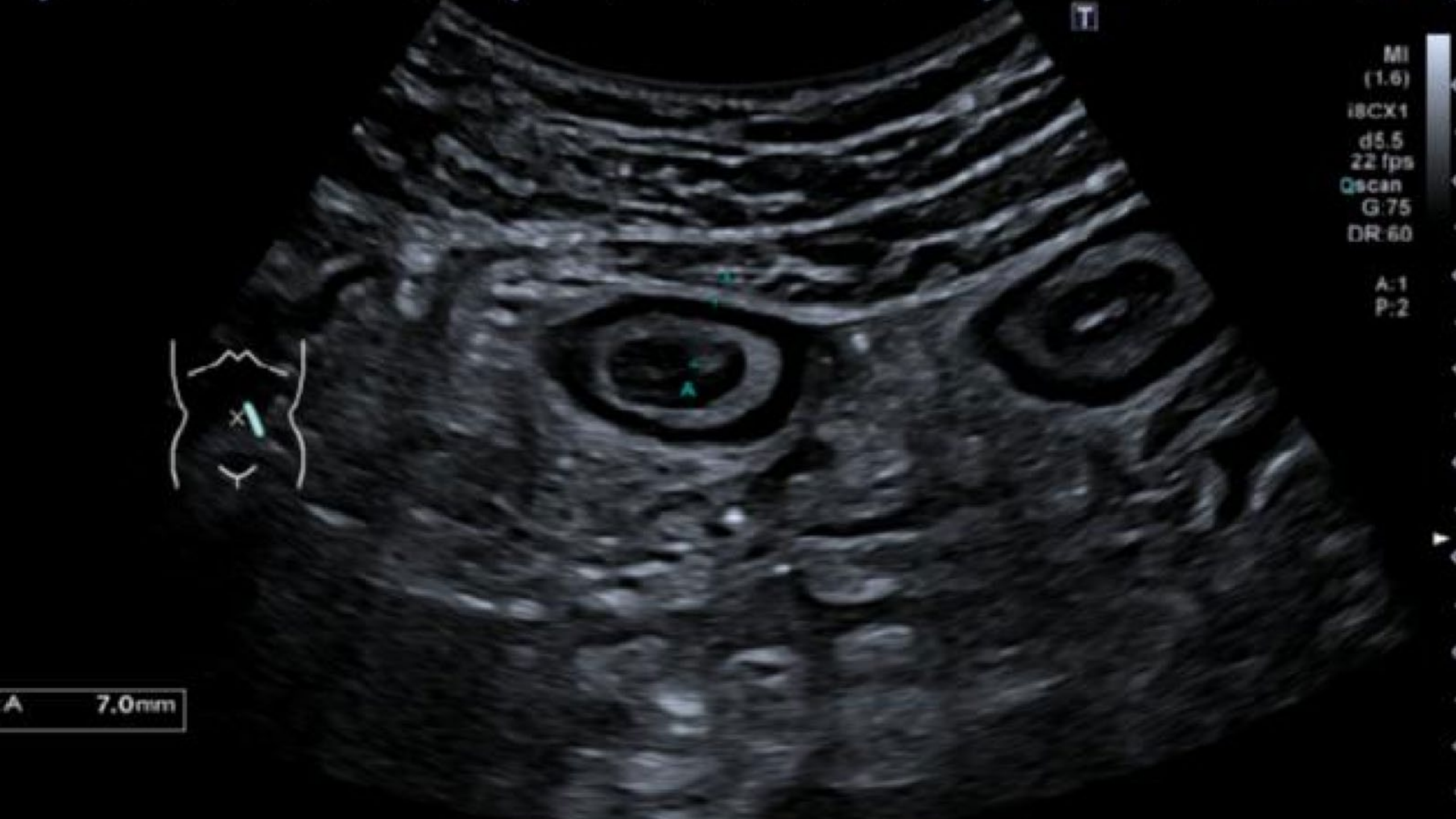
n/N = 24/131

[a]EAIRs were calculated as numbers of patients/PY × 100. [b]Total PY was defined as the sum of the numbers of years on study contributed by each patient from time of first dose to last date on study. [c]Laboratory values that qualified as AEs are reported in this table. [d]The case of symptomatic third-degree AV block was deemed to be unrelated to ozanimod but was related to a history of atherosclerotic cardiovascular disease. [e]The case of bradycardia occurred on Day 1 of the True North induction period, was considered mild and nonserious, did not require treatment interruption or hospitalization, and resolved on Day 7.
AE, adverse event; AESI, adverse event of special interest; AV, atrioventricular; ALT, alanine aminotransferase; GGT, gamma-glutamyl transferase; EAIR, exposure-adjusted incidence rate; OLE, open-label extension; PY, patient-years; TEAE, treatment-emergent adverse event.

Danese S et al. ECCO 2023.

Zusammenfassung

- Beta-Lactam Antibiotika können Schübe von IBD auslösen
- JAK Inhibitoren:
  - Upadacitinib auch bei M. Crohn wirksam
  - Keine vermehrten cardiovaskulären Ereignisse bei IBD Patienten bisher
- Auch in populationsbasierten Studien zeigen sich Vorteile einer frühen Resektion bei M. Crohn des terminalen Ileums
- Network Meta-Analysen zur Induktionstherapie bei M. Crohn: sehr gute RR für Infliximab, Risankizumab, Upadacitinib, Adalimumab (und Ustekinumab bei Biologika naiven Patienten)
- In einer Head-to-head-Studie war Risankizumab überlegen gegen Ustekinumab bei moderatem bis schwerem M. Crohn
- Mirikizumab und Guselkumab sind zur Induktionstherapie und zur Remissionserhaltung bei Colitis ulcerosa effektiv
- Ermutigende Daten für S1P1 Agonisten bei Colitis ulcerosa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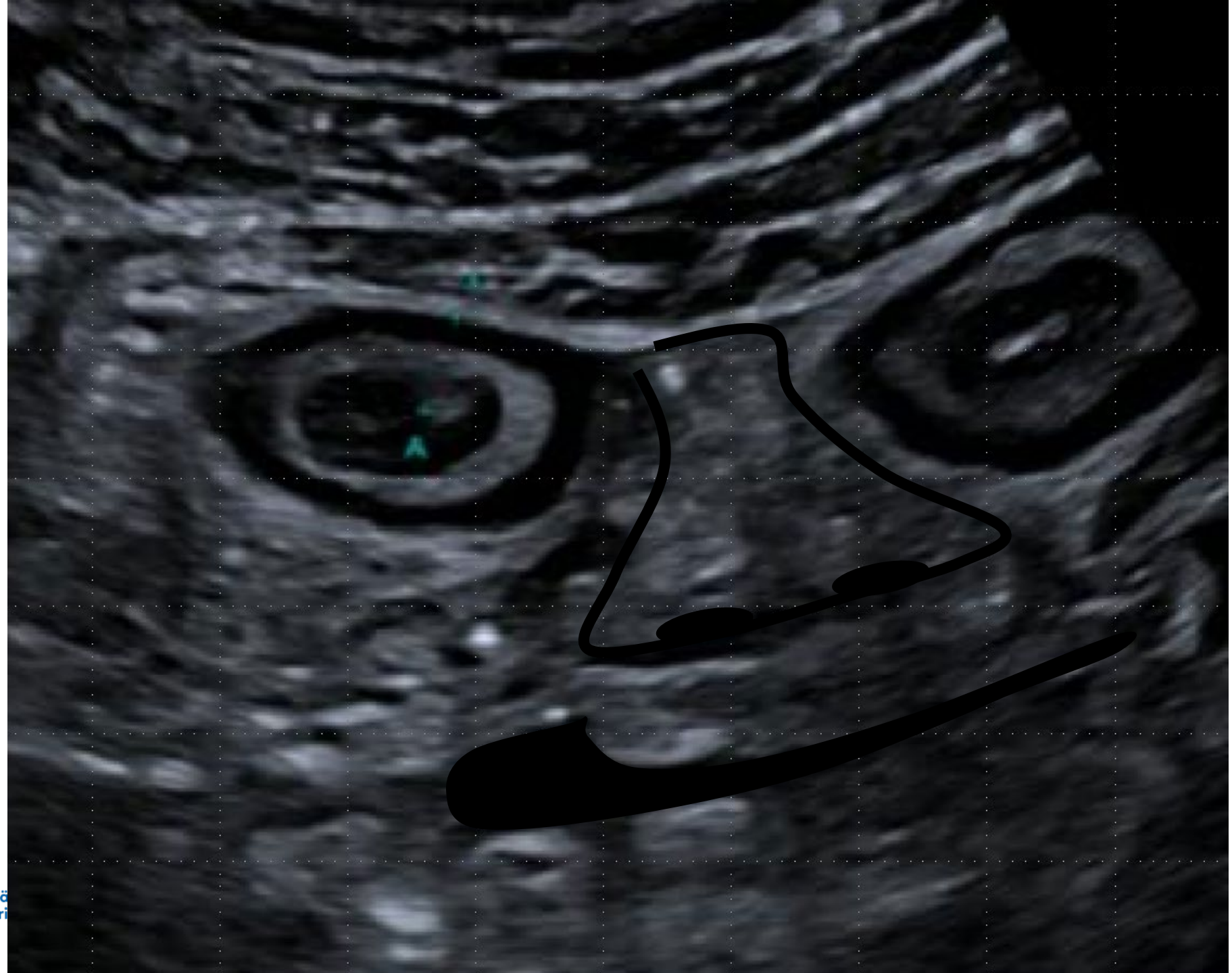
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Danke für die Aufmerksamkeit

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