The role of IUS in the treat-to-target concept

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Disclosures

- Lecture fees:
  - AbbVie, BMS, Celgene, Celltrion, Falk Pharma, Ferring, Galapagos, Gilead, MSD, Janssen, Lilly, Pfizer, Takeda, Tillotts, Sapphire Medical, Sandoz, Shire, Warner Chilcott

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Treating to target – the basics

Understand the need for TTT

Understand the concept of TTT

Understand the evidence for TTT

Overcome the challenges of TTT

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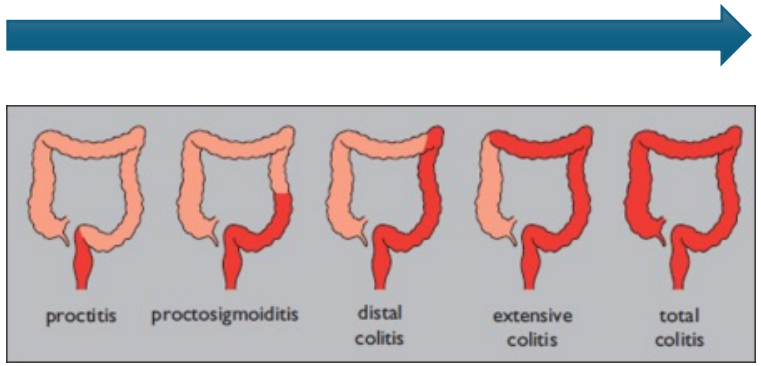
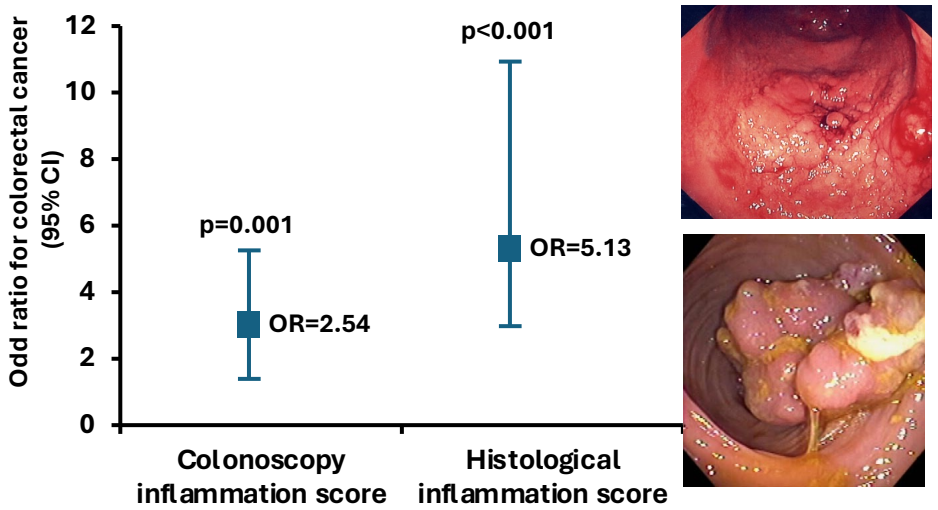
Crohn's and UC are long-term diseases

- ***Short-term thinking is the enemy of long-term success***

UC has long-term complications

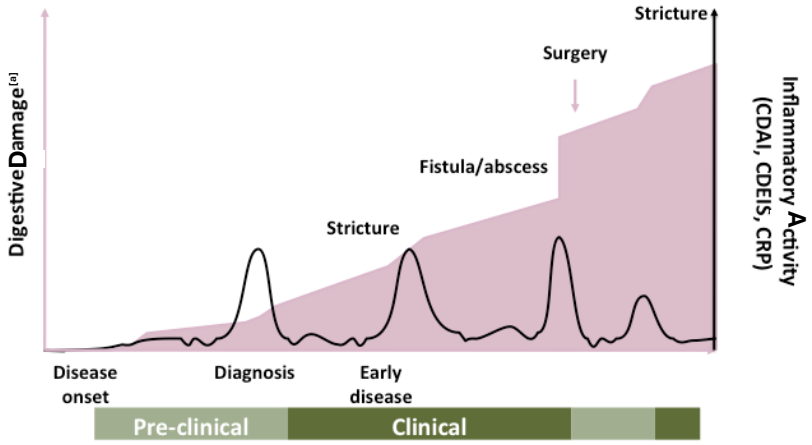


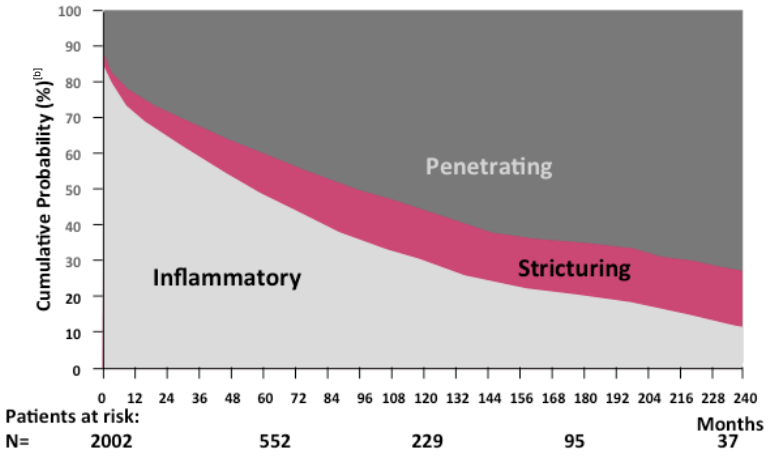


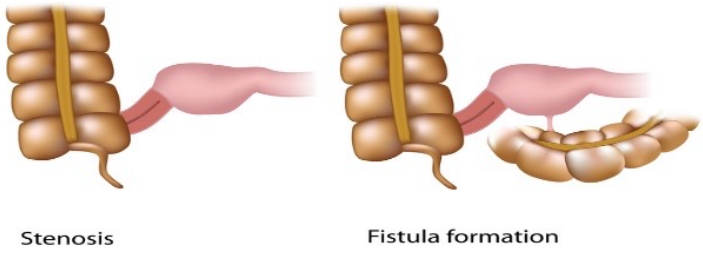
ORs for colorectal cancer are for each 1-point increase in inflammation score

- Rutter M, et al. Gastroenterology, 2004;126:451-9

CD Has Long-Term Complications







- Pariente B, et al. *Inflamm Bowel Dis*. 2011;17:1415-422.
- Cosnes J, et al. *Inflamm Bowel Dis*. 2002;8:244-250.

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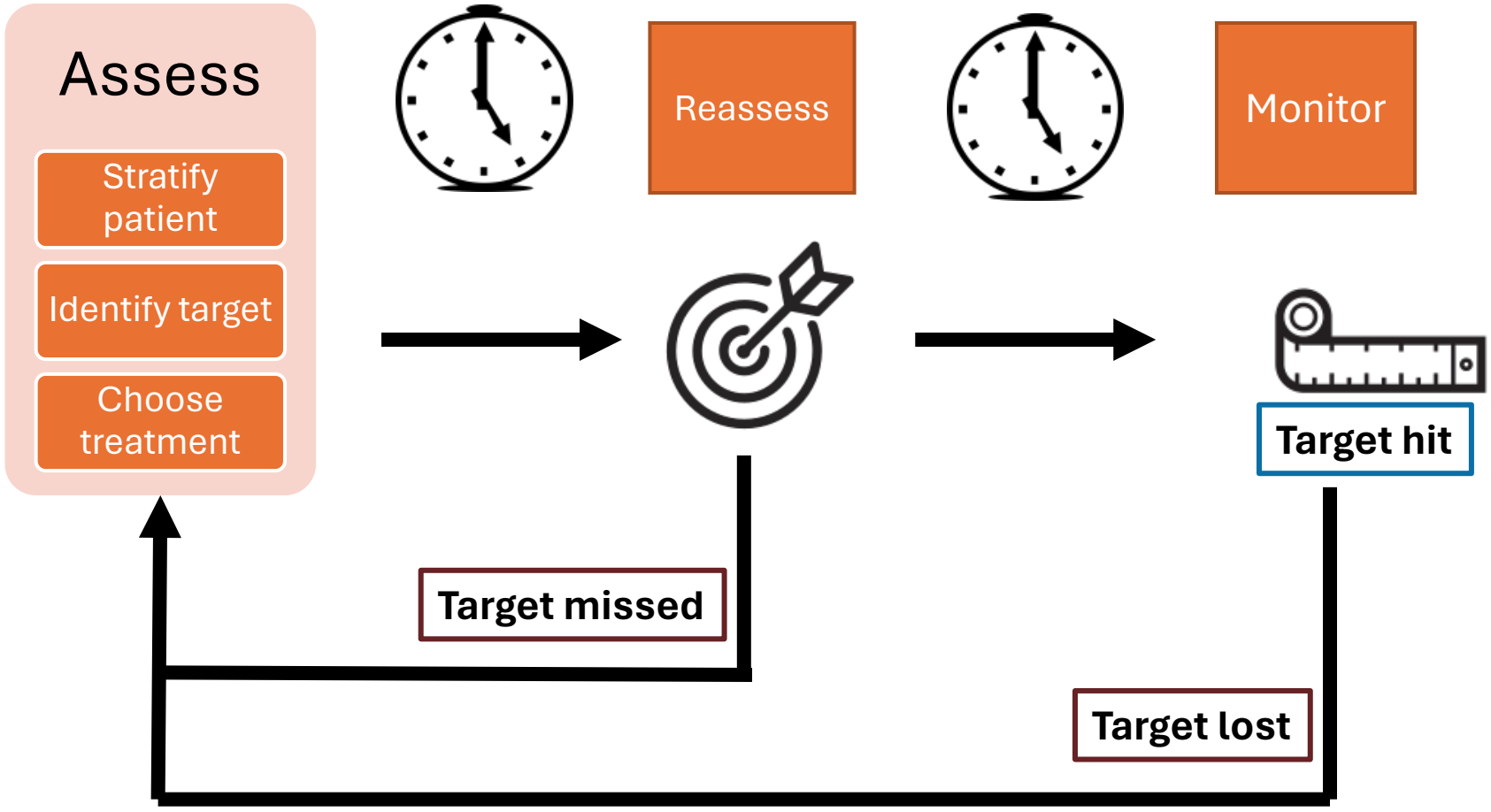
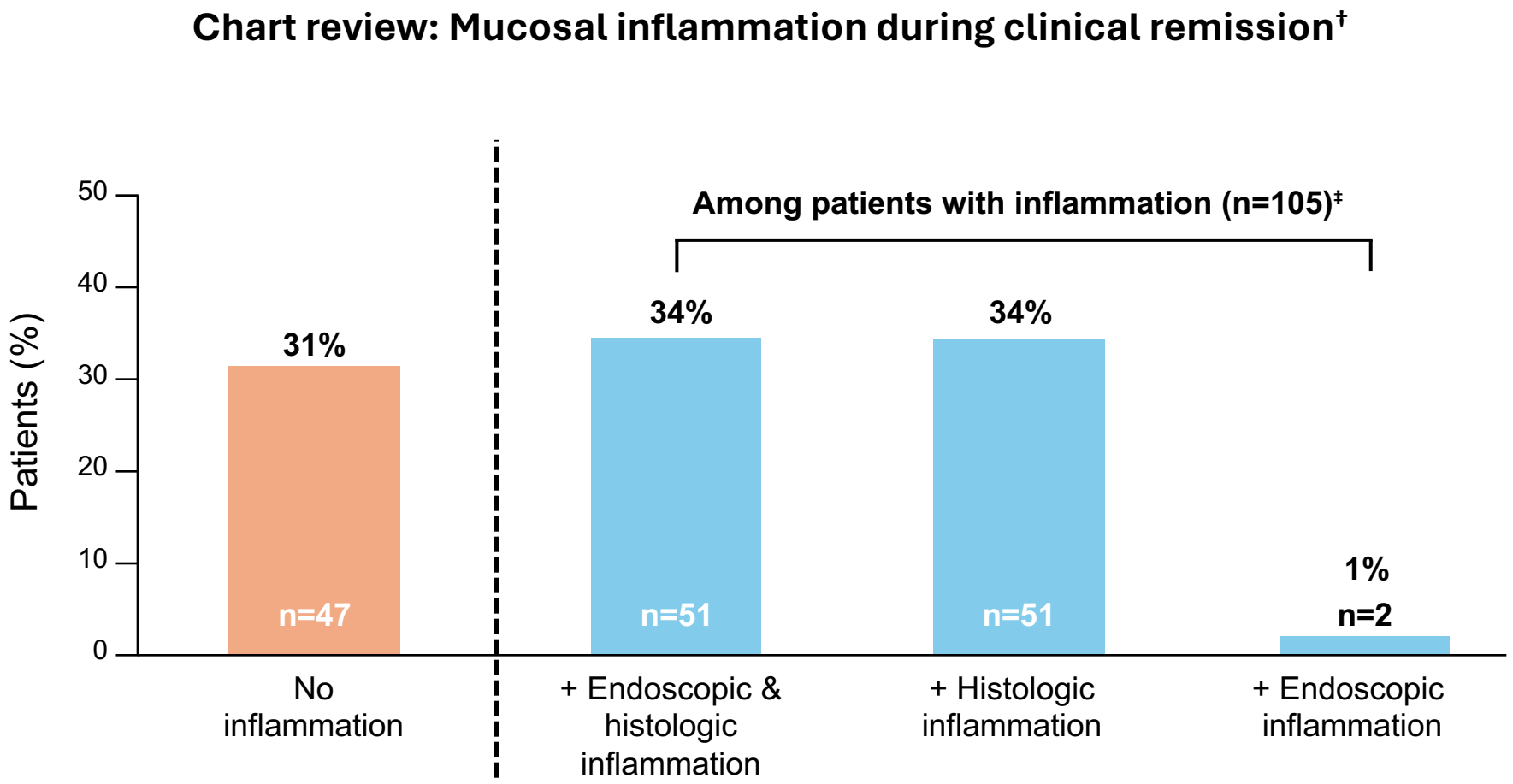
Treating to target is an attractive concept



The majority of IBD patients in clinical remission have mucosal inflammation



†N=152 IBD patients; 65% (n=98) UC patients. ‡Data on endoscopic inflammation missing in 1 patient.

Baars JE, et al. *Inflamm Bowel Dis*. 2012;18:1634-40.

What should the mucosal target be in ulcerative colitis?

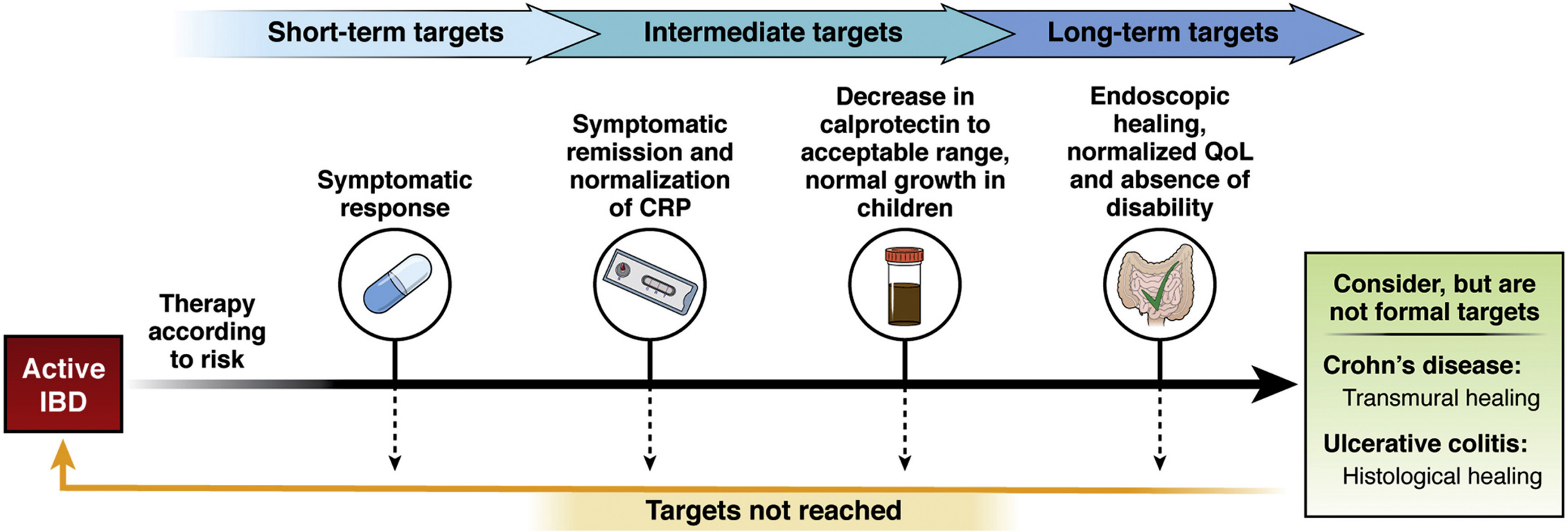
1. Mayo – 0
2. Mayo – 1
3. UCEIS – 0
4. UCEIS – 1
5. UCEIS – 2
6. Histological healing
7. Other
8. Errrrr….

What should the mucosal target be in Crohn's disease?

1) Complete mucosal normality
2) Lack of deep ulcers
3) Lack of shallow ulcers
4) Lack of any ulcers including aphthous ulcers
5) Other
6) Hmmmm….

Selecting targets of remission in inflammatory bowel disease

STRIDE II: “Treat-to-target in IBD”



Turner D *et al*. *Gastroenterology* 2021

Treating to target – the basics

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CALM: An open-label, multicentre study in moderate to severe Crohn's disease†

Treat-to-target (treatment escalation based on biomarkers) **vs Clinical management** (treatment escalation based on clinical symptoms)

Study overview

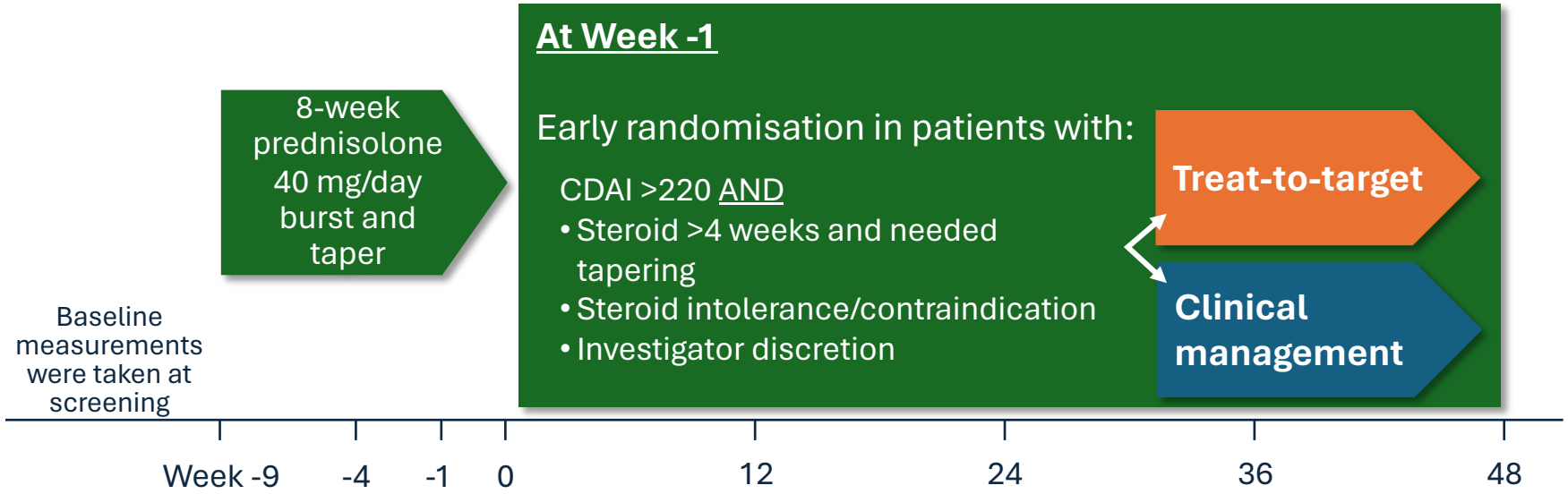
- Patients eligible for CALM as per **CDAI score** and **diagnosis**
- **All patients received steroids at baseline**
- Patients were randomised to **different treatment approaches:**
  - Treat-to-target
  - Clinical management
- These **approaches dictate the treatment** patients received **at randomisation and during the study**

CDAI, Crohn's Disease Activity Index.

Colombel JF, et al. *Lancet.* 2018;390:2779–89.

CALM study design

Open-label, multicentre study in moderate to severe Crohn's disease (n=244)



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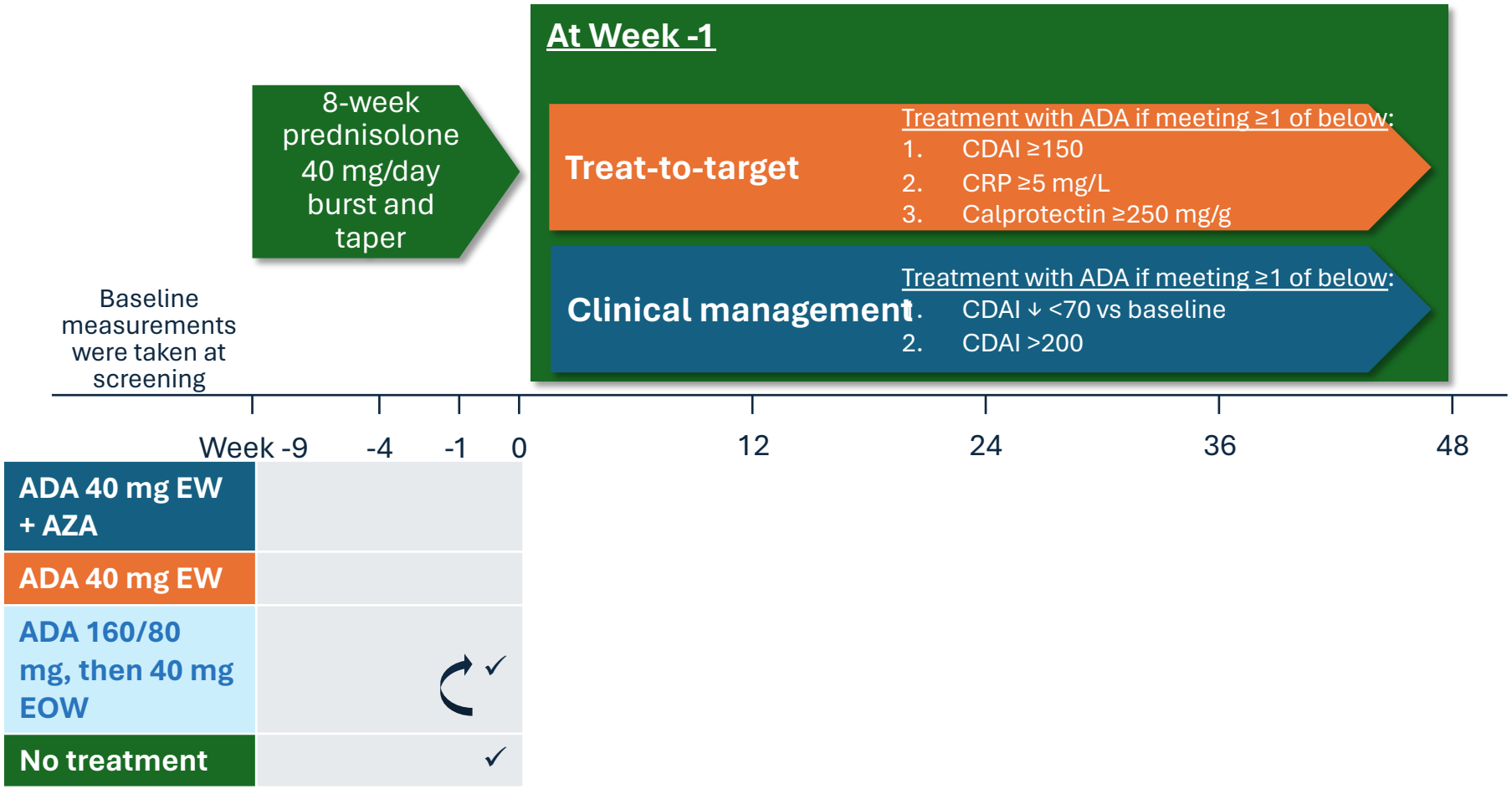

ADA, adalimumab; AZA, azathioprine; CDAI, Crohn's Disease Activity Index; EOW, every other week; EW, every week.
Colombel JF, et al. *Lancet*. 2018;390:2779–89.

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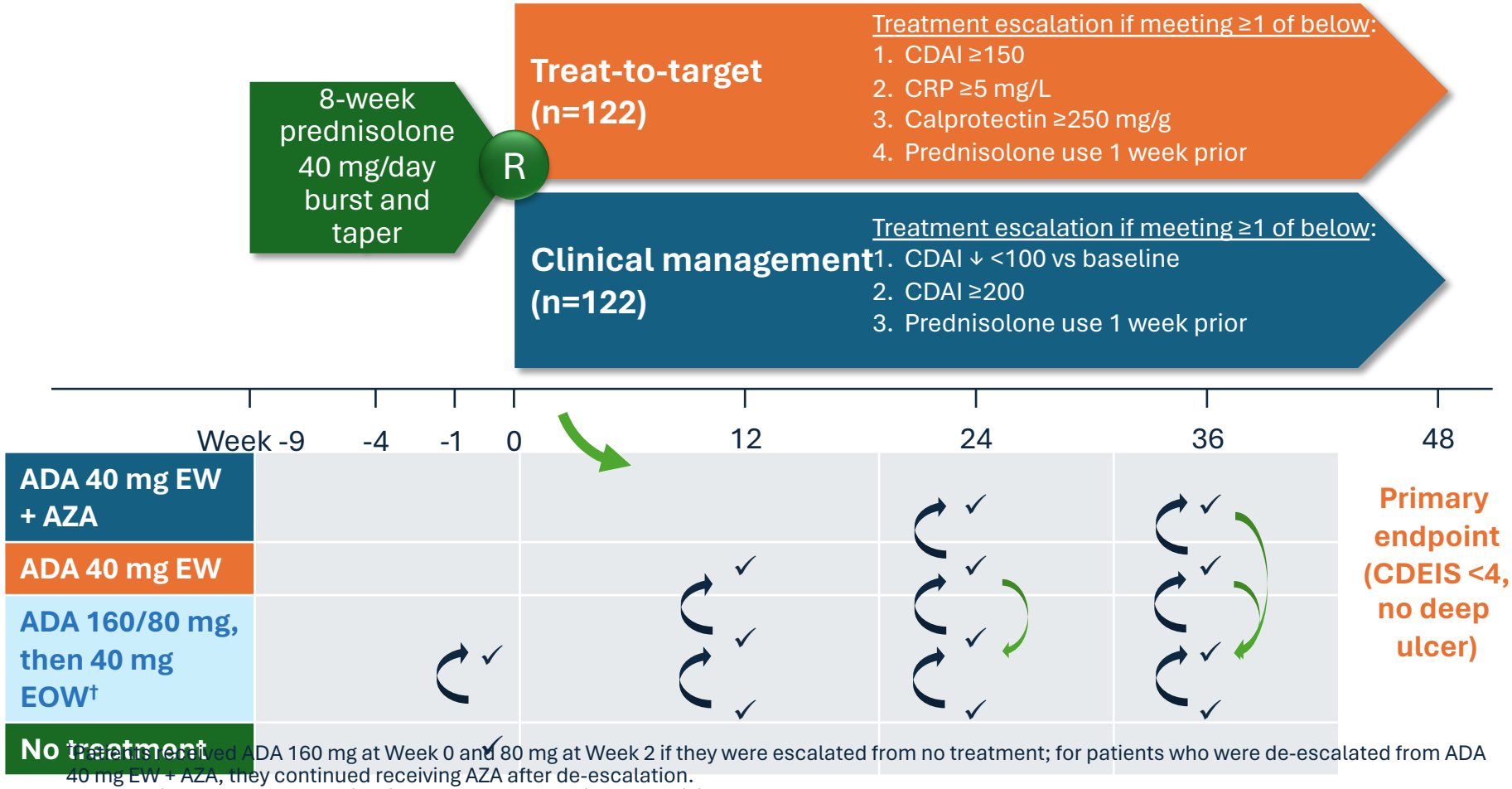
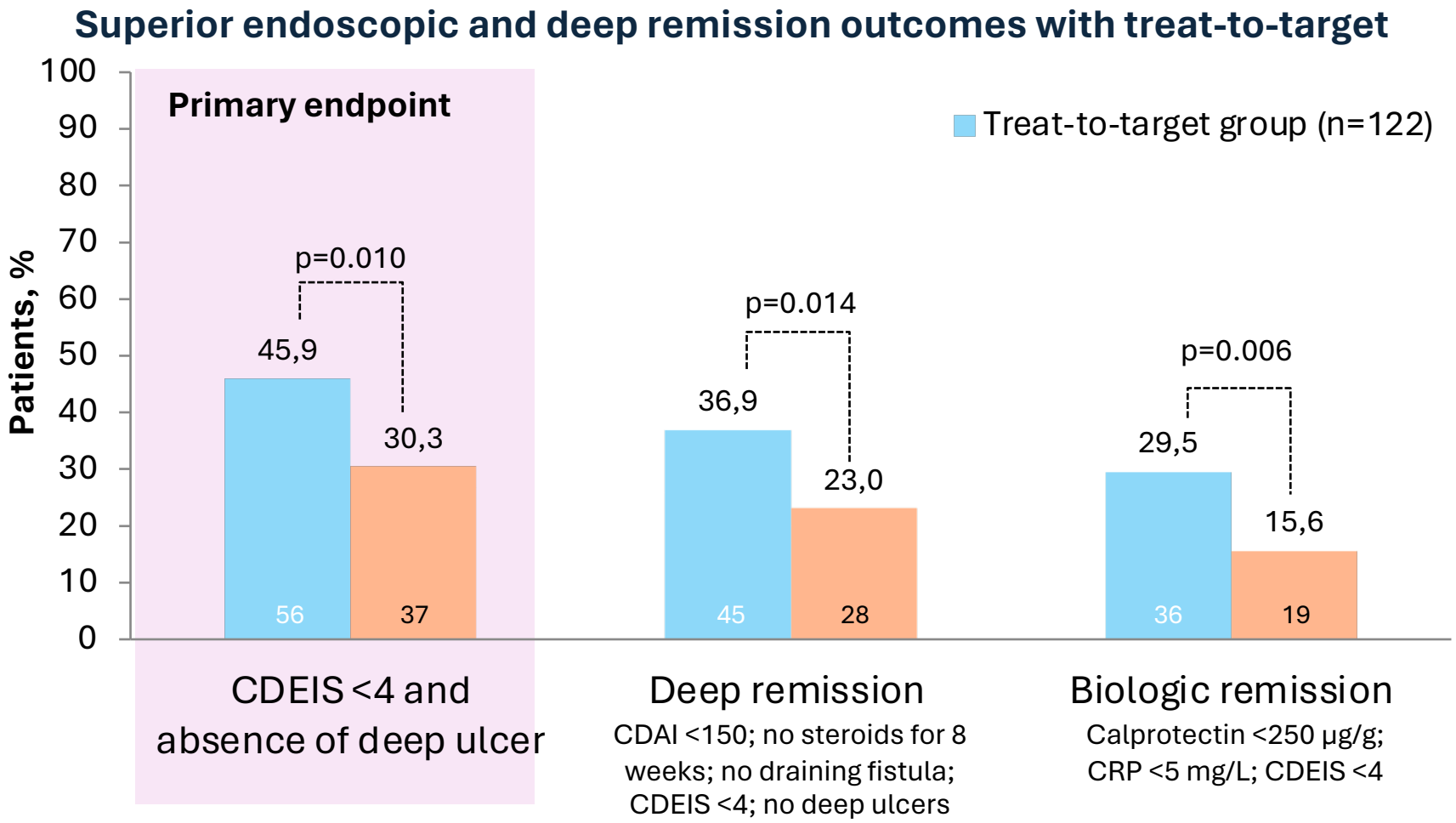


†Patients received ADA 160 mg at Week 0 and 80 mg at Week 2 if they were escalated from no treatment; for patients who were de-escalated from ADA 40 mg EW + AZA, they continued receiving AZA after de-escalation.

ADA, adalimumab; AZA, azathioprine; CDAI, Crohn's Disease Activity Index; EOW, every other week; EW, every week; T2T, treat-to-target.

Colombel JF, et al. *Lancet.* 2018;390:2779–89.

CALM: Significantly more patients in the T2T group achieved primary endpoint at 48 weeks than conventional management



CDAI, Crohn's Disease Activity Index; CDEIS, Crohn's Disease Endoscopic Index of Severity; T2T, treat to target.
Colombel JF, et al. *Lancet*. 2018;390:2779–89.

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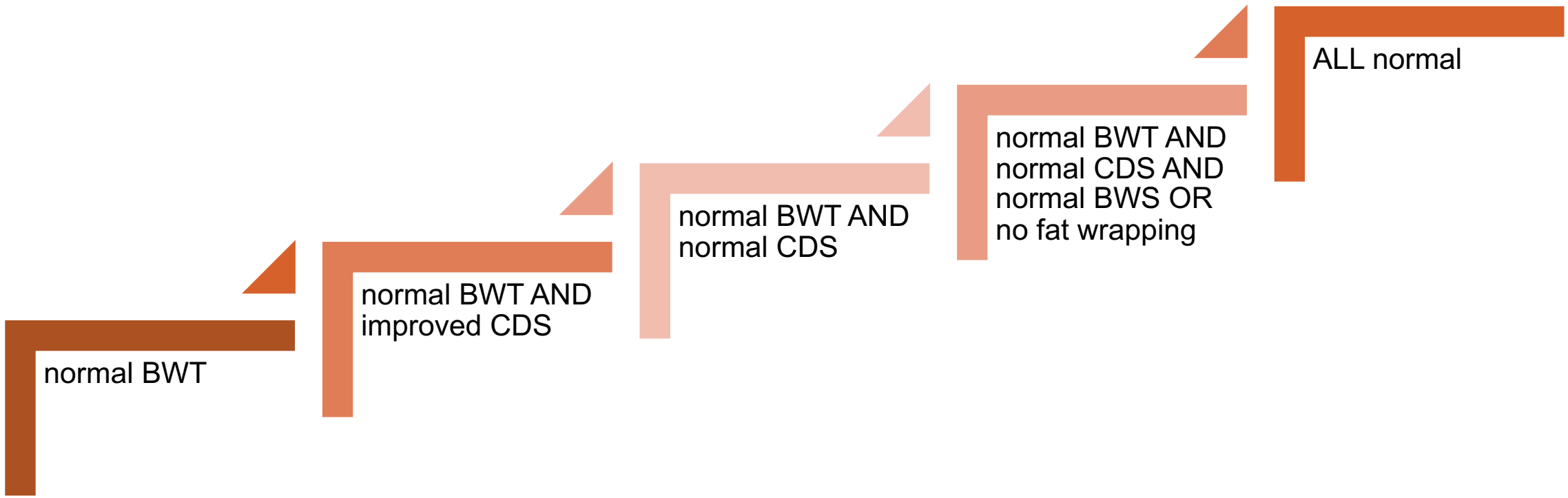
Treating to target: possible benefits and risks

Benefits	Risks

• Improved outcome through better monitoring
• Alteration of disease course
	• Over treatment
	  • Cost and safety
	• Increased monitoring
	  • Costs and safety
	• Failure to alter disease course

Potential caveats of transmural healing

Different definitions of transmural healing – no studies comparing the comparibility of these
Irreversible changes (fibrosis / penetration / dysfunction)
Transmural healing as a target - no interventional studies available… yet.

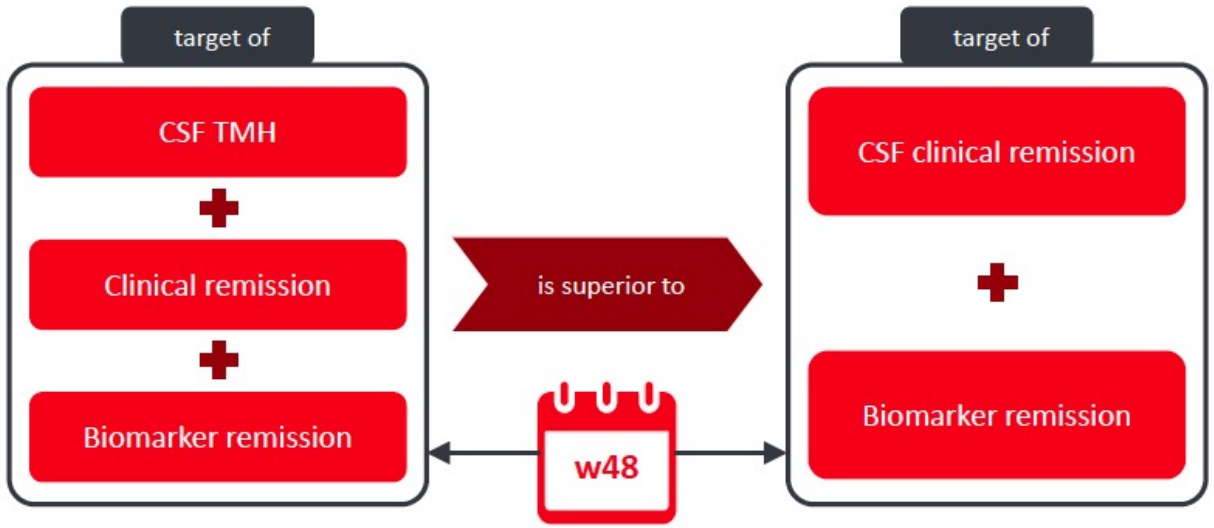


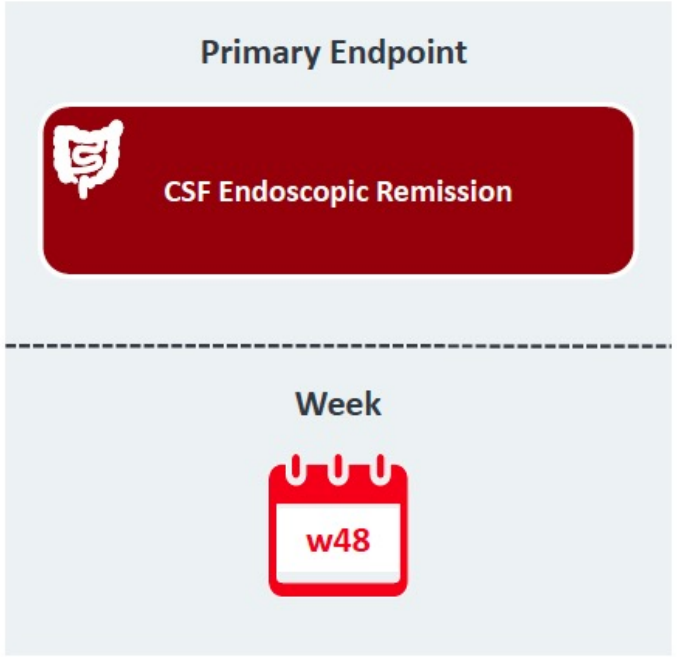
VECTORS

A Study to Evaluate Transmural Healing as a Treatment Target in Crohn's Disease

Primary Objective and Endpoint

Primary Objective: To demonstrate that treating to achieve:





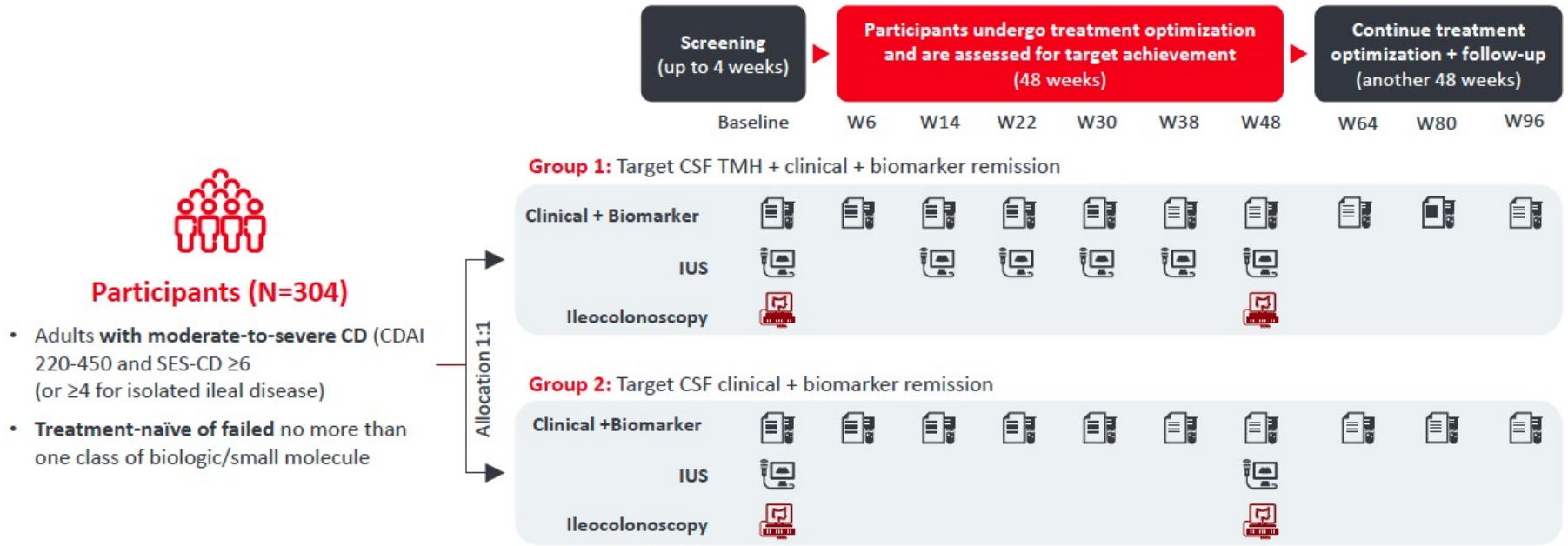
Endpoint Definitions:

- **TMH:** Bowel wall thickness (BWT) ≤3.0 mm and CDS 0 in all evaluable segments assessed by IUS and scored by a central reader.
- **Clinical remission:** Achievement of CDAI <150.
- **Biomarker remission:** Normalization of either CRP (<5 mg/mL) or FCP (<250 µg/g).

VECTORS

Study Design

Phase 4, open-label with no placebo arm, prospective, interventional, multicenter study.



Primary outcome: Corticosteroid-free (CSF) endoscopic remission at week 48.

Secondary outcome: Occurrence of CD-related complications at week 96.

Hypothesis: A treatment target of CSF TMH + clinical remission + biomarker remission is superior to a treatment target of CSF clinical remission + biomarker remission alone in achieving the primary endpoint of CSF endoscopic remission at week 48, measured by the SES-CD.

Conclusions

- TTT is starting to become embedded in clinical practice
- Attractive concept
- Need better definition of targets
- IUS is a potentially attractive target modality
- Limited evidence but
  - we all do it already anyway…..

Could treating to target be cost effective?

Evidence from RA

- 2 real-life cohorts of patients with RA
  - DREAM cohort T2T (treat-to-target)
  - Nijmegen early RA inception cohort (usual care)
- T2T = protocol-led care based on disease activity scores (DAS28)
- 3 year follow-up available
  - 127 patients (T2T)

  180 (usual care)

Results

- T2T resulted in greater remission rates (65% vs 30%) and higher QALYs
- After two years, costs were higher in T2T group largely driven by anti-TNF
- After 3 years, costs were lower in T2T group – very similar costs of anti-TNF

QALYs, quality adjusted life year; RA, rheumatoid arthritis

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