המרכז הרפואי
שערי צדק
SHAARE ZEDEK
MEDICAL CENTER

ANNE & JOE TURNER
PEDIATRIC IBD CENTER
Shaare Zedek Medical center

Use of Placebo in Pediatric trials in IBD

Cons

Dan Turner

Chair, Pediatric IBD Porto Group of ESPGHAN

Member, Pediatric ECCO committee (PECCO)

Shaare Zedek Medical Center

The Hebrew University of Jerusalem

Disclosures

Last 3 years received consultation fee, research grant, royalties, or honorarium from:

Janssen, Pfizer, SickKids, Ferring, MegaPharm, AstraZeneca, Abbvie, Takeda, Rafa/Falk, and BMS

Active (arm)

Placebo

ECCO

The Paediatric IBD Porto Group

ESPGHAN

Is there any role for placebo in children?

YES!

- Withdrawal in children with deep and longstanding remission
- Add-on to effective treatment (excluding failed maintenance treatment as with thiopurines)
- When the drug has not been evaluated previously in adults

These are not the circumstances of current typical clinical trials

Placebo can be used in children when all 4 criteria are met:

1) **Evidence for any particular treatment is lacking (i.e. equipoise between treatment and placebo)**
2) **The risks are minimal (favorable risk-benefit ratio)**
3) **Extrapolation from adult data is not considered adequate**
4) **Alternative study designs are not available**

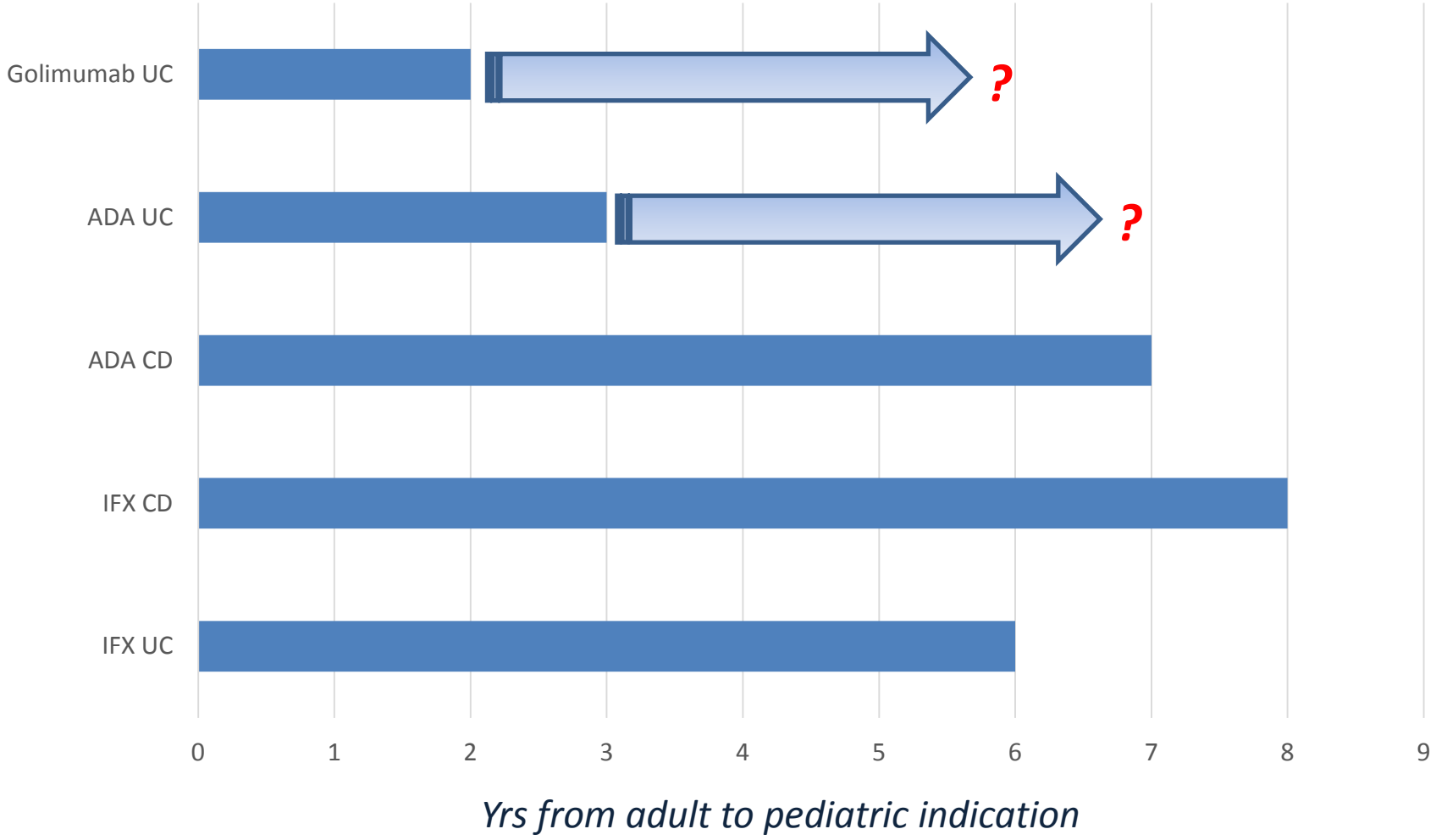
The four criteria do not hold in most paediatric IBD trials!

EU GCP Directive 2001/20/EC

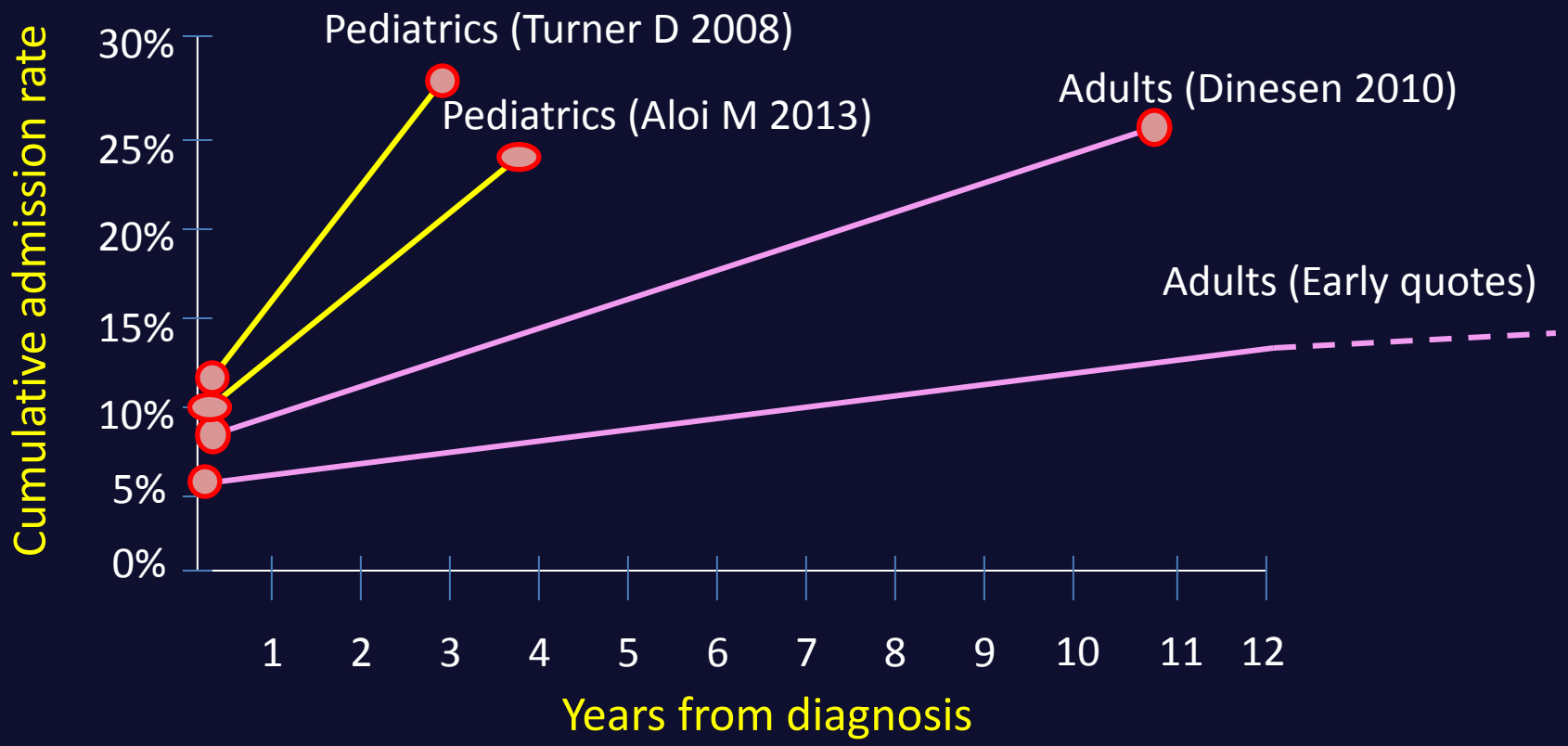
At present, why must pediatric trials be designed differently?

- A caregiver must make all choices for the best interest of his/her child and cannot consent to make his/her child altruistic as they can for themselves
- Adult data are available
- Placebo is less tolerated in children given the more severe disease
- Growth
- Feasibility issues

We must shorten time to pediatric indications!



Admission rate for severe colitis



The fact that the disease is more extensive/severe may reflect on dosing and the way the drug is given but the underlying response is similar

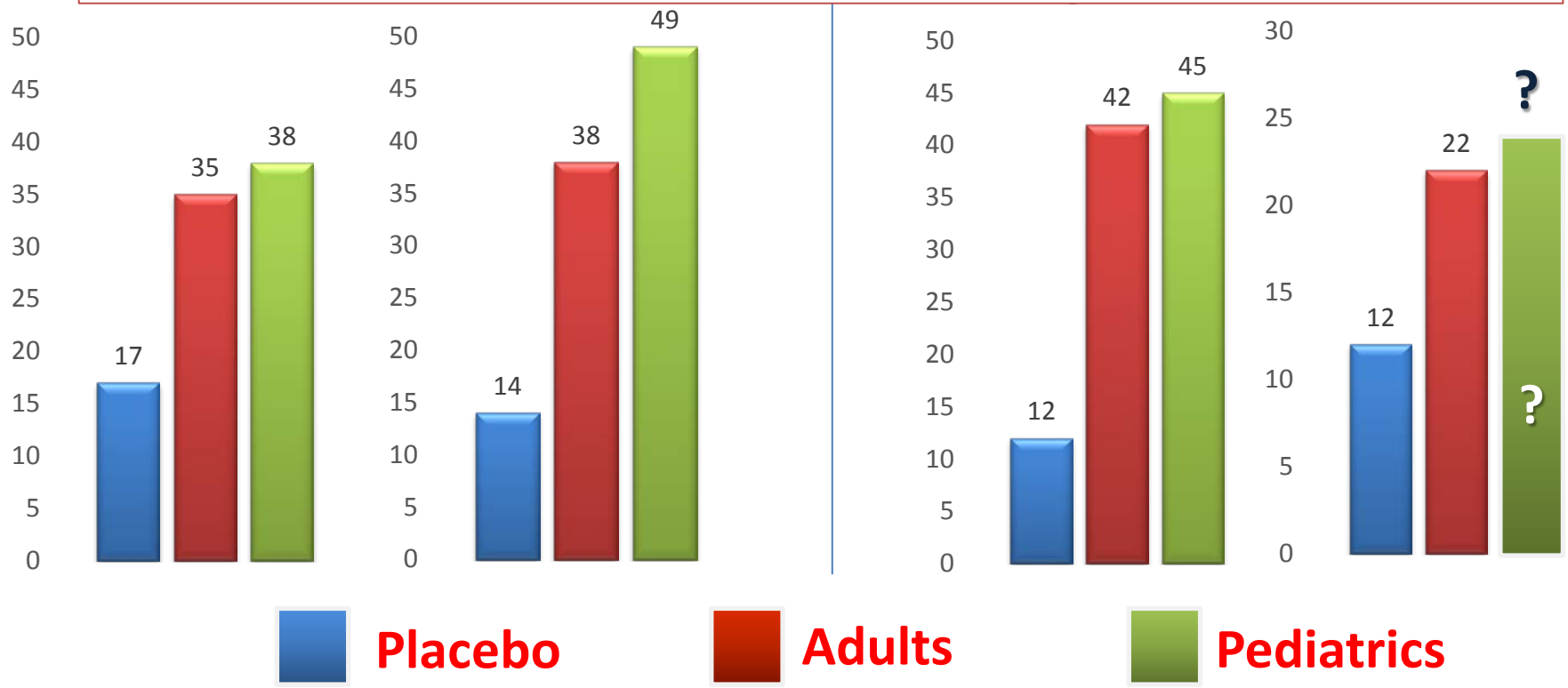
There are no examples of IBD drugs that work in adults, but do not work in children

Treatment	Adult	Children
5-ASAs	✓	✓
Corticosteroids	✓	✓
Immunomodulators (MTX and thiopurines)	✓	✓
Budesonide	✓	✓
Anti-TNFs	✓	✓

In 2015, there is certainty that an effective adult IBD therapy is effective also in children

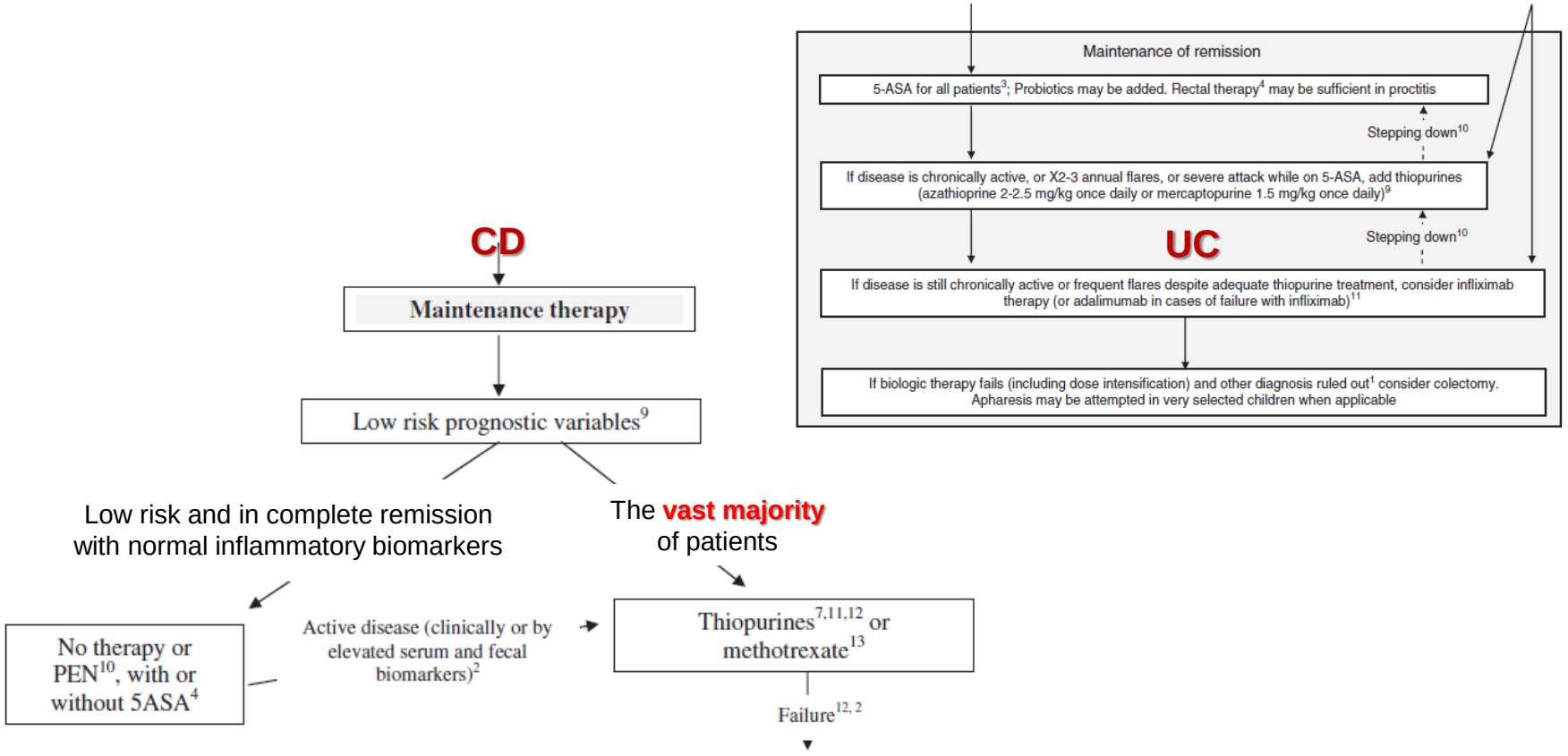
Equipoise "a genuine uncertainty on the part of the expert community about the therapeutic benefits of each arm"

"no one enrolled in a trial should receive a known inferior treatment"



The vast majority of children must be on maintenance Rx

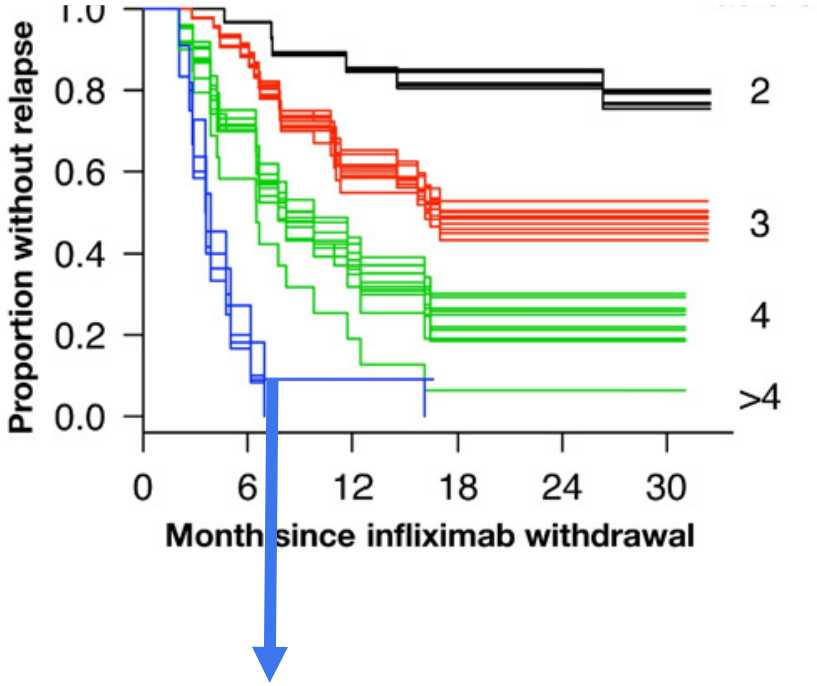
ECCO-ESPGHAN guidelines



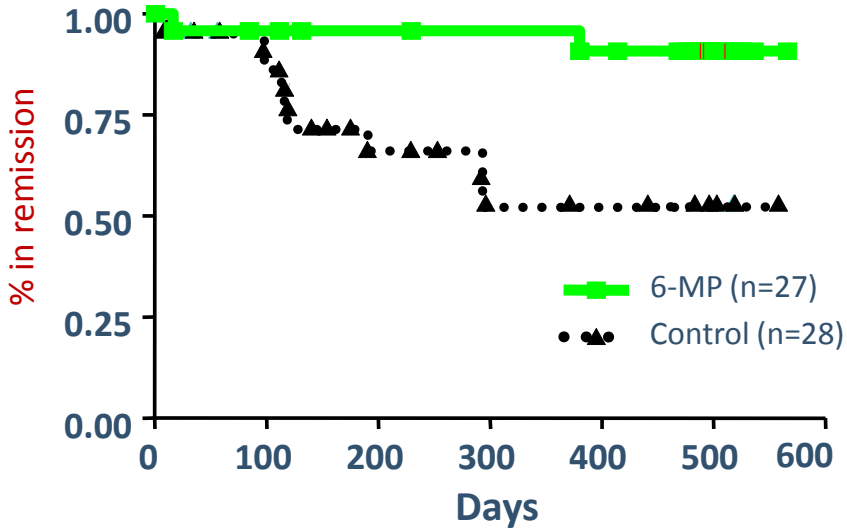
Ruemmele F et al. J Crohn Colitis 2014; 8:1179-1207
Turner D et al. JPGN 2012;55: 340–361

It's obvious that treatment is better than placebo! Exacerbation occurs unless there is a maintenance strategy!

STORI trial



Markowitz 2000



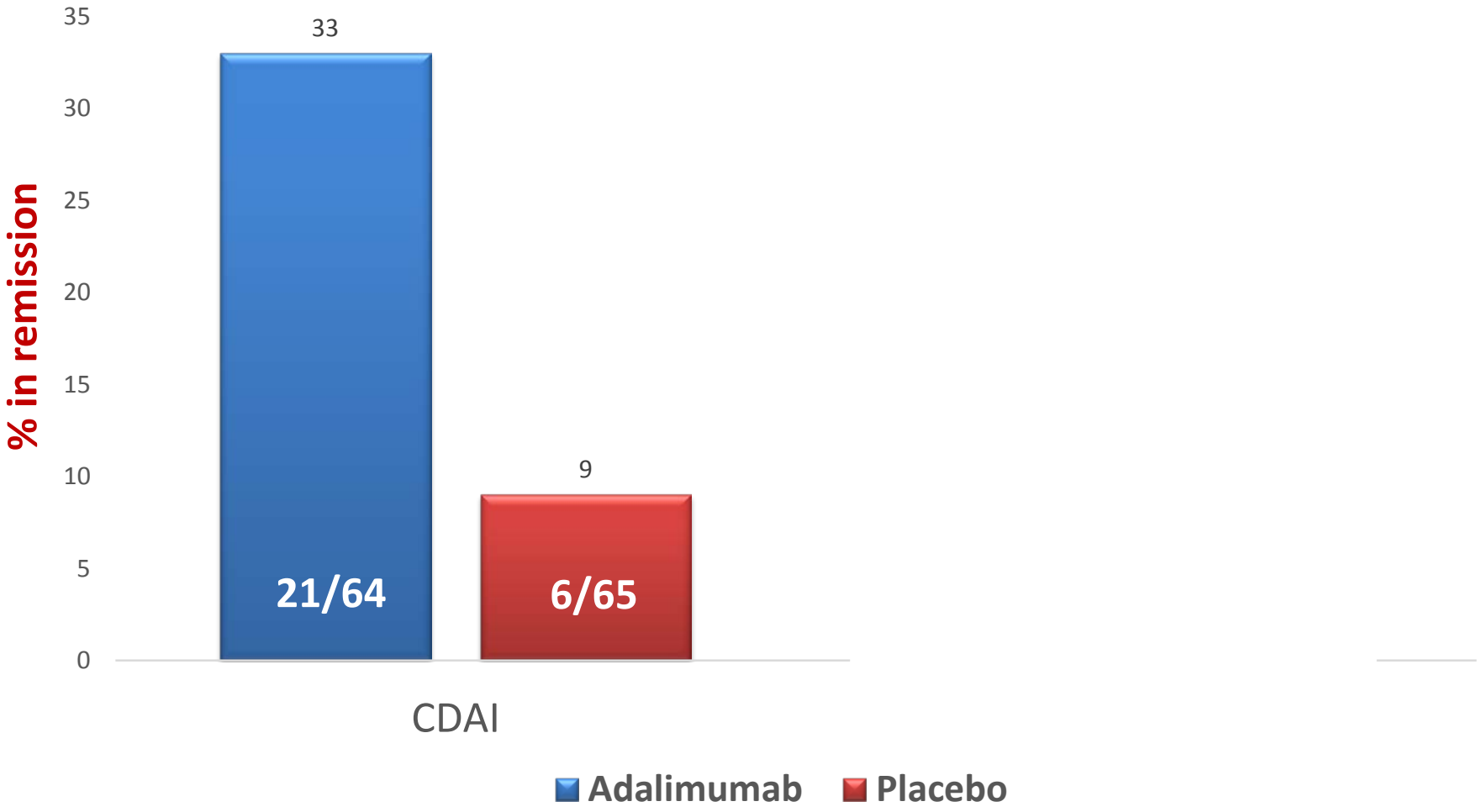
- **Those who were not in complete deep remission flared very rapidly (and <u>all were on thiopurines</u>!)**
- **Reintroduction was NOT successful in 100% (88%, <u>and all were on thiopurines</u>!)**

Markowitz J et al. Gastroenterol 2000;119:895

Loiuse, GASTROENTEROLOGY 2012;142:63–70

Placebo….is just placebo….

52wk remission in the EXTEND trial of adalimumab vs. placebo



Rutgeerts P et al. Gastroenterology. 2012 May;142(5):1102-1111.

Could the use of placebo cause harm?

- Losing effect of the drug and developing antibodies
- Use of corticosteroids
- Growth (shows only after 2-3 months)
- Emotional price of another flare/pain in a child

Even though the risks are hard to quantify, the overall risk appears to be greater than minimal

All anti-TNFs are immunogenic especially as episodic

		Patients, %			
		Episodic Maintenance		Scheduled Maintenance	
		IMS-	IMS+	IMS-	IMS+
Infliximab[1]	(CD 5 mg/kg)	38%	16%	11%	7%
	(CD 10 mg/kg)			8%	4%
Infliximab[2]	(UC 5 mg/kg)	No data		19%	2%
	(UC 10 mg/kg)			9%	4%
Certolizumab[3]	(PRECiSE I)			10%	4%
Certolizumab[4]	(PRECiSE II)	24%	8%	12%	2%
Golimumab	**(PURSUIT)**	**Placebo 7.1%**		**Active drug 3.4%**	
Adalimumab[5]	(RA, all doses)	No data		**28%**	**8%**
Adalimumab[6]	(CLASSIC II)			4%	0%

.

1.Hanauer SB et al. Clin Gastroenterol Hepatol. 2004;2:542-553; 2. Sandborn WJ et al. DDW 2007 Poster and abstract T1273; 3. Sandborn WJ et al. N Engl J Med. 2007;357:228-238; 4. Schreiber S et al. N Engl J Med. 2007;357:239-250; 5. Adalimumab [package insert]. Abbott Laboratories. July 2007; 6. Sandborn WJ et al. Gut. 2007;56:1232-1239. 7. JAMA, April 13, 2011—Vol 305, No. 14 Eur J Gastroenterol Hepatol 2012;24(9):1078–85.

Modified with permission from M. Abreu

Antibodies are associated with more serious infusion reactions

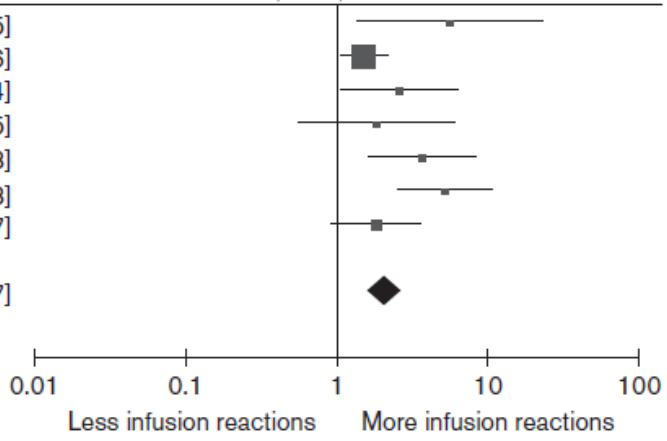
Anti-infliximab antibodies in inflammatory bowel disease: prevalence, infusion reactions, immunosuppression and response, a meta-analysis

Lennard Y.W. Lee, Jeremy D. Sanderson and Peter M. Irving

Study or subgroup	ATI +ve Events	ATI +ve Total	ATI –ve Events	ATI –ve Total	Weight	Risk ratio M-H, fixed, 95% CI
Farrell *et al.* [18]	10	25	2	28	3.5%	5.60 [1.35, 23.15]
Hanauer *et al.* [11]	29	80	71	297	56.4%	1.52 [1.06, 2.16]
Maser *et al.* [4]	11	22	5	26	8.6%	2.60 [1.07, 6.34]
Miele *et al.* [12]	4	12	4	22	5.3%	1.83 [0.56, 6.05]
Rutgeerts *et al.* [14]	5	14	21	215	4.8%	3.66 [1.62, 8.23]
Rutgeerts *et al.* [14]	6	12	17	176	4.1%	5.18 [2.51, 10.68]
Sands *et al.* [15]	13	44	13	80	17.3%	1.82 [0.93, 3.57]
Total (95% CI)		209		844	100.0%	2.07 [1.61, 2.67]
Total events	78		133			

Heterogenity: $\chi^2 = 13.32$, $d.f. = 6$ ($P = 0.04$); $I^2 = 55\%$

Test for overall effect: $Z = 5.67$ ($P < 0.00001$)



European J Gastroenter & Hepatol 2012, 24:1078–1085

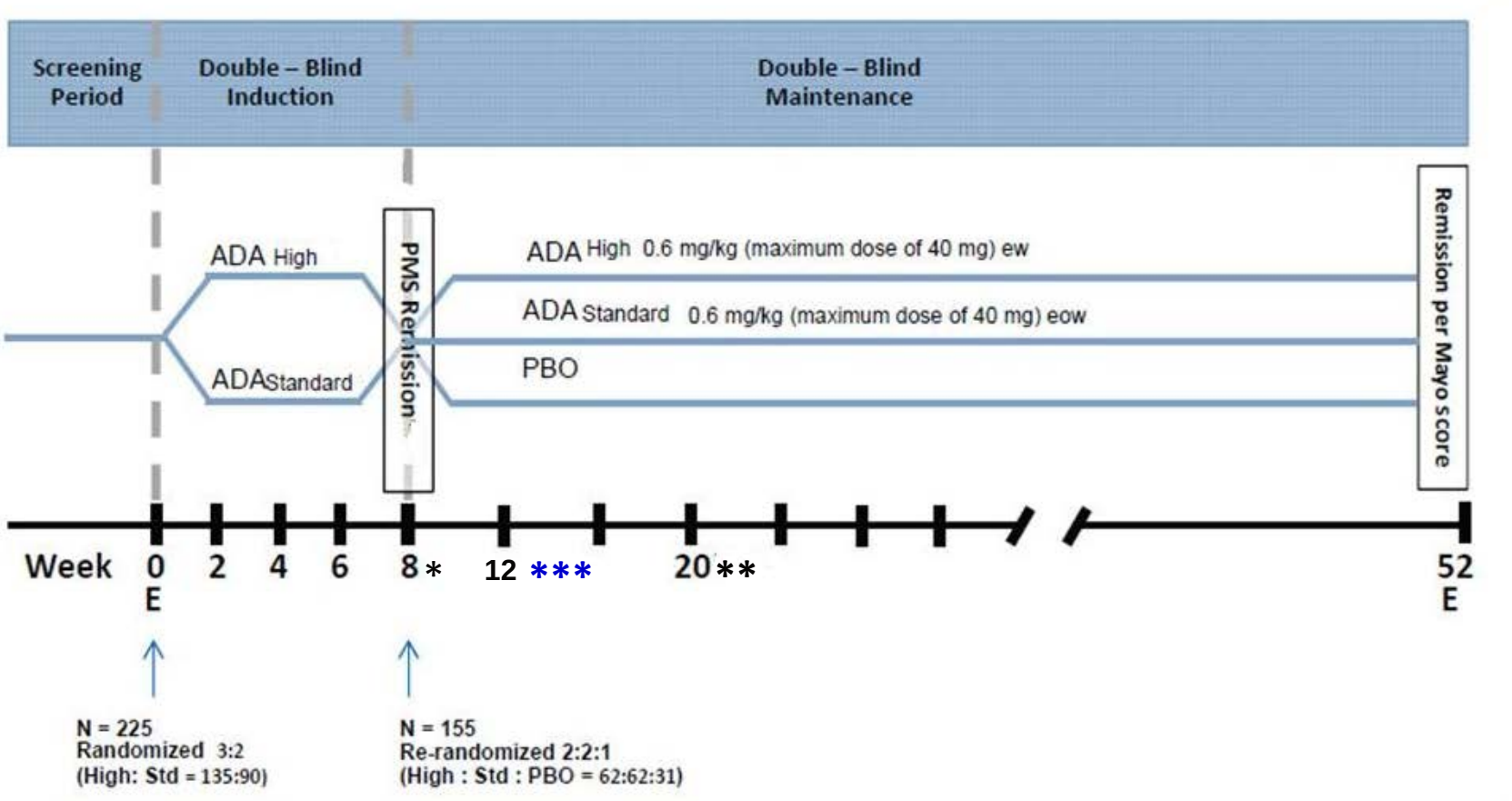
“Early” escape does not solve the problem

- **~10-15% of patients will lose response after a biological drug ‘holiday’** (meta-analysis of the 8 studies below and most were on thiopurines and discontinuation after prolonged remission).

- A drug holiday is associated with increased risk for serious infusion reactions *(n=614 in Leuven, Gut 2009;58:501–508; n=314, APT 2011; 34: 51–58)*

Scand J Gastroenterol 2012; 47: 518–527; Gastroenterology 2012;142:63-70; Br J Dermatol 2013;168:1325–1334; Gastroenterology 2004;126:402–413, CGH 2004;2:542–553; Inflamm Bowel Dis 2014;20:251-258; CGH 2014;12:1474-1481; APT 2009;12:1240-48

M11-290 Study Design



* Re-Randomization of responders and discontinuation of non-responders at Week 8.

** Current protocol: Rescue therapy with active drug for flare at/after Week **20**

*** Amendment 3: Rescue therapy with active drug for flare at/after Week **12**

approval code A4799588

Courtesy Abbvie

Response ≠ Remission

- A child may have 2-3 diarrhea with blood, abdominal pain, anemia and elevated CRP and still considered a "responder"

- **In the year of 2015, it is NOT accepted by ANY standards to withdraw treatment in a child with an active disease.** Both parents and physicians do not accept that

Randomized Withdrawal Study Design are not feasible/effective in the small pediatric population

- In a Peds study with 200 subjects enrolled into induction, and assuming **30%** remission (REACH, T72, IMAgINE):
  - **70** responders to enter maintenance
  - 3 treatment groups (Pbo, high-dose, low-dose) = **25** per group
  - Insufficient power to detect treatment differences:
    - <~20% for overall maintenance endpoint
    - <~10% to distinguish between dose groups if delta=10%

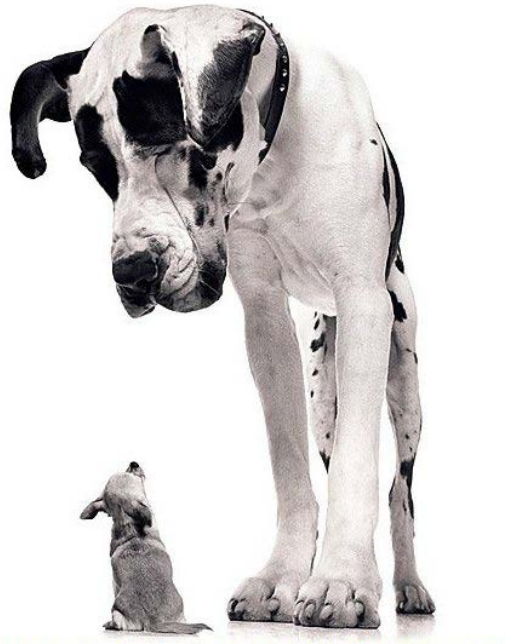
M11-290 Enrollment Barriers and Study Status

- ~200 sites were approached.
- Approximately 100 sites declined participation due to:
  - Ethical concerns associated with a paediatric placebo-controlled study
  - Competing studies without placebo
  - Complexity of the study and limited resources
  - No answer provided
- 30 sites currently active but only 13 sites have screened a patient
  - First study site activated June 2014
  - First patient enrolled in November 2014
  - 14 patients (6.2%) enrolled as of May 2015

Courtesy Abbvie

Children are not like adults make the limitations –a benefit!

"If I have seen further, it is by standing on the shoulders of giants"
(Isaac Newton 1676)



Build on adult trials and address open questions of HOW to use the drug

Given the more extensive and active disease in children

- Active comparison of standard of care
- Standard vs level-based strategy
- Standard dosing vs high doses (esp younger children <10yo)
- Dosing per/kg vs per/BSA
- Combination vs monotherapy

Placebo should not be used in current typical clinical trials!

Where we are asked to:

- Remove therapy from children with mod-severe disease who are improving, but have not necessarily achieved remission, or have had just a brief 6-8 week remission
- Remove therapy from children who may be just starting to achieve catch-up growth

While….

- Continuing treatment is the globally-accepted standard of care
- We know the drug works from adult trials
- Withholding treatment is associated with flares and possibly loss of response and adverse events

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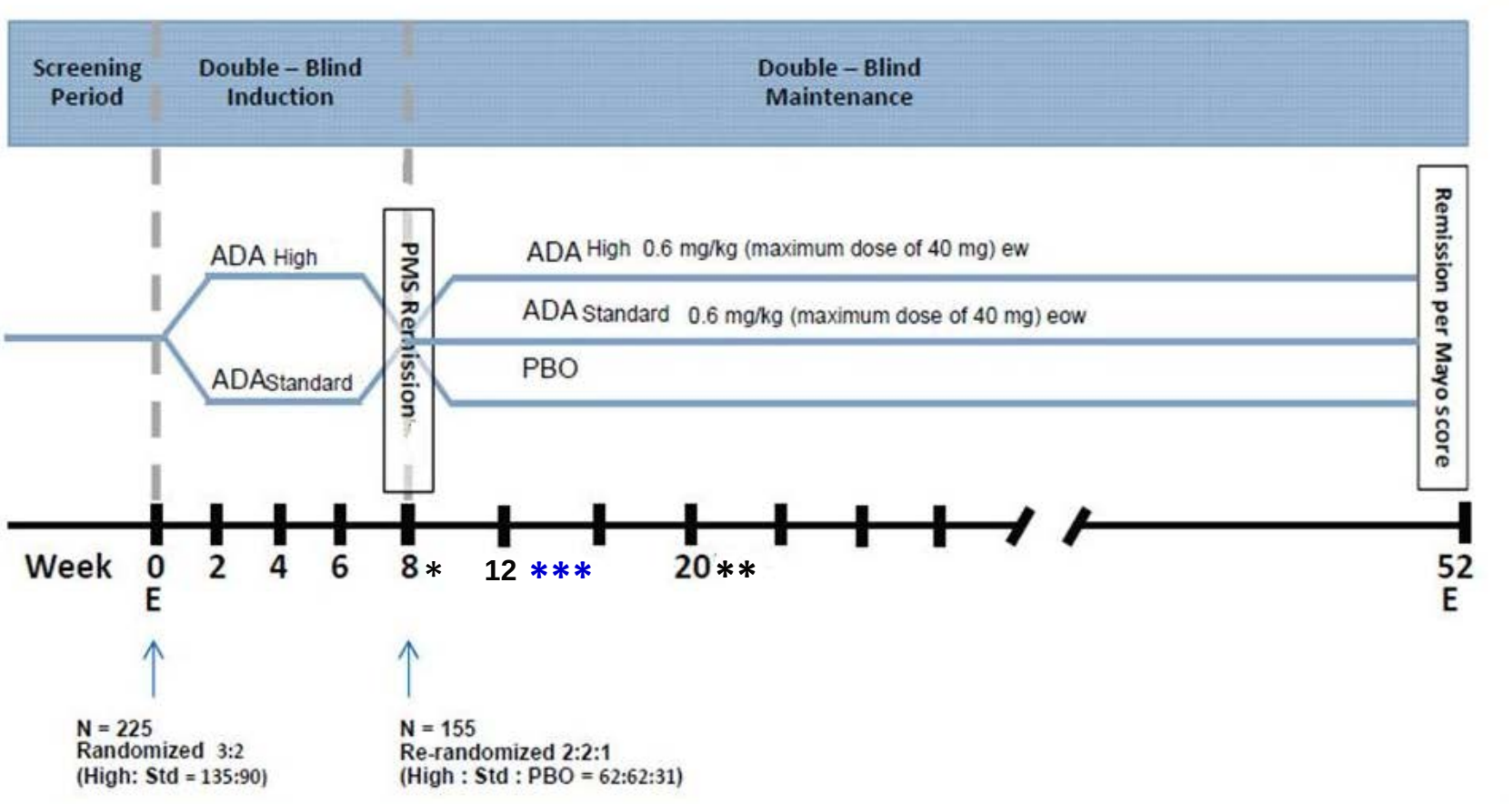
The Juliet Keidan Institute of
Paediatric Gastroenterology and Nutrition
Shaare Zedek Medical Center, Jerusalem, Israel

M11-290 Study Design



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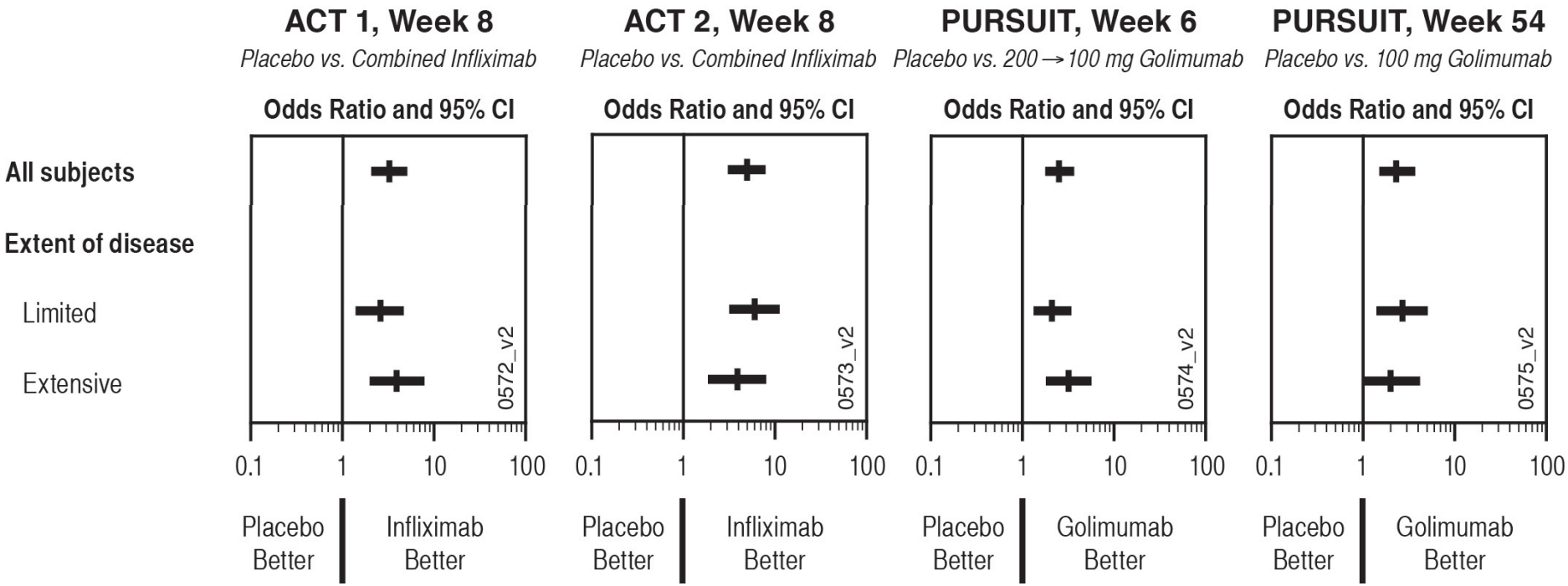
Similarity in treatment response: Extent of Disease



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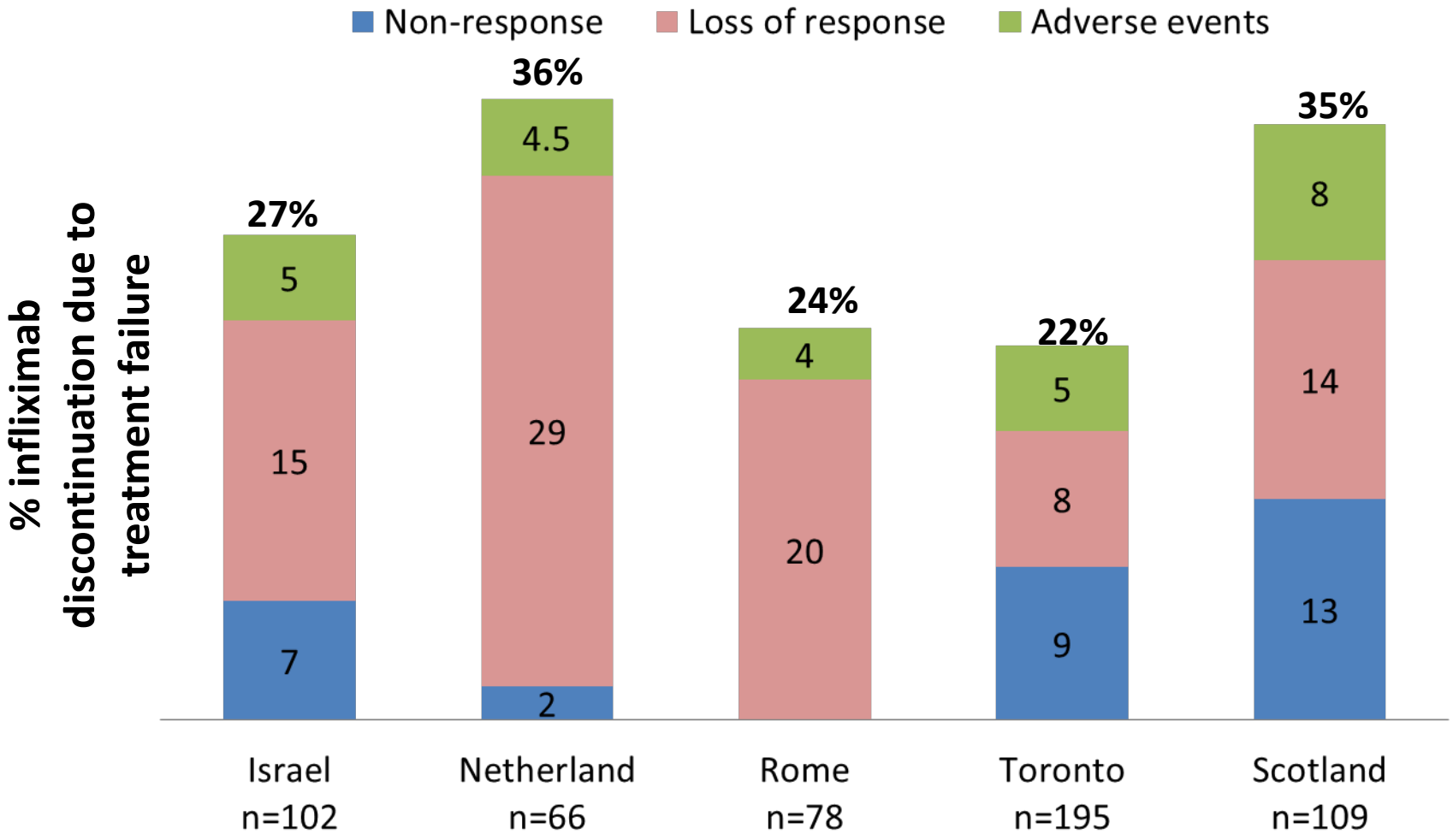
Slide- courtesy Janssen

Long term discontinuation rate of infliximab-CHILDREN

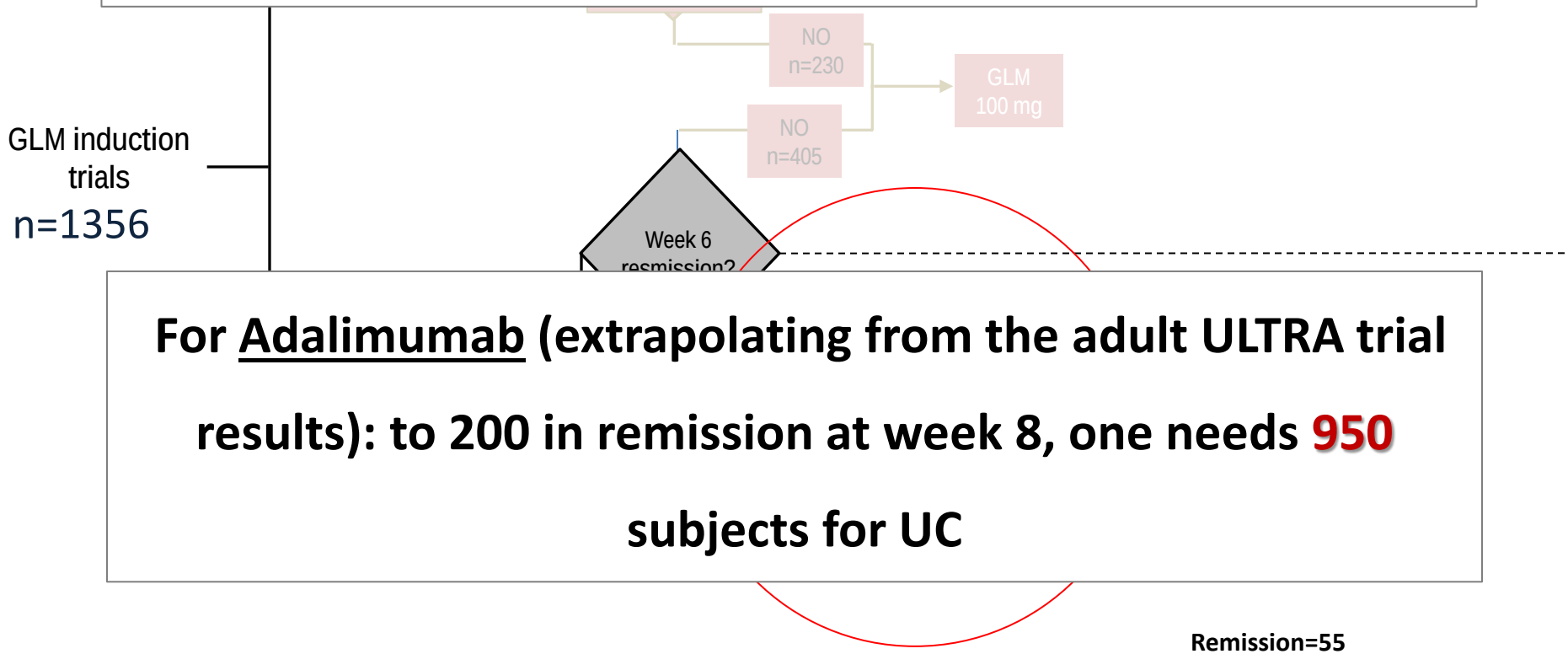


Median duration of FU (months)	15 (4-24)	41 (12-165)	27 (1.5-86)	21.5 (12-36)	23(2-81)
Period	1999-2011	1992-2007	2001-2011	2000-2011	2000-2010

Topf C, Turner D. Arch Dis Child 2015

Randomized Withdrawal Study Design are very inefficient

For <u>vedolizumab</u> (extrapolating from the adult GEMINI trials results): to obtain 200 in remission at week 6, one needs 1176 subjects for UC and 1333 subjects for CD



For <u>Adalimumab</u> (extrapolating from the adult ULTRA trial results): to 200 in remission at week 8, one needs 950 subjects for UC

Courtesy Janssen

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