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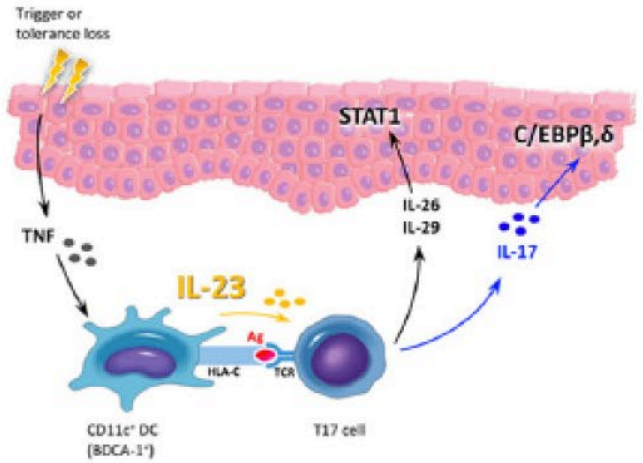
IL-23 Medications for Psoriasis

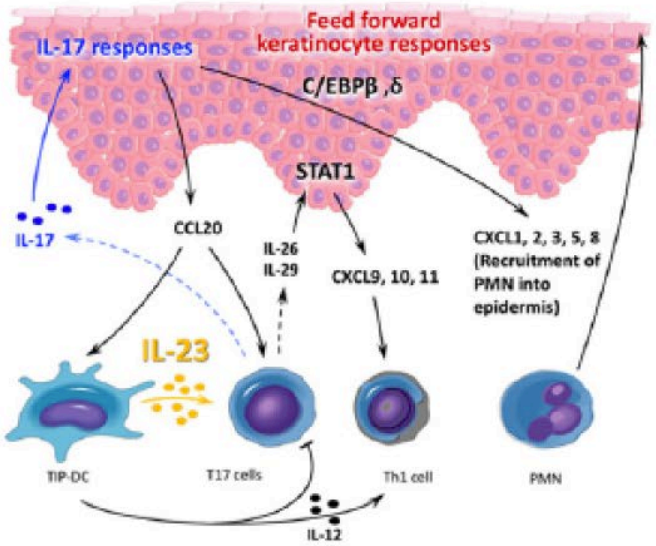
Paolo Romanelli, MD
Professor of Dermatology
Director of ACGME Dermatopathology Fellowship
Director of Psoriasis Clinic at UM/JHS

Pre-psoriatic skin



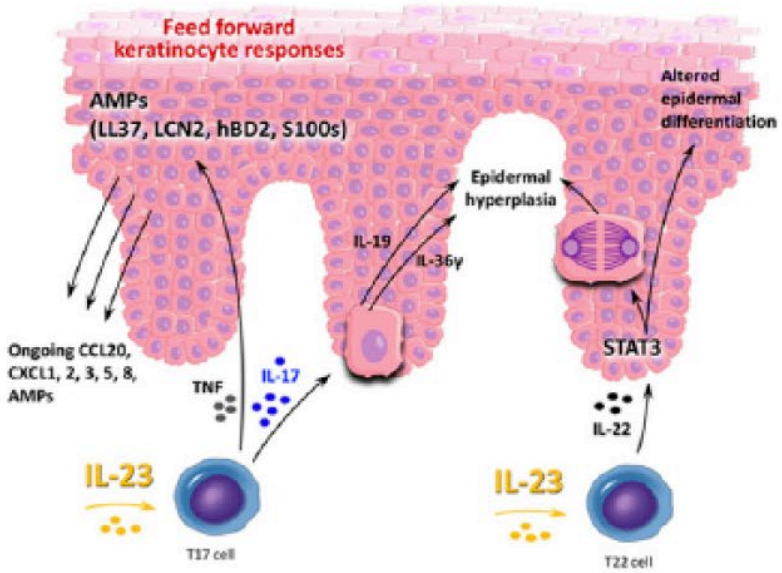
IL-23 initiates T17 cell activation and IL-17 production.

Early psoriatic lesion



IL-23 promotes survival and expansion of pathogenic T17 cells.

Chronic psoriatic plaque



Persistent high levels of IL-23 sustains the production of IL-17, which produces a feed-forward inflammatory reaction.

Chan, TC. *et al. Therapeutic Advances in Chronic Disease* (2018).

IL-23 FOUND IN LESIONAL SKIN IN PSORIASIS

Comparative Study > J Exp Med. 2004 Jan 5;199(1):125-30. doi: 10.1084/jem.20030451.

Increased expression of interleukin 23 p19 and p40 in lesional skin of patients with psoriasis vulgaris

Edmund Lee [1], William L Trepicchio, Judith L Oestreicher, Debra Pittman, Frank Wang, Francesca Chamian, Madhav Dhodapkar, James G Krueger

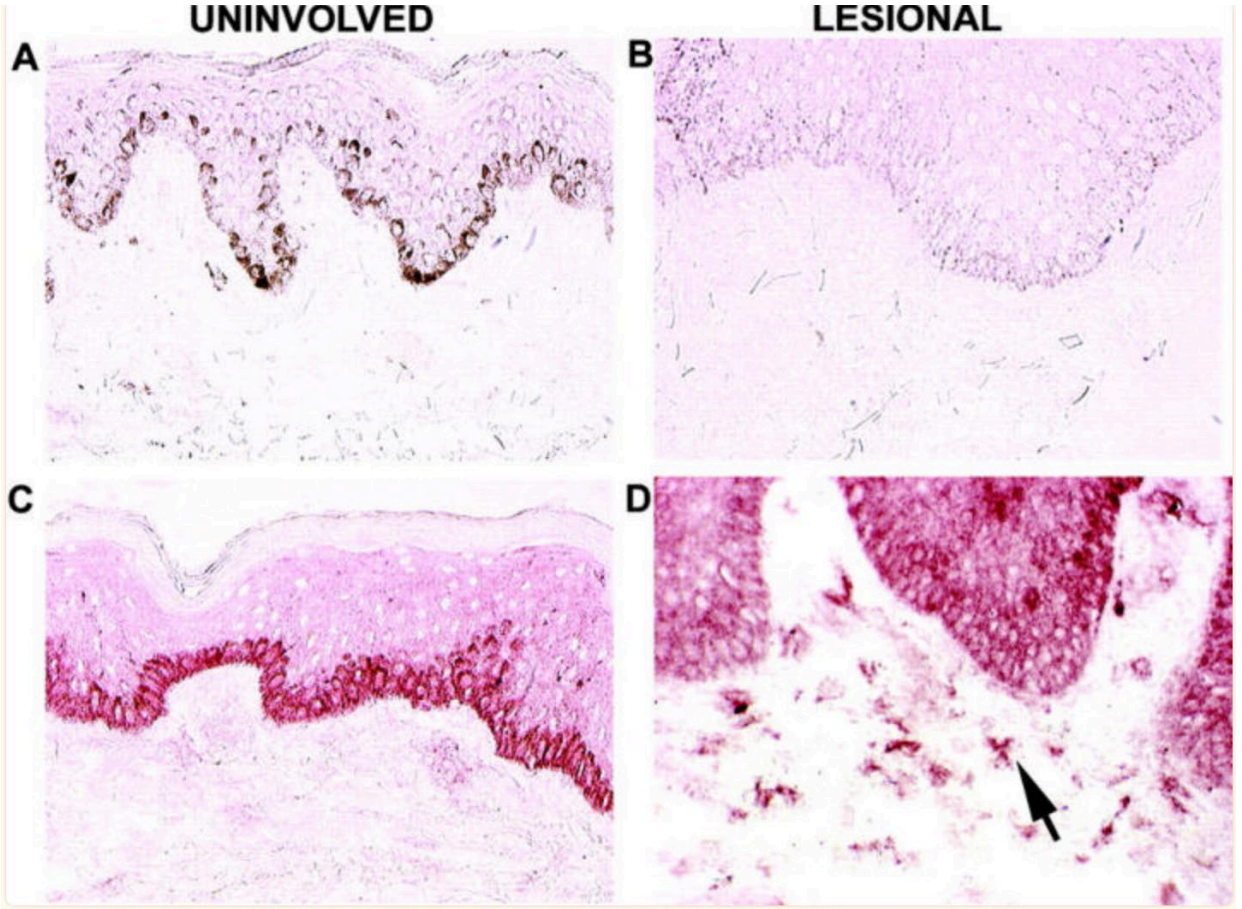
Results:
IL-23 was expressed mainly by dermal cells and increased p40 immunoreactivity was visualized in large dermal cells in the lesions.

The p40 subunit, shared by IL-12 and IL-23, was increased by 11.6-fold compared with nonlesional skin (P = 0.003)

There was increased IL-23 p19 subunit mRNA expressed by quantitative rtPCR in lesional skin compared with nonlesional skin (22.3-fold increase; P = 0.001)

IL-12 p35 subunit was not increased in lesional skin

IL-23 is playing a more dominant role than IL-12 in psoriasis



*Immunohistochemical localization of p40 in psoriatic skin. The four panels are from frozen sections of human skin from psoriasis patients. A and B are IgG isotype controls in uninvolved and lesional skin, respectively. C and D are stained with mouse anti–human IL-12p40 as indicated. The arrow indicates morphology consistent with DCs. The color represents 3-amino-9-ethylcarbazole deposition at the site of antibody binding. Melanin appears in A as dark stain in the basal cell layer

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Lee, E. *et al. Journal of Experimental Medicine* (2004).

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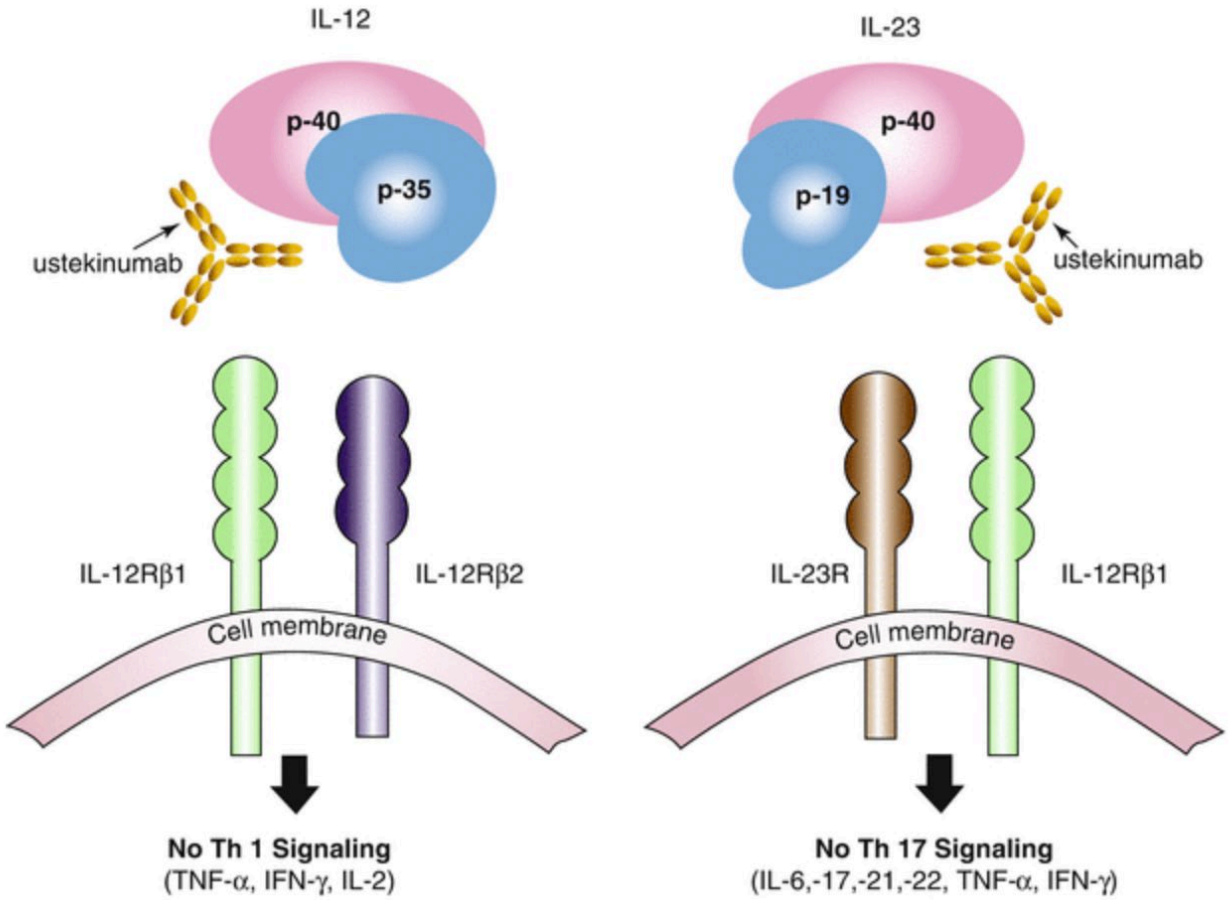
IL-23 Blockers

USTEKINUMAB
GUSELKUMAB
TILDRAKIZUMAB
RISANKIZUMAB

USTEKINUMAB- MECHANISM OF ACTION

Human monoclonal antibody that binds with high specificity and affinity to the P40 subunit of both IL-12 and IL-23



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Koutruba N. *et al. Therapeutics and Clinical Risk Management* (2010).

- Adult Chronic Plaque Psoriasis
- Pediatric Chronic Plaque Psoriasis >6 years old
- Psoriatic Arthritis
- Crohn's Disease
- Ulcerative Colitis
- Pediatric Psoriatic Arthritis >6 years old

USTEKINUMAB- LOTS OF EVIDENCE

Clinical Trial > Lancet. 2008 May 17;371(9625):16
doi: 10.1016/S0140-6736(08)60725-4.

**Efficacy and safety of ustekinu
interleukin-12/23 monoclonal
with psoriasis: 76-week result**

> Dermatol Ther (Heidelb). 2020 Aug;10(4):663-670. d
Epub 2020 May 15.

**Ixekizumab and Ustekinumab
Psoriasis in Patients with Mod
Psoriasis: 52-Week Results from a Phase 3, Head-to-
Head Study (IXORA-S)**

Norman Wasel [1], Diamant Thaçi [2], Lars E French [3], Curdin Conrad [4], Yves Dutr [5], Gaia Gallo [5], Lovisa Berggren [6], Jean-Philippe Lacour [7]

**with psoriasis: 52-week results from a ra
double-blind, placebo-controlled trial (PI**

Kim A Papp [1], Richard G Langley, Mark Lebwohl, Gerald G Krueger, Philippe Newman Yeilding, Cynthia Guzzo, Ming-Chun Hsu, Yuhua Wang, Shu Li, Lisa Kristian Reich; PHOENIX 2 study investigators

Clinical Trial > N Engl J Med. 2015 Oct;373(14):1318-28. doi: 10.1056/NEJMoa1503824.

**Phase 3 Studies Comparing Brodalumab with
Ustekinumab in Psoriasis**

Mark Lebwohl [1], Bruce Strober, Alan Menter, Kenneth Gordon, Jolanta Weglowska, Lluis Puig, Kim Papp, Lynda Spelman, Darryl Toth, Francisco Kerdel, April W Armstrong, Georg Stingl, Alexa B Kimball, Herve Bachelez, Jashin J Wu, Jeffrey Crowley, Richard G Langley, Tomasz Blicharski, Carle Paul, Jean-Philippe Lacour, Stephen Tyring, Leon Kircik, Sergio Chimenti, Kristina Callis Duffin, Jerry Bagel, John Koo, Gary Aras, Joanne Li, Wenjie Song, Cassandra E Milmont, Yifei Shi, Ngozi Erondu, Paul Klekotka, Brian Kotzin, Ajay Nirula

Randomized Controlled Trial > Lancet. 2021 Feb 6;397(10273):487-498.
doi: 10.1016/S0140-6736(21)00125-2.

**Bimekizumab versus ustekinumab for the treatment
of moderate to severe plaque psoriasis (BE VIVID):
efficacy and safety from a 52-week, multicentre,
double-blind, active comparator and placebo
controlled phase 3 trial**

Kristian Reich [1], Kim A Papp [2], Andrew Blauvelt [3], Richard G Langley [4], April Armstrong [5], Richard B Warren [6], Kenneth B Gordon [7], Joseph F Merola [8], Yukari Okubo [9], Cynthia Madden [10], Maggie Wang [10], Christopher Cioffi [10], Veerle Vanvoorden [11], Mark Lebwohl [12]

0-9. doi: 10.1016/j.jaad.2015.05.013.

**kinumab in clearing
severe plaque
controlled trial**

-Fang Tsai [4], Francisco Vanaclocha [5], t [9], Ruquan You [10],

Clinical Trial > N Engl J Med. 2017 Apr 20;376(16):1551-1560. doi: 10.1056/NEJMoa1607017.

Risankizumab versus Ustekinumab for Moderate-to-

derham [1], James G Krueger [1], ofen [1], Stephen Tyring [1], , Nathan Bennett [1],

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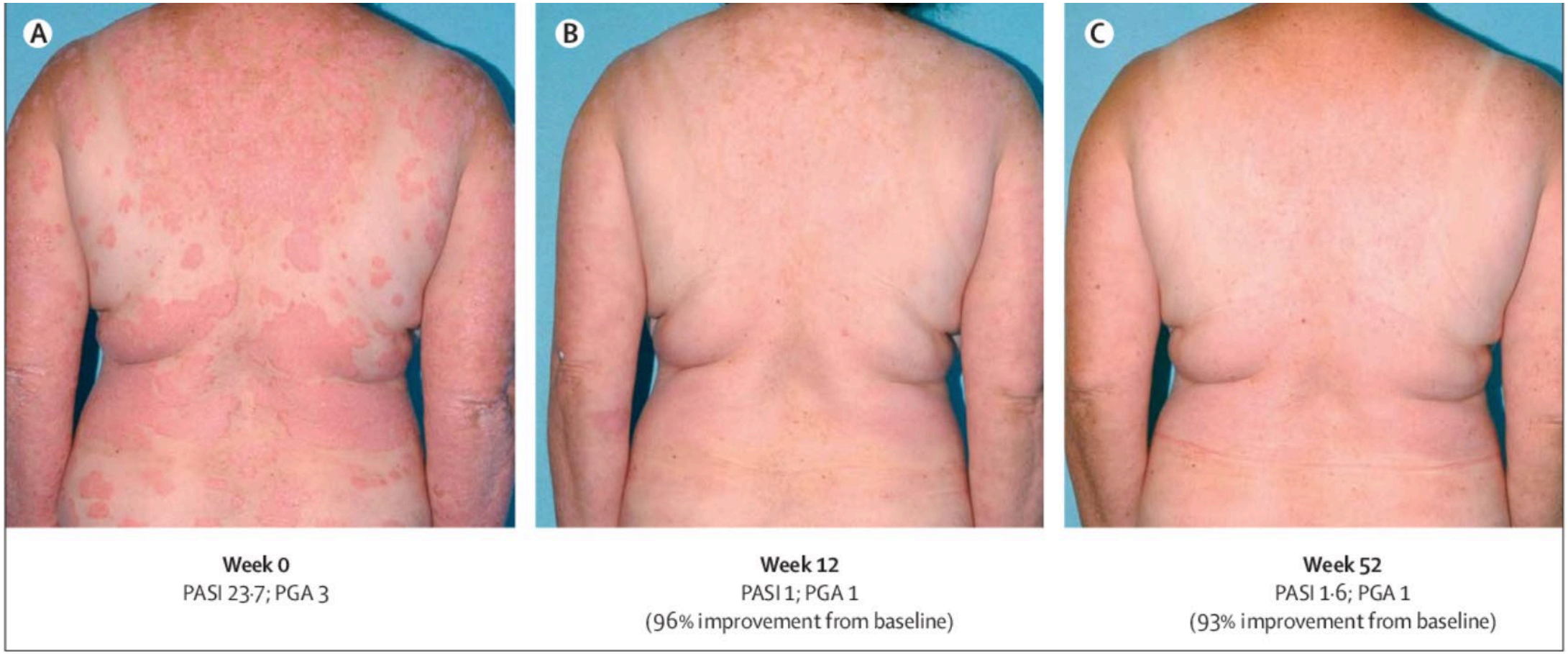

Figure 4: **Improvements in psoriasis in a patient treated with ustekinumab 90 mg every 12 weeks**
At baseline (A), week 12 (B), week 52 (C). PASI=psoriasis area and severity index. PGA=physician's global assessment.

Papp KA. *et al. Lancet* (2008).

USTEKINUMAB- SAFETY DATA POOLED ANALYSIS PHEONIX 1 AND PHEONIX 2 TRIALS

	Placebo	STELARA® 45 mg	STELARA® 90 mg
Patients treated	**665**	**664**	**666**
Nasopharyngitis, % (n)	8 (51)	8 (56)	7 (49)
Upper respiratory tract infection, % (n)	5 (30)	5 (36)	4 (28)
Headache, % (n)	3 (23)	5 (33)	5 (32)
Fatigue, % (n)	2 (14)	3 (18)	3 (17)
Diarrhea, % (n)	2 (12)	2 (13)	2 (13)
Back pain, % (n)	1 (8)	1 (9)	2 (14)
Dizziness, % (n)	1 (8)	1 (8)	2 (14)
Pharyngolaryngeal pain, % (n)	1 (7)	1 (9)	2 (12)
Pruritus, % (n)	1 (9)	2 (10)	1 (9)
Injection site erythema, % (n)	<1 (3)	1 (6)	2 (13)
Myalgia, % (n)	1 (4)	1 (7)	1 (8)
Depression, % (n)	<1 (3)	1 (8)	1 (4)

*Adverse reactions that occurred in less than 1% in the controlled period of PHOENIX 1 and PHOENIX 2 through Week 12 included: cellulitis, herpes zoster, diverticulitis, and certain injection site reactions (pain, swelling, pruritus, induration, hemorrhage, bruising, and irritation).
*One Case of Posterior Reversible Encephalopathy Syndrome (PRES) occurred during adult plaque psoriasis clinical studies.

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Leonard C. *et al. Lancet* (2008).
Papp KA. *et al. Lancet* (2008).

USTEKINUMAB- SAFETY DATA POOLED ANALYSIS PHEONIX 1 AND PHEONIX 2 TRIALS

	Placebo	45 mg	90 mg
Patients treated	**665**	**664**	**666**
Nasopharyngitis, % (n)	8 (51)	8 (56)	7 (49)
Upper respiratory tract infection, % (n)	5 (30)	5 (36)	4 (28)
Headache, % (n)	3 (23)	5 (33)	5 (32)
Fatigue, % (n)	2 (14)	3 (18)	3 (17)
Diarrhea, % (n)	2 (12)	2 (13)	2 (13)
Back pain, % (n)	1 (8)	1 (9)	2 (14)
Dizziness, % (n)	1 (8)	1 (8)	2 (14)
Pharyngolaryngeal pain, % (n)	1 (7)	1 (9)	2 (12)
Pruritus, % (n)	1 (9)	2 (10)	1 (9)
Injection site erythema, % (n)	<1 (3)	1 (6)	2 (13)
Myalgia, % (n)	1 (4)	1 (7)	1 (8)
Depression, % (n)	<1 (3)	1 (8)	1 (4)

*Adverse reactions that occurred in less than 1% in the controlled period of PHOENIX 1 and PHOENIX 2 through Week 12 included: cellulitis, herpes zoster, diverticulitis, and certain injection site reactions (pain, swelling, pruritus, induration, hemorrhage, bruising, and irritation).
*One Case of Posterior Reversible Encephalopathy Syndrome (PRES) occurred during adult plaque psoriasis clinical studies.

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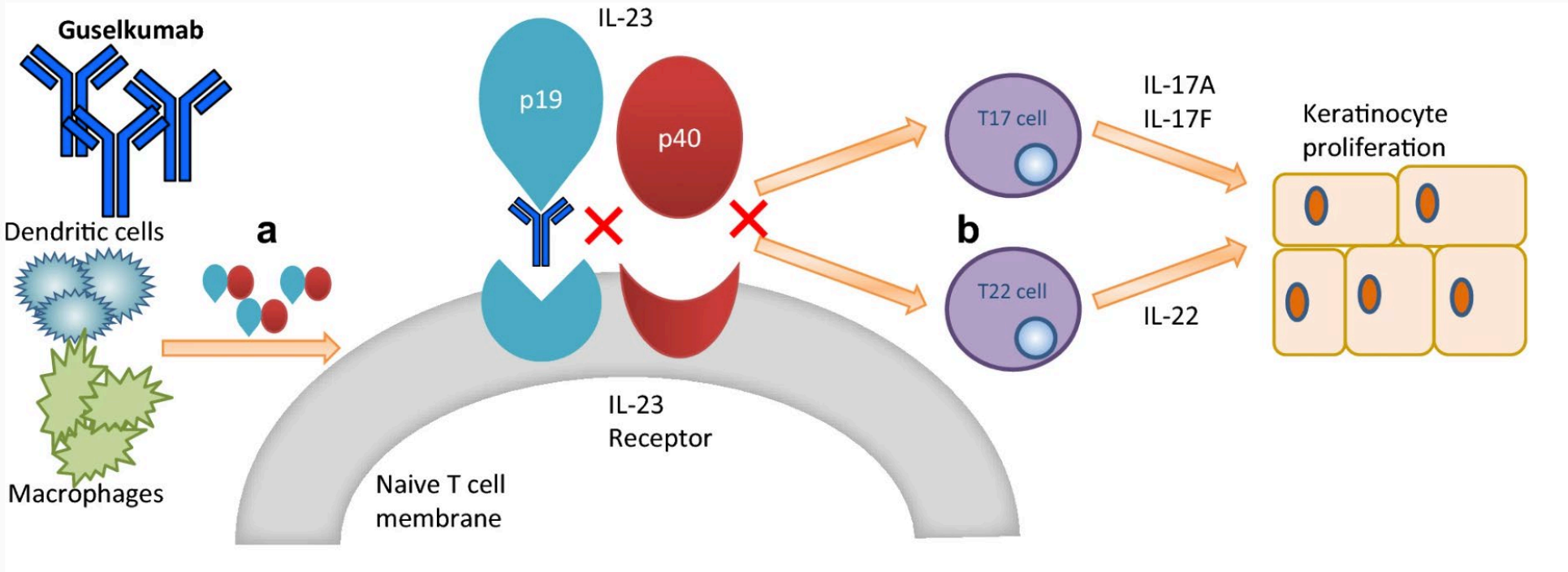
Leonard C. *et al. Lancet* (2008).
Papp KA. *et al. Lancet* (2008).

GUSELKUMAB- MECHANISM OF ACTION

Fully human IgG1 lambda monoclonal antibody that blocks the p19 subunit of IL-23



Approved for:

- Adult Plaque Psoriasis
- Adult Psoriatic Arthritis

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Al-Salama ZT. *et al. American Journal of Clinical Dermatol* (2018).

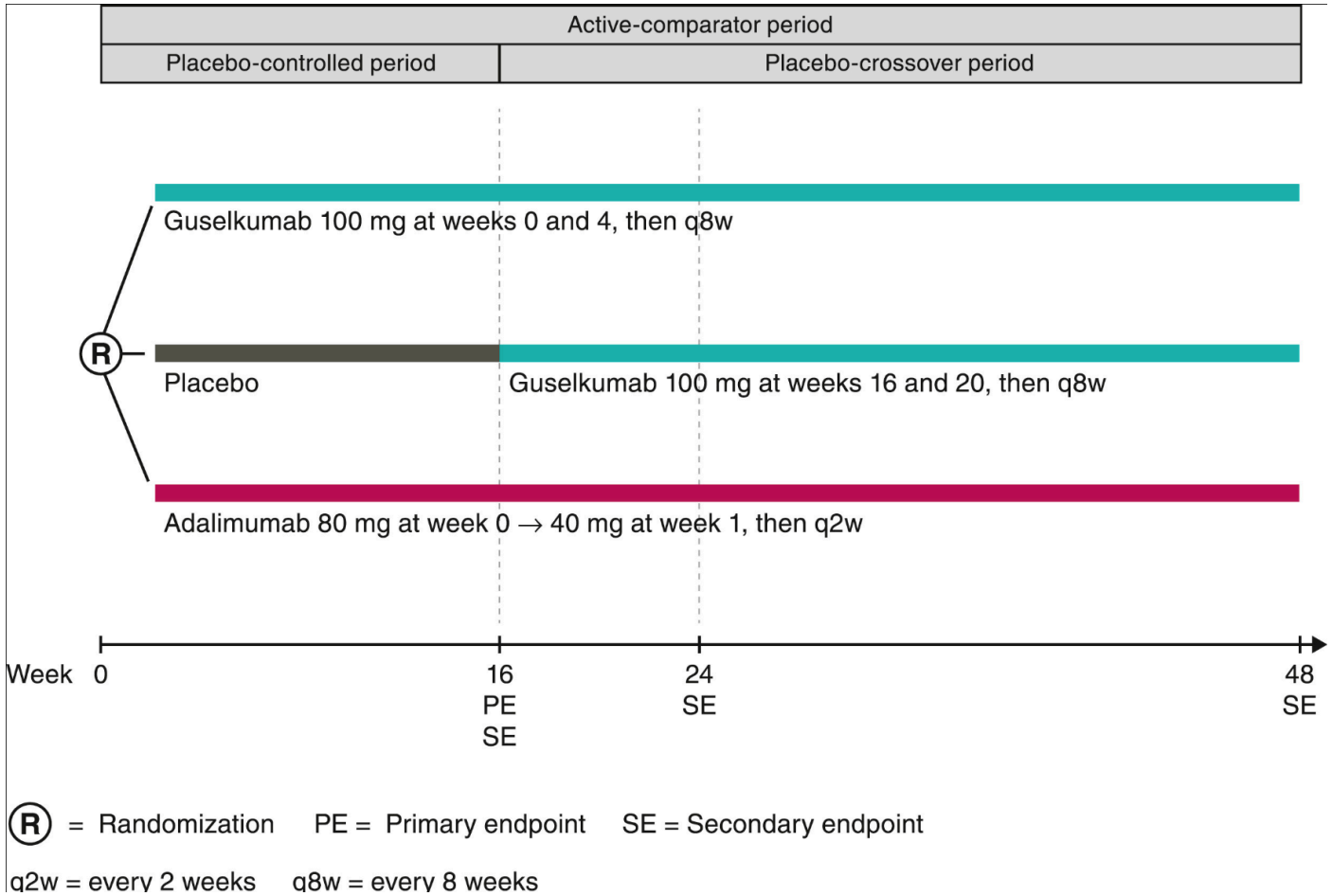
GUSELKUMAB- VOYAGE 1 TRIAL

Clinical Trial > J Am Acad Dermatol. 2017 Mar;76(3):405-417. doi: 10.1016/j.jaad.2016.11.041.
Epub 2017 Jan 2.

Efficacy and safety of guselkumab, an anti-interleukin-23 monoclonal antibody, compared with adalimumab for the continuous treatment of patients with moderate to severe psoriasis: Results from the phase III, double-blinded, placebo- and active comparator-controlled VOYAGE 1 trial

Andrew Blauvelt [1], Kim A Papp [2], Christopher E M Griffiths [3], Bruce Randazzo [4], Yasmine Wasfi [5], Yaung-Kaung Shen [5], Shu Li [5], Alexa B Kimball [6]

Study Design



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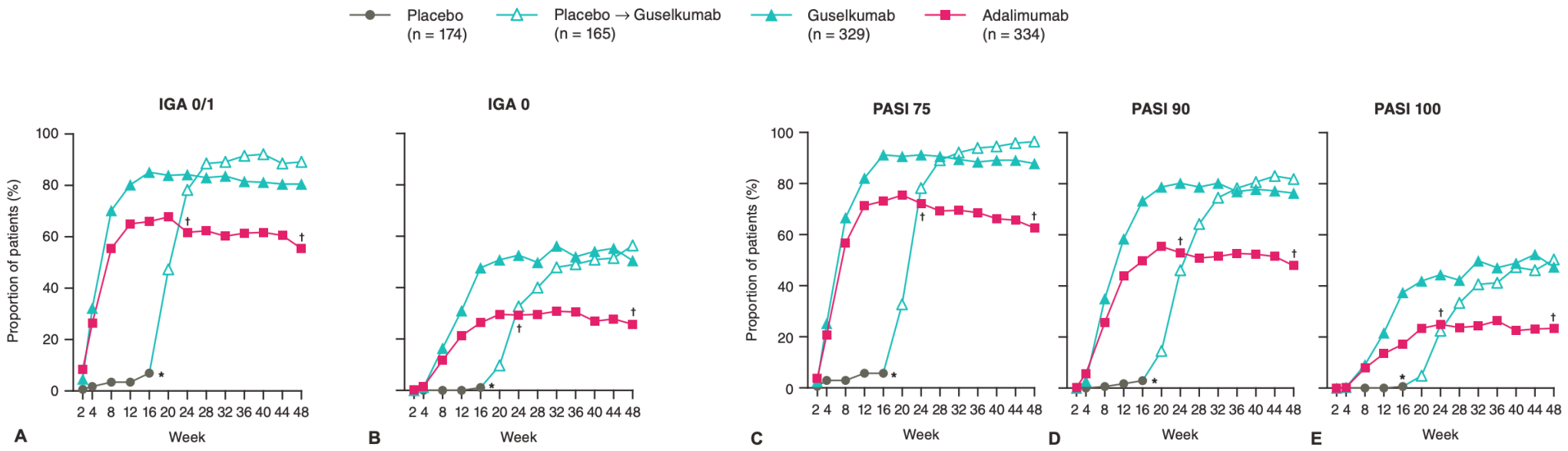
Reich K. *et al. J Am Acad Dermatol* (2017).

GUSELKUMAB- VOYAGE 1 TRIAL



	Week 16			Week 24		Week 48	
	Guselkumab	Adalimumab	Placebo	Guselkumab	Adalimumab	Guselkumab	Adalimumab
sIGA 0/1 (%)	85.1	65.9	6.9	84.2	61.7	80.5	55.4
PASI 75 (%)	91.2	73.1	5.7	91.2	72.2	87.8	63.6
PASI 90 (%)	73.3	49.7	2.9	80.2	53.0	76.3	47.9
PASI 100 (%)	37.4	17.1	0.6	44.4	24.9	47.4	23.4

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*Clinical Efficacy through week 48.

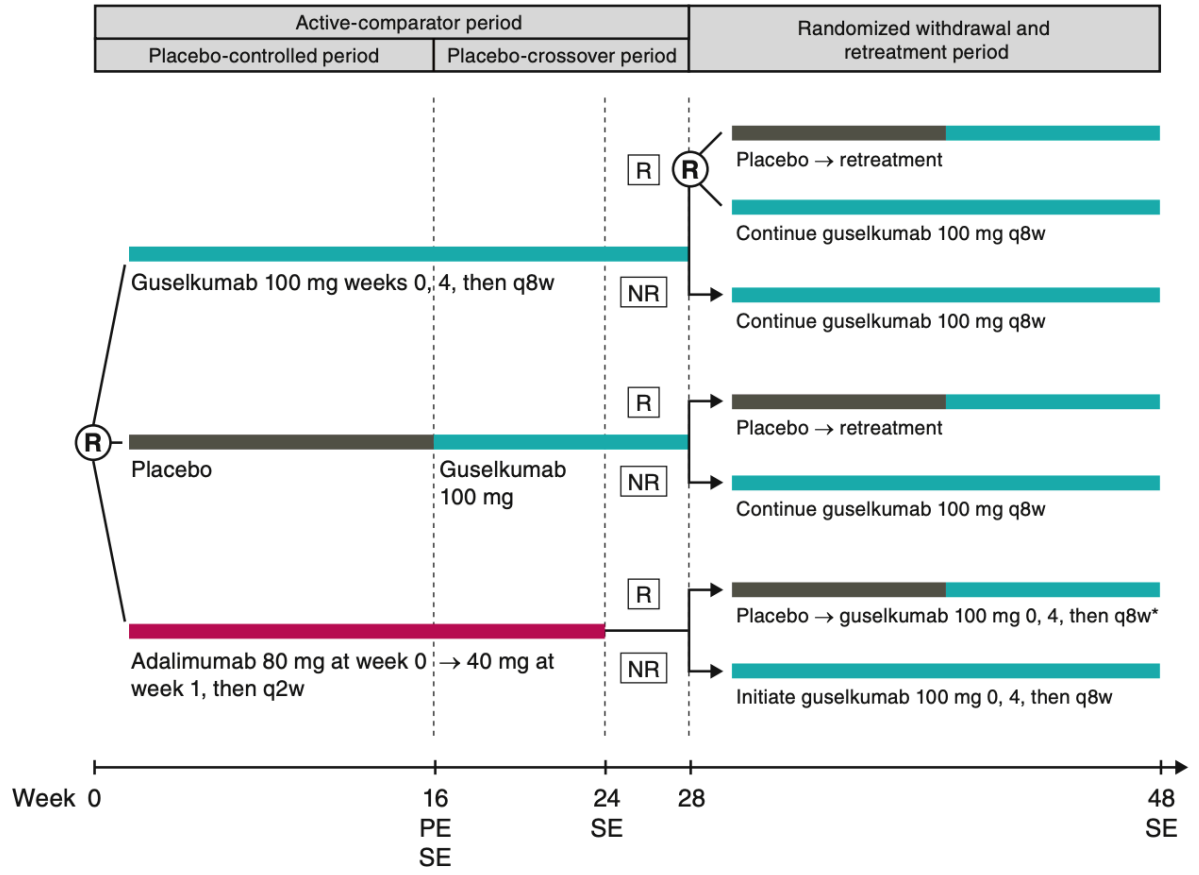
Blauvelt A. *et al. J Am Acad Dermatol* (2017).

Clinical Trial > J Am Acad Dermatol. 2017 Mar;76(3):418-431. doi: 10.1016/j.jaad.2016.11.042.
Epub 2017 Jan 2.

Efficacy and safety of guselkumab, an anti-interleukin-23 monoclonal antibody, compared with adalimumab for the treatment of patients with moderate to severe psoriasis with randomized withdrawal and retreatment: Results from the phase III, double-blind, placebo- and active comparator-controlled VOYAGE 2 trial

Kristian Reich [1], April W Armstrong [2], Peter Foley [3], Michael Song [4], Yasmine Wasfi [4], Bruce Randazzo [4], Shu Li [4], Y-K Shen [4], Kenneth B Gordon [5]

Study Design



R = Randomization PE = Primary endpoint SE = Secondary endpoint

q2w = every 2 weeks q8w = every 8 weeks

Responders R = 90% or greater improvement in Psoriasis Area and Severity Index (PASI 90)

Nonresponders NR = < PASI 90 response

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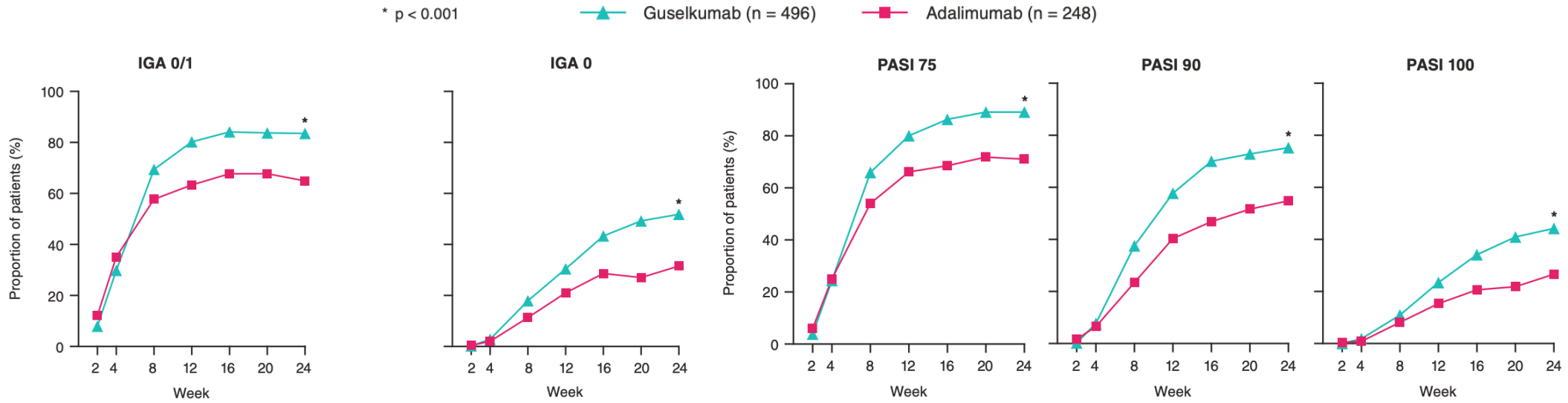
Blauvelt A. *et al. J Am Acad Dermatol* (2017).

GUSELKUMAB- VOYAGE 2 TRIAL



	Week 16			Week 24	
	Guselkumab	Adalimumab	Placebo	Guselkumab	Adalimumab
sIGA 0/1 (%)	84.1	67.7	8.5	83.5	64.9
PASI 75 (%)	86.3	68.5	8.1	89.1	71.0
PASI 90 (%)	70.0	46.8	2.4	75.2	54.8
PASI 100 (%)	34.1	20.6	0.8	44.2	26.6

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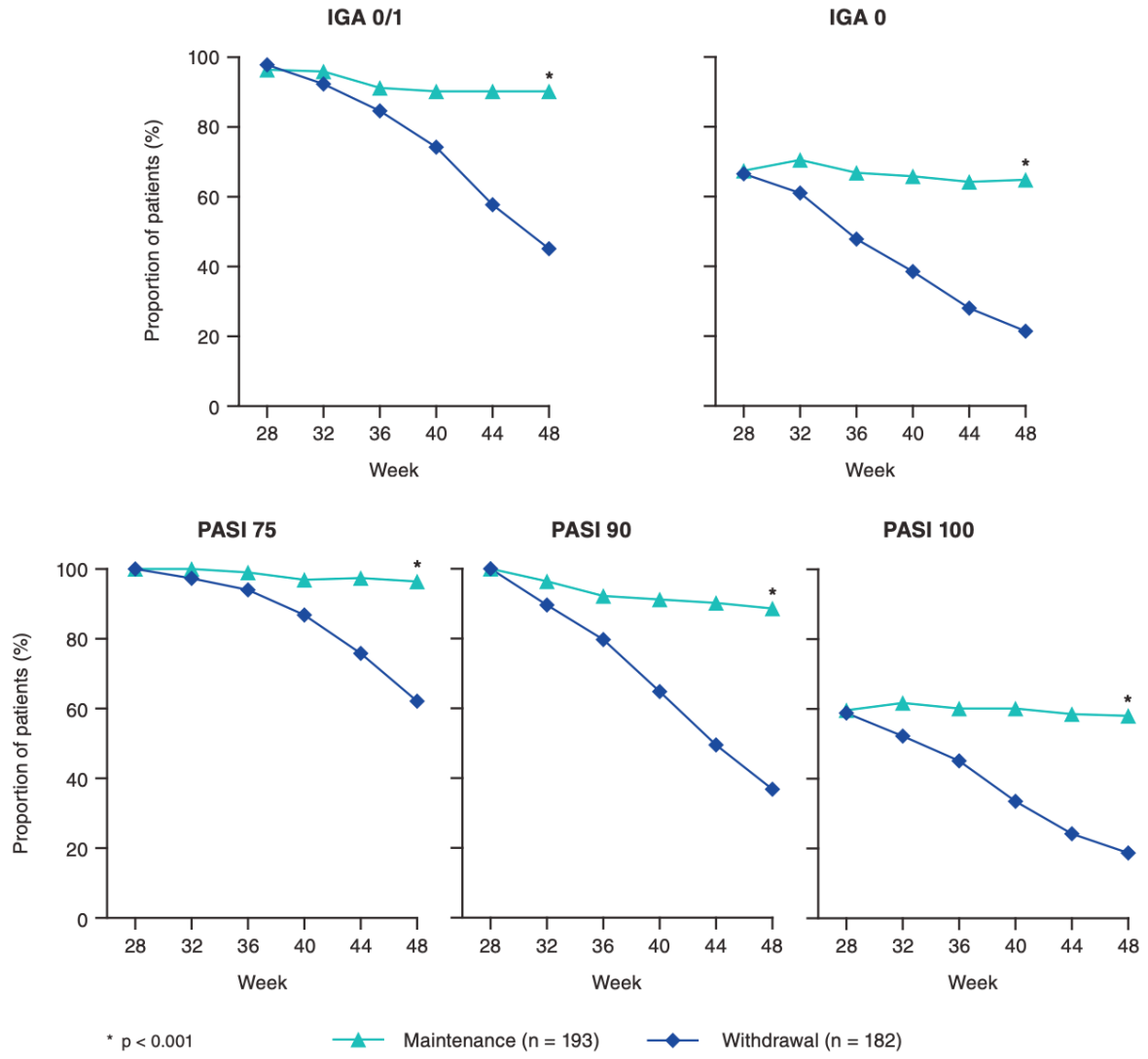
*Clinical Efficacy week 0 to week 24.

Reich K. *et al. J Am Acad Dermatol* (2017).

During the randomized withdrawal and retreatment period, PASI 90 responses were better maintained in guselkumab week-28 responders continuing guselkumab (maintenance group) vs responders rerandomized to placebo (withdrawal group).

At week 48, clinical responses (IGA, PASI) were significantly greater in the maintenance than in the withdrawal group ($p<0.001$)

Individuals that switched from adalimumab to guselkumab (n=112) had increased PASI 90 and PASI 100 response rates (66.1% and 28.6%, respectively) at week 48



*Clinical Efficacy of withdrawal and retreatment period from week 24 to week 48

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Reich K. *et al. J Am Acad Dermatol* (2017).

GUSELKUMAB- VOYAGE 2 CLINICAL PICTURES

*__Individual results may vary:__ Photos are of a real patient from VOYAGE 2 who received TREMFYA™ 100 mg at Weeks 0, 4, and 12.

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GUSELKUMAB- ADVERSE EVENTS FROM VOYAGE-1 AND VOYAGE-2 TRIALS

	Wk 0-16 Placebo-controlled period			Wk 0-48 Active comparator–controlled period		Wk 16-48
	Placebo	Guselkumab	Adalimumab	Guselkumab	Adalimumab	Placebo →guselkumab
Patients treated, n	174	329	333	329	333	165
Mean duration of follow-up, wk	15.88	16.27	16.14	46.47	45.56	31.88
At least 1 AE	86 (49.4)	170 (51.7)	170 (51.1)	243 (73.9)	248 (74.5)	107 (64.8)
Common AEs*						
Nasopharyngitis	17 (9.8)	30 (9.1)	35 (10.5)	83 (25.2)	74 (22.2)	34 (20.6)
Upper respiratory tract infection	9 (5.2)	25 (7.6)	16 (4.8)	47 (14.3)	42 (12.6)	17 (10.3)
Injection-site erythema	1 (0.6)	6 (1.8)	15 (4.5)	8 (2.4)	22 (6.6)	3 (1.8)
Headache	7 (4.0)	12 (3.6)	13 (3.9)	18 (5.5)	25 (7.5)	1 (0.6)
Arthralgia	3 (1.7)	11 (3.3)	9 (2.7)	18 (5.5)	16 (4.8)	2 (1.2)
Pruritus	10 (5.7)	5 (1.5)	7 (2.1)	8 (2.4)	12 (3.6)	0
Back pain	2 (1.1)	6 (1.8)	4 (1.2)	12 (3.6)	17 (5.1)	1 (0.6)
Discontinued study agent because of AE	2 (1.1)	4 (1.2)	3 (0.9)	9 (2.7)	12 (3.6)	1 (0.6)
At least 1 SAE	3 (1.7)	8 (2.4)	6 (1.8)	16 (4.9)	15 (4.5)	5 (3.0)
Infections	44 (25.3)	85 (25.8)	85 (25.5)	172 (52.3)	167 (50.2)	76 (46.1)
Requiring treatment	13 (7.5)	20 (6.1)	24 (7.2)	54 (16.4)	60 (18.0)	25 (15.2)
Serious infections	0	0	2 (0.6)	2 (0.6)	3 (0.9)	1 (0.6)
Malignancies†	0	0	0	2 (0.6)	0	0
NMSC‡	0	1 (0.3)	0	2 (0.6)	1 (0.3)	0
MACE§	0	1 (0.3)	1 (0.3)	1 (0.3)	1 (0.3)	0

Values are reported as n (%).
AE, Adverse event; *MACE*, major adverse cardiovascular events; *NMSC*, nonmelanoma skin cancers; *SAE*, serious adverse event.
*Occurred in at least 5% of patients in any treatment group through wk 48.
†Includes malignancies other than NMSC (ie, prostate and breast cancer).
‡Includes 3 basal cell carcinomas.
§Includes sudden cardiac death, myocardial infarction, and stroke.

*VOYAGE-1 Trial

*VOYAGE-2 Trial

	Wk 0-16 Placebo-controlled period			Wk 0-28 Active comparator-controlled period		Wk 16-28	Wk 28-48 Randomized withdrawal and retreatment period	
	Placebo	Guselkumab	Adalimumab	Guselkumab	Adalimumab	Placebo→guselkumab	Maintenance group*	Withdrawal group†
Patients treated, n	248	494	248	494	248	233	192	182
Mean duration of follow-up, wk	15.89	16.14	16.07	27.70	27.45	11.95	20.02	19.47
At least 1 AE	111 (44.8)	235 (47.6)	120 (48.4)	288 (58.3)	156 (62.9)	78 (33.5)	99 (51.6)	81 (44.5)
Common AEs‡								
Nasopharyngitis	16 (6.5)	35 (7.1)	20 (8.1)	51 (10.3)	34 (13.7)	12 (5.2)	22 (11.5)	23 (12.6)
Headache	7 (2.8)	25 (5.1)	5 (2.0)	29 (5.9)	9 (3.6)	5 (2.1)	3 (1.6)	2 (1.1)
Upper respiratory tract infection	10 (4.0)	16 (3.2)	4 (1.6)	25 (5.1)	10 (4.0)	5 (2.1)	9 (4.7)	10 (5.5)
Discontinued study agent because of AE	2 (0.8)	7 (1.4)	4 (1.6)	11 (2.2)	6 (2.4)	1 (0.4)	0 (0.0)	0 (0.0)
At least 1 SAE	3 (1.2)	8 (1.6)	6 (2.4)	18 (3.6)	9 (3.6)	4 (1.7)	2 (1.0)	3 (1.6)
Infections	46 (18.5)	106 (21.5)	58 (23.4)	153 (31.0)	87 (35.1)	41 (17.6)	55 (28.6)	50 (27.5)
Requiring treatment	17 (6.9)	35 (7.1)	19 (7.7)	58 (11.7)	29 (11.7)	19 (8.2)	23 (12.0)	9 (4.9)
Serious infections	1 (0.4)	1 (0.2)	2 (0.8)	3 (0.6)	3 (1.2)	1 (0.4)	1 (0.5)	0 (0.0)
Malignancies§	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
NMSC‖	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)
MACE¶	0 (0.0)	0 (0.0)	1 (0.4)	1 (0.2)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)

Values are n (%) unless otherwise indicated.
AE, Adverse event; *MACE*, major adverse cardiovascular event; *NMSC*, nonmelanoma skin cancer; *PASI*, Psoriasis Area and Severity Index; *SAE*, serious adverse event.
*Includes guselkumab wk-28 90% or greater improvement in PASI score from baseline (PASI 90) responders rerandomized at wk 28 to continue guselkumab 100 mg every 8 wk.
†Includes guselkumab wk-28 PASI 90 responders rerandomized at wk 28 to placebo (withdrawal), then retreated with guselkumab 100 mg every 8 wk after 50% or more loss of wk-28 PASI 90 response.
‡Occurred in at least 5% of patients in any treatment group.
§Includes malignancies other than NMSC (prostate cancer, n = 1).
‖Includes basal cell and squamous cell carcinomas.
¶Includes sudden cardiac death, myocardial infarction, and stroke.

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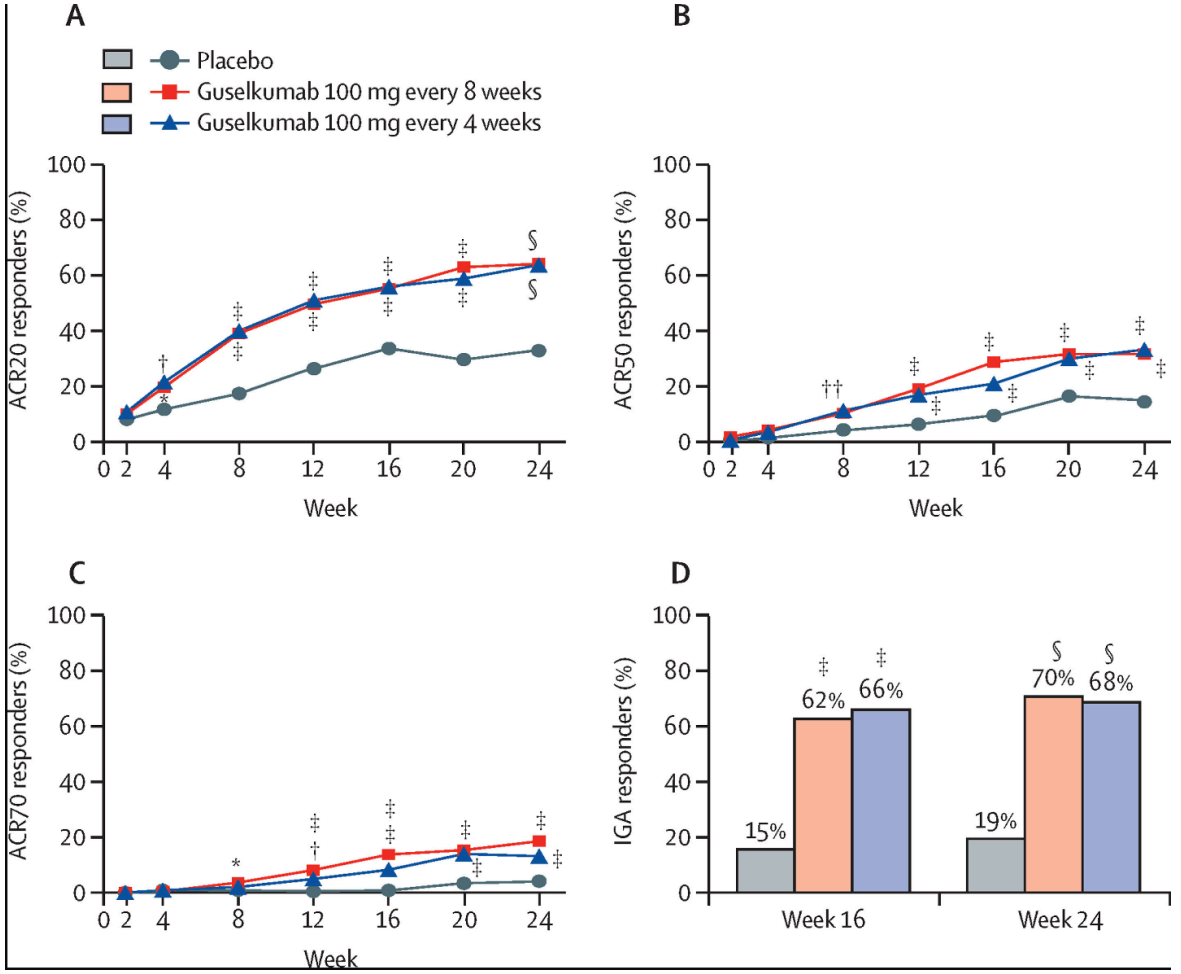
Blauvelt A. *et al. J Am Acad Dermatol* (2017).
Reich K. *et al. J Am Acad Dermatol* (2017).

Clinical Trial > Lancet. 2020 Apr 4;395(10230):1126-1136.
doi: 10.1016/S0140-6736(20)30263-4. Epub 2020 Mar 13.

Guselkumab in biologic-naive patients with active psoriatic arthritis (DISCOVER-2): a double-blind, randomised, placebo-controlled phase 3 trial

Philip J Mease [1], Proton Rahman [2], Alice B Gottlieb [3], Alexa P Kollmeier [4], Elizabeth C Hsia [5], Xie L Xu [4], Shihong Sheng [6], Prasheen Agarwal [6], Bei Zhou [6], Yanli Zhuang [7], Désirée van der Heijde [8], Iain B McInnes [9]; DISCOVER-2 Study Group

Guselkumab at two dosing regimens has been shown to be superior to placebo at alleviating psoriatic arthritis by week 24.



*Clinical efficacy of guselkumab for ACR20, ACR 50, ACR70 response rates. p< 0.05

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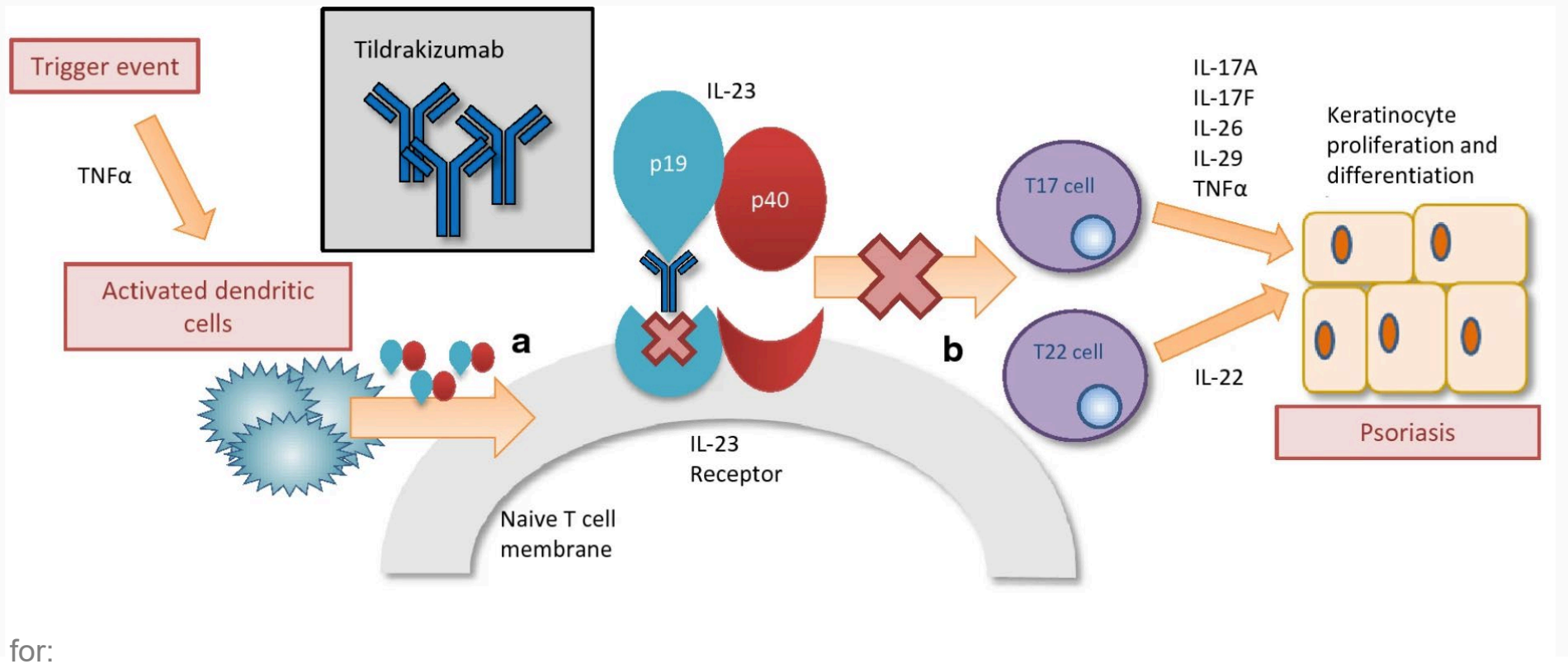
Mease, PJ. *et al. Lancet* (2020).

TILDRAKIZUMAB- MECHANISM OF ACTION

Humanized IgG1 monoclonal antibody that blocks the p19 subunit of IL-23



Approved for:

- Adult Plaque Psoriasis
- Adult Psoriatic Arthritis

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Frampton, J. *et al. American Journal of Clinical Dermatology* (2019).

TILDRAKIZUMAB- POOLED ANALYSIS RESURFACE 1 AND RESURFACE 2 TRIALS

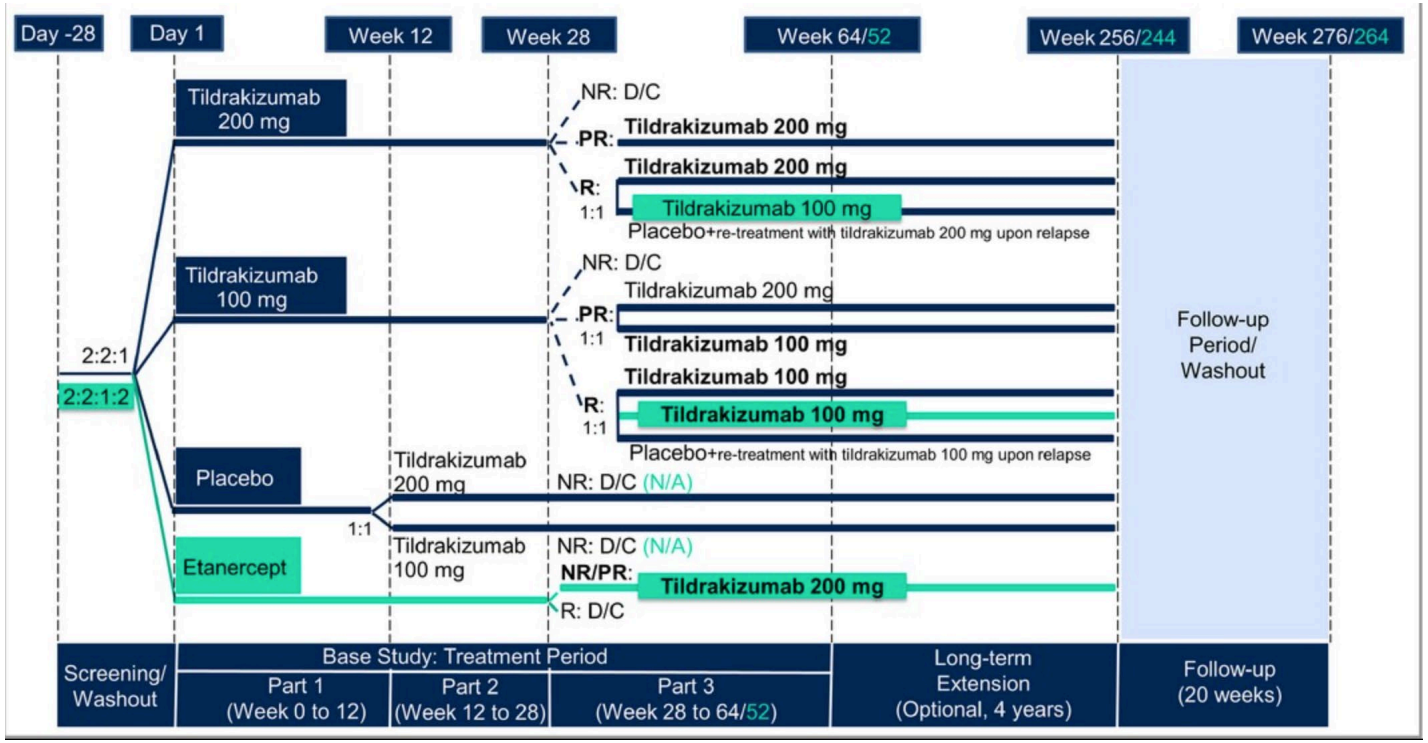
Clinical Trial > Lancet. 2017 Jul 15;390(10091):276-288.
doi: 10.1016/S0140-6736(17)31279-5. Epub 2017 Jun 6.

Tildrakizumab versus placebo or etanercept for chronic plaque psoriasis (reSURFACE 1 and reSURFACE 2): results from two randomised controlled, phase 3 trials

Kristian Reich [1], Kim A Papp [2], Andrew Blauvelt [3], Stephen K Tyring [4], Rodney Sinclair [5], Diamant Thaçi [6], Kristine Nograles [7], Anish Mehta [7], Nicole Cichanowitz [7], Qing Li [7], Kenneth Liu [7], Carmen La Rosa [7], Stuart Green [7], Alexa B Kimball [8]

reSURFACE 1: evaluating the efficacy of two tildrakizumab dosing regimens (200 mg or 100 mg) vs placebo

reSURFACE 2: evaluating the efficacy of two tildrakizumab dosing regimens (200 mg or 100 mg) vs placebo vs etanercept



*Integrated design of the reSURFACE 1 and reSURFACE 2 trials.
Differences in design for reSURFACE 2 vs. reSURFACE 1 are shown in turquoise color. Groups of interest for efficacy analyses are marked in bold.
D/C, discontinued; N/A, not applicable; NR, nonresponders [< PASI 50]; PR, partial responders (PASI 50–75); R, responders (PASI ≥ 75).

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Reich K. *et al. Lancet* (2017).

TILDRAKIZUMAB- POOLED ANALYSIS RESURFACE 1 AND RESURFACE 2 TRIALS

*Primary and Secondary Endpoints of tildrakizumab at week 12 (part 1)

	reSURFACE 1			reSURFACE 2			
	Tildrakizumab 200mg	Tildrakizumab 100mg	Placebo	Tildrakizumab 200mg	Tildrakizumab 100mg	Etanercept	Placebo
sIGA 0/1 (%)	59	58	7	59	55	48	4
PASI 75 (%)	62	64	9	66	61	48	6
PASI 90 (%)	35	35	3	37	39	21	1
PASI 100 (%)	14	14	1	12	12	5	0

*Primary and Secondary Endpoints of tildrakizumab between week 12 to week 28 (part 2)

	reSURFACE 1				reSURFACE 2				
	Tildra 200mg	Tildra 100mg	PBO→ Tildra 200mg	PBO→ Tildra 100mg	Tildra 200mg	Tildra 100mg	PBO→ Tildra 200mg	PBO→ Tildra 100mg	Etanercept
sIGA 0/1 (%)	69	66	71	76	69	65	64	48	45
PASI 75 (%)	82	80	86	77	73	73	69	55	54
PASI 90 (%)	59	52	52	59	58	56	49	39	31
PASI 100 (%)	32	24	26	31	27	23	19	14	11

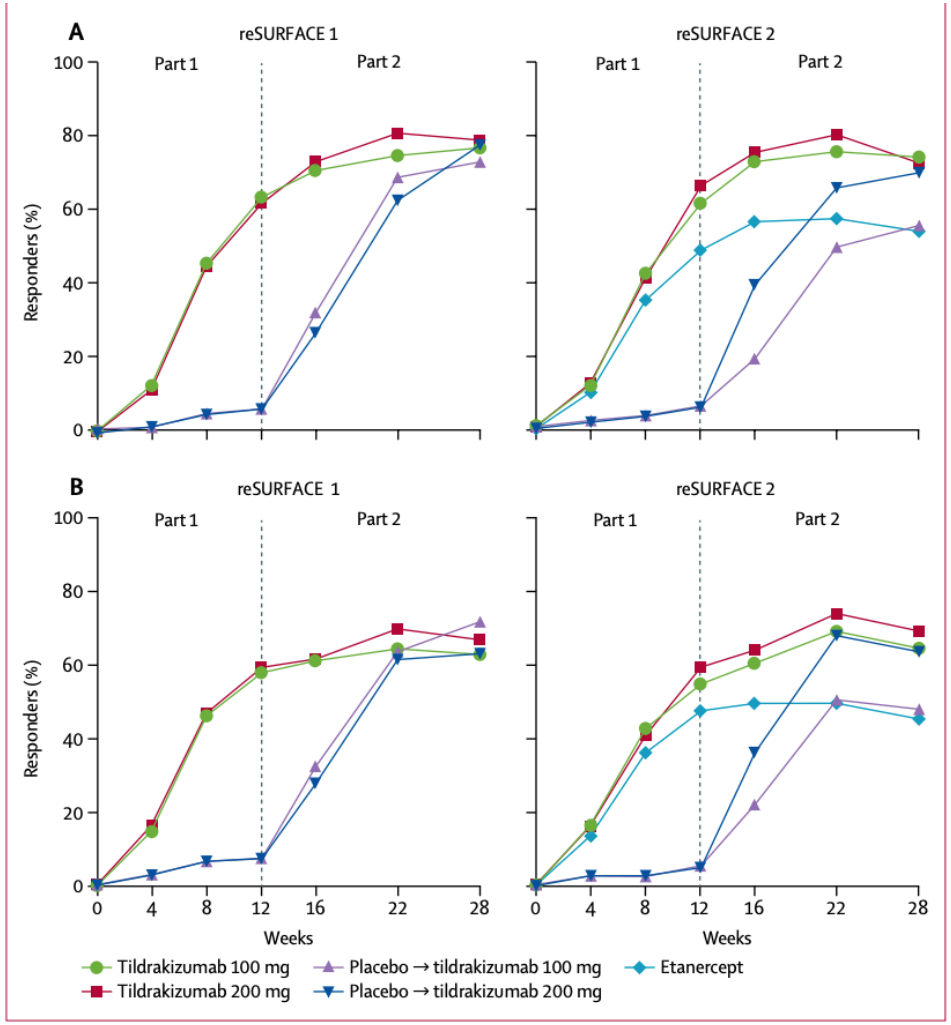

Figure 3: **Proportion of patients achieving PASI 75 (A) and PGA "clear" or "minimal" with at least 2 grade reduction (B) in reSURFACE 1 and reSURFACE 2**

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Reich K. *et al. Lancet* (2017).

TILDRAKIZUMAB- POOLED SAFETY DATA RESURFACE 1 AND RESURFACE 2 TRIALS

*reSURFACE 1

	Part 1			Part 2			
	Tildrakizumab 200 mg (n=308)	Tildrakizumab 100 mg (n=309)	Placebo N=154 n (%)	Tildrakizumab 200 mg → tildrakizumab 200 mg (n=298)	Tildrakizumab 100 mg → tildrakizumab 100 mg (n=300)	Placebo → tildrakizumab 200 mg (n=72)	Placebo → tildrakizumab 100 mg (n=74)
≥1 adverse events*	130 (42%)	146 (47%)	74 (48%)	118 (40%)	133 (44%)	29 (40%)	31 (42%)
Serious adverse events	8 (3%)	5 (2%)	1 (1%)	7 (2%)	6 (2%)	1 (1%)	1 (1%)
Deaths	0	0	0	0	0	0	0
Discontinued because of adverse events	5 (2%)	0	1 (1%)	3 (1%)	1 (<1%)	0	0
Most common adverse events							
Nasopharyngitis	20 (6%)	24 (8%)	8 (5%)	12 (4%)	20 (7%)	5 (7%)	4 (5%)
Upper respiratory tract infection	15 (5%)	10 (3%)	9 (6%)	20 (7%)	13 (4%)	0	3 (4%)
Psoriasis	0	3 (1%)	8 (5%)	0	0	0	0
Adverse events of special interest							
Severe infections†	1 (<1%)	1 (<1%)	0	1 (<1%)	2 (1%)	0	0
Malignancies‡	0	0	0	2 (1%)	1 (<1%)	0	1 (1%)
Non-melanoma skin cancer	0	0	0	1 (<1%)	1 (<1%)	0	1 (1%)
Confirmed major adverse cardiovascular events§	0	1 (<1%)	0	0	0	0	0
Drug-related hypersensitivity reactions	1 (<1%)	0	0	0	0	0	0

Data are n (%). *Participants who took at least one dose of part 1 study drug; based on the treatment actually received. †Infection meeting the regulatory definition of a serious adverse event, or any infection requiring intravenous antibiotics, irrespective of whether it was reported as a serious adverse event, as per the regulatory definition. ‡Excluding carcinoma in situ of the cervix. §Includes non-fatal myocardial infarction, non-fatal stroke, and cardiovascular deaths that are confirmed as "cardiovascular" or "sudden".

*reSURFACE 2

	Part 1				Part 2				
	Tildrakizumab 200 mg (n=314)	Tildrakizumab 100 mg (n=307)	Placebo (n=156)	Etanercept (n=313)	Tildrakizumab 200 mg→ tildrakizumab 200 mg (n=299)	Tildrakizumab 100 mg→ tildrakizumab 100 mg (n=294)	Etanercept→ etanercept (n=289)	Placebo→ tildrakizumab 200 mg (n=72)	Placebo→ tildrakizumab 100 mg (n=69)
≥1 adverse events*	155 (49%)	136 (44%)	86 (55%)	169 (54%)	135 (45%)	135 (46%)	164 (57%)	31 (43%)	37 (54%)
Serious adverse events	6 (2%)	4 (1%)	4 (3%)	7 (2%)	6 (2%)	9 (3%)	14 (5%)	2 (3%)	1 (1%)
Deaths†	0	1 (<1%)	0	0	0	0	0	0	0
Discontinued because of adverse events	3 (1%)	3 (1%)	2 (1%)	6 (2%)	1 (<1%)	1 (<1%)	3 (1%)	0	1 (1%)
Most common adverse events									
Injection site erythema	2 (1%)	2 (1%)	1 (1%)	27 (9%)	1 (<1%)	3 (1%)	3 (1%)	0	0
Nasopharyngitis	35 (11%)	41 (13%)	12 (8%)	36 (12%)	43 (14%)	23 (8%)	34 (12%)	3 (4%)	8 (12%)
Upper respiratory tract infection	0	0	0	0	6 (2%)	5 (2%)	7 (2%)	0	0
Adverse events of special interest									
Severe infections‡	1 (<1%)	0	1 (1%)	0	2 (1%)	1 (<1%)	3 (1%)	0	0
Malignancies§	1 (<1%)	1 (<1%)	0	1 (<1%)	0	0	3 (1%)	1 (1%)	1 (1%)
Non-melanoma skin cancer	1 (<1%)	1 (<1%)	0	1 (<1%)	0	0	1 (<1%)	1 (1%)	1 (1%)
Confirmed major adverse cardiovascular events¶	0	0	0	0	0	0	0	0	0
Drug-related hypersensitivity reactions	0	1 (<1%)	1 (1%)	0	0	0	0	0	2 (3%)

Data are n (%). *Participants who took at least one dose of part 1 study drug; based on the treatment actually received. †A patient on tildrakizumab 100 mg died; the patient had alcoholic cardiomyopathy and steatohepatitis, although adjudication was unable to determine the cause of death. ‡Infection meeting the regulatory definition of a serious adverse event, or any infection requiring intravenous antibiotics, irrespective of whether it was reported as a serious adverse event, as per the regulatory definition. §Excluding carcinoma in situ of the cervix. ¶Includes non-fatal myocardial infarction, non-fatal stroke, and cardiovascular deaths that are confirmed as "cardiovascular" or "sudden".

Most common adverse events in both studies:
Nasopharyngitis

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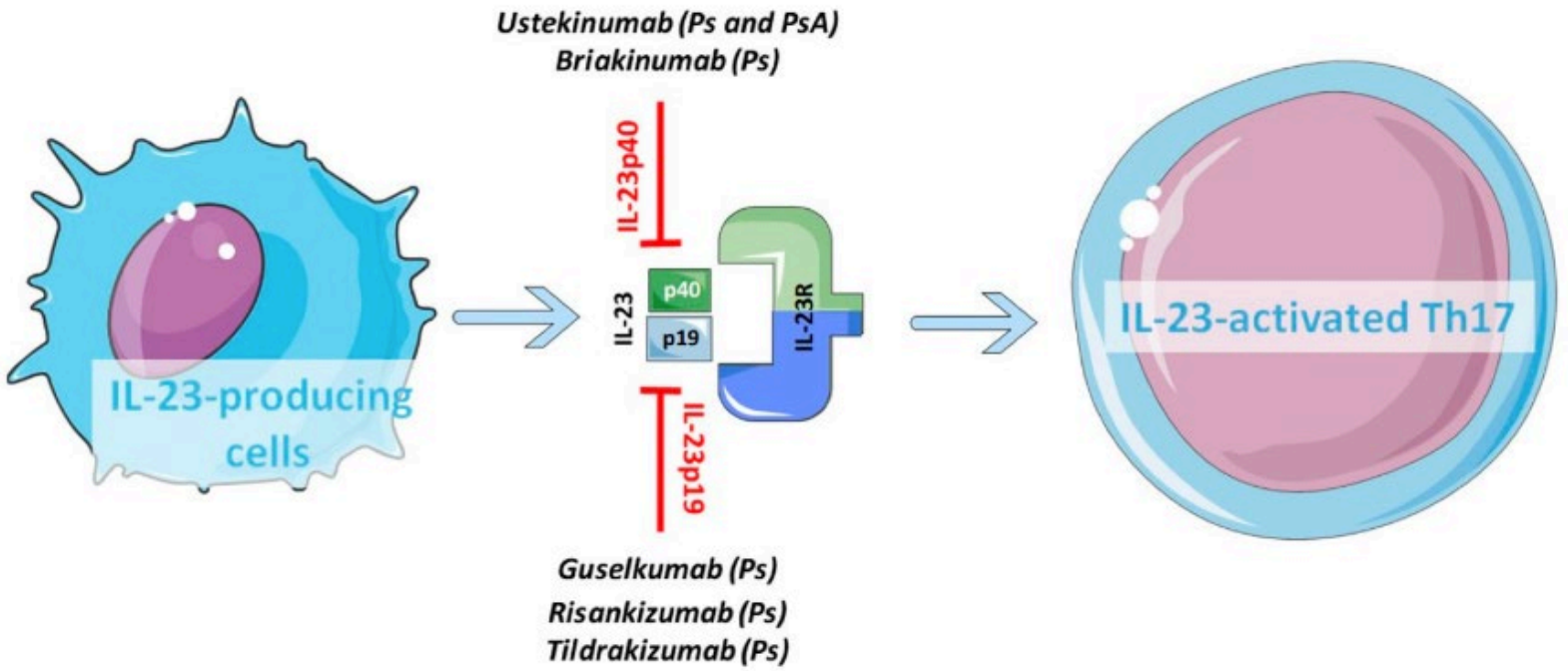
Reich K. *et al. Lancet* (2017).

RISANKIZUMAB- MECHANISM OF ACTION

Humanized IgG1 monoclonal antibody that blocks the p19 subunit of IL-23



Approved for:

- Adult Plaque Psoriasis
- Adult Psoriatic Arthritis
- Crohn's Disease

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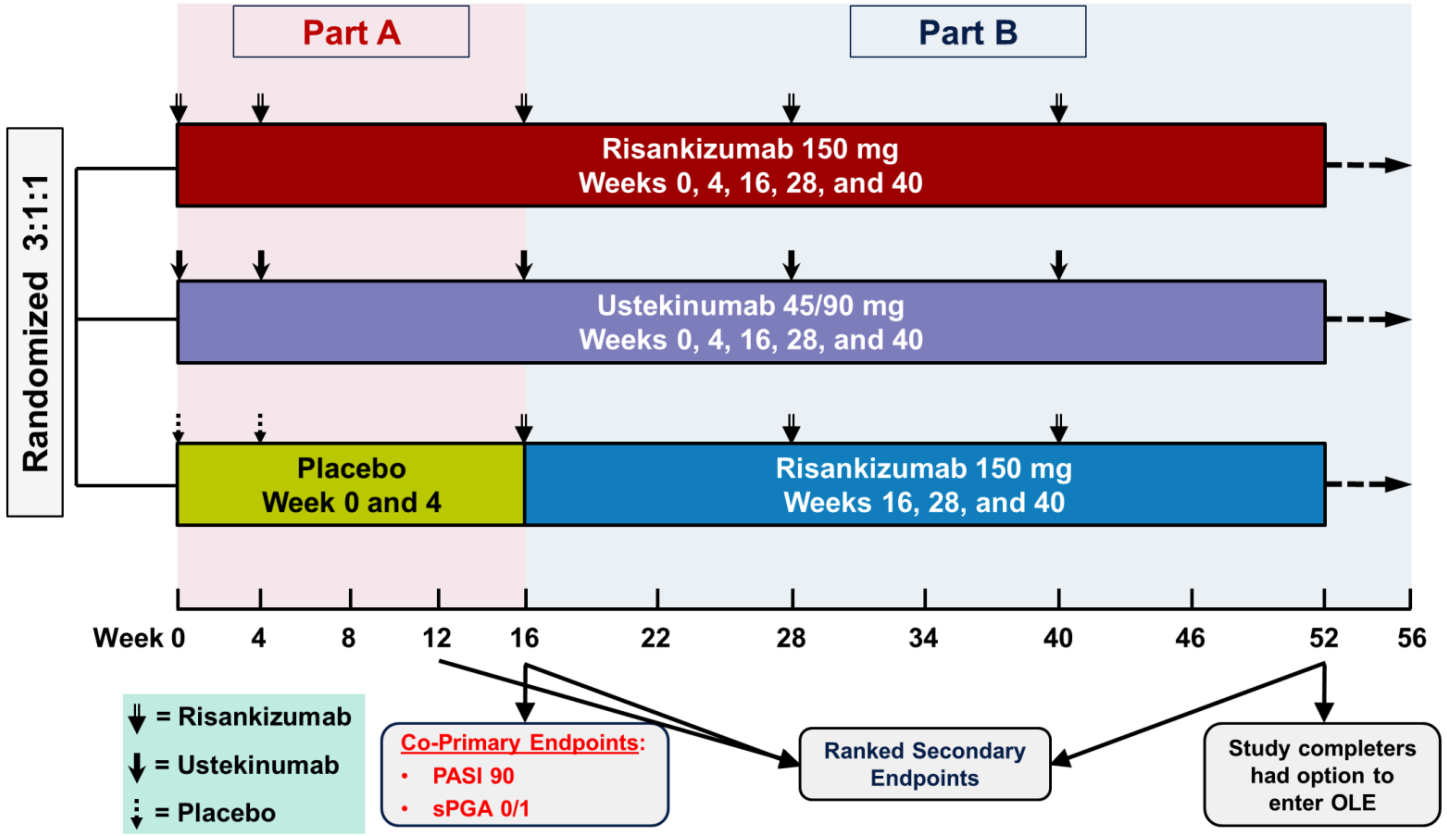
Boutet MB. *et al. International Journal of Molecular Sciences* (2018).

RISANKIZUMAB PIVOTAL TRIALS- ULTIMMA-1 AND ULTIMMA 2

Clinical Trial > Lancet. 2018 Aug 25;392(10148):650-661.
doi: 10.1016/S0140-6736(18)31713-6. Epub 2018 Aug 7.

Efficacy and safety of risankizumab in moderate-to-severe plaque psoriasis (UltIMMa-1 and UltIMMa-2): results from two double-blind, randomised, placebo-controlled and ustekinumab-controlled phase 3 trials

Kenneth B Gordon [1], Bruce Strober [2], Mark Lebwohl [3], Matthias Augustin [4], Andrew Blauvelt [5], Yves Poulin [6], Kim A Papp [7], Howard Sofen [8], Lluís Puig [9], Peter Foley [10], Mamitaro Ohtsuki [11], Mary Flack [12], Ziqian Geng [13], Yihua Gu [13], Joaquin M Valdes [13], Elizabeth H Z Thompson [14], Hervé Bachelez [15]



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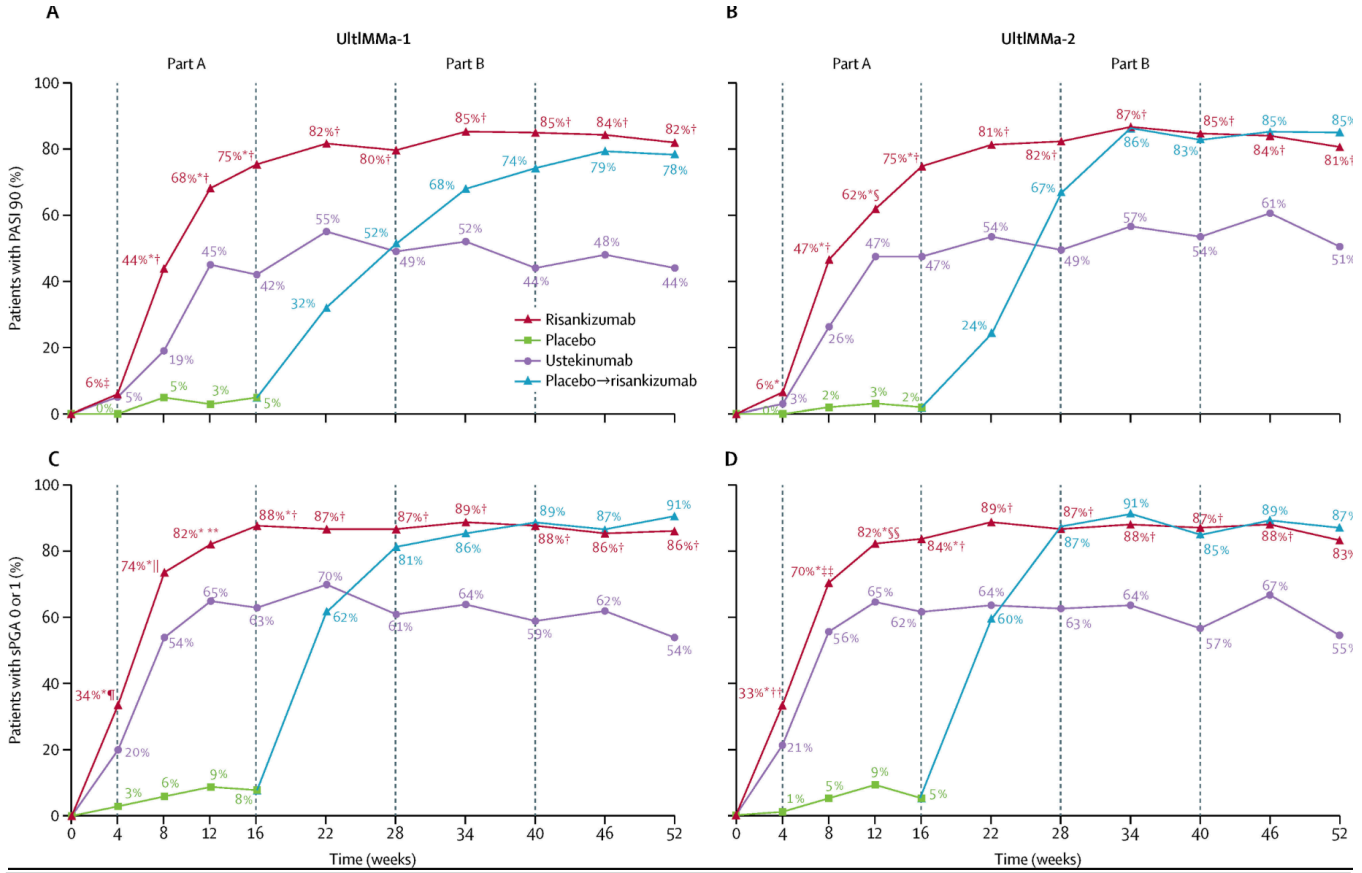
Gordon KB. *et al. Lancet* (2018).

RISANKIZUMAB PIVOTAL TRIALS- EFFICACY DATA ULTIMMA-1 AND ULTIMMA 2

In both studies, significantly greater proportions of patients receiving Risankizumab compared with those receiving placebo achieved the co-primary endpoints of PASI 90 and sPGA 0/1 at week 16 (p<0·0001 *vs* placebo)



*Proportions of patients (non-responder imputation) achieving PASI 90 and sPGA 0/1 through week 52 in UltIMMa-1 and UltIMMa-2

UltIMMa-1	Risankizumab (n=301)	Ustekinumab (n=98)	Placebo (n=102)	Difference from Ustekinumab (95% CI)	Difference from Placebo (95% CI)
PASI 90 at week 16	228 (75·7%)	41 (41·8%)	5 (4·9%)	34·1% (23·2, 45·0)*	70·8% (64·4, 77·1)*
sPGA 0/1 at week 16	266 (88·4%)	62 (63·3%)	8 (7·8%)	25·4% (15·4, 35·3)*	80·4% (74·1, 86·8)*
UltIMMa-2	Risankizumab (n=290)	Ustekinumab (n=98)	Placebo (n=98)	Difference from Ustekinumab (95% CI)	Difference from Placebo (95% CI)
PASI 90 at week 16	219 (75·5%)	47 (48·0%)	2 (2·0%)	27·8% (16·9, 38·8)*	73·2% (67·5, 78·9)*
sPGA 0/1 at week 16	245 (84·5%)	61 (62·2%)	5 (5·1%)	22·5% (12·3, 32·7)*	79·3% (73·3, 85·3)*

Data are least square mean (SE), n (%), or % (95% CI). Categorical variables were analysed using Cochran-Mantel-Haenszel (CMH) risk difference estimate stratified by baseline weight and prior exposure to TNFi. Missing data were imputed as non-responders. *P<0·0001 compared with placebo and ustekinumab. CI=Confidence Interval. PASI=Psoriasis Area and Severity Index. sPGA=static Physician's Global Assessment.

*Primary endpoints in UltIMMa-1 and UltIMMa-2

Gordon KB. *et al. Lancet* (2018).

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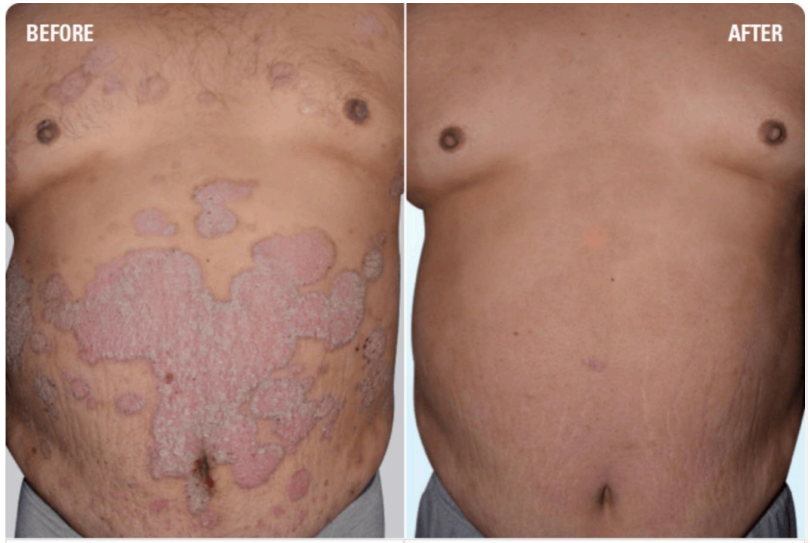
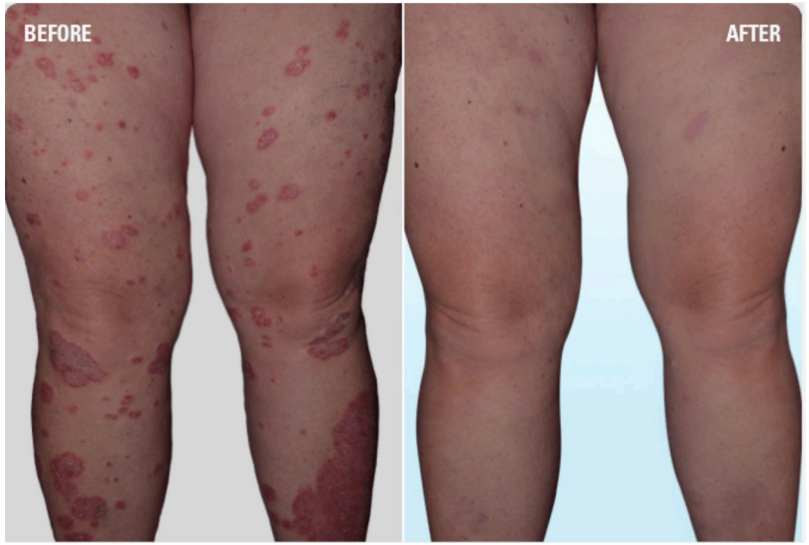
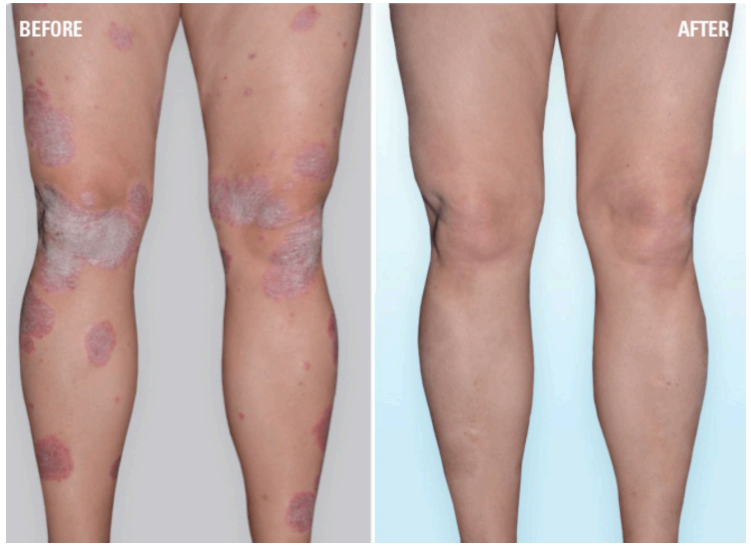
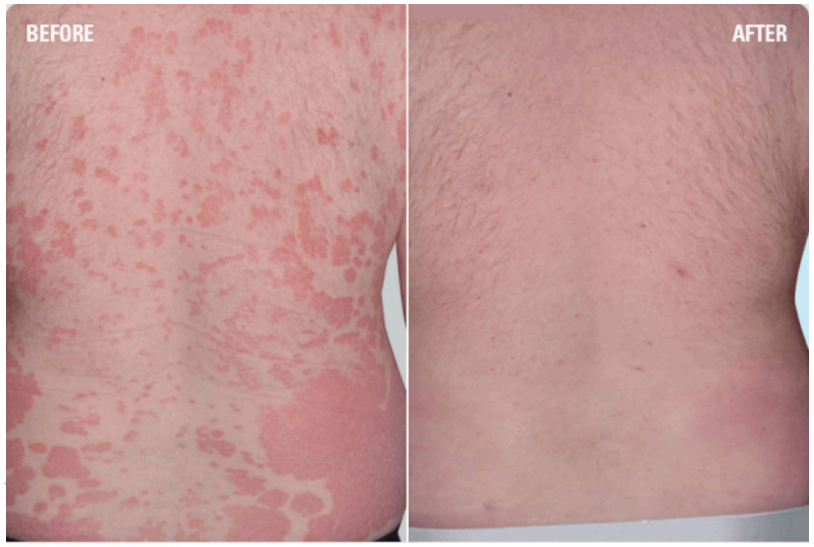
RISANKIZUMAB CLINICAL TRIAL PHOTOS









SKYRIZI clinical trial patient.

Skyrizi Clinical Report Data

RISANKIZUMAB- SAFETY DATA FOR ULTIMMA-1 AND ULTIMMA 2 TRIALS

Most common treatment-emergent adverse events reported by >5% in UltIMMA-1 and UltIMMA-2 trials

Part A	UltIMMA-1			UltIMMA-2		
	Risankizumab (n=304)	Ustekinumab (n=100)	Placebo (n=102)	Risankizumab (n=294)	Ustekinumab (n=99)	Placebo (n=98)
Viral upper respiratory tract infection	20 (6·6%)	6 (6·0%)	6 (5·9%)	10 (3·4%)	5 (5·1%)	2 (2·0%)
Upper respiratory tract infection	17 (5·6%)	6 (6·0%)	2 (2·0%)	11 (3·7%)	4 (4·0%)	2 (2·0%)
Psoriasis	0	1 (1·0%)	6 (5·9%)	0	1 (1·0%)	4 (4·1%)
Diarrhea	3 (1·0%)	2 (2·0%)	2 (2·0%)	3 (1·0%)	5 (5·1%)	3 (3·1%)
Part B	**UltIMMA-1**			**UltIMMA-2**		
	Risankizumab (n=297)	Ustekinumab (n=99)	Placebo → Risankizumab (n=97)	Risankizumab (n=291)	Ustekinumab (n=94)	Placebo → Risankizumab (n=94)
Viral upper respiratory tract infection	40 (13·5%)	18 (18·2%)	15 (15·5%)	34 (11·7%)	17 (18·1%)	14 (14·9%)
Upper respiratory tract infection	30 (10·1%)	11 (11·1%)	8 (8·2%)	24 (8·2%)	9 (9·6%)	8 (8·5%)
Urinary tract infection	3 (1·0%)	5 (5·1%)	0	6 (2·1%)	1 (1·1%)	0
Influenza	6 (2·0%)	2 (2·0%)	1 (1·0%)	4 (1·4%)	2 (2·1%)	5 (5·3%)
Headache	5 (1·7%)	5 (5·1%)	3 (3·1%)	7 (2·4%)	3 (3·2%)	2 (2·1%)

Gordon KB. *et al. Lancet* (2018).

FINAL SUMMARY OF AVAILABLE BIOLOGICS

	MOA[1]	Route[1]	Dose + Frequency[1]	FDA-Approved Indications[1]	Time to See Response[1]	Pros in Psoriasis[1]	Pros Overall	Cons[1]	Comorbidities in Which to Use[1-3]	Comorbidities in Which to Avoid[1-3]	PASI 75 SCORE [1]
Etanercept (Enbrel)	TNF-α Inhibitor	SQ -Fixed dosing	50mg 2x/week for 12 weeks, then 50mg weekly	- PsO - PsA - AS - RA - JIA	12–16 weeks	- Approved for patients ≥ age 4yrs - Scalp + nail PsO - Erythrodermic PsO - Palmoplantar PsO - Pustular PsO	- Anti-drug Abs not associated with loss of efficacy[1]	- Frequent SQ dosing - Slower onset of action compared to newer medications[4] - May worsen IBD[5]	- IBD+ (EXCEPTION: Etanercept) - CVD+ - HBV*, HCV** - HIV***	- MS (CI) - CHF Class III or IV (CI) - Concurrent or prior malignancy	At week 12: - 49% if 50mg twice per week - 33% if 50mg weekly
Adalimumab (Humira)	TNF-α Inhibitor	SQ -Fixed dosing	80mg at week 0, 40mg at week 1, then 40mg q2 weeks	- PsO (adults) - PsA - AS - RA - IBD - JIA - HS - Uveitis		- Scalp + nail PsO - Erythrodermic PsO - Palmoplantar PsO - Generalized pustular PsO	- Approved for adult and pediatric Crohn's[1]	- Frequent SQ dosing - Loss of efficacy via anti-drug Abs			At week 16: - 71%
Infliximab (Remicade)	TNF-α Inhibitor	IV -Weight-based dosing	5mg/kg at weeks 0, 2, 6, then q8 weeks	- PsO - PsA - AS - RA - IBD	8–10 weeks	- Scalp + nail PsO - Erythrodermic PsO - Palmoplantar PsO - Palmoplantar pustular PsO - Generalized pustular PsO	- Approved for adult and pediatric IBD[1]	- IV administration - Loss of efficacy via anti-drug Abs (prevention= MTX) - Infusion reactions			At week 10: - 75.5% if dosed at 5mg/kg - 70.3% if dosed at 3mg/kg
Certolizumab (Cimzia)	Pegylated TNF-α Inhibitor	SQ -Fixed dosing	- 400mg (as 2 200mg injections) q2 weeks - If ≤90kg: 400mg (as 2 200mg injections) at weeks 0, 2, 4, then 200mg q2 weeks	- PsO - PsA - AS - RA - Crohn's	12–16 weeks	- May be used in pregnancy-minimal crossing of placental barrier[6,7]	- Increased T1/2	- Frequent SQ dosing			At week 12: - 75% if 200mg q2 weeks - 83% if 400mg q2 weeks
Ustekinumab (Stelara)	IL-12 and IL-23 Inhibitor	SQ -Weight-based dosing	- If ≤100kg: 45mg at weeks 0 and 4, then q12 weeks - If >100kg: 90mg at weeks 0 and 4, then q12 weeks - If age 12–17yrs and <60kg: 0.75mg/kg at 0 and 4, then q12 weeks	- PsO - PsA - Crohn's	12 weeks	- Approved for patients ≥ age 12yrs - Scalp + nail PsO - Erythrodermic PsO - Palmoplantar PsO - Palmoplantar pustular PsO - Annular pustular PsO - Generalized pustular PsO	- q3mos dosing	- Less effective than TNF-α inhibitors for PsA - Loss of efficacy via anti-drug Abs	- IBD+ - Obesity+ - CHF+ - MS - HBV*, HCV** - HIV***		At week 12: - 66.7-67.1% if 45mg dose - 66.4-75.7% if 90mg dose
Guselkumab (Tremfya)	IL-23 Inhibitor	SQ	100mg at weeks 0 and 4, then q8 weeks	- PsO - PsA[8]	12 weeks	- Scalp + nail PsO - Palmoplantar PsO	- q2mos dosing - Neutralizing anti-drug Abs not associated with loss of efficacy or injection-site reactions[1]	- Slower onset of action + clinical improvement compared to IL-17 inhibitors[9]	- IBD - Obesity+ - CHF+ - HIV***		At week 16: - 86.3[10] - 91.2%[11]

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Dave R. *et al. Journal of Drugs in Dermatology* (2021).

FINAL SUMMARY OF AVAILABLE BIOLOGICS (CON'T)

	MOA[1]	Route[1]	Dose + Frequency[1]	FDA-Approved Indications[1]	Time to See Response[1]	Pros in Psoriasis[1]	Pros Overall	Cons[1]	Comorbidities in Which to Use[1-3]	Comorbidities in Which to Avoid[1-3]	PASI 75 SCORE [1]
Tildrakizumab (Ilumya)	IL-23 Inhibitor	SQ	100mg at weeks 0 and 4, then q12 weeks	- PsO			- q3mos dosing	- Slower onset of action + clinical improvement compared to IL-17 inhibitors[9] - Loss of efficacy via neutralizing anti-drug Abs			At week 12: - 61% if 100mg dose - 66% if 200mg dose
Risankizumab (Skyrizi)	IL-23 Inhibitor	SQ	150mg at weeks 0 and 4, then q12 weeks	- PsO[12]			- q3mos dosing	- Slower onset of action/clinical improvement compared to IL-17 inhibitors[9]			At week 12: - 63% if 18mg dose - 98% if 90mg dose - 88% if 180mg dose[13]
Secukinumab (Cosentyx)	IL-17A Inhibitor	SQ	300mg weekly at weeks 0–4, then q4 weeks	- PsO (adults) - PsA - AS - Non-radiographic axial spondylo-arthritis[14]	12 weeks	- Scalp + nail PsO - Erythrodermic PsO - Palmoplantar PsO - Generalized pustular PsO - Neck PsO	- Rapid onset of action[4] - Maintenance of response at 52 weeks of q4 week dosing - Neutralizing anti-drug Abs not associated with loss of efficacy[1]	- May worsen IBD[15] - Increased infection risk - Risk of mucocutaneous Candida infections	- Obesity+ - CHF+ - MS - HBV*, HCV** - HIV***	IBD (May worsen)	At week 12: - 71.6-77.1% if 150mg dose - 77.1-81.6% if 300mg dose
Ixekizumab (Taltz)	IL-17A Inhibitor	SQ	- Initial: 160mg at week 0, then 80mg q2 weeks from weeks 2–12 - Maintenance: 80mg q4 weeks - Some may require 80mg q2 weeks	- PsO - PsA - AS - Non-radiographic axial spondylo-arthritis[16]		- Approved for patients ≥ age 6yrs - Scalp + nail PsO - Erythrodermic PsO - Palmoplantar PsO - Generalized pustular PsO - Inverse PsO - Genital PsO	- Rapid onset of action[4]	- May worsen IBD[15] - Increased infection risk - Risk of mucocutaneous Candida infections - Loss of efficacy via neutralizing anti-drug Abs			At week 12: - 84.2%
Brodalumab (Siliq)	IL-17RA Antagonist	SQ	- Initial: 210mg weekly at weeks 0–2 - Maintenance: 210mg q2 weeks	- PsO		- Scalp + nail PsO - Erythrodermic PsO - Generalized pustular PsO	- Rapid onset of action[4] - No neutralizing anti-drug Abs[1]	- May worsen IBD[15] - Increased infection risk - Risk of mucocutaneous Candida infections - BBW: suicidal ideation and behavior[17]			At week 12: - 67-69% if 140mg dose - 85-86% if 210mg dose

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Dave R. *et al. Journal of Drugs in Dermatology* (2021).

REFERENCES

1. Menter A, Strober BE, Kaplan DH, et al. Joint AAD-NPF guidelines of care for the management and treatment of psoriasis with biologics. *J Am Acad Dermatol*. 2019;80(4):1029-1072. doi:10.1016/j.jaad.2018.11.057
2. Chan TC, Hawkes JE, Krueger JG. Interleukin 23 in the skin: role in psoriasis pathogenesis and selective interleukin 23 blockade as treatment. *Ther Adv Chronic Dis*. 2018;9(5):111-119. doi:10.1177/2040622318759282
3. Lee E, Trepicchio WL, Oestreicher JL, et al. Increased expression of interleukin 23 p19 and p40 in lesional skin of patients with psoriasis vulgaris. *J Exp Med*. 2004;199(1):125-130. doi:10.1084/jem.20030451
4. Koutruba N, Emer J, Lebwohl M. Review of ustekinumab, an interleukin-12 and interleukin-23 inhibitor used for the treatment of plaque psoriasis. *Ther Clin Risk Manag*. 2010;6:123-141. doi:10.2147/TCRM.S5599
5. Leonardi CL, Kimball AB, Papp KA, et al. Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 76-week results from a randomised, double-blind, placebo-controlled trial (PHOENIX 1). 2008;371.
6. Papp KA, Langley RG, Lebwohl M, et al. Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 52-week results from a randomised, double-blind, placebo-controlled trial (PHOENIX 2). *Lancet Lond Engl*. 2008;371(9625):1675-1684. doi:10.1016/S0140-6736(08)60726-6
7. Gordon KB, Strober B, Lebwohl M, et al. Efficacy and safety of risankizumab in moderate-to-severe plaque psoriasis (UltIMMa-1 and UltIMMa-2): results from two double-blind, randomised, placebo-controlled and ustekinumab-controlled phase 3 trials. *The Lancet*. 2018;392(10148):650-661. doi:10.1016/S0140-6736(18)31713-6
8. Lebwohl M, Strober B, Menter A, et al. Phase 3 Studies Comparing Brodalumab with Ustekinumab in Psoriasis. *N Engl J Med*. 2015;373(14):1318-1328. doi:10.1056/NEJMoa1503824
9. Thaçi D, Blauvelt A, Reich K, et al. Secukinumab is superior to ustekinumab in clearing skin of subjects with moderate to severe plaque psoriasis: CLEAR, a randomized controlled trial. *J Am Acad Dermatol*. 2015;73(3):400-409. doi:10.1016/j.jaad.2015.05.013
10. Al-Salama ZT, Scott LJ. Guselkumab: A Review in Moderate to Severe Plaque Psoriasis. *Am J Clin Dermatol*. 2018;19(6):907-918. doi:10.1007/s40257-018-0406-1
11. Reich K, Armstrong AW, Foley P, et al. Efficacy and safety of guselkumab, an anti-interleukin-23 monoclonal antibody, compared with adalimumab for the treatment of patients with moderate to severe psoriasis with randomized withdrawal and retreatment: Results from the phase III, double-blind, placebo- and active comparator-controlled VOYAGE 2 trial. *J Am Acad Dermatol*. 2017;76(3):418-431. doi:10.1016/j.jaad.2016.11.042
12. Blauvelt A, Papp KA, Griffiths CEM, et al. Efficacy and safety of guselkumab, an anti-interleukin-23 monoclonal antibody, compared with adalimumab for the continuous treatment of patients with moderate to severe psoriasis: Results from the phase III, double-blinded, placebo- and active comparator-controlled VOYAGE 1 trial. *J Am Acad Dermatol*. 2017;76(3):405-417. doi:10.1016/j.jaad.2016.11.041
13. Mease PJ, Rahman P, Gottlieb AB, et al. Guselkumab in biologic-naive patients with active psoriatic arthritis (DISCOVER-2): a double-blind, randomised, placebo-controlled phase 3 trial. *Lancet Lond Engl*. 2020;395(10230):1126-1136. doi:10.1016/S0140-6736(20)30263-4
14. Frampton JE. Tildrakizumab: A Review in Moderate-to-Severe Plaque Psoriasis. *Am J Clin Dermatol*. 2019;20(2):295-306. doi:10.1007/s40257-019-00435-9
15. Reich K, Papp KA, Blauvelt A, et al. Tildrakizumab versus placebo or etanercept for chronic plaque psoriasis (reSURFACE 1 and reSURFACE 2): results from two randomised controlled, phase 3 trials. *Lancet Lond Engl*. 2017;390(10091):276-288. doi:10.1016/S0140-6736(17)31279-5
16. Boutet MA, Nerviani A, Gallo Afflitto G, Pitzalis C. Role of the IL-23/IL-17 Axis in Psoriasis and Psoriatic Arthritis: The Clinical Importance of Its Divergence in Skin and Joints. *Int J Mol Sci*. 2018;19(2):530. doi:10.3390/ijms19020530
17. Dave R, Alkeswani A. An Overview of Biologics for Psoriasis. *J Drugs Dermatol JDD*. 2021;20(11):1246-1247. doi:10.36849/jdd.6040