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# Data wobbles in hidradenitis suppurativa clinical trials and potential contributing factors: a retrospective review

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# ABSTRACT

**Background:** In some hidradenitis suppurativa (HS) clinical trial study arms, there is an unexpected decline in efficacy between the penultimate visit and the prespecified primary endpoint week, which we have termed a "wobble."

Objective: We aimed to establish how often study arms in HS programs wobble.

**Methods:** In a retrospective review, we identified HS clinical trials listed on ClinicalTrials.gov testing systemic, nonantibiotic medications that utilized Hidradenitis Suppurativa Clinical Response (HiSCR) as an outcome measure. We identified study arms demonstrating greater improvement in a visit prior to the primary endpoint week. Baseline subject characteristics were compared between studies with HiSCR wobble and no HiSCR wobble.

**Results:** A total of 21 studies (randomized control trial [RCT], n = 14; open-label, n = 7) with 35 study drug arms (RCT, n = 27; open-label, n = 8) and 14 placebo arms were identified. HiSCR wobble occurred significantly more often in RCT compared to open-label study drug arms (11/27 [40.7%] vs 0/8 [0%]). In RCT study arms with HiSCR wobble, baseline draining fistula counts were significantly lower (2.3 vs 3.2), and numerically fewer Hurley stage 3 patients (33.2% vs 42.5%), lower weighted total abscess and nodule counts (12.1 vs 12.6), lower weighted dermatology life quality index scores (12.5 vs 14.5), and a higher proportion of female patients (63.9% vs 58.3%) were observed.

Limitations: Include low number of HS clinical trials and insufficient data reported in many studies to assess for wobble, degree of wobble, and to compare all baseline characteristics.

**Conclusion:** Nonlinear improvement in study arm response occurs in some HS RCTs. Potential contributing factors include a higher proportion of less severe patients at baseline and more female patients.

Keywords: acne inversa, biological products, clinical trial protocol, hidradenitis suppurativa, randomized controlled trial

## Introduction

Hidradenitis suppurativa (HS) is a chronic debilitating skin disorder characterized by recurrent inflammatory nodules, abscesses, fistulas, and scars.<sup>1</sup> Adalimumab (a tumor necrosis factor-alpha inhibitor) was approved by the Food and Drug Administration in 2015.<sup>2,3</sup> Over the past several years, clinical

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trials for HS increased dramatically, leading to the approval of secukinumab by the European Commission in 2023.<sup>4</sup> HS clinical trials typically utilize a placebo-controlled design using the Hidradenitis Suppurativa Clinical Response (HiSCR or HiSCR 50), at least a 50% reduction in total abscess and nodule (AN) count with no increase in abscess or draining fistula (DF) count, as the primary efficacy endpoint at either 12 or 16 weeks.<sup>2</sup>

What is known about this subject in regard to women and their families?

- In the United States, hidradenitis suppurativa is diagnosed approximately 3 times more often in women than men and can often affect multiple family members.
- Hidradenitis suppurativa is an incredibly difficult condition to treat with currently only one Food and Drug Administration-approved treatment. Several clinical trials are ongoing to increase effective treatment options.

# What is new from this article as messages for women and their families?

• This article uncovers nonlinear improvements found in hidradenitis suppurativa clinical trials, explores factors that may play a role, and suggests some strategies to help reduce this unexpected data outcome in future trials.

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Author/ sponsor	Drug name	Dosing	"	Age, mean (SD)	F, %	Duration years, mean (SD)	Hurley 1, 2, 3; (%)	BL AN count, mean (SD)	BL DF count, mean (SD)	BL pain, mean (SD)	BL DLQI, mean (SD)	Wobble- peak week	%HiSCR week 12	%HiSCR week 16
Glatt et al.,	Bimekizumab	320 mg Q2W <sup>a</sup>	46	37.4 (11.9)	65.2	9 (8.8)	0, 50, 50	14.5 (11.9)	ı	3.7 (2.4)	11.7 (8)	Yes-10	62.5 <sup>b</sup>	.
Glatt et al.	Adalimumab	$40\text{mg}~\text{Q2W}^{a}$	21	31.1 (9.4)	81	8.6 (5.7)	0, 48, 52	20 (11.5)	ı	5.8 (2.7)	14.5 (7.9)	No	66.7	
Glatt et al.	Placebo	Placebo	21	40.7 (12.8)	67	9.5 (8.4)	0, 48, 52	12.7 (5.7)	I	5.6 (2.7)	12.7 (5.7)	Yes-4	27.8	
2021' InflaRx GmbH	IFX-1	400 mg Q4W	34	39 (-)	47.1			6 (-)	ı		ı	Yes-12	45.2	40
2019° InflaRx GmbH	IFX-1	800 mg Q4W	35	35 (-)	51.4			8 (-)		·	ı	No	36.4	51.5
2019° InflaRx GmbH	IFX-1	800 mg Q2W	36	37 (-)	55.6			10 (-)	ı	·	ı	Yes-12	40.6	38.7
2019° InflaRx GmbH	IFX-1	1200 mg	36	33.5 (-)	63.9			12.5 (-)	ı	ı	ı	No	40.6	45.5
2019° InflaRx GmbH	Placebo	Placebo	36	34.5 (-)	58.3			9.5 (-)	ı		ı	No	41.2	47.1
ZUT9° Bechara et al.	Adalimumab	$40\text{mg}~\text{Q1}\text{W}^{a}$	103	38.5 (11.71)	49.5		0, 51, 49	10.3 (7.5)	3.6 (4)	ı	13.6 (7.3)	No	48 <sup>b</sup>	ı
2021 <sup>*</sup> Bechara et al.	Placebo	Placebo	103	36.8 (10.81)	53.4		0, 52, 49	11.3 (12.6)	4 (5.4)	ı	12.9 (7.1)	No	34	ı
کانکا Kimball et al.	Adalimumab	$40\text{mg}~\text{Q2W}^{a}$	45	36.1 (12.77)	73.3		15.6, 55.6, 28.9	ı		·	ı	Yes-8	35.6	33.3 <sup>b</sup>
2016² Kimball et al.	Adalimumab	$40\text{mg}~\text{Q}1\text{W}^{a}$	44	36.6 (10.68)	70.5	12.1 (9.34)	18.2, 56.8, 25	ı			ı	Yes-12	59.1	54.5 <sup>b</sup>
2016² Kimball et al.	Placebo	Placebo	43	37.7 (12.01)	67.4	13.3 (9.53)	14, 55.8, 30.2	ı	ı		ı	Yes-8	16.3	25.6
2016² Kimball et al.	Adalimumab	$40\text{mg}~\text{Q}1\text{W}^{a}$	153	36.2 (10.8)	59.5	8.8 (-)	0, 52.3, 47.7	14.3 (11.9)	4.6 (5.2)	6 (1.8)	16.3 (6.6)	No	41.8 <sup>b</sup>	·
ZUT6 <sup>3</sup> Kimball et al.	Placebo	Placebo	154	37.8 (11.3)	68.2	9.4 (-)	0, 52.6, 47.4	14.4 (14.8)	3.8 (4.4)	6 (2)	16 (7.1)	No	26	ı
ZUT6° Kimball et al.	Adalimumab	$40\text{mg}~\text{Q1}\text{W}^{a}$	163	34.9 (10)	66.3	(-) 6	0, 52.8, 47.2	10.7 (8.1)	3 (4.1)	5.7 (1.9)	14.1 (7.7)	No	58.9 <sup>b</sup>	
ZUTO Kimball et al.	Placebo	Placebo	163	36.1 (12.2)	69.3	(-) 6.6	0, 54.6, 45.4	11.9 (11)	3.7 (5.2)	6.2 (1.9)	14.9 (7.3)	No	27.6	ı
ZUT6° Kimball et al.	Secukinumab	300 mg Q4W <sup>a</sup>	180	35.5 (11.4)	57	8.2 (8.4)	3, 59, 38	13.3 (8.8)	2.5 (3.5)	4.6 (2.5)	ı	Yes-12	51	46.1 <sup>b</sup>
Kimball et al.	Secukinumab	300 mg Q2W <sup>a</sup>	180	37.3 (11.5)	54	7.1 (7)	3, 51, 46	13.9 (9.9)	3 (3.6)	4.8 (2.4)	ı	No	39.3	42.3 <sup>b</sup>
ZUZ3 <sup>7</sup> Kimball et al.	Placebo	Placebo	183	36.2 (11.3)	57	7 (6.7)	2, 60, 38	12.8 (8.5)	2.6 (3.2)	4.7 (2.4)	ı	No	24.7	31.2
∠ترحم Kimball et al.	Secukinumab	$300\text{mg}\text{Q4W}^{a}$	180	35.7 (11.7)	56	6.6 (6.7)	6, 59, 35	12.6 (8.4)	2.5 (3.5)	4.2 (2.5)	ı	No	39.5	41.8
∠∪∠ئ <sup>7</sup> Kimball et al. ک∩י2₄	Secukinumab	300 mg Q2W <sup>a</sup>	181	37.1 (12.5)	56	7.4 (8)	4, 58, 39	12.9 (9.6)	2.9 (3.4)	4.5 (2.5)	ı	No	43.3	45 <sup>b</sup>
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Match     Age and a bar of a	Application     Application     Application     Application     Building     Building<	Matrix     Age, main     Matrix     Matrix     Bear (sc) (sc)     Models     Sec (sc) (sc)     Se	Duration years, lacebo     Dosing $n$ Age, mean (SD)     Duration years, 7     Hu       lacebo     Placebo     180     35.5 (10.8)     57     7.5 (7)       lacebo     45 mg 0D     52     -     -     -       lacebo     45 mg 0D     47     -     -     -       lacebo     40 mg 0D     47     -     -     -       lacebo     Placebo     48     -     -     -     -       lacebo     Placebo     52     36.5 (-)     71.2     9.9 (8.1)     7       ovorcitinib     45 mg 0D     52     36.5 (-)     75     7     7       ovorcitinib     75 mg 0D     52     36.5 (-)     75     9.9 (8.1)     7       ovorcitinib     75 mg 0D     52     36.6 (-)     75     11.2 (11.5)     7       ovorcitinib     75 mg 0D     53     33.5 (-)     73.6     11.1 (6.7)     7       ovorcitinib     75 mg 0D     33.5 (-)     75     11.1 (6.7)     7 <	lurley 1, 2, 3; (%) 4, 67, 28 -	BL AN count,	DI DE count					
eneop     Facebo     Fac     55 (10)     57     75 (7)     4, 67, 28     12.8 (2.2)     2.4 (2.2)     4.3 (2.5)     ·     100     286     337       pocinitio     45mg QD     52     ·	cerebe     Paceleo     10     355 (10)     57     7.5 (7)     4.67.20     1.2 (8.2)     2.4 (3.2)     4.3 (2.3)     6.0     2.06     2.3 (7.3)       proteinin     457 mg UD     52     -     -     -     -     -     -     -     -     -     2.0	ebed     Pacado     Pacado <th>cebo     Placebo     180     35.5 (10.8)     57     7.5 (7)       pocifinib     45 mg dD     52     -     -     -       nlovisertib     400 mg dD     47     -     -     -       nlovisertib     400 mg dD     47     -     -     -       bsacitinib     400 mg dD     47     -     -     -       orcitinib     15 mg dD     52     36.5 (-)     71.2     9.9 (8.1)     5       vorcitinib     15 mg dD     52     36.5 (-)     71.2     9.9 (8.1)     5       vorcitinib     75 mg dD     52     35.(-)     75     11.2 (11.5)     7       vorcitinib     75 mg dD     52     35.(-)     73.6     12.1 (9.7)     7       vorcitinib     75 mg dD     53     38.(-)     73.6     11.2 (11.5)     7       vorcitinib     75 mg dD     53     35.(-)     73.6     11.1 (6.5)     7       vorcitinib     75 mg dD     9     42.8 (13.8)     44.4     12.6 (7)</th> <th>4, 67, 28 - -</th> <th>mean (SD)</th> <th>BL UF COUIL, mean (SD)</th> <th>bL pain, mean (SD)</th> <th>BL DLQI, mean (SD)</th> <th>Wobble- peak week</th> <th>%HISCR week 12</th> <th>%HiSCR week 16</th>	cebo     Placebo     180     35.5 (10.8)     57     7.5 (7)       pocifinib     45 mg dD     52     -     -     -       nlovisertib     400 mg dD     47     -     -     -       nlovisertib     400 mg dD     47     -     -     -       bsacitinib     400 mg dD     47     -     -     -       orcitinib     15 mg dD     52     36.5 (-)     71.2     9.9 (8.1)     5       vorcitinib     15 mg dD     52     36.5 (-)     71.2     9.9 (8.1)     5       vorcitinib     75 mg dD     52     35.(-)     75     11.2 (11.5)     7       vorcitinib     75 mg dD     52     35.(-)     73.6     12.1 (9.7)     7       vorcitinib     75 mg dD     53     38.(-)     73.6     11.2 (11.5)     7       vorcitinib     75 mg dD     53     35.(-)     73.6     11.1 (6.5)     7       vorcitinib     75 mg dD     9     42.8 (13.8)     44.4     12.6 (7)	4, 67, 28 - -	mean (SD)	BL UF COUIL, mean (SD)	bL pain, mean (SD)	BL DLQI, mean (SD)	Wobble- peak week	%HISCR week 12	%HiSCR week 16
spontinic     4 mg 00     52     ·	gooding     farge     is	Booking for group is in the second for gro	pocifinib     45 mg dD     52     -		12.8 (8.2)	2.4 (3.2)	4.3 (2.5)		No	28.6	33.7
Inorsertio     40 mg 00     7     ·	Indication     40 m con     47     5.	Indicating     40 mg CD     47     · · · · · · · · · · · · · · · · · · ·	Invisertib     400 mg QD     47     -		ı	ı			No		51.9 <sup>b</sup>
psection     400 mg 0     7     ·	protection     40m g0     7     ·	pspectipite     dom g0     47      -	psacifinib     400 mg QD     47     -	ı	ı	ı	ı	ı	Yes-4	ı	34
acebo     Pacebo     48     · · · ·     · · ·     · · ·     · · ·     · · ·     · · ·     · · ·     · · ·     · · ·     · · ·     · · ·     · · · ·     · · · ·     · · · ·     · · · ·     · · · ·     · · · · ·     · · · ·	acedite     Hacebite     48     -     -     -     -     -     -     -     -     -     -     -     333       oncitititititi     15mg 00     52     36.5(1)     712     99.8(1)     5.8.71.2.231     11.8(7.1)     2.4 (4.4)     4.6 (2.4)     11.2(7.1)     No     42.3     48.1       voncititititi     75mg 00     52     36.5(1)     7.15     11.2(1.5)     12.7 (3)     14.1     44.2     44.3     44.3     44.3     44.3     44.3     44.3     44.3     44.3     44.3     44.3     12.6 (6.9.7)     7.5 (6.9.2.2.5.1)     11.2 (5.1)     46.1     46.2     45.1     45.1     45.3     45.3       voncititititititititititititititititititit	accord     Placetion     48     · · · ·     · · ·     · · ·     · · ·     · · ·     · · ·     · · ·     · · ·     · · ·     · · ·     · · ·     · · ·     · · ·     · · ·     · · ·     · · ·      voctinin<     · · ·	acebo     Placebo     48     - <t< td=""><td></td><td>I</td><td>ı</td><td>ı</td><td>ı</td><td>Yes-6</td><td>ı</td><td>37</td></t<>		I	ı	ı	ı	Yes-6	ı	37
vorcinity     15 mg UD     52     35 (1)     71.2     9.9 (8.1)     5.8,71.2.231     118 (7.1)     2.4 (4.4)     4.6 (2.4)     11.2 (7.1)     No<     4.23     481       vorcinity     45 mg UD     52     35 (1)     75     11.2 (115)     7.7,693.23.1     12.9 (12.3)     2.1 (9.7)     856.12     481     442       vorcinity     75 mg UD     53     38 (1)     75     81.16.50     7.7,693.23.1     12.9 (12.3)     5.1 (2.3)     137.6)     Yes-12     685     45.3       vorcinity     75 mg OD     53     38 (1)     75     0.666,33.3     2.2 (4)     5.1 (2.3)     Yes-12     685     45.3       vorcinity     75 mg OD     52     77     12.1 (7.3)     Yes-12     58.5     45.3       vorcinity     75 mg OD     9     42.0 (13)     0.0     0.666,33.3     -     2.1 (12.7)     Yes-12     7.7 (9)     Yes-12     2.8 (7)     1.4 (7)     Yes-12     2.8 (7)     1.4 (7)     Yes-12     2.8 (7)     1.4 (7)     Yes-12     2.8 (7)	wording     15 mg QD     52     36.5 ()     71.2     9.8 (1)     5.7.12.23.1     11.8 (7.1)     2.4 (4.4)     4.6 (2.4)     11.2 (7.1)     No<     423     481       wording     45 mg QD     52     35 ()     75     11.2 (11.5)     7.7, 69.2.23.1     12.9 (12.3)     2.2 (4)     5.1 (2.3)     13.7 (3)     %e5.1 (2)     481     442       wording     75 mg QD     52     335 ()     7.3 (80.2.23.1)     12.9 (12.3)     2.2 (4)     5.1 (2.3)     13.7 (3)     %e5.1 (2)     481     442       wording     82     335 ()     7.3 (80.2.23.1)     11.0 (7.2)     11.2 (7.3)     %e5.1 (7.3)     %e5.1 (7.3)     %e5.1 (7.3)     481     442       wording     100 mg QD     9     428 (13.3)     0.4 (10.6)     7.7 (80.2.23.1)     11.2 (5.3)     12.1 (7.3)     %e5.1 (7.	worklink     15 mg QD     22     36.5 (-)     712     9.9 (B,1)     5.8.7.1.2.231     1.1.8 (T,1)     No<     4.23     4.81       morklink     45 mg QD     52     35 (-)     75     11.2 (115)     7.7.693.2.331     12.9 (12.3)     2.2 (4)     5.1 (2.3)     13.7 (5)     48-6 (12)	vorcitinib     15 mg QD     52     36.5 (-)     71.2     9.9 (8.1)     5.       vorcitinib     45 mg QD     52     35 (-)     75     11.2 (11.5)     7       vorcitinib     75 mg QD     53     38 (-)     75     11.2 (11.5)     7       vorcitinib     75 mg QD     53     38 (-)     73.6     12.1 (9.7)     7       acebo     Placebo     52     33.5 (-)     82.7     8.1 (6.5)     7       acebo     Placebo     52     33.5 (-)     82.7     8.1 (6.5)     7       acebo     Placebo     10     42.8 (13.8)     44.4     12.3 (6.7)     0       acebo     Placebo     10     36 (11.3)     50     11.1 (6.8)     7       acebo     Placebo     5     33.4 (8.2)     100     16 (7.1)     0       acebo     Placebo     5     33.4 (8.2)     100     16 (7.1)     0		ı	ı	ı	ı	Yes-8	ı	33.3
wordtink     45 mg db     52     35 (-)     75     112 (115)     77,692.231     129 (123)     22 (4)     51 (2.3)     13 (7.6)     Wes-6,12     48.1     44.2       wordtink     75 mg db     53     38 (-)     736     12.1 (9.7)     75,693.226     10.6 (7.2)     16 (2.9)     5.1 (2.3)     Yes-12     58.5     45.3       wordtink     75 mg db     52     33.5 (-)     82.7     81 (6.5)     77,692.231     11.2 (5.9)     5.4 (2.9)     Yes-12     58.5     45.3       acebo     Pacebo     10     36 (11.3)     50     11.1 (6.8)     0,40,60     -     2 (1)     Yes-12     58.1     17.8     28.3     -	wordinity     45 mg QD     52     35 (-)     75     112 (11.5)     7.7, 69.2.231     129 (12.3)     22 (4.1)     51 (2.3)     13 (7.6)     Yes-6.12     48.1     44.2       wordinity     75 mg QD     53     36 (-)     73.6     12.1 (1.6)     7.5, 69.8, 22.6     10.6 (7.2)     16 (2.9)     55 (2.7)     12.1 (7.3)     Yes-12     58.5     45.3       wordinity     75 mg QD     52     33.5 (-)     82.1 (8.5)     7.7, 69.3, 23.3     11.2 (15.9)     56.6 (1.3)     56.4 (1.3)     Yes-12     76.9     75.8     45.3       wordinity     70mg QD     9     42.8 (13.8)     44.4     12.3 (6.5)     7.7, 69.2 (2.3)     12.1 (1.5)     76.9     76.9     76.9     76.9     76.9     76.9     76.9     76.9     76.9     77.8     26.3     76.9     76.9     76.9     77.8     76.9     76.9     76.9     76.9     76.9     76.9     76.9     76.9     76.9     76.9     76.9     76.9     76.9     76.9     76.9     77.8     76.3     76.9 <td>concluitub     45mg CD     52     35()     75     112 (11.5)     77,692,231     123 (12.3)     13 (7.6)     Wee,112     481     442       concluitub     75 mg CD     53     38()     736     12.1 (9.7)     7.5,693,226     10.6 (7.2)     16 (2.9)     53.2 (2.7)     12.1 (7.3)     Wee,12     685     45.3       concluitub     75 mg CD     52     33.6 ()     82.1 (9.7)     7.5,693,226     10.6 (7.2)     16.6 (2.9)     53.4 (2.9)     Yee-12     685     45.3       abolitur     100 mg CD     9     42.8 (13.8)     44     12.3 (6.7)     0.6 (6.6, 33.3)     11.2 (5.9)     24.4 (2.9)     54.4 (2.9)     Yee-12     30.8     26.8       abolitur     100 mg CD     10     36 (11.3)     50     11.1 (6.8)     0.40, 60     -     21.9     Yee-12     30.8     26.8     33.8       abolitur     16     36.1 (1.3)     50     11.1 (6.8)     0.40, 60     -     21.7 (7.9)     Yee-12     30.8     33.8       abolitur     30.0 mg CD     5<!--</td--><td>Sourcitinib     45 mg QD     52     35 (-)     75     11.2 (11.5)     7       Suorcitinib     75 mg QD     53     38 (-)     73.6     12.1 (9.7)     7       Suorcitinib     75 mg QD     53     38 (-)     73.6     12.1 (9.7)     7       acebo     Placebo     52     33.5 (-)     82.7     8.1 (6.5)     7       acebo     Placebo     52     33.5 (-)     82.7     8.1 (6.5)     7       nakinra     100 mg QD     9     42.8 (13.8)     44.4     12.3 (6.7)     1       acebo     Placebo     10     36 (11.3)     50     11.1 (6.8)     1       acebo     15     35.7 (13)     80     21.6 (13)     1     1       acebo     Placebo     5     33.4 (8.2)     100     16 (7.1)     1</td><td>5.8, 71.2, 23.1</td><td>11.8 (7.1)</td><td>2.4 (4.4)</td><td>4.6 (2.4)</td><td>11.2 (7.1)</td><td>No</td><td>42.3</td><td>48.1</td></td>	concluitub     45mg CD     52     35()     75     112 (11.5)     77,692,231     123 (12.3)     13 (7.6)     Wee,112     481     442       concluitub     75 mg CD     53     38()     736     12.1 (9.7)     7.5,693,226     10.6 (7.2)     16 (2.9)     53.2 (2.7)     12.1 (7.3)     Wee,12     685     45.3       concluitub     75 mg CD     52     33.6 ()     82.1 (9.7)     7.5,693,226     10.6 (7.2)     16.6 (2.9)     53.4 (2.9)     Yee-12     685     45.3       abolitur     100 mg CD     9     42.8 (13.8)     44     12.3 (6.7)     0.6 (6.6, 33.3)     11.2 (5.9)     24.4 (2.9)     54.4 (2.9)     Yee-12     30.8     26.8       abolitur     100 mg CD     10     36 (11.3)     50     11.1 (6.8)     0.40, 60     -     21.9     Yee-12     30.8     26.8     33.8       abolitur     16     36.1 (1.3)     50     11.1 (6.8)     0.40, 60     -     21.7 (7.9)     Yee-12     30.8     33.8       abolitur     30.0 mg CD     5 </td <td>Sourcitinib     45 mg QD     52     35 (-)     75     11.2 (11.5)     7       Suorcitinib     75 mg QD     53     38 (-)     73.6     12.1 (9.7)     7       Suorcitinib     75 mg QD     53     38 (-)     73.6     12.1 (9.7)     7       acebo     Placebo     52     33.5 (-)     82.7     8.1 (6.5)     7       acebo     Placebo     52     33.5 (-)     82.7     8.1 (6.5)     7       nakinra     100 mg QD     9     42.8 (13.8)     44.4     12.3 (6.7)     1       acebo     Placebo     10     36 (11.3)     50     11.1 (6.8)     1       acebo     15     35.7 (13)     80     21.6 (13)     1     1       acebo     Placebo     5     33.4 (8.2)     100     16 (7.1)     1</td> <td>5.8, 71.2, 23.1</td> <td>11.8 (7.1)</td> <td>2.4 (4.4)</td> <td>4.6 (2.4)</td> <td>11.2 (7.1)</td> <td>No</td> <td>42.3</td> <td>48.1</td>	Sourcitinib     45 mg QD     52     35 (-)     75     11.2 (11.5)     7       Suorcitinib     75 mg QD     53     38 (-)     73.6     12.1 (9.7)     7       Suorcitinib     75 mg QD     53     38 (-)     73.6     12.1 (9.7)     7       acebo     Placebo     52     33.5 (-)     82.7     8.1 (6.5)     7       acebo     Placebo     52     33.5 (-)     82.7     8.1 (6.5)     7       nakinra     100 mg QD     9     42.8 (13.8)     44.4     12.3 (6.7)     1       acebo     Placebo     10     36 (11.3)     50     11.1 (6.8)     1       acebo     15     35.7 (13)     80     21.6 (13)     1     1       acebo     Placebo     5     33.4 (8.2)     100     16 (7.1)     1	5.8, 71.2, 23.1	11.8 (7.1)	2.4 (4.4)	4.6 (2.4)	11.2 (7.1)	No	42.3	48.1
vorcititity     75mg 0D     53     38(-)     736     12.1 (9.7)     7.5, 63.8, 22.6     10.6 (7.2)     1.6 (2.9)     5.2 (2.7)     12.1 (7.3)     Ves-12     58.5     45.3       accotititity     Pacebo     52     33.5 (-)     82.7     81 (6.5)     7.7, 69.2.23.1     11.2 (5.9)     2.4 (4)     5.4 (2.8)     12.7 (7.3)     Ves-12     30.8     28.8       nakina     100 mg 0D     9     42.8 (13.8)     44.4     12.3 (6.7)     0, 66.6, 33.3     -     3 (1)     5.4 (2.9)     No <sup>-1</sup> 30.8     28.8       akina     100 mg 0D     9     42.8 (13.8)     44.4     12.3 (6.7)     0, 66.6, 33.3     -     3 (1)     No <sup>-1</sup> 2 (2)     No <sup>-1</sup> 2 (7, 6)     20.8     23.8       akina     100 mg 0D     9     42.8 (13.8)     44.4     12.3 (6.7)     0, 66.6, 33.3     -     2 (1)     0     0     2 (1, 7)     1 (2, 7)     1 (2)     1 (2)     2 (2)     2 (2)     2 (2)     2 (2)     2 (2)     2 (2)     2 (2)     2 (2)     2 (2)	outocitituity     75 mg QD     53     38 (-)     736     12.1 (-)     52 (-)     12.1 (-)     18-12     58.5     45.3       lateboo     Placeboo     52     33.5 (-)     82.1 (-)     82.1 (-)     7.5, 69.8, 25.3 1     11.2 (-)     54 (-)     12.1 (-)     Yes-12     30.8     28.8       nakina     100 mg QD     9     42.8 (13.8)     84.1     0.5 (6.6, 33.3)     -     2 (-)     12.4 (-)     Yes-12     30.8     28.8       nakina     100 mg QD     9     42.8 (13.8)     84.1     0.5 (6.6, 33.3)     -     2 (-)     12.4 (-)     77.8°     77.8°     2     35.7       nakina     100 mg DD     10     36 (11.3)     50     0.40, 60     -     2 (-)     14.6 (-)     Yes 7     14.8 (-)     77.8°     5     35.3       nakina     30 mg BD     15     35.7 (13)     80     216.7 (-)     14.6 (-)     Yes 7     14.6 (-)     77.8°     5     35.3       nakina     30 mg BD     15     35.7 (13)     81.2 (-) <td>outor (till)     75 mg QD     53     38 (1)     73 (5     13.1 (3.7)     75. (5.9.3, 2.2)     10.6 (7.2)     10.2 (7.3)     Ves-12     53.5     45.3       lacebo     52     33.5 (1)     82.7     81.1 (6.5)     7.7, 69.2, 23.1     11.2 (5.9)     2.4 (4)     5.4 (2.9)     Ves-12     30.8     28.8       nakina     100 mg QD     9     42.8 (13.8)     84.1     12.3 (6.7)     0.66.6, 33.3     -     2 (1)     Nes-12     30.8     28.8       nakina     100 mg QD     9     42.8 (13.8)     81.1 (1.6.8)     0, 40, 60     -     2 (1)     86.5 (21.7)<sup>6</sup>     14.3 (8.4)     Nes-12     30.8     28.3       nakina     30 mg BD     15     35.7 (13)     80     11.1 (6.8)     0, 40, 60     -     2 (1)     86.5 (21.7)<sup>6</sup>     14.3 (8.4)     Ne     77.8<sup>9</sup>     53.3     53.3     53.3     53.3     53.3     53.3     53.3     53.3     53.3     53.3     53.3     53.3     53.3     53.3     53.3     53.3     53.3     53.3     53.3<td>ovorcitinib     75 mg QD     53     38 (-)     73.6     12.1 (9.7)     7       lacebo     Placebo     52     33.5 (-)     82.7     8.1 (6.5)     7       nakinra     100 mg QD     9     42.8 (13.8)     44.4     12.3 (6.7)     7       nakinra     100 mg QD     9     42.8 (13.8)     44.4     12.3 (6.7)     7       lacebo     Placebo     10     36 (11.3)     50     11.1 (6.8)     7       premilast     30 mg BID     15     35.7 (13)     80     21.6 (13)     1       lacebo     Placebo     5     33.4 (8.2)     100     16 (7.1)     1       intekizumab     320 mg Q2W     289     -     -     -     -     -</td><td>7.7, 69.2, 23.1</td><td>12.9 (12.3)</td><td>2.2 (4)</td><td>5.1 (2.3)</td><td>13 (7.6)</td><td>Yes-6,12</td><td>48.1</td><td>44.2</td></td>	outor (till)     75 mg QD     53     38 (1)     73 (5     13.1 (3.7)     75. (5.9.3, 2.2)     10.6 (7.2)     10.2 (7.3)     Ves-12     53.5     45.3       lacebo     52     33.5 (1)     82.7     81.1 (6.5)     7.7, 69.2, 23.1     11.2 (5.9)     2.4 (4)     5.4 (2.9)     Ves-12     30.8     28.8       nakina     100 mg QD     9     42.8 (13.8)     84.1     12.3 (6.7)     0.66.6, 33.3     -     2 (1)     Nes-12     30.8     28.8       nakina     100 mg QD     9     42.8 (13.8)     81.1 (1.6.8)     0, 40, 60     -     2 (1)     86.5 (21.7) <sup>6</sup> 14.3 (8.4)     Nes-12     30.8     28.3       nakina     30 mg BD     15     35.7 (13)     80     11.1 (6.8)     0, 40, 60     -     2 (1)     86.5 (21.7) <sup>6</sup> 14.3 (8.4)     Ne     77.8 <sup>9</sup> 53.3     53.3     53.3     53.3     53.3     53.3     53.3     53.3     53.3     53.3     53.3     53.3     53.3     53.3     53.3     53.3     53.3     53.3     53.3 <td>ovorcitinib     75 mg QD     53     38 (-)     73.6     12.1 (9.7)     7       lacebo     Placebo     52     33.5 (-)     82.7     8.1 (6.5)     7       nakinra     100 mg QD     9     42.8 (13.8)     44.4     12.3 (6.7)     7       nakinra     100 mg QD     9     42.8 (13.8)     44.4     12.3 (6.7)     7       lacebo     Placebo     10     36 (11.3)     50     11.1 (6.8)     7       premilast     30 mg BID     15     35.7 (13)     80     21.6 (13)     1       lacebo     Placebo     5     33.4 (8.2)     100     16 (7.1)     1       intekizumab     320 mg Q2W     289     -     -     -     -     -</td> <td>7.7, 69.2, 23.1</td> <td>12.9 (12.3)</td> <td>2.2 (4)</td> <td>5.1 (2.3)</td> <td>13 (7.6)</td> <td>Yes-6,12</td> <td>48.1</td> <td>44.2</td>	ovorcitinib     75 mg QD     53     38 (-)     73.6     12.1 (9.7)     7       lacebo     Placebo     52     33.5 (-)     82.7     8.1 (6.5)     7       nakinra     100 mg QD     9     42.8 (13.8)     44.4     12.3 (6.7)     7       nakinra     100 mg QD     9     42.8 (13.8)     44.4     12.3 (6.7)     7       lacebo     Placebo     10     36 (11.3)     50     11.1 (6.8)     7       premilast     30 mg BID     15     35.7 (13)     80     21.6 (13)     1       lacebo     Placebo     5     33.4 (8.2)     100     16 (7.1)     1       intekizumab     320 mg Q2W     289     -     -     -     -     -	7.7, 69.2, 23.1	12.9 (12.3)	2.2 (4)	5.1 (2.3)	13 (7.6)	Yes-6,12	48.1	44.2
lacebo     Flacebo     52     33.5 (-)     82.7     81 (6.5)     7.7, 69.2, 23.1     11.2 (5.9)     2.4 (4)     5.4 (2.8)     12.7 (7.3)     Yes-12     30.8     28.8       nakirat     100 mg 0D     9     42.8 (13.8)     44.4     12.3 (6.7)     0, 66.6, 33.3     -     3 (-)     54.4 (2.9)     20.7 (5.9)     No     77.8°     -       lacebo     Placebo     10     36 (11.3)     50     11.1 (6.8)     0, 40, 60     -     2 (-)     60.5 (21.7)°     14.3 (8.4)     No     77.8°     -       premiast     30 mg BID     15     35.7 (13)     80     21.6 (13)     -     2 (-)     6.4 (2.4)     14.6 (7.6)     Yes-2     53.3     53.3       acebo     Placebo     5     33.4 (8.2)     100     16 (7.1)     -     5.8 (2.4)     -     5.8 (2.3)     53.3     53.3     53.3     53.3       acebo     Placebo     7     2     5.8 (2.4)     -     5.8 (2.2)     11.8 (5.9)     Yes-2     0     0     0     0<	lacebo     Pacebo     52     33.5 (-)     82.1     81.16.5)     7.7, 69.2, 2.3.1     11.2 (5.9)     2.4 (4)     5.4 (2.8)     12.7 (7.3)     Yes-12     30.8     28.8       nakina     100mg 0D     9     42.8 (13.8)     44.4     12.3 (6.7)     0, 66.6, 33.3     -     3 (-)     54.4 (2.9)     No     77.8'     -	lacebo     Pacebo     2     33.5 (1)     82.1     81.1 (6.5)     7.7, 69.2, 23.1     11.2 (5.9)     24.4 (2.9)     12.7 (7.3)     Vest 12     30.9     28.8       nakina     100 mg 0D     9     42.8 (13.3)     44.4     12.3 (6.7)     0, 66.6, 33.3     -     3 (1)     54.4 (2.9)     70.7 (5.9)     No     77.8°     -     -       lacebo     Pacebo     10     36 (11.3)     50     11.1 (6.8)     0, 40, 60     -     2 (1)     64.4 (2.9)     10.7 (5.9)     No     77.8°     - <t< td=""><td>lacebo     Placebo     52     33.5 (-)     82.7     8.1 (6.5)     7.       nakinra     100 mg QD     9     42.8 (13.8)     44.4     12.3 (6.7)     (1111)       lacebo     Placebo     10     36 (11.3)     50     11.1 (6.8)     (1111)       premilast     30 mg BID     15     35.7 (13)     80     21.6 (13)     (1111)       lacebo     Placebo     5     33.4 (8.2)     100     16 (7.1)     (1111)       lacebo     Placebo     5     33.4 (8.2)     100     16 (7.1)     (111)</td><td>7.5, 69.8, 22.6</td><td>10.6 (7.2)</td><td>1.6 (2.9)</td><td>5.2 (2.7)</td><td>12.1 (7.3)</td><td>Yes-12</td><td>58.5</td><td>45.3</td></t<>	lacebo     Placebo     52     33.5 (-)     82.7     8.1 (6.5)     7.       nakinra     100 mg QD     9     42.8 (13.8)     44.4     12.3 (6.7)     (1111)       lacebo     Placebo     10     36 (11.3)     50     11.1 (6.8)     (1111)       premilast     30 mg BID     15     35.7 (13)     80     21.6 (13)     (1111)       lacebo     Placebo     5     33.4 (8.2)     100     16 (7.1)     (1111)       lacebo     Placebo     5     33.4 (8.2)     100     16 (7.1)     (111)	7.5, 69.8, 22.6	10.6 (7.2)	1.6 (2.9)	5.2 (2.7)	12.1 (7.3)	Yes-12	58.5	45.3
ankiration     100mg QD     9     42.8 (13.8)     44.4     12.3 (6.7)     0, 66.6, 33.3     -     3 (-)     54.4 (22.9) <sup>c</sup> 20.7 (5.9)     No     77.8 <sup>o</sup> -       Iacebo     Placebo     10     36 (11.3)     50     11.1 (6.8)     0, 40, 60     -     2 (-)     60.5 (21.7) <sup>c</sup> 14.6 (7.6)     Yes-2     53.3     53.3       premiast     30mg BID     15     35.7 (13)     80     21.6 (13)     -     6.1 (1.7)     -     6.4 (2.4)     14.6 (7.6)     Yes-2     53.3     53.3       nemiast     30mg BID     15     33.4 (8.2)     100     16 (7.1)     -     6.4 (2.4)     14.6 (7.6)     Yes-2     53.3     53.3       facebo     Placebo     7     33.4 (8.2)     100     16 (7.1)     -     5.8 (2.2)     11.8 (5.9)     Yes-2     0     0     0     7.6     45.3       inekizumab     320mg Q2W     74     -     5.8 (2.4)     -     5.8 (2.2)     11.8 (5.9)     Yes-2     0     0     0     74.5	Indicational     100 mg 00     9     42.8 (13.8)     44.4     12.3 (6.7)     0, 66.6, 33.3     5     11.1 (6.8)     0, 66.6, 33.3     5     11.1 (6.8)     0, 40, 60     5     44.2 (2.9)     No     77.8 <sup>o</sup> 77.8 <sup>o</sup> 5       Incerbo     10     36 (11.3)     50     11.1 (6.8)     0, 40, 60     -     2 (7)     60.5 (21.7) <sup>o</sup> 14.6 (7.6)     No     77.8 <sup>o</sup> -     -	Indicational     100 mg QD     9     42.8 (1.3.8)     44.4     12.3 (6.7)     0, 66.6, 33.3     -     3(1)     54.4 (2.5.9)     No     77.8 <sup>1</sup> -       Incerbo     10     36 (11.3)     50     11.1 (6.8)     0, 40.60     -     2 (.)     60.5 (21.7) <sup>o</sup> 14.3 (6.4)     No     77.8 <sup>1</sup> -       Interbinant     30 mg BD     15     35.7 (13)     80     21.6 (13)     -     5 (1.1.7)     14.6 (7.6)     No     70     30     -     -       Interbinant     30 mg BD     15     35.7 (13)     80     21.6 (13)     -     5 (2.4)     14.6 (7.6)     No     70     30     0	inakima     100 mg QD     9     42.8 (13.8)     44.4     12.3 (6.7)     (11,1)       lacebo     Placebo     10     36 (11.3)     50     11.1 (6.8)       premilast     30 mg BID     15     35.7 (13)     80     21.6 (13)       lacebo     Placebo     5     33.4 (8.2)     100     16 (7.1)       imekizumab     320 mg 02W     289     -     -     -	7.7, 69.2, 23.1	11.2 (5.9)	2.4 (4)	5.4 (2.8)	12.7 (7.3)	Yes-12	30.8	28.8
Iacebo     Placebo     10     36 (11.3)     50     11.1 (6.8)     0, 40, 60     -     2 (-)     60.5 (21.7) <sup>c</sup> 14.3 (8.4)     No     30     -     30.3     53.3     <	Include     Include <t< td=""><td>lacebo     Placebo     10     36 (11.3)     50     11.1 (6.3)     0, 40, 60     -     2 (+)     60.5 (21.7)<sup>c</sup>     14.3 (8.4)     No     30     33.3 (8.4)     No     30     33.3 (8.4)     No     30.3 (8.2)     53.3 (8.3)     53</td><td>lacebo Placebo 10 36 (11.3) 50 11.1 (6.8) premilast 30 mg BID 15 35.7 (13) 80 21.6 (13) lacebo Placebo 5 33.4 (8.2) 100 16 (7.1) imekizumab 320 mg Q2W 289</td><td>0, 66.6, 33.3</td><td>ı</td><td>3 (-)</td><td>54.4 (22.9)°</td><td>20.7 (5.9)</td><td>No</td><td>77.8<sup>b</sup></td><td>ı</td></t<>	lacebo     Placebo     10     36 (11.3)     50     11.1 (6.3)     0, 40, 60     -     2 (+)     60.5 (21.7) <sup>c</sup> 14.3 (8.4)     No     30     33.3 (8.4)     No     30     33.3 (8.4)     No     30.3 (8.2)     53.3 (8.3)     53	lacebo Placebo 10 36 (11.3) 50 11.1 (6.8) premilast 30 mg BID 15 35.7 (13) 80 21.6 (13) lacebo Placebo 5 33.4 (8.2) 100 16 (7.1) imekizumab 320 mg Q2W 289	0, 66.6, 33.3	ı	3 (-)	54.4 (22.9)°	20.7 (5.9)	No	77.8 <sup>b</sup>	ı
premilast     30 mg BlD     15     35.7 (13)     80     21.6 (13)     -     6.1 (1.7)     -     6.4 (2.4)     14.6 (7.6)     Yes-2     53.3     53.3     53.3       lacebo     Placebo     5     33.4 (8.2)     100     16 (7.1)     -     5.8 (2.2)     11.8 (5.9)     Yes-2     5.3.3     53.3     53.3       inekizumab     320 mg Q2W     289     -     5.8 (2.4)     -     5.8 (2.2)     11.8 (5.9)     Yes-2     0     0     0       inekizumab     320 mg Q2W     289     -     -     5.8 (2.2)     11.8 (5.9)     Yes-2     0	premilast     30 mg BlD     15     35.7 (13)     80     21.6 (13)     -     6.1 (1.7)     -     6.4 (2.4)     14.6 (7.6)     Yes-2     53.3     53.3     53.3       acebo     Placebo     5     33.4 (8.2)     100     16 (7.1)     -     5.8 (2.4)     -     5.8 (2.2)     11.8 (5.9)     Yes-2     0     0       innekizumab     320 mg Q2W     289     -     -     5.8 (2.4)     -     5.8 (2.2)     11.8 (5.9)     Yes-2     0     0     0       innekizumab     320 mg Q2W     289     -     -     -     5.8 (2.4)     -     5.8 (2.2)     11.8 (5.9)     Yes-2     0     0     0       innekizumab     320 mg Q2W     289     -     -     -     -     47.8 <sup>1</sup> innekizumab     320 mg Q2W     281     -     -     -     -     47.8 <sup>1</sup> innekizumab     320 mg Q2W     281     -     -     -     -     -     -     -     -     -     -	premilast     30 mg Bl0     15     35.7 (13)     80     21.6 (13)     6     6.1 (1.7)     6     6.4 (2.4)     14.6 (7.6)     Yes-2     5.3.3     5.3.3     5.3.3       lacebo     Placebo     5     33.4 (8.2)     100     16 (7.1)     -     5.8 (2.4)     -     5.8 (2.2)     11.8 (5.9)     Yes-2     0     0     0       innekizumab     320 mg Q2W     72     -     -     5.8 (2.4)     -     5.8 (2.2)     11.8 (5.9)     Yes-2     0     0     0     0       innekizumab     320 mg Q2W     72     -     -     -     5.8 (2.4)     -     -     -     47.8%       innekizumab     320 mg Q2W     72     - </td <td>premilast 30 mg BID 15 35.7 (13) 80 21.6 (13) lacebo Placebo 5 33.4 (8.2) 100 16 (7.1) imekizumab 320 mg Q2W 289</td> <td>0, 40, 60</td> <td>I</td> <td>2 (-)</td> <td>60.5 (21.7)°</td> <td>14.3 (8.4)</td> <td>No</td> <td>30</td> <td>ı</td>	premilast 30 mg BID 15 35.7 (13) 80 21.6 (13) lacebo Placebo 5 33.4 (8.2) 100 16 (7.1) imekizumab 320 mg Q2W 289	0, 40, 60	I	2 (-)	60.5 (21.7)°	14.3 (8.4)	No	30	ı
lacebo     Placebo     5     33.4 (8.2)     100     16 (7.1)     -     5.8 (2.4)     -     5.8 (2.2)     11.8 (5.9)     Yes-2     0     0       innekizumab     320 mg Q2W     289     -     -     -     -     47.8 <sup>b</sup> innekizumab     320 mg Q2W     289     -     -     -     -     47.8 <sup>b</sup> innekizumab     320 mg Q4W     144     -     -     -     -     45.3       innekizumab     320 mg Q4W     144     -     -     -     -     -     45.3       innekizumab     320 mg Q2W     291     -     -     -     -     28.7       innekizumab     320 mg Q2W     291     -     -     -     -     28.7       innekizumab     320 mg Q2W     74     -     -     -     -     -     55.8 <sup>o</sup> innekizumab     320 mg Q4W     144     -     -     -     -     55.8 <sup>o</sup> innekizumab     320 mg Q4W     -	Iacebo     Flacebo     5     33.4 (8.2)     100     16 (7.1)     5     5.8 (2.4)     5     5.8 (2.2)     11.8 (5.9)     Yes-2     0     0       innekizumab     320 mg Q2W     899     -     -     -     5.8 (2.2)     11.8 (5.9)     Yes-2     0     0     0       innekizumab     320 mg Q2W     72     -     -     -     -     -     45.3       innekizumab     320 mg Q2W     72     -     -     -     -     -     -     45.3       innekizumab     320 mg Q2W     74     -     -     -     -     -     -     45.3       innekizumab     320 mg Q2W     74     -	Including     Flacebo     5     33.4 (8.2)     100     16 (7.1)     5     5.8 (2.4)     5.8 (2.2)     11.8 (5.9)     Ves-2     0     0     0       innekizumab     320 mg Q4W     144     -     -     -     -     -     -     47.8 <sup>b</sup> innekizumab     320 mg Q4W     144     -     -     -     -     -     47.8 <sup>b</sup> innekizumab     320 mg Q4W     144     -     -     -     -     -     45.3       Incebo     72     -     -     -     -     -     -     -     -     45.3       Incebo     72     -<	lacebo Placebo 5 33.4 (8.2) 100 16 (7.1) imekizumab 320 mg Q2W 289		6.1 (1.7)	ı	6.4 (2.4)	14.6 (7.6)	Yes-2	53.3	53.3
imekizumab   320 mg Q2W   289   -   -   -   47.8 <sup>1</sup> inekizumab   320 mg Q4W   144   -   -   -   45.3     lacebo   Placebo   72   -   -   -   -   45.3     lacebo   Placebo   72   -   -   -   -   -   45.3     imekizumab   320 mg Q2W   72   -   -   -   -   28.7     imekizumab   320 mg Q2W   72   -   -   -   -   28.7     imekizumab   320 mg Q2W   74   -   -   -   -   52°     inekizumab   320 mg Q2W   74   -   -   -   -   52°     lacebo   74   -   -   -   -   -   53.8°     lacebo   74   -   -   -   -   -   -   32.2     lacebo   74   -   -   -   -   -   -   -   32.2     lacebo   74   -   -   -	imekizumab     320 mg Q2W     144     -     -     -     47.8°       imekizumab     320 mg Q4W     144     -     -     -     46.3       acebo     72     -     -     -     -     -     45.3       acebo     72     -     -     -     -     -     -     45.3       imekizumab     320 mg Q2W     74     -     -     -     -     -     45.3       imekizumab     320 mg Q2W     74     -	Intekizumab     320 mg Q4W     144     -     -     47.8°       intekizumab     320 mg Q4W     144     -     -     -     47.8°       intekizumab     320 mg Q4W     144     -     -     -     47.8°       intekizumab     320 mg Q4W     144     -     -     -     45.3       intekizumab     320 mg Q4W     144     -     -     -     -     45.3       intekizumab     320 mg Q2W     291     -     -     -     -     -     28.7       intekizumab     320 mg Q2W     144     -     -     -     -     -     28.7       intekizumab     320 mg Q4W     144     -     -     -     -     -     28.7       intekizumab     320 mg Q4W     144     -     -     -     -     -     57.8       intekizumab     320 mg Q4W     144     -     -     -     -     -     57.8       intekizumab     142.6     - <td< td=""><td>imekizumab 320 mg Q2W 289</td><td></td><td>5.8 (2.4)</td><td>ı</td><td>5.8 (2.2)</td><td>11.8 (5.9)</td><td>Yes-2</td><td>0</td><td>0</td></td<>	imekizumab 320 mg Q2W 289		5.8 (2.4)	ı	5.8 (2.2)	11.8 (5.9)	Yes-2	0	0
Imekizumab 320 mg 04W 144 - - - 45.3   Iacebo 72 - - - - - 45.3   Iacebo 72 - - - - - 28.7   Intekizumab 320 mg 02W 291 - - - 28.7   Imekizumab 320 mg 02W 291 - - - 52 <sup>b</sup> Imekizumab 320 mg 04W 144 - - 53.8 <sup>b</sup> Iacebo 74 - - - - 53.8 <sup>b</sup> Iacebo 74 - - - - - 32.2	imekizumab   320 mg d4W   144   -   -   -   45.3     lacebo   72   -   -   -   -   45.3     lacebo   72   -   -   -   -   45.3     imekizumab   320 mg 02W   291   -   -   -   28.7     imekizumab   320 mg 02W   291   -   -   -   -   52 <sup>b</sup> imekizumab   320 mg 04W   144   -   -   -   -   -   53.8 <sup>b</sup> lacebo   74   -   -   -   -   -   -   -   53.8 <sup>b</sup> lacebo   74   -   -   -   -   -   -   53.8 <sup>b</sup> lacebo   74   -   -   -   -   -   -   53.8 <sup>b</sup> lacebo   74   -   -   -   -   -   -   53.8 <sup>b</sup> lacebo   74   -   -   -   -   -   -   -   -   -   -   53.8 <sup>b</sup> -   -   -<	Imekizumab   320 mg daw   144   -   -   -   -   45.3     lacebo   72   -   -   -   -   -   -   45.3     lacebo   72   -   -   -   -   -   -   -   45.3     imekizumab   320 mg QaW   74   -	minimit 220 mag 200 mag	ı		I			Nod		47.8 <sup>b</sup>
acebo Placebo 72 28.7 mekizumab 320mg Q2W 291 5 55 <sup>b</sup> mekizumab 320mg Q4W 144 5 53.8 <sup>b</sup> acebo Placebo 74 80 <sup>d</sup> - 53.8 <sup>b</sup>	acebo     Placebo     72     -     -     -     28.7       mekizumab     320 mg Q2W     291     -     -     -     28.7       mekizumab     320 mg Q2W     291     -     -     -     52 <sup>b</sup> mekizumab     320 mg Q4W     144     -     -     -     53.8 <sup>b</sup> acebo     Placebo     74     -     -     -     -     53.8 <sup>b</sup> acebo     Placebo     74     -     -     -     -     -     53.8 <sup>b</sup> acebo     Placebo     74     -     -     -     -     -     -     53.8 <sup>b</sup> acebo     74     -<	acebo     Placebo     72     -     -     -     -     28.7       imekizumab     320 mg Q2W     291     -     -     -     -     0d     -     52 <sup>b</sup> imekizumab     320 mg Q2W     291     -     -     -     -     No <sup>d</sup> -     52 <sup>b</sup> imekizumab     320 mg Q4W     144     -     -     -     -     No <sup>d</sup> -     52 <sup>b</sup> acebo     74     -     -     -     -     -     No <sup>d</sup> -     52 <sup>b</sup> acebo     74     -     -     -     -     -     -     53.8 <sup>b</sup> acebo     74     -     -     -     -     -     -     53.8 <sup>b</sup> acebo     74     -     -     -     -     -     -     -     53.8 <sup>b</sup> acebo     74     -     -     -     -     -     -     -     -     -     -     -     -     -		ı	ı		,	ı	Nod	·	45.3
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Fig. 1. Inclusion/exclusion algorithm. HiSCR, Hidradenitis Suppurativa Clinical Response; RCT, randomized control trial.

We have observed that in some HS studies, there is an unexpected declining efficacy between the penultimate visit and the prespecified primary endpoint week. For example, adalimumab's phase 2 study used a primary endpoint of 16 weeks, but both study drug arms demonstrated a higher HiSCR response at week 12.<sup>2</sup> Subsequently, adalimumab's phase 3 study used a primary endpoint week of 12 with maximum HiSCR response at week 12.<sup>3</sup> In this study, we established how often nonlinear improvement occurs in HS programs and explored possible trial design and data analysis implications.

#### Methods

A retrospective review of randomized control trials (RCTs) and open-label studies of systemic, nonantibiotic medications for HS on ClinicalTrials.gov as of March 27, 2023, was performed. Study results were obtained from ClinicalTrials.gov and augmented with press releases and dermatology conference presentations. Inclusion criteria included the employment of HiSCR as an outcome measure and the availability of HiSCR data at the primary endpoint week and at least one additional time point prior to the primary endpoint week. Studies were excluded if they included conditions other than HS, had a primary endpoint week before 12 weeks, did not investigate a systemic medication, or were not an RCT or open-label study.

Data collected included baseline patient characteristics, HiSCR response rates, dermatology life quality index (DLQI) scores, HS pain, and the International HS severity score system (IHS4). In RCT studies, study drug arms were considered "successful" if the HiSCR response at the primary endpoint week was significant compared with placebo or "failed" if found nonsignificant. The maximum value for each outcome measure was assessed through week 16 by comparing values reported in tables or text, if available, or peak graphical points. A "wobble" was defined as outcome measure efficacy that peaked prior to the primary endpoint week.

The proportions of study drug arms that displayed a wobble were compared using Fisher exact test in RStudio (2022.07.01, Boston, Massachusetts). Significance was set to a

P < .05. Means, weighted based on sample size, were calculated for baseline characteristics, Hurley stage, AN count, total DF count, pain scores, DLQI scores, and proportion of females, in study drug arms and compared between groups with HiSCR wobble and no HiSCR wobble using a Mann–Whitney *U* test in Microsoft Excel 2016 (16.0.5378.1000). Study arms that reported HiSCR response data beyond the primary endpoint were also assessed for the timing of maximum response. The proportion of study drug arms that displayed a wobble in quality of life (QoL) measures (DLQI and pain scores) and IHS4 was also assessed.

## Results

A total of 21 studies (RCT, n = 14; open-label, n = 7), with 35 study drug arms (RCT, n = 27; open-label, n = 8) and 14 placebo arms, were included (Table 1; Fig. 1).<sup>2–19</sup> Among RCTs, 9 studies (21 study drug arms, 9 placebo arms) designated the primary endpoint at week 16, and 5 studies (6 study drug arms, 5 placebo arms) designated at week 12 (Table 1). Significance tests/designation as success or failure was not performed for the adalimumab arm in Glatt et al., since it was used as a comparator arm and not designed for statistical testing. In total, 14 study drug arms were considered successful and 12 failed.

HiSCR wobble occurred significantly more often in RCTs compared with open-label study drug arms (11/27 [40.7%] vs 0/8 [0%], respectively, P = .0292) (Table 2). Within RCTs, HiSCR wobble occurred significantly more often in study drug arms with sample sizes of less than 50 patients than in those with more than 50 patients (8/12 [66.7%] vs 3/15 [20%], respectively, P = .022). Among RCTs, HiSCR wobble occurred numerically more often in failed versus successful study drug arms (7/12 [58.3%] vs 4/14 [28.6%], respectively, P = .2329) and in those with a primary endpoint week of 16 versus 12 (10/21 [47.6%] vs 1/6 [16.7%], respectively, P = .3497). HiSCR wobble also occurred in 5 (35.7%) of the placebo arms (Table 2).

Baseline DF counts were significantly lower in study drug arms with HiSCR wobble (2.3 vs 3.2, u = 1, P < .05). Study drug

Table	2			
Wobble	breakdown	based	on	HiSCR

	Wobble	No wobble	<i>P</i> value/ <i>u</i> value
Open-label (n = 8), n (%)	0 (0)	8 (100)	.0292ª
RCT			
Placebo arms (n = 14), n (%)	5 (35.7)	9 (64.3)	
Study drug arms (n = $27)^{b}$ , n (%)	11 (40.7)	13 (48.1)	
Successful (n = 14), n (%)	4 (28.6)	10 (71.4)	.2329
Failed (n = 12), n (%)	7 (58.3)	5 (41.7)	
Primary endpoint week 12 ( $n = 6$ ), n (%)	1 (16.7)	5 (83.3)	.3497
Primary endpoint week 16 ( $n = 21$ ), n (%)	10 (47.6)	11 (52.4)	
Sample size >50 (n = 15), n (%)	3 (20)	12 (80)	.022
Sample size $<50$ (n = 12), n (%)	8 (66.7)	4 (33.3)	
Baseline characteristics <sup>c</sup>			
Hurley 1/2, mean %	66.8	57.7	14.5
Hurley 3, mean %	33.2	42.5	13.5
AN count, mean	12.1	12.6	26.5
DF count, mean	2.3	3.2	<b>1</b> <sup>d</sup>
Pain score, mean	4.7	5	18.5
DLQI score, mean	12.5	14.5	7
Female, mean %	63.9	58.3	31

AN, total abscess and nodule count; DF, draining fistula; DLQI, dermatology life quality index; HiSCR, Hidradenitis Suppurativa Clinical Response; RCT, randomized control trial. <sup>a</sup>Open-label compared to RCT study drug arms.

<sup>b</sup>Total number of study drug arms is one greater than successful and failed trials because Glatt et al. contained an extra study drug arm that served as a comparator and no statistics were run for significance compared to the placebo arm.

<sup>c</sup>Not all study drug arms reported baseline characteristics. For those that displayed a wobble: 6/11 supplied Hurley stage breakdown, 7/11 AN count, 3/11 DF, 5/11 pain score, 9/11 female percentage. For those that displayed no wobble: 9/16 supplied Hurley stage breakdown, 10/16 AN count, 8/16 DF, 8/16 pain score, 11/16 female percentage.

<sup>d</sup>DF counts were found to be significantly different between the 2 groups.

arms where HiSCR wobble occurred had less severe populations, that is, fewer Hurley stage 3 patients (33.2% vs 42.5%), lower weighted AN counts (12.1 vs 12.6), lower weighted pain scores (4.7 vs 5), lower weighted DLQI scores (12.5 vs 14.5), and a higher proportion of female patients (63.9% vs 58.3%) (Table 2).

Twelve of the RCT study drug arms across 7 trials reported HiSCR response data beyond their original primary endpoint week as part of an extension study. The majority of these extensions were not placebo-controlled (10/12 [83.3%]). Most study drug arms had greater HiSCR responses beyond their primary endpoint week (10/11 [90.9%]). Two of the study drug arms from a single study had their extension periods pooled together.

Fifteen study drug arms reported sufficient data to assess QoL measures for wobble including DLQI (n = 7) and pain scores (n = 9). DLQI wobble occurred in 2/7 (28.6%) of study arms, and pain score wobble occurred in 8/9 (88.9%) of study arms. QoL outcome measures reached maximum improvement earlier than maximum HiSCR response in 6 (40%) instances, at the same time in 5 (33.3%) instances, and after in 4 (26.7%) instances.

Six RCT study drug arms in 2 studies used the IHS4 with a primary endpoint week of 16, and half displayed an IHS4 wobble.<sup>5,6</sup>

#### Discussion

In these studies, nonlinear improvement or wobble was observed in drug and placebo arms in HS studies across multiple outcomes including HiSCR, IHS4, and patient-reported outcome measures. Factors associated with HiSCR wobble included smaller sample sizes, RCT study design, a primary endpoint week of 16, study drugs failing to demonstrate significance compared to their placebo arm, and studies including patients with lower baseline disease severity (lower DF counts and more Hurley 1/2 vs Hurley 3 patients) or female gender, although only the first 2 were significant.

The finding that study drug arms with less severe patients displayed greater HiSCR wobble could be due to the prior observation that less severe patients at baseline may be more susceptible to HS disease fluctuation and variability compared with patients with more severe disease at baseline. Indeed, Frew

et al.20 demonstrated that increasing inclusion criteria to 7 nodules may decrease the placebo rate in HS studies by reducing variability; however, they did not recommend this approach due to the potential reduction in external validity of future trials. In our experience, folliculonodular disease, which may affect women more frequently, is characterized by relapsing/remitting primarily inflammatory nodules and papules sensitive to hormonal triggers. The higher proportion of female patients noted in study drug arms that displayed HiSCR wobble is consistent with the concept that hormonal fluctuations may contribute to disease flares and disease variability in trials with HiSCR wobble.<sup>1</sup> Currently, disease triggers and clinically relevant HS phenotypes are not captured in HS clinical trials. Validation and subsequent incorporation of phenotypes in clinical trials, along with tracking of disease triggers such as dates of menses, could add further insight into the interpretation of placebo responses, HiSCR wobble, and differences in treatment response based on disease phenotype in HS trials. These data also reinforce the clinical concept that patients with HS can experience significant variability in their disease, even as their overall trajectory is improving. Longterm studies, especially, against active controls may help us better understand and predict their improvement course.

In contrast to clinical care, where providers often overlap therapies to avoid flaring disease, HS clinical trials require washout periods of systemic and topical treatments that often last from 4 to 12 weeks prior to enrollment. For biologics, this time frame is often 5 half-lives or 12 weeks, whichever is longer.<sup>2,3</sup> Thus, patients enrolled into placebo arms of placebocontrolled trials may go without treatment for months, resulting in rebound, recurrence, and unknown impact on their long-term prognosis or disease progression. Because long washout periods can unpredictably disrupt stable moderate to severe disease in both placebo subjects and those on active therapy, we recommend reducing washout periods to no longer than 5 half-lives or 12 weeks, whichever is shorter. Since we found that a large proportion of study drug arms with primary endpoint at week 16 demonstrated HiSCR wobble, with many peaking at week 12, it may also be appropriate to limit placebo-controlled periods to 12 weeks or consider active-controlled arms, which would also allow for much longer controlled periods.

#### Limitations

Limitations include low number of HS clinical trials and insufficient/incomplete data reported in many studies to assess for wobble, degree of wobble, and to compare all baseline characteristics. Further, we were unable to assess if trials with primary endpoint week 12 would have met maximum response at a later week and the dataset was limited to trials listed on ClinicalTrials.gov.

#### Conclusion

Nonlinear improvement in study arm response occurs in HS RCTs across several outcome measures. Potential contributing factors include a higher proportion of less severe patients at baseline and more female patients, which could represent a particular HS phenotype that has more underlying variability. Study designers may wish to incorporate 12-week endpoints to help mitigate this problem, bearing in mind that some drugs may not have reached peak efficacy at this time.

#### **Conflicts of interest**

The authors made the following disclosures: A.B.K.'s institution received grants from Abbvie, Admirx, Anapyts Bio, Aristea, Bristol Myers Squibb, Chemocentryx, Eli Lilly, Incyte, Janssen, Moonlake, Novartis, Pfizer, Prometheus, UCB; Sonoma Bio. she received consulting fees from Abbvie, Alumis, Bayer, Bristol Myers Squibb, Boehringer Ingelheim, Eli Lilly, Janssen, Moonlake Novartis, Pfizer, Priovant, Sonoma Bio, Sanofi, UCB; Target RWE, Ventyx; and serves on the board of directors of Almirall. M.L.P. is a consultant and/or investigator for Abbvie, Alumis, Anaptys Bio, Aristea, Bayer, Bristol Meyers Squibb, Janssen, Eli Lilly, Moonlake, Novartis, Pfizer, Prometheus, Trifecta Clinical, UCB, Regeneron, Innovoderm, Bayer, Prometheus, and Incyte. S.X.C. is an investigator for Novartis, Moonlake, Prometheus, and UCB. R.S.G.'s fellowship was funded through the National Psoriasis Foundation. R.S.G. is an investigator for Abbvie, Janssen, Regeneron, Eli Lilly, Novartis, UCB, Aristea, Incyte, Innovoderm, Bayer, and Moonlake. C.L.S. declares no conflicts of interest.

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#### Study approval

N/A

#### **Author contributions**

CLS: Participated in research design, data collection, data analysis, writing of the manuscript, and manuscript review. RSG and SXC: Participated in writing of the manuscript and manuscript review. MLP and ABK: Participated in research design, writing of the manuscript, and manuscript review.

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