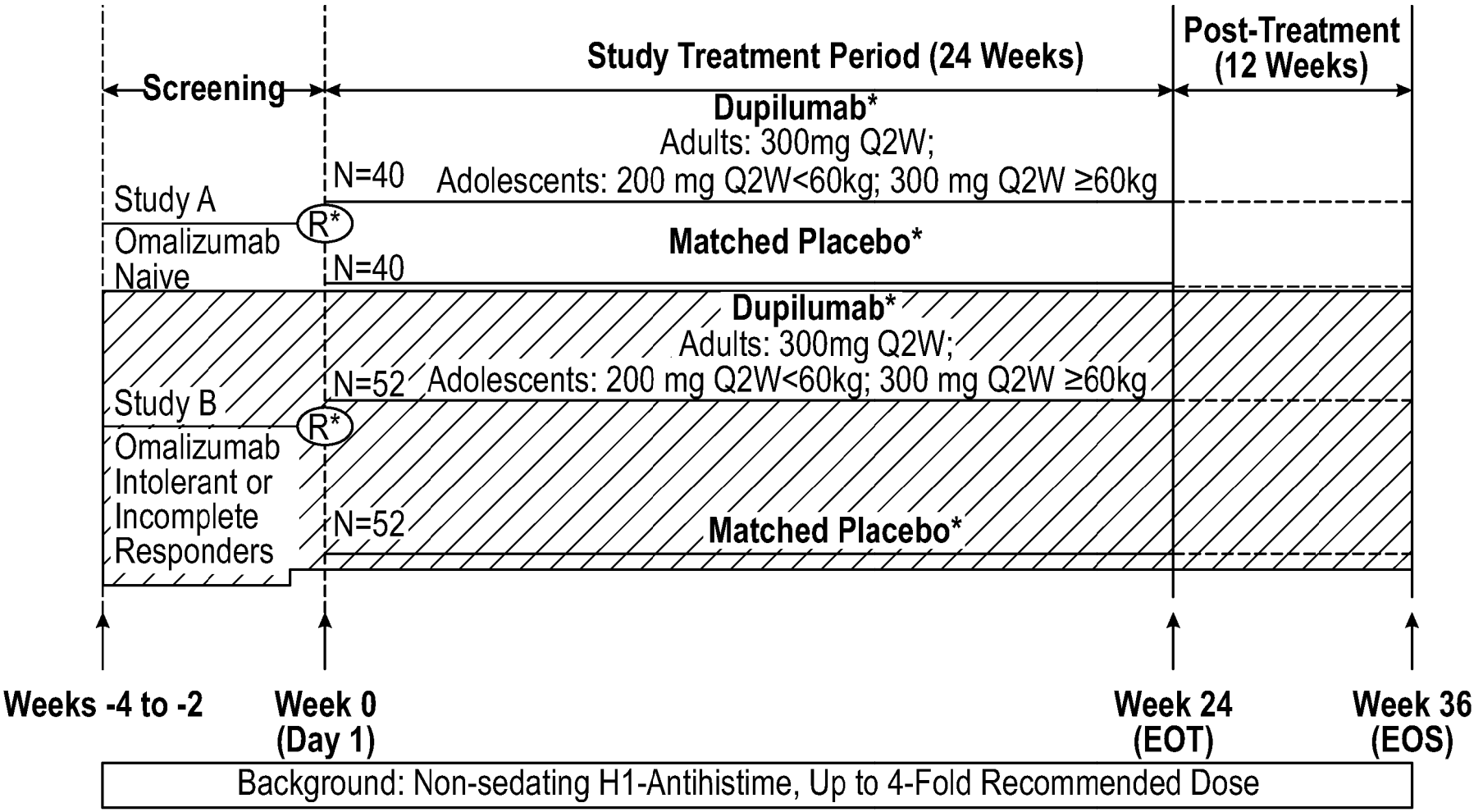


Dupilumab 300 mg Q2W,Administered as 1 SC Injection of Dupilumab 300 mg (2 mL)

Dupilumab 200 mg Q2W,Administered as 1 SC Injection of Dupilumab 200 mg (1.14 mL)

Matched Placebo is Prepared in the Same Formulation Without the Addition of Protein (i.e, the Active Substance)
A Loading Dose Equivalent to Treatment Group Assigned Will be Administered on Day 1.

FIG. 1

Procedures	Screening (2 to 4 Weeks Before Day 1)	Intervention Period (Weeks)			Follow-Up (12 Weeks)	Notes
		0 (Day 1)	12	24	36	Visit Window: ±3 Days for Visits 3, 4, and 5
Visit	1	2[a]	3	4 (EOT)[b]	5 (EOS)	
Screening/Baseline:						
Informed Consent	X					
Medical History	X					
Prior and Concomitant Medication	X	X	X	X	X	Concomitant Medication Including Rescue OCS Taken Since Last Visit Will be Collected Throughout the Study
Demographics	X					
Inclusion/Exclusion Criteria	X	X				
Patient E-Diary Training	X	X				
Randomization		X				
Study Intervention						
Call IVRS/IWRS	X	X	X	X	X	
IMP Administration		X[c]				IMP Will be Administered Every Other Week Except (for Study A) for Children <30 Kg and ≥15kg Where it Will be Administered Every 4 Weeks. The Planned Last Dose is at Week 22 Except (for Study A) for Children <30kg and ≥15 Kg Where it Will be Administered at Week 20. Patients are Allowed to Self-inject IMP at Home
Dispense/Upload Electronic Diary[d]	X	X				Device is Dispensed at Screening (Including Instructions for Use). At the EOS, the E-diary is Returned to the Site

FIG. 2A

Procedures	Screening (2 to 4 Weeks Before Day 1)	Intervention Period (Weeks)			Follow-Up (12 Weeks)	Notes
		0 (Day 1)	12	24	36	Visit Window: ±3 Days for Visits 3, 4, and 5
Visit	1	2[a]	3	4 (EOT)[b]	5 (EOS)	
Safety[e]						
Physical Examination[f]	X	X		X	X	
Vital Signs[g]	X	X	X	X	X	
Electrocardiogram(12 lead)	X			X		ECG to be Locally Collected and Read
Hematology, Biochemistry, Urine Analysis[h]	X	X	X	X	X	
Hepatitis, HIV Serology,TB Test[i]	X					
Pregnancy Test[i]	Serum	Ur	Ur	Ur	Ur	In Between Visit Urine Pregnancy Tests Must be Performed at Home (weeks 4, 8, 16, 20, 28 And 32)
AE Reporting, Including SAEs	X	X	X	X	X	
Pharmacokinetics and ADA[e]						
Serum PK Samples for Dupilumab Concentration[k]		X	X	X	X	
Anti-Dupilumab Antibody[k]		X	X	X	X	
Biomakers[e]						
Total Serum IgE		X	X	X	X	
Basophil Activation Test (Optional Sub-Study)[l]		X	X	X		
Skin Biopsy (Optional Sub-Study)[m]		X		X		
Archive Serum and Plasma Samples (Optional)[n]		X	X	X	X	Archive Serum and Plasma Samples (Optional) are Collected for Future Analysis of Potential Biomarkers of Drug Response, Disease Activity, Safety and the Type 2 Inflammation Pathway

FIG. 2B

Procedures	Screening (2 to 4 Weeks Before Day 1)	Intervention Period (Weeks)			Follow-Up (12 Weeks)	Notes
		0 (Day 1)	12	24	36	Visit Window: ±3 Days for Visits 3, 4, and 5
Visit	1	2[a]	3	4 (EOT)[b]	5 (EOS)	
DNA (Whole Blood) Samples - Optional[o]		X				
RNA (Whole Blood) Samples - Optional[p]		X		X		
Efficacy[d,e]						
UAS7	UAS7 (Includes ISS7 and HSS7 as Components), Once Daily From Screening to EOS					To be Recorded in E-diary on the Same Time of the Day
AAS7	AAS7,Once Daily From Screening to EOS					To be Recorded in E-diary on the Same Time of the Day
UCT		X	X	X	X	
DLQI/CDLQI		X	X	X	X	
CU-Q2oL		X	X	X	X	
PGIC			X	X		
PGIS	X	X	X	X		
EQ-5D-5L/EQ-5D-Y		X	X	X	X	
Missed School/Work Days[q]		X	X	X	X	
Photographs CSU Representative Area for Commercial Activities (at Selected Sites in Selected Countries)[r]		X	X	X	X	

FIG. 2C

Score*	Hives (Wheals)	Score*	Itch Severity Score (ISS)
0	None	0	None
1	Mild (<20 Hives/24 h)	1	Mild (Present, but not Annoying or Troublesome)
2	Moderate (20-50 Hives/24 h)	2	Moderate (Troublesome, but Does not Interfere With Normal Daily Activity or Sleep)
3	Intense (50 Hives/24 h or Large Confluent Areas of Hives)	3	Intense (Severe itch, Which is Sufficiently Troublesome to Interfere With Normal Daily Activity or Sleep)

FIG. 3

Urticaria Control Test

Patient Name: _____ Date: (dd mmm yyyy): __ ___ ____

Date of Birth (dd mmm yyyy):__ ___ ____

Instructions : You have Urticaria. The Following Questions Should Help us Understand Your Current Health Situation. Please Read Through Each Question Carefully and Choose an Answer From the Five Options That Best Fits Your Situation. Please Limit Yourself to the Last Four Weeks. Please Don't Think About the Questions for a Long Time, and do Remember to Answer all Questions and to Provide Only One Answer to each Question.

1. How Much Have You Suffered From the Physical Symptoms of the Urticaria (Itch, Hives (Welts) and/or Swelling) in the Last Four Weeks?
   ○ Very Much ○ Much ○ Somewhat ○ A Little ○ Not at All

2. How Much was Your Quality of Life Affected by the Urticaria in the Last 4 Weeks?
   ○ Very Much ○ Much ○ Somewhat ○ A Little ○ Not at All

3. How Often was the Treatment for Your Urticaria in the Last 4 Weeks not Enough to Control Your Urticaria Symptoms?
   ○ Very Often ○ Often ○ Sometimes ○ Seldom ○ Not at All

4. Overall, How Well Have you Had Your Urticaria Under Control in the Last 4 Weeks?
   ○ Not at All ○ A Little ○ Somewhat ○ Well ○ Very Well

FIG. 4

Chronic Urticaria Quality of Life Questionnaire
(CU-Q_2oL)

How Bothered Have you Been by the Following Symptoms in the Last Two Weeks?

1 Itching
▫ Not At All ▫ A Little ▫ Moderately ▫ Very Much ▫ Extremely

2 Hives
▫ Not At All ▫ A Little ▫ Moderately ▫ Very Much ▫ Extremely

3 Swelling of the Eyes
▫ Not At All ▫ A Little ▫ Moderately ▫ Very Much ▫ Extremely

4 Swelling of the Lips
▫ Not At All ▫ A Little ▫ Moderately ▫ Very Much ▫ Extremely

Please Indicate if Urticaria has Limited You in the Following Daily Activities During the Last Two Weeks.

5 Work
▫ Not At All ▫ A Little ▫ Moderately ▫ Very Much ▫ Extremely

6 Physical Activity
▫ Not At All ▫ A Little ▫ Moderately ▫ Very Much ▫ Extremely

FIG. 5A

7 Sleep
□ Not At All □ A Little □ Moderately □ Very Much □ Extremely

8 Free Time
□ Not At All □ A Little □ Moderately □ Very Much □ Extremely

9 Relationships with Other People
□ Not At All □ A Little □ Moderately □ Very Much □ Extremely

10 Eating
□ Not At All □ A Little □ Moderately □ Very Much □ Extremely

Answer the Following Questions Regarding Difficulties and Problems That You May Have Experienced in Association With Urticaria (In the Last Two Weeks)

11 Do You Have Difficulty Falling Asleep?
□ Not At All □ A Little □ Moderately □ Very Much □ Extremely

12 Do You Wake Up During the Night?
□ Not At All □ A Little □ Moderately □ Very Much □ Extremely

13 Are You Tired During the Day Due to a Lack of Sleep at Night?
□ Not At All □ A Little □ Moderately □ Very Much □ Extremely

14 Do You Have Difficulty Concentrating?
□ Not At All □ A Little □ Moderately □ Very Much □ Extremely

15 Do You Feel Nervous?
□ Not At All □ A Little □ Moderately □ Very Much □ Extremely

FIG. 5B

16 Do You Feel Down?

▫ Not At All ▫ A Little ▫ Moderately ▫ Very Much ▫ Extremely

17 Do You have to Limit Your Choice of Foods?

▫ Not At All ▫ A Little ▫ Moderately ▫ Very Much ▫ Extremely

18 Are You Embarrassed by the Marks that Appear on Your Body Due to Urticaria?

▫ Not At All ▫ A Little ▫ Moderately ▫ Very Much ▫ Extremely

19 Are You Embarrassed to go Out in Public?

▫ Not At All ▫ A Little ▫ Moderately ▫ Very Much ▫ Extremely

20 Do You Have Difficulty Using Cosmetics (For Example, Perfumes, Creams, Lotions, Bubble Bath, Makeup)?

▫ Not At All ▫ A Little ▫ Moderately ▫ Very Much ▫ Extremely

21 Is Your Choice of Clothing Affected?

▫ Not At All ▫ A Little ▫ Moderately ▫ Very Much ▫ Extremely

22 Do You Limit Your Sports Activities Because of Urticaria?

▫ Not At All ▫ A Little ▫ Moderately ▫ Very Much ▫ Extremely

23 Are You Bothered by Side Effects from the Medication You Take for Urticaria?

▫ Not At All ▫ A Little ▫ Moderately ▫ Very Much ▫ Extremely

FIG. 5C

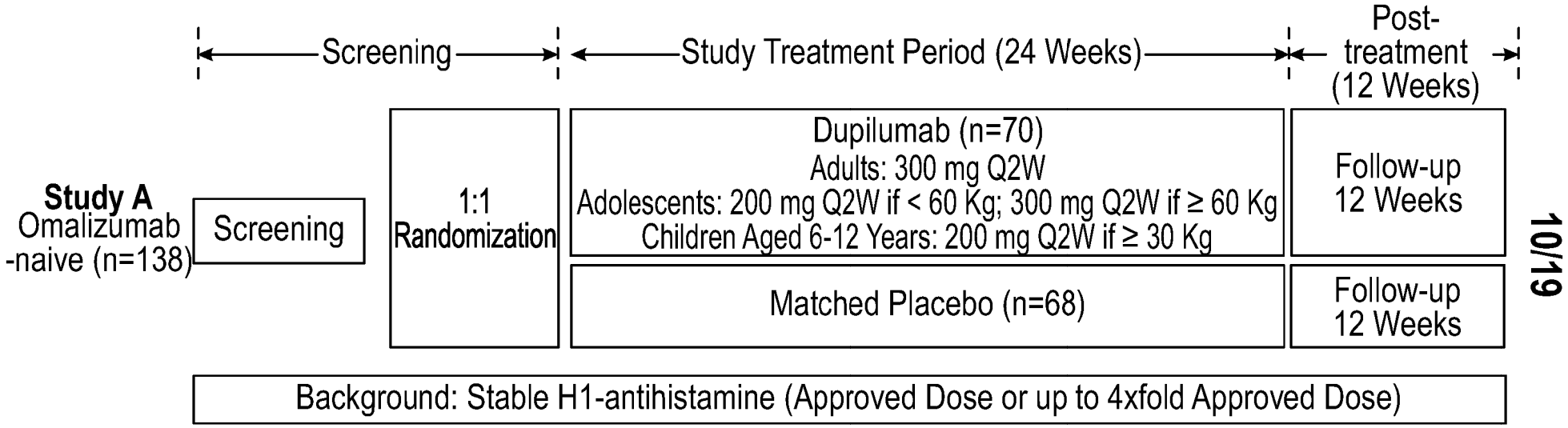

Screening
Study Treatment Period (24 Weeks)
Post-treatment (12 Weeks)
Study A
Omalizumab -naive (n=138)
Screening
1:1 Randomization
Dupilumab (n=70)
Adults: 300 mg Q2W
Adolescents: 200 mg Q2W if < 60 Kg; 300 mg Q2W if ≥ 60 Kg
Children Aged 6-12 Years: 200 mg Q2W if ≥ 30 Kg
Follow-up 12 Weeks
Matched Placebo (n=68)
Follow-up 12 Weeks
Background: Stable H1-antihistamine (Approved Dose or up to 4xfold Approved Dose)

FIG. 6

CUPID Study A: Statistical Testing Hierarchy

Endpoint (Primary for US/EU as Noted; Key Secondary Otherwise, Unless Bold Which is Other Secondary)		Placebo[a] N=68 (SD)	Dupilumab[a] N=70 (SD)	Treatment Effect Dupl vs. Pbo (95% CI)[b]	P-value	EU Hierarchy	US Hierarchy
ISS7 (0-21)	@wk 24, Δ from BL	-6.01 (0.94)	-10.24 (0.91)	-4.23 (-6.63, -1.84)	0.0005	2	1-Primary
UAS7 (0-42)	@wk 24, Δ from BL	-12.00 (1.81)	-20.53 (1.76)	-8.53 (13.16, -3.90)	0.0003	1-Primary	2
UAS7≤6	@wk 24, % of pts [Partial Responder]	16 (23.5)	32 (45.7)	2.848 (1.301, 6.234)	0.0075	3	3
UAS7=0	@wk 24, % of pts [Complete Responder]	9 (13.2)	22 (31.4)	2.908 (1.173, 7.209)	0.0199	4	4
HSS7(0-21)	@wk 24, Δ from BL	-5.90 (0.93)	-10.28 (0.91)	-4.38 (-6.78, -1.98)	0.0003	5	5
ISS7	@wk 12, Δ from BL	-6.01 (0.85)	-8.37 (0.84)	-2.37 (-4.60, -0.13)	0.0377	6	6
UAS7	@wk 12, Δ from BL	-11.79 (1.64)	-16.81 (1.62)	-5.02 (-9.32, -0.72)	0.0223	7	7
UAS7≤6	@wk 12, % of pts [Partial Responder]	12 (17.6)	24 (34.3)	2.645 (1.154, 6.061)	0.0215	8	8
ISS MID ≥5	@wk 24, % of pts [itch MID]	29 (42.6)	51 (72.9)	3.413 (1.596, 7.299)	0.0014	9	9
Hierarchy Break (Nominal p-value)							
ISS MID ≥5	@wk 12, % of pts [itch MID]	36 (52.9)	49 (70.0)	1.872 (0.893, 3.923)	**0.0971**	10	10
HSS7	@wk 12, Δ from BL	-5.69 (0.83)	-8.39 (0.83)	-2.70 (-4.90, -0.50)	0.0160	11	11
UAS7=0	@wk 12, % of pts [Complete Responder]	6 (8.8)	11 (15.7)	1.970 (0.676, 5.743)	**0.2152**	12	12
UCT (0-16)	@wk 24, Δ from BL	4.88 (0.61)	7.71 (0.59)	2.84 (1.27, 4.40)	0.0004	13	13
UCT	@wk 12, Δ from BL	4.62 (0.57)	6.48 (0.57)	1.86 (0.35, 3.36)	0.0155	14	14

FIG. 7

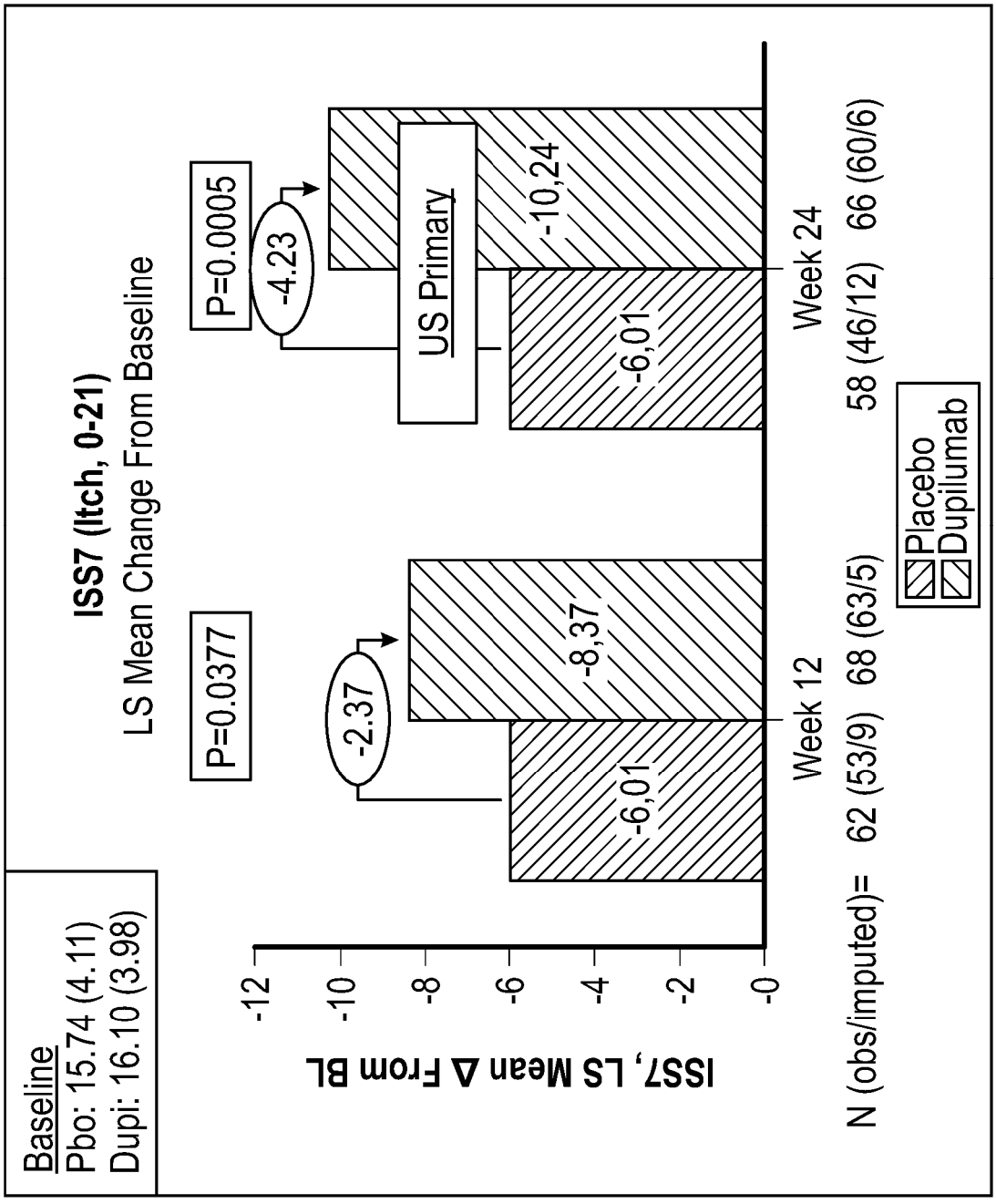
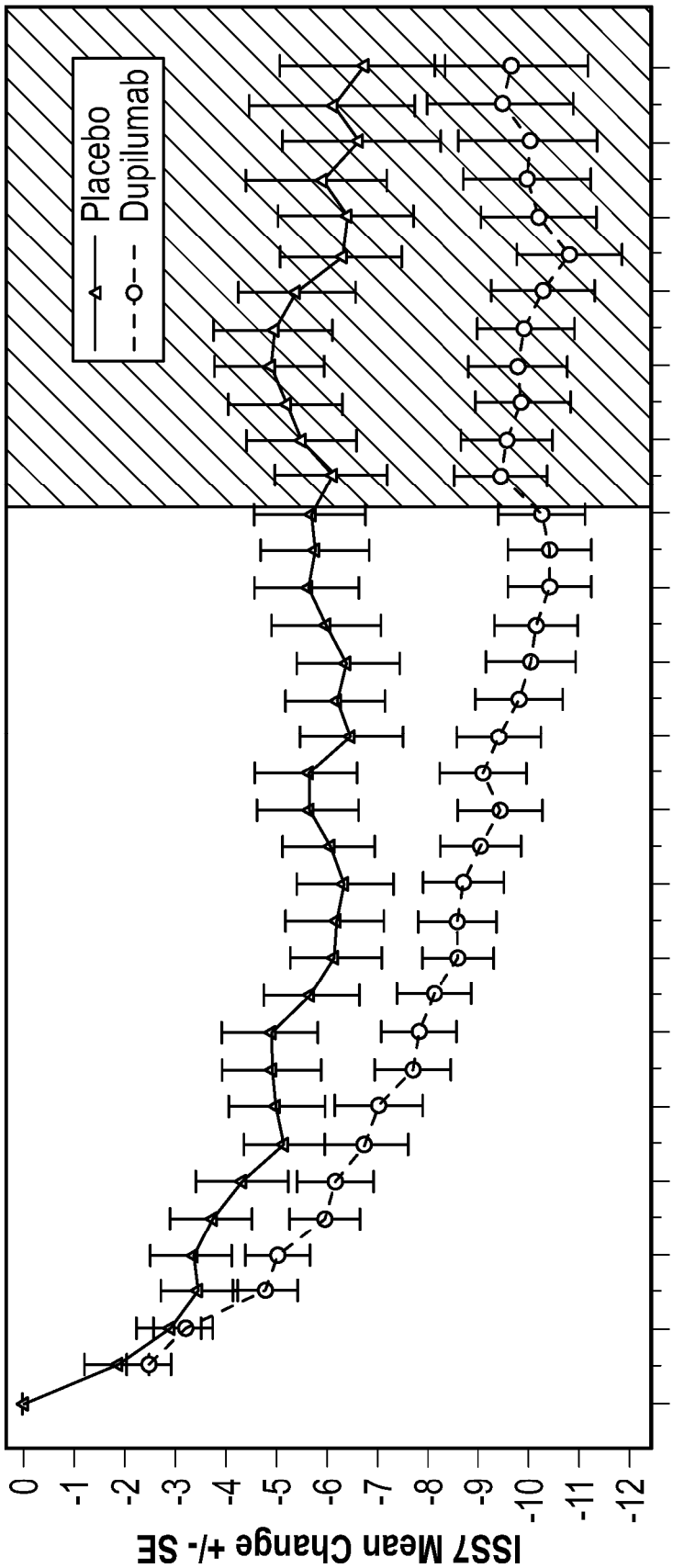

Baseline
Pbo: 15.74 (4.11)
Dupi: 16.10 (3.98)
ISS7 (Itch, 0-21)
LS Mean Change From Baseline
P=0.0377
-2.37
P=0.0005
-4.23
US Primary
-10,24
-8,37
-6,01
-6,01
ISS7, LS Mean Δ From BL
-12
-10
-8
-6
-4
-2
-0
Week 12
Week 24
N (obs/imputed)= 62 (53/9) 68 (63/5) 58 (46/12) 66 (60/6)
Placebo
Dupilumab

FIG. 8



#Subjects																			
Placebo	68	66	65	62	62	58	62	59	58	66	65	59	58	64	57	58	66	63	55	53	41	31	26
Dupilumab	70	69	70	68	68	66	68	66	66	66	65	59	58	66	64	58	66	63	55	55	48	32	27

FIG. 9

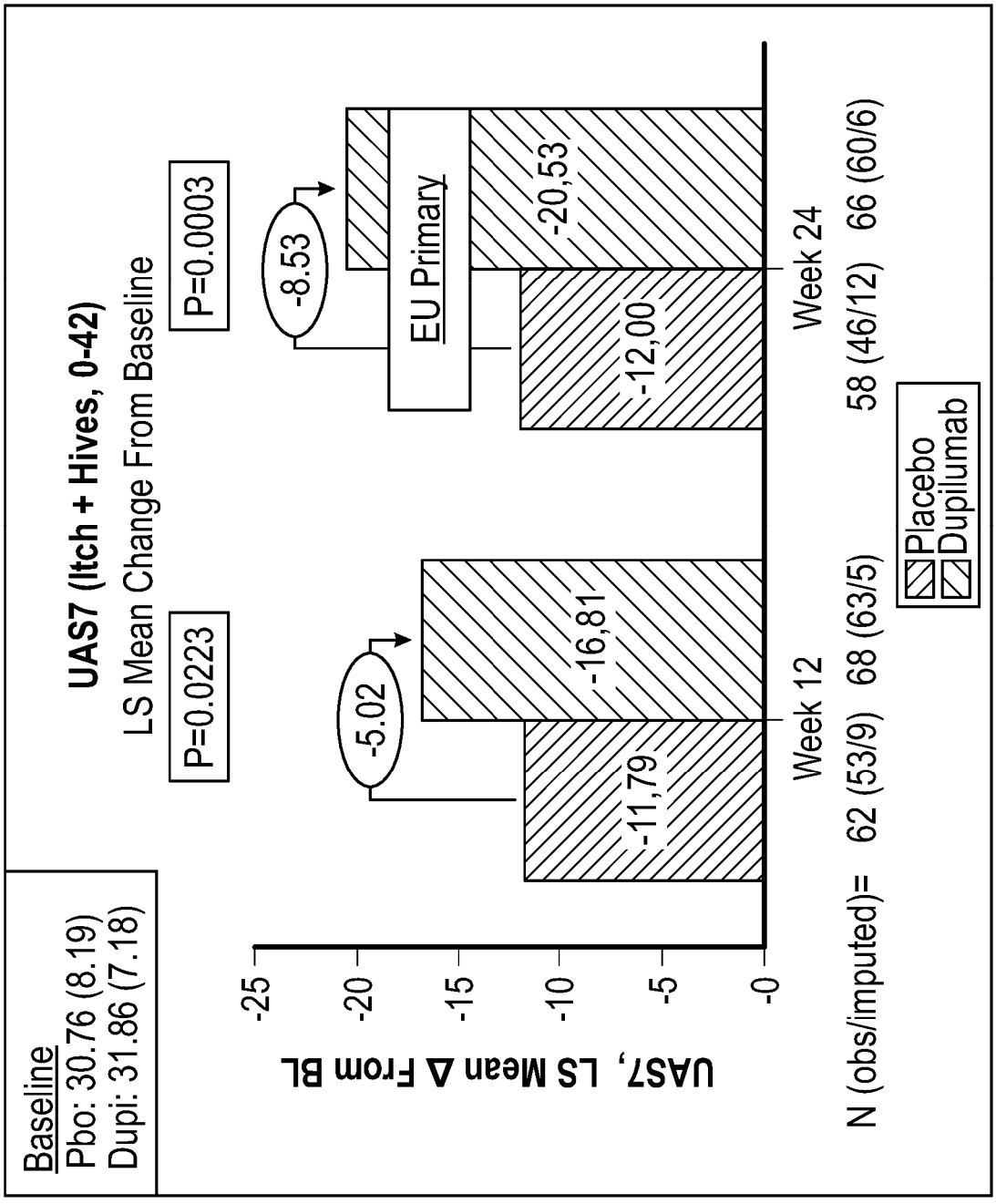

Baseline
Pbo: 30.76 (8.19)
Dupi: 31.86 (7.18)
UAS7 (Itch + Hives, 0-42)
LS Mean Change From Baseline
P=0.0223
P=0.0003
-5.02
-8.53
EU Primary
-16,81
-11,79
-20,53
-12,00
UAS7, LS Mean Δ From BL
-25
-20
-15
-10
-5
-0
Week 12
Week 24
N (obs/imputed)= 62 (53/9) 68 (63/5) 58 (46/12) 66 (60/6)
Placebo
Dupilumab

FIG. 10

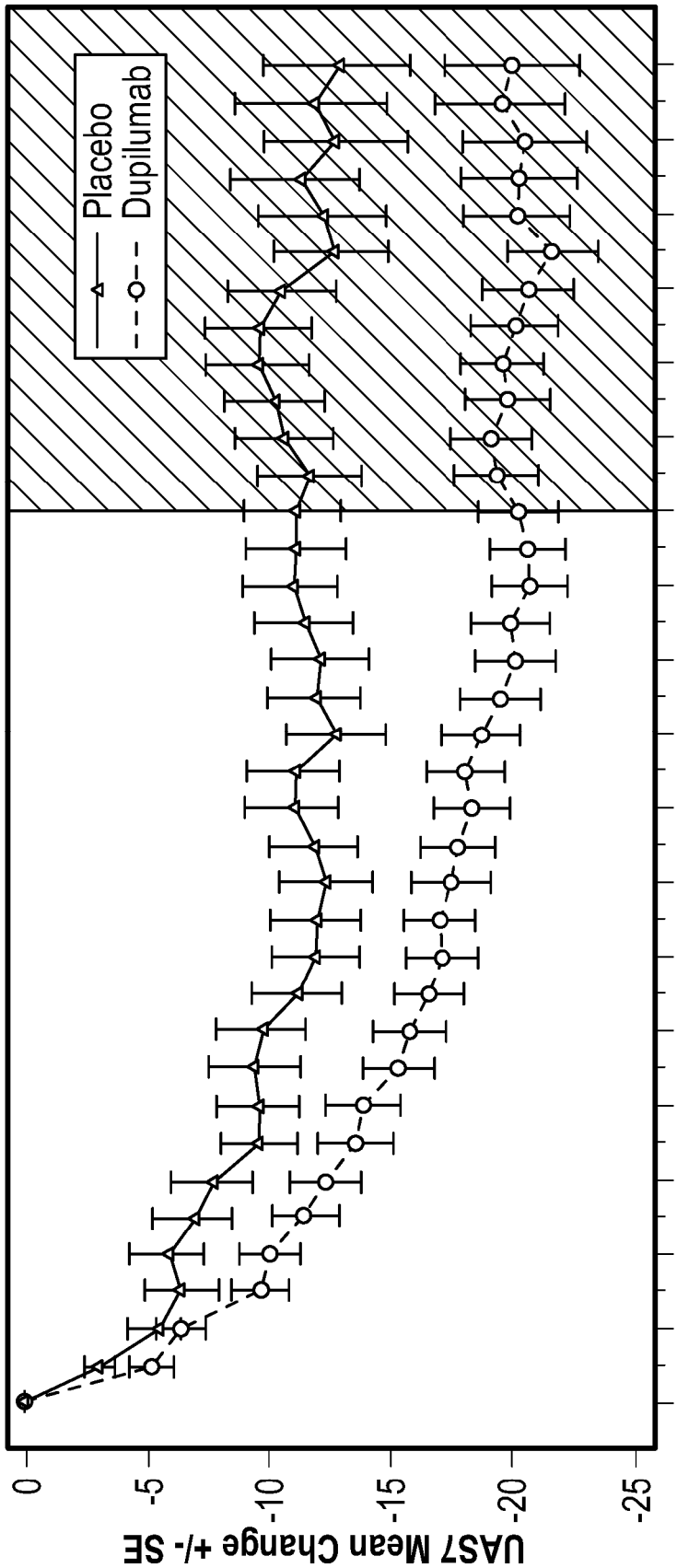

Placebo
Dupilumab
UAS7 Mean Change +/- SE
0
-5
-10
-15
-20
-25
BL 2 4 6 8 10 12 14 16 18 20 22 24 26 28 30 32 34 36
Week
#Subjects
Placebo 68 66 65 62 62 58 66 68 62 59 58 66 65 64 57 58 66 63 55 53 41 31 26
Dupilumab 70 69 70 68 68 66 68 66 66 66 58 66 63 63 55 55 48 32 27

FIG. 11

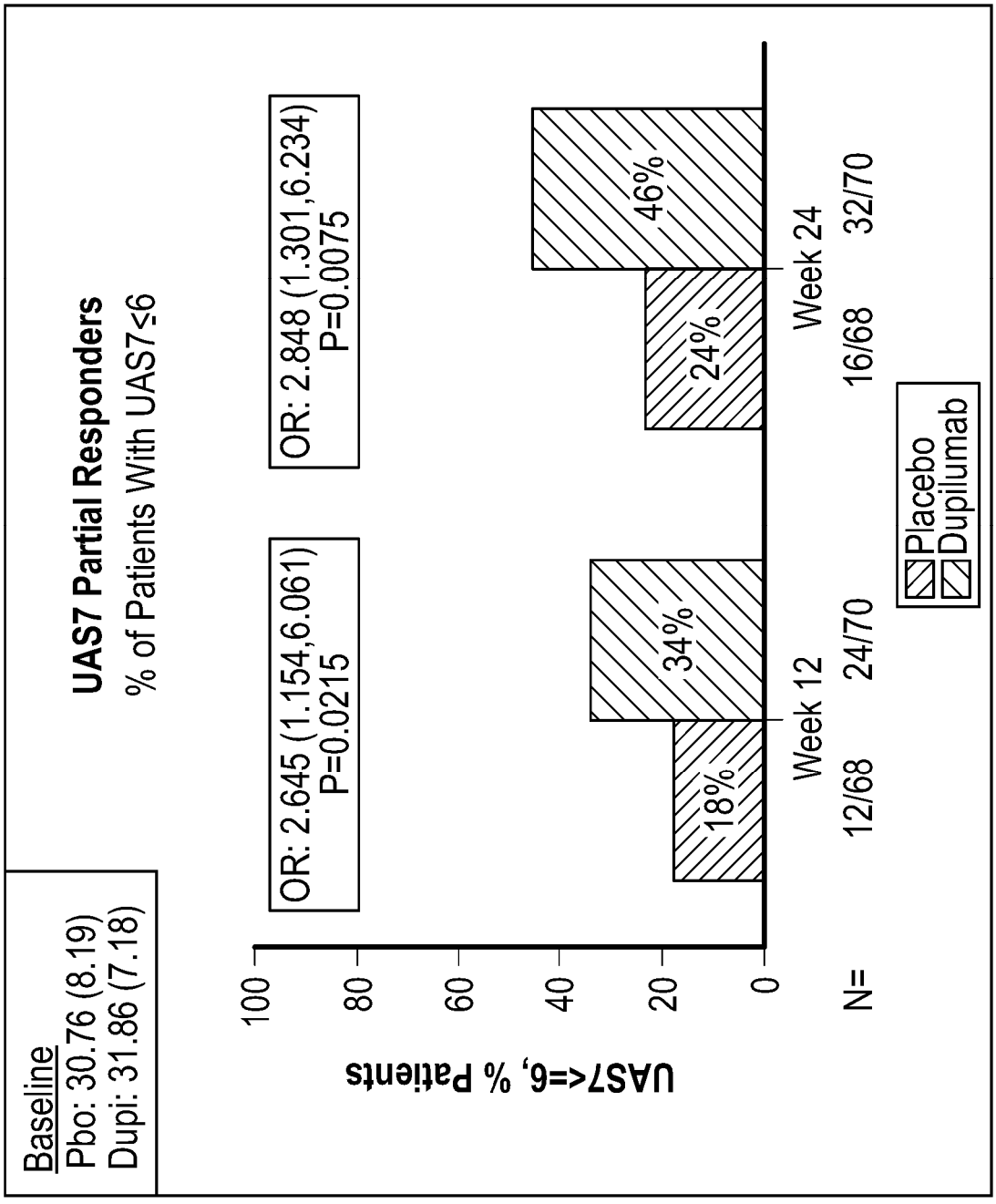

Baseline
Pbo: 30.76 (8.19)
Dupi: 31.86 (7.18)
UAS7 Partial Responders
% of Patients With UAS7≤6
OR: 2.645 (1.154,6.061)
P=0.0215
OR: 2.848 (1.301,6.234)
P=0.0075
UAS7<=6, % Patients
100
80
60
40
20
0
34%
18%
46%
24%
Week 12
Week 24
N=
12/68
24/70
16/68
32/70
Placebo
Dupilumab

FIG. 12

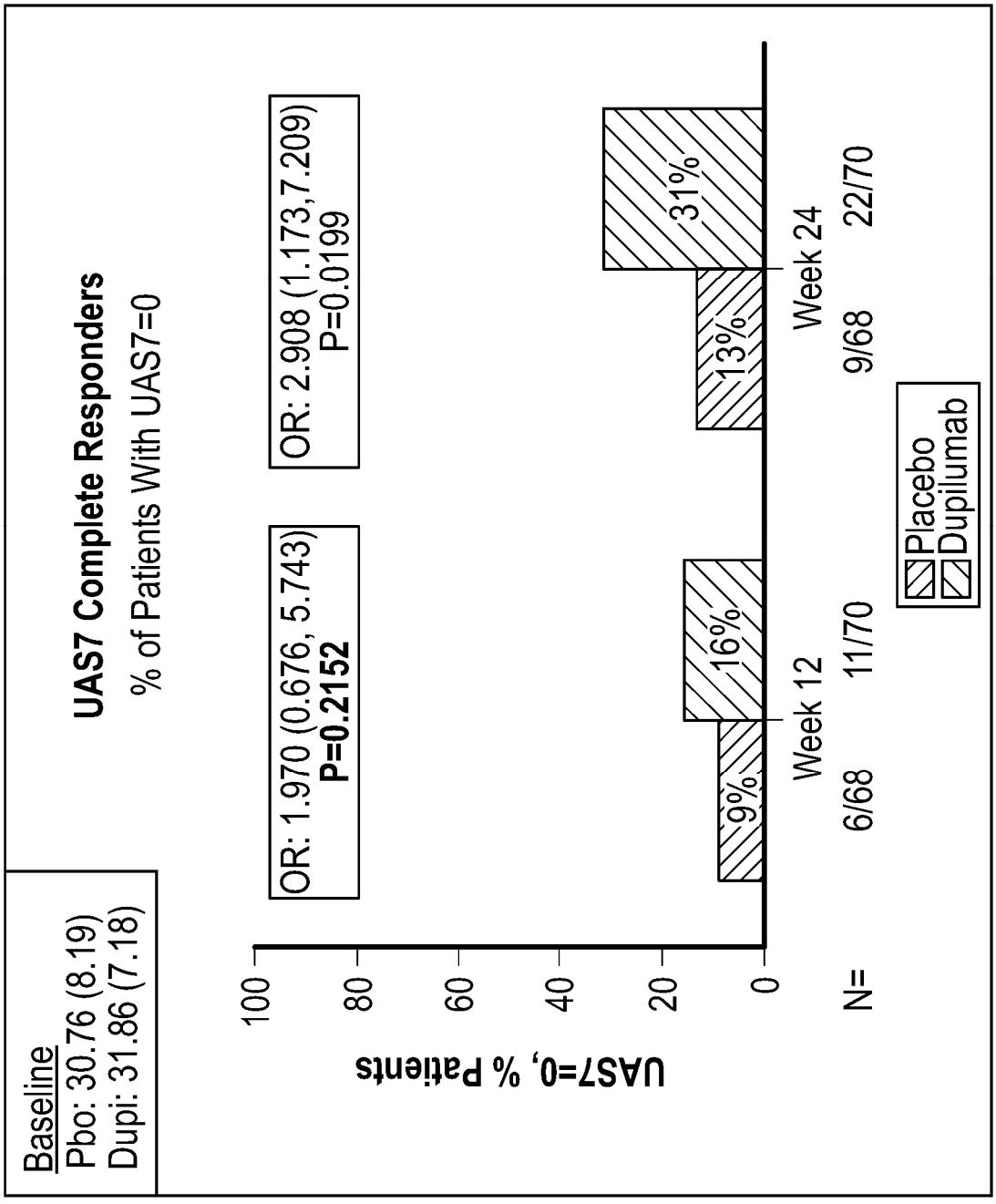

Baseline
Pbo: 30.76 (8.19)
Dupi: 31.86 (7.18)
UAS7 Complete Responders
% of Patients With UAS7=0
OR: 1.970 (0.676, 5.743)
P=0.2152
OR: 2.908 (1.173,7.209)
P=0.0199
UAS7=0, % Patients
100
80
60
40
20
0
9%
16%
13%
31%
Week 12
Week 24
N=
6/68
11/70
9/68
22/70
Placebo
Dupilumab

FIG. 13

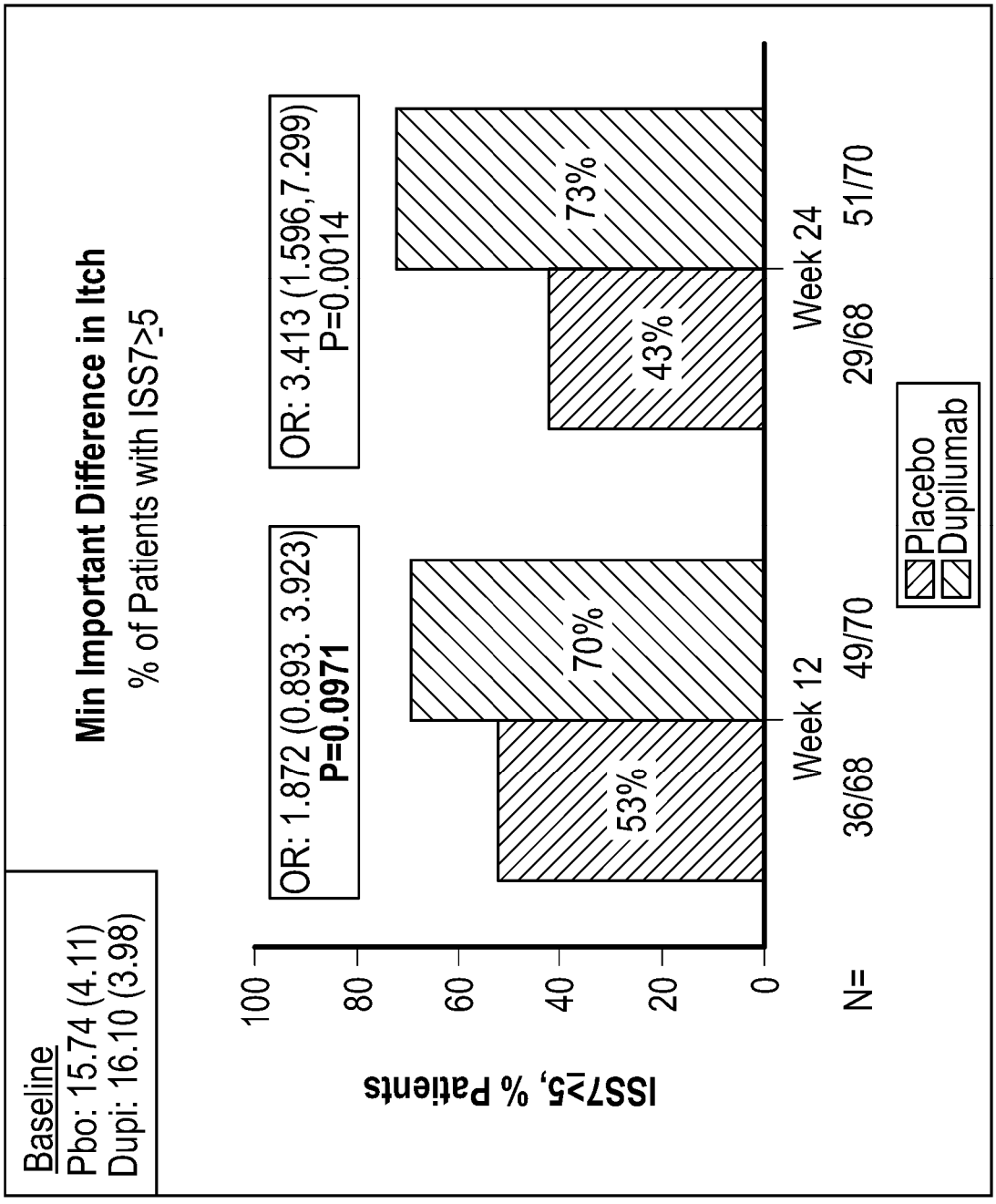
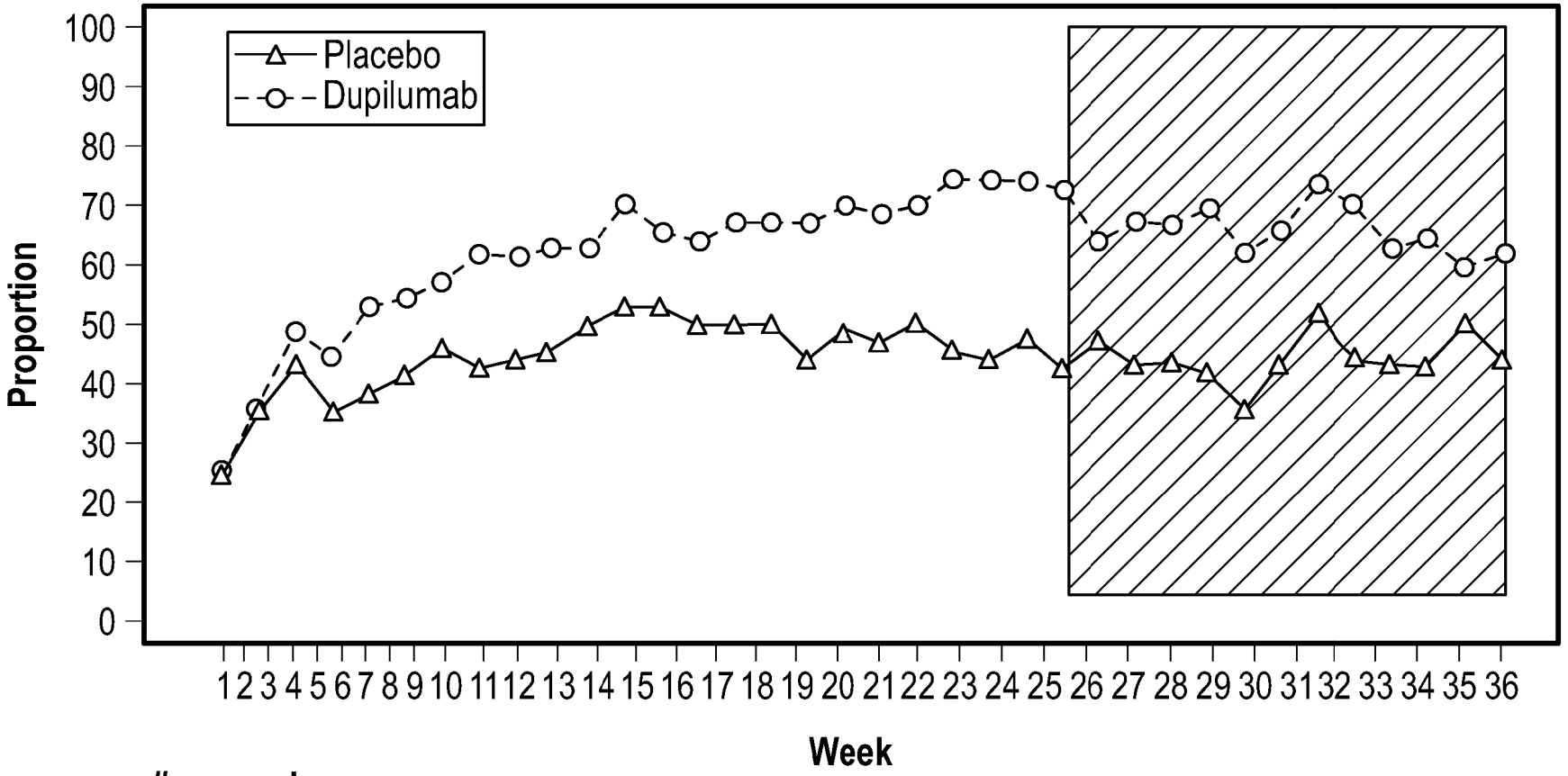

Min Important Difference in Itch
% of Patients with ISS7>5
Baseline
Pbo: 15.74 (4.11)
Dupi: 16.10 (3.98)
OR: 1.872 (0.893. 3.923)
P=0.0971
OR: 3.413 (1.596,7.299)
P=0.0014
ISS7≥5, % Patients
100
80
60
40
20
0
53%
70%
43%
73%
Week 12
Week 24
N=
36/68
49/70
29/68
51/70
Placebo
Dupilumab

FIG. 14



#responders

Placebo	24	24	28	29	31	36	34	34	33	34	30	29	29	28	28	23	18	16
Dupilumab	25	31	38	43	44	49	45	47	49	49	52	51	47	48	42	38	25	21

FIG. 15