**Supplementary Figure1:** A forest plot of the change in FENO (ppb) at week 12.

	Dup	ilumab		Pla	acebo			Mean Difference	Mean Difference
Study or Subgroup	Mean		Total	Mean	SD	Total	Weight	IV, Random, 95% Cl	IV, Random, 95% Cl
1.5.1 Dupilumab 100-2	200 mg q2\	N							
Bacharier et al. 2021 <b>Subtotal (95% Cl)</b>	-16.95	24.49	247 <b>247</b>	-0.15	32.57	126 <b>126</b>		-16.80 [-23.26, -10.34] - <b>16.80 [-23.26, -10.34]</b>	
Heterogeneity: Not app	olicable								
Test for overall effect: 2	Z= 5.10 (P	< 0.000	101)						
1.5.2 Dupilumab 200 n	ng q2w								
Castro et al. 2018	-14.9	31.3	631	-2.5	21	313	18.8%	-12.40 [-15.77, -9.03]	+
Wenzel et al. 2016 Subtotal (95% Cl)	-24.02	76.4	150 <b>781</b>	11.58	77	131 <b>444</b>	4.5% <b>23.2</b> %	-35.60 [-53.58, -17.62] -22.25 [-44.73, 0.23]	
Heterogeneity: Tau <sup>2</sup> = : Test for overall effect: 2	•		8, df = 1	(P = 0.0	1); I² = 8	4%			
		- 0.05)							
1.5.3 Dupilumab 200 n	ng q4w								
Wenzel et al. 2016 Subtotal (95% Cl)	2.45	76.34	114 <b>114</b>	11.58	77	131 <b>131</b>	4.0% <b>4.0</b> %	-9.13 [-28.37, 10.11] - <b>9.13 [-28.37, 10.11]</b>	
Heterogeneity: Not app	olicable								
Test for overall effect: 2	Z = 0.93 (P	= 0.35)							
1.5.4 Dupilumab 300 n	ng q2w								
Castro et al. 2018	-15.6	25.3	632	-3.6	29.6	321	18.2%	-12.00 [-15.79, -8.21]	+
Rape et al. 2018	-18.7	28.24	83	-2.755	31.34	93	11.2%	-15.95 [-24.75, -7.14]	
Wechsler et al. 2021	-7.908		58	6.906	26.46	49	11.1%	-14.81 [-23.72, -5.91]	
Wenzel et al. 2013	-17.862			10.363	24.2	44		-28.22 [-39.21, -17.24]	
Wenzel et al. 2016	-28.04	77.28	157	11.58	77	131		-39.62 [-57.51, -21.73]	
Subtotal (95% CI)	54 00. OK 3	45.00	970	(D 0 0	0.41.17	638	55.9%	-19.56 [-27.21, -11.90]	•
Heterogeneity: Tau² = : Test for overall effect: 2				(P = 0.0	04); 1*=	/4%			
1.5.5 Dupilumab 300 n	ng q4w								
Wenzel et al. 2016	-9.97	76.23	157	11.58	77	131	4.6%	-21.55 [-39.33, -3.77]	
Subtotal (95% CI)			157			131	4.6%	-21.55 [-39.33, -3.77]	
Heterogeneity: Not app Test for overall effect: 2		= 0.02)							
Total (95% CI)			2269			1470	100.0%	-17.58 [-21.87, -13.29]	•
Heterogeneity: Tau <sup>2</sup> = 1	22.54: Chi⁼	<sup>2</sup> = 23.53		(P = 0.0)	05); I <sup>2</sup> =				
Test for overall effect: 2			-	ų. 0.0	// -				-100 -50 Ó 50 10
Test for subgroup diffe			r .	4 (P = 0.9	$(A) = \mathbf{E} = 1$	n %.			Favours (Dupilumab) Favours (Placebo)

	Du	pilumab		Р	lacebo			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% Cl	IV, Random, 95% Cl
1.6.1 Dupilumab 100-2	00 mg qi	2w							
Bacharier et al. 2021 Subtotal (95% Cl)	-16.8	24.77	242 242	2.66	37.54	123 <b>123</b>		-19.46 [-26.79, -12.13] - <b>19.46 [-26.79, -12.13]</b>	<b>→</b>
Heterogeneity: Not app Test for overall effect: Z		⊃ < 0.00	001)						
1.6.2 Dupilumab 200 n	ng q2w								
Castro et al. 2018	-16.2	32.6	631	-2.8	21.2	313	20.1%	-13.40 [-16.86, -9.94]	+
Wenzel et al. 2016 Subtotal (95% Cl)	-21.86	59.68	114 745	10.91	59	120 <b>433</b>	7.7% <b>27.8</b> %	-32.77 [-47.98, -17.56] -21.61 [-40.37, -2.85]	
Heterogeneity: Tau² = 1 Test for overall effect: Z			-	1 (P = (	).01); I²∘	= 83%			
1.6.3 Dupilumab 200 n	ng q4w								
Wenzel et al. 2016 Subtotal (95% Cl)	-5.47	58	102 <b>102</b>	10.91	59	120 <b>120</b>	7.6% <b>7.6</b> %	-16.38 [-31.81, -0.95] - <b>16.38 [-31.81, -0.95]</b>	•
Heterogeneity: Not app	licable								
Test for overall effect: Z	. = 2.08 (ł	P = 0.04	)						
1.6.4 Dupilumab 300 n	ng q2w								
Castro et al. 2018	-16.2	26	632	-4.6	30.5	321	19.7%	-11.60 [-15.50, -7.70]	+
Rape et al. 2018	-17.3		88	0.3	29.9	89	13.9%	-17.60 [-26.18, -9.02]	
Wenzel et al. 2016 Subtotal (95% Cl)	-29.39	60.6	124 <b>844</b>	10.91	59	120 530	7.9% 41.4%	-40.30 [-55.31, -25.29] - <b>21.18 [-33.97, -8.38]</b>	
Heterogeneity: Tau² = 1 Test for overall effect: Z				= 2 (P =	0.0009	); <b> ²</b> = 8	6%		
1.6.5 Dupilumab 300 n	ng q4w								
Wenzel et al. 2016 Subtotal (95% Cl)	-16.61	59.5	115 <b>115</b>	10.91	59	120 <b>120</b>		-27.52 [-42.68, -12.36] - <b>27.52 [-42.68, -12.36]</b>	•
Heterogeneity: Not app Test for overall effect: Z		P = 0.00	04)						
Total (95% CI)			2048			1326	<b>100.0</b> %	-19.50 [-24.74, -14.25]	◆
Heterogeneity: Tau <sup>2</sup> = 3	32.49: Ch	$i^{2} = 24.3$	32. df =	7 (P = 0)	).001): F	r = 71%	6		-100 -50 0 50 1

Supplementary Figures 2B: A forest plot of the change in FENO (ppb) at week 24 after sensitivity analysis.

	Dupilumab		-	lacebo			Mean Difference	Mean Difference	
Study or Subgroup	Mean		Total	Mean	SD	Total	Weight	IV, Random, 95% Cl	IV, Random, 95% Cl
1.6.1 Dupilumab 100-2	200 mg q2	2w							
Bacharier et al. 2021 Subtotal (95% CI)	-16.8	24.77	242 <b>242</b>	2.66	37.54	123 <b>123</b>		-19.46 [-26.79, -12.13] - <b>19.46 [-26.79, -12.13]</b>	•
Heterogeneity: Not app	olicable								
Test for overall effect: 2	Z = 5.20 (P	P < 0.00	001)						
1.6.2 Dupilumab 200 n	ng q2w								
Castro et al. 2018	-16.2	32.6	631	-2.8	21.2	313	26.5%	-13.40 [-16.86, -9.94]	+
Wenzel et al. 2016	-21.86	59.68	114	10.91	59	120	6.1%		<b>.</b>
Subtotal (95% CI)			745			433	32.6%	-21.61 [-40.37, -2.85]	
Heterogeneity: Tau <sup>2</sup> = 1				1 (P = 0)	).01); <mark>I</mark> ≧:	= 83%			
Test for overall effect: 2	Z = 2.26 (F	P = 0.02	)						
1.6.3 Dupilumab 200 n	ng q4w								
Wenzel et al. 2016 Subtotal (95% Cl)	-5.47	58	102 <b>102</b>	10.91	59	120 <b>120</b>	6.0% <b>6.0</b> %	-16.38 [-31.81, -0.95] - <b>16.38 [-31.81, -0.95]</b>	-
Heterogeneity: Not app	olicable								
Test for overall effect: 2	Z = 2.08 (F	P = 0.04	)						
1.6.4 Dupilumab 300 n	ng q2w								
Castro et al. 2018	-16.2	26	632	-4.6	30.5	321	25.3%	-11.60 [-15.50, -7.70]	₽
Rape et al. 2018	-17.3	28.3	88	0.3	29.9	89	13.7%	-17.60 [-26.18, -9.02]	
Wenzel et al. 2016	-29.39	60.6		10.91	59	120		Not estimable	
Subtotal (95% CI)			720			410	39.0%	-13.34 [-18.67, -8.00]	•
Heterogeneity: Tau <sup>2</sup> = I				(P = 0.2)	1); I² = 3	36%			
Test for overall effect: 2	Z = 4.90 (F	P < 0.00	001)						
1.6.5 Dupilumab 300 n	ng q4w								
Wenzel et al. 2016	-16.61	59.5		10.91	59			-27.52 [-42.68, -12.36]	
Subtotal (95% CI)			115			120	6.2%	-27.52 [-42.68, -12.36]	$\bullet$
Heterogeneity: Not app									
Test for overall effect: 2	Z= 3.56 (F	P = 0.00	04)						
Total (95% CI)			1924			1206	<b>100.0</b> %	-16.74 [-20.93, -12.56]	•
Heterogeneity: Tau <sup>2</sup> = 1	14.08; Ch	i <b>²</b> = 13.2	20, df =	6 (P = 0	0.04); I²∶	= 55%			-100 -50 0 50 10
Test for overall effect: 2				-					-100 -50 0 50 10 Favours (Dupilumab) Favours (Placebo)
Test for subgroup diffe	rences: C	⊳hi <b>²</b> = 4.	29, df=	= 4 (P = I	0.37), <b>I</b> ²	= 6.8%	5		ravers [Dubininab] ravers [riacebo]

**Supplementary Figure 3:** A forest plot of the change in blood eosinophils (cells/mm<sup>3</sup>) at week 12.

	Dupilumab		PI	acebo			Mean Difference	Mean Difference	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% Cl	IV, Random, 95% Cl
1.7.1 Dupilumab 100-200	mg q2v	1							
Bacharier et al. 2021 Subtotal (95% CI)	126.6	936	255 <b>255</b>	63.8	622	131 <b>131</b>	5.2% <b>5.2</b> %	62.80 [-93.86, 219.46] 62.80 [-93.86, 219.46]	
Heterogeneity: Not applica	able								
Test for overall effect: Z =	0.79 (P =	= 0.43	)						
1.7.2 Dupilumab 200 mg	q2w								
Castro et al. 2018 Subtotal (95% CI)	117	537	631 <b>631</b>	-12	269	313 <b>313</b>	47.9% <b>47.9</b> %	129.00 (77.58, 180.42) <b>129.00 (77.58, 180.42)</b>	
Heterogeneity: Not applica	able								
Test for overall effect: Z =	4.92 (P <	< 0.00	001)						
1.7.3 Dupilumab 300 mg	q2w								
Castro et al. 2018	86	528	632	-43	350	321	40.1%	129.00 [72.78, 185.22]	
Wechsler et al. 2021 2	98.624	647	56	-3.517	329.5	52	3.4%	302.14 [110.47, 493.81]	
Wenzel et al. 2013 Subtotal (95% CI)	171	597	44 732	-2	262.2	43 416	3.4% <b>46.9</b> %	173.00 [-20.02, 366.02] 168.27 [76.12, 260.41]	•
Heterogeneity: Tau <sup>2</sup> = 263	3.61; CI	ni <b>≊</b> = 2	.97, df :	= 2 (P = I	0.23); <b>I</b> ²	= 33%			
Test for overall effect: Z = 3	3.58 (P =	= 0.00	03)						
Total (95% CI)			1618			860	100.0%	133.05 [97.46, 168.64]	•
Heterogeneity: $Tau^2 = 0.00$ Test for overall effect: $Z = 7$ Test for subgroup differen	7.33 (P -	< 0.00	001)						-500 -250 0 250 500 Favours (Dupilumab) Favours (Placebo)

**Supplementary Figure 4:** A forest plot of the change in blood eosinophils (cells/mm<sup>3</sup>) at week 24.

	Dupilumab			Р	lacebo			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% Cl	IV, Random, 95% Cl
1.8.1 Dupilumab 100-20	0 mg a	2w							
Bacharier et al. 2021 Subtotal (95% Cl)	75.15	865	250 <b>250</b>	-6.16	553.1	127 <b>127</b>	7.6% <b>7.6</b> %	81.31 [-62.74, 225.36] 81.31 [-62.74, 225.36]	
Heterogeneity: Not appli	cable								
Test for overall effect: Z =	= 1.11 (	(P = 0	.27)						
1.8.2 Dupilumab 200 mg	g q2w								
Castro et al. 2018 Subtotal (95% CI)	84	617	631 <b>631</b>	-23	333	313 <b>313</b>	42.9% <b>42.9</b> %	107.00 [46.35, 167.65] 107.00 [46.35, 167.65]	
Heterogeneity: Not appli Test for overall effect: Z =		(P = 0	.0005)						
1.8.3 Dupilumab 300 mg	g q2w								
Castro et al. 2018 Subtotal (95% Cl)	54	500	632 <b>632</b>	-32	374	321 <b>321</b>	49.5% <b>49.5</b> %	86.00 [29.49, 142.51] <b>86.00 [29.49, 142.51]</b>	
Heterogeneity: Not appli	cable								
Test for overall effect: Z =		(P = 0	.003)						
Total (95% CI)			1513			761	100.0%	94.66 [54.92, 134.40]	•
Heterogeneity: Tau <sup>2</sup> = 0.	00; Chi	i <sup>z</sup> = 0.3	28, df=	2 (P = 0	l.87); <b>I</b> ²	= 0%		-	
Test for overall effect: Z =	= 4.67 (	(P < 0	.00001	)					-200 -100 Ó 100 200 Favours (Dupilumab) Favours (Placebo)
Test for subgroup differe	ences:	Chi <b></b> ⁼=	0.28, 0	lf = 2 (P	= 0.87)	. I <sup>z</sup> = 09	6		

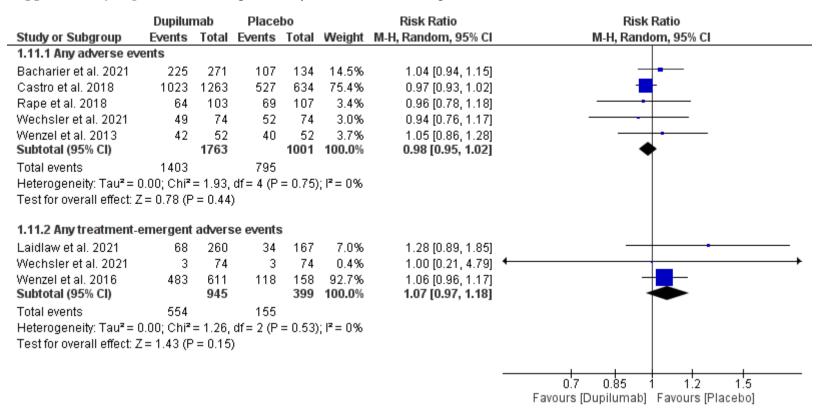
## **Supplementary Figure 5:** A forest plot of the change in IgE (IU/mL) at week 12.

	Dupilur			Pla	acebo			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% Cl	IV, Random, 95% Cl
1.9.1 Dupilumab 200 m	ng q2w								
Castro et al. 2018 Subtotal (95% Cl)	-161.4	326.6	631 <b>631</b>	11.5	306.6	313 <b>313</b>		-172.90 [-215.36, -130.44] - <b>172.90 [-215.36, -130.44]</b>	<b>+</b> ♦
Heterogeneity: Not app	licable								
Test for overall effect: Z	(= 7.98 (P =	< 0.0000	)1)						
1.9.2 Dupilumab 300 m	ng q2w								
Castro et al. 2018	-143.4	303.6	632	-4.5	174.1	321	56.2%	-138.90 [-169.28, -108.52]	•
Wechsler et al. 2021	-132.515	258	63	-29.141	254.4	56	8.3%	-103.37 [-195.56, -11.19]	_ <b></b>
Wenzel et al. 2013	-273.32	638.2		-37.022	175.1	44	1.9%	-236.30 [-429.81, -42.79]	
Subtotal (95% CI)			740			421	66.4%	-137.61 [-166.15, -109.08]	•
Heterogeneity: Tau² = 0 Test for overall effect: Z				= 0.46); l²	= 0%				
Total (95% CI)			1371			734	<b>100.0</b> %	-149.27 [-176.39, -122.16]	•
Heterogeneity: Tau <sup>2</sup> = 1	00.24; Chi <sup>a</sup>	<sup>2</sup> = 3.36,	df = 3	(P = 0.34)	; <b>I</b> ² = 11	%		-	
Test for overall effect: Z	•			, ,					-500 -250 Ó 250 500
Test for subgroup diffe				(P = 0.18)	), l² = 46	5.3%			Favours (Dupilumab) Favours (Placebo)

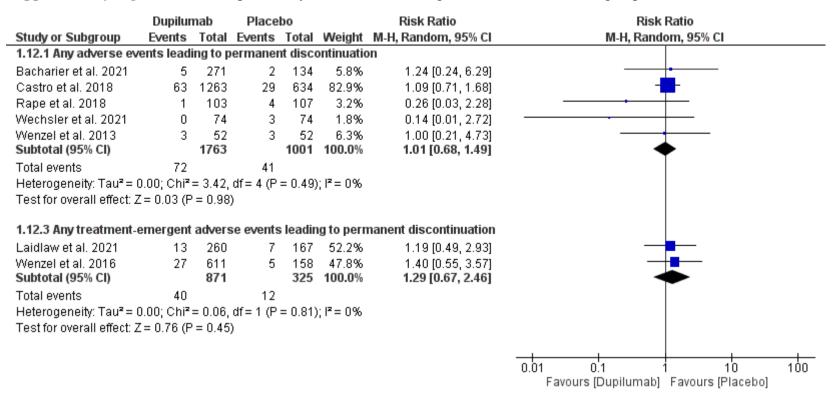
## **Supplementary Figure 6:** A forest plot of the change in IgE (IU/mL) at week 24.

	Dupilumab			F	Placebo			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% Cl	IV, Random, 95% Cl
1.10.1 Dupilumab 100	-200 mg q2	w							
Bacharier et al. 2021 Subtotal (95% Cl)	-431.75	1,292	265 <b>265</b>	-15.91	1,580.7	130 <b>130</b>		-415.84 [-728.94, -102.74] -4 <b>15.84 [-728.94, -102.74]</b>	
Heterogeneity: Not app	olicable								
Test for overall effect: 2	Z = 2.60 (P :	= 0.009)							
1.10.2 Dupilumab 200	mg q2w								
Castro et al. 2018 Subtotal (95% Cl)	-245.6	461.1	631 <b>631</b>	10.5	303.7	313 <b>313</b>	28.6% <b>28.6</b> %	-256.10 [-305.36, -206.84] - <b>256.10 [-305.36, -206.84]</b>	•
Heterogeneity: Not app	olicable								
Test for overall effect: 2	Z = 10.19 (F	° < 0.000	101)						
1.10.3 Dupilumab 300	mg q2w								
Bachert et al. 2020	-36.81	120.21	297	2.72	49.25	150	29.4%	-39.53 [-55.31, -23.75]	•
Castro et al. 2018 Subtotal (95% CI)	-210.4	367.6	632 <b>929</b>	33.5	372.2	321 <b>471</b>	28.6% <b>58.0</b> %	-243.90 [-293.69, -194.11] - <b>140.29 [-340.55, 59.96]</b>	+
Heterogeneity: Tau <sup>2</sup> = 3			.81, df:	= 1 (P ≺	0.00001);	<b>I</b> ² = 98	%		
Test for overall effect: 2	Z=1.37 (P:	= 0.17)							
Total (95% CI)			1825			914	<b>100.0</b> %	-210.28 [-365.02, -55.55]	
Heterogeneity: Tau <sup>2</sup> = 3				f=3(P <	< 0.00001	); <b>I</b> ² = 9	8%		-500 -250 0 250 500
Test for overall effect: 2				-					Favours [Dupilumab] Favours [Placebo]
Test for subgroup diffe	erences: Ch	ll <sup>≠</sup> = 2.27	, df = 2	(P = 0.3)	2), I <sup>z</sup> = 11.	.9%			

Supplementary Figure 7: A forest plot of any and treatment-emergent adverse events.



Supplementary Figure 8: A forest plot of any and treatment-emergent adverse events leading to permanent discontinuation.

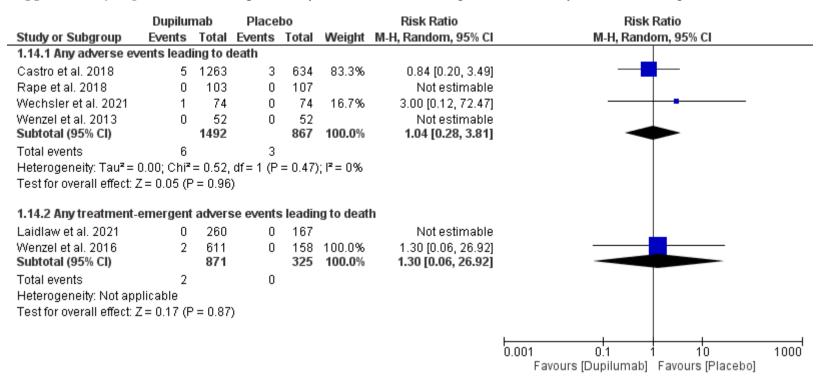


Supplementary Figure 9: A forest plot of serious and treatment-emergent adverse events.

	Dupilur	nab	Place	bo		Risk Ratio		Risk Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl		M-H, Random, 95% Cl	
1.13.1 Serious advers	se events								
Bacharier et al. 2021	13	271	6	134	9.1%	1.07 [0.42, 2.76]			
Castro et al. 2018	104	1263	53	634	81.1%	0.99 [0.72, 1.35]			
Rape et al. 2018	9	103	6	107	8.2%	1.56 [0.58, 4.22]			
Wenzel et al. 2013 Subtotal (95% CI)	1	52 <b>1689</b>	3	52 <b>927</b>	1.6% <b>100.0</b> %	0.33 [0.04, 3.10] 1.01 [0.76, 1.35]	-	•	
Total events	127		68						
Heterogeneity: Tau <sup>2</sup> =	0.00: Chi <sup>z</sup>	= 1.71.	df = 3 (P	= 0.63)	: <b>I</b> ² = 0%				
Test for overall effect: 2	•			,					
			, ,						
1.13.2 Serious treatm	ient-emer	gent ad	verse ev	ents					
Laidlaw et al. 2021	13	260	7	167	37.4%	1.19 [0.49, 2.93]		<b>_</b>	
Wenzel et al. 2016	45	611	9	158	62.6%	1.29 [0.65, 2.59]			
Subtotal (95% CI)		871		325	<b>100.0</b> %	1.25 [0.72, 2.17]			
Total events	58		16						
Heterogeneity: Tau <sup>2</sup> = I	0.00; Chi <sup>z</sup>	= 0.02,	df = 1 (P	= 0.89)	; I² = 0%				
Test for overall effect: 2				,					
	- · · ·		r						
							L		100

Favours (Dupilumab) Favours (Placebo)

Supplementary Figure 10: A forest plot of any adverse events leading to death and any treatment-emergent adverse events leading to death.



Supplementary Figure 11: A forest plot of upper respiratory tract infection, viral upper respiratory tract infection, and influenza adverse events.

	Dupilur	nab	Place	bo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
1.15.1 Upper respirato	ry tract ii	fection	1				
3acharier et al. 2021	35	271	18	134	12.1%	0.96 [0.57, 1.63]	
Castro et al. 2018	146	1263	86	634	54.8%	0.85 [0.66, 1.09]	•
⊥aidlaw et al. 2021	9	260	10	167	4.4%	0.58 [0.24, 1.39]	
Nechsler et al. 2021	4	74	7	74	2.4%	0.57 [0.17, 1.87]	
Venzel et al. 2013	7	52	9	52	4.1%	0.78 [0.31, 1.93]	
Venzel et al. 2016	83	611	28	158	22.2%	0.77 [0.52, 1.13]	
Subtotal (95% Cl)		2531		1219	100.0%	0.82 [0.68, 0.99]	•
Fotal events	284		158				
Heterogeneity: Tau² = (	•	•		= 0.91)	; l² = 0%		
Fest for overall effect: Z	.= 2.12 (P	= 0.03)	I				
I.15.2 Viral upper resp	oiratory tr	act infe	ection				
Bacharier et al. 2021	33	271	13	134	24.5%	1.26 [0.68, 2.30]	
Castro et al. 2018	230	1263	124	634	49.0%	0.93 [0.77, 1.13]	🖷
Rape et al. 2018	9	103	19	107	19.1%	0.49 [0.23, 1.04]	
Nechsler et al. 2021	2	74	5	74	5.6%	0.40 [0.08, 2.00]	
Venzel et al. 2013	3	52	0	52	1.8%	7.00 [0.37, 132.23]	
Subtotal (95% Cl)		1763		1001	<b>100.0</b> %	0.88 [0.59, 1.31]	♠
Fotal events	277		161				
Heterogeneity: Tau <sup>2</sup> = (	).08; Chi <mark></mark> ≇	= 6.59,	df = 4 (P	= 0.16)	; I <sup>z</sup> = 39%		
Fest for overall effect: Z	C= 0.64 (P	= 0.52)	I				
1.15.3 Influenza							
Castro et al. 2018	74	1263	51	634	52.3%	0.73 [0.52, 1.03]	
Rape et al. 2018	3	103	6	107	18.2%	0.52 [0.13, 2.02]	
Venzel et al. 2016	38	611	5	158	29.4%	1.97 [0.79, 4.91]	
Subtotal (95% CI)		1977		899	100.0%	0.92 [0.46, 1.84]	<b>•</b>
Fotal events	115		62				
Heterogeneity: Tau <sup>2</sup> = (	).21; Chi <mark></mark> ≇	= 4.43,	df = 2 (P	= 0.11)	; I <sup>z</sup> = 55%	, ,	
Fest for overall effect: Z					-		
							, ,   ,
							0.005 0.1 1 10 200
							Favours [Dupilumab] Favours [Placebo]

Supplementary Figure 12: A forest plot of nasopharyngitis, sinusitis, and bronchitis adverse events.

	Dupilur	nab	Place	bo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
1.16.1 Nasopharyngiti	is						
Bacharier et al. 2021	50	271	29	134	39.0%	0.85 [0.57, 1.28]	- <b>-</b> -
Laidlaw et al. 2021	33	260	24	167	27.2%	0.88 [0.54, 1.44]	<b>_</b>
Wechsler et al. 2021	9	74	9	74	8.7%	1.00 [0.42, 2.38]	
Wenzel et al. 2013	7	52	2	52	2.8%	3.50 [0.76, 16.06]	
Wenzel et al. 2016	59	611	15	158	22.3%	1.02 [0.59, 1.74]	
Subtotal (95% CI)		1268		585	100.0%	0.94 [0.73, 1.22]	•
Total events	158		79				
Heterogeneity: Tau² =	•		•	= 0.51)	; I² = 0%		
Test for overall effect: 2	Z=0.44 (P	= 0.66	)				
1.16.2 Sinusitis							
Bacharier et al. 2021	9	271	7	134	27.0%	0.64 [0.24, 1.67]	
Rape et al. 2018	7	103	4	107	19.0%	1.82 [0.55, 6.03]	
Wenzel et al. 2013	1	52	5	52	6.8%	0.20 [0.02, 1.65]	
Wenzel et al. 2016	36	611	11	158	47.1%	0.85 [0.44, 1.62]	
Subtotal (95% CI)		1037		451	100.0%	0.82 [0.47, 1.45]	
Total events	53		27				
Heterogeneity: Tau² =				= 0.30)	; I <sup>z</sup> = 19%	)	
Test for overall effect: 2	Z = 0.68 (P	= 0.50	)				
1.16.4 Bronchitis							
Bacharier et al. 2021	17	271	14	134	9.6%	0.60 [0.31, 1.18]	
Castro et al. 2018	144	1263	89	634	72.0%	0.81 [0.63, 1.04]	
Rape et al. 2018	7	103	6	107	3.9%	1.21 [0.42, 3.49]	
Wenzel et al. 2016	51	611	15	158	14.5%	0.88 [0.51, 1.52]	
Subtotal (95% Cl)		2248		1033	<b>100.0</b> %	0.81 [0.66, 1.00]	◆
Total events	219		124				
Heterogeneity: Tau² =				= 0.71)	; I² = 0%		
Test for overall effect: 2	Z = 1.97 (P	= 0.05	)				
							Favours [Dupilumab] Favours [Placebo]
							, areas a feature and a state fride and

Supplementary Figure 13: A forest plot of injection site reaction, eosinophilia, and headache adverse events.

	Dupilur	nab	Place	bo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
1.17.1 Injection-site re	eaction						
Bacharier et al. 2021	80	271	23	134	19.8%	1.72 [1.14, 2.60]	
Castro et al. 2018	212	1263	50	634	29.0%	2.13 [1.59, 2.85]	+
_aidlaw et al. 2021	60	260	33	167	22.2%	1.17 [0.80, 1.70]	
Rape et al. 2018	9	103	4	107	3.8%	2.34 [0.74, 7.35]	
Nechsler et al. 2021	4	74	4	74	2.8%	1.00 [0.26, 3.85]	
Veinstein et al. 2018	60	249	19	140	16.7%	1.78 [1.11, 2.85]	_ <b></b>
Venzel et al. 2013	15	52	5	52	5.5%	3.00 [1.18, 7.65]	
Subtotal (95% CI)		2272		1308	100.0%	1.73 [1.37, 2.19]	◆
Fotal events	440		138				
Heterogeneity: Tau <sup>2</sup> =	0.03; Chi <b></b> ²÷	= 8.38,	df = 6 (P :	= 0.21);	, <b>I</b> ² = 28%		
Fest for overall effect: 2	Z=4.64 (P	< 0.000	001)				
1.17.2 Eosinophilia							
Bacharier et al. 2021	16	271	1	134	50.0%	7.91 [1.06, 59.03]	
Rape et al. 2018	14	103	1	107	50.0%	14.54 [1.95, 108.61]	
Subtotal (95% Cl)		374		241	<b>100.0</b> %	10.73 [2.59, 44.43]	
Fotal events	30		2				
Heterogeneity: Tau² =	0.00; Chi <b></b> r:	•	df=1 (P:	= 0.67);	<sup>2</sup> = 0%		
	0.00; Chi <b></b> r:	•	df=1 (P:	= 0.67);	; I² = 0%		
Heterogeneity: Tau² = Fest for overall effect: 2	0.00; Chi <b></b> r:	•	df=1 (P:	= 0.67);	; I² = 0%		
Heterogeneity: Tau <sup>2</sup> = Fest for overall effect: 2 I.17.3 Headache	0.00; Chi <sup>z</sup> : Z = 3.27 (P	= 0.00'	df = 1 (P : l)				
Heterogeneity: Tau <sup>2</sup> = Fest for overall effect: 2 I. <b>17.3 Headache</b> Bacharier et al. 2021	0.00; Chi <sup>z</sup> : Z= 3.27 (P 19	= 0.00 <sup>2</sup> 271	df = 1 (P = 1) 10	134	9.4%	0.94 [0.45, 1.96]	
Heterogeneity: Tau <sup>2</sup> = Fest for overall effect: 2 I. <b>17.3 Headache</b> Bacharier et al. 2021 Castro et al. 2018	0.00; Chi <sup>‡</sup> : Z= 3.27 (P 19 86	= 0.00 <sup>2</sup> 271 1263	df = 1 (P = 1) 10 51	134 634	9.4% 45.9%	0.85 [0.61, 1.18]	
Heterogeneity: Tau <sup>2</sup> = Fest for overall effect: 2 I.17.3 Headache Bacharier et al. 2021 Castro et al. 2018 Laidlaw et al. 2021	0.00; Chi <sup>≉</sup> : Z = 3.27 (P 19 86 20	= 0.00 <sup>4</sup> 271 1263 260	df = 1 (P = 1) 10 51 16	134 634 167	9.4% 45.9% 12.9%	0.85 [0.61, 1.18] 0.80 [0.43, 1.50]	
Heterogeneity: Tau <sup>2</sup> = Fest for overall effect: 2 I.17.3 Headache Bacharier et al. 2021 Castro et al. 2018 Laidlaw et al. 2021 Wechsler et al. 2021	0.00; Chi <sup>≉</sup> : Z = 3.27 (P 19 86 20 10	= 0.00 <sup>4</sup> 271 1263 260 74	df = 1 (P = 1) 10 51 16 7	134 634 167 74	9.4% 45.9% 12.9% 6.1%	0.85 [0.61, 1.18] 0.80 [0.43, 1.50] 1.43 [0.57, 3.55]	
Heterogeneity: Tau <sup>2</sup> = Fest for overall effect: 2 I.17.3 Headache Bacharier et al. 2021 Castro et al. 2018 Laidlaw et al. 2021 Wechsler et al. 2021 Wenzel et al. 2013	0.00; Chi <sup>≉</sup> : Z = 3.27 (P 19 86 20 10 6	= 0.00 <sup>4</sup> 271 1263 260 74 52	df = 1 (P = 1) 10 51 16 7 3	134 634 167 74 52	9.4% 45.9% 12.9% 6.1% 2.9%	0.85 [0.61, 1.18] 0.80 [0.43, 1.50] 1.43 [0.57, 3.55] 2.00 [0.53, 7.57]	
Heterogeneity: Tau <sup>2</sup> = Fest for overall effect: 2 <b>I.17.3 Headache</b> Bacharier et al. 2021 Castro et al. 2018 Laidlaw et al. 2021 Wechsler et al. 2021 Wenzel et al. 2013 Wenzel et al. 2016	0.00; Chi <sup>≉</sup> : Z = 3.27 (P 19 86 20 10	= 0.00 <sup>4</sup> 271 1263 260 74 52 611	df = 1 (P = 1) 10 51 16 7	134 634 167 74 52 158	9.4% 45.9% 12.9% 6.1% 2.9% 22.8%	0.85 [0.61, 1.18] 0.80 [0.43, 1.50] 1.43 [0.57, 3.55] 2.00 [0.53, 7.57] 0.80 [0.50, 1.29]	
Heterogeneity: Tau <sup>2</sup> = Fest for overall effect: 2 <b>I.17.3 Headache</b> Bacharier et al. 2021 Castro et al. 2018 Laidlaw et al. 2021 Wechsler et al. 2021 Wenzel et al. 2013 Wenzel et al. 2016 Subtotal (95% CI)	0.00; Chi <sup>a</sup> : Z = 3.27 (P 19 86 20 10 62	= 0.00 <sup>4</sup> 271 1263 260 74 52	df = 1 (P 1) 10 51 16 7 3 20	134 634 167 74 52 158	9.4% 45.9% 12.9% 6.1% 2.9%	0.85 [0.61, 1.18] 0.80 [0.43, 1.50] 1.43 [0.57, 3.55] 2.00 [0.53, 7.57]	
Heterogeneity: Tau <sup>2</sup> = Fest for overall effect: 2 <b>I.17.3 Headache</b> Bacharier et al. 2021 Castro et al. 2018 Laidlaw et al. 2021 Wechsler et al. 2021 Wenzel et al. 2013 Wenzel et al. 2016 <b>Subtotal (95% CI)</b> Fotal events	0.00; Chi <sup>a</sup> : Z = 3.27 (P 19 86 20 10 62 203	= 0.00 <sup>°</sup> 271 1263 260 74 52 611 <b>2531</b>	df = 1 (P = 1) 10 51 16 7 3 20 107	134 634 167 74 52 158 <b>1219</b>	9.4% 45.9% 12.9% 6.1% 2.9% 22.8% <b>100.0</b> %	0.85 [0.61, 1.18] 0.80 [0.43, 1.50] 1.43 [0.57, 3.55] 2.00 [0.53, 7.57] 0.80 [0.50, 1.29]	
Heterogeneity: Tau <sup>2</sup> = Fest for overall effect: 2 <b>I.17.3 Headache</b> Bacharier et al. 2021 Castro et al. 2018 Laidlaw et al. 2021 Wechsler et al. 2021 Wenzel et al. 2013 Wenzel et al. 2016 <b>Subtotal (95% CI)</b> Fotal events Heterogeneity: Tau <sup>2</sup> =	0.00; Chi <sup>≆</sup> : Z = 3.27 (P 19 86 20 10 62 203 0.00; Chi <sup>≇</sup> :	= 0.00 <sup>°</sup> 271 1263 260 74 52 611 <b>2531</b> = 2.86,	df = 1 (P = 1) 10 51 16 7 3 20 107 df = 5 (P =	134 634 167 74 52 158 <b>1219</b>	9.4% 45.9% 12.9% 6.1% 2.9% 22.8% <b>100.0</b> %	0.85 [0.61, 1.18] 0.80 [0.43, 1.50] 1.43 [0.57, 3.55] 2.00 [0.53, 7.57] 0.80 [0.50, 1.29]	
Heterogeneity: Tau <sup>2</sup> = Fest for overall effect: 2 <b>I.17.3 Headache</b> Bacharier et al. 2021 Castro et al. 2018 Laidlaw et al. 2021 Wechsler et al. 2021 Wenzel et al. 2013 Wenzel et al. 2016 <b>Subtotal (95% CI)</b> Fotal events	0.00; Chi <sup>≆</sup> : Z = 3.27 (P 19 86 20 10 62 203 0.00; Chi <sup>≇</sup> :	= 0.00 <sup>°</sup> 271 1263 260 74 52 611 <b>2531</b> = 2.86,	df = 1 (P = 1) 10 51 16 7 3 20 107 df = 5 (P =	134 634 167 74 52 158 <b>1219</b>	9.4% 45.9% 12.9% 6.1% 2.9% 22.8% <b>100.0</b> %	0.85 [0.61, 1.18] 0.80 [0.43, 1.50] 1.43 [0.57, 3.55] 2.00 [0.53, 7.57] 0.80 [0.50, 1.29]	
Heterogeneity: Tau <sup>2</sup> = Fest for overall effect: 2 <b>I.17.3 Headache</b> Bacharier et al. 2021 Castro et al. 2018 Laidlaw et al. 2021 Wechsler et al. 2021 Wenzel et al. 2013 Wenzel et al. 2016 <b>Subtotal (95% CI)</b> Fotal events Heterogeneity: Tau <sup>2</sup> =	0.00; Chi <sup>≆</sup> : Z = 3.27 (P 19 86 20 10 62 203 0.00; Chi <sup>≇</sup> :	= 0.00 <sup>°</sup> 271 1263 260 74 52 611 <b>2531</b> = 2.86,	df = 1 (P = 1) 10 51 16 7 3 20 107 df = 5 (P =	134 634 167 74 52 158 <b>1219</b>	9.4% 45.9% 12.9% 6.1% 2.9% 22.8% <b>100.0</b> %	0.85 [0.61, 1.18] 0.80 [0.43, 1.50] 1.43 [0.57, 3.55] 2.00 [0.53, 7.57] 0.80 [0.50, 1.29]	
Heterogeneity: Tau <sup>2</sup> = Fest for overall effect: 2 <b>I.17.3 Headache</b> Bacharier et al. 2021 Castro et al. 2018 Laidlaw et al. 2021 Wechsler et al. 2021 Wenzel et al. 2013 Wenzel et al. 2016 <b>Subtotal (95% CI)</b> Fotal events Heterogeneity: Tau <sup>2</sup> =	0.00; Chi <sup>≆</sup> : Z = 3.27 (P 19 86 20 10 62 203 0.00; Chi <sup>≇</sup> :	= 0.00 <sup>°</sup> 271 1263 260 74 52 611 <b>2531</b> = 2.86,	df = 1 (P = 1) 10 51 16 7 3 20 107 df = 5 (P =	134 634 167 74 52 158 <b>1219</b>	9.4% 45.9% 12.9% 6.1% 2.9% 22.8% <b>100.0</b> %	0.85 [0.61, 1.18] 0.80 [0.43, 1.50] 1.43 [0.57, 3.55] 2.00 [0.53, 7.57] 0.80 [0.50, 1.29]	

Supplementary Figure 14: A forest plot of allergic rhinitis, cough, urinary tract infection, back pain, and erythema adverse events.

	Dupilur	nab	Place	bo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
1.18.1 Allergic rhinitis							
Bacharier et al. 2021	16	271	16	134	40.5%	0.49 [0.26, 0.96]	
Castro et al. 2018	39	1263	31	634	50.9%	0.63 [0.40, 1.00]	
Wechsler et al. 2021	5	74	1	74	8.6%	5.00 [0.60, 41.77]	
Subtotal (95% CI)		1608		842	100.0%	0.68 [0.35, 1.33]	-
Total events	60		48				
Heterogeneity: Tau <sup>2</sup> = 0				= 0.12)	); <b>I</b> ² = 53%		
Test for overall effect: Z	= 1.12 (P	= 0.26	)				
1.18.2 Cough							
Bacharier et al. 2021	15	271	9	134	74.5%	0.82 [0.37, 1.83]	
Wechsler et al. 2021	10	74	9 5	74		0.20 [0.02, 1.67]	
Subtotal (95% CI)	1	345	5		100.0%	0.57 [0.17, 1.96]	
Total events	16	0.0	14	200			
Heterogeneity: Tau <sup>2</sup> = 0		= 1.54		= 0.22	: I <b>≧</b> = 35%	5	
Test for overall effect: Z	•			0.22,	,		
	(-		,				
1.18.3 Urinary tract inf	ection						_
Castro et al. 2018	36	1263	29	634	93.1%	0.62 [0.39, 1.01]	
Wechsler et al. 2021	3	74	2	74	6.9%	1.50 [0.26, 8.72]	
Subtotal (95% CI)		1337		708	100.0%	0.66 [0.42, 1.05]	•
Total events	39		31				
Heterogeneity: Tau <sup>2</sup> = 0	•			= 0.35)	; I² = 0%		
Test for overall effect: Z	= 1.75 (P	' = 0.08	)				
1.18.4 Back pain							
Castro et al. 2018	55	1263	23	634	95.7%	1.20 [0.74, 1.93]	
Wechsler et al. 2021	3	74		74	4.3%	3.00 [0.32, 28.18]	
Subtotal (95% CI)	-	1337			100.0%	1.25 [0.78, 1.99]	
Total events	58		24				_
Heterogeneity: Tau <sup>2</sup> = 0	.00; Chi²	= 0.62,	df = 1 (P	= 0.43)	; I² = 0%		
Test for overall effect: Z	= 0.93 (P	= 0.35	)				
4 49 E Endhoma							
1.18.5 Erythema	0.5	074	4.0	404	5 4 O.Y	4 00 10 70 0 401	
Bacharier et al. 2021	35				54.8%		
Laidlaw et al. 2021 Subtotal (95% Cl)	19	260 531	14	167	45.2% <b>100.0</b> %	0.87 [0.45, 1.69] 1.10 [0.70, 1.72]	
Total events	54	551	27	301	100.070	1.10[0.10, 1.12]	
Heterogeneity: Tau <sup>2</sup> = 0		<u> 99 0 -</u>		= 0.26	· IZ = 0.94		
Test for overall effect: Z		-	-	- 0.50,	, i = 0 %		
Cottor overall ellett. Z	- 0.42 (F	- 0.00	/				
							0.01 0.1 1 10 100
							Favours [Dupilumab] Favours [Placebo]