

## Supplementary materials

**Table S1: Ethics Committees**

<i>BULGARIA</i>
Ethics Committee for Multicentre Trials, Sofia
<i>CZECH REPUBLIC</i>
Ethics Committee Faculty Hospital Kralovske Vinohrady, Prague
<i>GERMANY</i>
Ethics Committee of Hessen State Medical Association, Frankfurt
<i>HUNGARY</i>
Medical Research Council Ethics Committee for Clinical Pharmacology, Budapest
<i>LATVIA</i>
Ethics Committee for Clinical Research at Development Society of Pauls Stradins, Riga
<i>LITHUANIA</i>
Lithuanian Bioethics Committee, Vilnius
<i>MACEDONIA</i>
Macedonian Agency for Medicines and Medical Devices, Ethics Committee for Clinical and Other Trials Related to Medicines and Medical Devices, Skopje
<i>POLAND</i>
Bioethics Committee at the Regional Chamber of Physicians in Cracow, Kraków
<i>ROMANIA</i>
The National Ethics Committee for the Clinical Study of Medicine, Bucharest
<i>RUSSIA</i>
Ethics Committee under Federal State Budgetary Institution Federal Scientific Clinical Center of Specialized Medical Care and Medical Technologies of Federal Medical and Biological Agency, Moscow
Joint Local Ethics Committee of the Municipal Budgetary Healthcare Institution, Kemerovo Cardiologic Healthcare Centre and Federal State Budgetary Institution Research Institute of Complex Cardiovascular Problems of the Siberian Division of the Russian Academy of Medical Sciences, Kemerovo
Ethics Committee at the State Budgetary Educational Institution of Higher Professional Education, Siberian State Medical University of the Ministry of Health of the Russian Federation, Tomsk
Ethics Committee at the Municipal Budgetary Healthcare Institution City Clinical Hospital No. 3 named after M.A. Podgorbunskiy, Kemerovo
Ethics Committee at the Federal State Budgetary Institution Research Institute of Internal Medicine and Preventative Care of the Siberian Branch of Russian Academy of Medical Sciences, Novosibirsk

Local Ethics Committee at State Budgetary Healthcare Institution of Leningrad Region Centre for Occupational Pathology, Saint Petersburg
Ethics Committee at the State Budgetary Educational Institution of Higher Professional Education First Saint Petersburg State Medical University named after I.P. Pavlov of the Ministry of Health of the Russian Federation, Saint Petersburg
Ethics Committee at State Budgetary Healthcare Institution of Novosibirsk Region, City Clinical Hospital of Emergency Medical Care No. 2, Novosibirsk
Ethics Committee at State Budgetary Educational Institution of Higher Professional Education Orenburg State Medical Academy of the Ministry of Healthcare of the Russian Federation, Orenburg
Ethics Committee at First Moscow State Medical University named after I.M. Sechenov of the Ministry of Health of the Russian Federation, Moscow
Ethics Committee at State Healthcare Institution of Yaroslavl Region, Clinical Hospital No. 2, Yaroslavl
Ethics Committee at State Healthcare Institution, City Clinical Hospital No. 51 of the Department of Health of the city of Moscow, Moscow
<i>SLOVAKIA</i>
Ethics Committee Self-Governing Region of Kosice, Kosice
<i>SOUTH AFRICA</i>
Pharma-Ethics (Pty) Ltd, Pretoria
<i>SOUTH KOREA</i>
Konkuk University Medical Center IRB, Seoul
Seoul St. Mary's Hospital IRB, Seoul
Hallym University Sacred Heart Hospital IRB, Gyeonggi-do
Yonsei University Wonju Severance Christian Hospital IRB, Gangwon-do
Korea University Guro Hospital IRB, Seoul
Yeungnam University Hospital IRB, Daegu
Soon Chun Hyang University Hospital Bucheon IRB, Gyeonggi-do
Yonsei University Health System Severance Hospital IRB, Seoul
<i>SPAIN</i>
Clinical Research Ethics Committee Parc de Salut MAR, Barcelona
<i>UKRAINE</i>
Local Ethics Commission of the Communal Healthcare Institution "Kharkiv City Multidisciplinary Hospital No 18", Kharkiv
Local Ethics Commission of the State Institution "F.H. Yanovskyi National Phthiology and Pulmonology Institute of the National Academy of Medical Sciences of Ukraine", Kyiv
Local Ethics Commission of the Communal Healthcare Institution "Oblast Clinical Hospital – Centre of Emergency Medical Care and Disaster Medicine", Kharkiv
Local Bioethics Commission of the Oblast Phthiopulmonology Center of the City of Ivano-Frankivsk, Ivano-Frankivsk
Local Bioethics Commission of the State Institution "Ukrainian State Scientific Research Institute of the Medical and Social Problems of Disability of the Ministry of Health of Ukraine", Dnipropetrovsk
Local Ethics Commission of the Communal Institution of Sumy Oblast Council "Sumy Oblast Clinical Hospital", Sumy
Local Ethics Commission of the Kyiv City Clinical Hospital No.8, Kyiv

Local Ethics Commission of the Communal Institution "M.V. Sklifosovskyi Poltava Oblast Clinical Hospital", Poltava
Local Ethics Commission of the Communal Institution "City Hospital No.7", Zaporizhzhia
Local Ethics Commission of the Communal Healthcare Institution "Prof. O.I Meshchaninov, Kharkiv City Clinical Hospital of Emergency and Urgent Clinical Care", Kharkiv
Local Ethics Commission of the State Institution "F.H. Yanovskyi National Phthisiology and Pulmonology Institute of the National Academy of Medical Sciences of Ukraine", Kyiv
Local Ethics Commission of the Communal Institution "Uzhhorod Raion Hospital", Uzhhorod
Local Ethics Commission of the Communal Institution "Zaporizhzhia City Clinical Hospital No. 10", Zaporizhzhia
Local Ethics Commission of City Clinical Hospital No. 1 of the City of Vinnytsia, Vinnytsia
Local Ethics Commission of the Communal Institution "Odessa Oblast Clinical Hospital", Odessa
Local Ethics Commission of the Communal Institution "Sumy City Clinical Hospital No. 1", Sumy
Local Ethics Commission of the Scientific and Practical Medical Centre of Kharkiv National Medical University, Kharkiv
<i>UNITED KINGDOM</i>
NRES Committee: South West – Exeter, Bristol

**Table S2: *Post hoc* analysis of blood eosinophils at baseline (Full Analysis Population)**

	<b>FP/FORM 500/20</b>	<b>FP/FORM 250/10</b>	<b>FORM 12</b>
Blood eosinophils (%)			
< 2%	37.3	36.9	39.8
≥ 2% to < 3%	22.7	24.8	23.2
≥ 3% to < 4%	15.8	16.7	13.9
≥ 4%	24.2	21.6	23.1

Fluticasone propionate, FP; Formoterol fumarate, FORM.

**Table S3: *Post hoc* analysis of annualized rate of moderate / severe exacerbations by baseline blood eosinophil category (Full Analysis Population)**

<b>Blood eosinophils &lt;2% or ≥2%</b>			
<b>Subgroup with baseline blood eosinophils &lt;2%</b>			
	<b>FP/FORM 500/20 N=219</b>	<b>FP/FORM 250/10 N=217</b>	<b>FORM 12 N=235</b>
LSM rate moderate / severe exacerbations (events/patient/year)	0.70	0.77	0.84
Rate ratio (95% CIs) versus FORM	0.83 (0.63, 1.08)	0.92 (0.70, 1.20)	
	p=0.170	p=0.532	
<b>Subgroup with baseline blood eosinophils ≥2%</b>			
	<b>FP/FORM 500/20 N=368</b>	<b>FP/FORM 250/10 N=371</b>	<b>FORM N=355</b>
LSM rate moderate / severe exacerbations (events/patient/year)	0.88	0.83	0.88
Rate ratio (95% CIs) versus FORM	1.00 (0.81, 1.24)	0.95 (0.77, 1.18)	
	p=0.984	p=0.634	
<b>Blood eosinophils &lt;3% or ≥3%</b>			
<b>Subgroup with baseline blood eosinophils &lt;3%</b>			
	<b>FP/FORM 500/20 N=352</b>	<b>FP/FORM 250/10 N=363</b>	<b>FORM 12 N=372</b>
LSM rate moderate / severe exacerbations (events/patient/year)	0.73	0.73	0.79
Rate ratio (95% CIs) versus FORM	0.93 (0.74, 1.15)	0.92 (0.74, 1.14)	
	p=0.487	p=0.423	
<b>Subgroup with baseline blood eosinophils ≥3%</b>			
	<b>FP/FORM 500/20 N=235</b>	<b>FP/FORM 250/10 N=225</b>	<b>FORM 12 N=218</b>
LSM rate moderate / severe exacerbations (events/patient/year)	0.94	0.92	0.98
Rate ratio (95% CIs) versus FORM	0.97 (0.74, 1.26)	0.94 (0.73, 1.22)	
	p=0.803	p=0.654	
<b>Blood eosinophils &lt;4% or ≥4%</b>			
<b>Subgroup with baseline blood eosinophils &lt;4%</b>			
	<b>FP/FORM 500/20 N=445</b>	<b>FP/FORM 250/10 N=461</b>	<b>FORM 12 N=454</b>
LSM rate moderate / severe exacerbations	0.76	0.80	0.86

(events/patient/year)			
Rate ratio (95% CIs) versus FORM	0.88 (0.73, 1.07)	0.93 (0.77, 1.12)	
	p=0.202	p=0.438	
<b>Subgroup with baseline blood eosinophils ≥4%</b>			
	<b>FP/FORM 500/20 N=142</b>	<b>FP/FORM 250/10 N=127</b>	<b>FORM 12 N=136</b>
LSM rate moderate / severe exacerbations (events/patient/year)	0.94	0.80	0.82
Rate ratio (95% CIs) versus FORM	1.14 (0.81, 1.61)	0.97 (0.67, 1.39)	
	p=0.445	p=0.864	

Fluticasone propionate, FP; Formoterol fumarate, FORM; Least squares mean, LS mean; Confidence Interval, CI;

**Table S4: SP-D at baseline and week 6 (Full Analysis Population)**

	<b>FP/FORM 500/20</b>		<b>FP/FORM 250/10</b>		<b>FORM 12</b>	
	Value (ng/mL)	Change from Baseline	Value (ng/mL)	Change from Baseline	Value (ng/mL)	Change from Baseline
<b>Baseline</b>						
n	117		114		111	
Mean (SD)	202.2(111.1)		191.7 (108.8)		196.5 (126.5)	
Median	187.0		175.5		175.0	
Q1, Q3	124.0, 263.0		118.0, 254.0		119.0, 254.0	
Min, Max	35.4, 682.0		39.7, 612.0		36.6, 878.0	
<b>Week 6</b>						
n	105	100	102	98	101	94
Mean (SD)	191.8 (110.3)	-4.1 (68.4)	194.4 (102.6)	5.2 (49.2)	178.9 (96.0)	-3.1 (62.6)
Median	185.0	-4.5	182.0	1.0	159.0	-3.5
Q1, Q3	123.0, 248.0	-22.5, 22.5	123.0, 246.0	-24.0, 22.0	118.0, 213.0	-25.0, 14.0
Min, Max	31.4, 633.0	-410.0, 187.0	34.8, 578.0	-87.0, 223.0	25.8, 576.0	-208.0, 366.9

Surfactant protein D, SP-D; Fluticasone propionate, FP; Formoterol fumarate, FORM; Standard Deviation, SD; Quartile, Q; Minimum, Min; Maximum, Max.

**Table S5: CCL-18 at baseline and week 6 (Full Analysis Population)**

	FP/FORM 500/20		FP/FORM 250/10		FORM 12	
	Value (ng/mL)	Change from Baseline	Value (ng/mL)	Change from Baseline	Value (ng/mL)	Change from Baseline
Baseline						
n	120		115		111	
Mean (SD)	137.2 (68.7)		141.3 (77.7)		141.2 (68.4)	
Median	127.5		117.0		130.0	
Q1, Q3	84.0, 171.5		92.0, 189.0		87.0, 168.0	
Min, Max	1, 361		41, 553		32, 383	
Week 6						
n	103	100	103	100	101	94
Mean (SD)	147.8 (79.8)	9.8 (62.0)	138.5 (69.2)	-1.5 (49.7)	137.7 (73.8)	-4.9 (43.7)
Median	133.0	6.0	119.0	0.5	121.0	-5.0
Q1, Q3	96.0, 180.0	-12.0, 20.5	89.0, 176.0	-24.0, 19.0	87.0, 163.0	-24.0, 11.0
Min, Max	48, 645	-130, 470	44, 483	-152, 285	35, 461	-191, 123

CC chemokine ligand 18, CCL-18; Fluticasone propionate, FP; Formoterol fumarate, FORM; Standard Deviation, SD; Quartile, Q; Minimum, Min; Maximum, Max.

**Table S6: Incidence (n [%]) of individual adverse events occurring in ≥1% of patients in any treatment group**

	<b>FP/FORM 500/20</b>	<b>FP/FORM 250/10</b>	<b>FORM 12</b>
<b>CARDIAC DISORDERS</b>			
Angina pectoris	3 (0.5)	7 (1.2)	2 (0.3)
Atrial fibrillation	5 (0.9)	4 (0.7)	10 (1.7)
Cardiac failure	9 (1.5)	6 (1.0)	3 (0.5)
Tachycardia	7 (1.2)	2 (0.3)	4 (0.7)
Ventricular extrasystoles	4 (0.7)	6 (1.0)	4 (0.7)
Ventricular tachycardia	6 (1.0)	9 (1.5)	4 (0.7)
<b>GENERAL DISORDERS</b>			
Oedema peripheral	4 (0.7)	3 (0.5)	6 (1.0)
<b>INFECTIONS AND INFESTATIONS</b>			
Influenza	2 (0.3)	7 (1.2)	5 (0.8)
Nasopharyngitis	31 (5.3)	30 (5.1)	30 (5.1)
Pneumonia	17 (2.9)	21 (3.6)	11 (1.9)
Respiratory tract infection	4 (0.7)	6 (1.0)	4 (0.7)
Respiratory tract infection viral	2 (0.3)	3 (0.5)	8 (1.4)
Upper respiratory tract infection	9 (1.5)	9 (1.5)	9 (1.5)
<b>INVESTIGATIONS</b>			
Blood uric acid increased	1 (0.2)	7 (1.2)	3 (0.5)
Gamma-glutamyltransferase increased	2 (0.3)	7 (1.2)	3 (0.5)
<b>METABOLISM AND NUTRITION DISORDERS</b>			
Hypercholesterolaemia	6 (1.0)	7 (1.2)	6 (1.0)
Hypertriglyceridaemia	3 (0.5)	6 (1.0)	4 (0.7)
<b>MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS</b>			
Back pain	6 (1.0)	9 (1.5)	3 (0.5)
Muscle spasms	1 (0.2)	6 (1.0)	1 (0.2)
<b>NERVOUS SYSTEM DISORDERS</b>			
Headache	7 (1.2)	8 (1.4)	8 (1.4)
<b>RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS</b>			
Chronic obstructive pulmonary disease	8 (1.4)	6 (1.0)	4 (0.7)
Cough	5 (0.9)	9 (1.5)	1 (0.2)
Dyspnoea	10 (1.7)	6 (1.0)	10 (1.7)
<b>VASCULAR DISORDERS</b>			
Hypertension	19 (3.2)	16 (2.7)	13 (2.2)

Fluticasone propionate, FP; Formoterol fumarate, FORM.



