

**Supplementary Table 1.** List of Independent Ethics Committees for ACLIFORM COPD

<b>Country</b>	<b>Name and address of central IEC</b>	<b>Name and address of local IEC</b>
Austria	Ethikkommission der Medizinischen, Universität Graz, Auenbruggerplatz 2, 8036 Graz	Ethics committee of the Medical University Graz, Auenbruggerplatz 2, 8036 Graz
		Ethics committee of the country Salzburg, Sebastian- Stief-Gasse 2, 5010 Salzburg
Belgium	Ethisch Comité UZA, Wilrijkstraat 10, Edegem 2650	NA
Bulgaria	Ethics Committee for Multicenter Trials (ECMT), 5, “Sveta Nedelya” Square, 1000 Sofia	Local Ethics Committee UMHAT Aleksandrovska EAD, 3, Georgi Sofiyski Str. 1431 Sofia
		Local Ethics Committee SHATTPD-Ruse EOOD, 1, Aleya Lilia Str. 7002 Ruse
		Local Ethics Committee SHATPFD-Sofia District EOOD, 309, “Slivnitsa” Blvd, 1234 Sofia
		Local Ethics Committee DCC Sveta Anna EOOD, 1, Dimitar Mollov Str. 1709 Sofia
		Local Ethics Committee DCC “Akta Medika” EOOD, 60, “Nikola Petkov” Str., 5400 Sevlievo

Croatia	Agency for Medicinal Product and Medical Devices of Croatia, Central Ethics Committee, Ksaverska cesta 4, Zagreb, 10000	NA
Czech Republic	Multicentricka eticka komise Fakultni nemocnice u sv. Anny v Brne, Vystavni 17/19, Brno, 656	NA
Denmark	De Videnskabsetiske Komitéer for Region Hovedstaden, Kongens Vænge 2, 3400 Hillerød	NA
Finland	Keski-Suomen sairaanhoitopiiri, Eettinen toimikunta, Sairaan hoitopiirin toimisto Rak. 6/2, Keskussairaalantie 19, 40620 Jyväskylä	NA
France	Comité de Protection des Personnes Sud Ouest et Outre Mer III, Place Amélie Raba-Léon, Groupe Hospitalier Pellegrin – Service de Pharmacologie Clinique, Bât 1 A, Bordeaux cedex, 33076	NA
Germany	Landesärztekammer Rheinland-Pfalz, Postfach 29 26, 55019 Mainz	Landesamt für Gesundheit und Soziales Berlin, Geschäftsstelle der Ethik-Kommission des Landes Berlin, Fehrbelliner Platz 1, 10707 Berlin
		Ethik-Kommission des Landes Sachsen-Anhalt, Geschäftsstelle, Kühnauer Str. 70, 06846 Dessau-Roßlau

		Ethik-Kommission der Ärztekammer Westfalen-Lippe und der Medizinischen Fakultät der Westfälischen Wilhelms-Universität Münster, Gartenstr. 210–214, 48147 Münster
		Landesärztekammer Hessen, Ethikkommission, Im Vogelsang 3, 60488 Frankfurt am Main
		Sächsische Landesärztekammer, Ethikkommission, Schützenhöhe 16–18, 01099 Dresden
		Ärztekammer Hamburg, Ethikkommission, Humboldtstr. 67a, 22083 Hamburg
		Landesärztekammer Rheinland-Pfalz, Ethikkommission, Deutschhausplatz 3, 55116 Mainz
		Ärztekammer Nordrhein, Ethikkommission, Tersteegenstr. 9, 40474 Düsseldorf
		Ethikkommission der Medizinischen Fakultät der Universität Rostock, Institut für Rechtsmedizin, St. Georg-Str. 108
		Ärztekammer Niedersachsen, Ethikkommission, Berliner Allee 20, 30175 Hannover

		Bayerische Landesärztekammer, Ethikkommission, Mühlbauerstr. 16, 81677 München
Hungary	Egészségügyi Tudományos Tanács Klinikai Farmakológiai Etikai Bizottsága, Arany J. u. 6–8, Budapest, H-1051	NA
Italy	Comitato Etico Locale per la Sperimentazione Clinica dei Medicinali dell'Azienda Ospedaliero ra Universitaria ria Senese di Siena, c/o Farmacia AOUS Viale Bracci, Siena, 53100	Comitato Etico Unico per la Provincia di Parma, Via Gramsci, 14, Parma, 43100
		Comitato per la Sperimentazione Clinica Medicinali dell'Azienda Ospedaliero Universitaria Pisana di Pisa, Via Roma 67, Pisa, 56100
		Comitato Etico Locale per la Sperimentazione Clinica dei Medicinali dell'Azienda Ospedaliero ra Universitaria ria Senese di Siena, c/o Farmacia AOUS Viale Bracci, Siena, 53100
		Comitato Etico dell'Azienda Ospedaliero Universitaria S.Martino di Genova, Largo Rosanna Benzi, 10, Genova, 16132
Republic of Korea	NA	IRB of Ewha Womans University Mokdong Hospital, 1071, Anyangcheon-ro, Yangcheon-Ku, Seoul, 158-710
		IRB of Korea University Anam Hospital, 73

		Inchon-ro, Seongbuk-Gu, Seoul, 136-705
		IRB of Hallym University Sacred Heart Hospital, 896 Pyeongchon-dong, Dongan-gu, Anyang-si, 431-070
		IRB of The Catholic University of Korea, Seoul St.Mary's Hospital 222 Banpo-Daero, Seocho-gu, Seoul, 137-701
		IRB of Soonchunhyang University Bucheon Hospital, 1174 Joong-dong, Wonmi-gu, Buchon-si, 420-767
		IRB of Korea University Guro Hospital, 148 Gurodong-ro, Guro-Gu, Seoul, 152-703
		IRB of Yonsei University Wonju Christian Hospital, 20 Ilsan-Ro, Wonju-Si, 220-701
		IRB of Seoul National Hospital, 101 Daehak-ro Jongno-gu, Seoul, 110-744
Netherlands	METC Catharina ziekenhuis, Michelangelo laan 2, Eindhoven, 5623 EJ	NA
Poland	Komisja Bioetyczna przy Instytucie Gruźlicy I Chorob Płuc, ul. Płocka 26, Warszawa, 01-138	NA
Romania	Comisia Nationala de Etica, Str. Aviator Sanatescu Nr. 48,	NA

	Bucuresti, Sector 1,01	
Russian Federation	Ethical Council at the MoH of RF, 3 Rakhmanovsky Pereulok, Moscow, 127994	LEC at City Clinical Hospital #23 n.a. Medsantrud, 11, Yauzskaya str, Moscow, 109240
		LEC FA of HealthCare andSD StP Rheumatology Clinical Hosp.#25, 47, Piskarevsky prospect, St. Petersburg, 195067
		LEC at SRI of Therapy of Siberian branch of Russian Academy of Medical Sciences, 175/1, B.Bogatkova str, Novosibirsk, 630089
		LEC at StP SMU n.a. acad. I.P. Pavlov, 10, Rentgena str.Saint-Petersburg, 197101
		LEC at FSd ESMC of presed. RF City Hospital #17, Volynskaya, 7, Moscow, 119620
Slovakia	Fakultná nemocnica s poliklinikou F.D. Roosevelta, Nám. L. Svobodu 1, 975 17 Banská Bystrica	Nitriansky samosprávny kraj Úrad Nitrianskeho samosprávneho kraja Etická komisia, Štefánikova tr. 69, 949 01 Nitra
		Bratislavský samosprávny kraj, Úrad samosprávneho kraja, Etická komisia, Sabinovská 16, P.O. Box 106, 820 05 Bratislava 25
		Košický samosprávny kraj, Úrad Košického

		samosprávneho kraja Etická komisia, Námestie Maratónu mieru 1, 042 66 Košice
		NsP Sv. Jakuba, n.o., Bardejov, ul. Sv. Jakuba 21, 085 01 Bardejov
		Fakultná nemocnica s poliklinikou F.D. Roosevelta, Nám. L. Svobodu 1, 975 17 Banská Bystrica
		EK-Narodny ustav TBC, pľucnych chorob a hrudnikovej chirurgie, Vysne Hagy, Vysne Hagy, 05984
		Nitriansky samosprávny kraj Úrad Nitrianskeho samosprávneho kraja Etická komisia, Štefánikova tr. 69, 949 01 Nitra
South Africa	NA	Pharma Ethics, 123 Amcor Road, Lyttelton Manor 0157
		University of Cape Town Ethics Committee, Faculty of Health Sciences Research EC, E52-24 Old Main Building, Groote Schuur Hospital, Observatory, Cape Town, 7925
		University of Stellenbosch Ethics Committee, Faculty of Health Sciences, Francie van Zijl Drive, Cape Town, 7505

		Pharma Ethics, 123 Amcor Road, Lyttelton Manor 0157
		University of Pretoria, Research Ethics Committee, 31 Bophelo Road, HW Snyman South Building, Level 2, Room 2:34, Pretoria, Gauteng, 0001
Spain	CEIC Hospital Universitario Puerta de Hierro Majadahonda, Planta 1ª, Pasillo unidades, administrativas de servicios, c/ Manuel de Falla, 1, Majadahonda, 28222	CEIC Institut Municipal d'Assistència Sanitària, C/ Doctor Aiguader, 88 Edifici PRBB Barcelona, 08003
		Comité Ético de Investigación Clínica de Asturias, C/ Celestino Villamil, s/n Oviedo, 33006
		CEIC Hospital virgen de la Macarena, Dirección: Avda. Dr. Fedriani, 3 – Unidad de Investigación 2ª planta Sevilla, 41071
		CEIC del Complejo Hospitalario de Cáceres, Avda. Pablo Naranjo s/n Caceres, 10003
		CEIC del IDIAP Jordi Gol i Gurina, Gran Via de les Corts Catalanes, 587 atico Barcelona, 08007
		CEIC Hospital Germans Trias i Pujol, Ctra. Canyet, s/n Badalona, 08916,



		CEIC Hospital general Carlos Haya, Avda. Carlos Haya, s/n Málaga, 29010
Sweden	Regionala etikprövningsnämnden i Lund, Box 133, Östra Vallgatan, 14/Östervångsvägen 1, Lund, 22100	NA
Ukraine	Central Ethics Commission of the Ministry of Health of Ukraine, 5, Narodnogo Opolchennya St., Kyiv, 03680	LEC "Kharkiv City Clinical Hospital # 13", 137, Gagarin Av. Kharkiv, 61035
		LEC SI "National Institute of Phthisiology and Pulmonology named F.G.Yanovskyy of AMS of Ukr, 10, Amosova Str., Kyiv, 03680
United Kingdom	NRES Committee North West, 3rd Floor, Barlow House, 4 Minshull Street, Manchester, M1 3DZ	NRES Committee North West, 3rd Floor Barlow House, 4 Minshull Street, Manchester, M1 3DZ
		Bart 's Health NHS Trust, Joint Research and Development Office, Queen Mary Innovation Centre, 5 Walden Street, London, E1 2EF
		The Royal Wolverhampton Hospitals NHS Trust, Research & Development Directorate, The Chestnuts, Wolverhampton, West Midlands, WV10 0QP
		Cambridge University Hospitals NHS Foundation Trust, Addenbrookes Hospital, Hills Road, Cambridge, CB2 0QQ

		<p>Hull &amp; East Yorkshire Hospitals NHS Trust,  Research &amp; Development Department, 2nd  Floor Daisy Building, Castle Hill Hospital,  Castle Road, Cottingham, East Yorkshire, HU16  5JQ</p>
		<p>Bradford Teaching Hospitals NHS Foundation  Trust, Bradford Royal Infirmary, Room 6,  Pharmacy Stores, Gate 7, Smith Lane, Bradford  West Yorkshire, BD9 6RJ</p>
		<p>NRES Committee West Midlands, Prospect  House, Fishing Line Road, Enfield, Redditch,  B97 6EW</p>
		<p>NRES Committee South Central, Building L27,  University of Reading, London Road, Reading,  RG1 5AQ</p>
		<p>North Tees &amp; Hartlepool NHS Foundation Trust  – R&amp;D, Hardwick Road, Stockton on Tees,  TS19 8PE</p>
		<p>Wirral University Teaching Hospital NHS  Foundation Trust, Arrowe Park Hospital,  Arrowe Park Road, Upton, Wirral, CH49 5PE</p>
		<p>NHS Royal Victoria Infirmary, Queen Victoria  Road, Newcastle Upon Tyne, Newcastle, NE1</p>

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IEC, Independent Ethics Committee

**Supplementary Table 2.** List of Institutional Review Boards for AUGMENT COPD

List of Institutional Review Boards for AUGMENT COPD
<p>Multi-region Ethics Committee  c/- Ministry of Health  PO Box 5013  1 the Terrace  Wellington  Phone: (04) 816 2655  Fax: (04) 496 2343  Email:  multiregion_ethicscommittee@moh.govt.nz</p>
<p>IRB Services (Institutional Review Board Services) (central)  372 Hollandview Trail, Suite 300 Aurora,  Ontario L4G 0A5  Canada  Phone: 905-727-7989  Fax: 905-727-7990</p>
<p>Quorum Institutional Review Board (central)  1601 Fifth Avenue, Suite 1000  Seattle, WA 98101  Phone: 877-472-9883</p>
<p>Bellberry Human Research Ethics Committee  229 Greenhill Road  Dulwich SA 5065  Australia</p>
<p>Human Studies Subcommittee  Bay Pines VA Healthcare System  Research and Development Service (151)  10000 Bay Pines Blvd.  Bay Pines, FL 33744  (local)</p>

<p>Flinders Clinical Research Ethics Committee  Bedford Park SA 5042  Australia</p>
<p>Western Institutional Review Board (local)  3535 7th Avenue SW  Olympia, WA 98502</p>
<p>St. Luke's IRB (local)  232 S. Woods Mill Rd.  Chesterfield, MO 63017</p>
<p>Human Research Ethics Committee - D  St Vincent's Health Melbourne  PO Box 2900  Fitzroy, Vic 3065  Australia</p>
<p>Royal Adelaide Hospital Research Ethics Committee  North Terrace  Adelaide SA 5000  Australia</p>
<p>Concordia Hospital Ethics Committee (local)  Concordia Hospital  1095 Concordia Avenue  Winnipeg, Manitoba, Canada  R2K 3S8</p>
<p>Hunter New England Human Research Ethics Committee  Locked Bag 1  New Lambton NSW 2305  Australia</p>
<p>University of Saskatchewan Biomedical Ethics Review Board (local)  Research Ethics Office  University of Saskatchewan  Box 5000 RPO University  Saskatoon, Saskatchewan S7N 4J8 Canada</p>

<p>Telephone: 306-966-2975  Facsimile: 306-966-2069</p>
<p>Sparks Institutional Review Board (local)  1001 Towson Avenue  PO Box 2406  Fort Smith, AR 72902-2406</p>
<p>Kansas City Veterans Affairs Medical Center IRB (local)  4801 East Linwood Blvd.  #151  Kansas City, MO64128</p>
<p>University of California San Diego  Human Research Protections Program (local)  9500 Gilman Drive, Mail Code 0052  La Jolla, California 92093-0052</p>
<p>University of British Columbia, Clinical Research Ethics Board Office (local)  Room 210, Research pavilion  828 West 10th Avenue  Vancouver, British Columbia  Canada  V5Z 1L8</p>
<p>Mayo Clinic  Office for Human Research Protection  Institutional Review Board (IRB) (local)  201 Building Room 4-60  200 1st Street SW  Rochester, MN 55905</p>
<p>Creighton University IRB (local)  2500 California Plaza  Omaha, NE 68178</p>
<p>Institutional Review Board  University of Texas Health Science  Center at Tyler (local)</p>

11937 US Highway 271 Tyler, TX 75708
University of Illinois College of Medicine of Peoria Institutional Review Board (local) One Illini Drive Box 1649 Peoria, Illinois 61656-1649
Mercy St. Vincent Medical Center Adult Investigational Review Board (local) 2213 Cherry St. Toledo, OH 43608
Gold Coast Health Service District Human Research Ethics Committee 108 Nerang Street Southport Qld 4215 Australia
GLA-VA IRB (local) 11301 Wilshire Blvd. Building 114 Room 325 Los Angeles, CA 90073

**Supplementary Table 3.** Baseline demographics and patient characteristics of treatment groups by less symptomatic and more symptomatic patients according to baseline E-RS and BDI

	Acclidinium/formoterol 400/12 µg				Acclidinium 400 µg				Formoterol 12 µg				Placebo			
	E-RS		BDI		E-RS		BDI		E-RS		BDI		E-RS		BDI	
Demographic parameter	E-RS <10 n=230	E-RS ≥10 n=480	BDI ≥7 n=305	BDI <7 n=393	E-RS <10 n=252	E-RS ≥10 n=455	BDI ≥7 n=332	BDI <7 n=371	E-RS <10 n=267	E-RS ≥10 n=434	BDI ≥7 n=313	BDI <7 n=385	E-RS <10 n=180	E-RS ≥10 n=337	BDI ≥7 n=246	BDI <7 n=262
Age, mean (SD)	63.1 (8.4)	63.5 (8.6)	63.5 (8.5)	63.2 (8.6)	64.8 (8.1)	63.0 (8.6)	63.5 (7.8)	63.8 (9.1)	64.6 (7.9)	62.8 (8.2)	63.7 (8.4)	63.4 (8.2)	64.9 (8.1)	63.0 (8.7)	63.2 (8.3)	63.8 (8.8)
Sex, male, %	57.8	60.4	63.9	56.2	59.5	62.6	59.6	63.9	57.7	60.1	63.3	56.4	58.9	59.6	57.3	62.2
<b>COPD severity (GOLD stages) (%)</b>																
Stage II (Moderate)	70.0	52.8	69.1	49.6	65.2	52.6	64.8	49.5	71.4	53.2	66.5	55.7	64.4	50.9	63.8	49.2
Stage III (Severe)	30.0	46.6	30.9	49.6	34.8	46.5	34.2	50.3	27.8	46.1	32.6	43.8	35.6	47.9	35.4	50.0
Current smoker, %	45.7	50.8	47.9	50.4	43.7	51.4	47.0	50.1	43.1	51.8	48.6	49.1	46.1	52.2	56.1	45.4



<b>Smoking history, pack-years (SD)</b>	47.7 (25.0)	46.1 (25.0)	45.7 (23.7)	47.1 (26.1)	47.3 (24.0)	43.7 (23.3)	45.0 (22.8)	44.8 (24.4)	45.9 (22.2)	45.5 (22.2)	45.1 (22.7)	46.2 (22.2)	50.2 (28.3)	48.7 (25.9)	47.8 (25.8)	49.9 (26.4)
<b>No. exacerbations in previous 12 months, mean (SD)</b>	0.3 (0.7)	0.5 (1.0)	0.4 (0.7)	0.5 (1.0)	0.3 (0.7)	0.5 (0.9)	0.4 (0.7)	0.5 (0.9)	0.3 (0.6)	0.5 (0.9)	0.3 (0.6)	0.5 (0.9)	0.3 (0.6)	0.4 (0.7)	0.2 (0.6)	0.4 (0.7)
<b>Baseline post-dose FEV<sub>1</sub>, L, mean (SD)</b>	1.50 (0.51)	1.34 (0.52)	1.49 (0.52)	1.31 (0.51)	1.43 (0.52)	1.35 (0.52)	1.44 (0.53)	1.31 (0.50)	1.46 (0.51)	1.35 (0.51)	1.50 (0.52)	1.31 (0.49)	1.44 (0.53)	1.36 (0.56)	1.46 (0.54)	1.32 (0.55)
<b>Baseline FVC, L, mean (SD)</b>	2.9 (0.9)	2.8 (0.8)	3.0 (1.0)	2.7 (0.8)	2.9 (0.9)	2.8 (0.8)	2.9 (0.9)	2.8 (0.9)	2.9 (0.9)	2.8 (0.8)	3.0 (0.8)	2.7 (0.8)	2.9 (1.0)	2.8 (0.9)	3.0 (1.0)	2.8 (0.9)
<b>FEV<sub>1</sub>/FVC, %, mean (SD)</b>	49.7 (10.7)	46.9 (10.5)	48.3 (10.6)	47.1 (10.7)	47.7 (10.1)	47.9 (11.2)	49.3 (10.2)	46.2 (11.0)	49.1 (10.6)	46.7 (10.8)	49.3 (10.6)	46.0 (10.7)	48.3 (10.2)	47.2 (11.2)	49.0 (10.1)	45.6 (11.5)
<b>E-RS total score at baseline (SD)</b>	5.5 (2.9)	16.5 (4.9)	11.0 (6.0)	14.4 (6.9)	5.9 (2.7)	16.2 (4.6)	9.9 (5.4)	14.8 (6.3)	5.6 (2.9)	16.5 (4.4)	10.1 (6.3)	14.3 (6.3)	5.6 (2.9)	15.7 (4.5)	9.7 (5.4)	14.5 (6.1)
<b>BDI score at baseline (SD)</b>	7.28 (1.93)	5.98 (2.01)	8.2 (1.4)	5.0 (1.3)	7.53 (2.14)	5.93 (1.95)	8.2 (1.4)	4.9 (1.4)	7.51 (2.12)	5.81 (2.00)	8.4 (1.4)	4.9 (1.3)	7.48 (2.05)	5.93 (2.16)	8.2 (1.4)	4.8 (1.5)

BDI, Baseline Dyspnea Index; COPD, chronic obstructive pulmonary disease; E-RS, Evaluating Respiratory Symptoms; FEV<sub>1</sub>, forced expiratory volume in 1 second; FVC, forced vital capacity; GOLD, Global initiative for chronic Obstructive Lung Disease; SD, standard deviation