

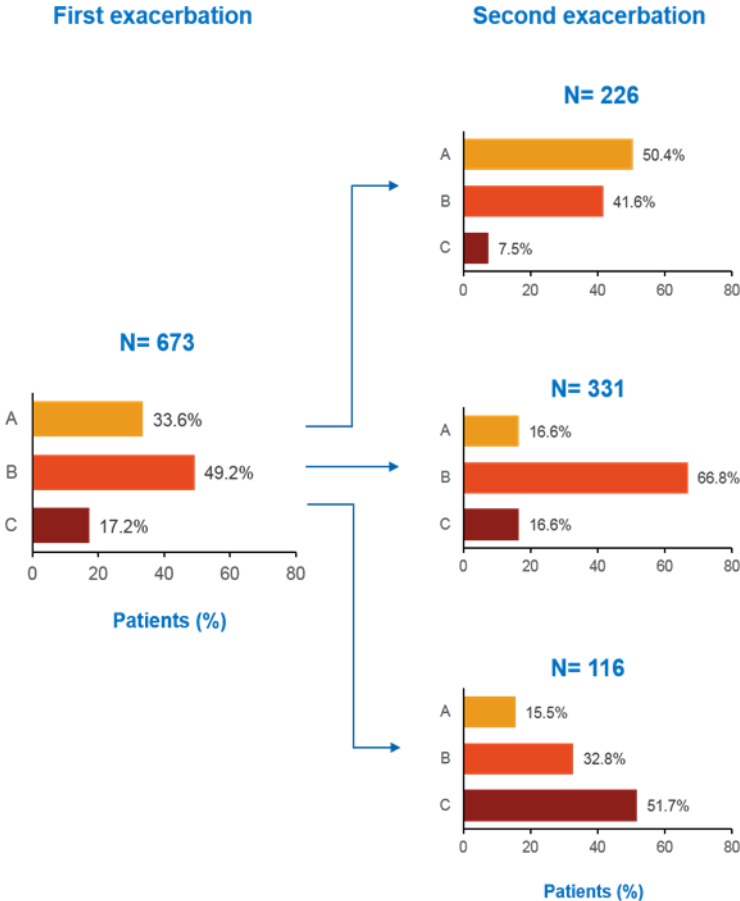
**Online supplement**

- Patients were recruited between July 2013 and September 2015 from 356 investigational centres in 43 countries

Supplemental figures:

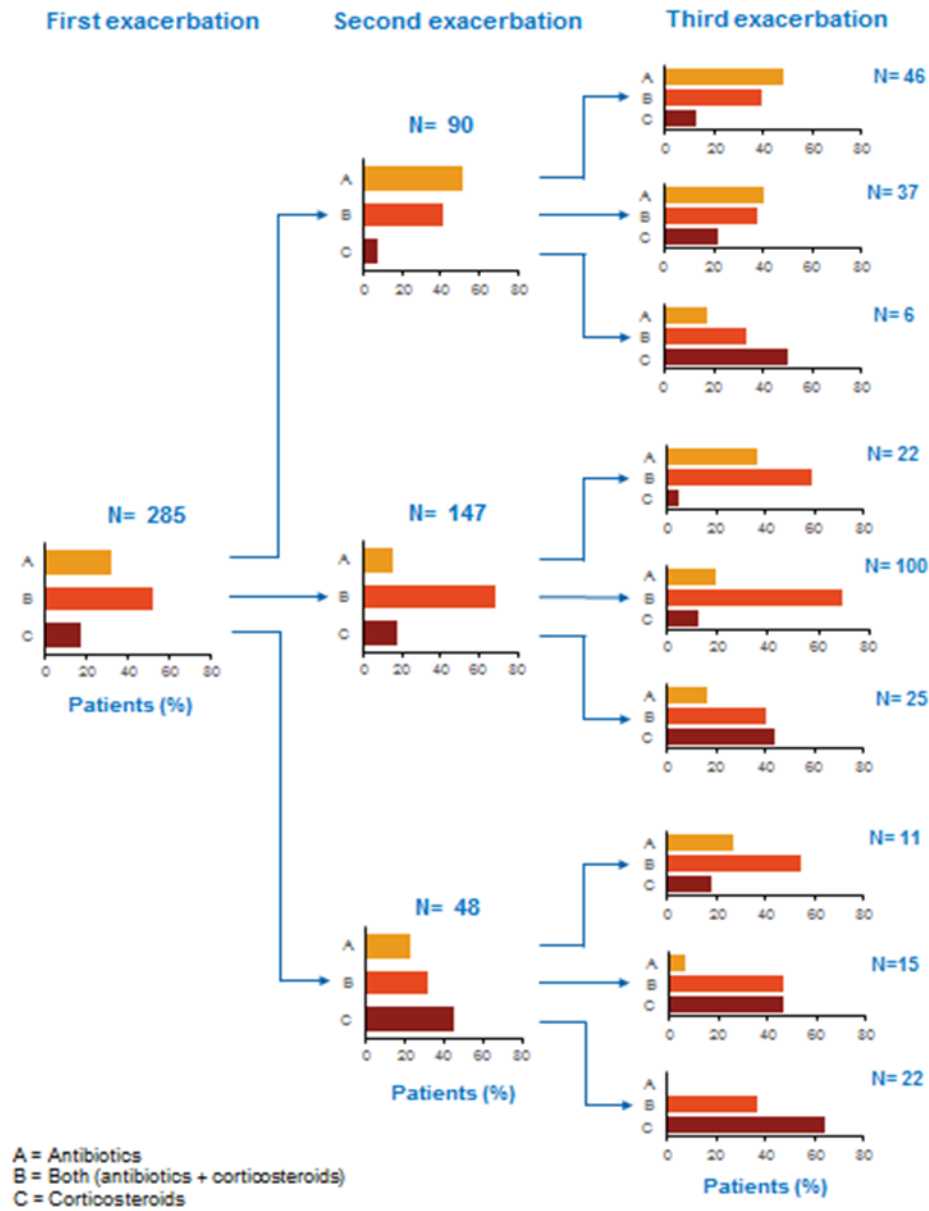
Figure 1. Evolution of the management of exacerbations in patients with >1 event

i) Patients with  $\geq 2$  exacerbations



A = Antibiotics  
B = Both (antibiotics + corticosteroids)  
C = Corticosteroids

ii) Patients with  $\geq 3$  exacerbations



Treatment was evaluated according to the use of antibiotics (A), corticosteroids (C) or both (B).

i) Patients that presented  $\geq 2$  events ii) Patients that presented  $\geq 3$  events. Patients who presented with  $>3$  events are a subpopulation of patients who presented with  $\geq 2$  events.

**Table 1.** List of institutional review boards or ethics committees.

#	EC/IRB country	Site Number(s)	EC/IRB Name	EC/IRB Department	EC/IRB City (State/Province)
	Argentina	4003;#4008;#4011;#4014;#4017;#4019;#4023;#4027;#4029	Comite Independiente de Etica para Ensayos en Farmacologia Clinica	NA	CABA (Buenos Aires)
	Argentina	4001;#4002;#4004;#4007;#4013;#4018;#4021;#4025	Comite de Etica en Investigacion Clinica	NA	CABA (Buenos Aires)
	Argentina	4005	Comite Independiente de etica para ensayos en farmacologia clinica del centro medico Dra. De Salvo	NA	CABA (Buenos Aires)
	Argentina	4010	Comite de etica en Investigaciones Biomedicas Sanatorio Otamendi y Miroli S.A	NA	CABA (Buenos Aires)
	Argentina	4016	Comite de Bioetica CIMEL	NA	Lanus Este (Buenos Aires)
	Argentina	4020	Comite de Etica en Inestigacion	NA	CABA (Buenos Aires)
	Argentina	4022	Comite de Etica en Investigacion Instituto de Investigaciones Clinicas	NA	Mar del Plata (Buenos Aires)
	Argentina	4024;#4028	Comite de Etica en Investigacion Instituto Ave Pulmo	NA	Mar del Plata (Buenos Aires)
	Argentina	4030	Comite de Etica en Investigacion de INAER	NA	CABA (Buenos Aires)

	Austria	4110;#4111;#4112;#4113;#4114;#4115;#4116;#4117;#4118;#4119	Ethikkommission des Landes Oberösterreich		Linz (Oberösterreich)
	Belgium	4140;#4141;#4142;#4143;#4145;#4146;#4147;#4148;#4149;#4150;#4151;#4152;#4153;#4155;#4156;#4159;#4160;#4161	Commissie Medische Ethiek UZ Brussel		Brussels
	Bulgaria	4200;#4201;#4202;#4203;#4204;#4205;#4206;#4207;#4208;#4209;#4210	Ethics Committee for Multicenter Trials		Sofia
	Canada	4232;#4233;#4234;#4247;#4236;#4238;#4245;#4243;#4246;#4244	Institutional Review Board Services		Aurora (Ontario)
	Canada	4239	Comité d'éthique de la recherche sur l'humain du Centre hospitalier universitaire de Sherbrooke		Fleurimont (Quebec)
	Canada	4235	Conjoint Health Research Ethics Board	Research Services Office	Calgary (Alberta)
	Chile	4263	Comité Ético Científico Hospital Dr. Gustavo Fricke. Servicio de Salud Viña del Mar - Quillota		Viña del Mar
	Chile	4261	Comité de Ética Científico Servicio de Salud Metropolitano Oriente		Santiago, Providencia (Región Metropolitana)
	Chile	4266	Comité Ético Científico Servicio de Salud Metropolitano Sur		Santiago, San Miguel

					(Región Metropolitana)
	China	4300	Ethical Committee of the First Affiliated Hospital of Guangzhou Medical University		Guangzhou (Guangdong Province)
	China	4302	Ethical Committee of the First Affiliated Hospital of Chinese PLA General Hospital		Beijing (Beijing)
	China	4301	Ethical Committee of the General Hospital of Guangzhou Military Command of PLA		Guangzhou (Guangdong Province)
	China	4303	Ethical Committee of Beijing Friendship Hospital, Capital Medical University		Beijing (Beijing)
	China	4304	Ethical Committee of Peking Union Medical College Hospital		Beijing (Beijing Province)
	China	4305	Ethical Committee of The Third Xiangya Hospital of Central South University		Changsha (Hunan Province)
	China	4306	Ethical Committee of West China Hospital of Sichuan University		Chengdu (Sichuan)
	China	4307	Ethical Committee of Southwest Hospital, the Third Military Medical University		Chongqing (Chongqing)
	China	4308	Ethical Committee of The Second Affiliated Hospital of		Chongqing (Chongqing)

			Third Military Medical University	
	China	4309	Ethical Committee of Hainan provincial people's Hospital	Haikou (Hainan Province)
	China	4310	Ethical Committee of Hangzhou First People's Hospital	Hangzhou (Zhejiang Province)
	China	4312	Ethical Committee of The Jiangxi Provincial People's Hospital	Nanchang (Jiangxi Province)
	China	4313	Ethical Committee of The First Affiliated Hospital of Nanchang University	Nanchang (Jiangxi Province)
	China	4315	Ethical Committee of Shanghai Pulmonary Hospital	Shanghai (Shanghai)
	China	4316	Ethical Committee of Ruijin Hospital Affiliated to Shanghai JiaoTong University School of Medicine	Shanghai (Shanghai)
	China	4317	Ethical Committee of The General Hospital of Shenyang Military Region	Shenyang (Liaoning Province)
	China	4318	Ethical Committee of The Second Hospital of Hebei Medical University	Shijiazhuang (Hebei Province)
	China	4320	Ethical Committee of The First Affiliated Hospital of Soochow	Suzhou (Jiangsu)

			University		Province)
	China	4321	Ethical Committee of The General Hospital Tianjin Medical University		Tianjin (Tianjin)
	China	4322	Ethical Committee of The First Affiliated Hospital of the Fourth Military Medical University		Xi'an (Shanxi Province)
	China	4323	Ethical Committee of Jiangsu Province Hospital		Nanjing (Jiangsu Province)
	Colombia	4400	Comité de ética en Investigación - Fundación Cardiomet Eje Cafetero	NA	Manizales (Caldas)
	Colombia	4401	Comité de Etica de la investigación CAIMED	NA	Bogotá (Cundinamarca)
	Colombia	4402	Comité Medico, Etico, Científico Asesor - Clínica Soma	NA	Medellín (Antioquia)
	Colombia	4403	Comité de ética en Investigación CEI- FOSCAL	NA	Floridablanca (Santander)
	Croatia	1770;#1771;#1772	SEP - Sredisnje eticko povjerenstvo		Zagreb
	Czech Republic	4420;#4421;#4422;#4423;#4424;#4426;#4427;#4432;#4425;#4436	Etická komise IKEM a TN	Thomayerov a nemocnice	Praha 4 -Krc
	Czech Republic	4430;#4435	Eticka komise	Vitkovicka nemocnice a.s.	Ostrava - Vitkovice
	Czech	4433	Eticka komise	Nemocnice	Melnik



	Republic			Melnik	
	Czech Republic	4434	Etická komise	Nemocnice Rudolfa a Stefanie Benešov, a.s.	Benešov
	Czech Republic	4437	Etiická komise FN a LF UP Olomouc		Olomouc
	Czech Republic	4428;#4429;#4431	Etická komise IKEM a TN	Thomayerov a nemocnice	Praha 4 - Krc
	Denmark	4460;#4461;#4462;#4463;#4464;#4465;#4466;#4467;#4468	De Videnskabsetiske Komiteer	Region Hovedstaden	Hillerød
	Estonia	4500;#4501;#4502	Tallinn Medical Research Ethics Committee	NA	Tallinn (NA)
	Finland	All sites/central Vote;#4520;#4521;#4523;#4524;#4525;#4526	Keski-Suomen sairaanhoitopiirintieteellinen toimikunta		Jyväskylä
	France	4540;#4541;#4542;#4543;#4544;#4545;#4546;#4548;#4551;#4552;#4554;#4555	CPP Ile de France XI	Centre Hospitalier de Saint-Germain-Laye	Saint Germain en Laye Cedex (NA)
	Germany	All sites/central Vote	Ethikkommission Medizinische Fakultät Heidelberg	Medizinische Fakultät Heidelberg	Heidelberg (Baden-Württemberg)
	Greece	4710;#4711;#4712;#4713;#4714;#4715;#4717;#4718;#4719;#4720;#4721	National Ethics Committee (EED)		Cholargos (Attiki)

	Guatemala	4740;#4741;#4742;#4743;#4745	Comité de Ética Independiente ZUGUEME		Guatemala City (Guatemala)
	Hong Kong	4761	Joint Chinese University of Hong Kong- New territories East cluster Clinical Research Ethics Committee	NA	Hong Kong (NA)
	Hong Kong	4762	Kowloon West Cluster Research Ethics Committee	NA	Hong Kong (NA)
	Hungary	All sites/central Vote	Medical Research Council	Ethics Committee for Clinical Pharmacology	Budapest
	Iceland	4810	The National Bioethics Committee		Reykjavik
	India	4823	Institutional Ethical Review Board		Bangalore (Karnataka)
	India	4827	KRIMS Ethics Committee		Nagpur (Maharashtra)
	India	4828	Institutional Ethics Committee		Coimbatore (Tamil Nadu)
	India	4830	Institutional Ethics Committee		Visakhapatnam (Andhra Pradesh)
	India	4831	Fortis Hospital Ethics Committee		Kolkata (West Bengal)
	India	4833	Ethics Committee of Care Institute of Medical Sciences		Ahmedabad (Gujarat)

	India	4835	Drug Trial Ethics Committee		Ludhiana (Punjab)
	India	4837	Institutional Human Ethics Committee		Coimbatore (Tamil Nadu)
	India	4838	AMC MET Ethics Committee		Ahmedabad (Gujarat)
	India	4840	Paras Hospital Ethics Committee		Gurgaon (Harayana)
	India	4841	Institutional Ethics Committee		Hyderabad (Andhra Pradesh)
	India	4843	Getwell Institutional Ethics Committee (GIEC)		Nagpur (Maharashtra)
	Italy	4890	Comitato per la Sperimentazione Clinica dei Medicinali Area Vasta Nord	c/o Azienda Ospedaliero Universitaria Pisana di Pisa	Pisa
	Italy	4891	Comitato Etico per le Sperimentazioni Cliniche della Provincia di Padova	C/O AOU Padova	Padova
	Italy	4892	Comitato Etico Regionale Unico (CERU)	c/o Azienda Ospedaliero universitaria	Udine
	Italy	4893	Comitato Etico Area di Pavia	c/o Fondazione Irccs Policlinico	Pavia

				San	
	Italy	4894	Comitato Etico Seconda Universita' Degli Studi di Napoli	Aou Sunaorn	Napoli
	Italy	4895	Comitato Etico Provinciale di Varese	c/o Ospedale di Circolo e	Varese
	Italy	4897	Comitato Etico Dell'Azienda Ospedaliero-Universitaria Ospedali Riuniti		Foggia
	Italy	4898	Comitato Etico Milano Area C	c/o Azienda Ospedaliera Ospedale Niguarda Ca'	Milano
	Italy	4899	Comitato Etico per la Sperimentazione Clinica delle Province di Verona	C/O AOUI Verona	Verona
	Italy	4900	Comitato Etico Provinciale di Reggio Emilia	c/o Azienda Ospedaliera Arcispedale S. Maria Nuova/IRCC S	Reggio emilia
	Italy	4901	Comitato Etico Dell'IRCCS Fondazione Don Carlo Gnocchi di Milano	Centro S. Maria Nascente	Milano
	Italy	4902	Comitato Etico Della Provincia di	C/O Azienda	Modena

			Modena	Policlinico,	
	Italy	4903	Comitato Etico Aree Cremona, Mantova e Lodi	c/o AO di Cremona	Cremona
	Italy	4904	Comitato Etico Regionale (CER)	c/o Azienda Ospedaliera Universitaria Ospedali Riuniti Umberto I- Lancisi-Gm Salesi di Ancona	Ancona
	Italy	4906;#4905	Comitato Etico Centrale Dell'IRCCS Fondazione Salvatore Maugeri (IRCCS) di Pavia		Pavia
	Italy	4908	Comitato Etico Dell' IRCCS Ospedale Oncologico di Bari		Bari
	Italy	4909	Comitato Etico Regione Liguria	c/o IRCCS Aou San Martino - Ist Istituto Nazionale per la Ricerca Sul Cancro	Genova
	Japan	1009;#1011;#1014;#1020;#1006;#1012	National Hospital Organization CRB	National Hospital	Meguro-ku (Tokyo)

				Organization	
	Japan	1000	Nihon Koukan Hospital IRB	Nihon Koukan Hospital	Kawasaki (Kanagawa)
	Japan	1001	Tokyo-Eki Center-building Clinic IRB		Chuo-ku (Tokyo)
	Japan	1002	Nakatani Hospital IRB		Himeji (Hyogo)
	Japan	1003	JCHO Hokkaido Hospital IRB		Sapporo (Hokkaido)
	Japan	1004	Tenryu Hospital IRB		Hamamatsu (Shizuoka)
	Japan	1005	Kishiwada City Hospital IRB		Kishiwada (Osaka)
	Japan	1007	Sakaide City Hospital IRB		Sakaide (Kagawa)
	Japan	1008	Hamamatsu Rosai Hospital IRB		Hamamatsu (Shizuoka)
	Japan	1010	Matsusaka City Hospital IRB		Matsusaka (Mie)
	Japan	1013	Tosei General Hospital IRB		Seto (Aichi)
	Japan	1015	Obihiro Kokyukika Naika Hospital IRB		Obihiro (Japan)
	Japan	1016	Iwata City Hospital IRB		Iwata (Shizuoka)
	Japan	1017	Takamatsu Manicipal Hospital		Takamatsu

			IRB		(Kagawa)
	Japan	1018	Daido Hospital IRB		Nagoya (Aichi)
	Japan	1019	Nagata Hospital IRB		Yanagawa (Fukuoka)
	Japan	1021	Harasanshin Hospital IRB		Fukuoka (Fukuoka)
	Japan	1022	Tohoku University Hospital IRB		Sendai (Miyagi)
	Japan	1023	Nihon University Hospitals' Joint IRB	Nihon University Hospitals	Itabashi-ku (Tokyo)
	Japan	1024	Juntendo University Hospitals IRB		Bunkyo-ku (Tokyo)
	Japan	1025	Hokkaido University Hospital IRB		Sapporo (Tokyo)
	Japan	1026	Fujita Health University hospital IRB		Toyoake (Aichi)
	Japan	1027	Kyoto University Hospital IRB		Kyoto (Kyoto)
	Japan	1028	ICR Clinical Research Tokyo Hospital IRB	ICR Clinical Research Tokyo Hospital	Shinjuku-ku (Tokyo)
	Japan	1029	Kimura Hospital IRB	Kimura Hospital	Ota-ku (Tokyo)
	Latvia	1230;#1231;#12 33	P. Stradins Clinical University		Riga

			Hospital EC		
	Lithuania	1250;#1251;#1252;#1253;#1254;#1255;#1257;#1259;#1260	Lietuvos bioetikos komitetas (Lithuanian Bioethics Committee)		Vilnius
	Mexico	1280;#1284	Comité Bioético para la Investigación Clínica S.C.	NA	Mexico City (Mexico City)
	Mexico	1281	Comité de Ética del Hospital General de México "Dr. Eduardo Liceaga"	Dirección de Investigación	Mexico City (Mexico City)
	Mexico	1282	Comité de Ciencia y Bioética en Investigación del Instituto Nacional de Enfermedades Respiratorias "Ismael Cosío Villegas"	NA	Mexico City (Mexico City)
	Mexico	1283	Comité de Ética del Hospital Ángel Leaño	NA	Guadalajara (Jalisco)
	Mexico	1285	Comité de Bioética en Investigación Christus Muguerza Hospital UPAEP	NA	Puebla (Puebla)
	Mexico	1286	Centro de Investigación Médico Biológica y Terapia Avanzada S.C.	NA	Guadalajara (Jalisco)
	Netherlands	1310;#1311;#1312;#1315;#1313;#1316;#1317;#1318;#1319;#All sites/central Vote	MEC-U (Medical Research Ethics Committees United)		Eindhoven
	Norway	All sites/central Vote	Regionale komiteer for medisinsk og helsefaglig	REK Sør-øst B	Oslo



			forskningsetikk (REK)		
	Philippines	1380	Lung Center of the Philippines	Institutional Ethics Review Board	Quezon City (Quezon Avenue Extension)
	Philippines	1381	University of the Philippines Manila	Research Ethics Board	Manila (Pedro Gil St. Ermita)
	Philippines	1382	Mary Mediatrix Medical Center	Research Ethics Committee	Batangas, Lipa City (J.P. Laurel Highway)
	Poland	1401;#1400;#1402;#1403;#1404;#1405;#1406	Komisja Bioetyki Uniwersytetu Medycznego w Łodzi	NA	Łódź (NA)
	Portugal	1430;#1431;#1432;#1433;#1434;#1435;#1436;#1437;#1438;#1439;#1440	CEIC - Parque da Saúde de Lisboa	Not Applicable	Lisbon (Lisbon)
	Republic of korea	1205	Kyunghee University Medical Center	IRB	Seoul (1, Heogi-dong, Dongdaemun-gu)
	Republic of korea	1207	Seoul National University Hospital	IRB	Seoul (103, Daehak-ro, Jongno-gu)
	Republic of korea	1200	Korea University Anam Hospital	IRB	Seoul (126-1, Anam- dong 5-ga, Sungbuk-gu)
	Republic of	1202	The Catholic University of Korea	IRB	Seoul

	korea		Seoul St. Mary's Hospital		(505, Banpo-dong, Seocho-gu)
	Republic of korea	1203	Chungang University Hospital	IRB	Seoul (224-1 Heukseok-dong, Dongjak-gu)
	Republic of korea	1204	Soonchunhyang University Hospital_Bucheon	IRB	Gyeonggi-do (1174, Jung-dong, Wonmi-gu, Bucheon-si)
	Republic of korea	1201	The Catholic University of St Paul's Hospital	IRB	Seoul (Jeonnong 1-dong, Dongdaemun-gu)
	Republic of korea	1206	The Catholic University of Korea Incheon St. Mary's Hospital	IRB	Incheon (665-8, Bupyeong-dong, Bupyeong-gu)
	Republic of korea	1209	Chonbuk National University Hospital	IRB	Chonbuk (634-18, Geumam-dong, Deokjin-gu, Jeonju-si, Jeollabuk-do)
	Romania	All sites/central Vote	Comisia Nationala de Bioetica a Medicamentului si Dispozitivelor Medicale		Bucharest

	Russian federation	All sites/central Vote	Ethics committee of Russian Federation		Moscow
	Serbia	1790	EC of Clinical Centre Nis		Nis
	Serbia	1791	EC of Clinical Centre Kragujevac		Kragujevac
	Serbia	1792	EC of Clinical Centre of Serbia		Belgrade
	Serbia	1793	EC of Clinical Hospital Centre Bezanijska Kosa		Belgrade
	Slovakia	1540;#1545;#1541;#1542;#1543;#1544;#1546;#1547;#1548;#1549;#1551;#1552;#1553;#1554;#1555;#1556	Eticka komisia Kosickeho samospravneho kraja	Odbor Zdravotnictva	Kosice (NA)
	South africa	1570;#1571;#1572;#1573;#1574;#1576;#1578;#1579;#1580	Pharma Ethics Independent Research Ethics Committee		Pretoria (Gauteng)
	South africa	1581	University of Stellenbosch Human Research Ethics Committee	Division of research development and support	Cape Town (Western Cape)
	South africa	1575	University of Cape Town Human Research Ethics Committee	Faculty of Health Sciences	Cape Town (Western Cape)
	Spain	1602;#1601;#1603;#1604;#1605;#1607;#1610;#1611;#1612;#1614;#1613;#1617;#1616;#1618;#1620;#1623;#1624;#1626;#1631;#1630;#1629;#1628;#1627	FUNDACIÓ UNIÓ CATALANA D'HOSPITALS	Comité Ético Investigación Clínica	Barcelona (Barcelona)
	Sweden	1651;#1650;#1652;#1655;#1656;#1657	Regionala etikprövningsnämnden i Lund	Box 133	Lund

	Taiwan	1670	Institutional Review Board	Taipei Veterans General Hospital	Taipei
	Taiwan	1671	Research Ethics Committee	National Taiwan University Hospital	Taipei
	Taiwan	1672	Research Ethics Review Committee	Far Eastern Memorial Hospital	Taipei
	Taiwan	1673	Research Ethics Committee	China Medical University Hospital	Taichuang
	Taiwan	1674	The Institution Review Board of Taichuang Veterans General Hospital	Taichuang Veterans General Hospital	Taichuang
	Taiwan	1675	Institutional Review Board	Chang Gung Medical Foundation	Taoyuan County
	Taiwan	1676	Institutional Review Board	National Cheng Kung University Hospital	Tainan

	Taiwan	1677	Institutional Review Board	Chang Gung Medical Foundation	Taoyuan County
	Thailand	1751	The Office of Human Research Ethics	Khon Kaen University	Khon Kaen
	Thailand	1752	Research Ethics Committee	Faculty of Medicine,Ch iang Mai University	Chiang Mai
	Thailand	1753	The Research Ethics Committee	Faculty of Medicine, Prince of Songkla University	Songkla
	Turkey	1697;#1696;#1695;#1694;#1693;#1692;#1691;#1690	Baskent University Medical Faculty Clinical Research Ethics Committee	-	Ankara (Besevler)
	United Kingdom	All sites/central Vote	Yorkshire & The Humber - Leeds West	TEDCO Business Centre	Rolling Mill Road (Jarrow)
	Argentina	4003;#4008;#4011;#4014;#4017;#4019;#4023;#4027;#4029	Comite Independiente de Etica para Ensayos en Farmacologia Clinica	NA	CABA (Buenos Aires)

**Notes:**

**Abbreviations:** NA, not available.