Supplemental Materials

List of investigators and hospitals

Argentina

Sanatorio de La Trinidad Mitre, Buenos Aires, Argentina. Javier Altclas, MD, Mariana Patricia Berte, Adriana Victoria Diaz Balocchi, Maria Verónica Latini, Daniela Malano Barletta, Claudia Cristina Salgueira, MD, Analia Rosana Santa Maria.

Sanatorio Mayo Privado Sanatoria Allende S.A, Cordoba, Argentina. German Ambasch, MD, Jorge Luis Tambini Diaz.

Clinica Montegrande-Clinica Privada Monte Grande, Buenos Aires, Argentina. Pedro Xavier Bocca Ruiz, MD, Xavier Antonio Bocca Pereira, Sebastian Caravaggio, Victor Hugo Pecci, Feliciano Petro Moreno.

Clinca Privada Colombo, Cordoba, Argentina. Hugo Raul Colombo, MD, PhD, Marianela Colombo.

Clínica Privada Independencia de Munro, Buenos Aires, Argentina. Pablo Alexis Christian Doreski, MD, MBA, Jorge Oscar Fandi, Celia Sara Giler, Fernando Ricardo Racca Velasquez, Damian Gonzalo Rutolo, Oscar Alberto Salva.

Instituto de Cardiologia Juana F. Cabral, Corrientes, Argentina. Angel Esteban Piacenza, M.D, Leonardo Mariano Braccini, Jorge Matias Ochoa.

Sanatorio Allende S.A., Córdoba, Argentina. Fernando Oscar Riera, MD, Aldana Mano, Gabriela Virginia Peukert, Carlos Federico Romero.

Belgium

CHU Dinant Godinne, Cliniques Universitaires Catholic University of Louvain Namur, Yvoir, Belgium. Nathalie Ausselet, MD, Pierre Bulpa, MD, Benedicte MJB, Delaere, MD, Alain M. Dive, MD, Patrick Evrard, MD, Geoffrey Horlait, MD, Isabelle Michaux, MD, Pascal Reper, MD.

UZ Brussel, Brussels, Belgium. Elisabeth De Waele, MD, PhD, Marc W. Diltoer, MD, PhD, Steven Hendrickx, Joop Jonckheer, MD, Michael Mekeirele, MD, Duc Nam Nguyen, MD, PhD, Matthias Raes, MD, Simon de Ridder, MD, Alex R. Van Hoorn, Ruth Van Lacker, Wout Van Oosterwyck, Domien Vanhonacker, MD.

Brazil

Hospital São Paulo – UNIFESP, São Paulo, Brazil. Jaquelina Sonoe Ota Arakaki, MD, PhD, Oliver Augusto Nascimento, Daniella Silva de Almeida.

Santa Casa de Misericordia de Belo Horizonte, Belo Horizonte, Brazil. Antonio Tarcisio Freire, MD, Thayse Kayser, Claudia Oliveira.

Instituto de Infectologia Emilio Ribas, São Paulo, Brazil. Luiz Carlos Pereira Junior, MD, Amanda Bittencourt, Gustavo Dittmar, Bernardo Porto Maia, Denise Pacola, Vistor Passarelli, Maria Silvia Biagioni Santos, Tamara Newman Lobato Azevedo Souza, Ana Luiza de Castro Conde Toscano.

Hospital das Clinicas da Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brazil. Esper Georges Kallas, MD, PhD, Angela Carvalho Freitas, Gabriel Fialkovitz da Costa Leite, Lucas Chaves Netto.

Universidade Federal de Minas Gerais, Minas Gerais, Brazil. Jorge Andrade Pinto, MD, Thiago Bragança Lana Silveira Ataide, Renan Detoffol Bragança, Helena Duani, Flavia Gomes Faleiro Ferreira.

Rua Oswaldo Oscar Barthelson, Campinas, Brazil. José Francisco Saraiva, MD, Matheus Nascimento, Hugo Bertipaglia.

Hospital Alemão Oswaldo Cruz, Hospital Sirio Libanes Instituto de Ciências, São Paulo, Brazil. Victor Augusto Hamamoto Sato, MD, Daniela Ghidetti Mangas Catarino, Jose Victor Gomes Costa, Erico Souza De Oliveira, MD, Bernadete Ferreira, Sara Mohrbacher, MD, Leonardo Victor Barbosa Pereira, MD, PhD.

Hospital de Clínicas de Porto Alegre, Porto Alegre, Brazil. Eduardo Sprinz, MD, PhD, MSc, Gustavo Leal Agune, Beatriz Arns, Giulia Baldissera, Ana Elize Barin, Murillo Machado Cipolat, Julio Cezar Gonçalves Cordeiro dos Santos, Mariana Falcetta, Leonardo Martins Pires, Guilherme Geraldo Lovato Sorio, Tarsila Vieceli.

Canada

Hôpital du Sacré Cœur de Montréal, Montréal, Québec, Canada. Martin Albert, MD, Francis Bernard, Yiorgos Alexandros Cavayas, MD, Karim Serri, David Williamson.

UBC James Hogg Research Centre Saint Paul's Hospital, Vancouver, British Columbia, Canada. John Boyd, MD, Adam Peets, Demetrios Sirounis.

The Ottawa Hospital, Ottawa, Ontario, Canada. Shane W. English BSc, MD, FRCPC, MSc, Scott J Millington, MD, FRCPC.

CISSS de la Montérégie-Centre/Hôpital Charles Le Moyne, Taschereau, Québec, Canada. Germain Poirier, MD, CM, FRCPC, Antoine Delage, Louise Passerini.

Unite de recherche Clinique du CISSS des Laurentides, Saint-Jerome, Québec, Canada. Sebastien Poulin, MD, Louay Mardini, MD, Yves Pesant, MD.

Chile

Hospital Barros Luco, Santiago, Chile. Luis Benito Fuenzalida Castillo, Ronald Edgar Pairumani Medrano, MD.

Clinica Las Condes, Las Condes, Santiago, Chile. Tomas Regueira Heskia, MD, PhD, Andrés Alberto Ferre Contreras, MD.

Centro Respiratorio Integral Ltda, Region de Valparaiso, Chile. Juana Rosa Pavie Gallegos, MD, Patricia Alexandra Intriago Alcivar, Baird Ibn Zegpi Keller, MD.

Hospital Regional de Talca, Región Del Maule, Chile. Absalón Rafael Sergio Silva Orellana, MD, Carolina Paz González Navarro, MD.

Columbia

Hospital Universitario San Ignacio, Bogotá, Colombia. Luis Carlos Triana Moreno, Stela del Pilar Baracaldo Gomez, MD, Maria Alejandra Betancur Diaz, MD, Angel Alberto Garcia, MD.

France

HCL – Centre Hospitalier Lyon Sud, Pierre-Bénite, France. Bernard Allaouchiche, MD, PhD, Marie Darien, MD, Donatien De Seissan De Marignan, MD, Marion Didier, MD, Lucille Jay,

MD, Emilie Joffredo, MD, Maxime Lecocq, MD, Alain Lepape, MD, Mélanie Levrard, MD, Fabrice Thiolliera, MD, Florent Wallet, MD.

CHU d'Angers, Angers, France. Pierre Asfar, MD, PhD, François Beloncle, MD, Julien Demiselle, MD, Hélène Julien, MD, Achille Kouatchet, MD, Satar Mortaza, MD, Pierre-Yves Olivier, MD, Marc Pierrot, MD, Vincent Souday, MD.

CH Valenciennes - Hôpital Jean Bernard, Valenciennes, France. Hatem Boughanmi, MD, Fabien Lambiotte, MD, Piehr Saint Leger, MD.

GH Pitié-Salpêtrière, Paris, France. Jean-Michel Constantin, MD, PhD, Mona Assefi, MD, Marine Le Corre, MD, Bao-Long Nguyen, MD, Cyril Quemeneur, MD, Guillaume Savary, MD, Agathe Selves, MD.

Centre Hospitalier Universitaire de Limoges, Limoges, France. Bruno François, MD, Thomas Daix, MD, Arnaud Desachy, MD, Bruno Evrard, MD, Anne-Laure Fedou, MD, Guillaume Gilbert, MD, Marine Goudelin, MD, Amandine Sanson, MD, Julien Vaidie, MD, Philippe Vignon, MD, PhD.

CHR de Metz-Thionville – Hôpital Mercy, Service de Réanimation Polyvalente, Ars-Laquenexy, France. Rostane Gaci, MD, Cyril Cadoz, MD, Serge Le Tacon, MD, Guillame Louis, MD, Adeline Perrein, MDCHD Vendée – Site De La Roche-sur-Yon, La Roche-Sur-Yon, France. Jean-Claude Lacherade, MD, Marie-Ange Azais, MD, Konstantinos Bachoumas, MD, Rémi Bernardon, MD, Gauthier Blonz, MD, Gwenhaël Colin, MD, Luc Desmedt, MD, Maud Fiancette, MD, Matthieu Henry-Lagarrigue, MD, Hugo Hille, MD, Christine Lebert, MD, Laurent Martin-Lefevre, MD, Caroline Pouplet, MD, Aurélia Toussaint, MD, Isabelle Vinatier, MD, Aihem Yehia, MD.

CHU Amiens-Picardie - Site Sud, Amiens, France. Julien Maizel, MD, PhD, Abdallah Al Salameh, MD, Damien Basille, MD, Mélanie Drucbert, MD, Mathieu Guilbart, MD, Jean-Philippe Lanoix, MD, Michel Slama, MD, Sandrine Soriot-Thomas, MD, Yoann Zerbib, MD.

Hôpitaux Universitaires de Strasbourg - Nouvel Hôpital Civil, Strasbourg, France. Ferhat Meziani, MD, PhD, Jessy Cattelan, M.D., Raphaël Clere-Jehl, MD, Julien Demiselle, MD, Julie Helms, MD, Louise-Marie Jandeaux, MD, Christine Kummerlen, MD, Hamid Merdji, MD, Alexandra Monnier, MD, Hassene Rahmani, MD, Antoine Studer, MD.

Groupe Hospitalier Sud Ile de France, Melun, France. Mehran Monchi, MD, Esther Mbakulu Muanda, MD, Franck Pourcine, MD.

Centre Hospitalier Victor Dupouy, Argenteuil, France. Gaëtan Plantefeve, MD, Damien Contou, MD, Megan Fraisse, MD, Paul Desaint, MD, Elsa Logre, MD, Olivia Picq, MD, Florence Sarfati, MD, Joanna Tirolien, MD.

Hôpitaux Universitaires de Strasbourg - Hôpital de Hautepierre, Service de Médecine Intensive et Réanimation, Strasbourg, France. Francis Schneider, MD, PhD, Mathieu Baldacini, MD, Thien Nga Chamaraux, MD, Pierre Diemunsch, MD, Sophie Diemunsch, MD, Max Guillot, MD, Jean-Etienne Herbrecht, MD, Pierre-Olivier Ludes, MD, Guillaume Morel, MD, Eric Noll, MD, Julien Pottecher, MD.

CHU Grenoble Alpes – Site Nord La Tronche - Hôpital Michallon, La Tronche, France. Nicolas Terzi, MD, Joanna Bougnaud, MD, Anaïs Dartevel, MD, Louis-Marie Galerneau, MD, Côme Gerard, MD, Guillaume Rigault, MD, Carole Schwebel, MD, Florian Sigaud, MD.

Germany

University Hospital Aachen, Department of Pneumology and Critical Care, Nordrhein-Westfalen, Germany. Michael Dreher, MD, Maria Aetou MD, Christian Cornelissen, MD, Ayham Daher, MD, Alexander Kersten, MD, Tobias Mueller, MD, Annegret Mueller, MD, Judith Smith, MD, Robert Stoehr, MD.

Universitaetsmedizin Goettingen, Goettingen, Germany. Onnen Moerer, MD, Martin Winkler, MD.

Medizinische Hochschule Hannover, Hospital of Pneumology, Hannover, Niedersachsen, Germany. Tobias Welte, MD, Torben Brod, MD, Nora Drick, MD.

Krankenhaus Merheim, Koeln, Nordrhein-Westfalen, Germany. Wolfram Windisch, MD, Laura Emrich, MD, Danial Majorski, MD, Sarah Schwarz, MD, Maximillian Wollsching-Strobel, MD.

Charité - Universitätsmedizin Berlin, Berlin, Germany. Martin Witzenrath, MD, Phillipp Enghard, MD, Moritz Mueller-Plathe, MD.

India

Max Smart Super Speciality Hospital (A Unit of Gujarmal Modi Hospital and Research Centre for Medical Sciences), New Delhi, India. Ritesh Aggarwal, MBBS, DNB, Arun Dewan.

Medica Superspecialty Hospital, Kolkata, India. Tanmay Banerjee, MD, MBBS, Anirban Bose, MD, Amitabha Saha, MD.

Government Medical College, Aurangabad, India. Meenakshi Bhattacharya, MD, MBBS, Aditya Gudhate, Avinash Humbe.

Saint Theresas Hospital, Hyderabad, India. Nagaraju Boyilla, MD, MBBS, Akula Venkateshwar Rao.

Government Medical College and Hospital Nagpur, Nagpur, India. Dipti Chand, MD, MBBS, Nikhil Agarwal, Chandrashekhar Atkar, Sagar Khandare.

Metas Adventis Hospital, Surat, India. Chirag Chhatwani, MD, MBBS, Amit Shah, Ramesh Surati.

Peerless Hospitex Hospital and research center limited, Kolkata, India. Rimita Dey, MD, MBBS, Subhrojyoti Bhowmik, MD.

Kasturba Hospital for Infectious Disease, Mumbai, India. Ajay Jhaveri, MBBS, DNB, Chandrakant Pandurang Pawar, MD.

Noble Hospital Private Limited, Pune, India. Reema Kashiva, MD, MBBS, Prashant Raghunath Potdar.

SMS Medical College and Attached Hospitals Jaipur, Jaipur, India. Chhuttan Lal Nawal, MD, MBBS, Radhey Shyam Chejara, MD, Vinaykumar Meena, MD, Hazari Lal Saini, MD.

MGM Medical College and Hospital, Aurangabad, India. Umar Quadri Syed, MD, MBBS, Rohit Jacob, Nilofer Bano Patel.

Ruby Hall Clinic, Cancer Centre, Pune, India. Kapil Zirpe, MD, Abhijit Deshmukh.

Italy

Istituto Nazionale Malattie Infettive – INMI L. Spallanzani IRCCS, U.O.C. Immunodeficienze Virali, Roma, Italy. Andrea Antinori MD, Marta Camici, Ilaria Mastrorosa, Valentina Mazzotta, Carmela Pinnetti, Alessandra Vergori.

Fondazione S. Raffaele del Monte Tabor, Unita' di Reumatologia e Immunologia Clinica, Divisione di Medicina, Milano, Italy. Lorenzo Dagna, MD, Alessandro Tomelleri.

AO Ospedali dei Colli, 1 UTSIR COVID, Napoli, Italy. Guiseppe Fiorentino, MD, Anna Annuzianta, Novella Carannante, Valentina Si Spirito, Pasquale Imitazione, Maurizia Lanza, Antonelle Marotta, Giorgio Emanuele Polistina.

Azienda Ospedaliero-Universitaria "Policlinico Riuniti" di Foggia, Dipartimento di Medicina Specialistica, Foggia, Italy. Maria Pia Foschino Barbaro, MD, Donato Lacedonia, Giorgia Lepore, Carla Maria Irene Quarato, Pasquale Tondo.

Ospedale Luigi Sacco – Azienda Ospedaliera e Polo Universitario, Dipartimento Malattie Infettive 1° Divisione Malattie Infettive ed Allergologia, Milan, Italy. Giuliano Rizzardini, MD, Amedeo F. Capetti, MD, Massimo Coen, Maria V Cossu, MD, Ivano Faggion, Guido Gubertini, Matteo Passerini, Monica Schiavini.

Japan

Shonan Fujisawa Tokushukai Hospital, Kanagawa, Japan. Makoto Hibino, MD, Shigeto Horiuchi, Tetsuri Kondo, Kazunari Maeda, Shunichi Tobe.

Tokyo Nishi Tokushukai Hospital, Tokyo, Japan. Hirokazu Iijima, MD, Ryo Ga, Mutsuo Takaki.

Funabashi Central Hospital, Internal Medicine, Chiba, Japan. Satoru Ishikawa, MD, Akira Kojima.

National Center for Global Health and Medicine, Tokyo, Japan. Shinyu Izumi, MD, PhD, Kazuo Hakkaku, Masao Hashimoto, Masayuki Hojo, Motoyasu Iikura, Takashi Katsuno, Kazuki Kawajiri, Yusaku Kusaba, Ayako Mikami, Momoko Morishita, Chie Morita, Go Naka, Susumu Saito, Keita Sakamoto, Yuriko Sugiura, Manabu Suzuki, Jin Takasaki, Hiroshi Takumida, Yoshie Tsujimoto, Akinari Tsukada, Hiromu Watanabe, Yoh Yamaguchi.

Japanese Red Cross Medical Center, Tokyo, Japan. Takehiro Izumo, PhD, MD, Nobuyasu Awano, Kazushi Fujimoto, Munehiro Hayashi, Minoru Inomata, Yu Ito, Yuji Kondo, Kana Kono, Naoyuki Kuse, Kenro Maki, Haruko Mastsumoto, Yuta Moroe, Shun Muramatsu, Yutaka Muto, Akira Nomi, Shogo Sagisaka, Ayae Saiki, Keita Sakamoto, Kohei Takada, Mari Tone, Ryuta Yamashita, Tomoyuki Yamashita.

Yokohama City Minato Red Cross Hospital, Kanagawa, Japan. Isao Nagata, MD, Michiko Fujisawa, Shinsuke Karatsu, Eisaku Nashiki, Kei Sugiki, Taketo Suzuki, Tetsuhiro Takei, Hiroyuki Yamada, Naoki Yonezawa.

Nozaki Tokushukai Hospital, Neurosurgery, Osaka, Japan. Hidemitsu Nakagawa, MD, Shin Hirayama, Masakazu Tamura, Masanobu Yamada.

Tokyo Medical and Dental University, Tokyo, Japan. Yasuhiro Otomo, MD, Akira Endo, Kenichi Hondo, Takahiro Mitsumura, Yasunari Miyazaki, Koji Morishita, Kanae Ochiai, Keisuke Suzuki, Wataru Takayama.

Tokyo Shinjuku Medical Center, Tokyo, Japan. Hidefumi Shimizu, MD, Yoshimasa Horie, Hiroshi Kojima, Akira Mizoo.

Osaka City General Hospital, Osaka, Japan. Michinori Shirano, MD, PhD, Tomohiro Asaoka, Tetsushi Goto, Ko Iida, Keiji Konishi, Hidenori Nakagawa.

Saitama Medical University Hospital, Saitama, Japan. Norihito Tarumoto, MD, Kazuo Imai, Noriomi Ishibashi, Shigefumi Maesaki, Jun Sakai.

Fujita Health University Hospital, Aichi, Japan. Norimichi Uenishi, MD, Daichi Arakaki, Yohei Doi, Kenichiro Fujii, Masaya Hibino, Takao, Yuki Osuki, Hirotaka Otake.

Mexico

Fundacion Santos y de la Garza Evia I.B.P. Hospital San José TecSalud, Monterrey, Mexico. José-Fernando Castilleja-Leal, MD, Daniel Davila-Gonzalez, Alberto Garcia-Vega, Arturo Adrian Martinez-Ibarra, Juan Francisco Moreno-Hoyos Abril.

Hospital Civil Fray Antonio Alcalde, Guadalajara, Mexico. Pedro Martinez-Ayala, MD, Sara-Alejandra Aguirre-Diaz, Alfredo Gutierrez-Marin.

Instituto Nacional de Enfermedades Respiratorias “Ismael Cosío Villegas”, Mexico City, Mexico. Amy-Bethel Peralta-Prado, MD, Victor Hugo Ahumada-Topete, Maria Isabel Leon-Rodriguez.

Instituto Nacional de Ciencias Medicas y Nutricion Salvador Zubiran, Mexico City, Mexico. Juan Gerardo Sierra-Madero, MD, Claudia Paola Alarcon-Murra, Jose Guillermo Dominguez-Cherit, Karen-Aranza Marañon-Solorio, Bernardo Alfonso Martínez-Guerra, Carlos Torruco-Sotelo.

Netherlands

Medisch Spectrum Twente, Enschede, Netherlands. Albertus (Bert) Beishuizen, MD, PhD, Alexander D. Cornet, MD, PhD, Bob Oude Velthuis, MD, Jan W. Vermeijden, MD, PhD.

Canisius Wilhelmina Ziekenhuis, Nijmegen, Netherlands. Oscar Hoiting, MD, Marco A.A. Peters, MD, Els Rengers, MD.

Jeroen Bosch Ziekenhuis, Den Bosch, Netherlands. Frans W. (Wim) Rozendaal, MD, Cornelis P.C. de. Jager, MD, PhD, Miriam A.M. Moviat, MD, PhD, Anne J. Paling, MD, Florens N. Polderman, MD, G.A.M. (Astrid) Salet, MD, Koen S. Simons, MD, PhD.

Amphia Ziekenhuis, Breda, Netherlands. Simone van der Sar, MD, Remco S. Djamin, MD, PhD, Klaas M. (Merijn) Kant, MD, Kornelis H. van der Leest, MD, PhD, Sander Talman, MD.

Ikazia Ziekenhuis, Rotterdam, Netherlands. Fenna J. Schoonderbeek, MD, PhD, Maaike Muller-Ekas, MD, Ralph V. Pruijsten, MD, Anna F.C. Schut-Houtgraaf, MD, PhD, Susanne Stads, MD, Walter van den Tempel, MD, Henriette F.E.M. Willems, MD.

Peru

Clínica Internacional - Seda Lima, Lima, Peru. José Luis Cabrera Rivero, Alfredo Gilberto Guerreros Benavides, Edwin Hernando Herrera Flores, MD, Eneyda Giuvanela Llerena Zegarra, Lorena Mata Juarez, Teresa Jhovina Perez Rodriguez, Raúl Ruiz Castellanos, MD, Karla Ysabel Sánchez Vallejos, MD, Hernando Torres Zevallos, MD.

Centro de Investigación del Hospital Militar Central, Lima, Peru. Victoria Chavez Miñano, MD, Aida Miluska Delgado Flores, Raul Ernesto Porras Serna, Giovanna Rosa Trujillo Velita, MD.

Hospital Nacional Alberto Sabogal Sologuren, Lima, Peru. Luis Enrique Hercilla Vásquez, MD, Erika Cecilia Agurto Lescano, Ysabel Marlene Chavez Santillan, Ronald Nilton Guzman Ramos, Freddy Roberto Marchand Gago, Fernando Franz Namuche Ojeda, D'yanira Felieva Rojas Montaño, Miguel Angel Tapia Paredes, Carmen Sara Terrazas Obregon, MD, Nora Isabel Villoslada Contreras.

Hospital Nacional Edgardo Rebagliati Martins, Lima, Peru. Fernando Cruz Mendo Urbina, MD, Oscar Melitón Reyna Vargas, Jose Carlos Ruelas Figueroa.

Poland

Wojewodzki Szpital Obserwacyjno-Zakazny, Bydgoszcz, Poland. Dorota Anna Dybowska, MD, PhD, Dorota Kozielewicz, Przemyslaw Slomkowski.

Centralny Szpital Kliniczny MSWiA w Warszawie, Warszawa, Poland. Andrzej M. Fal, MD, PhD, Kamil Adamczyk, Malgorzata Dorobek, Maciej Jankowski, Anna Jasinska, Antoni Okninski, Iwona Pikto-Pietkiewicz, Katarzyna Przybylowska, MD, Monika Maria Swiderska, Ewa Szczesniak, Konstanty Szuldrzynski, Rafal Wojtowicz, Justyna Zielinska-Turek.

Wielospecjalistyczny Szpital Miejski im. J. Strusia, City Hospital of Poznan, Poznan, Poland. Blazej Rozplochowski, MD, PhD, Teresa Ganowicz-Kaatz, Jakub Kopaczynski, Sylwia Michalik, Iwona Mozer-Lisewska, Maja Szczerbakowska.

Szpital Uniwersytecki w Krakowie, Oddzial Kliniczny Chorob Zakaznych, Krakow, Poland. Wojciech Serednicki, MD, PhD, Tomasz Gazda, Teresa Kowal, Anna Kwinta, Rafal Swistek, Wojciech Szpunar.

Wojewodzki Szpital Specjalistyczny im. J. Gromkowskiego, Oddzial Chorob Zakaznych ul, Wroclaw, Poland. Krzysztof Simon, MD, PhD, Justyna Janocha, Anna Szymanek-Pasternak, Aleksander Zinczuk.

Russian Federation

Clinic of Bashkir State Medical University, Ufa, Russian Federation. Bulat Bakirov, MD, PhD, Ruslan Maier, MD.

State Budget Healthcare Institution City Clinical Hospital #15 n.a. O.M.Filatov, Moscow, Russian Federation. Ivan G. Gordeev, MD, PhD, Vitaliy Firstov, Vartan Grigoryan, Ilia Kokorin, Ksenia Komissarova, Anna Kozlova, Nina Lapochkina, MD, Sevinch Mamedguseyinova, MD, Ksenia Polubatonova, MD, Natalia Alexandrovna Suvorova, MD.

Regional Clinical Hospital #4, Chelyabinsk, Russian Federation. Galina L Ignatova, MD, Vladimir Antonov MD, Olga V. Rodionova, MD.

Budgetary Healthcare Institution of the Voronezh region 'Voronezh Regional Clinical Hospital #1,' Voronezh, Russian Federation. Natalia E. Kostina, MD, PhD, Svetlana Chuprina, MD, Olga M. Korolkova, MD, PhD, Andrey Vorobyev, MD.

BUZ of Omsk Region, Regional Clinical Hospital, Omsk, Russian Federation. Tatiana Kropotina, MD, Julia Arbuzova, MD, Evgeniya Baygozina, MD, Elena Elokhina, MD, Irina Menschikova, MD, Ekaterina Shelyagina, MD, Boris Statsenko, MD, Yuliya Zakharevich, MD.

Nizhniy Novgorod City Clinical Hospital #10, Nizhniy Novgorod, Russian Federation. Ekaterina V. Makarova, MD, PhD, Ludmila Alexandrovna Lomakina, MD, Natalya Lyubavina, Vladimir Vakhlamov.

Saint Petersburg State Healthcare Institution City Mariinsky Hospital, Saint Petersburg, Russian Federation. Aleksey G. Mamonov, MD, Vladimir Okhritckii.

State Budget Institution of Health, City Hospital #5, Barnaul, Russian Federation. Tatiana Martynenko, MD, PhD, DNSc, Konstantin Gatalskiy, MD, Ilya Lazarenko, MD, Olga Paraeva, MD, Anastasiya Shek, Elena A Vasilkova, Olga Ganova, MD.

Perm Regional Clinical Hospital #1, Perm, Russian Federation. Yuliya Trefilova, MD, PhD, Galina Bykova, MD, Anna Ershova, MD, Natalia Grigoriadi, MD, Natalia Komarovskaya, MD, Kseniya Trenogina, MD, Vera Vustina, MD, Tatiana Yakovleva, MD, Yulia Zhelnina, MD.

City Clinical Hospital #14, Ekaterinburg, Russian Federation. Elena Mikhailovna Vishneva, MD, PhD, Ekaterina A. Egorova, MD, Anna Pavlovna Isakova.

South Africa

Jakaranda Hospital, Pretoria, South Africa. Johannes Breedt, MBChB, DOH.

MERC SiReN, Metcare Milpark Hospital, Johannesburg, South Africa. Natasha Joseph. MB ChB, Safiyya Chohan MB ChB, Shiraaz Bhamjee, MB ChB.

University of Stellenbosch, Cape Town, South Africa. Coenraad F.N. Koegelenberg, PhD, MB ChB, MMed, Brian William Allwood, MB ChB, PhD, Usha Lalla, MB ChB.

Durban International Clinical research site, Enhancing Care Foundation, Durban, South Africa. Rosie Mngqibisa, MB ChB, Umesh Gangharam Lalloo, MB ChB, Sajeeda Mawlana, MB ChB, Sundrapragasen Pillay, MB ChB, Natasha Lalloo, MB ChB.

Mzansi Ethical Research Centre – Middleburg, Middleburg, South Africa. Friedrich Georg Petrick. MB ChB, Augustine Chaumba, MB ChB, Gertruida Magdalena, MB ChB, Maxine Stephany Sampson, MB ChB, Mohammed Siddique Tayob, MB ChB.

Panorama Research, Cape Town, South Africa. Johan Theron, MB ChB, Daphne Charlotte Richter, MB ChB, Morne Johan Vorster, MB ChB.

Clinical Projects Research SA pty Ltd, Worcester, South Africa. Louis J. van Zyl, MB ChB, MMed, Marina Naude, MB ChB, Christo van Dyk, MB ChB, MMed, Francois H. van Zyl, MB ChB.

Life The Glynnwood Hospital, Eastrand Physicians, Benoni, South Africa. Agatha C. Wilhase, MB ChB, MCFP, MFamMed, Reece Boosi, MB ChB, Nabeela Kajee, MB ChB, MMed, Jayseelan Naidu, MB ChB, MMed, Kuven Naidu, MB ChB, Mirriam Patel, Bilaal Wadee, MB ChB

Spain

Hospital Universitario La Princesa, Madrid, Spain. Tamara Alonso Pérez, MD, María de Churruca Arróspide.

Hospital Universitario Gregorio Marañón, Madrid, Spain. Javier de Miguel Díez, MD, PhD, Walther Iván Girón Matute, Zichen Ji, Luis Puente Maestu, José Rafael Terán Tinedo.

H.E. Enferma Isabel Zendal, Madrid, Spain. Pedro Landete Rodríguez, MD, Clotilde Funes Moreno, Daniel Laorden Escudero, Eva Prats Gracia, José Rafael Terán Tinedo.

Hospital del Mar-IMIM, Barcelona, Spain. Rosana Muñoz Bermúdez, MD, PhD, Judith Marín Corral, MD, PhD, Francisco José Parrilla Gómez, MD, Clara Vilà Vilardell, MD.

Fundación Jiménez Díaz, Madrid, Spain. Germán Peces-Barba Romero, MD, PhD, Laura Álvarez Suárez, Elena Cabezas Pastor, Itziar Fernández Ormaechea, Andrés Giménez Velando, Carolina María Gotera Rivera, Pablo López Yeste, Marcel José Rodríguez Guzmán, Arnoldo de Jesús Santos Oviedo.

Hospital de San Pedro, Logroño, Spain. Carlos Ruíz Martínez, MD, PhD, Jorge Alba Fernández, Adolfo Calvo Martínez, Dolores del Puerto García, José Andrés Molina Espejo, Alejandra Roncero Lázaro, Esther Saiz Rodrigo, Javier Ugedo Urruela.

Hospital Universitario de Bellvitge, Barcelona, Spain. Salud Santos Pérez, MD, PhD, Ester Cuevas Sales, Mercè Gasa Galmes, Yolanda Ruiz Albert, Mikel Sarasate Azkona, Guillermo Rafael Suárez Cuartín, Pere Trias Sabrià.

Hospital Universitario Infanta Sofia, Madrid, Spain. Llanos Soler Rangel, MD, PhD, Miguel Ángel González Gallego, María Teresa Ramírez Prieto, Pilar Ruiz Seco, Inés María Suárez García, Miguel Ángel Vázquez Ronda.

United Kingdom

The James Cook University Hospital, Middlesbrough, United Kingdom. Stephen Bonner. MBBS, David Robert Chadwick, Nicola Cree, Uwe Franke, Isabel Gonzalez, Jeremy Henning, Alexander Scott, Michelle Shaw, Judith Wright.

Royal Victoria Infirmary, Newcastle Upon Tyne, United Kingdom. John Isaacs, PhD, FRCP, BSc(Hon.), MBBS, Andrew Barr, Ian Clement, Iain McCullagh, David Ashley Price, Amada Sanchez Gonzalez.

Bradford Teaching Hospitals, Bradford Royal Infirmary, Bradford, United Kingdom. Tom Lawton, BM, BCh, MA, MSc, MRCP, FRCA, FFICM, James Morgan, Dinesh Saralaya, Paul Whitaker.

Wythenshawe Hospital, Manchester, United Kingdom. Andrew David Martin, MB ChB, MRCP, FRCA, FFICM, CCT, Peter David Gregory Alexander, Andrew Mark Bentley, Tim Felton, Tolga Turgut.

Manchester University, Manchester Royal Infirmary, United Kingdom. Andrew Martin, MB ChB, MRCP, FRCA, FFICM, CCT, Jonathan Bannard-Smith, Steve Benington, Patrick Hamilton, James Hanison, Nina Rendell, Anthony Wilson.

Royal Liverpool University Hospital, Liverpool, United Kingdom. Ingeborg Dorothea Maria Welters, MD, PhD, Oliver Hamilton, Brian Johnston, Suleman Mulla, Alicia Waite, Richard Wenstone.

United States

University of California, Davis Medical Center, Sacramento, California, United States. Timothy Albertson, MD, PhD, Stuart H. Cohen, M.D., Brian M. Morrissey, MD, Christian Sandrock, MD.

Baltimore VA Medical Center, Baltimore, Maryland, United States. Jacqueline Bork, MD, Jennifer Y. So, MD, Rohit Talwani, MD.

Maine Medical Center, Portland, Maine, United Stated. Kathryn Marie Brouillete, MD, CM, Sarah Marie Bray, MD, Raymond M Klein, MD, Katherine T. Liu, MD, Daniel A. Meyer, MD.

G.V.(Sonny) Montgomery Veterans Administration Medical Center, Jackson, Mississippi, United States. Mary Jane Burton, MD, Gwendolyn Adams-McAlpine, NP, Christian D. Weaver, MD.

Temple University Hospital, Philadelphia, Pennsylvania, United States. Gerard J. Criner, MD, James C. Brown, MD, Junad Mir Chowdhury, MD, Stephen E. Codella, MD, Parag B. Desai, MD, Gustavo Adolfo Fernandez Romero, MD, Rohit Gupta, MD, Fredric Jaffe, DO, Navjot Ariyana Kaur, MD, Samuel L. Krachman, DO, Albert James Mamary, MD, Nathaniel Marchetti, DO, Janpreet Mokha, MD, Oisin O'Corragain, MD, Maulin Patel, MD, Parth M. Rali, MD, Ekamjeet Singh Randhawa, MD, Daniel Alejandro Salerno, MD, MS, Kartik V. Shenoy, MD, Omar Sheriff, MD, Jeffrey I. Stewart, MD, Maria Elena Vega-Sanchez, MD, Steven R. Verga, MD, Ibraheem Fares Mohammad Yousef, MD, Matthew Zheng, MD.

Carilion Roanoke Memorial Hospital Carilion Clinic, Roanoke, Virginia, United States. Dorothy C. Garner, MD, Ekta N. Bansal, MD, Mariana Gomez De La Espriella, MD, Ruth Ndolo, RN, Fazili Tasaduq, MD, FACP, Jim Wong, MD.

The Lundquist Institute for Biomedical Innovation, Harbor UCLA Medical Center, Torrance, California, United States. Timothy J. Hatlen, MD, Eric S. Daar, MD.

Broward Health Medical Center, Florida, United States. Frank P. Hull, MD.

Mercy Health– Saint Vincent Medical Center, Toledo, Ohio, United States. Luis E. Jauregui-Peredo, MD, Salil Avasthi, MD, Tanyanyiwa W. Chinyadza, MD, Srinivas Katragadda, MD, James A. Tita, DO.

Renown Regional Medical Centre, Reno, Nevada, United States. Farah K. Madhani-Lovely, MD, Daniel Antwi-Amoabeng, MD, Rudy Tedja, DO.

Clement J Zablocki Veterans Administration Medical Center, Milwaukee, Wisconsin, United States. Sheran Mahatme, MD, Nathan D. Gundacker, MD.

Northwestern Medicine Central DuPage Hospital, Winfield, Illinois, United States. Luis A. Manrique, MD, Daniel Boyle, MD.

Regions Hospital, Saint Paul, Minnesota, United States. Charlene E. McEvoy, MD MPH, Omobosola O. Akinsete, MD, Charles A. Bruen, MD, Kealy Rae Ham, MD, Sarah Rebecca Peglow, MD.

Methodist Hospital, St. Louis Park, Minnesota, United States. Charlene E. McEvoy, MD MPH, Amanda Calvin, MD, Elizabeth Miller, MD.

Multicare Institute for Research & Innovation, Tacoma, Washington, United States. Patrick Scott Meehan, Jr., MD, Vinay Malhotra, MD.

University of Arkansas for Medical Sciences, Little Rock, Arkansas, United States. Nikhil Kumar Meena, MD, Jose Diego Caceres, MD, Harmeen Goraya, MD, Larry Galdoc Johnson, MD.

Loma Linda University Medical Center, California, United States. H. Bryant Nguyen, MD, Terri Granillo, PA.

Memorial Hermann Hospital – Texas Medical Center, Texas, United States. Bela Patel, MD, Bindu Akkanti, MD, Luis Zeichner Ostrosky, MD.

Veterans Administration Western New York Healthcare System, New York, United States. Karin A. Provost, DO, PhD, Gregory Scott Fuhrer, MD, Jeffery M Mador, MD, Archana Mishra, MD.

Holy Cross Hospital, Silver Spring, Maryland, United States. Lee Edward Schwab, MD, Bernice Wiredu Aidoo, MD, Miriam Louise Cameron, MD, Ramani Reddy, MD.

Holy Cross Germantown Hospital, Germantown, Maryland, United States. Lee Edward Schwab, MD, Miriam Louise Cameron, MD, Farah Munnir Cheema, MD, Sameer B. Ismailjee, MD.

Pulmonary Associates of Mobile, Mobile, Alabama, United States. Allan F. Seibert, IV, MD, Michele L. Hemphill, RN, Daniel Joseph Pollman, MD.

Atrium Health, Charlotte, North Carolina, United States. Zainab Shahid, MD, Michael Sean Boger, MD, Yvonne Lynnette Carter, MD, Tedra Claytor, MD, Lisa E. Davidson, MD, Azeem Elahi, MD, Joseph P. Lang, MD, Michael K. Leonard, MD, Lewis Hall McCurdy, MD, Leigh Ann Medaris, MD, Tue H. Ngo, MD, Fred C. Papali, MD, CM, Christopher Polk, MD, Nestor Manuel Quezada, MD, Mindy M. Sampson, MD, DO, Jaspal Singh, MD, Kranthi K. Sitammagari, MD, Stephanie L. Strollo, MD, Brice Thomas Taylor, MD, Shelley S. Towery, RN, David Allan Weinrib, MD, Michael Zgoda, MD, Sara Zulfigar, MD.

North Florida South Georgia Veterans Health System, Gainesville, Florida, United States. Peruvemba S. Sriram, MD.

Doylestown Hospital, Doylestown, Pennsylvania, United States. Les A. Szekely, MD, Pinak Sumant Acharya, MD, Manuel Jose Jimenez-Serrano, MD, Kathy Tran-Gast, DO.

Supplementary Methods

Modified World Health Organisation (WHO) Ordinal Scale

1 = not hospitalised, no limitation of activity

2 = not hospitalised, limitation of activity

3 = hospitalised, no oxygen therapy

4 = hospitalised, low-flow oxygen by mask or nasal prongs

5 = hospitalised, high-flow oxygen (≥15 L/min), continuous positive airway pressure, bilevel positive airway pressure, non-invasive ventilation

6 = hospitalised, intubation and mechanical ventilation

7 = hospitalised, mechanical ventilation plus additional organ support

8 = death.

Blinding

An unblinded pharmacist dispensed the study intervention, ensuring no differences in labelling or time taken to dispense between the two interventions. Investigators who enrolled the patients, and the patients remained blinded to assigned study intervention.

Endpoints and assessments

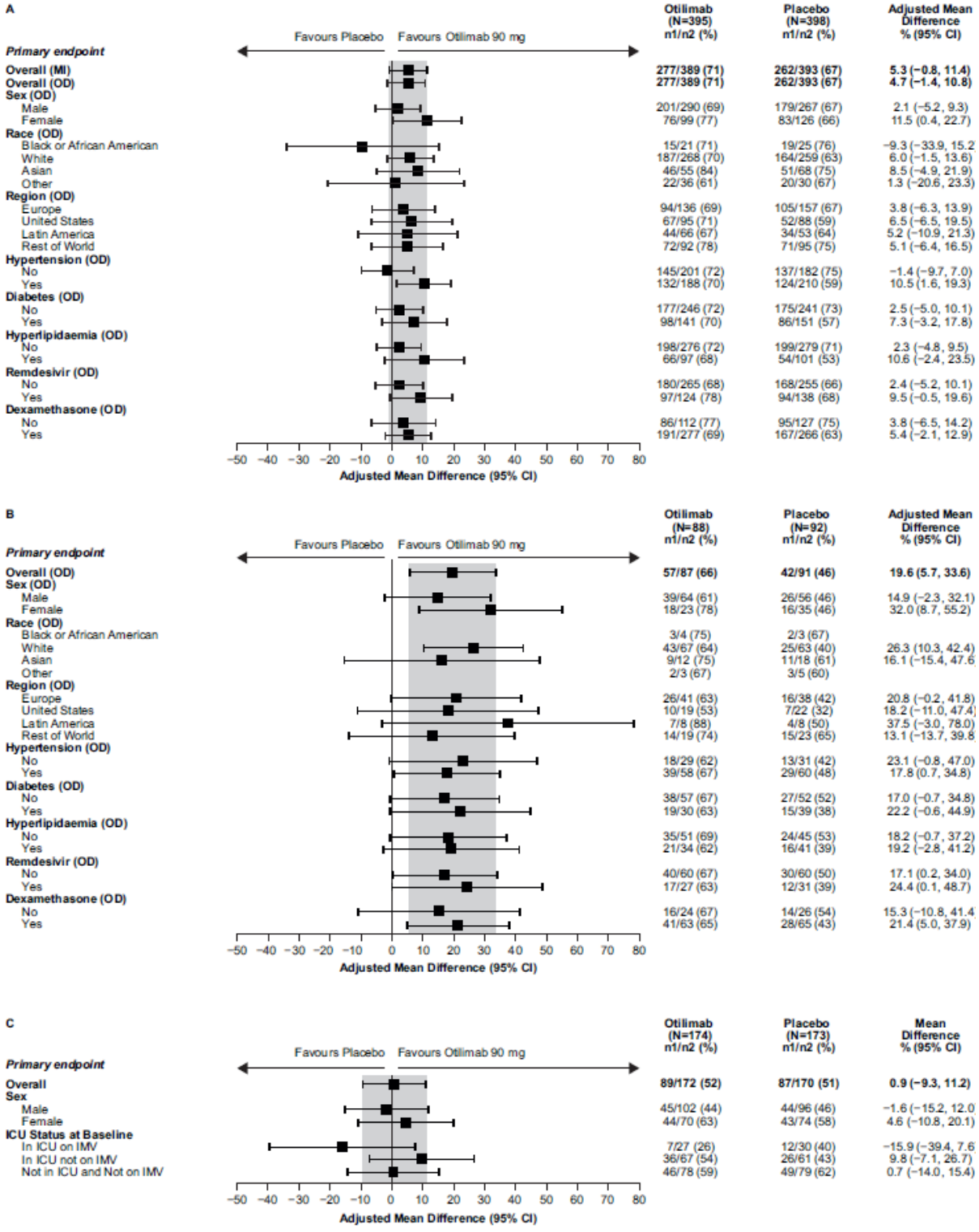
Exploratory endpoints (to Day 28, unless otherwise specified) included time to IMV (if not previously initiated); time to extubation; improvement, relative to baseline, in fraction of inspired oxygen (FiO_2) (estimated using the 3%-formula [1]); time to clinical status improvement of ≥2 categories, relative to baseline (to Day 60), PK parameters (to Day 14); exposure-response relationship for key efficacy, safety, and

PD biomarker endpoints; and change in markers of inflammation including, but not limited to, CRP, ferritin and inflammatory cytokines.

Pharmacokinetic (PK) and exposure-response analysis

A two-compartment PK model with first-order elimination from the central compartment with the covariate bodyweight on clearance and volume terms was developed using combined PK data from both parts and prior PK model information from 4 previous otilimab studies (EudraCT2007-007614-11, EudraCT2011-001809-27, [2, 3]). The model was used to derive the individual exposure metrics of area under the concentration-time curve (AUC) and maximum concentration (C_{max}) that were then used for exploratory exposure-response analysis for key efficacy, safety, and pharmacodynamic (PD) biomarker endpoints.

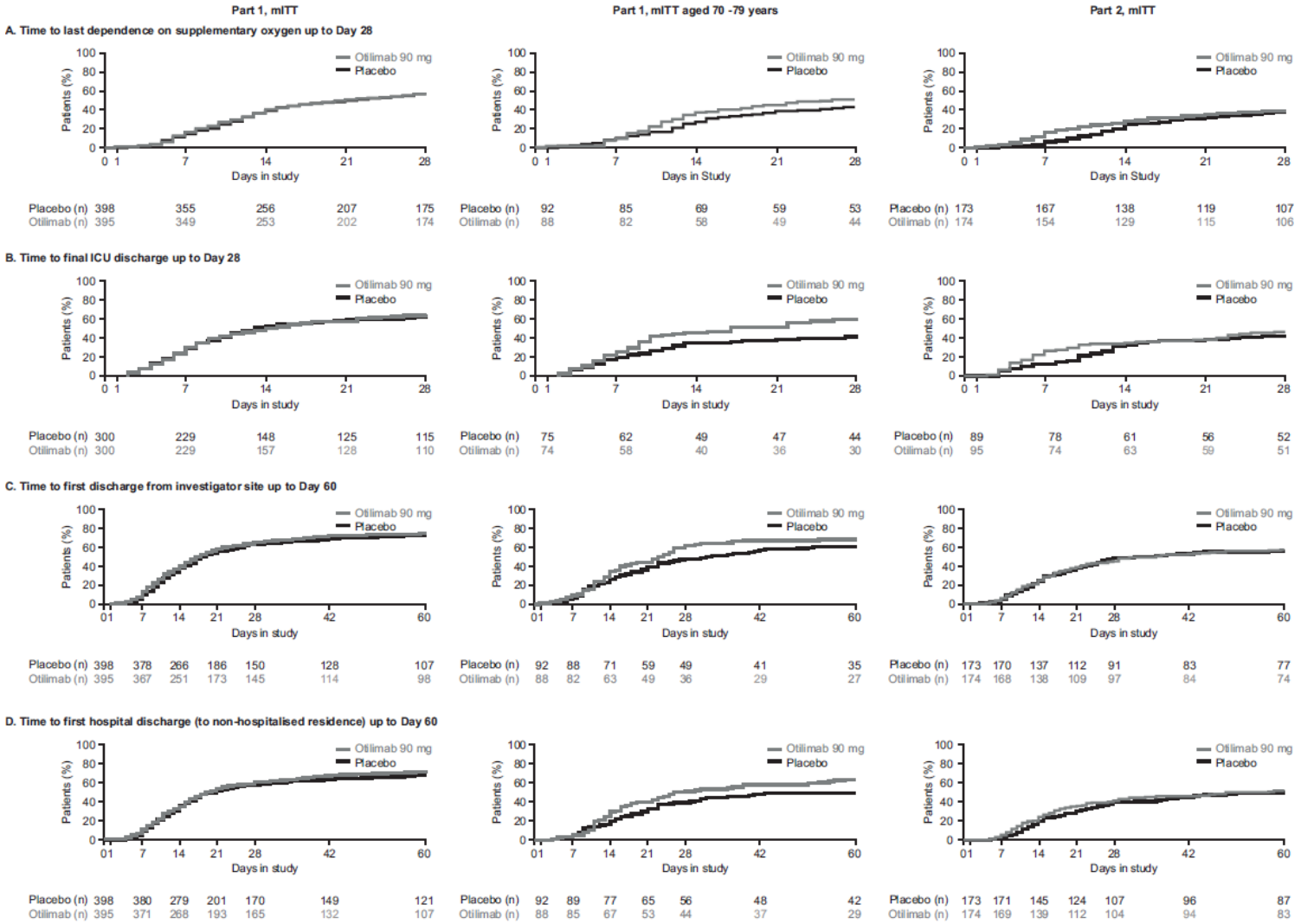
Figure S1. Patients alive and free of respiratory failure at Day 28 (primary endpoint) by baseline characteristic in Part 1 (A), Part 1 ≥70 years age subgroup (post hoc analysis; B), and Part 2 (C)

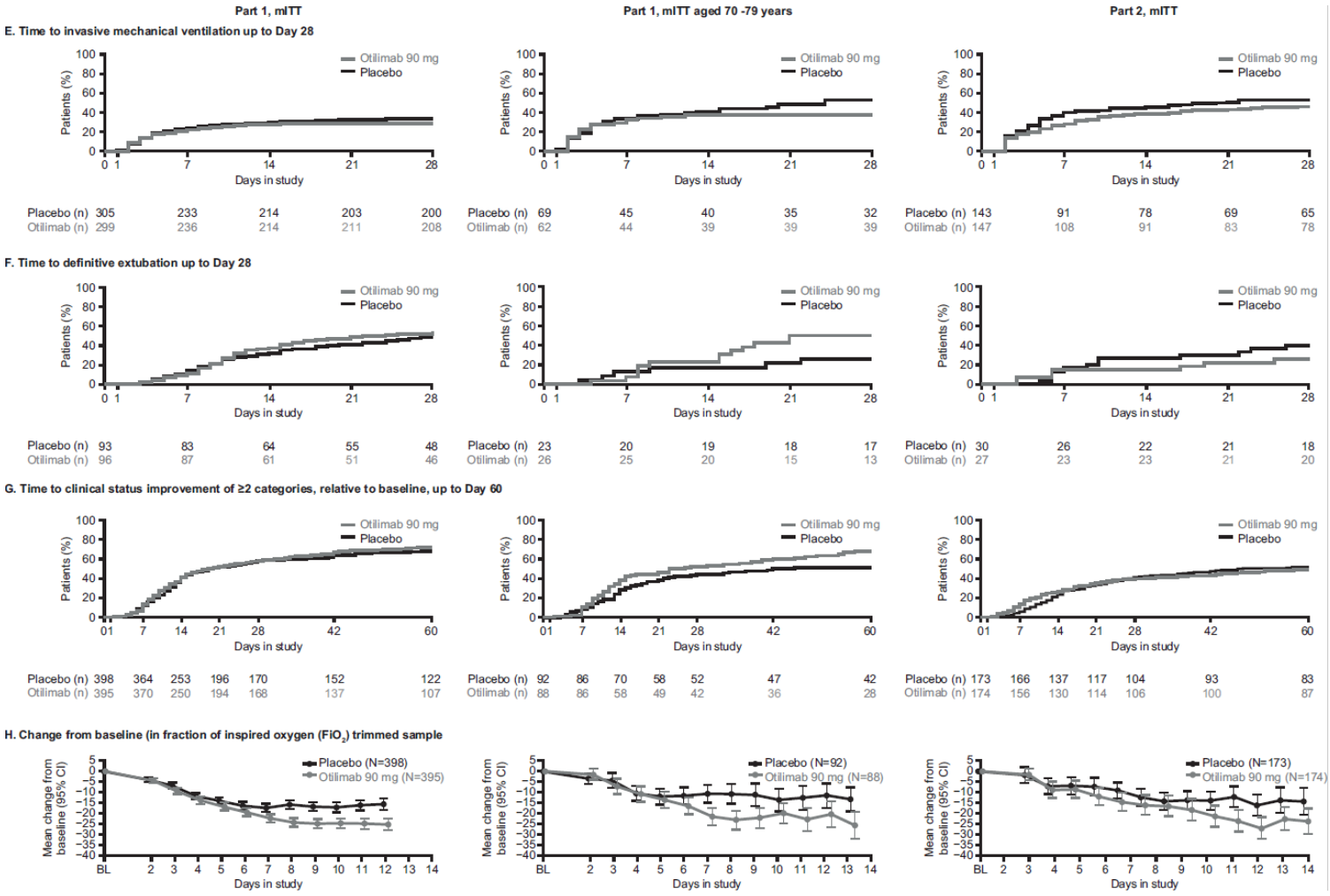


CI, confidence interval; ICU, intensive care unit; IMV, invasive mechanical ventilation; MI, multiple imputation; OD, observed data.

Figure S2. Kaplan-Meier plots of time-to-event analyses

Secondary endpoints: Kaplan-Meier time to last dependence on supplementary oxygen up to Day 28 (A); Kaplan-Meier time to final ICU discharge up to Day 28 (B); Kaplan-Meier time to first discharge from investigator site up to Day 60 (C); Kaplan-Meier time to first hospital discharge (to non-hospitalised residence) up to Day 60 (D); exploratory endpoints: Kaplan-Meier time to invasive mechanical ventilation up to Day 28 (E); Kaplan-Meier time to definitive extubation up to Day 28 (F); Kaplan-Meier time to clinical status improvement of ≥2 categories, relative to baseline, up to Day 60 (G);mean change from baseline (95% CI) in fraction of inspired oxygen (FiO_2) trimmed sample (H) in the mITT population of Part 1, post hoc ≥70-year age group of Part 1, and in the mITT population of Part 2





BL, baseline; CI, confidence interval; ICU, intensive care unit; mITT, modified intent-to-treat.

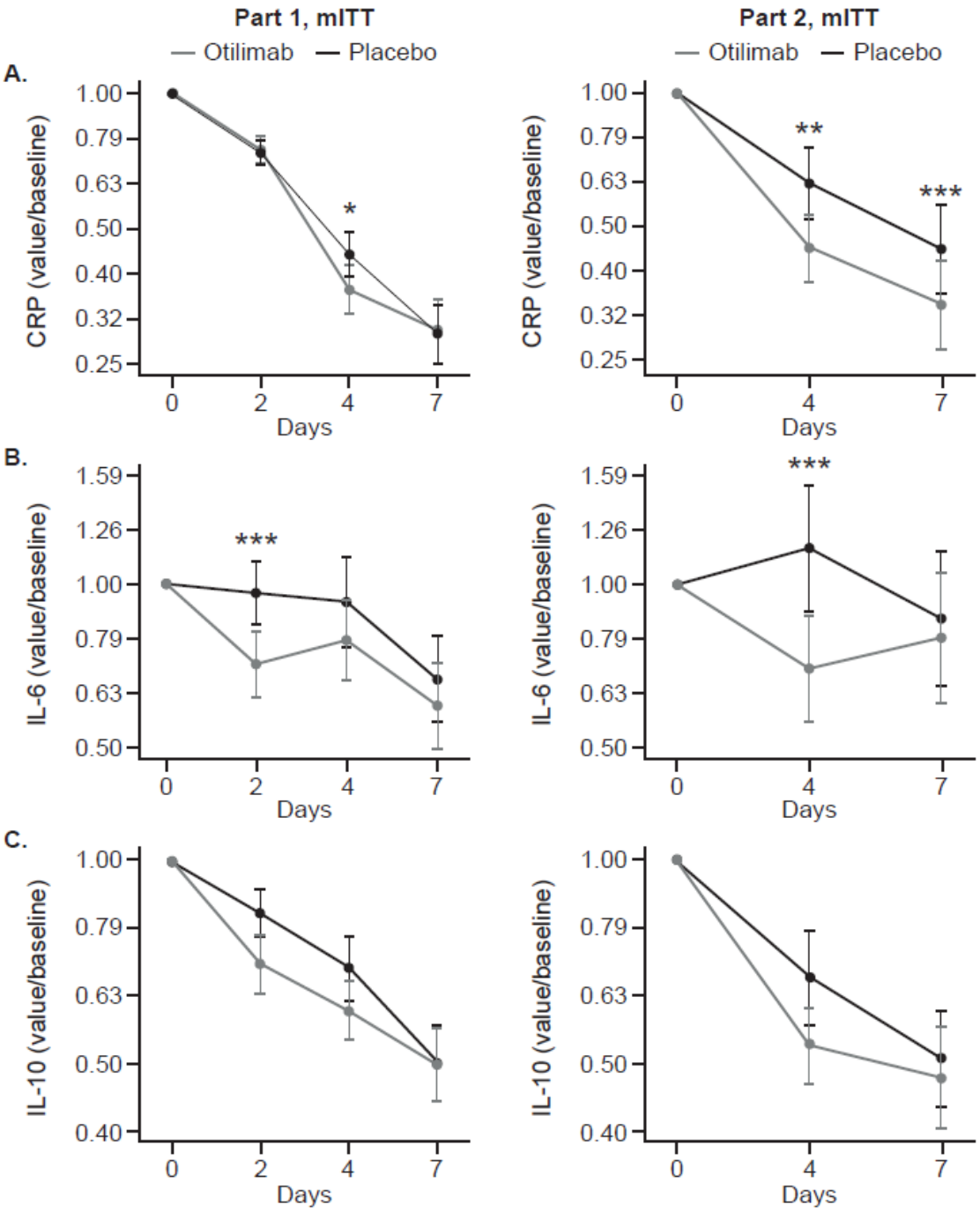
Table S1. Otilimab, free GM-CSF, and GM-CSF–otilimab complex concentrations

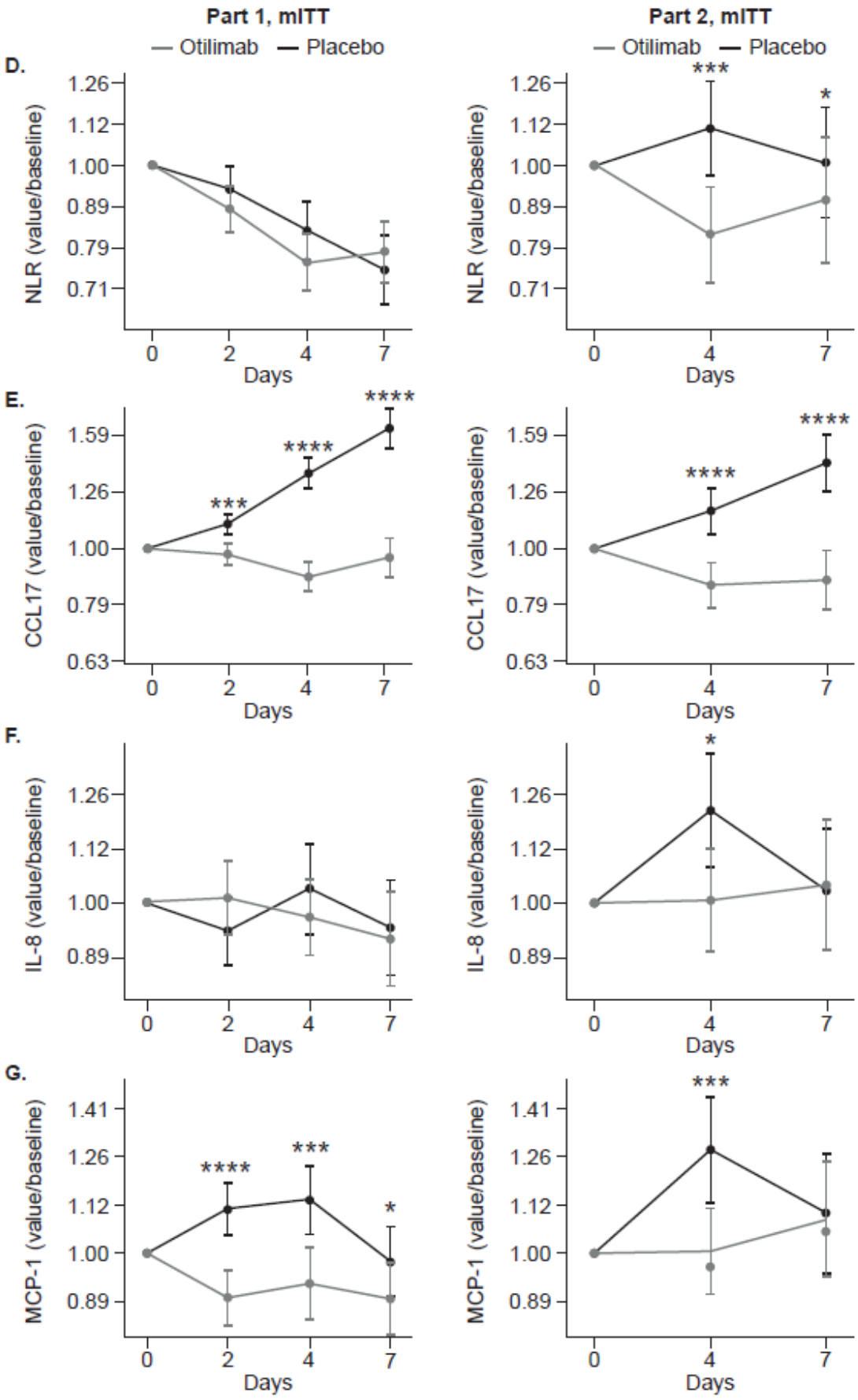
Variable	Part 1	Part 2
Otilimab serum concentration (ng/mL), median (min, max)		
Day 1	19600 (277, 584000)	20100 (339, 183000)
Day 2	12600 (226, 35300)	12700 (790, 35200)
Day 7	1840 (208, 17100)	1780 (394, 6930)
Day 14	336 (202, 2400)	314 (202, 1410)
Free GM-CSF concentration (pg/mL), median (min, max)		
Day 1	0.480 (0.0550, 9.70)	0.460 (0.0500, 13.0)
GM-CSF–otilimab complex concentration (pg/mL), median (min, max)		
Day 1	13.8 (5.81, 40.3)	11.7 (7.79, 20.8)
Day 2	24.7 (5.29, 953)	24.6 (6.15, 221)
Day 7	191 (6.29, 1290)	166 (7.96, 1540)
Day 14	54.6 (6.11, 599)	55.2 (7.36, 528)

GM-CSF, granulocyte-macrophage colony-stimulating factor.

Figure S3. Change from baseline in clinical biomarkers using linear mixed modelling

Fold change from baseline in CRP (A), IL-6 (B), IL-10 (C), neutrophil-to-lymphocyte ratio (D), CCL17 (E), IL-8 (F), and MCP-1 (G) in the mITT population of Part 1 and Part 2. Data presented as geometric mean with 95% CI derived from standard error (P*<0.05, ***P*<0.01, ****P*<0.001 and *****P*<0.0001, for otilimab versus placebo, by analysis of variance [ANOVA] F-test).**





CRP, C-reactive protein; IL, interleukin; MCP, macrophage chemotactic protein-1; mITT, modified intent-to-treat; NLR, neutrophil-to-lymphocyte ratio.

Figure S4. Otilimab concentration-time curves

Overlay of individual observed otilimab serum concentrations over time for the OSCAR pharmacokinetics population datasets for Part 1 and Part 2 in their respective overall (A) and age ≥70 years (B) subgroups.

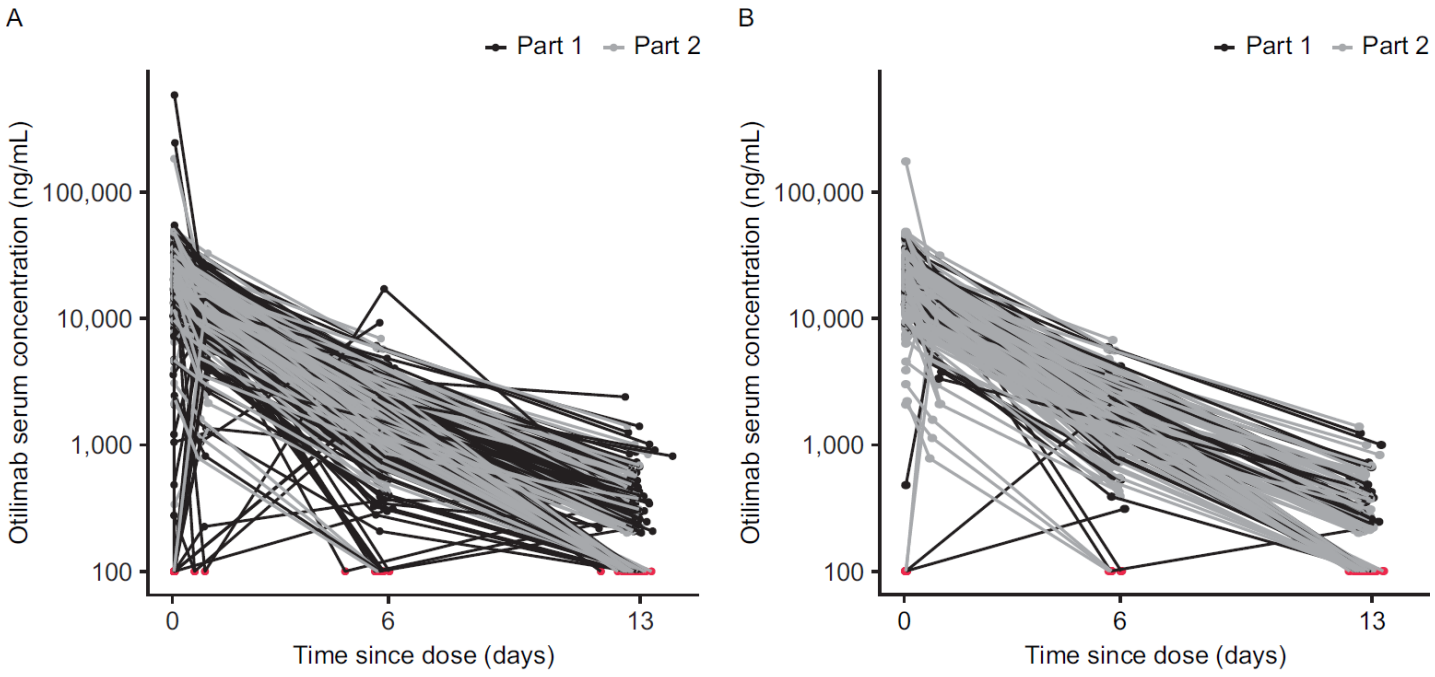
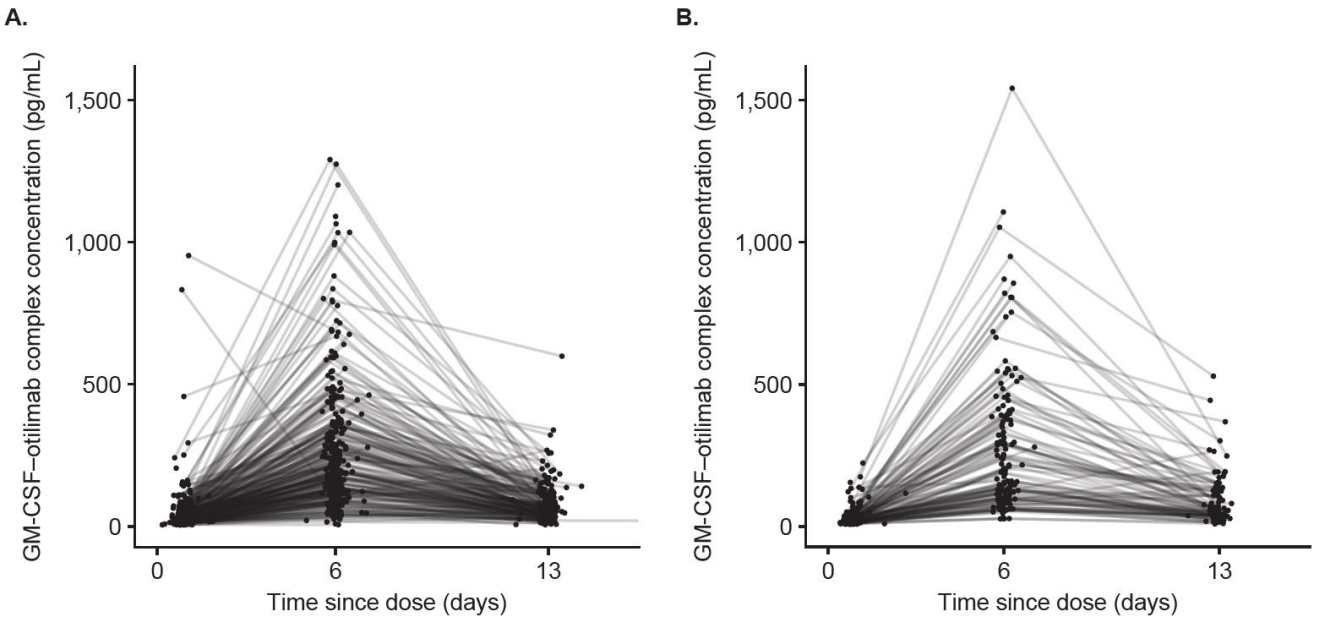


Figure S5. GM-CSF–otilimab complex concentration-time curve

Overlay of individual observed GM-CSF–otilimab complex concentrations versus time after first dose for the COVID-19 patients in the otilimab target engagement analysis

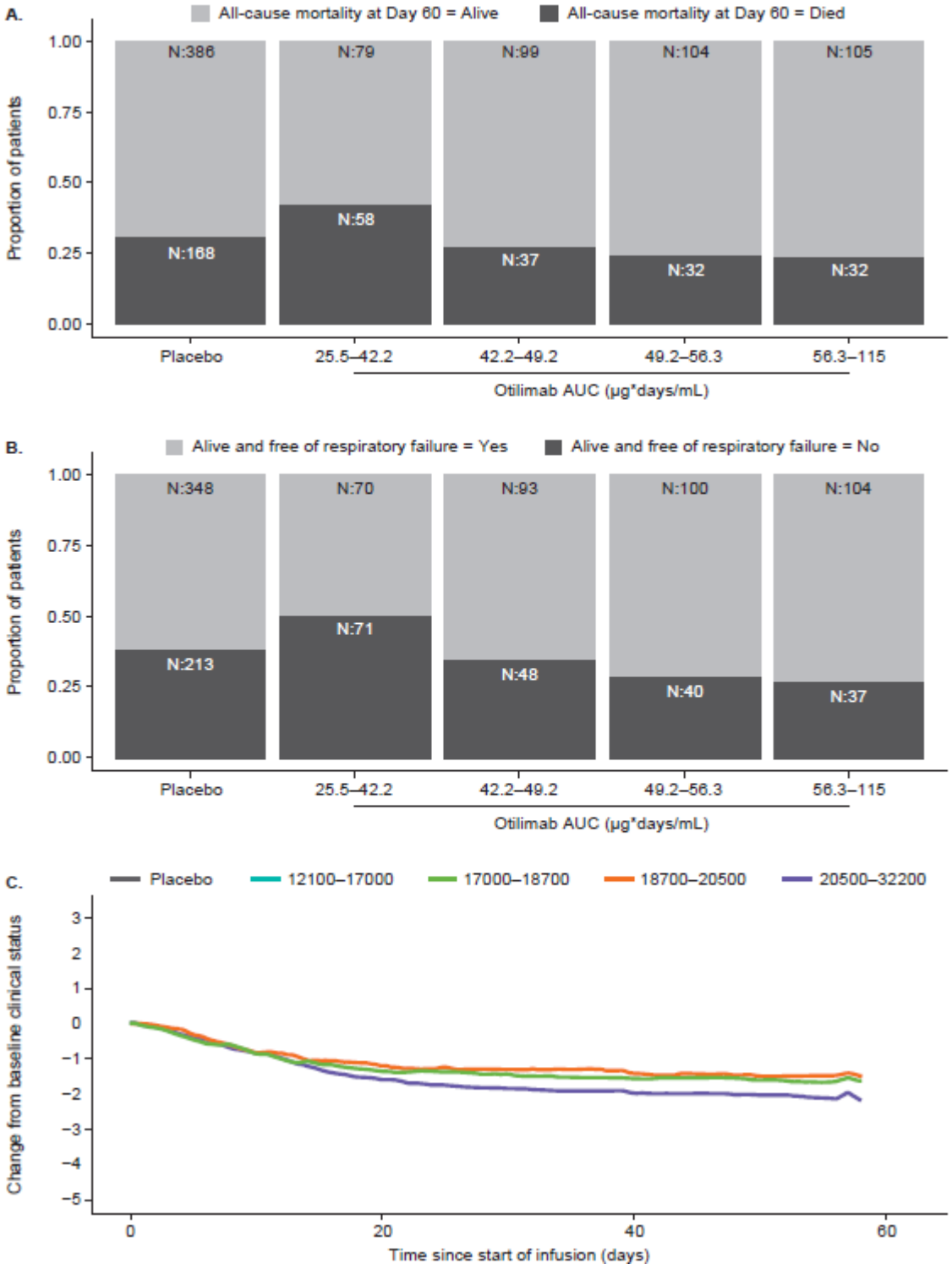


data set for Part 1 (A) and Part 2 (B).

GM-CSF, granulocyte-macrophage colony-stimulating factor.

Figure S6. Proportion of patients alive and free of respiratory failure at Day 28 (A) and all-cause mortality at Day 60 (B) versus the AUC percentile.

Mean change from baseline in clinical status over time grouped by C_{max} percentile (C). Percentiles: ≤25th; >25th to ≤50th; >50th to ≤75th; >75th to <Max.



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