Supplementary Appendix

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This appendix has been provided by the authors to give readers additional information about the work.

CONTENTS

APOLLO-B STUDY INVESTIGATORS AND COLLABORATORS

Karolinska Universitetssjukhuset, Solna, Sweden

Investigators: Per Eldhagen Principal Investigator, Michael Melin Sub-Investigator, Ida Löfman Sub-Investigator, Emil Najjar Sub-Investigator, Gianluigi Savarese Sub-Investigator, Lars Lund Sub-Investigator, Jonas Faxén Sub-Investigator, Tonje Thorvaldsen Sub-Investigator

Site staff: Ann Hultman Cadring Study Nurse, Karin Safbom Pharmacist, Emma Jönsson Study Coordinator, Camilla Hage Study Coordinator, Isabel Tronstad Study Nurse, Liselott Söderström Radiology Technician, Cristina Oliveira da Silva Radiology Technician, Matthias Lidin Nurse, Kerstin Höglund Study Coordinator, Agneta Segerlund Pharmacist, Leila Niknam Pharmacist, Christina Fiebig Pharmacist, Zina Majid Pharmacist, Ashwin Venkateshvaran Echocardiographist

Odense Universitetshospital, Odense, Denmark

Investigators: Jens Flensted Lassen Principal Investigator, Michael Maiborg Sub-Investigator, Søren Kristian Nielsen Sub-Investigator, Julie Hempel Larsen Sub-Investigator, Selma Hasific Sub-Investigator, Jens Mogensen Principal Investigator, Nils Sofus Borg Mogensen Sub-Investigator, Alexander Chemnitz Sub-Investigator, Kalle Brunebjerg Engdam Sub-Investigator

Site staff: Lene Sehested Pharmacist, Helle Tveskov Primary Study Coordinator, Maybritt Grundt Rønn Study Coordinator, Therese Gents Primary Study Coordinator, Ida Rosenlund Study Coordinator, Astrid Trangbaek Unblinded Team Member, Helle Cappelen Study Coordinator, Marianne Augustenborg Lab Personnel, Tina Mwaipaya Lab Personnel, Sussi Faxoe Unblinded Team Member, Heidi Helk Olesen Pharmacy Personnel, Alice Mätzke Tandrup Unblinded Team Member, Bente Helgeneseth Pharmacist, Marie Brunsgaard Krogh Unblinded Team Member, Linda Hammer Lab Personnel

Copenhagen University Hospital, Copenhagen, Denmark

Investigators: Finn Gustafsson Principal Investigator, Søren Lund Kristensen Sub-Investigator, Westin Oscar Sub-Investigator

Site staff: Ditte Marie Andersen Study Nurse, Anna Wieland Study Nurse, Katrine Bavnbek Unblinded Team Member, Rosenberg Tine Study Coordinator, Christina Møller Primary Study Coordinator, Kirsten Thrysøe Study Coordinator, Sisse Maj Lund Jensen Study Coordinator, Lene Kløvgaard Study Coordinator, Anne Lavigne Study Nurse, Elsebet Eriksen Study Coordinator, Aslaug Karlsdottir Study Coordinator, Bente Brodersen Unblinded Team Member, Berit Thomsen Unblinded Team Member, Mie Christa Jensen Larsen Unblinded Team Member, Satu Laukka Unblinded Team Member

Hospital de São Teotónio, Viseu Dão Lafões, Portugal

Investigators: Emanuel Correia Principal Investigator, Inês Pires Sub-Investigator, Vanda Neto Sub-Investigator, Joana Correia Sub-Investigator, João Santos Sub-Investigator

Site staff: Gonçalo Ferreira Safety Contact, João Pedro Alves Lab Personnel, Ana Margarida Correia Radiology Technician, Monica Leite Unblinded Team Member, Ana Catarina Dias Lab Personnel, Ana Cristina Andrade Unblinded Team Member, Susana Carvalho Unblinded Team Member, Anabela Santos Study Nurse

CLINICOR Clinica Radiologica Ribeirao Preto, São Paulo, Brazil

Investigators: Pedro Vellosa Schwartzmann Principal Investigator, Breno de Paiva Eto Sub-Investigator

Site staff: Gabriela Gimenez Faustino Ilana Study Coordinator, Debora Duarte Galeriani Research Assistant, Adailza Braz o Rosario Pharmacist, Rossana Falcone Study Coordinator, Vivian do Prado Martins Nurse, Vanessa Cristina Miranda Takahagi Physiotherapist, Roberta Bardella Mendonça Nurse, Henrique Trad Research Clinician, Daiane de Jesus Exam Assistant, Leticia Nayara Prado Research Assistant, Bianca Ferreira Research Assistant, Guilherme Tosato Chinelli Research Clinician, Bruna Lopes Consolo Research Clinician, Luciana Ribeiro Jarduli Pharmacist

Azienda Ospedaliera Universitaria Careggi, Florence, Italy

Investigators: Federico Perfetto Principal Investigator, Mattia Zampieri Sub-Investigator, Martina Gabriele Sub-Investigator

Site staff: Alessia Argirò Unblinded Team Member, Susanna Citernesi Unblinded Team Member, Monica Albissi Nurse, Katia Baldini Nurse, Michela Pucatti Pharmacist, Alessia Tomberli Primary Study Coordinator, Sara Giovani Study Coordinator, Marco Allinovi Unblinded Team Member, Lino Cirami Unblinded Team Member, Francesco Cappelli Safety Contact, Carla Pecoraro Unblinded Team Member

Fondazione IRCCS Policlinico San Matteo di Pavia, Pavia, Italy

Investigators: Laura Obici Principal Investigator, Roberta Mussinelli Sub-Investigator, Francesca Benigna Sub-Investigator, Andrea Foli Sub-Investigator, Stefano Perlini Sub-Investigator, Vittorio Rosti Sub-Investigator, Paolo Milani Sub-Investigator

Site staff: Eleonora Di Buduo Primary Study Coordinator, Nicole Pinocchio Study Coordinator, Federica Bocchio Pharmacist, Rosa Colella Unblinded Team Member, Giulia Rebagliati Pharmacist, Lucia Pasqualicchio Unblinded Team Member, Patrizia Maestri Nurse, Simona Casarini Lab Personnel, Anna Racchi Pharmacist, Maria Cusato Pharmacist, Cristina Meazza Pharmacist, Alice Di Benedetto Pharmacist, Claudia Sforzini Study coordinator, Renza Zucchini Nurse

Azienda Ospedaliero Universitaria Di Bologna - Policlinico S Orsola Malpighi, Bologna, Italy

Investigators: Igor Diemberger Principal Investigator, Claudio Rapezzi Principal Investigator, Alberto Ponziani Sub-Investigator, Rachele Bonfiglioli Sub-Investigator, Luigi Lovato Sub-Investigator, Giulia Saturi Sub-Investigator, Angelo Giuseppe Caponetti Sub-Investigator, Simone Longhi Sub-Investigator

Site staff: Christian Gagliardi Safety Contact, Fabrizio Bassetta Unblinded Team Member, Salvatore Re Unblinded Team Member, Patrizia De Feudis Unblinded Team Member, Gianpaolo Fini MRI Technician, Concetta Distefano Study Coordinator, Anna Maria GuarguAglini Pharmacist, Vincenzo Cambria Unblinded Team Member, Lucia Bernardo Unblinded Team Member, Irene Martens Pharmacist, Michele Meneghello Unblinded Team Member, Silvia Restuccia Unblinded Team Member

Az Ospedaliera Universitaria Policlinico G Martino, Messina, Italy

Investigators: Gianluca Di Bella Principal Investigator, Giancarlo Trimarchi Sub-Investigator, Fabio Minutoli Sub-Investigator, Pietro Pugliatti Sub-Investigator, Mariapaola Campisi Sub Investigator

Site staff: Debora Bonfiglio Unblinded Team Member, Anna Paola Capra Lab Personnel, Sara Briguori Lab Personnel, Petronilla Daniela Romeo Lab Personnel, Silvana Briuglia Lab Personnel, Maria Angela La Rosa Lab Personnel, Nicola Pellegrino Pharmacist, Tiziana Genovese Pharmacist, Lida Lombardo Pharmacist, Giulia Giuffrida Study Coordinator

Universitair Medisch Centrum Groningen, Groningen, The Netherlands

Investigators: Peter van der Meer Principal Investigator, Alwin Tubben Sub-Investigator, Hans Nienhuis Sub-Investigator, Remco de Brouwer Sub-Investigator, Sebastiaan Klaassen Sub-Investigator

Site staff: Bart van Essen Safety Contact, Gonda Renkema Back-Up Study Coordinator, Zwanet Wiering Study Nurse, Carin Pauline Boogerd Study Nurse, Josephine Riley Study Nurse, Carina Hooghiemstra Radiology Technician, Henriette Oosterhoff Research Assistant, Marcha Mollema Pharmacy Personnel, Karin Rutgers Pharmacy Personnel, Trieneke Brink Pharmacy Personnel, Irma Doeleman Pharmacy Personnel, Karin Hoomoedt Pharmacy Personnel, Robert Samwels Radiology Technician, Sandra Terpstra Research Assistant, Greetje de Jong Primary Study Coordinator, Geert Bokhorst Study Coordinator, Margriet Couperus Study Nurse, Hendrikus Boersma Pharmacist, Marissa Heijnen Pharmacist, Jerome Appeldoorn Pharmacist, Jenny Jongsma Radiology Technician

Hospital Das Clinicas da Faculdade de Medicina de Ribeirão Preto – USP, São Paulo, Brazil

Investigators: Marcus Simoes Principal Investigator

Site staff: Jaqueline de Andrade Unblinded Team Member, Pedro Henrique Leite da Silva Unblinded Team Member, Andre Phillipe Villanova, Research Assistant, Leonardo Chara Vieira Research Assistant, Julia Casagrande Coletti Back-Up Study Coordinator, Daiane Fernanda dos Santos Lab Personnel, Flávio Henrique Valicelli Safety Contact, Henrique Carvalho Clé Back-Up Study

Coordinator, Pedro Henrique Marques Research Assistant, Andreia Fernanda Leone Aguiar Lab Personnel, Joao Paulo Resende do Nascimento Study Coordinator, Barbara Coutinho Research Assistant, Antonio Carlos Merger Junior Research Assistant, Izabela Cristina Rodrigues Primary Study Coordinator, Henrique Pereira Administration, Amanda Seiscentos Lab Personnel, Taiz Francine Brasil Bazo Lab Personnel, Samantha Silveira Study Coordinator, Rosemeire Rosa Tritola Regulatory Coordinator, Vinicius de Paula Pereira Regulatory Coordinator, Augusto Cesar Martins Galante Unblinded Team Member, Lilian Sonobe Research Assistant, Tulio Queiroz de Paula Research Assistant, Antonio Carlos Leite de Barros Filho Research Clinician, Stela Passos Regulatory Coordinator, Luiz Rodrigo Valvassoura Nurse, Jessica Stephanie Santos de Campos Nurse, Bianca Nardini de Freitas Research Assistant, Elaine Ribeiro Nurse, Julio Gabaldi Unblinded Team Member

Instituto do Coração – HCFMUSP, São Paulo, Brazil

Investigators: Fabio Fernandes Principal Investigator, Aristoteles Alencar Sub-Investigator, Bruno Vaz Kerges Bueno Sub-Investigator, Charles Mady Sub-Investigator, Felix Ramires Sub-Investigator, João Henrique Rissato Sub-Investigator, Natalia de Melo Pereira Sub-Investigator

Site staff: Caio Rebouças Fonseca Cafezeiro Research Assistant, Claudia Curcio Administration, Renata do Val Research Director, Cesar Higa Nomura Medical Imaging Director, Graziele Pereira Lunas Safety Contact, Heloisa Schurig Unblinded Team Member, José Soares Junior Director of Nuclear Medicine and Molecular Imaging, Maria Cristina Abduh Research Clinician, Wilson Mathias Junior Research Clinician, Suênia Carvalhal Study Coordinator, Rosimeiri Oliveira Back Up Study Coordinator, Thais Borges Study Coordinator, Roberto Kalil Filho Clinical Cardiology Department Director, Carlos Eduardo Rochitte Associate Professor and Academic Vice-Coordinator for the Cardiac Magnetic Resonance and Cardiac Tomography, Natalia Cirilio Caio Unblinded Team Member

Hospital Pró Cardíaco, Rio de Janeiro, Brazil

Investigators: Cláudio Mesquita Principal Investigator, Diane de Ávila Sub-Investigator, Isabella Palazzo Sub-Investigator

Site staff: Roberta dos Santos Study Coordinator, Aline dos Santos da Silva Unblinded Team Member, Leandra de Oliveira Souza Unblinded Team Member, Thalita Gonçalves do Nascimento Camilo Research Assistant, Eliza de Almeida Gripp Research Clinician, Lidielle dos Santos Pimenta Rodrigues Pereira Unblinded Team, Alice Baptista de Oliveira Unblinded Team Member, Beatriz Robert Moreira Research Assistant, Roberta Valle dos Santos Said Study Coordinator, Marli Dominici Research Assistant

Hospital de Clinicas de Porto Alegre (HCPA) – PPDS, Porto Alegre, Brazil

Investigators: Andreia Biolo Principal Investigator, Anderson da Silveira Sub-Investigator, Humberto Butzke da Motta Sub-Investigator

Site staff: Vera Lorentz Unblinded Team Member, Lucas Saboia Bertoni Study Coordinator, Simone Gottfried Scherer Safety Contact, Adriana Cardoso Unblinded Team Member, Juliana Borges Study Nurse, Paola Maciel Unblinded Team Member, Jessica Rosa Custia Study Nurse, Carolina Maciel Pharmacist, Giovanni Costa Research Assistant, Jessica Valadas Da Silva Unblinded Team Member, Marilze Alves Quessada Safety Contact

Hôpital de Rangueil, Toulouse, France

Investigators: Olivier Lairez Principal Investigator, Pauline Fournier Principal Investigator, Romain Itier Sub-Investigator, Eve Cariou Sub-Investigator, Yoan Lavie-Badie Sub-Investigator

Site staff: Emeline Hoarau Back-Up Study Coordinator, Lydie Sanchez Study Coordinator, Christine Lagente Back-Up Study Coordinator, Anne-Laure Sarda Pharmacist, Virginie Blanchard Radiology Technician, Barbara Terre Administration, Sandrine Gascon Administration, Laetitia Caturla Pharmacist, Nathalie Rosolin Study Coordinator

Hôpital Henri Mondor, Paris, France

Investigators: Thibaud Damy Principal Investigator, Denis Bernard Tixier Sub-Investigator, Gagan Deep Singh Chadha Sub-

Investigator, Arnault Galat Sub-Investigator, Soulef Guendouz Sub-Investigator, Coraline Chalard Sub-Investigator, Fatima Djellaili Sub-Investigator, Sophie Mallet Sub-Investigator

Site staff: Anisse Medane Study Coordinator, Steven Maupou Study Nurse, Amira Zaroui Research Clinician, Sidney Silva Study Coordinator, Hanna Roubache Study Coordinator, Mounira Kharoubi Safety Contact, Ani Vardanyan Back-Up Study Coordinator, Elodie Allouis Pharmacist, Gregoire Planchais Study Coordinator, Maryam Remdane Back-Up Study Coordinator, Karim Bouadam Pharmacy Personnel, Elodie Faye Pharmacist, Amandine Berrebi Nurse, Saeed Wissam Pharmacist, Kahina Rebiai Study Coordinator, Delphine Le Febvre De Nailly Pharmacist, Alaki Thiemele Pharmacist, Muriel Carvalho Pharmacy Personnel

Hôpital Pontchaillou, Rennes, France

Investigators: Erwan Donal Principal Investigator, Bruno Laviolle Sub-Investigator, Elise Paven Sub-Investigator, Jean Charles Leroy Sub-Investigator, Jean-Sébastien Allain Sub-Investigator, Marie Dewitte Sub-Investigator, Fabrice Lainé Sub-Investigator

Site staff: Laurene Masson Study Nurse, Sophie Caradec Back-Up Study Coordinator, Amélie Martin EDC Access (Study Coordinator), Elena Galli Radiology Technician, Arnaud Hubert Radiology Technician, Aurélie Heinry Study Nurse, Dominique Fargeaud Study Coordinator, Catherine Hamon Pharmacist, David Vallée Site Manager, Marie Le Bourlais Study Coordinator, Solène Rautureau Study Nurse, Anne-Sophie Charpentier Study Nurse, Viviane Fortuna Study Nurse, Anne Claire Gaudin Study Nurse, Anne Goupil Study Nurse, Nolwenn Boissel Study Nurse, Helene Dubois Study Nurse, Sabrina Cochennec Back-Up Study Coordinator, Coleen Tanguy Safety Contact (Study Coordinator), Baptiste Belline Back-Up Study Coordinator, Lucie Gouin Back-Up Study Coordinator, Adeline Chanat Pharmacist, Guillaume Jego Study Nurse, Lisa Ménager Study Nurse, Nadège Prodhomme Lab Technician, Zahia Droniou Study Nurse, Cécile Reminiac Study Nurse

Boston University School Of Medicine, Boston, MA, USA

Investigators: John Berk Principal Investigator, Omar Siddiqi Sub-Investigator

Site staff: Tennyson Hunt Site Manager, Vanessa Bahnam Primary Study Coordinator, Olivia Mueller Primary Study Coordinator, Caitlin Breuckner Study Coordinator, Taylor Jarzombek Study Coordinator, Charlotte Jean Michel Study Coordinator, Victoria Lazarri Back-Up Study Coordinator, Oltion Sina Back-Up Study Coordinator, Tiana Mason Back-Up Study Coordinator, Alejandro Perez Echocardiographer, Jean Doricent Echocardiographer, Stephen Zalewski Pharmacy Manager, Nitasha Sanil Pharmacy Manager, Michael Camuso Pharmacist, Husam Dennaoui Pharmacist, Crystal Ng Pharmacist, Ratna Dodhia Pharmacist, Nisha Verma Pharmacy Personnel (Technician), Della Carter Laboratory Manager, Ridiane Denis Nurse Manager, Yuri Kim Research Nurse, Anh Tran Research Nurse, Jennifer Johns Research Nurse, Mona Lauture Research Nurse, Mary Barbara Walsh Research Nurse

Mayo Clinic – PPDS, Rochester, MN, USA

Investigators: Martha Grogan Principal Investigator, Omar Abou Ezzeddine Sub-Investigator, Morris Gertz Sub-Investigator, Angela Dispenzieri Sub-Investigator, Janell Grazzini Frantz Sub-Investigator, Wayne Miller Sub-Investigator, Grace Lin Sub-Investigator

Site staff: Wanda Rhodes Regulatory Coordinator, Kirstin Stalnaker Pharmacy Personnel, Kimberly Warrington Pharmacy Personnel, Erin Stern Pharmacy Personnel, Sara Jones Pharmacy Personnel, Derek Roadway Pharmacy Personnel, Gregory Brunn Pharmacist, Binh Luu Research Clinician, Karin Ferden RN Study Coordinator, Lisa Ehleiter Back-Up Study Coordinator, Julie Wissink Safety Contact, Eliza Griggs RN Study Coordinator, Kristina Franta Unblinded Team Member, Janel Tesmer Administration, Kris Leibfried Study Coordinator, Melissa Rott RN Study Coordinator, Shane Melver Pharmacy Personnel, Eleonor Olson Study Coordinator, Diane Schmidt RN Study Coordinator, Patricia Aggen Administration, Susanna Miller Primary Study Coordinator, Brandon Trammell Regulatory Coordinator, Patricia Mohs Research Clinician, Teresa Pfiefer Research Clinician, Chad Gerken Pharmacy Personnel

Johns Hopkins Hospital, Baltimore, MD, USA

Investigators: Michael Polydefkis Principal Investigator, Mohammad "Nima" Khoshnoodi Sub-Investigator, Xiaoling Li Sub-Investigator, Qingfeng Liu Sub-Investigator, Kavita Sharma Sub-Investigator, Joban Vaishnav Sub-Investigator

Site staff: Lauren Crabtree Administration, Daniel Tsottles Data Manager, Lucyna Trzeciak Pharmacist, Erika Gailunas Administration, Jared Nipper Administration, Kimberly Keck Research Clinician, Jing Ye Primary Study Coordinator, Laurie Bienert Pharmacist, Donna Boone Lab Personnel

Washington University in St. Louis, St. Louis, MO, USA

Investigators: Daniel Lenihan Principal Investigator, Joshua Mitchell Principal Investigator, Molly Rater Sub-Investigator, Jesus Jimenez Sub-Investigator, Justin Vader Sub-Investigator, Jose Alvarez-Cardona Sub-Investigator

Site staff: Madison Alexander Study Coordinator, Rachel Meyers Research Clinician, Pattie Lenzen Research Clinician, Anne Dirks Study Coordinator, Ashley Toenjes Research Clinician, Margaret Jarriett Unblinded Team Member, Kristopher Bakos Unblinded Team Member, Kathryn Vehe Unblinded Team Member, Sandy Hutton Study Coordinator, Emily Terrebonne Study Coordinator, Joshua Mitchell Principal Investigator, Jean Flanagan Administration, Caroline Kempter Study Coordinator

Penn Presbyterian Medical Center, Philadelphia, PA, USA

Investigators: Brian Drachman Principal Investigator, Margaret Shanks Sub-Investigator, Hansie Mathelier Sub-Investigator

Site staff: Elizabeth Medenilla Administration, Patricia DiVito Primary Study Coordinator, Patricia Clements Research Clinician, Teresa Schwarz Research Clinician, Karen Maslowski Back-Up Study Coordinator, Michele Wisniewski Pharmacist, Jason DeWitt Pharmacist

Mount Sinai Hospital, New York, NY, USA

Investigators: Sumeet Mitter Principal Investigator, Cristina Surach Sub-Investigator, Anuradha Lala-Trindade Sub-Investigator

Site staff: Wenli Zhao Research Clinician, Ivy Cohen Pharmacist, Eugene Royzman Study Coordinator, Katherine Wang Study Coordinator, Danielle Brunjes Study Coordinator, Tiffany Soto Study Coordinator, Lovelyne Julien Study Coordinator, Pilar Tlachi Primary Study Coordinator

University of Kansas Medical Center, Kansas City, KS, USA

Investigators: Zubair Shah Principal Investigator, Bhanu Gupta Sub-Investigator, Thomas Rosamond Sub-Investigator, Dana Miller Sub-Investigator, Amandeep Goyal Sub-Investigator

Site staff: Tanya Eckhardt Nurse, Eva Adams Back-Up Study Coordinator, Sonja Way Legal Contact, Lori Neece Administration, Tiana Moala Research Assistant, Lanecia Wright EDC Access, Yolanda Murr Primary Study Coordinator, Alyssa Boyce-White Study Coordinator, Denetta Nelson Research Assistant, Tilitha Shawgo Research Assistant, Kelsey Williams Research Assistant, Kartik Munshi Back-Up Study Coordinator, KUMC Research Institute Finance Administration, Chasity Ward EDC Access, Rocio Lager Unblinded Team Member, Mia Hard Unblinded Team Member, Kirsten Filby Unblinded Team Member, Barbara Couldry Unblinded Team Member, Tyler Zimmer Regulatory Coordinator

Columbia University Medical Center, New York, NY, USA

Investigators: Mathew Maurer Principal Investigator, Dia Smiley Sub-Investigator, Hannah Rosenblum Sub-Investigator, Sunil Saith Sub-Investigator, Jan Griffin Sub-Investigator, Margaret Cuomo Sub-Investigator, Karan Wats Sub-Investigator, Nicholas Chan Sub-Investigator, Priyanka Bhattacharya Sub-Investigator

Site staff: Massiel Jimenez Research Assistant, Leonid Zaurov Sonographer, Angela Bustamante Back-Up Study Coordinator, Luz Paredes Back-Up Study Coordinator, Carlos Rodriguez Research Assistant, Henry Arango Research Assistant, Donalrey Nieva Pharmacy Personnel, Connie Eng Pharmacist, Lourdes Vasquez Administration, Collin Glidewell Legal Contact, Marta Scotto Pharmacist, Sergio Teruya Study Coordinator, Elnaz Anjom Pharmacy Directory, Shiney Kunjukutty Administration, Melissa Valarezo EDC Access, Danilo Gamino Research Assistant, Jeffeny De Los Santos Site Coordinator, Stephen Helmke Sonographer, Samantha Guadalupe Regulatory Coordinator, Kimberly Mateo Research Assistant, Denisse Santana Del Rosario Research Assistant, Alfonsina Mirabal Back-Up Study Coordinator, Andie - Duong Nguyen Payment Contact, Mary Paulino Primary Study Coordinator, Tanja Holgate Pharmacy Personnel, Oriel Averion Pharmacist

University of Chicago Hospitals, Chicago, IL, USA

Investigators: Nitasha Sarswat Principal Investigator, Sean Pinney Sub-Investigator, Patrick Sung Sub-Investigator, Jonathan Grinstein Sub-Investigator, Ann Nguyen Sub-Investigator, Daniel Rodgers Sub-Investigator, Gene Kim Sub-Investigator, Sara Kalantari Sub-Investigator, Bryan Smith Sub-Investigator, Bow "Ben" Chung Sub-Investigator

Site staff: Tiffany Hart Primary Study Coordinator, Corinne Stonebraker Research Assistant, Kyle Hipke Research Assistant, Edward Kazyanskaya Pharmacist, Victoria Andrade Pharmacy Personnel, Jaime Nowik Pharmacy Personnel, Jessica Vega Pharmacy Personnel, Ramon Murphy Pharmacy Personnel, Tanja Alavanja Pharmacist, Eric Kruse Research Clinician, Amy Bennett Study Coordinator, Caroline Taromino Back-Up Study Coordinator, Jessica Lyons Legal Contact, Laura Krupa Regulatory Coordinator, Judy Pi Pharmacist, Tracey Silverstein Primary Study Coordinator, Jennifer Regan Administration

Vanderbilt University Medical Center, Nashville, TN, USA

Investigators: Rebecca Hung Principal Investigator, Amanda Peltier Sub-Investigator, Hasan Siddiqi Sub-Investigator, Douglas Brinkley Sub-Investigator, Lynn Punnoose Sub-Investigator, Natalie Castillo Sub-Investigator

Site staff: John Oleis Pharmacist, Ursula Powell Unblinded Team Member, Emma Claire Gauthier Pharmacy Personnel, Terry Weyand Research Assistant, Christy McDougall Research Assistant, Sherron Crook Research Assistant, Jaime Rich Study Coordinator, Melissa Lowe Primary Study Coordinator, Ellen Hathcock Primary Study Coordinator, Leslie Cornell Back-Up Study Coordinator, Mary Gordon Primary Study Coordinator, Felicia Lowe Study Coordinator, Martha Fraley Regulatory Coordinator, Shane Moore Pharmacist, Sherry Bowman Site Manager, Gail Gabhart Legal Contact, Vicky Gibson Legal Contact, Leslie Stiles Unblinded Team Member, Meryk Moore Unblinded Team Member, Tara Evans Unblinded Team Member, Cindy Bridges Infusion Nurse, Ben Small Infusion Nurse, Tim Smith Infusion Nurse, Bianca Plunkett Infusion Nurse, Melissa Lehman Infusion Nurse, Millicent Johnson Infusion Nurse, Sherri Hails Infusion Nurse, Diane Anders Infusion Nurse, Stacy Gilbert Infusion Nurse, Robin Perkins Infusion Nurse, Connie Dotye Infusion Nurse, Betsy Parker Infusion Nurse

Instituto Nacional de Ciencias Medicas y Nutricion Salvador Zubiran, Mexico City, Mexico

Investigators: Maria Gonzalez Duarte Briseno Principal Investigator, Jose Pablo Hernandez Reyes Sub-Investigator, Karla Cardenas Soto Sub-Investigator

Site staff: Aldo Reyes Study Coordinator, Sandra Lorena Perez Castañeda Unblinded Team Member, Jonathan Zepeda Leon Nurse, Andrea Fiscal Carvajal Pharmacy Personnel

The Cleveland Clinic Foundation, Cleveland, OH, USA

Investigators: Wai Hong Wilson Tang Principal Investigator, J. Emanuel Finet Sub-Investigator, Jerry Estep Sub-Investigator, Jill Kandrac Sub-Investigator, Mazen Hanna Sub-Investigator

Site staff: Colleen Cummins Study Coordinator, Sonya Mihalus Study Coordinator, Danielle Kellner Study Coordinator, Rachael Yim Pharmacist, Susan Hejl Regulatory Coordinator, Jenna Titus Pharmacy Personnel, Jackie Indre Pharmacy Personnel, Bill Palmer Budget Contact, Lauren Ives Study Coordinator, Laurie Ann Moennich Study Coordinator, Theresa Fonk Study Coordinator, Barbara Gus Study Coordinator, Alice Bereznay Research Clinician, Katy Rutkowski Primary Study Coordinator, Michelle Homner-Leanza Pharmacy Personnel

Cedars Sinai Medical Center, Los Angeles, CA, USA

Investigators: Jignesh Patel Principal Investigator, Andriana Nikolova Principal Investigator, Michelle Kittleson Sub-Investigator, Babak Azarbal Sub-Investigator, David Chang Sub-Investigator, Lawrence Czer Sub-Investigator, Robert Cole Sub-Investigator, Michele Hamilton Sub-Investigator, Jon Kobashigawa Sub-Investigator, Robert Vescio Sub-Investigator, Dael Geft Sub-Investigator, Richard Lewis Sub-Investigator, Jaime Moriguchi Sub-Investigator, Antoine Hage Sub-Investigator, Evan Kransdorf Sub-Investigator

Site staff: Lucilla Garcia Study Coordinator, Bo Ran Kang Pharmacy Personnel, Alen Hakimi Pharmacy Personnel, Janell Dunn Pharmacy Personnel, Trung Tran Pharmacy Personnel, Vanessa Wilson Primary Study Coordinator, Monica Toscano Regulatory Coordinator, Tyler Fernholz Research Assistant, Kiana Achoy Research Assistant, Eliot Han Pharmacy Personnel, Liliana Huitron

Research Clinician, Heidi Hagena Pharmacist, Marissa Horrigan Pharmacist, Sylvia Bendimez Study Coordinator, Lauren Escobar Unblinded Team Member, Paul Chung Unblinded Team Member, Sami Naber Payment Contact, Irina Cozianu Administration, Monica Guerrero Regulatory Coordinator, Jack Haslett Study Coordinator, Annie Yi Pharmacist, Sean Sana Study Coordinator, Maria Thottam Study Coordinator

Taipei Veterans General Hospital, Taipei City, Taiwan

Investigators: Wen-Chung Yu Principal Investigator, Wei-Ting Wang Sub-Investigator, Kon-Ping Lin Sub-Investigator, Shih-Hsien Sung Sub-Investigator, Jo-Nan Liao Sub-Investigator, Wei-Ming Huang Sub-Investigator

Site staff: Pei-Ru Yen Lab Personnel, Wan-I Yang Research Assistant, Yu-Juan Chen Unblinded Team Member, Han-Jei Chen Unblinded Team Member, Pao-Hsiang Chiu Pharmacist, Ya-Ju Wen Pharmacist, Ying-Ju Chen Pharmacist, Cheng-Fang Chuang Pharmacist, Nai-Chi Chen Pharmacist, Ying-Luan Wang Primary Study Coordinator, Chuen-Yu Li Lab Personnel

Seoul National University Hospital, Seongnam, South Korea

Investigators: Hyun-Jai Cho Principal Investigator, Seung-Pyo Lee Sub-Investigator, Hae-Young Lee Sub-Investigator

Site staff: Hong Won Jang Unblinded Team Member, Suyeon Park Radiology Technician, SuJung Choi Radiology Technician, Ji-Yei Seo Unblinded Team Member, Juyeon Kim Pharmacist, Han Sol Lee Pharmacist, Jihyun Kim Unblinded Team Member, Min-kyoung Kim Unblinded Team Member, Eunjin Hur Primary Study Coordinator, HyeLee Song Unblinded Team Member, DaeHyun Han Unblinded Team Member, Inyoung Lee Unblinded Team Member, Seungyeon Hong Pharmacist, MoonJu Kim Unblinded Team Member, Minjeong Seo Unblinded Team Member, Hyeonjin Goh Back-Up Study Coordinator, Mikyoung Hong Study Coordinator, Da-jung Son Unblinded Team Member, Minju Seo Unblinded Team Member, Hyeonjin Kim Back-Up Study Coordinator

Medical Center Convex EOOD, Sofia, Bulgaria

Investigators: Mariana Gospodinova Principal Investigator, Nora Milcheva Sub-Investigator, Yosif Peychev Sub-Investigator

Site staff: Srebrina Taseva Unblinded Team Member, Elka Vasileva-Ganova Safety Contact, Nikolina Dragoilova Nurse, Raina Ivanova Pharmacist

Vseobecna Fakultni Nemocnice V Praze, Prague, Czech Republic

Investigators: Tomas Palecek Principal Investigator, Lenka Roblova Sub-Investigator, Petr Kuchynka Sub-Investigator

Site staff: David Zogala Radiology Technician, Petra Zavadilova Primary Study Coordinator, Milada Behounkova Pharmacist Jaroslava Rihova Study Nurse, Jana Papackova Pharmacist, Andrea Hvozdova Unblinded Team Member, Jakub Halad Pharmacist, Veronika Bauerova Pharmacist

Fakultni nemocnice u sv. Anny v Brne, Brno, Czech Republic

Investigators: Jan Krejci Principal Investigator, Petr Hude Sub-Investigator, Eva Ozabalova Sub-Investigator, Julius Godava Sub-Investigator, Tomas Honek Sub-Investigator, Hana Poloczkova Sub-Investigator

Site staff: Lucie Cernoskova Unblinded Team Member, Monika Cerna Study Nurse, Zuzana Hrdlickova Study Coordinator, Zdenka Povolna Radiology Technician

Institut Klinicke A Experimentalni Mediciny, Prague, Czech Republic

Investigators: Milos Kubanek Principal Investigator, Jana Binova Sub-Investigator

Site staff: Linda Havranová Study Nurse, Ivana Kuklova Study Nurse, Lenka Leva Study Nurse, Petr Lupinek Radiology Technician, Romana Kadlecova Pharmacist, Marie Buncova Radiology Technician, Dana Kautznerova MRI Technician, Jaroslav Tintera MRI Technician, Martin Kotrc Radiology Technician, Jiri Ters Radiology Technician, Jirina Kralova Unblinded Team Member, Eva Kasalova Unblinded Team Member, Ivana Horakova Primary Study Coordinator, Jana Frantova Unblinded Team Member, Sylva Klovrzova Pharmacist

AES - DRS - Synexus Czech s.r.o., Prague, Czech Republic

Investigators: Iva Skarpova Principal Investigator, Denisa Kraftova Sub-Investigator, Jaroslav Brotanek Sub-Investigator, Lucie Veberova Sub-Investigator, Marketa Hraskova Sub-Investigator

Site staff: Nikola Cervenakova Study Coordinator, Anna Voborilova Study Coordinator, Natalie Lakostikova Research Assistant, Helen Konasova Pharmacist, Tomas Palyza Pharmacist, Petra Adamkova Study Nurse, Jiri Bartonicek Unblinded Team Member, Eva Adamova Unblinded Team Member, Jan Lami Radiology Technician, Katerina Wernerova Unblinded Team Member, Miroslav Rubacek Radiology Technician, Pavel Hajdusek Radiology Technician, Jana Skolilova Nurse, Katerina Janickova Study Nurse, Marie Miličková Study Coordinator, Aneta Oliveirová Study Coordinator, Martina Švecová Study Coordinator, Zuzana Mikulová Research Assistant, Petra Nebeská Research Assistant

Kumamoto University Hospital, Kumamoto, Japan

Investigators: Kenichi Tsujita Principal Investigator, Seiji Takashio Sub-Investigator

Nagoya University Hospital, Nagoya, Japan

Investigators: Takahiro Okumura Principal Investigator, Toyoaki Murohara Sub-Investigator, Kenji Furusawa Sub-Investigator, Shingo Kazama Sub-Investigator, Yuki Kimura Sub-Investigator, Ryota Morimoto Sub-Investigator, Ryota Ito Sub-Investigator, Yuichiro Koyama Sub-Investigator, Hiroaki Hiraiwa Sub-Investigator

Site staff: Sachiko Iida Primary Study Coordinator, Naomi Masuda Study Coordinatorm Yumi Fujita Study Coordinator Yosuke Niwa Site Manager, Kana Ogura Pharmacist, Saori Kinoshita Pharmacist, Hirotake Hida Pharmacist, Hiroshi Kato Pharmacist, Takako Morooka Lab Personnel, Aiko Okuma Lab Personnel, Rie Nagaya Study Nurse, Mariko Nakamura Study Nurse, Katsuko Takenaka Study Nurse, Ayako Morihara Study Nurse, Akiko Okada Study Nurse, Keiko Teshirawara Study Nurse, Norie Kanada Study Nurse, Tomoko Nakashima Study Nurse, Fukuko Nishio Study Nurse, Nami Takai Study Nurse, Miyu Osako Study Nurse, Shino Sakakibara Study Nurse

Shinshu University Hospital, Matsumoto, Japan

Investigators: Yoshiki Sekijima Principal Investigator, Nagaaki Kato Sub-Investigator, Minori Kodaira Sub-Investigator, Katsuya Nakamura Sub-Investigator, Akiyo Hineno Sub-Investigator, Daigo Miyazaki Sub-Investigator, Yusuke Mochizuki Sub-Investigator, Yuske Mochizuki Sub-Investigator

Site staff: Chieko Nagashima Study Coordinator, Yuka Nakazawa Pharmacist, Takashi Takezawa Pharmacist, Erina Motoki Pharmacist, Yuki Uematsu Pharmacist, Yukari Inoue Pharmacist, Akane Tachibana Nurse, Reiko Yamamoto Nurse, Hiroshi Horiuchi Research Assistant, Shota Ikegami Research Assistant, Kouhei Nagamine Research Assistant, Yoko Usami Lab Personnel, Junichi Kurata Lab Personnel, Jun Sasaki MRI Technician, Eri Katsuyama MRI Technician, Hiroaki Watanabe Pharmacist, Chie Omori Primary Study Coordinator, Miho Obara Pharmacist, Chizuru Higuchi Nurse, Takayuki Ide Pharmacist, Megumi Iimori Nurse, Hisataka Itoh Pharmacist, Tsukuru Iwama Pharmacist, Hiroko Kitamura Pharmacist, Katsuhiro Nagai Pharmacist, Shusuke Ozawa Pharmacist, Wakana Iwashita Pharmacist, Genki Suzuki Pharmacist, Kazumasa Narita Pharmacist, Mitsutoshi Asakura Pharmacist, Yumi Yoshikawa Pharmacist, Airi Ishii Study Coordinator, Junko Hiroma Study Coordinator, Mao Iwamoto Study Coordinator, Miho Suzuki Nurse, Mai Nakamura Nurse, Mizuki Okada Nurse, Moyo Watanabe Nurse, Miho Terasawa Pharmacist, Sachi Koiwai Pharmacist, Susumu Sakaue Pharmacist, Natsumi Seki Pharmacist, Keita Hirai Pharmacist

Kurume University Hospital, Kurume, Japan

Investigators: Nobuhiro Tahara Principal Investigator, Mika Enomoto Sub-Investigator, Jinya Takahashi Sub-Investigator, Akihiro Honda Sub-Investigator, Jun Kumanomido Sub-Investigator, Kazutoshi Mawatari Sub-Investigator, Masanori Ohtsuka Sub-Investigator, Shoko Ogata Sub-Investigator, Hanae Yoshimura Sub-Investigator, Satoko Ohno Sub-Investigator, Yoichi Sugiyama Sub-Investigator, Team Member, Yuka Sato Unblinded Team Member, Takashi Ishimatsu Sub-Investigator, Norifumi Nishida Sub-Investigator, Munehisa Bekki Sub-Investigator

Site staff: Makiko Iwai Study Coordinator, Yuriko Murayama Study Coordinator, Ryuji Ikematsu Radiology Technician, Kazutaka Nashiki MRI Technician, Kanae Tateishi Study Coordinator, Takuya Kubota Study Coordinator, Takayuki Sasano Study Coordinator,

Shinichiro Ito Lab Personnel, Minako Hashimoto Study Coordinator, Kotone Zushi Primary Study Coordinator, Satoko Kajihara Unblinded Team Member, Takatoshi Komiya Unblinded Team Member, Tomomi Kumashiro Unblinded Team Member, Chiharu Morimitsu Unblinded Team Member, Naoko Nakashima Unblinded Team Member, Makoto Takahashi Unblinded Team Member, Mariko Yanaga Unblinded Team Member, Megumi Hidaka Unblinded

The Royal Free Hospital, London, UK

Investigators: Marianna Fontana Principal Investigator, Julian Gillmore Sub-Investigator, Liza Chacko Sub-Investigator, Oliver Cohen Sub-Investigator, Steven Law Sub-Investigator, Carol Whelan Sub-Investigator, Ana Martinez De Azcona Naharro Sub-Investigator

Site staff: Elizabeth Woodford Pharmacy Personnel, Jashreebahen Gosai Pharmacy Personnel, Angelique Smit Study Nurse, Amanda Bidle Administration, Svetla Strehina Study Nurse, Ruth Staunton Primary Study Coordinator, Michael Wood Study Nurse, Bella Ruth Sombrito Study Nurse, Beth Clarkson-Dodd Study Nurse, Jyoti Vakharia Data Manager, Sindhu Varughese Study Nurse, Darren Foard Study Nurse, Vietland Le Pharmacy Personnel, Lisa Rannigan Study Coordinator, Aarti Nandani Pharmacist

Richmond Pharmacology Limited, London, UK

Investigators: Jorg Taubel Principal Investigator, Laura Edwards Sub-Investigator, Vishal Aggarwal Sub-Investigator, Kruti Patel Sub-Investigator, Robert Dunn Sub-Investigator, Tamer Rezk Sub-Investigator, Ben Hutter Sub-Investigator, James Mitchell Sub-Investigator, Junko Ono Sub-Investigator, Lisa Whittington Sub-Investigator, Naomi How Sub-Investigator, Samuel Cole Sub-Investigator, Ulrike Lorch Sub-Investigator, James Hilton Sub-Investigator, Matthew Cheaveau Sub-Investigator, Priyank Shah Sub-Investigator, Richard Francis-Sakai Sub-Investigator, Sebastian Grant Sub-Investigator, Sid Kona Sub-Investigator, Mark Loughrey Sub-Investigator, Dominic Pimenta Sub-Investigator, Emily Duggan Sub-Investigator, Faser Peck Sub-Investigator, Talia Shively Sub-Investigator, Thomas York Sub-Investigator, Clara Haroulis Sub-Investigator, Lucy Fulford-Smith Sub-Investigator, Andrew Stokes Sub-Investigator, Thomas Ashdown Sub-Investigator, Christian Coles Sub-Investigator, Hugh Furness Sub-Investigator,

Matej Goricar Sub-Investigator, Edward Jackson Sub-Investigator, Amir Majid Sub-Investigator, Delphine Nkuliza Sub-Investigator, Priscilla Ochuba Sub-Investigator, Hannah Plaschkes Sub-Investigator, Keneolisa Udoji Sub-Investigator, Andrew Want Sub-Investigator, Laura Wojtowitz Sub-Investigator

Site staff: Stefan Lewandowski Primary Study Coordinator, Samsam Abdi Site Manager, Khaled Aboullo Clinical Staff, Salma Aden Lab Personnel, Dara Adeyemi Site Manager, Farhan Adib Siam Data Manager, Dilawaiz Afaqui Pharmacy Personnel, Priya Agarwal Clinical Staff, Helen Aguolu Site Manager, Fatima Ahmed Site Manager, Mohamed Alam Data Manager, David Applegate Recruitment, Tamanna Aziz Site Manager, April Balud Data Manager, Haaris Barkatli Clinical Staff, Kris Dannelle Bautista Reyes Site Manager, Ema Begum Clinical Staff, Pooyan Behbahani Study Coordinator, Keith Berelowitz Site Manager, Alisha Blackman-Asante Site Manager, William Bowler Lab Personnel, Reagan Bradley Site Manager, Mubiyna Braithwaite Site Manager, Sarah Brown Lab Personnel, Mihaela Cardas Data Manager, Ching Fung Chan Data Manager, Yen-Yu Chen Site Manager, Sue Cheung Lab Personnel, Carmen Cheung Site Manager, Daniel Chung Site Manager, Olivia Clarke Study Coordinator, Odiesia Daley Lab Personnel, Maria Damai Clinical Staff, Omari Jordan Daniel Recruitment, Kris Dannelle Bautista Site Manager, Sofia David Clinical Staff, Kyron Desuze Clinical Staff, Manmohan Dhamu Data Manager, Anastaija Drobysevskaja Lab Personnel, Amal Egah Site Manager, Mary Elizabeth McCorkindale Site Manager, Silvia Fernandez Clinical Staff, Luis Ferreira Site Manager, Scarlett Flourendzoi Site Manager, Odiesia Daley Lab Personnel, Ronnie Gansah Pharmacy Personnel, Yasmeen- Gibbs Study Coordinator, Aarthi Girithananda Site Manager, Lorenzo Glancristofaro Site Manager, Maria Gomes Pharmacist, James Goodman Clinical Staff, Clare Griffiths Clinical Staff, Ameena Gull Recruiter, Joseph Hallett Site Manager, Mia Hawkins Site Manager, Sally Higgins Site Manager, Thomas Higgs Lab Personnel, Jack Holland Site Manager, Matthew Holloway Lab Personnel, Yurika Hoshimi Clinical Staff, Haruna Ioka Clinical Staff, Nabihah Jaigirdar Clinical Staff, Bolor Jamsranjav Site Manager, Fanny Jaso Clinical Staff, Derrell Jennings Data Manager, Noelle Jordaan Data Manager, Maki Kasahara Clinical Staff, Hotaru Kato Clinical Staff, Matthew Kemball-Cook Lab Personnel, Shuhada Khanum Site Manager, Yuki Kodama Clinical Staff, Yuki Kodamama Site Manager, Klevi Kola Clinical Staff, Mizuki Konno Pharmacy Personnel, Rajeev Kumar Site Manager, Krishana Kumari Data Manager, Fazley Lahany Data

Manager, Rowland Lewis Lab Personnel, Teresa Liu Clinical Staff, James Liu Clinical Staff, Haruna Loca Site Manager, Laura Lyons Project Manager, Abbie Macleod Study Coordinator, Mohamed Mahamud Study Nurse, Yaasir Mahamuud Lab Personnel, Alex Markulis Primary Study Coordinator, Matthew Maroney Lab Personnel, Kadeem Marsall Data Manager, Catherine Mazzi Clinical Staff, Jonil Mehmeti Data Manager, Emmanuel Mensah Site Manager, Jeannie Miles Site Manager, Mariia Moiseeva Data Manager, Prince Kwasi Mpiani Site Manager, Donovan Nei Study Coordinator, Wako Nihei Data Manager, Ayana Ninoi Clinical Staff, Yuki Nomura Site Manager, Abdifatah Noor Data Manager, Daniel Owen Project Manager, Emmanuelle Owoyele Clinical Staff, Janki Patel Data Manager, Kastur Patel Pharmacist, Pooja Patel Safety Contact, Nigel Pereira Project Manager, Jedi Perkins Data Manager, Matthew Porter Clinical Staff, Matthew Portwe Site Manager, Tamanna Rana Lab Personnel, Llion Roberts Site Manager, Marina Rubcova Data Manager, Nagisa Sato Data Manager, Karolina Sek Clinical Staff, Alexios Serefas Pharmacy Personnel, Kami Shouur PV Team, Wendy Simkin Data Manager, Miriam Snowball Clinical Staff, Olasubomi Sotunde Lab Personnel, Sethuvani Srinivasan Data Manager, Alisha Swizal Vas Pharmacy Personnel, Mayi Taichi Site Manager, PV Team RPL Research Assistant, Satoshi Takahashi Clinical Staff, Anna Takata Clinical Staff, Satomi Tanaka Site Manager, Faris Taslim Clinical Staff, Carlo Testore Site Manager, Yuka Tokunaga Clinical Staff, Janice Tong Site Manager, Harvey Turnbull Clinical Staff, Naseer Ud Din Data Manager, Kapil Undaviya Site Manager, Ana Utea Site Manager, Alisha Vas Pharmacy Personnel, Apple Ventura Pharmacy Personnel, Mark Vernon Site Manager, Anna Visipkova Clinical Staff, Millie Voitovich Data Manager, Rosa Vojdani Project Manager, Liat Yefet EDC Access, Hysen Yulika Site Manager

AES - DRS - Synexus Midlands Clinical Research Centre, Birmingham, UK

Investigators: Karen Faulkner Principal Investigator, Christina Kyriakidou Sub-Investigator, Mariana Carreno Sub-Investigator, Desislav Gunchev Sub-Investigator, Madhu Gowda Sub-Investigator, Victoria Grinstead Sub-Investigator, Peter Keighley Sub-Investigator, Rohan Ahmed Sub-Investigator, Imrozia Munsoor Sub-Investigator, Marlies Viljoen Sub-Investigator

Site staff: Juliana Ying Bong Lab Personnel, Fayza Kauser Research Assistant, Natasha Stanley Study Nurse, Ali Hamaad Research Clinician, Dawn McIlhone Study Coordinator, Lacey Butlin Study Coordinator, Melissa Kenney Unblinded Team Member,

Oliver Jenks Study Coordinator, Jessica Kirszniok Primary Study Coordinator, Minal Patel Data Manager, Jeremiah Chimeura Unblinded Team Member, Gift Nyatsuro Study Nurse, Libby Marcus Study Nurse, Oluwaseun Adebayo Unblinded Team Member, Fatoumata Bah Lab Personnel, John Haynes Research Assistant, Aisling Deeney Lab Personnel, Sanjit Chaggar Study Coordinator, Cristina Constantinescu Study Coordinator, Shivani Baghral Lab Personnel, Kavitha Shetty Study Coordinator, Alexandra Radu Study Coordinator, Sandra McCalla Research Assistant, Natalia Daniliuc Research Assistant, Elaine Riding Research Assistant, Auguszta Mako Research Assistant, Katie Saunders Back-up Lab Personnel, Mahvish Mahmood Study Coordinator, Angela Jones Research Assistant, Elizabeth Pennington Research Assistant, Shumon Ahmed Research Assistant, Shamim Onyango-Odera Study Nurse, Olusolafunmi Agbeyi Study Nurse, Fabio Bento Study Nurse, Asiah Shaheen Research Assistant, Kiran Takhar Research Assistant

AES - DRS - Synexus Wales Clinical Research Centre, Gwaelod-y-Garth, UK

Investigators: Christina Kyriakidou Principal Investigator, Karen Faulkner Principal Investigator, Darius Williams Principal Investigator, Mustafe Ali Sub-Investigator, Kathleen Martin Sub-Investigator, Hawys Thomas Sub-Investigator, Natalie Duric Sub-Investigator, Marianne (Marlies) Viljoen Sub-Investigator, Madhu Gowda Sub-Investigator, Imrozia Munsoor Sub-Investigator, Lucy Wilks Sub-Investigator, Helen Nicholls Sub-Investigator

Site staff: Rebecca Crossley Study Nurse, Richard Abraham Study Coordinator, Mafeliza Dela Cruz Study Nurse, Louise Richards Safety Contact, Jeremiah Chimeura Study Nurse, Michaela Cox Study Coordinator, Jodie Cooper Study Coordinator, Carol Wynne Study Coordinator, Paul Davies Unblinded Team Member, Leanne Walker Unblinded Team Member, Emma Rees Radiology Technician, Katie Saunders Lab Personnel, Alison Elliot-Garwood Recruiter, Danielle Matthews Study Coordinator, Cerys Saunders Subject Recruiter, Samantha Heslop Lab Personnel, Julie Crandon Recruiter

AES - DRS - Synexus North Teeside Clinical Research Centre, Stockton-on-Tees, UK

Investigators: Lisa Husband Principal Investigator, Shalini Iyengar Principal Investigator, Hussam Mohamed Sub-Investigator, Dominique Lentchou Sub-Investigator, Vivek Krishna Sub-Investigator, Sandra Connell Sub-Investigator

Site staff: Lisa Crawford Lab Personnel, Lorna Ramsey Study Nurse, Eileen Turnbull Study Nurse, Andrew Sowerby Lab Personnel, Ruth Graham Unblinded Team Member, Sarah Kitchen Study Coordinator, Aimee Leath Research Assistant, Susan Slaney Unblinded Team Member, Matt Holmes Study Coordinator, Rebecca Ferguson Research Assistant, Suzanne Hirst Study Nurse, Jennifer Morgan Study Nurse, Kirsty Reeve-Butterworth Lab Personnel, Victoria Frank Safety Contact, Corinne Riley Study Nurse, Kirsty Baillie Study Coordinator, Ashleigh Popple Data Manager, Emma Allan Data Manager, Siobhan Allison Data Manager, Kylie Jackson Study Nurse, Deborah Lowery Lab Personnel, Caroline Allison Study Nurse, Jane Everson Site Manager, Susan Morgan Study Nurse, Katie Saunders Lab Personnel, Helen Esplin Data Manager, Graham Le Sueur Study Nurse, Frances Marshall Study Nurse, Danielle Ashton Study Nurse, Sinqobile Sibanda Unblinded Team Member, Frances O'Rourke Lab Personnel, Amy Wallace Lab Personnel, Andrew Pegg Lab Personnel

Westmead Hospital, Westmead, Australia

Investigators: Mark Taylor Principal Investigator, Graeme Stewart Principal Investigator, Fiona Kwok Sub- Investigator, Daniel Suan Sub-Investigator

Site staff: Helen Knight Senior Study Coordinator/ Clinical Trial Manager, Cavelyn Jones Study Coordinator, Mark Clifford Pharmacist, Mercy Owusu-Sekyere Pharmacist, Elizabeth Tran Administration Pharmacy, Cassandra Thompson 6-MWT Accessor, Robert Robles 6-MWT Accessor, Catherine Farrow 6-MWT Accessor, Rochelle McCredie Radiology Technician, Paula Brown Chief Cardiac Physiologist, Amenze Uyagu Infusion Nurse Manager, Kate Eisenhuth Infusion Nurse in Charge, Ann Madrid Primary Study Coordinator, Anie Barnsdall-Krikorian Study Coordinator, Prerana Nasikkar Study Coordinator

Box Hill Hospital, Box Hill, Australia

Investigators: Simon Gibbs Principal Investigator, Shreerang Sirdesai Principal Investigator, Tamara Marconi Sub-Investigator, Shi Qin Kimberly Wong Sub-Investigator, Stephen Ting Sub-Investigator, Kah Yong Peck Sub-Investigator

Site staff: Ian Ngo Unblinded Team Member, Jayasinghe Pharmacy Personnel, Nadia Chee Pharmacist, Elizabeth Arnold Study Coordinator, Paula Lee Pharmacist, Suzi Jakicic Study Coordinator, Carol Sung Unblinded Team Member, Jessa Chacko Varghese Safety Contact, Carmel Corfield Primary Study Coordinator, Selene Mourikis Study Coordinator, Kate Dunstan Study Coordinator, Tarni Gould Back-Up Study Coordinator, Zoe Meyer 6 MWT Administrators, Catherine Lai 6-MWT Administrators, Emma Smith 6-MWT Administrator, Elenora Del Colle 6-MWT Administrator, Claire Gollogly Study Coordinator, Fiona Hosking Study Coordinator, Samara Halkett Study Coordinator, Ranita Nalini Charitra Study Coordinator, Bonnie Jongue Pharmacist, Glen Hastings Cardiac Ultrasonographer

Christchurch Hospital, Christchurch, New Zealand

Investigators: Ian Crozier Principal Investigator, John Elliott Principal Investigator

Site staff: Michael Hume Blinded Study Coordinator, Laura Perston Radiology Technician, Amanda Scull Back-Up Study Coordinator, Catherine Cruickshank Blinded Study Coordinator, Houda El Banna Unblinded Study Coordinator, Kim Clark Back-Up Unblinded Study Coordinator

Waikato Hospital, Hamilton, New Zealand

Investigators: Hugh Goodman Principal Investigator, Fraser Hamilton Sub-Investigator

Site staff: Melissa Kirk Primary Study Coordinator, Liz Low Unblinded Team Member, Sharon Jaques Study Coordinator, Rajan Ragupathy Pharmacist

Instituto Cardiovascular de Rosario, Rosario, Argentina

Investigators: Alejandro Meiriño Principal Investigator, Juan Escalante Sub-Investigator, Gerardo Zapata Sub-Investigator

Site staff: Franco Marino Study Coordinator, Juan Manuel Dominguez Unblinded Team Member, Ruben Chavez Caballero MRI Technician, Alejandra Passafiume Lab Personnel, Magali Mure Study Coordinator, Silvana Lopez MRI Technician

Hospital Privado Centro Médico de Córdoba, Córdoba, Argentina

Investigators: Oscar Salomone Principal Investigator, Alejandro Marcos Amuchastegui Sub-Investigator

Site staff: María Jose Cáceres Study Coordinator, Miguela Bono Unblinded Team Member, Nora Konicoff Regulatory Coordinator, Maria Cecilia Gonzalez Unblinded Team Member, Erica Geraudo Unblinded Team Member, Paula Salomone Unblinded Team Member, Vanesa Carnero Unblinded Team Member, Mailen Konicoff Unblinded Team Member

Instituto Médico de la Fundación Estudios Clínicos, Rosario, Argentina

Investigators: Ezequiel Vottero Principal Investigator, Amarú Lopez Sub-Investigator, Federico Ferraro Sub-Investigator

Site staff: Luciana Zanchi Unblinded Team Member, María Fernanda Ghiara Unblinded Team Member, Sofia Perotti Unblinded Team Member, Claudia Victoria Pizurno Study Coordinator, Marcia Lopez Primary Study Coordinator, Valentina Ermini Primary Study Coordinator, Norma Jacobi Lab Personnel

Maastricht University Medical Center, Maastricht, Netherlands

Investigators: Christian Knackstedt Principal Investigator, Vanessa Van Empel Sub-Investigator, Vanessa Van Empel Sub-Investigator, Hans Peter Brunner-La Rocca Sub-Investigator

Site staff: Luciana Bianca Borghans Pharmacy Personnel, Odile Schoffelen Pharmacy Personnel, Jen Offermans Pharmacy Personnel, Beitske Smick Pharmacist, Monique Goessens Lab Personnel, Mireille Spanjers Primary Study coordinator and Safety

Contact, Roger de Rooij Pharmacist, Arlette Peters Study Coordinator, Kelly Heitlager Nurse, Simone Schoonbroodt Echo Technician, Alissa Thomassen Echo Technician

AZ Delta, Roeselare, Belgium

Investigators: Karl Dujardin Principal Investigator, Michel De Ceuninck Sub-Investigator

Site staff: Hannah Vandergucht Study Coordinator, Wannes Deprez Back-Up Study Coordinator, Nicolas Wyseure Study Nurse, Tessy Van Tomme Study Coordinator, Barbara De Naeyer Study Nurse, Inge Bolle Primary Study Coordinator, Els Vancayseele Study Coordinator, Anja Depoortere Pharmacist, Cléo Van de Velde Pharmacist, Veroniek Ryssaert Pharmacist, Vera Lateur Study Coordinator, Eveline Vercaigne Study Nurse, Ingeborg Maddens Study Nurse

CHR de la Citadelle, Liège, Belgium

Investigators: Pierre Troisfontaines Principal Investigator, Maria Melissopoulou Sub-Investigator

Site staff: Thi Nguyen Pharmacy Personnel, Annick Peters Pharmacy Personnel, Alexa Jonas Pharmacist, Danielle Malmendier Nurse, Sonia Nardulli Primary Study Coordinator, Etienne Hoffer Research Clinician, Mireille Massoz Study Coordinator, Valentine Lesenfants Pharmacist, Sophie Jacquet Study Coordinator, Marine Delhasse Pharmacy Assistant, Audrey Moxhet Pharmacy Assistant

Onze-Lieve-Vrouwziekenhuis, Aalst, Belgium

Investigators: Sofie Verstreken Sub-Investigator, Marc Vanderheyden Principal Investigator, Riet Dierckx Sub-Investigator, Ward Heggermont Sub-Investigator, Jozef Bartunek Sub-Investigator

Site staff: Steve Aerts Safety Contact, Kathy De Knijf Study Coordinator, Leen Pierssens Lab Personnel, Marijke Sleeuwagen Lab Personnel, Tanja De Meyer Pharmacist, Katrien Uyttendaele Pharmacist, Hedwig Batjoens Study Coordinator

AES - DRS - Synexus Scotland Clinical Research Centre, Bellshill, UK

Investigators: Puneet Agarwal Principal Investigator, Imrozia Munsoor Principal Investigator, Holly Ross Principal Investigator, Donald McVinnie Principal Investigator, Tamer Yousef Sub-Investigator, Karen Faulkner Sub-Investigator (OOH Doctor), Madhu Venkate Gowda Sub-Investigator (OOH Doctor), Marianne (Marlies) Viljoen Sub-Investigator (OOH Doctor), Shalini Iyengar Sub-Investigator

Site Staff: Maheswari Alapati Data Compliance Specialist, Adrian Mooty Research Assistant, Graham Le Sueur Study Nurse, Caroline Colquhoun Research Assistant, Eva Jardine Research Assistant, Cheryl Marmion Data Compliance Specialist, Tracy Kelt Manager Data Compliance, Frances Marshall Unblinded Team Member, Darren Clyde Study Nurse, Billie Jean Connolly Research Assistant

The University of Tokyo Hospital, Tokyo, Japan

Investigators: Masaru Hatano Principal Investigator, Junichi Ishida Sub-Investigator, Eisuke Amiya Sub-Investigator, Koichi Narita Sub-Investigator, Nobutaka Kakuda Sub-Investigator, Satoshi Ishii Sub-Investigator, Takanobu Yamada Sub-Investigator, Akihito Saito Unblinded Sub-Investigator, Mai Shimbo Unblinded Sub-Investigator, Masaki Tsuji Unblinded Sub-Investigator, Chie Bujo Unblinded Sub-Investigator

Site Staff: Masao Daimon Sonographer, Tomoko Nakao Sonographer, Hirohide Suzuki Sonographer, Kazuno Sasaki Sonographer, Yoshimi Suto Sonographer, Shota Inoue Sonographer, Miho Echizenya Unblinded Pharmacist, Masami Kaneko Unblinded Pharmacist, Maika Kissei Unblinded Pharmacist, Naoko Yamada Unblinded Pharmacist, Yugo Kunibe Unblinded Physician, Risa Kishikawa Unblinded Physician, Hiroshi Takiguchi Unblinded Physician, Masaki Hashimoto Unblinded Physician, Zhehao Dai Unblinded Physician, Takahiro Jimba Unblinded Physician, Atushi Kobayashi Unblinded Physician, Madoka Iwaizumi Study Nurse, Yukiko Suzuki Study Nurse, Naoko Sato Study Nurse, Ayaki Ehara Study Nurse, Ari Muramori Study Nurse, Naoko Takayama Study Nurse, Satoshi Nagai Study Nurse, Maiko Haramura CRC, Mami Okanaga CRC, Chika Ohara CRC, Haruko Kuzuyama CRC, Mao Machida CRC, Miho Kato CRC, Chihiro Kaminaga CRC, Yuka Suzuki CRC, Atsuko Watanabe CRC, Miyu Ogata CRC, Sanae Sato

CRC, Rika Takeuchi CRC, Mizuki Soga CRC, Masayoshi Onuki CRC, Mayumi Mizuguchi CRC, Serina Sato CRC, Juri Nakasako Unblinded Pharmacist, Miho Sato Unblinded Pharmacist, Kaori Sako Study Nurse, Minako Takahashi Study Nurse, Ikuko Tanaka Study Nurse, Yoko Hirao Study Nurse, Hisai Furusawa Study Nurse, Kanako Hyoudou Study Nurse, Megumi Tamada Study Nurse, Akina Kunihiro Study Nurse, Yasue Tamami Study Nurse, Yurie Wakabayashi Study Nurse, Hisae Yamaguchi Study Nurse, Rie Yoshiwara Study Nurse

Kyushu University Hospital, Fukuoka, Japan

Investigators: Toru Hashimoto Principal Investigator, Soichiro Ikeda Sub-Investigator, Shoji Matsushima Sub-Investigator, Keisuke Shinohara Sub-Investigator, Taiki Higo Sub-Investigator, Masato Katsuki Sub-Investigator, Takeo Fujino Sub-Investigator, Tomomi Ide Sub-Investigator

Site Staff: Chikage Kubota Primary Study Coordinator, Goro Kawahara Radiology Technician, Takafumi Sakamoto Unblinded Team Member, Chiharu Tanaka Study Coordinator, Soichiro Tajima Unblinded Team Member, Yuriko Ryokai Unblinded Team Member, Masae Takagi Unblinded Team Member, Masatoshi Mine Unblinded Team Member, Yuichi Tsuchiya Unblinded Team Member, Satoshi Hirai Unblinded Team Member, Hideki Ochiai Unblinded Team Member, Maki Iwamoto Unblinded Team Member, Rumi Tanaka Unblinded Team Member, Yusuke Ishikawa Unblinded Team Member, Tomoko Nishida Unblinded Team Member, Yui Hasebe Unblinded Team Member, Shogo Miki Unblinded Team Member, Hiromi Sakaguchi Unblinded Team Member, Chika Tanaka Unblinded Team Member, Ken Utsunomiya Unblinded Team Member, Mayu Kubota Unblinded Team Member, Akari Shimauchi Unblinded Team Member, Makoto Takahira Unblinded Team Member, Ai Koyanagi Study Coordinator, Tomoko Sumitomo Study Coordinator, Hatsuyo Makino Study Coordinator, Rika Iwasaki Study Coordinator

Enroll SpA PPDS, Santiago, Chile

Investigators: Luis Morales Principal Investigator, Jaime Vergara Nuñez Sub-Investigator, Lia Miranda Assef Sub-Investigator, Sebastian Vazquez Sub-Investigator

Site Staff: Alessandra Mafucci Primary Study Coordinator, Ximena Vargas Study Coordinator, Belen Andrea de Miguel Jorquera Study Coordinator, Pamela Gallardo Unblinded Team Member, Rosario Garcia Study Coordinator, Marisol Fernandez Study Coordinator, Rosa Arenas Laboratory Technician

Instituto Dante Pazzanese de Cardiologia, São Paolo, Brazil

Investigators: Edileide De Barros Correia Principal Investigator, Berenice Cataldo Oliveira Valerio Sub Investigator, Larissa Venture Ribeiro Bruscky Sub Investigator, Fabiano Castro Albrecht Sub Investigator, Ana Cristina De Souza Murta Sub Investigator, Yoná Francisco Sub Investigator, Liria Maria Lima Silva Sub Investigator, Priscila Cestari Quagliato Sub Investigator, Kelin Chen Sub Investigator

Site Staff: Patricia Paiva Back Up Study Coordinator, Carlos Eduardo Pinto Lab Personnel, Mayara Cortez Silva Safety Contact, Renata Pimentel Leite Research Assistant, Rubens Avelino Oliveira Filho Study Nurse, Ana Paula Conceição Unblinded Team Member, Gabriela Santos Unblinded Team Member, Marilia Amorim Souza Leão Research Assistant

Aarhus University Hospital, Aarhus N, Denmark

Investigators: Steen Poulsen Principal Investigator, Jens Kæstel Skov Sub-Investigator, Bertil Thyrsted Ladefoged Sub-Investigator, Thorsten Bloch Rasmussen Sub-Investigator, Anders Dahl Pedersen Sub-Investigator

Site Staff: Louise Health Bertelsen Pharmacy Personnel, Karen Valdimarsdottir Primary Study Coordinator, Lene Lindencrone Kondrad Primary Study Coordinator, Kristine Serup-Hansen Study Coordinator, Gitte Udsen Study Coordinator, Marianne Leth Study Coordinator, Lone Romby Nurse, Line Jaquet Sørensen Pharmacy Personnel, Lene Holm Ahrendt Pharmacy Personnel, Anne Dybroe Unblinded Team Member, Morten Bank Troelsen Pharmacy Personnel, Meri Olsen Pharmacy Personnel, Ulla Brandstrup Pharmacy Personnel, Birgitte Madsen Pharmacy Personnel

National Cerebral and Cardiovascular Center, Ôsaka, Japan

Investigators: Chisato Izumi Principal Investigator, Hiroyuki Takahama Sub-Investigator, Atsushi Okada Sub-Investigator, Hideaki Kanzaki Sub-Investigator, Makoto Amaki Sub-Investigator, Masashi Amano Sub-Investigator, Takeshi Kitai Sub-Investigator

Site Staff: Emi Tateishi Radiology Technician, Kenji Moriuchi Unblinded Team Member, Hiromi Nakano Unblinded Team Member, Keiko Waku Study Coordinator, Yukihiro Shimada Research Assistant, Megumi Yasunobe Unblinded Team Member, Taisuke Sugino Unblinded Team Member, Mai Narukawa Unblinded Team Member, Miyu Masaki Unblinded Team Member, Airi Mizukami Unblinded Team Member, Tasuku Hada Unblinded Team Member, Kohei Kaneta Unblinded Team Member, Marina Arai Unblinded Team Member, Akemi Furukawa Study Coordinator, Yoshito Jo Sonographer, Ayaka Mizumoto Sonographer, Rika Yonezawa Sonographer, Hitomi Nishimura Sonographer, Hiromasa Ikariyama Rehabilitation Technician, Noriyuki Fukui Rehabilitation Technician, Kenji Furuta Lab Technician, Yoshiyuki Sumita Lab Technician, Narumi Matsumura Unblind Pharmacist, Mai Takano Unblind Pharmacist, Hiroki Nakamura Unblind Pharmacist, Shoko Amano Unblind Pharmacist, Kaori Imanishi Unblind Pharmacist, Akie Kitaba Unblind Pharmacist, Saya Tanaka Unblind Pharmacist, Rikako Nagata Unblind Pharmacist, Ayano Habe Unblind Pharmacist, Nagisa Hamamoto Unblind Pharmacist, Masaki Abe Unblind Pharmacist, Yuki Irie Unblinded Team Member, Yu Kawada Unblinded Team Member, Nami Omori Unblinded Team Member, Shoko Nakagawa Unblinded Team Member, Reiko Adachi Unblinded Team Member, Reiko Nakao Unblinded Team Member

Jessa Ziekenhuis, Hasselt, Belgium

Investigators: Jan Verwerft Principal Investigator, Philippe Timmermans Sub-Investigator

Site Staff: Emily Dekimpe Primary Study Coordinator, Charlotte Baecke Study Coordinator, Anuschka De Clercq Pharmacist, An Lambaerts Pharmacist, Arne Janssen Site Manager, Inge Dreesen Pharmacist, Emelien Putzeys Pharmacy Personnel

AES-DRS-NW Consortium Manchester, Manchester UK

Investigators: MadhuVenkate Gowda Principal Investigator, Marianne (Marlies) Viljoen Sub-Investigator

Site Staff: Tracey Gillon Lab Personnel, Lauren Stopford Study Coordinator, Inge Ghysels Study Nurse, Alison Merrick Study Nurse, Olga Littler Site Manager, Lena Al-Sheikhly Primary Study Coordinator, Angela Fallows Associate Manager, Jacqueline Clowes Patient Services Coordinator, Cathrine Basikalo Study Nurse

Instituto CAICI, Santa Fe, Argentina

Investigators: Martin Najenson Principal Investigator, Martin Viso Sub-Investigator, Juan Loureyro Sub-Investigator

Site Staff: Sofia Fernandez Study Coordinator

Baylor University Medical Center, Dallas, Texas, USA

Investigators: Parag Kale Principal Investigator, Amarinder Bindra Sub-Investigator, Robert Gottlieb Sub-Investigator, Melody Sherwood Sub-Investigator, Cesar Guerrero-Miranda Sub-Investigator, Timothy Gong Sub-Investigator, Sandra Carey Sub-Investigator, Shelley Hall Sub-Investigator

Site Staff: Arizbe Reyes Administration, Adriana Palacios Pharmacy Personnel, Lily Nguyen Pharmacy Personnel, Aaron Killian Pharmacist, Leslie Jacob Administration, Tein Luu Study Coordinator, Kiersten Schenider Study Coordinator, Shelby Shull Back-Up Study Coordinator, Edilia Solis Pharmacy Personnel, Eva Patel Regulatory Coordinator, Aayla Jamil Regulatory Coordinator, Amanda Doss Research Staff, Donna Michelle Clark Research Staff, Karen Castro Research Staff, Wenqin Du Research Staff, Ramatoulaye Diallo Research Staff, Olivia Larkins Research Staff, Melissa Gayheart Research Nurse, Russelia Jackson Research Staff, Tatyana Ganz Research Staff, Hira Zafar Research Staff, Shane Blakenship Research Staff, Joost Felius Research Staff, Edward Mercer Research Staff

Princess Margaret Hospital, Lai Chi Kok, Hong Kong

Investigators: Bun Sheng Principal Investigator, Ka Fai Johnny Ma Sub-Investigator, Wing Hang Luk Sub-Investigator, Cheuk Hang Tsang Sub-Investigator, Lun Pei Ng Sub-Investigator, Chun Hin Eric Cheung Sub-Investigator, Yan Lok Tiffany Lam Sub-Investigator

Site Staff: Pui Ki Peggy Chan Back-Up Study Coordinator, Winnie Yau Study Coordinator, Shuk King Eva Chan Pharmacist, Ka Kin Tom Chan Pharmacist, Kei Hong Tom Chan Pharmacist, Tsz Ka Simon Kwok Pharmacist, Yi Ka Kelly Ng Pharmacist, In Yung Alison So Pharmacist, Ka Wai Queenie Wong Pharmacist, Tsun Ting Brian You Pharmacist, Ka Ying Elza Wong Senior Dispenser, Wai Man Raymond Wong Senior Dispenser, Yeuk Fei Au Study Nurse, Ka Ho Ray Tjong Primary Study Coordinator, Yan Yu Leung Study Coordinator

NorthShore University HealthSystem, Evanston, Illinois, USA

Investigators: Nitasha Sarswat Principal Investigator, Robert Gordon Sub-Investigator, Charu Gupta Sub-Investigator

Site Staff: Linda Pierchala Back-Up Study Coordinator, Bernardo Vargas Regulatory Coordinator, Saritha Theegala Back-Up Study Coordinator, Tracey Silverstein Study Coordinator, Annalise Thomsen Unblinded Team Member, Diana Di Domenico Administration, Kamila Lepkowska Site Manager, Izabela Wozniak Pharmacist, Karen Kaul Laboratory Director, Karen Kelly Unblinded Team Member, Amber Meigs Unblinded Team Member, Lisa Patel Unblinded Team Member, Shayna Acance Unblinded Team Member, Annalise Thomsen Unblinded Team Member, Hardy Sandefur Back-Up Study Coordinator, Ujala Bokhar Site Manager, Adam Vanderloo Legal Contact

APOLLO-B Study Team

Rita Amirana, Raina Leahy, Brittany McLaughlin, Christine Snow, Vanessa Bahnam, James Keegan, Erik Sokolowski, David Keller, Ariel Kalotkin, Kailey Walsh, Joshua Emerson, Rick Falzone, Audrey Recupero, Amita Karre, Lingjiao Qi, Amanda Plaisted, and D’dra Octavia

ADDITIONAL METHODOLOGICAL DETAILS

INCLUSION CRITERIA

Age and Sex

1. Age 18 (or age of legal consent, whichever is older) to 85 years, inclusive.

Patient and Disease Characteristics

2. Documented diagnosis of transthyretin cardiac amyloidosis, also called ATTR cardiac amyloidosis, classified as either hereditary, also known as variant, ATTR cardiac amyloidosis or wild-type ATTR cardiac amyloidosis.

Variant ATTR cardiac amyloidosis diagnosed based on meeting all of the following criteria:

a. Pathogenic transthyretin (*TTR*) variant consistent with variant ATTR amyloidosis.

b. Evidence of cardiac involvement by echocardiography with an end-diastolic interventricular septal wall thickness greater than 12 mm (based on central echocardiogram reading at screening).

c. Amyloid deposits in cardiac or noncardiac tissue (e.g., fat pad aspirate, salivary gland, median nerve connective sheath) confirmed by Congo Red (or equivalent) staining **OR** technetium (^{99m}Tc) scintigraphy (^{99m}Tc-3,3-diphosphono-1,2-propanodicarboxylic acid [DPD-Tc], ^{99m}Tc-pyrophosphate [PYP-Tc], or ^{99m}Tc-hydroxymethylene diphosphonate [HMDP]) with grade 2 or 3 cardiac uptake, if monoclonal gammopathy of undetermined significance (MGUS) has been excluded.

d. If MGUS, confirm TTR protein in tissue with immunohistochemistry (IHC) or mass spectrometry.

Wild-type ATTR cardiac amyloidosis diagnosed based on meeting all of the following criteria:

a. Absence of pathogenic *TTR* variant.

b. Evidence of cardiac involvement by echocardiography with an end-diastolic interventricular septal wall thickness greater than 12 mm (based on central echocardiogram reading at screening).

c. Amyloid deposits in cardiac tissue with TTR precursor identification by IHC, mass spectrometry, **OR** ^{99m}Tc scintigraphy (DPD-Tc, PYP-Tc, or HMDP) with grade 2 or 3 cardiac uptake, if MGUS has been excluded.

d. If MGUS, confirm TTR protein in cardiac tissue with IHC or mass spectrometry.

3. Medical history of heart failure (HF) with at least one prior hospitalization for HF (not due to arrhythmia or a conduction system disturbance treated with a permanent pacemaker) **OR** clinical evidence of HF (with or without hospitalization) manifested by signs and symptoms of volume overload or elevated intracardiac pressures (e.g., elevated jugular venous pressure, shortness of breath or signs of pulmonary congestion on X-ray or auscultation, peripheral edema) that currently requires treatment with a diuretic.

4. Patient meets one of the following criteria:

a. Tafamidis naïve; in addition to patients who have never taken tafamidis, those who have been on tafamidis for 30 days total or fewer and have not received any tafamidis in the 6 months prior to baseline will be considered tafamidis naïve and may qualify for the study.

b. Currently on tafamidis (for at least 6 months) and has demonstrated disease progression, as determined by the Investigator (at the time of study entry, tafamidis treatment must be on-label use of commercial tafamidis for the treatment of ATTR cardiac amyloidosis at the approved dose in the country of use).

5. Patient is clinically stable, with no cardiovascular (CV)-related hospitalizations within 6 weeks prior to randomization, as assessed by the Investigator.

6. Able to complete at least 150 m on the 6-minute walk test (6-MWT) at screening.

7. Screening *N*-terminal prohormone of B-type natriuretic protein (NT-proBNP) greater than 300 pg/ml and less than 8500 pg/ml; in patients with permanent or persistent atrial fibrillation, screening NT-proBNP greater than 600 pg/ml and less than 8500 pg/ml.

EXCLUSION CRITERIA

1. Has known primary amyloidosis or leptomeningeal amyloidosis.

2. New York Heart Association (NYHA) class III **AND** ATTR amyloidosis disease stage 3 (defined as both NT-proBNP >3000 pg/ml and estimated glomerular filtration rate [eGFR] <45 ml/min/1.73 m^2).

3. NYHA class IV at the screening visit.

4. Has a polyneuropathy disability score IIIa, IIIb, or IV (requires cane or stick to walk, or is wheelchair bound) at the screening visit.

5. Has any of the following laboratory parameter assessments at screening:

    a. Aspartate transaminase or alanine transaminase levels greater than 2.0 × the upper limit of normal (ULN).

    b. Total bilirubin greater than 2 × ULN.

    c. International normalized ratio (INR) greater than 1.5 (unless patient is on anticoagulant therapy, in which case excluded if INR >3.5).

6. Has eGFR less than 30 ml/min/1.73 m^2 (using the modification of diet in renal disease formula).

7. Has known human immunodeficiency virus infection, or evidence of current or chronic hepatitis C virus or hepatitis B virus infection.

8. Tafamidis-naïve patients (at baseline) for whom the Investigator actively plans or anticipates commencing treatment with tafamidis during the 12-month double-blind period, taking into consideration clinical status, patient preference, and/or commercial availability of tafamidis.

9. Is currently taking diflunisal; if previously on this agent, must have at least a 30-day washout prior to dosing (day 1).

10. Is currently taking doxycycline, ursodeoxycholic acid, or tauroursodeoxycholic acid; if previously on any of these agents, must have completed a 30-day washout prior to dosing (day 1).

11. Received prior TTR-lowering treatment (including patisiran) or participated in a gene therapy trial for variant ATTR amyloidosis.

12. Current or future participation in another investigational device or drug study, scheduled to occur during this study, or has received an investigational agent or device within 30 days (or five half-lives of the investigational drug, whichever is longer) prior to dosing (day 1). In the case of investigational TTR stabilizer drugs, washout for 6 months prior to dosing (day 1) is required; this does not apply to patients who are on tafamidis at baseline (per inclusion criterion 4).

13. Requires chronic treatment with nondihydropyridine calcium channel blockers (e.g., verapamil, diltiazem).

Medical Conditions

14. Other non-TTR cardiomyopathy, hypertensive cardiomyopathy, cardiomyopathy due to valvular heart disease, or cardiomyopathy due to ischemic heart disease (e.g., prior myocardial infarction with documented history of cardiac enzymes and electrocardiogram changes).

15. Has nonamyloid disease affecting exercise testing (e.g., severe chronic obstructive pulmonary disease, severe arthritis, or peripheral vascular disease affecting ambulation).

16. Recent or planned orthopedic procedure during the double-blind period (e.g., lower extremity or back surgery) that could impact 6-MWT.

17. Unstable congestive HF (e.g., no adjustment of diuretics at time of screening required to achieve optimal treatment of congestive HF).

18. Had acute coronary syndrome or unstable angina within the past 3 months.

19. Has history of sustained ventricular tachycardia or aborted ventricular fibrillation.

20. Has history of atrioventricular nodal or sinoatrial nodal dysfunction for which a pacemaker is indicated but will not be placed.

21. Has persistent elevation of systolic (>180 mmHg) and diastolic (>100 mmHg) blood pressure that is considered uncontrolled by physician.

22. Has untreated hypo- or hyperthyroidism.

23. Prior or planned heart, liver, or other organ transplant.

24. Had a malignancy within 5 years, except for basal or squamous cell carcinoma of the skin or carcinoma in situ of the cervix that has been successfully treated.

25. Has other medical conditions or comorbidities which, in the opinion of the Investigator, would interfere with study compliance or data interpretation; or, in the opinion of the Investigator, taking part in the study would jeopardize the safety of the patient.

26. Has a history of severe hypersensitivity (e.g., anaphylaxis) to any of the excipients in patisiran.

Contraception, Pregnancy, and Breastfeeding

27. Is not willing to comply with the contraceptive requirements during the study period.

28. Female patient is pregnant or breastfeeding.

Alcohol Use

29. Has a known history of alcohol abuse within the past 2 years or daily heavy alcohol consumption (for females, >14 units of alcohol per week; for males, >21 units of alcohol per week [unit: 1 glass of wine [125 ml] = 1 measure of spirits = ½ pint of beer]).

30. History of illicit drug abuse within the past 5 years that, in the opinion of the Investigator, would interfere with compliance with study procedures or follow-up visits.

PREMEDICATION REQUIREMENTS

All patients in both treatment arms received premedication approximately 60 minutes prior to an infusion comprising an intravenous (IV) corticosteroid (dexamethasone 10 mg or equivalent), paracetamol 500 mg orally, and IV H1 blocker (diphenhydramine 50 mg, or equivalent; IV or oral nonsedating H1 blockers are acceptable) or IV H2 blocker (ranitidine 50 mg, or equivalent).

Patients who had received at least two doses of study drug at a study center and were considered to have tolerated the infusion were permitted to have study drug administered at a location other than the study center (e.g., at home), where applicable country and local regulations allowed.

PRIMARY AND SECONDARY EFFICACY END POINT MEASURES

The functional exercise capacity assessment, 6-MWT, was performed at screening, baseline, month 6, month 9, and month 12. To avoid the potential training effect from repeated 6-MWT assessments within a short period of time, only one 6-MWT assessment was collected for the following time periods: day 2 to day 214 (for month 6), day 215 to day 319 (for month 9), and day 320 to day 417 (for month 12). During the double-blind period, a patient could opt to begin tafamidis treatment or to discontinue study treatment, in which case they completed a 6-MWT at the pre-tafamidis drop-in visit (occurring prior to starting concomitant tafamidis and, where possible, 7 to 14 days post-dose), or at the early treatment discontinuation visit (occurring at month 12 for patients who discontinued treatment early, i.e., prior to month 12, and chose to remain in the study), respectively.

Health status was measured using the 23-item self-administered Kansas City Cardiomyopathy Questionnaire (KCCQ), which measures HF symptoms, impact on physical and social function, and how HF impacts patient quality of life within a 2-week recall period (scores range from 0 to 100, with a score of 0 to 24 indicating very poor to poor quality of life, 25 to 49 poor to fair, 50 to 74 fair to good, and 75 to 100 good to excellent). The KCCQ was completed at baseline, month 6, month 9, and month 12, in addition to the pre-tafamidis drop-in visit or the early treatment discontinuation visit, if applicable. The KCCQ Overall Summary (KCCQ-OS) score is reported, which

summarizes six domains (symptoms, physical function, quality of life, social limitation, self-efficacy, and symptom stability).

All deaths and hospitalizations including urgent visits for HF were recorded from day 1 post-dose and continuously throughout the study. Reasons for deaths, urgent visits for HF, and nonelective hospitalizations were adjudicated by an independent adjudication committee.

EXPLORATORY EFFICACY END POINT MEASURES

The cardiac biomarkers NT-proBNP and troponin I were used to assess cardiac stress and HF severity. Blood samples to assess these biomarkers were taken at screening, baseline, month 3, month 6, month 9, and month 12, or at the early treatment discontinuation visit, if applicable. Biomarker levels were measured at a central laboratory.

Echocardiograms were taken at screening and month 12 and analyzed at a central cardiac imaging core laboratory to assess cardiac structure and function parameters. Change from baseline at month 12 in select echocardiographic parameters (mean left ventricular [LV] wall thickness, LV mass, and global LV longitudinal strain) was assessed.

STATISTICAL ANALYSES

The primary analysis for 6-MWT using the stratified Wilcoxon rank-sum test, stratified by baseline tafamidis use (yes vs. no), was based on the following assumptions for missing data at month 12:

1. Patients who die during the 12-month double-blind period (not due to coronavirus disease 2019 [Covid-19]) or who have become unable to walk due to progression of ATTR amyloidosis by month 12 and have missing data: Assuming that deaths observed in the study will likely be related to worsening of disease, the missing month 12 6-MWT change from baseline was imputed as the worst 10th percentile change, capped by the worst possible change for the patient (i.e., 0 – baseline 6-MWT).

2. Patients who have missing data due to other reasons were imputed assuming data were missing at random (MAR). Since the pattern of missing data within patients

may be nonmonotone, multiple imputation was conducted separately by treatment arm and baseline tafamidis use group using the Markov Chain Monte Carlo method. For each treatment arm/baseline tafamidis use group, the imputation model included type of amyloidosis (variant ATTR vs. wild-type ATTR), NYHA class (I/II vs. III), age at randomization (<75 vs. ≥75), baseline NT-proBNP (≤3000 pg/ml vs. >3000 pg/ml), baseline 6-MWT, and all calculated values of change from baseline in 6-MWT at prespecified visits.

Missing values were imputed 100 times to generate 100 complete data sets using the procedures described above. The stratified Wilcoxon rank-sum test was applied to each imputed data set for the change from baseline in 6-MWT at month 12. The Z-scores estimated from the stratified Wilcoxon rank-sum test fit to each imputed data set were combined by applying Rubin's rules using SAS PROC MIANALYZE to produce inferential results for the p-value.

The effect size comparing treatment groups was estimated using the stratified Hodges–Lehmann (H–L) estimate (stratified by baseline tafamidis use) of the median difference in the change from baseline between patisiran and placebo, together with its 95% confidence interval (CI). The stratified H–L is an estimate of the median value of all paired differences between observations in the patisiran vs. placebo groups accounting for baseline tafamidis use, calculated using the imputed data sets. The calculation was repeated for each imputed data set, and the results were combined by applying Rubin's rules using SAS PROC MIANALYZE to obtain the stratified H–L estimate and corresponding 95% CI.

A parametric sensitivity analysis using a mixed-effects model repeated measures (MMRM) was also performed. The MMRM included baseline 6-MWT as the continuous covariate and treatment arm, visit (month 6, month 9, or month 12), baseline tafamidis use (yes vs. no), type of amyloidosis (variant ATTR vs. wild-type ATTR), age at randomization (<75 vs. ≥75 years), treatment-by-visit interaction, treatment-by-baseline tafamidis interaction, visit-by-baseline tafamidis interaction, and treatment-by-visit-by-baseline tafamidis interaction as fixed factors. Assessments obtained on or after the onset of a serious Covid-19 adverse event were treated as missing and assumed to be MAR. An unstructured covariance structure was used to model the within-patient errors.

The primary comparison was the contrast (difference in least-squares [LS] means) between the patisiran and placebo arms at month 12. The LS mean coefficients were computed using the observed proportions of the categorical covariates (baseline tafamidis use, type of ATTR amyloidosis, and age) in the full analysis set. The analysis was implemented with SAS PROC MIXED. The MMRM analysis assumes multivariate normality for the error term in the analysis model. This normality assumption was assessed by inspection of residual plots, along with a formal test for normality using the Shapiro–Wilk test.

Additional sensitivity analyses based on the stratified Wilcoxon rank-sum test were conducted as follows: 1) including all 6-MWT assessments, i.e., not censoring assessments after tafamidis drop-in or assessments impacted by Covid-19; 2) where missing data from off-treatment patisiran patients were imputed based on data from the placebo group, thus accommodating situations where the missingness mechanism may be missing not at random.

A post hoc analysis of 6-MWT, as described for the primary analysis above, was also performed in patients with a polyneuropathy disability (PND) score of 0 at baseline.

The primary analysis of the change from baseline at month 12 in KCCQ-OS was analyzed using an MMRM model similar to the MMRM model for 6-MWT described above but adjusting for baseline KCCQ-OS as a continuous covariate.

The composite end point of death from any cause, frequency of CV events, and change from baseline in 6-MWT over the double-blind period was analyzed using the stratified win ratio method,[1] stratified by baseline tafamidis use. This method makes within-stratum pairwise comparisons for all patisiran–placebo patient pairs in a sequential manner (first mortality, then CV events, then 6-MWT), with later steps evaluated only in the case of a tie on the prior step (see Section 6.6.2.2.2 of the Statistical Analysis Plan v2.1 for additional details).

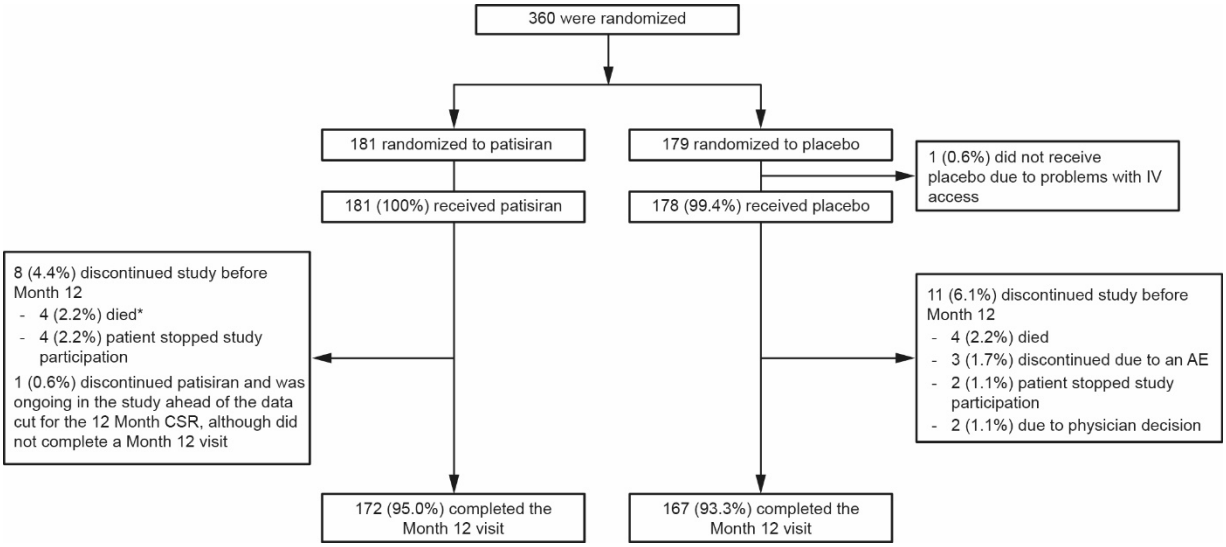
The prespecified analysis for the composite end point of death from any cause and frequency of hospitalizations for any cause and urgent visits for HF in the overall population was a modified Andersen–Gill model stratified by baseline tafamidis (yes vs. no), including treatment, type of amyloidosis (variant ATTR vs. wild-type ATTR), baseline NYHA class (I/II vs. III), and age at randomization (<75 vs. ≥75 years) as covariates.

This composite end point was also assessed in patients not on tafamidis at baseline, with a prespecified Andersen–Gill model, including treatment, type of amyloidosis, baseline NYHA class, and age at randomization as covariates. The proportional hazards (PH) assumption was assessed by including an interaction term between treatment and log(time) in the models. The PH assumption was not met for the prespecified Andersen–Gill models, and post hoc analyses for the composite end points were also conducted using negative binomial regression models. Both models included treatment arm, type of ATTR amyloidosis, baseline NYHA class, and age group as covariates, and for the analysis in the overall population, the model also included baseline tafamidis use and the treatment-by-baseline tafamidis use interaction as covariates.

Echocardiographic parameters were assessed using analysis of covariance models, which included the baseline value for the parameter, treatment arm, baseline tafamidis use (yes vs. no), type of amyloidosis (wild-type ATTR vs. variant ATTR), age at randomization (<75 vs. ≥75 years), and treatment-by-baseline tafamidis use interaction as covariates.

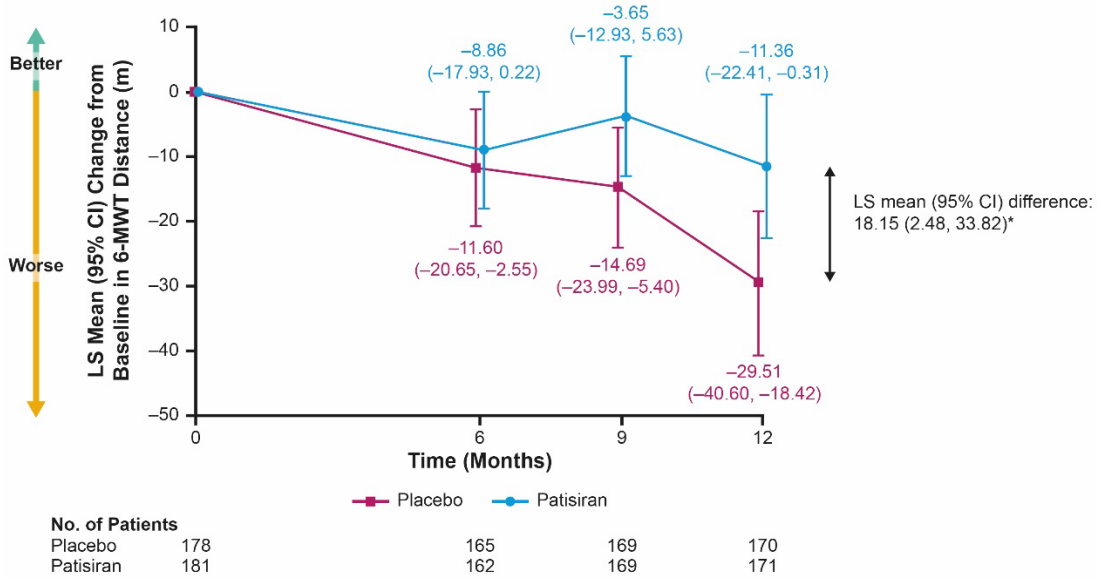
SUPPLEMENTARY FIGURES

Figure S1. Randomization and Follow-up at Month 12.



The figure includes all patients in APOLLO-B who were randomized at a 1:1 ratio to the patisiran or the placebo group. Reasons for discontinuation of the study are shown as reported by the Investigator. Two patients in the placebo group had a heart transplant during the double-blind period; one was reported as discontinuing the study due to an AE, one was reported as discontinuing the study due to physician decision. Deaths were collected during participation in the study and by assessment of vital status after withdrawal from the study. If a patient died during participation in the study, the primary reason for discontinuation of the study was reported as death. If a patient withdrew from the study and was reported as dead during assessment of vital status after the study, the primary reasons that led to withdrawal from the study are listed. In the patisiran group, five patients died; of these patients, four died during participation in the study (*includes one death due to Covid-19) and one patient who stopped participation died after the study. In the placebo group, eight patients died; of these, four patients died during participation in the study and four patients died after study withdrawal (reasons for withdrawal included adverse event [one patient], patient stopped study participation [two patients], and physician decision [one patient]). AE, adverse event; IV, intravenous.

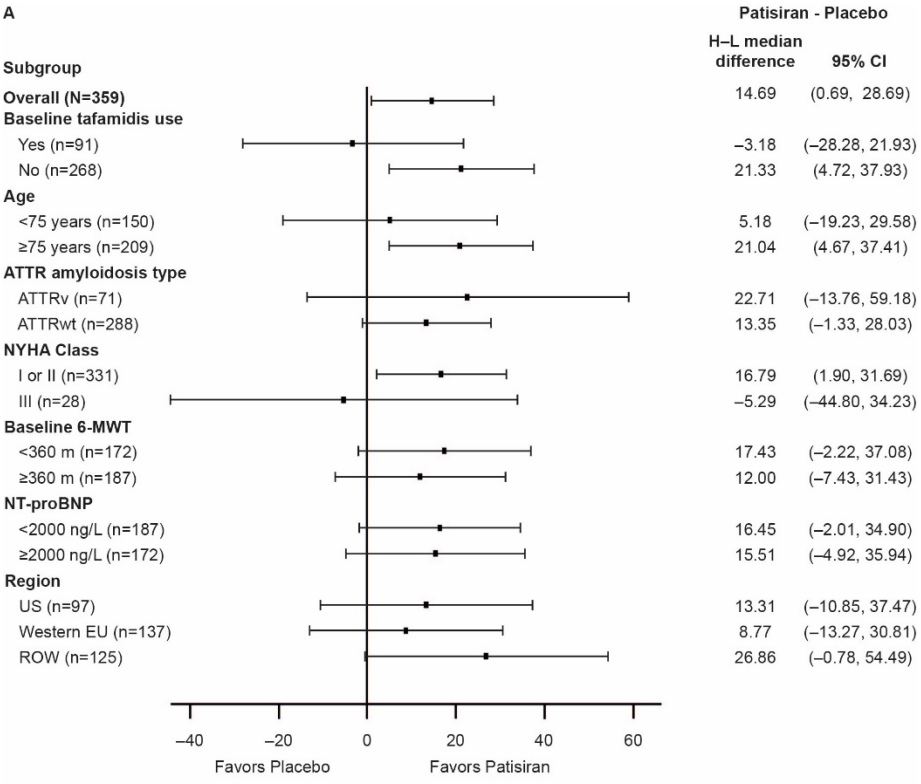
Figure S2. Prespecified Sensitivity Analysis of 6-MWT vs. Placebo Using the MMRM.

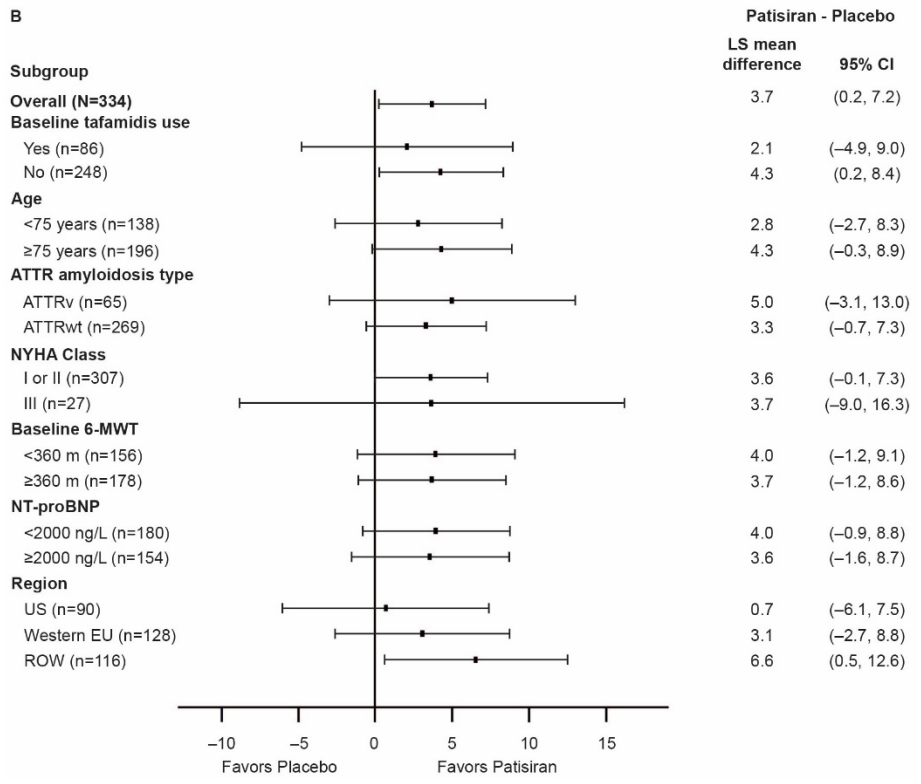


A further distance walked indicates better function. The number of patients in this MMRM analysis at month 12 include both non-missing 6-MWT assessments (166 patisiran, 161 placebo) and the imputed values for patients who died (not due to Covid-19) or who became unable to walk due to ATTR amyloidosis disease progression (5 patisiran, 9 placebo). The numbers differ from the study patient disposition at month 12 in Figure S1 due to multiple factors. Among patients who completed the month 12 visit in Figure S1 (172 patisiran, 167 placebo), one patisiran patient was unable to walk due to ATTR amyloidosis disease progression and had the month 12 change from baseline imputed as the worst 10th percentile change observed across all patients in the DB period, capped by the worst possible change for the patient (i.e., 0 minus baseline 6-MWT). Month 12 assessments obtained on or after the onset of a serious Covid-19 adverse event were treated as missing (one patisiran, three placebo). Additionally, seven patients (four patisiran, three placebo) completed the month 12 visit but did not have a valid 6-MWT assessment. *MMRM sensitivity analysis. LS means (95% CI) and LS mean (95% CI) difference were estimated from the MMRM analysis. The LS mean coefficients were computed using the observed proportions of the categorical covariates (baseline tafamidis use, type of ATTR amyloidosis, and age group). At baseline, the mean (SD) 6-MWT was 360.47 (102.27) in the patisiran group and 374.65 (102.39) in the placebo

group. 6-MWT data for two patisiran patients were updated for this analysis following database lock, as updated by the Investigator. CI widths have not been adjusted for multiplicity and may not be used in place of hypothesis testing. 6-MWT, 6-minute walk test; ATTR, transthyretin-mediated; CI, confidence interval; DB, double-blind; LS, least-squares; MMRM, mixed-effects model repeated measures; SD, standard deviation.

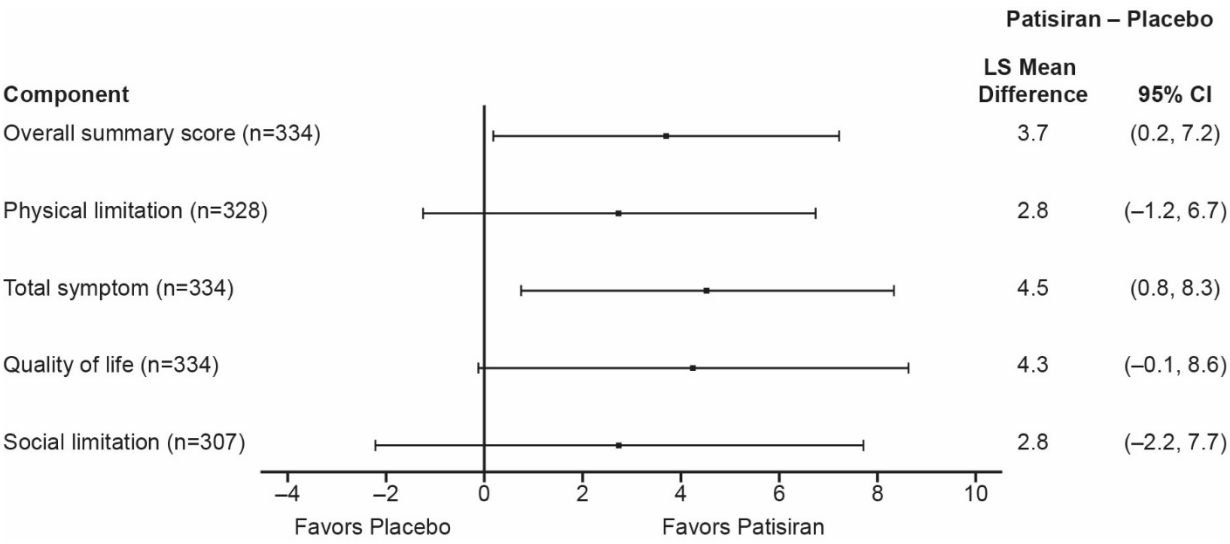
Figure S3. Subgroup Analysis of Change from Baseline to Month 12 in (A) 6-MWT and (B) KCCQ-OS.





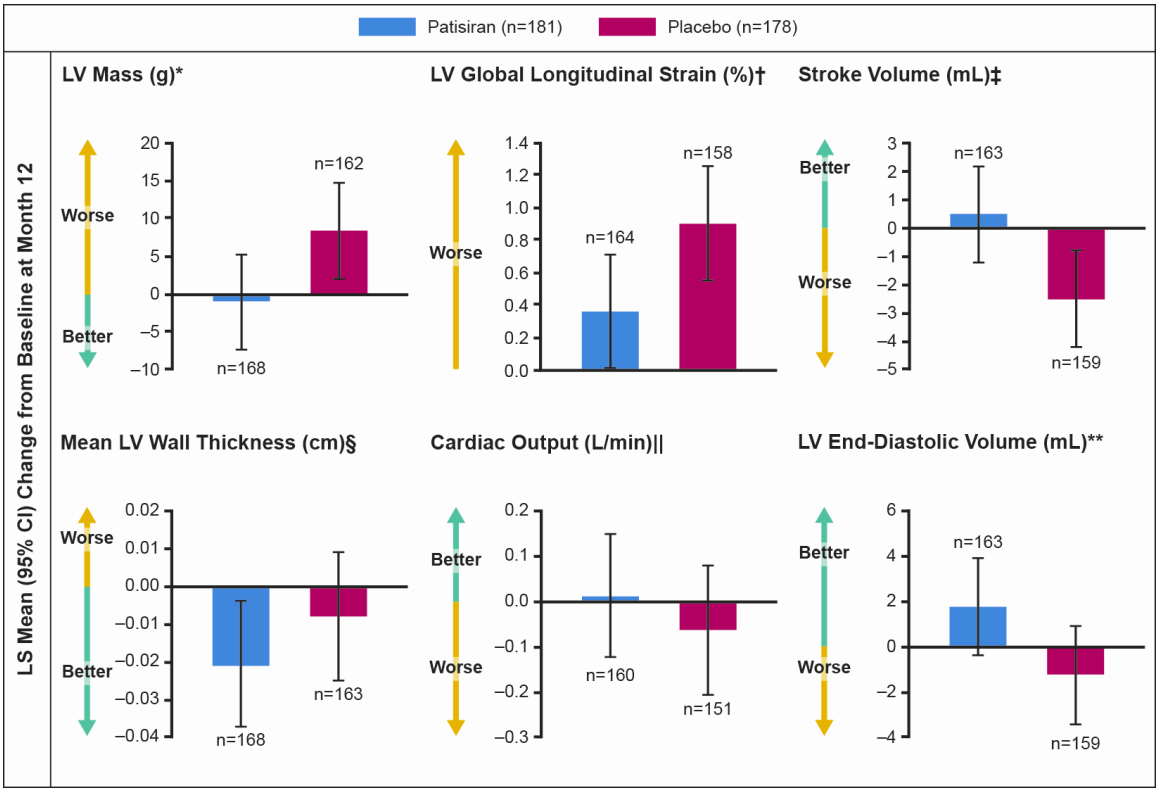
(A) H–L median difference in change from baseline to month 12 in 6-MWT between patisiran- and placebo-treated patients within subgroups. A further distance walked indicates better function. (B) LS mean difference from baseline to month 12 in KCCQ-OS between patisiran- and placebo-treated patients within subgroups. Lower KCCQ-OS values indicate worse quality of life. CI widths have not been adjusted for multiplicity and may not be used in place of hypothesis testing. Baseline 6-MWT, NT-proBNP, and region were not prespecified subgroups and have been included in the analysis to contextualize the results in terms of disease severity and global representation. 6-MWT, 6-minute walk test; ATTR, transthyretin-mediated; ATTRv, variant transthyretin; ATTRwt, wild-type ATTR; CI, confidence interval; H–L, Hodges–Lehmann; KCCQ-OS, Kansas City Cardiomyopathy Questionnaire Overall Summary; NT-proBNP, *N*-terminal prohormone B-type natriuretic peptide; NYHA, New York Heart Association; ROW, rest of world.

Figure S4. LS Mean Difference Between Patisiran and Placebo Treatment Groups in Change from Baseline to Month 12 in KCCQ Domains.



Lower KCCQ values indicate worse quality of life. CI widths have not been adjusted for multiplicity and may not be used in place of hypothesis testing. CI, confidence interval; KCCQ, Kansas City Cardiomyopathy Questionnaire; LS, least-squares.

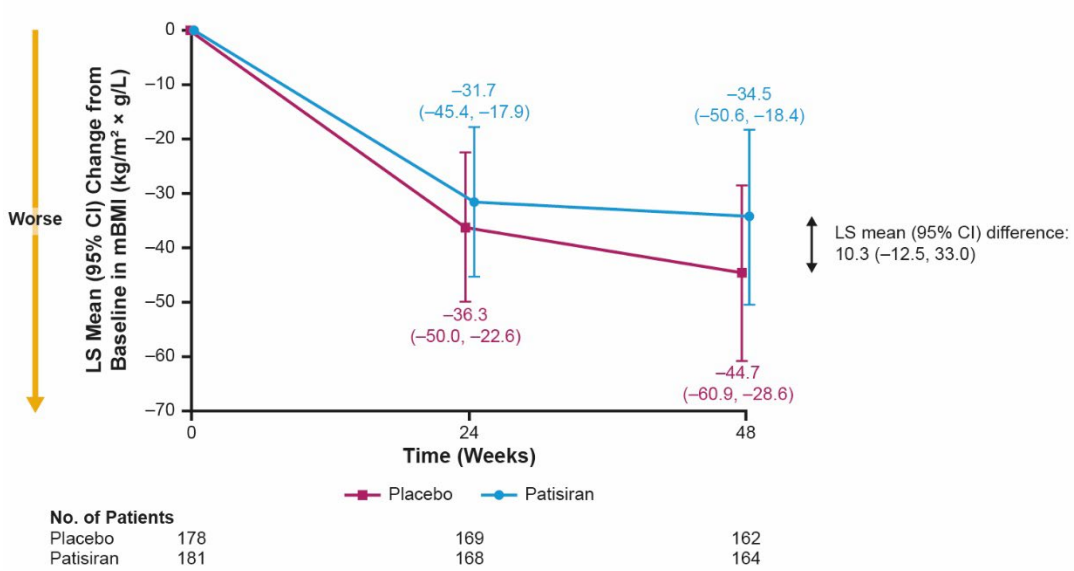
Figure S5. LS Mean Change from Baseline in Echocardiographic Parameters at Month 12 in Patisiran- and Placebo-treated Patients.



*All patients had a baseline LV mass measurement; 9% and 7% of patients in the placebo and patisiran groups, respectively, had missing measurements at month 12. †A decrease from baseline in LV longitudinal strain represents an improvement. In the placebo and patisiran groups, respectively, LV longitudinal strain measurements were missing at baseline in 3% and 1% of patients, and at month 12, in 10% and 9% of patients. ‡Stroke volume was calculated as LV end-diastolic volume – LV end-systolic volume. In the placebo and patisiran groups, respectively, stroke volume measurements were missing at baseline in 2% and 2% of patients, and at month 12, in 9% and 8% of patients. §All patients had a baseline LV wall thickness measurement; 8% and 7% of patients in the placebo and patisiran groups, respectively, had missing measurements at month 12. ||Cardiac output was calculated as heart rate × LV stroke volume. In the placebo and patisiran groups, respectively, cardiac output measurements were missing at baseline in 4% and 3% of patients, and at month 12, in 12% and 9% of patients. **An increase in the change from baseline in LV end-diastolic volume represents an improvement in patients with ATTR cardiomyopathy; i.e., in patients with ATTR

amyloidosis with restrictive cardiomyopathy, LV end-diastolic volume decreases as the LV wall thickens. In the placebo and patisiran groups, respectively, LV end-diastolic volume measurements were missing at baseline in 2% and 2% of patients, and at month 12, in 9% and 8% of patients. CI widths have not been adjusted for multiplicity and may not be used in place of hypothesis testing. ATTR, transthyretin-mediated; CI, confidence interval; LS, least-squares; LV, left ventricular.

Figure S6. LS Mean Change from Baseline in mBMI* over 48 Weeks



Higher mBMI values indicate better nutritional status. LS means were estimated from the MMRM analysis. CI widths have not been adjusted for multiplicity and may not be used in place of hypothesis testing. At baseline, the median (IQR) values were 1147.0 kg/m^2 × g/L (988.4 to 1273.8) for the patisiran group and 1134.0 (1018.7 to 1259.1) for the placebo group. All patients had a baseline mBMI measurement; 9% of patients each in the placebo and patisiran groups had missing measurements at week 48. *mBMI was calculated as BMI (weight in kilograms divided by square of height in meters) × albumin level in grams per liter. BMI, body mass index, CI, confidence interval; IQR, interquartile range; LS, least-squares; mBMI, modified BMI; MMRM, mixed-effects model repeated measures.

SUPPLEMENTARY TABLES

Table S1. Baseline Echocardiographic Parameters

	Patisiran (n=181)	Placebo (n=178)
LV ejection fraction, %, median (IQR)	58.0 (46.0 to 66.4)	60.3 (45.5 to 65.4)
LV global longitudinal strain, %, median (IQR)	–10.7 (–13.2 to –8.5)	–10.9 (–13.0 to –9.4)
Stroke volume, ml, median (IQR)	47.0 (38.2 to 57.8)	50.7 (39.7 to 60.9)
Cardiac output, l/min, median (IQR)	3.3 (2.7 to 4.0)	3.5 (2.8 to 4.2)
LV end-diastolic volume, ml, median (IQR)	89.9 (71.3 to 104.7)	91.1 (70.9 to 110.0)
Mean LV wall thickness, cm, median (IQR)	1.8 (1.6 to 1.9)	1.8 (1.6 to 2.0)
LV mass, g, median (IQR)	332.5 (275.7 to 391.5)	325.1 (270.3 to 371.1)

IQR, interquartile range; LV, left ventricular.

Table S2. Representativeness of Study Participants

Category	Description
Disease, problem, or condition under investigation	ATTR cardiac amyloidosis (Inclusive of both variant and wild-type forms)
Special consideration related to:	
Sex and gender	• A higher prevalence (69 to 94%) of ATTR cardiac amyloidosis occurs in men compared with women, with a male prevalence of 81 to 97% reported for wild-type ATTR cardiac amyloidosis and 69 to 76% reported for variant ATTR cardiac amyloidosis[2-5]
Age	• Most cases of ATTR cardiac amyloidosis occur in patients greater than 65 years of age[6] • Observational studies have reported a higher age at diagnosis in patients with wild-type ATTR cardiac amyloidosis (75 to 79 years) versus patients with non-V122I variant ATTR cardiac amyloidosis (67 years) with this age varying between 70 and 77 years for patients with the V122I variant[2,5,7] • The onset of disease has also been reported to be higher in patients with wild-type ATTR cardiac amyloidosis (>60 years) compared with variant ATTR cardiac amyloidosis (>45 to >65 years depending on the variant type)[8]
Race or ethnic group	• In the global ATTR-ACT clinical trial, the majority of enrolled patients with ATTR cardiac amyloidosis were White (81%) with 14% and 4% of patients being Black and Asian, respectively[9] • In patients with wild-type ATTR cardiac amyloidosis enrolled in the THAOS registry, 3% of patients were of African descent[10] • In patients with variant ATTR amyloidosis enrolled in the THAOS registry, who have cardiac variants (V122I, T60A, I68L), 48% of patients were of African descent[10] • The TTR V122I variant, associated with cardiomyopathy, is more prevalent in people with African ancestry, with ~4% of African Americans and up to 5% of West Africans carrying the variant.[9] In patients with V122I ATTR cardiac amyloidosis enrolled in registries, 87% to 100% were African American[4,7] • Other common TTR variants (e.g., V30M) that are present in patients with ATTR amyloidosis with both polyneuropathy and cardiomyopathy occur in people of White and Hispanic/Latin American ethnicity[11]

Geography	• In the THAOS registry, most North American and European patients with a predominant cardiac phenotype had wild-type ATTR amyloidosis[10] • The TTR V122I variant is the most common variant in the US[11] • The TTR V30M variant is endemic in Portugal, Sweden, Brazil, and Japan[11]
Other considerations	• Data are limited for wild-type ATTR amyloidosis, which is underdiagnosed. Based on the increased aging of the global population and growing awareness of the disease and developments in diagnostic techniques (e.g. scintigraphy), wild-type ATTR amyloidosis is more common than variant ATTR amyloidosis and likely to become more so[12]
Overall representativeness of this trial	• As observed in ATTR cardiac amyloidosis populations, a high proportion of patients in the APOLLO-B study were male (patisiran group 89%; placebo group, 90%) • In line with the higher disease prevalence in the elderly population, the median ages (range) of the patisiran group and placebo group were 76 years (47 to 85) and 76 years (41 to 85), respectively • The majority of patients were White (patisiran 76%; placebo 79%), with the rest of patients being Asian (patisiran 13%; placebo 8%), Black/African American (patisiran 9%; placebo 8%), or Other/not reported (patisiran 2%; placebo 4%). In the patisiran group, 12% of patients were of Hispanic/Latin American ethnicity compared with 11% in the placebo group • Study inclusion criteria required patients to have any variant ATTR cardiac amyloidosis or wild-type ATTR cardiac amyloidosis. The enrolled population comprised 80% of patients with wild-type ATTR cardiac amyloidosis and 20% patients with variant ATTR cardiac amyloidosis who had a wide range of 16 TTR variants, with the most common variants being V122I (41%), T60A (17%), and A97S (14%)

The data regarding ATTR amyloidosis epidemiology and demographics were synthesized from reports of real-world studies, observational studies, and clinical trials. A literature search was conducted using PubMed and concatenation of key terms of: 'ATTR amyloidosis', 'epidemiology', 'statistics', and 'global'. Specific references cited to support the epidemiologic observations noted are listed in the references section (at the end of this document).

ATTR, transthyretin-mediated; TTR, transthyretin.

Table S3. TTR Variants among Patients with ATTRv Amyloidosis Enrolled in APOLLO-B.

Genotype, n (%)	Placebo (n=34)	Patisiran (n=37)	Total (N=71)
V122I	12 (35)	17 (46)	29 (41)
T60A	6 (18)	6 (16)	12 (17)
A97S	3 (9)	7 (19)	10 (14)
I68L	3 (9)	1 (3)	4 (6)
S50R	2 (6)	1 (3)	3 (4)
V30M	1 (3)	1 (3)	2 (3)
E89Q	0	2 (5)	2 (3)
A19D	1 (3)	0	1 (1)
A45S	0	1 (3)	1 (1)
D38A	1 (3)	0	1 (1)
D38G	0	1 (3)	1 (1)
E92K	1 (3)	0	1 (1)
I73V	1 (3)	0	1 (1)
T59K	1 (3)	0	1 (1)
V122A	1 (3)	0	1 (1)
V122L	1 (3)	0	1 (1)

ATTRv, variant transthyretin; TTR, transthyretin.

Table S4. Baseline Disease Characteristics of Patients with ATTRv Amyloidosis with a Mixed Phenotype* of Cardiomyopathy and Polyneuropathy Enrolled in APOLLO-B.

Baseline Characteristics	Patisiran (n=34)	Placebo (n=31)
Age at screening, years, median (range)	70 (47 to 85)	66 (41 to 85)
Male sex, n (%)	20 (59)	24 (77)
V122I, n (%)	17 (50)	11 (35)
Baseline tafamidis use, n (%)	4 (12)	5 (16)
NYHA class, n (%)		
I	1 (3)	4 (13)
II	31 (91)	25 (81)
III	2 (6)	2 (6)
ATTR amyloidosis stage,[13] n (%)		
1	21 (62)	20 (65)
2	10 (29)	9 (29)
3	3 (9)	2 (6)
6-MWT, m, mean (SD)	319.6 (89.6)	377.1 (107.2)
KCCQ-OS, mean (SD)	58.6 (21.6)	67.7 (22.1)
NT-proBNP, pg/ml, mean (SD)	2550.9 (2072.7)	2810.8 (2649.5)
PND score, n (%)		
0	6 (18)	10 (32)
I	19 (56)	17 (55)
II	9 (26)	4 (13)

*Mixed-phenotype patients in this analysis had ATTRv amyloidosis **AND** one of the following without a known cause of polyneuropathy unrelated to ATTRv amyloidosis: 1) a history of polyneuropathy, 2) PND score at least I, 3) Norfolk QOL-DN score at least 30, or 4) plasma neurofilament light chain level greater than the upper limit of the age-based reference value established by Mayo Clinic laboratories. 6-MWT, 6-minute walk test; ATTR, transthyretin-mediated; ATTRv, variant transthyretin; KCCQ-OS, Kansas City Cardiomyopathy Questionnaire Overall Summary; NT-proBNP, *N*-terminal prohormone B-type natriuretic peptide; Norfolk QOL-DN, Norfolk Quality of Life-Diabetic Neuropathy;

NYHA, New York Heart Association; PND, polyneuropathy disability; SD, standard deviation.

Table S5. Concomitant Cardiac Medications Used During the 12-Month Double-Blind Treatment Period.

Medication, n (%)	Patisiran (n=181)	Placebo (n=178)
Diuretics		
High-ceiling diuretics*	166 (92)	158 (89)
Low-ceiling diuretics, thiazides†	18 (10)	17 (10)
Low-ceiling diuretics, excluding thiazides‡	11 (6)	17 (10)
Diuretics and potassium-sparing agents in combination	3 (2)	3 (2)
Other diuretics	1 (1)	3 (2)
Antithrombotic agents	150 (83)	154 (87)
Lipid-modifying agents		
In combination	105 (58)	110 (62)
Monotherapy	0	5 (3)
Potassium-sparing agents	109 (60)	97 (54)
Beta blocking agents	78 (43)	91 (51)
ACE inhibitors		
Monotherapy	35 (19)	49 (28)
In combination	1 (1)	1 (1)
ARBs		
Monotherapy	41 (23)	16 (9)
In combination	12 (7)	12 (7)
Antiarrhythmics, class I and III	39 (22)	43 (24)
Vasodilators used in cardiac diseases	19 (10)	20 (11)
Selective CCBs		
With mainly vascular effects	9 (5)	16 (9)
With direct cardiac effects	2 (1)	2 (1)
Cardiac glycosides	6 (3)	5 (3)

*High-ceiling diuretics include azosemide, bumetanide, furosemide, and torasemide. †Low-ceiling diuretics, thiazides include bendroflumethiazide, benzylhydrochlorothiazide, hydrochlorothiazide, and trichlormethiazide. ‡Low-ceiling diuretics, excluding thiazides

include chlortalidone, indapamide, and metolazone. ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; CCB, calcium channel blocker.

Table S6. Sensitivity Analyses for 6-MWT.

Pre-planned Analysis	Analysis Method	Intercurrent Events and Missing Data Handling	Treatment Difference (95% CI)
Primary analysis	Stratified Wilcoxon rank-sum test for p-value HL estimate for median difference	• Assessments obtained after Covid-19 SAE treated as missing • Missing data due to death or inability to walk* imputed with worst 10th percentile change • Other missing data assumed MAR	14.7 (0.7, 28.7)
Sensitivity 1		• Same as primary analysis except assessments obtained after Covid-19 SAE not treated as missing	14.1 (0.3, 27.9)
Sensitivity 2		• Same as primary analysis except assuming MNAR for off-treatment patisiran patients (missing data assumed to follow placebo trajectory using copy reference approach)	14.5 (0.4, 28.5)
Sensitivity 3†	MMRM	• Same as primary analysis	18.1 (2.5, 33.8)

A further distance walked indicates better function. *Deaths (not due to Covid-19) and patients who were unable to walk due to progression of ATTR amyloidosis. †6-MWT data for two patisiran patients were updated for this analysis following database lock, as updated by the Investigator. 6-MWT, 6-minute walk test; CI, confidence interval; Covid-19, coronavirus disease 2019; HL, Hodges–Lehmann; MAR, missing at random; MMRM, mixed-effects model repeated measures; MNAR, missing not at random; SAE, serious adverse event.

Table S7. Post hoc Analysis for 6-MWT in Patients Without Impairment of Walking by Neuropathy (PND score 0) at Baseline

	Patisiran (n=96)	Placebo (n=109)
Baseline, m, median (IQR)	363.42 (304.18, 425.40)	377.10 (307.72, 443.35)
Change from baseline at month 12,*† m, median (95% CI)	–5.48 (–15.48, 13.25)	–17.20 (–36.60, –4.35)
H–L median difference for change from baseline at month 12 (patisiran vs placebo),*‡ m, (95% CI)	20.02 (2.41, 37.63)	

A further distance walked indicates better function. *Missing assessments due to non-Covid-19 death or inability to walk due to ATTR amyloidosis disease progression were imputed as the worst 10th percentile change observed across all patients in the DB period. Other missing data (including assessments obtained after a serious Covid-19 adverse event which were treated as missing) were multiply imputed assuming data were missing at random (see SAP for details). Missing data were imputed 100 times to create 100 complete data sets. †For each patient, the change from baseline is averaged across the 100 complete data sets. ‡The stratified H–L estimate was generated for each of the 100 complete data sets, and the results were combined using Rubin's rules. 6-MWT, 6-minute walk test; CI, confidence interval; H-L, Hodges–Lehmann; IQR, interquartile range; PND, polyneuropathy disability.

Table S8. Secondary Composite Outcome End Points over 12 Months.

	Patisiran	Placebo
Composite of death from any cause, frequency of CV events,* and change from baseline in 6-MWT over 12 months†		
Stratified win ratio (95% CI) for patisiran vs. placebo‡	1.27 (0.99, 1.61)	
Composite of death from any cause and frequency of hospitalizations for any cause and urgent visits for HF in patients not on tafamidis at baseline†		
Number of patients	135	133
Total number of events, n	57	55
Death from any cause	3	7
Hospitalizations for any cause	50	47
Urgent visits for HF	4	1
HR (95% CI) for patisiran vs. placebo§‖	0.997 (0.62, 1.60)	
Incidence rate ratio (patisiran/placebo)§**	0.97 (0.58, 1.63)	
Composite of death from any cause and frequency of hospitalizations for any cause and urgent visits for HF in the overall population†		
Number of patients	181	178
Total number of events, n	73	79
Death from any cause	4	10
Hospitalizations for any cause	65	65
Urgent visits for HF	4	4
HR (95% CI) for patisiran vs. placebo§‖	0.88 (0.58, 1.34)	
Incidence rate ratio (patisiran/placebo)§**	0.87 (0.55, 1.36)	

*CV events were defined as CV hospitalizations and urgent visits for HF. †Deaths, hospitalizations, and urgent visits for HF due to Covid-19 were not treated as events in the analysis, in accordance with the pre-defined statistical analysis plan. Patients who underwent heart transplantation and/or ventricular assist device placement after randomization were handled in the same manner as death in the analysis. ‡The first composite end point was analyzed using a generalized rank-based win ratio method stratified by baseline tafamidis use (yes vs. no), which made within-stratum pairwise comparisons for all possible patisiran–placebo patient pairs in a sequential manner (first mortality, then CV events, then 6-MWT). The point estimate and 95% CI for the stratified win ratio were based on Dong et al. 2018.[1] §Patients who died due to Covid-19 (1 patisiran patient) were censored at the date of death, and cardiac transplants were handled in the same manner as death (two placebo patients). ||The hazard ratio and 95% CI were derived using an Andersen–Gill model, including treatment arm, type of ATTR amyloidosis, baseline NYHA class, and age group as covariates. For the analysis in the overall population, the model was also stratified by baseline tafamidis use. A hazard ratio less than 1 represents a favorable outcome for patisiran. **The incidence rate ratio and 95% CI were derived using a negative binomial model, including treatment arm, type of ATTR amyloidosis, baseline NYHA class, and age group as covariates. For the analysis in the overall population, the model also included baseline tafamidis use

and the treatment-by-baseline tafamidis use interaction as covariates. An incidence rate ratio less than 1 represents a favorable outcome for patisiran. CI widths have not been adjusted for multiplicity and may not be used in place of hypothesis testing. 6-MWT, 6-minute walk test; ATTR, transthyretin-mediated; CI, confidence interval; CV, cardiovascular; HF, heart failure; HR, hazard ratio; NYHA, New York Heart Association.

Table S9. Serious Adverse Events Reported During the 12-Month Double-Blind Treatment Period

Event, n (%)	Patisiran (n=181)	Placebo (n=178)
Any serious adverse event	61 (34)	63 (35)
Blood and lymphatic system disorders	2 (1)	0
Anemia	1 (1)	0
Blood loss anemia	1 (1)	0
Cardiac disorders	32 (18)	28 (16)
Acute myocardial infarction	0	2 (1)
Angina unstable	0	1 (1)
Atrial fibrillation	5 (3)	4 (2)
Atrial flutter	2 (1)	0
Atrioventricular block	1 (1)	0
Atrioventricular block complete	2 (1)	4 (2)
Atrioventricular block first degree	1 (1)	0
Atrioventricular block second degree	0	2 (1)
Bradycardia	2 (1)	0
Cardiac amyloidosis	1 (1)	0
Cardiac arrest	1 (1)	0
Cardiac failure	15 (8)	13 (7)
Cardiac failure acute	1 (1)	2 (1)
Cardiac failure congestive	1 (1)	1 (1)
Chronotropic incompetence	1 (1)	0
Conduction disorder	0	1 (1)
Coronary artery disease	0	3 (2)
Hypertensive heart disease	0	1 (1)
Myocardial infarction	1 (1)	0
Pericarditis	0	1 (1)
Sinus node dysfunction	0	1 (1)

Supraventricular tachycardia	1 (1)	0
Tachyarrhythmia	1 (1)	0
Ventricular fibrillation	0	1 (1)
Ventricular tachycardia	1 (1)	0
Gastrointestinal disorders	8 (4)	4 (2)
Abdominal pain upper	1 (1)	0
Colitis ulcerative	0	1 (1)
Enteritis	0	1 (1)
Functional gastrointestinal disorder	0	1 (1)
Gastric ulcer	1 (1)	0
Gastritis erosive	1 (1)	0
Gastrointestinal hemorrhage	1 (1)	1 (1)
Hemorrhoids	1 (1)	0
Ileus paralytic	1 (1)	0
Impaired gastric emptying	1 (1)	0
Incarcerated umbilical hernia	1 (1)	0
Large intestine polyp	0	1 (1)
Pancreatitis	1 (1)	0
Small intestinal obstruction	2 (1)	0
Upper gastrointestinal hemorrhage	1 (1)	0
General disorders and administration site conditions	1 (1)	7 (4)
Asthenia	0	1 (1)
Chest discomfort	0	1 (1)
Chest pain	0	3 (2)
Infusion site phlebitis	1 (1)	0
Pyrexia	0	1 (1)
Vessel puncture site hematoma	0	1 (1)
Hepatobiliary disorders	1 (1)	1 (1)
Cholangitis	0	1 (1)

Cholecystitis	1 (1)	0
Immune system disorders	1 (1)	5 (3)
Amyloidosis	1 (1)	4 (2)
Drug hypersensitivity	0	1 (1)
Infections and infestations	8 (4)	15 (8)
Appendicitis	0	1 (1)
Bacterial sepsis	1 (1)	0
Coronavirus disease 2019	2 (1)	3 (2)
Cellulitis	0	2 (1)
Dengue fever	0	1 (1)
Diverticulitis	0	2 (1)
Erysipelas	2 (1)	0
Gastroenteritis	0	1 (1)
Infected bite	0	1 (1)
Ophthalmic herpes zoster	0	1 (1)
Pneumonia	1 (1)	3 (2)
Sepsis	1 (1)	0
Urinary tract infection	1 (1)	2 (1)
Urosepsis	2 (1)	0
Injury, poisoning and procedural complications	7 (4)	6 (3)
Contusion	1 (1)	0
Fall	1 (1)	2 (1)
Foot fracture	1 (1)	0
Head injury	1 (1)	1 (1)
Post procedural hemorrhage	0	1 (1)
Road traffic accident	2 (1)	0
Skull fracture	1 (1)	0
Subdural hemorrhage	1 (1)	0
Urinary retention postoperative	0	1 (1)

Vascular pseudoaneurysm	1 (1)	1 (1)
Investigations	2 (1)	2 (1)
Blood ethanol increased	0	1 (1)
Heart rate irregular	0	1 (1)
Hepatic enzyme increased	1 (1)	0
Troponin I increased	1 (1)	0
Metabolism and nutrition disorders	0	2 (1)
Dehydration	0	1 (1)
Hypokalemia	0	1 (1)
Musculoskeletal and connective tissue disorders	4 (2)	4 (2)
Arthralgia	0	1 (1)
Arthropathy	1 (1)	0
Lumbar spinal stenosis	2 (1)	0
Osteoarthritis	1 (1)	3 (2)
Rhabdomyolysis	1 (1)	0
Neoplasms benign, malignant, and unspecified (including cysts and polyps)	2 (1)	3 (2)
Hepatocellular carcinoma	0	1 (1)
Lip squamous cell carcinoma	0	1 (1)
Pancreatic carcinoma metastatic	0	1 (1)
Rectosigmoid cancer	1 (1)	0
Squamous cell carcinoma	1 (1)	0
Nervous system disorders	7 (4)	7 (4)
Cerebral infarction	1 (1)	0
Cerebrovascular accident	1 (1)	1 (1)
Ischemic stroke	3 (2)	0
Seizure	0	1 (1)
Syncope	2 (1)	4 (2)
Transient ischemic attack	0	1 (1)
Renal and urinary disorders	3 (2)	2 (1)

Acute kidney injury	2 (1)	0
Chronic kidney disease	0	1 (1)
Cystitis hemorrhagic	1 (1)	0
Hematuria	0	1 (1)
Respiratory, thoracic, and mediastinal disorders	4 (2)	2 (1)
Chronic obstructive pulmonary disease	1 (1)	0
Dyspnea exertional	0	1 (1)
Pleural effusion	1 (1)	0
Pneumonia aspiration	0	1 (1)
Pneumothorax	1 (1)	0
Pulmonary embolism	1 (1)	0
Surgical and medical procedures	1 (1)	0
Hip arthroplasty	1 (1)	0

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