Supplementary Appendix

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

Supplement to: Bhatt DL, Steg PG, Miller M, et al. Cardiovascular risk reduction with icosapent ethyl for hypertriglyceridemia. N Engl J Med 2019;380:11-22. DOI: 10.1056/NEJMoa1812792

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Country listing by enrollment; N=number of participants randomized per country; (site number)

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Emily Ensminger, Hillary Garcia, (190) Dawn Robinson, Carolyn Tran, Jeffrey Jacqmein, Darlene Bartilucci, Michael Koren / Barbara Maluchnik, Melissa Parks, Jennifer Miller, (191) / Cynthia DeFosse, (192) Albert B. Knouse, Jr / Amy Delancey, (193) Stephanie Chin, Thomas Stephens / Mag Sohal, Juana Ingram, (194) Swarooparani Kumar / Heather Foley, Nina Smith, (196) / Vera McKinney, Linda Schwarz, Judith Moore, (197) H.V. Anderson, Stefano Sdringola-Maranga, Ali Denktas / Elizabeth Turrentine, Rhonda Patterson, (199) John Marshall / Terri Tolar, Donna Patrick, (203) / Pamela Schwartzkopf, (204) Anthony M. Fletcher, Frances R. Harris / Sherry Clements, Tiffany Brown, (205) William Smith / Stacey J. Baehl, Robin Fluty, (206) Daniel VanHamersveld, Dennis Breen, Nancy Bender / Beverly Stafford, Tamika Washington, (207) / Margaret N. Pike, (208) Mark A. Stich, / (209) Evyan Jawad, Amin Nadeem / Jill Nyland, (211) / Rhonda Hamer, Kendra Calhoun, Charlotte Mall, Samuel Cadogan, Kati Raynes, (212) Richard Katz / Lorraine Marshall, (213) Rashida Abbas, Jay L. Dinerman, John T. Hartley, III / Beth Lamb, Lisa Eskridge, Donna Raymond, (214) / Kristy Clemmer, (215) / Denise M. Fine, Paula Beardsley, (216) / Janet Werner, Bette Mahan, Courtney VanTol, (217) Robert Herman / Christine Raiser-Vignola, Felicia McShan, (220) Stefanie A. Neill, David R. Blick, Michael J. Liston / Denetta K. Nelson, Sandra K. Dorrell, Patricia Wyman, (221) Ambereen Quraishi, Fernando Ferro, Frank Morris / Vicki J. Coombs, Autumn M. Mains, Austin A. Campbell, Jeanne Phelps, Cheryl A. Geary, Ellen G. Sheridan, Jean M. Downing, (222) Arie Swatkowski, Tish Redden / Brian Dragutsky, Susan Thomas, Candace Mitchell, Diana Barker, Elanie Turcotte, Deborah Segerson, Jill Guy, (223) / Karena De La Mora, Jennifer Hong, Dennis Do, Rose Norris, (224) Faisal Khan / Hector Montero, (225) Stacy Kelly-White, Alan Cleland, Rosalyn Alcalde-Crawford, Melissa Morgan, Brijmohan Sarabu, Megan Minor / Shweta Kamat, Stephanie M. Estes, Nancee Harless, Alicia Disney, (226) / Jodi L. Pagano, (227) Chad M. Alford, Noel W. Bedwell, Warren D. Hardy, Kevin DeAndrade / Jessica G. Elmore, (228) Eric G. Auerbach, Anthony W. Haney / Miriam H. Brooks, (229) Jose Torres, Lois Roper, Terry Backer, Katie Backer / Lois Roper, (230) John G. Evans, James S. Magee, Ricardo A. Silva, Lorraine H. Dajani, Scott A. Segel / Veronica Yousif, Tammy Ross, Rebecca F. Goldfaden, (231) Sion K. Roy, Ronald Oudiz / Sajad Hamal, Ferdinand Flores, (233) / Amor Leahy, Debra Ayer, (234) Swapna George / Chrisi Carine Stewart, Elvira Orellana, (235) Cristina Boccalandro / Mary Rangel, (237) Suzanne Hennings, Carl Vanselow, Teri Victor, Darlene Birdwell, Paul Haas, Anthony Sandoval / Gina Ciavarella, Caroline Saglam, (239) / Amy Bird, (240) Keith Beck, Brian Poliquin, David Dominguez, Brittany Tenorio / Harvonya Perkins, Esther San Roman, (241) Paris Bransford, Christy Lowrance, Marcy Broussard / Mary Ellis, Bobbi Skiles, Jessica Hamilton, Kathryn Hall, Diego Olvera, (243) / Kathleen Maloney, (244) / Julee A. Hartwell, (246) / Nevien Sorial, (248) Kishlay Anand, Mary Rickman, Kevin Berman, Nirav Mehta / Annie Laborin, Caroline Saglam, (249) Rodger Rothenberger / Sarah Beauvilliers, (250) / Kathy Morrell, (251) Michael P. Schachter, Cindy L. Perkins, Elizabeth A. Gordon / Jennifer Lauer, Kim Bichsel, Kelly Oliver, (252) / Leslie J. Mellor, (253) Candice Demattia / Jennifer Schomburg, Yenniffer Moreno, Eduardo Mansur-Garza, (255) Lena Rippstein / Lorie Chacon, Andrea Pena, (256) Michelle King / Susan Richardson, Annette Jessop, Nicole Tucker, Whitney Royer, (257) Gilbert Templeton, Ann Moell, Christine Weller / Melissa J. Botts, Gretel Hollon, (258) / Elsa Homberg-Pinassi, (259) Paula Forest, Aref Bin Abhulhak / Devona Chun-Furlong, Deborah Harrington, Emily Harlynn, Marjorie Schmitt, Constance Shelsky, Patricia Feldick,

Mary Cherrico, (260) Courtney Jagle, Nicholas Warnecke, Debra Myer / Deanna J. Ruder, Albina Underwood, (261) Alan Rauba, George Carr / Barbara Oberhaus, Jessica Vanderfeltz, (263) Mary Jo Stucky-Heil, Dale R. Gibson / Vonnie Fuentes, (264) Kimberly L. Talbot, William C. Simon / Katlyn J. Grimes, Christina R. Wheeler, Cassaundra Shultz, Rhonda A. Metcalf, Jennifer L. Hill, Michelle R. Oliver, (265) / Basharat Ahmad, Fouzal Azeem, Abdul Rahim, (267) George H. Freeman, Dawn Bloch / Heather Freeman, (268) Jamie Brown / Sarah Rosbach, Pamela Melander, Nick Taralson, Alex Liu, Katlyn Harms, (269) Mahfouz Michale / Jose Lopez, (270) Maria Revoredo, / (272) / Shari Edevane, Sarah Shawley, (273) Timothy L. Jackson, Michael J. Oliver / Dina DeSalle, (274) Patricia J. Matlock, Ionna M. Beraun / Heather Hendrix, Garrett Bromley, Ashley Niemerski, Gabby Teran, Sonia Guerrero, Murtaza Marvi, Zehra Palanpurwala, Andrea Torres, Patty Gloyd, Michelle Conger, Andrea Pena, (275) Aziz Laurent / Olia Nayor, (277) Catalina S. Villanueva, (278) Munira Khambati / Tabetha J. Mumford, Melanie J. Castillo, (279) Taddese Desta, Jerome Robinson / La Shawn Woods, Anita H. Bahri, Nancy Herrera, (280) Cecilia Casaclang, Jeffrey R. Unger, Geraldine Martinez, Mia K. Moon, Stephen M. Mohaupt / Larry Sandoval, Louisito Valenzuela, Victora Ramirez, Nelly Mata, Veronica Avila, Marisol Patino, Cynthia Montano-Pereira, Omar Barnett, (281) William M. Webster / Lorraine M. Christensen, Leighna Bofman, Melanie Livingston, Stacey Adams, (283) Joseph Hobbs / Stacey Adams, Leesa Koskela, Mia Katz, (284) Samuel Mujica-Trenche / Franklin Cala, Noreen T. Rana, Jennifer Scarlett, Milagros Cala Anaya, (285) / Marsha R. Jones, Kelly D. Hollis, Debbie Roth, Kristin Eads, Tina Watts, (287) / Judy Perkins, (289) / Alice Arnold, (290) Daniel C. Ginsberg / Denise Quinn, (291) / Nicole Cureton, (292) David B. Fittingoff, Mohammed I. Iqbal, Stephen R. White / Edith Sisneros, Michelle Ducca, David Streja, Danny Campos, (293) / Jennifer L. Boak, (295) / Farzeen Amir, (296) / Felice Anderson, (297) James J. Kmetzo / Mary O. Bongarzone, Dawn Scott, (298) / Mary Grace De Leon, (299) / Cynthia Buda, (350) William Graettinger, Michelle Alex, William Graettinger, / (353) Erika Hess, James Govoni / Melissa Bartel, (356) Travis L. Monchamp / Julie S. Roach, Sara Gibson, (357) / Amy M. Allfrey, Kristen Timpy, Kathy Bott, Karin A. Soucy, (358) / Jean Willis, (359) / Cecilia A. Valerio, Anusha Chunduri, (360) / Rebecca Coker, Nicole Vidrine, (362) Ellen A. Thompson, Mark A. Studeny / Melissa K. Marcum, Tammy S. Monway, (363) Douglas L. Kosmicki / Melissa J. Kelley, Corey M. Godfrey, Susan L. Krenk, Randy R. Holcomb, Deb K. Baehr, Mary K. Trauernicht, (364) David Rowland Lowry, Betty Bondy Herts, Jeanne E Phelps, Jean-Marie Downing, Carol Gamer Dignon, (365) / Elisabeth S. Cockrill, (367) Pravinchandra G. Chapla / Diane Fera, (368) Margaret Chang, Patricia Fredette / Tamie Ashby, Renee Bergin, (370) Zebediah A. Stearns, David B. Ware / Rachael M. Boudreaux, (371) Francisco G. Miranda / Joanna Rodriguez, (373) Robert McKenzie, Amanda Huber, Rebecca Sommers, Heather Rowe, Stacy McLallen, Michale Haynes / Ashley Adamson, Janice Henderson, Lori McClure, (374) / Beverly A. Harris, (375) / Laura Ference, Sue Meissner-Dengler, (376) / Lisa Treasure, Doreen Nicely, (377) Timothy L. Light / Tracey A. Osborn, Kimberly J. Mai, (379) Pablo Vivas, Jose Rios / Dunia Rodriguez, (380) Roger DeRaad, James Walder, Oscar Bailon / Denice Hockett, Debbie Anderson, Kelli McIntosh, Amber Odegard, Andrew Shepherd, Mary Seifert, (381) Laurence Kelley, Rajendra Shetty, Michael Castine, David Brill, Gregory Fisher / Nicole Richmond, Kathleen Gray, Patricia Miller, (383) / Charlene Coneys, (384) / Yarixa Chanza, Monica Sumoza, (386) Victoria M. Caudill, Kelly D. Harris, Courtney A. Manion / Melody J.

Lineberger-Moore, Julie J. Wolfe, Barbara J. Rosen, (387) / Patricia DiVito, (388) / Janet L. Moffat, (389) Christina Michaelis, Prashant Koshy / Diana Perea, Ghaith Al Yacoub, Stephanie Sadeghi, (393) Thomas D. LeGalley, Rudolph F. Evonich, William J. Jean, Gary M. Friesen, John M. Pap, David A. Pesola, Mark D. Cowan, Kristofer M. Dosh / Dianna Larson, Adele M. Price, Jodi A. Nease, Jane E. Anderson, Lori A. Piggott, (394) Robert Iwaoka, Kevin Sharkey, Edward McMillan / Laurie Lowder, Latisha Morgan, Kyle Davis, Tara Caldwell, Erica Breglio, Jasmine Summers, Rachel Poulimas, (396) / Muhammad Zahid, Hamid Syed, Maria Escobar, Jacob Levy, Rahma Warsi, (398) Carol Ma, Puxiao Cen / Kimberly A. Cawthon, Delores B. Barnes, Deanna G. Allen, Margaret L. Warrington, Carol R. Stastny, Robin J. Michaels, (399) / Mohamad Saleh, (653) John Sorin / Sunny Rathod, Urakay Juett, (654) Steven Spencer, Aziza Keval, Jill McBride, Shane Young, Catherine Baxter, Carol Rasmussen, Shari L. Coxe / (655) Luis Campos, Shahin Tavackoli / Diana Beckham, Darlynee Sanchez, (656) Karanjit Basrai / Dorian Helms, Erica Clinton, Kasie Smith, (657) Arnold Ghitis, Henry Cusnir / Mary Klaus Clark, (661) Madhavagopal V. Cherukuri / Ameta Scarfaru, (662) Stephen D. Nash / Jeannine Moore, Helene Wallace, (663) Loretta C. Grimm, / (664) / Anna Grace, Kylie McElheran, (665) / Dino Subasic, (668) / Zedrick Buhay, (669) / Janet Litvinoff, Tamika Washington, (670) Deepak Shah / Shannon Cervantes, Freda Usher, (671) Farra Yasser, Theodore Trusevich, Ronnie L. Garcia, Jamison Wyatt, Rahul Bose / Holllilyn Miska, Traci Spivey, (672) Amy B. Wren, Katie E. Vance / Lani L. Holman, Pam Gibbons, (678) / Elaine Eby, Sandra Shepard, (679) Soratree Charoenthongtrakul, (680) / Brett Snodgrass, Mohammed Nazem, Shelly Keteenburg, Prathima Murthy, (681) Frederic Prater / Ashley Rumfelt, (683) / Christina Eizensmits, (685) / Lisa Iannuzzi, (686) / Pourus R. Patel, (687) / Clellia Bergamino, Elizabeth McFeaters, (688) Botros Rizk, Emiljia Pflaum / Danny Kalish, (690) / Rex Ambatali, Mona Ameli, Delaina Sanguinetti / Mona Ameli, (691) Rakesh Vaidya / Karen Blinson, Lynda Doomy, Vickie Wayne

<u>The Netherlands</u> N=1678 ***WCN*** (701) Rob J. Bos, Alexandra Wils / Tamara Jacobs, (702) Erik A. Badings / Lillian A. Ebels-Tuinbeek, Mayke L. Scholten, (703) / Esther Bayraktar-Verver, Debby Zweers, Manoek Schiks, Carolien Kalkman, (704) / Tineke Tiemes, Jeanette Mulderij, (705) W Hermans / K Dabrowska, W Wijnakker, R Vd Loo, J DeGraauw, (706) / Giny Reijnierse, (707) / Mirjam van der Zeijst, (708) / Mariska Scholten, (709) / Henk R. Hofmeijer, Antoinette van Dijk-van der Zanden, (719) / Dineke J. van Belle, (720) Jan Van Es / Gera Van Buchem, Wendy Zijda, Harald Verheij, Linnea Oldenhof-Janssen, Martina Bader, Marije Löwik, (721) / Sandra Stuij, (722) Pascal Vantrimpont / Krista van Aken, Karen Hamilton, (723) Arno van der Weerdt / Han Blömer, Gabriela van Laerhoven, (724) Raymond Tukkie, Maarten Janssen, Gerard Verdel, Jon Funke Küpper, Bob van Vlies / Caroline Kalkman, Joke Vooges, Marinella Vermaas, (725) / Jeanne de Graauw, Riny Van de Loo, Rachel Langenberg, (726) Niek Haenen, Frans Smeets, Arko Scheepmaker, Marcel Grosfeld / Ilvy Van Lieshout, Marleen van den Berg, (727) / Marian Wittekoek, (728) / Petra Mol, Antionette Stapel, (729) M. Sierevogel / N vd Ven, A. Berkelmans, (731) Eric Viergever / Hanneke Kramer, Wilma Engelen, Karen V. Houwelingen, (732) Thierry X. Wildbergh, Arend Mosterd / Coriet Hobé-Rap, Marjan van Doorn, Petra Bunschoten, (733) Michel Freericks, Mireille Emans / Petra Den Boer-Penning, Els Verlek, Christine Freericks, (734) Cornelis de Nooijer / Christina Welten, Ingrid Groenenberg, (735) / C van der Horst, E Vonk, (736) Geert Tjeerdsma, Gerard M. Jochemsen /

Corinne van Daalen, (737) / Ingrid Y. Danse, (738) / Lucy Kuipers, Anke Pieterse, (739) Antonius Oomen, Daan de Waard, Willem Jan Flu, Zusan Kromhout / Petra Van der Bij, (740) Rob Feld / Brigitta Hessels-Linnemeijer, Rob Lardinois, (741) Jan L. Posma / Zwanette R. Aukema-Wouda, Marjolijn Hendriks-van Woerden, (742) / Desiree van Wijk, (743) Driek P. Beelen / Ingrid H. Hendriks; ***non-WCN*** (710) Jan J. Jonker, Stefanie Schipperen, Vicdan Köse, Gloria Rojas / Linda Goedhart, Hanneke van Meurs, Rachel Langenberg, Jacqueline Rijssemus, (711) Jacqueline Hoogendijk, Lindy Swinkels-Diepenmaat, Wouter van Kempen / Marloes de Louw-Jansen, Dominique Bierens-Peters, (712) Willem W. van Kempen, Marianne E. Wittekoek, Irmaina Agous / Geert Schenk, (713) Willem W. van Kempen, Janneke Wittekoek, Kevin Cox, Deborah F. Julia, Jan JC Jonker / Roel Janssen, (714) Willem W. van Kempen, Marianne E. Wittekoek, Melchor Nierman, Hilligje Katerberg, Jan JC Jonker / Irene van der Haar, (715) Willem W. Van Kempen, Taco van Mesdag, Janneke Wittekoek, Jan JC Jonker, Leyda M. Alvarez Costa / Manon Schensema, (716) Salomé Zweekhorst, Lindy Swinkels-Diepenmaat, Stefanie Schipperen, Willem W. van Kempen, Deborah Font Julia, Jan JC Jonker, Lauri Hanewinckel / Joyce Olsthoorn, (718) Johan C. Berends, Arie C. van der Spek, Roy van der Berg, Rob J. Timmermann / Ingrid Boerema

<u>Ukraine</u> N=836 (885) Iryna Mudruk, Anna Khrystoforova, / (886) Serhii Kyselov, / (887) Yaroslava V. Hilova, / (888) Pavlo Logoida / Pavlo Logoida, (889) Nataliia A. Sanina, / (890) Ilona P. Golikova, Olena O. Nemchyna / Ilona P. Golikova, Ilona P. Golikova, (891) Ivan I. Isaichikov, Olga B. Potapova / Iurii V. Gura, (892) Larysa Berestetska, / (893) Olena O. Kulianda, / (895) Oleksandr Tantsura, / (897) Oleksandr S. Kulbachuk, / (898) Volodymyr Petsentiy, Ihor Biskub / Ihor Biskub, (899) Tetyana Handych, (900) Oleg Lagkuti, Alyna Gagarina, / (937) Taras Chendey, / (938) Oksana F. Bilonko, / (939) Olena Matova, Larysa Bezrodna, Olena Yarynkina, Tetiana Ovdiienko, Volodymyr Randchenko, Maryna Mospan / Tetiana Ovdiienko, (940) Olena Butko, Olga Romanenko, / (941) Mykhailo Pavelko, Iryna Sichkaruk, / (942) Svitlana O. Lazareva, Olena A. Kudryk / Inessa M. Koltsun, Inessa M. Koltsun, (943) Tetiana Magdalits, / (944) Sergei Zadorozhniy, Kira Kompaniiets, / (945) Andrii Ivanov, Sergiy Romanenko, Pavlo Kaplan, / (946) Vadym Y. Romanov, / (947) Oksana P. Mykytyuk / Nataliia S. Zaitseva, (948) Sergiy N. Pyvovar, / (949) Lyudmyla Burdeuna, / (951) Emerita Serdobinska, / (952) Tatiana I. Shevchenko, Igor I. Ivanytskyi / Igor I. Ivanytskyi, Igor I. Ivanytskyi, (953) / Olena V. Khyzhnyak, (954) Ganna Smirnova, Nataliya Kalinkina, Olena Keting, Olena Sklyanna, Olga Kashanska, Anna Shevelok, Marina Khristichenko, / (955) Ievgenii Y. Titov, Danilenko O. Oleksander / Nataliia S. Polenova, (956) Nataliia Altunina, / (957) Viktoriia Kororaieva, / (958) Stanislav Zborovskiy, Leonid Kholopov, Iurii Suliman, Lanna Lukashenko, / (959) Stanislav Shvaykin, (960) Olexandr M. Glavatskiy, Roman O. Sychov, Roman L. Kulynych, / (961) Oleksandr A. Skarzhevskyi, Nataliia V. Dovgan, / (962) Marta Horbach, / (964) Olga Cherkasova, Iryna Tyshchenko, / (965) Liudmyla Todoriuk, Svitlana Kizim, Nataliia Brodi, Oleksandr Ivanko / Olga Garbarchuk, (985) Liudmyla Alieksieieva, / (992) Tetiana L. Shandra, / (994) Olena Beregova, / (996) Larisa An Bodretska, / (997) Svitlana S. Naskalova / Ivanna A. Antoniuk-Shcheglova, Olena V. Bondarenko, (998) / Natalia G. Andreeva, (999) Iryna I. Vakalyuk, Olha S. Chovganyuk, Nataliya R. Artemenko /

<u>Russian Federation</u> N=709 (850) Kiril A. Maltsev, / (851) Natalia Kalishevich, / (901) Natalia G. Kondratyeva, Svetlana A. Nikitina, Maria V. Martjanova, / (902) Anna V. Sokolova, Dmitrii O. Dragunov, / (903) Olga Kolesnik, / (904) / Vera Larina, (905) / Oxana V. Tsygankova, (906) Maria Ivanova, Illia A Karpov, Elena M Aronova, Ekaterina S. Vedernikova, / (908) / Ekaterina I. Lubinskaya, (909) Taras Y. Burak, / (910) Sergey I. Skichko, Farhad Rasulev / Ekaterina B. Soldatova, (911) Alexander L. Fenin / Ilya I. Laptev, (912) Elena E. Luchinkina, (913) Alexandr Akatov, Natalia V Polenova, Natalia N Slavina, Irina N. Korovnika, Marina Yu Prochorova, / (914) Regina Shakirova, / (915) Elena N. Andreicheva, / (916) Olga A. Krasnova, / (917) Tinatin V. Lobzhanidze, Tatiana B. Dmitrova, / (918) Viktoriya V. Stakhiv, Maria I Pechatnikova, Alexandra V Panova, Maria Y. Tipikina, / (919) / Oxana P. Rotar, (921) Nikolay A. Bokovin, Saule K. Karabalieva, Farid Y. Tumarov / Elena V. Vasileva, (922) / Natalya Gennadevna Lozhkina, (923) Ekaterina V. Filippova, Alisa I. Sharkaeva / Ekanerina V. Filippova (Deilik), (924) Natalia Yu Tolkacheva, Elena N. Domracheva, Andrey N. Ryabikov, / (925) Inga T. Abesadze / Marianna Z. Alugishvili, (926) Elena P. Nikolaeva / Nadezda V. Smirnova, Valentina I. Rodionova, (927) Polina V. Dolovstaya, / (928) Igor E. Yunonin, / (929) Sergey V. Kadin, Tatyana S. Sveklina, / (930) Anna V. Bushmanova / Anna V. Bushmanova, (931) Elena L. Barkova, Irina S. Gomova, Yana V. Brytkova / Tatiana B. Ivanova, (932) Marina Y. Zubareva, / (933) Inga Skopets, / (934) Lybov A. Galashevskaya, / (935) Emilia D. Butinskaya / Olga G. Gusarova, (936) Natalia B. Kalishevich, Yana R Pavlova, Marianna P Serebrenitskaya, Vitalina F. Grygorieva, Gulnara R. Kuchaeva, / (966) Inna A. Vasileva, / (968) Gulnara I. Ospanova, (969) / Yulia V. Vahrusheva, Irina A. Semenova, (970) Irina E E. Mikhailova, Olga O. Kvasova, Valeria D. Shurygina, Alexey E. Rivin, Alexey O. Savelyev / Alexey A. Savelyev, (972) Olesya O. Milyaeva, Nadezhda N. Lapshina, Ninel A. Lantsova, / (973) Pavel V. Alexandrov, / (974) / Evgeniy A. Orlikov, (975) Alla Falkovskaya, Tatiana Ripp, Sergei Triss, Stanislav Pekarskiy / Sitkova Ekaterina, (976) / Evgeniya N. Zhuravleva, (977) Olga Perova, / (978) Galina Kovaleva, Liubov Koroleva / Liubov Koroleva, (979) Lydia Mishchenko, (980) Boris P. Garshin, / (982) Svetlana A. Kutuzova, Lyudmila I. Provotorova / Igor P. Zadvorny, (983) Olga V. Okhapkina / Anatoly O. Khrustalev, (987) Tatiana Suvorova, / (988) / Elena S. Shaf, (989) Varvara A. Vershinina, Andrey A. Kozulin, / (990) Oxana A. Oleynik / Irina Y. Martynova, (991) Natalia V. Kizhvatova, / (993) Alla S. Salasyuk, Vera V. Tsoma, Alla A. Ledyaeva, Elena V. Chumachek /

<u>South Africa</u> N=414 (416) SC Blignaut / Tersia Y. Alexander, Chano Du Plessis, (417) Thirumani Govender, Samatha M. Du Toit, Leya Motala / Areesh Gassiep, Christina Naude (Smit), Marli Terblanche, Marlien Snoer (Kruger), Berenice Pillay, (418) De Vries Basson, Clive H. Corbett / Marisa E. Theron, (419) / Bianca Fouche, Mareli E. Coetzee, (420) Pieter Odendall / Frederik H. Van Wijk, Anna-Mari Conradie, Trudie Van der Westhuizen, (421) / Carine Tredoux, (422) Mohamed S. Mookdam, Andie J. Van der Merwe / Karin Snyman, Gerda Smal, (423) / Yvonne De Jager, (424) Thomas A. Mabin / Annusca King, (425) / Lindy L. Henley, (426) / Brenda M. Zwane, Jane Robinson, (427) / Marinda Karsten, Andonia M. Page, Valerie Nsabiyumva, Charmaine Krahenbuhl, (430) Jaiprakash D. Patel, Yunus E. Motala / Ayesha Dawood, Nondumiso B. Koza, Lenore MS Peters, Shavashni Ramlachan, (431) Wilhelm J. Bodenstein, Pierre Roux / Lizelle Fouche, Cecilia M. Boshoff, (432) Haroon M. Mitha / Fathima Khan, (433) Henry P. Cyster / Helen Cyster, (435) E. C. Wessels / Florence J. Jacobs, (437)

Melanie A. Sebastian / Deborah A. Sebastian, Nadia Mahomed, (439) Ignatius P. Immink / Celia Cotzee, (440) Tanja Cronje / Madele Roscher, Maria Le Roux, (441) Yvonne A. Trinder /

Poland N=359 (602) Renata Wnętrzak-Michalska / Magdalena Piszczek, (603) Andrzej Piela, Ewa Czernecka, Dorota Knychas, Alina Walczak, Izabella Gładysz / Katarzyna Filas, Ewelina Kiluk, Krzysztof Świgło, Iwona Jędrzejczyk, Kamila Łuczyńska, (604) / Katarzyna Tymendorf, (605) Wojciech Piesiewicz, (606) Wojciech L. Kinasz / Stefan Samborski, Ilona Bartuś, (607) / Gramzyna Latocha Korecka, Ewa Gulaj, (608) / Jolanta Sopa, (609) Bogusław Derlaga, / (610) Marcin Baisiak, / (612) Allicia Kowalisko, Edyta Stainszewska-Marasazlek, Bartosz Szafran / Malgorzata Swiatkiewicz, (613) Artur Racewicz, Sławomir Grycel, Jerzy Supronik / Sylwia Walendziuk, Magdalena Tarantowicz, Agata Stasiak, (614) Anna Sidorowicz-Białynicka, Marek Dwojak, Ewa Jaźwińska-Tarnawska / Katarzyna Kupczyk, Kamila Martowska, Kamila Kulon, (617) / Katarzyna Gajda

India N=262 (501) Bivin Wilson / Krithika Velusamy, Swaidha S. Sadhiq, (502) / Bhavani Siddeshi, (503) M Bhanukumar / Abhishek Srivatsav, Madhan Ramesh, Sri Harsha Chalasani, Mini Johnson, Prashanth Gopu, Jeesa George, Sowmya Reddy, Swetha Tessy Thara Eleena (504) Damodara Rao Kodem / Haritha N. Nakkella, Padma Kumari Mandula, Anjan Kumar Vuriya, Syamala Rajana, (505) / Aruna Kale, (506) Tiwari Rajeev / Raina Jain, Vipin Jain, (507) Srilakshmi Mandayam Adhyapak / Lumin Sheeba, Uma C R, Ramya R, (509) Aditya V. Kulkarni / M S. Ganachari, Ruma Sambrekar, (510) / Mohammad Bilal, Nungshijungla (511) Kalyan Chakravarthy / Ravi Badhavath, Sravan Kumar, Meenakshi Simhadri, Farooque Salamuddin, Venkat Prasad, (513) Vivek Dwivedi, Sudha Sarna / Tilak Arora, Deepak Chawla, (514) Archana Sathe / Chaware Gayatree, (515) / Ajeet Nanda, Ram Avtar, Jyoti Sharma, (516) Vaibhavi P S Sasirekha D, Deepthi Kobbajji / Ramya Ningappa, Shwetha Shree, Chandrashekar K Nandini M R Sowjanya S Devika I G Yashaswini N Sonika G Rathna L Priyanka R (517) / Rupal J. Shrimanker, (518) Lakshmi Vinutha Reddy, K Sumathi, Babitha Devi / Bina N. Naik, Rohini Manjunath, Rajeshwari Ashok, (524) / Tony V. Kunjumon, Jesline Thomas, (525) / Shaik Samdhani, (526) Kasthuri Selvam / Poongothai Subramani, Nandakumar Parthasarathy, (527) Nirmal K. Bohra / Anvesh K. Gatla

Canada N=250 (172) / Cheryl Horbatuk, (173) / Julie Sills, (175) E B. Davey / Liz Paramonczyk, Olga Racanelli, (176) David Crowley / Sandy Strybosch, (177) Andre Belanger, Jean Palardy, Alicia Schiffrin / Sylvie Gauthier, (178) Norman Kalyniuk, Shawn D. Whatley / Heather Lappala, Grishma Patel, Matthew Reeve, (181) Catherine Moran / Jody Everitt, (182) / Teresa Ferrari, (188) / Christine Bouffard, (200) Jirir Frohlich, Gordon Francis, John Mancini, Gregory Bondy, Debbie DeAngelis, Patricia Fulton / Debbie DeAngelis, Patricia Fulton, (201) David W. Blank / Angela Lombardo, Mylène Roy, (202) / Jackie Chow, (219) Hyman Fox, William J. Grootendorst, Angela Hutchinson, Hyman Fox / Sharon M. Chan, (271) / Christie Fitzgerald, (361) / Teresa Ferrari, (395) / Lynn Wilkins, Rebecca L. Raymond, Arlene Reyes (397) Lavoie Marc André / Denis Fortin, (659) Hélène Ouimet, Thanh-Thao Tôn-Nu, Martine Dussureault, Marie-Hélène Blain / Madeleine Roy, Nathalie Kopajko, Chantal Fleury, (660) / Karine Maheux

Romania N=202 (801) Gabriela Valentina Ciobotaru, / (803) Maria C. Constantinescu / Carmen-Lucia Gherghinescu, (804) Ana-Maria Avram, / (805) Ioan Manitiu / Radu I. Cojan, (806) Octavian M. Pirvu, (808) Aura Sinpetrean, Lucian Pop, Delia Lupu, / (809) Radu Usvat, Ana Petrisor, / (810) Nicoleta Dumitru, / (811) Camelia Moruju, / (812) / Adelina Gheorghita, (813) Magda V. Mitu, / (814) Cosmin Macarie, / (815) Ana Maria Pop, / (816) Maria-Catalina Diaconu, / (817) Iulia Grancea, / (818) Mihaela Cosma / Mihaela Cosma, (819) Mihaela Crisan /

Australia N=189 (301) / Elizabeth Herron, (302) Anthony M. Dart, Paul Nestel / Sally B. Kay, Kaye S. Carter, (303) Imran Badshah, Ashley Makepeace / Jocelyn Drinkwater, Michelle England, (304) / Azette Rafei, Kylie Patterson, (305) Alicia Jenkins, Sybil McAuley / Sue M. Kent, (306) / Joy E. Vibert, Leonie Perrett, (307) Thomas David / Samantha L. Kaye, Monika O'Connor, (308) Nimalie J. Perera / Nicole T. Lai, Kerry A. Kearins, (309) Christinia Dicamillo, Heather Anderson / Louise Ferguson, (310) / Sharon D. Radtke, (311) Charles T. Thamarappillil / Janice M. Boys, (312) / Anita K. Long, Toni Shanahan, (313) Michael Nyguyen / Nicole Forrest, Gill Tulloch, Della Greenwell, (314) Sarah L. Price, Aye N. Tint, Priya K. Sumithran / Tamara L. Debreceni, Lisa Walker, Mary Caruana, Kira Edwards, Maria Stathopoulos, Cilla Haywood, (316) Dimitar Sajkov / Sharen Pringle, Anne Tabner, Kathrina Bartolay, Chamindi Abeyratne, Kylie Bragg, (317) Patrick Mulhern, Peter Purnell, Randall Hendriks / Gill Tulloch, (319) Lyn Williams, Jane Hamlyn / Aurelia Connelly, Jan Hoffman

New Zealand N=134 (402) Samantha Bailey, Jane Kerr / Zarnia Morrison, Sarah Maeder, Roberta McEwan, Prasanna Kunasekera, Patrice McGregor, Jo Young, Sharon Berry, (405) Rick Cutfield, Michelle Choe, Catherine McNamara / Narrinder K. Shergill, (406) / Petra Crone, (408) Miles G. Williams, Keith Dyson / Diana H. Schmid, Audrey C. Doak, Melissa Spooner, (411) Colin Edwards / Anne Turner, Grainne M. McAnnalley, (414) Raewyn A. Fisher, Fraser B. Hamilton, Denis H. Friedlander / Melissa R. Kirk, Jayne E. Scales, (415) / Marguerite A. McLelland, (442) Neelam A. Dalman / Cathy E. Vickers, Carolyn Jackson, (444) / Wendy Coleman, (445) Phillip I. Garden / Wendy F. Arnold

Institutions

Country listing by enrollment; N=number of participants randomized per country; (site number)

United States N=3146 (100) The Center for Clinical Trials, Inc., Biloxi, MS, (101) The Center for Clinical Trials, Mobile, AL, (102) Velella Research, Sarasota, FL, (103) Yale New Haven Health, North Haven, CT, (104) Nature Coast Clinical Research, Inverness, FL, (105) Biofortis, Inc, Addison, IL, (106) North Ohio Heart Center, Sandusky, OH, (107) New York University School of Medicine, New York, NY, (108) Maine Research Associates, Lewiston, ME, (110) Heartland Research Associates, LLC, Wichita, KS, (111) Merced Heart Associates, Merced, CA, (114) Aurora Denver Cardiology, Aurora, CO, (115) Clearwater Cardiovascular Consultants, Clearwater, FL, (116) Alfieri Cardiology, Wilmington, DE, (117) East-West Medical Research Institute, Honolulu, HI, (118) Westlake Medical Research, Westlake Village, CA, (119) Ventura Cardiology Consultants Medical Group, Inc., Ventura, CA, (120) Ocala Research Institute, Inc, Ocala, FL, (121) Altus Research, Inc, Lake Worth, FL, (122) L-Marc Research Center, Louisville, KY, (124) Carient Heart & Vascular, Manassas, VA, (125) Hartford Hospital, Hartford, CT, (129) Chi Health Research Center, Omaha, NE, (130) John Muir Physician

Network Clinical Research Center, Concord, CA, (131) New West Physicians, Golden, CO, (132) St. Vincent's Research - Southside, Jacksonville, FL, (135) Rockdale Medical Research Associates, Conyers, GA, (136) Centracare Heart & Vascular Center, St. Cloud, MN, (137) Georgia Heart Specialists, LLC, Covington, GA, (138) Daniel W. Gottlieb, M.D., P.S., Burien, WA, (139) Cardiology Consultants of Philadelphia, Yardley, PA, (140) Duke University Medical Center, Durham, NC, (141) Baylor College of Medicine, Houston, TX, (142) Trinity Clinical Research Associates, Inc., Carrollton, TX, (143) Westside Medical Associates of Los Angeles, Beverly Hills, CA, (144) Jellinger and Lerman, MD PA Dba The Center for Diabetes and Endocrine Care, Fort Lauderdale, FL, (146) West Jefferson Heart Clinic of Louisiana, Marrero, LA, (147) North Ohio Heart Center, Lorain, OH, (149) Penn State Health Medical Group - Berks Cardiology, Wyomissing, PA, (151) PMG Research of Raleigh, Raleigh, NC, (152) East Coast Institute for Research, LLC, Jacksonville, FL, (154) Gables Research, Miami, FL, (155) Steljes Cardiology, Henderson, NV, (156) Birmingham Heart Clinic, Birmingham, AL, (158) Cardiovascular Associates of Virginia, Bon Secours St. Mary's Hospital, Midlothian, VA, (161) Foundation Research, Key West, FL, (162) Melbourne Internal Medicine Associates, Melbourne, FL, (164) Cardiovascular Research Institute of Dallas, Dallas, TX, (165) Metabolic Research Institute, Inc., West Palm Beach, FL, (166) Legacy Heart Center, Plano, TX, (167) Longmont Medical Research Network, Longmont, CO, (169) Southgate Medical Group, LLP, West Seneca, NY, (171) Syracuse Preventive Cardiology, Syracuse, NY, (185) Wake Forest University Health Sciences, Winston-Salem, NC, (186) University of Maryland School of Medicine, Baltimore, MD, (189) Memorial Hospital, University of Colorado Health, Colorado Springs, CO, (190) Jacksonville Center for Clinical Research Ltd, Jacksonville, FL, (191) The Lindner Research Center, Cincinnati, OH, (192) Capital Area Research, Newport, PA, (193) University Healthcare Alliances/Cardiology Consultants Medical Group, Walnut Creek, CA, (194) Nature Coast Clinical Research, Crystal River, FL, (196) Doylestown Health Cardiology, Doylestown, PA, (197) University of Texas Health Science Center of Houston, Houston, TX, (199) Northeast Georgia Heart Center, Gainesville, GA, (203) Advocate Medical Group Cardiology/Pulmonology, Normal, IL, (204) Cardiology and Medicine Clinic, P.A., Little Rock, AR, (205) Research Institute of Deaconess Clinic, Evansville, IN, (206) Sacramento Heart and Vascular Research, Sacramento, CA, (207) University of Alabama at Birmingham, Birmingham, AL, (208) Westside Center for Clinical Research, Jacksonville, FL, (209) Captain James A. Lovell Federal Health Care Center, North Chicago, IL, (211) Atlanta Heart Specialists, LLC, Cumming, GA, (212) George Washington University School of Medicine and Health Sciences - Medical Faculty Associates, Washington, DC, (213) Heart Center Research, LLC, Huntsville, AL, (214) Baptist Heart Specialists, Jacksonville, FL, (215) Boston Medical Center, Boston, MA, (216) San Diego Cardiac Center, San Diego, CA, (217) Long Island Gastrointestinal Research Group LLP, Great Neck, NY, (220) Kansas City Cardiology, Lee's Summit, MA, (221) Spectrum Clinical Research at Overlea Personal Physicians, Baltimore, MD, (222) Stern Cardiovascular Foundation, Germantown, TN, (223) Orange County Heart Institute & Research Center, Orange, CA, (224) Metabolic Clinic and Research Center, Los Angeles, CA, (225) Baptist Endocrinology, Jacksonville, FL, (226) Washington University School of Medicine, St. Louis, MO, (227) Mobile Heart Specialists, Mobile, AL, (228) Oklahoma Heart Institute, Tulsa, OK, (229) Atlanta Cardiology Consultants, Roswell, GA, (230) East Coast Institute for

Research, LLC, Jacksonville, FL, (231) Los Angeles Biomedical Research Institute at Harbor UCLA Medical Center, Torrance, CA, (233) Broward Health, Fort Lauderdale, FL, (234) Seven Corners Medical Research Center, Falls Church, VA, (235) Office of Dr. Alan S. Hoffman, Houston, TX, (237) Clinical Research Advantage Inc., Glendale, AZ, (239) New Mexico Heart Institute, PA, Albuquerque, NM, (240) BFHC Research, San Antonio, TX, (241) Southeast Texas Clinical Research Center, Beaumont, TX, (243) Clearwater Cardiovascular Consultants, Safety Harbor, FL, (244) United Medical Associates, Vestal, NY, (246) N & N Research and Management Corp., Fall River, MA, (248) Clinical Research Advantage, Phoenix, AZ, (249) PMA Medical Specialists, LLC, Phoenixville, PA, (250) PMG Research of Bristol, Bristol, TN, (251) Prime Care Research, LLC, Florissant, MS, (252) Med Center Medical Clinic, Carmichael, CA, (253) DM Clinical Research, Houston, TX, (255) Texas Medical Research Associates, LLC, San Antonio, TX, (256) Advanced Clinical Research, West Jordan, UT, (257) Primed Clinical Research, Dayton, OH, (258) NYU Langone Medical Associates Chelsea, New York, NY, (259) University of Iowa, College of Public Health, Preventive Intervention Center, Iowa City, IA, (260) Methodist Medical Center of Illinois, Peoria, IL, (261) Jefferson City Medical Group, P.C., Jefferson City, MS, (263) Cardiovascular Associates of Mesa, Mesa, AZ, (264) Professional Research Network of Kansas, LLC, Wichita, KS, (265) DiGiovanna Institute for Medical Education & Research, North Massapequa, NY, (267) Health Research of Hamilton Roads, Newport News, VA, (268) Lillestol Research LLC, Fargo, ND, (269) Clinica Medica San Miguel, Los Angeles, CA, (270) Pembroke Clinical Trials, Miami Lakes, FL, (272) Clinical Research Associates of Central PA, LLC, Altoona, PA, (273) Heritage Valley Medical Group, Inc., Beaver, PA, (274) Martin Diagnostic Clinic/DM Clinical Research, Tomball, TX, (275) Austin Center for Clinical Research, Austin, TX, (277) Center for Clinical Trials, LLC, Paramount, CA, (278) Family Practice Center South, Austin, TX, (279) Precision Research Institute, San Diego, CA, (280) Catalina Research Institute, LLC, Montclair, CA, (281) Sierra Clinical Research, Roseville, CA, (283) Clinical Trials Research, Lincoln, CA, (284) Viable Research Management; Alas Science Clinical Research, Las Vegas, NV, (285) Cardiology Associates Research, LLC, Tupelo, MS, (287) Arcturus Healthcare, Plc, Troy Internal Medicine Research Division, Troy, MI, (289) Terence Hart MD, Tuscumbia, AL, (290) Multicare Research Institute, Tacoma, WA, (291) Quality Clinical Research, Omaha, NE, (292) Infosphere Clinical Research, INC., Omaha, NE, (293) Sparrow Clinical Research Institute, Lansing, MI, (295) Dairy Ashford Family Practice, Houston, TX, (296) Eclipse Clinical Research, Tucson, AZ, (297) Doylestown Health Cardiology, Doylestown, PA, (298) American Clinical Trials, Hawaiian Gardens, CA, (299) Fleming Island Center for Clinical Research, Fleming Island, FL, (350) Reno Clinical Trials, Sparks, NV, (353) Panacea Clinical Research, San Antonio, TX, (356) Endocrinology Services Northwest, Bend, OR, (357) Monmouth Cardiology Associates, Eatontown, NJ, (358) Christiana Care Health System, Newark, DE, (359) Angiocardiac Care of Texas, Houston, TX, (360) Alexandria Cardiology Clinic/Cambridge Medical Trials, Alexadria, LA, (362) Marshall Cardiology, Huntington, WV, (363) Nebraska Heart Institute, Hastings, NE, (364) Lutherville Personal Physicians, Lutherville, MD, (365) Hillcrest Clinical Research, LLC, Simpsonville, SC, (367) Lycoming Internal Medicine, Inc., Jersey Shore, PA, (368) Riverside Clinical Research, Edgewater, FL, (370) Horizon Research Group of Opelousas, LLC, Eunice, LA, (371) New Horizon Research Center, Miami, FL, (373) HCCA Clinical Research Solutions,

Smryna, TN, (374) HCCA Clinical Research Solutions, Columbia, TN, (375) Grandview Lehigh Valley Health Services, Buxmont Cardiology Division, Sellersville, PA, (376) Cardiovascular Research of Knoxville, Knoxville, TN, (377) Innovative Research of West Florida, Clearwater, FL, (379) Research Physicians Network Alliance, Miami Beach, FL, (380) Black Hills Cardiovascular Research, Rapid City, SD, (381) Adventist Health Care Inc., Takoma Park, MD, (383) Joslin Diabetes Center, Boston, MA, (384) Research Physicians Network Alliance, Pembroke, FL, (386) CaroMont Heart & Vascular, Gastonia, NC, (387) Penn Presbyterian Medical Center, Philadelphia, PA, (388) Dupage Medical Group Cardiology, Winfield, IL, (389) Endocrine IPS, PLLC, Houston, TX, (393) UP Health System Marquette, Marquette, MI, (394) Novant Health Clinical Research, Charlotte, NC, (396) VA Medical Center, Philadelphia, Philadelphia, PA, (398) Florida Hospital, Orlando, FL, (399) Beth Israel Deaconess Medical Center, Boston, MA, (653) Diverse Clinical Research Center of Chicago, LLC, Chicago, IL, (654) Exodus Healthcare Network, Magna, UT, (655) Med-Tech LP, Houston, TX, (656) Trinity Medical Research, Inc, Roseville, CA, (657) Heart & Health Institute Westside, Plantation, FL, (661) Biltmore Cardiology, Phoenix, AZ, (662) SJH Cardiology, Liverpool, NY, (663) Albany Medical Center, Division of Community Endocrine, Albany, NY, (664) Oregon Health and Science University, Portland, OR, (665) Triwest Research Associates, El Cajon, CA, (668) Mercury Clinical Research, Inc, Houston, TX, (669) Shahram Jacobs, MD Inc, Sherman Oaks, CA, (670) Carolina Heart Specialists, LLC, Lancaster, SC, (671) Mission Research Institute, New Braunfels, TX, (672) Apex Cardiology, P.C., Jackson, TN, (678) Nova Clinical Research, Bradenton, FL, (679) Professional Health Care of Pinellas, St. Petersburg, FL, (680) Center for Advanced Medicine and Research, St. Peters, MO, (681) Clinical Research Professionals, Chesterfield, MO, (683) Protenium Clinical Research, Hurst, TX, (685) Endocrine Associates of Long Island, PC, Smithtown, NY, (686) Synergist Research, LLC, Lancaster, CA, (687) Geodyssey Research, LLC, Vero Beach, FL, (688) The Center for Clinical Trials, Saraland, AL, (690) Manshadi Heart Institute, Inc, Stockton, CA, (691) W.G. (Bill) Hefner Salisbury VA Medical Center/ Kernersville Health Care Center, Kernersville, NC

The Netherlands N=1678 ***WCN*** (701) Bravis Hospital, Roosendaal, (702) Deventer Hospital, Cardiology Department, Deventer, (703) Spaarnegasthuis, Hoofddorp, (704) Gelre Ziekenhuis, Zutphen, (705) Tweesteden Ziekenhuis, Tilburg, (706) Admiraal De Ruyter Ziekenhuis, Goes, (707) Tergooi, Blaricum, (708) Canisius Wilhelmina Ziekenhuis, Nijmegen, (709) Alrijne Hospital, Leiderdorp, (719) HMC Bronovo, Den Haag, (720) Stichting CRE Enschede, Thoraxcentrum Twente, Medisch Spectrum Twente, Enschede, (721) Beatrix Hospital, Gorinchem, (722) Langeland Ziekenhuis, Cardiology Department, Zoetermeer, (723) Medisch Centrum Leeuwarden, Leeuwarden, (724) Spaarne Gasthuis, Haarlem, (725) St Elisabeth Hospital, Tilburg, (726) Bernhoven Hospital, Uden, (727) Franciscus Gasthuis & Vlietland, Schiedam, (728) Noordwest Ziekenhuis, Den Helder, (729) Jeroen Bosch Hospital, Hertogenbosch, (731) Groene Hart Ziekenhuis, Gouda, (732) Meander Medical Center, Amersfoort, (733) Ikazia Hospital Rotterdam, Rotterdam, (734) Máxima Medisch Centrum, Veldhoven, (735) Ziekenhuis Stjansdal, Harderwijk, (736) Tjongerschans Ziekenhuis, Cardiology Department, Heerenveen, (737) Franciscus Gasthuis, Rotterdam, (738) ZGT, Almelo and Hengelo, (739) D & A Research, Sneek, (740) Zuyderland Mc, Heerlen, (741) Martini Ziekenhuis, Groningen, (742) Gelderse Vallei Ziekenhuis, EDE, (743) Ijsselland Ziekenhuis,

Capelle aan den Ijssel; ***non-WCN*** (710) Andromed Rotterdam, Rotterdam, (711) Andromed Eindhoven, Eindhoven, (712) Andromed Leiden, Leiderdorp, (713) Andromed Oost BV, Velp, (714) Andromed Zoetermeer BV, Zoetermeer, (715) Andromed Noord, Groningen, (716) Andromed Breda, Breda, (718) Gemini Ziekenhuis, Den Helder

Ukraine N=836 (885) State Institutio, D.F.Chebotarev Institute of Gerontology of NAMS, Kiev, (886) Department of Internal Diseases-1 of Zaporizhzhya State Medical University, Zaporizhzhya City Clinical Hospital of Emergency Care, Zaporizhzhya, (887) The State Institute of Therapy, L.T. Malaya of Ukrainian National Academy of Medical Science, Kharkov, (888) Policlinic of Administration of Medical Services and Rehabilitation of Artem State Holding, Kiev, (889) State Institution, Ukrainian State Scientific and Research Institute of Medical and Social Problems of Disability of Ministry of Health of Ukraine, Dnipro, (890) National Scientific Center M.D. Strazhesko Institute of Cardiology, Kiev, (891) Communal Institution, Central Clinical Hospital #4 of Zavodsky District, Zaporizhzhia, (892) Kiev City Clinical Hospital #7, Therapeutic dpt #2, Kiev, (893) Medical Center, Desna, Ltd, Ternopil, (894) LTD Cardiology Clinic, Heart and Vessels, Kiev, (895) Clinic of State Institution, Ukrainian State Institute of Medical and Social Problems of Disability Ministry of Public Health, Dnipro, (897) State Institute, Zaporizhzhia Medical Academy of Postgraduate Education of Ministry of Health of Ukraine, Department of Family Medicine With Course of Dermatovenereology and Psychiatry Based On Municipal Institution: Zaporyzhzhya 9th City Multidisciplinary Clinical Hospital, Cardiology Department, Zaporizhzhia, (898) Volyn Regional Clinical Hospital, Department of Cardiosurgery, Lutsk, (899) Zakarpatskyi Oblasnyi Klinichnyi Kardiolohichnyi Dyspanser, m. Uzhhorod, (900) Infarction Dprt of City Clinic Hosp. #6, Simferopol, AR Crimea, (937) Zakarpattya Regional Clinical Cardiology Dispensary, Dept. of General Cardiology, Uzhhorod National University, Chair of Hospital Therapy, Uzhhorod, (938) City Clinical Hospital #1, Vinnitsa, (939) State Institution, National Scientific Center, NAMS Institute of Cardiology M.D. Strazhesko, Department of Essential Hypertension, Kiev, (940) Kharkiv Medical Academy of Postgraduate Education, City Clinical Hospital #8, Kharkiv, (941) Lutsk City Clinical Hospital, Lutsk, (942) Kharkiv City Clinical Hospital #27, Kharkiv, (943) Kharkiv Medical Academy of Postgraduate Education, Kharkiv, (944) Lugansk Regional Cardiological Dispensary, Luhansk, (945) Dnipropetrovsk Medical Academy, Dnipropetrovsk Joint Emergency Hospital, Dnipro, (946) State Institution, National Scientific Center, The M.D. Strazhesko Institute of Cardiology, National Academy of Medical Sciences of Ukraine, Kiev, (947) City Clinical Hospital №3, Chernivtsi, (948) National Institute of Therapy N.A. L. Malaya NAMS, Kharkiv, (949) National Pirogov Memorial Medical University, Vinnytsya, (951) Clinic of State Institution, Institute of Therapy NAMS Ukraine L.T. Maloy, Kharkiv, (952) HSEE of Ukraine, Ukrainian Medical Stomatological Academy, Poltava, (953) Odessa National Medical University, Center of Reconstructive and Recovery Medicine (University Clinic), Odessa, (954) Institute of Urgent and Recovery Surgery, Donetsk, (955) State Institution National Scientific Centre, Acad. M.D. Strazhesko Institute of Cardiology of Nacional Ams of Ukraine, Kiev, (956) Kiev Municipal Clinical Hospital #12, Department of Cardiology; O. O. Bogomolets National Medical University, Kiev, (957) Saint Catherine Odessa, Treatmnent and Diagnostic Center LLC, Odesa, (958) Central City Clinical Hospital #1, Donetsk, (959) Communal Institution, Odesa Regional Cardiological Dispensary, Odesa, (960) Zaporizhzhia Regional Clinical Hospital, Zaporizhzhea,

(961) National Scientific Center, NAMS Strazhesko Institute of Cardiology, Kiev, (962) Communal City Clinical Hospital #8, Lviv, (963) Ivano-Frankivsk Regional Clinical Cardiological Center, Ivano-Frankivsk, (964) City Clinical Hospital #9, Department of Cardiology; State Institution, Dnipropetrovsk Medical Academy of Moh, Dnipro, (965) Kyiv City Clinical Hospital #1, Department of Emergency Cardiology, Kiev, (985) Kyiv City Oleksandrivska Clinical Hospital, Kiev, (992) Cherkasy Regional Cardiological Center, Cherkasy, (994) Kyiv Emergency Care Hospital, Infarction Department, Kiev, (996) The Institute of Gerontology NAMS D.F.Chebotarev, Kiev, (997) D.F. Chebotarev Institute of Gerontology, National Academy of Medical Sciences, Kiev, (998) Odesa Regional Clinical Hospital, Department of Cardiosurgery, Odesa, (999) Ivano-Frankivsk National Medical University, Ivano-Frankivsk

Russian Federation N=709 (850) State Budget Healthcare Institution of City Moscow, City Clinical Hospital N.A. M.P. Konchalovskogo of Healthcare Department, Zelenograd, (851) Saint Petersburg State Budget Healthcare Institution, City Consultative and Diagnostic Center #1, Saint Petersburg, (901) State Health Care Institution City Hospital #117, Saint Petersburg, (902) State Budget Healthcare Institution of Moscow, City Clinical Hospital #4 of The Healthcare Department, Moscow, (903) First Saint Petersburg State Medical University N.A.Acad.I.P.Pavlov of The Ministry of Healthcare of Russian Federation, Saint Petersburg, (904) Pirogov Russian National Research Medical University, Moscow, (905) City Clinical Emergency Hospital#2, Novosibirsk, (906) State Inst City Multidiscipline Hospital# 2, Saint Petersburg, (908) Almazov National Medical Research Centre, Saint Petersburg, (909) Autonomous Non-Profit Organization: Medical Center Alliance, Kirovsk, (910) Central Clinical Hospital of The Russian Academy of Sciences, Moscow, (911) Saint Petersburg State Budget Institution of Healthcare, City Hospital #15, Saint Petersburg, (912) City Clinical Hospital #15 O.M.Filatov, Moscow, (913) FSBHI Clinical Hospital #123 of FMBA, Moscow, (914) Kazan State Medical University, Kazan, (915) Scientific Research Medical Complex, State Budget Institution of Healthcare Clinical Hospital #2, LLC, Kazan, (916) Saint Petersburg State Budget Institution of Healthcare, City Hospital #9, Saint Petersburg, (917) State Budget Healthcare Institution of City Moscow, City Clinical Hospital N.A. V.V.Vinogradova of Healthcare Department, Moscow, (918) International Clinic MEDEM, LLC, Saint Petersburg, (919) Almazov National Medical Research Centre, Saint Petersburg, (921) Saint Petersburg State Budget Institution of Healthcare, City Outpatient Clinic #109, Saint Petersburg, (922) Novosibirsk State Medical University, Novosibirsk, (923) Medinet, LLC, Saint Petersburg, (924) Research Institute of Internal and Preventive Medicine, Branch of The Institute of Cytology and Genetics, Siberian Branch of Russian Academy of Sciences, Novosibirsk, (925) Almazov National Medical Research Centre, Saint Petersburg, (926) Saint Petersburg State Budgetary Healthcare Institution, City Pokrovskaya Hospital, Saint Petersburg, (927) Saratov Regional Veterans Hospital, Saratov, (928) State Healthcare Institution of Yaroslavl Region, Clinical Hospital #8, Yaroslavl, (929) Federal State Budget Military Educational Institution of Higher Professional Education, Military Medical Academy, S.M. Kirov of Ministry of Defence of Russian Federation, Saint Petersburg, (930) The Federal State Autonomous Educational Institution of Higher Education I.M. Sechenov First Moscow State Medical University of Ministry of Healthcare of The Russian Federation (Sechenovskiy University), Moscow, (931)

Moscow State Medical and Dental University N.A A.I. Evdokimov of The Ministry of Health, Moscow, (932) FGBU, National Medical Research Center of Cardiology, Ministry of Health Care of Russia, Moscow, (933) State Budget Institution of Healthcare, Republican Hospital V.A. Baranov, of The Ministry of Healthcare of Karelia Republic, Petrozavodsk, (934) State Budget Healthcare Institution of Arkhangelsk Region, Arkhangelsk Regional Clinical Hospital, Arkhangelsk, (935) Leningrad Regional Cliical Hospital, Saint Petersburg, (936) Science and Research Institute of Experimental Medicine, Saint Petersburg, (966) Saint Petersburg State Budget Healthcare Institution, City Hospital #40 of Kurortniy District, Saint Petersburg, (967) Federal State Budget Institution of Healthcare, Clinical Hospital #122 N.A. L.G. Sokolov Under Federal Medical and Biological Agency of Russia, Saint Petersburg, (968) City Hospital # 38 N A Semashko, Saint Petersburg, (969) State Budget Institution of Healthcare of Arkhangelsk Region, The First City Clinical Hospital E.E. Volosevich, Arkhangelsk, (970) Cardio-Centre, Chernaja Rechka, Saint Petersburg, (971) Central Outpatient Department at Federal State Budget Institution of Healthcare, Northern Medical Clinical Center N.A. Semashko of Federal Medical-Biological Agency, Arkhangelsk, (972) Saint Petersburg State Official Institution of Healthcare, Mariinskaya Ambulatory, Saint Petersburg, (973) Sanatorium Chernaya Rechka, Saint Petersburg, (974) State Healthcare Institution, Regional Clinical Cardiology Dispensary, Saratov, (975) Cardiology Research Institute, Tomsk National Research Medical Center of Russian Academy of Sciences, Tomsk, (976) Research Institute of Complex Issues of Cardiovascular Diseases (NII KPSSZ), Kemerovo, (977) Panaceya Clinic, LLC, Moscow, (978) Nizhny Novgorod Regional Clinical Hospital N.A.Semashko, Nizhny Novgorod, (979) Moscow Hospital #15 O.M.Filatov, Moscow, (980) Budgetary Healthcare Institution of Voronezh Region, Voronezh City Clinical Hospital of Emergency Medical Care #1, Voronezh, (982) Autonomous Healthcare Institution, Voronezh Regional Clinical Consultative and Diagnostic Center, Voronezh, (983) Yaroslavl Regional Clinical Hospital, Yaroslavl, (987) Medical Union New Hospital, LLC, Ekaterinburg, (988) Hospital of Veterans Wars, Kemerovo, (989) State Budget Healthcare Institution of Sverdlovsk Region, Sverdlovsk Regional Clinical Hospital #1, Ekaterinburg, (990) Siberian State Medical University, Tomsk, (991) State Budget Healthcare Institution, Scientific and Research Institute, Regional Clinical Hospital #1 N.A., Krasnodar, (993) Volgograd State Medical University, Department of Therapy and Endocrinology, Volgograd

South Africa N=414 (416) Paarl Research Centre, Paarl, (417) TREAD Research cc, Cape Town, (418) Durbanville Medi-Clinic, Durbanville, (419) Unitas Hospital, Pretoria, (420) Somerset West Clinical Trial Unit, Somerset West, (421) Tiervlei Trial Centre, Bellville, (422) Langeberg Clinical Trials, Cape Town, (423) Synexus Helderberg, Somerset West, (424) Helderberg Research Institute, Somerset West, (425) Vincent Pallotti Hospital, Cape Town, (426) Wits Clinical Research Bara, Soweto, (427) Cardiology Research, Bloemfontein, (430) Newkwa Medical Centre, Durban, (431) Corbod Research Pty Ltd, Panorma, (432) Worthwhile Clinical Trials, Johannesburg, (433) Dr HFM Nortje Clinical Trials, Cape Town, (435) Drs' Joynt Venter and Associates, Witbank, (437) Dr P J Sebastian, Durban, (439) Boanerges Clinical Research, Bloemenstein, Free State, (440) Clinical Projects Research Centre, Worcester, (441) University of Cape Town, Cape Town

Poland N=359 (602) Synexus Polska Sp. Z O.o., Katowice, (603) Synexus Sp. Z O.o., Warsaw, (604) Centrum Medyczne Ogrodowa, Skierniewice, (605) Centrum Medyczne Nzoz As-Medica Sp.Z O.o., Zgierz, (606) ZSGL LeK, Mikołów, (607) Podlaski Osrodek Kardiologiczny, Bialystok, (608) Institute of Cardiology, Warsaw, (609) Specjalistyczny Gabinet Lekarski Internistyczno-Kardiologiczny Ewa Laskowska-Derlaga, Tarnów, (610) NZOZ SALVIA, Katowice, (612) Centrum Kardiologiczne Pro Corde Sp. Z O.o., Wroclaw, (613) Osteo-Medic Sc, Bialystok, (614) Synexus Sp. Z O.o., Wrocław, (616) Przychodnia Specjalistyczna PROSEN; Department of Experimental and Clinical Physiology, Laboratory of Center for Preclinical Research, Medical University of Warsaw, Warsaw, (617) Centrum Nowoczesnych Terapii, Dobry Lekarz, Krakow

India N=262 (501) G.Kuppuswamy Naidu Memorial Hospital, Coimbatore, Tamilnadu, (502) Medwin Hospitals, Hyderabad, Telangana, (503) JSS Medical College Hospital, Mysuru, Karnataka, (504) Mycure Hospital, Visakhapatnam, Andhra Pradesh, (505) Shatabdi Super Specialty Hospital, Suyojit City Center, Opp. Mahamarg Bus Stand, Nashik, Maharashtra, (506) SR Kalla Memorial Gastro and General Hospital, Jaipur, (507) St. John's Medical College Hospital, Koramangla, Karnataka, (509) KLE Dr. Prabhakar Kore Hospital, Nehru Nagar, (510) Fortis Escorts Heart Institute, New Delhi, (511) Gleneagle Global Hospitals, Hyderabad, Telangana, (513) Monilek Hospital and Research Center, Jaipur, (514) Cardiac Care & Counselling Center, Pune, Maharashtra, (515) Dharma Vira Heart Cente, Sir Ganga Ram Hospital, New Delhi, (516) Vikram Hospital Pvt. Ltd, Mysore, Karnataka, (517) Bhatia Hospital, Mumbai, Maharastra, (518) Endocrinology Diabetes Centre, Bangalore, Karnataka, (524) Caritas Hospital, Kottayam, Kerala, (525) Vikram Hospital, Bangalore, Karnataka, (526) Madras Diabetes Research Foundation, Chennai, Tamilnadu, (527) Krishna Institute of Medical Sciences, Secunderabad, Telanagana

Canada N=250 (172) Recherche Clinique London, Sherbrooke, Québec, (173) Clinique Des Maladies Lipidiques De Québec, Québec, (175) Ronald Collette, MD, Burnaby, (176) DCTM Clinical Trials Group, Strathroy, Ontario, (177) Centre de recherche clinique de Laval, Laval, Québec, (178) SKDS Research Inc., Newmarket, Ontario, (181) Moran Medical Centre, Collingwood, Ontario, (182) Corunna Clinical Research Centre, Corunna, Ontario, (188) London Road Diagnostic Clinic, Sarnia, Ontario, (200) Heathy Heart Program, Vancouver, (201) McGill University Health Centre, Royal Victoria Hospital, Montreal, Québec, (202) Vancouver General Hospital, Vancouver, British Columbia, (219) North Road Clinical Research, Coquitlam, British Columbia, (271) Brampton Research Associates, Brampton, Ontario, (361) Sarnia Institute of Clinical Research, Sarnia, Ontario, (395) Alta Clinical Research Inc, Edmonton, Alberta, (397) Montreal Heart Institute, Montreal, Québec, (659) Centre de Sante et de Services Sociaux de Lanaudière, St-Charles-Borromée, Québec, (660) Institut Universitaire De Cardiologie Et De Pneumologie Du Québec, Université Laval, Québec

Romania N=202 (801) Medical Center Medcalis SRL, Timisoara, (803) Universitary Emergency Hospital, Cardiology Ward I, Bucuresti, (804) Centrul Medical International Bucuresti Dacia, Bucuresti, (805) Emergency County Hospital, Sibiu, (806) Mediclass Sananova SRL, Bucharest, (808) Clinic County Emergency Hospital Cluj-Napoca, Cluj-Napoca, (809)

Universitary Emergency Hospital Bucharest, Bucharest, (810) Ilro Medical Clinic, Bucharest, (811) CardioMed SRL, Craiova, (812) Spitalul Judetean De Urgenta Braila, Braila, (813) University of Medicine and Pharmacy Grigore T. Popa, Rehabilitation Hospital, Department of Cardiovascular Rehabilitation, Lasi, (814) Spitalul Clinic Judetean De Urgenta, Tirgu Mures, (815) Spitalul Clinic Judetean De Urgenta, Sibiu, (816) Centrul Med Plus SRL Bucuresti, Bucuresti, (817) Centrul Medical Galenus, Tirgu Mures, (818) CMI Cardiologie, Baia Mare, (819) SC Clinica Angiomed, Bucharest, (820) Spitalul De Urgenta Arges, Pitesti, (821) CMI Cardiologie, Constanta

Australia N=189 (301) Holy Spirit Northside Hospital, Brisbane, QLD, (302) The Alfred Hospital Heart Centre, Melbourne, VIC, (303) Fremantle Hospital, Fremantle, WA, (304) Dr Heart Pty Ltd, Woolloongabba, QLD, (305) St. Vincents Hospital (Melb) Dept. of Medicine, Fitzroy, VIC, (306) Joondalup Cardiovascular Trials Foundation, Joondalup, WA, (307) Launceston General Hospital, Launceston, TAS, (308) Royal Prince Alfred Hospital, Sydney, NSW, (309) Sir Charles Gairdner Hospital, Nedlands, (310) Royal Perth Hospital, School of Medicine and Pharmacology, Medical Research Foundation, Perth, WA, (311) Lismore Base Hospital Cardiac Catheter Lab, Northern Rivers Cardiovascular Clinic, Lismore, NSW, (312) Barwon Health University Hospital Geelong, Geelong, VIC, (313) Fiona Stanley Hospital, Murdoch, WA, (314) Austin Health, Heidelberg Heights, VIC, (316) Flinders Medical Centre and Flinders University, Bedford Park, SA, (317) Cardiovascular Trials WA (South), Bateman, WA, (319) Core Research Group Pty Ltd, Brisbane, QLD

New Zealand N=134 (402) Lipid and Diabetes Research, Christchurch, (405) Waitemata District Health Board, Diabetes Service, Auckland, (406) Cardiology Department, Nelson Hospital, Nelson, (408) Hawke's Bay District Health Board, Hastings, (411) Waitemata District Health Board, Auckland, (414) Cardiology Clinical Trials Unit, Waikato District Health Board, Hamilton, (415) Southern District Health Board, Dunedin Hospital, Dunedin, (442) Taranaki Base Hospital, New Plymouth, (444) Northland District Health Board, Whangarei, (445) Bay of Plenty Clinical Trials Unit, Tauranga

Supplemental Information: Prespecified Exploratory Analyses

SAP-Prespecified Tertiary Endpoints and Analyses

- Total CV events analysis defined as the time from randomization to occurrence of the first and all recurrent major CV events defined as CV death, nonfatal MI (including silent MI), nonfatal stroke, coronary revascularization, or unstable angina determined to be caused by myocardial ischemia by invasive/non-invasive testing and requiring emergent hospitalization
- Primary composite endpoint in subset of patients with diabetes mellitus at baseline;
- Primary composite endpoint in the subset of patients with metabolic syndrome at baseline as defined in *A Joint Interim Statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity*;[1] with cut points of parameters as defined in Table 1 of Alberti *et al.* and waist circumference cut points further guided by Table 2 of Alberti *et al.* and specifically set at ≥35 inches (88 cm) for all women and Asian, Hispanic, or Latino men, and ≥40 inches (102 cm) for all other men
- Primary composite endpoint in the subset of patients with impaired glucose metabolism at baseline (Visit 2 FBG of 100-125 mg/dL)
- Key secondary composite endpoint in the subset of patients with impaired glucose metabolism at baseline (Visit 2 FBG 100-125 mg/dL)
- Composite of CV death, nonfatal MI (including silent MI), nonfatal stroke, cardiac arrhythmia requiring hospitalization of ≥24 hours, or cardiac arrest
- Composite of CV death, nonfatal MI (including silent MI), non-elective coronary revascularizations (defined as emergent or urgent classifications), or unstable angina determined to be caused by myocardial ischemia by invasive/non-invasive testing and requiring emergent hospitalization
- Composite of CV death, nonfatal MI (including silent MI), non-elective coronary revascularizations (defined as emergent or urgent classifications), unstable angina determined to be caused by myocardial ischemia by invasive/non-invasive testing and requiring emergent hospitalization, nonfatal stroke, or PVD requiring intervention, such as angioplasty, bypass surgery, or aneurysm repair
- Composite of CV death, nonfatal MI (including silent MI), non-elective coronary revascularizations (defined as emergent or urgent classifications), unstable angina determined to be caused by myocardial ischemia by invasive/non-invasive testing and requiring emergent hospitalization, PVD requiring intervention, or cardiac arrhythmia requiring hospitalization of ≥24 hours
- New CHF
- New CHF as the primary cause of hospitalization;
- Transient ischemic attack (TIA)
- Amputation for peripheral vascular disease (PVD)
- Carotid revascularization
- All coronary revascularizations defined as the composite of emergent, urgent, elective, or salvage
- Emergent coronary revascularizations
- Urgent coronary revascularizations

- Elective coronary revascularizations
- Salvage coronary revascularizations
- Cardiac arrhythmias requiring hospitalization of ≥24 hours
- Cardiac arrest
- Ischemic stroke
- Hemorrhagic stroke
- Fatal or nonfatal stroke in the subset of patients with a history of stroke prior to baseline;
- New onset diabetes, defined as Type 2 diabetes newly diagnosed during the treatment/follow-up period
- New onset hypertension, defined as blood pressure ≥140 mmHg systolic OR ≥90 mmHg diastolic newly diagnosed during the treatment/follow-up period
- Fasting TG, TC, LDL-C, HDL-C, non-HDL-C, VLDL-C, apo B, hs-CRP (hsCRP and log[hsCRP]), hsTnT, and RLP-C (to be estimated from standard lipid panel, RLP-C = TC – HDL-C – LDL-C [2] (based on ITT estimands)
    - Assessment of the relationship between baseline biomarker values and treatment effects within the primary and key secondary composite endpoints,
    - Assessment of the effect of icosapent ethyl on each marker,
    - Assessment of the relationship between post-baseline biomarker values and treatment effects within the primary and key secondary composite endpoints by including post-baseline biomarker values (for example, at 4 months, or at 1 year) as a covariate.
- Continuous tertiary endpoints include:
    - Change from baseline and percent change from baseline in fasting TG, TC, LDL-C, HDL-C, non-HDL-C, VLDL-C, apo B, hs-CRP (hsCRP and log[hsCRP]), hsTnT, and RLP-C (to be estimated from standard lipid panel, RLP-C = TC – HDL-C – LDL-C [2] (based on ITT estimands)
    - Change in body weight
    - Change in waist circumference

The fasting lipid panel is tested at Screening (Visit 1 or Visit 1.1), Randomization visit (Visit 2; Day 0), Visit 3 (Day 120; ~4 Months) and all other follow-up visits including the last visit. For change from baseline to 1-year Preparative Ultracentrifugation measurements for LDL-C will be analyzed, unless this value is missing. As described in SAP Section 4.3.3, if the LDL-C Preparative Ultracentrifugation values is missing, then another LDL-C value will be used, with prioritization of values obtained from LDL-C Direct measurements, followed by LDL-C derived by the Friedewald calculation (only for patients with TG <400 mg/dL), and finally LDL-C derived using the calculation published by Johns Hopkins University investigators.[3] In addition, change from baseline to day 120 in LDL-C utilizing Friedewald and Hopkins methods will be analyzed, using the arithmetic mean of LDL-C obtained at Visit 2 (Day 0) and the preceding Visit 1 (or Visit 1.1). If one of these values is missing, the single available LDL-C value will be used. LDL-C according to Hopkins will be calculated at each visit.

The randomization visit will be considered Baseline. If a baseline value is not available from the randomization visit, then the latest screening value will be used.

For measurements of lipids, lipoproteins, and inflammatory markers, change from baseline and percent change will be summarized at each visit. Since these parameters are typically not normally distributed, the Wilcoxon rank-sum test will be used for treatment comparisons of percent change from baseline, and medians and quartiles will be provided for each treatment group. The medians of the differences between the treatment groups and 95% CIs will be estimated with the Hodges-Lehman method. In addition, shift–tables may be generated as appropriate.

As an additional exploratory analysis, the relationship between post-baseline biomarker values and treatment effects with the primary and key secondary composite endpoints will be assessed by adding biomarker values (for example, at 4 months, or at 1 year, etc.) as time-dependent covariates in the Cox proportional hazards model. Diagnostic plots for the proportional hazards assumption will be evaluated.

Weight is measured at screening and all follow-up visits, including last visit of study. Waist circumference will be measured at randomization visit (Visit 2; Day 0), Visit 5 (Day 720) and last visit of the study. Descriptive statistics will be presented by visit and treatment group for baseline, post-treatment change from baseline, and the percent change from baseline. Analysis methods for repeated measurements will be used to compare percent change from baseline between treatments.

SAP Addendum Prespecified Exploratory Analyses

Additional prespecified efficacy endpoints and analyses outlined below in the SAP Addendum are exploratory in nature and were not included in the formal SAP testing scheme:

- Time-to-event analyses as done for the primary analysis will be carried out at 1-year and 2-year landmarks for the ITT Population.

- For recurrent CV events analyses based on 5-component MACE (CV death, non-fatal MI, non-fatal stroke, unstable angina requiring hospitalization, or coronary revascularization), in addition to the Anderson and Gill, and Li and Lagakos methods specified in the SAP dated 08 July 2016, a total CV event analysis will be performed using a Negative Binomial Model.[4-6]

- An on-treatment sensitivity analysis will be performed including primary events with onset up to 0 and 30 days after permanent discontinuation of study drug.

- As done for the primary analysis, time-to-event analyses at 1-year and 2-year landmarks for the key secondary endpoints for the ITT Population.

- An analysis of the following clinical events that are positively adjudicated by the CEC as tertiary endpoints for the ITT Population:
    - Composite of total mortality, or new congestive heart failure (CHF)
    - Composite of CV death, or new CHF
    - Sudden cardiac death
    - Peripheral artery disease (PAD)
    - Atrial fibrillation or atrial flutter

- An analysis of the following as tertiary endpoints for the ITT Population:
    - Relationship between on-treatment hsCRP and primary and key secondary endpoints
    - Relationship between on-treatment serum EPA and primary and key secondary endpoints

- To assess relationships between on-treatment hsCRP and primary and key secondary endpoints, subgroup analyses as done for the ITT population for patients grouped according to values greater or equal to or less than 2 mg/dL at baseline and at 2 years.

- To assess relationships between on-treatment serum EPA and primary and key secondary endpoints, KM curves for icosapent ethyl patients grouped into tertiles based on values at year 1 compared with placebo patients.

- The following will be added to the subgroup analyses:
    - Baseline HbA1c value (<6.5%, ≥6.5%)
    - Baseline PAD
    - Baseline TG ≥ 150mg/dL with HDL-C ≤ 40 mg/dL for males and ≤ 50 mg/dL for females

Prespecified List of Additional Exploratory Analyses

The following list presents additional pre-specified exploratory efficacy analyses that could be of particular interest to the general clinical and scientific community:

- Non-fatal myocardial infarction (MI) (including both clinical manifestation and silent MI categorizations) – ITT Population

- Evaluation of effect of time-weighted (or area under the curve [AUC]) EPA data on the primary and key secondary composite endpoints – ITT Population

- Sensitivity analyses on primary and key secondary composite endpoints by excluding elective coronary artery revascularizations if onset is <3 months post randomization; and also excluding peri-procedural MIs – ITT Population

- Two silent MI (SMI) sensitivity analyses on primary and key secondary composite endpoints – ITT Population:

    - Counting all potential SMIs identified by CEC ECG reviewer, whether confirmed at final ECG or not, and,
    - Counting only potential SMIs that have at least one confirmatory ECG showing persistence of Q-waves (even if not present at final ECG)

- Non-alcoholic fatty liver disease (NAFLD) analyses using NAFLD Fibrosis Score (NFS), assessing – ITT Population:

    - Effect on primary and key secondary composite endpoints by baseline NFS category, and,
    - Treatment effect on change from baseline in NFS at 1 and 5 years

- Individual and combined on-treatment goal achievement of triglyceride (TG) ≤ 150 mg/dL and hsCRP ≤ 2 mg/L at 2 years, and end of study – ITT Population

- Additional renal function (eGFR) analyses – ITT Population:

    - Primary and key secondary composite endpoints for patients with baseline renal dysfunction [eGFR] ≥60 and <90 mL/min/1.73m^2
    - Treatment effect on change from baseline in renal function (eGFR) at 1 and 5 years

- Sensitivity analyses on primary and key secondary composite endpoints by excluding patients with post-randomization LDL-C values >100 mg/dL; and another for >70 mg/dL – ITT Population

- Analyses of hospitalization data (pooled, positively-adjudicated unstable angina requiring hospitalization, congestive heart failure [CHF] requiring hospitalization, and cardiac arrhythmia requiring hospitalization) – ITT Population

    - Time from randomization to first hospitalization
    - Recurrent event analysis on hospitalizations

- Additional subgroup analyses (US versus Non-US) on the primary and key secondary composite endpoints; also potentially other endpoints – ITT Population

- Additional subgroup analyses for patients with very high-risk cardiovascular disease (CVD) (defined as recurrent cardiovascular [CV] events or CV events in more than one vascular bed, i.e., polyvascular disease) on the primary and key secondary composite endpoints; also potentially other endpoints – ITT Population

- Sensitivity analyses for apo B to assess whether subgroup(s) with apo B reductions from baseline beyond certain threshold(s) have corresponding incremental reductions in clinical endpoint events

- Sensitivity analyses for myocardial infarction endpoints excluding peri-procedural MIs (Type 4a)

    - Additional analyses factoring for recency and number of prior MIs

- Sensitivity analyses for stroke, factoring for patients with history of stroke

- Sensitivity analyses for heart failure, factoring for patients with history of heart failure

- Sensitivity analyses for endpoints comprised of coronary revascularizations which exclude early elective revascularizations (e.g., within 30-90 days post-randomization)

- Subgroup analyses of primary (and potentially key secondary) endpoint(s) among following cohorts:

    - High risk patients with "the hypertriglyceridemic waist" (obese patients at high CV risk)
    - High risk subgroup defined by baseline hsTNT level (and potentially by NT-proBNP from archived frozen samples)
    - High TG/low LDL-C phenotypes beyond those currently specified in SAP and SAP Addendum
    - High-risk patients as defined by their atherothrombotic risk score[7]

- Treatment effect on:

    - Peripheral arterial events (e.g., major adverse limb events [MALE])
    - Hypertension, using BP as a continuous variable

- Using archived frozen serum biosamples: additional analyses of fatty-acid levels (and ratios), including baseline and on-treatment effects on EPA, DHA, DPA, AA (and associated ratios) and relationships between fatty-acid levels and cardiovascular outcomes.

    - Relationship between on-treatment fatty-acid levels and
        - Baseline fatty-acid levels and
        - Study medication compliance

- Using archived frozen biosamples (serum and whole blood); potential analyses of treatment effects on biomarkers and genetic markers and associations with outcomes, including but not limited to the following:

    - LDL-P
    - RLP-C (measured)
    - LDL-TG
    - Ox-LDL
    - Galectin-3
    - Lp(a) at baseline, as a predictor of CVD benefit
    - LpPLA2
    - HDL2, HDL3, apo A-I, apo A-II, HDL-P, apo C-III (and apo C-III in apo-B containing proteins), apo A-V, Apo E subtypes (2, 3, 4), IL-6, LPL

- Analyses may include change (and percent change) from baseline, and on-treatment comparisons between treatment groups with testing as predictors of CV risk

- Exploratory analyses of differential treatment effects for potential benefit (from adverse event reports) of:
  - Ophthalmologic changes (e.g., incidence of age-related macular degeneration, progression of diabetic retinopathy)
  - Cognitive impairment[8]
  - Erectile dysfunction[9]
  - Ischemic cardiomyopathy (as indicated by hospitalization for CHF, ICD placement etc.)

- Additional genetic bioassays including genes which may relate to triglyceride, lipid metabolism, and CVD

- Effects of potential mediators identified *post hoc* on primary/key secondary outcome measures[10]

SAP-Prespecified Exploratory Subgroups and Analyses

Analyses of effects of patients off study drug and withdrawn from study have on primary endpoint.

Subgroup analyses of the primary and key secondary endpoints as described for the primary endpoint. For each subgroup, Kaplan-Meier estimates, the log-rank test stratified by stratification factors used at randomization (except where the subgroup is a stratification factor), and HRs and CIs from the Cox proportional hazards model as specified for the primary efficacy endpoint, will be summarized by treatment group.

The following subgroups will be explored:

Demographic Parameters

- sex;
- age (<65 years and ≥65 years);
- race (white and non-white, or any other subset with at least 10% of the total number of patients);
- geography (Westernized, Eastern European, and Asia Pacific countries); and
- baseline ezetimibe use (yes/no).

Disease Parameters:

- CV risk category;
- the presence/absence of diabetes at baseline; and
- renal dysfunction (estimated glomerular filtration rate [eGFR] <60 mL/min/1.73m^2) using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation as follows:

$$eGFR = 141 \times \min(S_{cr}/\kappa, 1)^{\alpha} \times \max(S_{cr}/\kappa, 1)^{-1.209} \times 0.993^{Age} \times 1.018 \text{ [if female]} \times 1.159 \text{ [if black]}$$

Where:
S_{cr} is serum creatinine in mg/dL,
κ is 0.7 for females and 0.9 for males,
α is -0.329 for females and -0.411 for males,
min indicates the minimum of S_{cr}/κ or 1, and
max indicates the maximum of S_{cr}/κ or 1.

Treatment Parameters:

- Statin intensity at baseline (statin type and regimen)

Statin intensity categories as defined in ACC/AHA Cholesterol Guidelines[11] and patient's 10-year CV Risk Score[12] will be considered.

Baseline Lipid and Lipoprotein and Inflammatory Marker Parameters:

- LDL-C (by tertile);
- HDL-C (by tertile, and tertile by gender);
- TG (by tertile, and tertile by gender);
- RLP-C (by tertile);
- TG ≥150 mg/dL and TG <150 mg/dL;
- TG ≥200 mg/dL and TG <200 mg/dL;
- TG ≥ median, TG < median;
- combined highest tertile for TG and lowest tertile for HDL-C;
- gender-specific highest tertile for TG and lowest tertile for HDL-C;
- TG ≥ 200 mg/dL with HDL-C ≤35 mg/dL;
- hs-CRP (≤3 mg/L and >3 mg/L) and by gender;
- hs-CRP (≤2 mg/L and >2 mg/L) and by gender;
- Apo B (by tertile); and
- non-HDL-C (by tertile).

Adjustment for Baseline TG Level: Following a protocol amendment (May 2013), only patients with qualifying TG ≥200 mg/dL were enrolled in the study. Prior to that, patients with qualifying TG levels as low as approximately 135 mg/dL were permitted. To account and adjust for differing follow-up times depending on baseline TG level, a Cox PH model as described above but including baseline TG as a covariate will be fitted to the data at each interim. Diagnostic plots for the PH assumption will be evaluated.

The consistency of the treatment effects in subgroups will be assessed for the primary and key secondary efficacy endpoints. For each subgroup variable, a Cox proportional hazards model with terms for treatment, stratification factors (with the exception of those subgroup variables related to the stratification factors, i.e., CV risk category), subgroup, and treatment-by-subgroup interaction will be performed. The main treatment effect will not be tested with this model. P-values for testing the interaction terms <0.15 will be considered significant. Results will be presented in a Forest plot.

All subgroup analyses will be conducted for the ITT, mITT and PP populations.

Trial Registration

Due to a misunderstanding by a former employee of the sponsor, the trial was registered with ClinicalTrials.gov on December 15, 2011, which was 18 days after the first patient was randomized (November 28, 2011) and after 3 of the 8179 patients had been randomized, while still in compliance with FDA regulations.

Supplementary Table 1. Inclusion Criteria.[13]

1. Men or women ≥45 years of age with established CVD (Primary Prevention Risk Category; see Table 1a) *or* ≥50 years of age with diabetes in combination with one additional risk factor for CVD (Secondary Prevention Risk Category; see Table 1b)
2. Fasting TG levels ≥150 mg/dL and <500 mg/dL*
3. LDL-C >40 mg/dL and ≤100 mg/dL and on stable statin therapy (± ezetimibe) for ≥4 weeks prior to the LDL-C and TG qualifying measurements for randomization
4. Women who are not pregnant, not breastfeeding, not planning on becoming pregnant, and using an acceptable form of birth control during the study (if of child-bearing potential)
5. Able to provide informed consent and adhere to study schedules
6. Agree to follow and maintain a physician-recommended diet during the study

Table 1a. Inclusion Criteria for Secondary Prevention Risk Category.

Defined as men and women ≥45 years of age with one or more of the following:

1. Documented coronary artery disease (CAD; one or more of the following primary criteria must be satisfied):
    - Documented multi vessel CAD (≥50% stenosis in at least two major epicardial coronary arteries – with or without antecedent revascularization);
    - Documented prior MI;
    - Hospitalization for high-risk non-ST-segment elevation acute coronary syndrome (NSTE-ACS) (with objective evidence of ischemia: ST-segment deviation or biomarker positivity).
2. Documented cerebrovascular or carotid disease (one of the following primary criteria must be satisfied):
    - Documented prior ischemic stroke;
    - Symptomatic carotid artery disease with ≥50% carotid arterial stenosis;
    - Asymptomatic carotid artery disease with ≥70% carotid arterial stenosis per angiography or duplex ultrasound;
    - History of carotid revascularization (catheter-based or surgical).
3. Documented peripheral arterial disease (PAD; one or more of the following primary criteria must be satisfied):
    - Ankle-brachial index (ABI) <0.9 with symptoms of intermittent claudication;
    - History of aorto-iliac or peripheral arterial intervention (catheter-based or surgical).

Table 1b. Inclusion Criteria for Primary Prevention Risk Category.

Defined as patients with:

1. Diabetes mellitus (Type 1 or Type 2) requiring treatment with medication AND
2. Men and women ≥50 years of age AND
3. One of the following at Visit 1 (additional risk factor for CVD):
    - Men ≥55 years of age and Women ≥65 years of age;
    - Cigarette smoker or stopped smoking within 3 months before Visit 1;
    - Hypertension (blood pressure ≥140 mmHg systolic OR ≥90 mmHg diastolic) or on antihypertensive medication;
    - HDL-C ≤40 mg/dL for men or ≤50 mg/dL for women;
    - Hs-CRP >3.00 mg/L (0.3 mg/dL);
    - Renal dysfunction: Creatinine clearance (CrCL) >30 and <60 mL/min;
    - Retinopathy, defined as any of the following: non-proliferative retinopathy, pre-proliferative retinopathy, proliferative retinopathy, maculopathy, advanced diabetic eye disease or a history of photocoagulation;
    - Micro- or macroalbuminuria. Microalbuminuria is defined as either a positive micral or other strip test (may be obtained from medical records), an albumin/creatinine ratio ≥2.5 mg/mmol or an albumin excretion rate on timed collection ≥20 mg/min all on at least two successive occasions; macroalbuminuria, defined as Albustix or other dipstick evidence of gross proteinuria, an albumin/creatinine ratio ≥25 mg/mmol or an albumin excretion rate on timed collection ≥200 mg/min all on at least two successive occasions;
    - ABI <0.9 without symptoms of intermittent claudication (patients with ABI <0.9 with symptoms of intermittent claudication are counted under Secondary Prevention Risk Category).

Note: Patients with diabetes and CVD as defined above are eligible based on the CVD requirements and will be counted under CV Risk Stratum 1. Only patients with diabetes and no documented CVD as defined above need at least one additional risk factor as listed, and will be counted under Primary Prevention Risk Category.

*A study amendment (May 2013) was made, increasing the lower end of the fasting TG level from ≥150 mg/dL to ≥200 mg/dL to increase enrollment of patients with TG at or above 200 mg/dL.

ABI denotes ankle-brachial index, CAD coronary artery disease, CrCL creatinine clearance, CV cardiovascular, CVD cardiovascular disease, HDL-C high-density lipoprotein cholesterol, Hs-CRP high-sensitivity C-reactive protein, LDL-C low-density lipoprotein cholesterol, MI myocardial infarction, PAD peripheral arterial disease, TG triglyceride.

Supplementary Table 2. Exclusion Criteria.[13]

1. Severe (New York Heart Association [NYHA] class IV) heart failure
2. Any life-threatening disease expected to result in death within the next 2 years (other than CVD)
3. Diagnosis or laboratory evidence of active severe liver disease
4. Hemoglobin A1c >10.0% at screening
5. Poorly controlled hypertension: SBP ≥200 mmHg or DBP ≥100 mmHg (despite antihypertensive therapy)
6. Planned coronary intervention or any non-cardiac major surgical procedure
7. Known familial lipoprotein lipase deficiency (Fredrickson Type I), apolipoprotein C-II deficiency, or familial dysbetalipoproteinemia (Fredrickson Type III)
8. Participation in another clinical trial involving an investigational agent within 90 days prior to screening
9. Intolerance or hypersensitivity to statin therapy
10. Known hypersensitivity to fish and/or shellfish, or ingredients of the study product or placebo
11. History of acute or chronic pancreatitis
12. Malabsorption syndrome and/or chronic diarrhea
13. Use of non-study drug-related, non-statin, lipid-altering medications, dietary supplements, or foods during the screening period (after Visit 1) and/or plans for use during the treatment/follow-up period including:
    a. Niacin (>200 mg/d) or fibrates (unless ≥28-day washout)
    b. Any OM-3 fatty acid medications (unless ≥28-day washout)
    c. Dietary supplements containing OM-3 fatty acids (eg, flaxseed, fish, krill, or algal oils; unless ≥28-day washout)
    d. Bile acid sequestrants (unless ≥7-day washout)
    e. PCSK9 inhibitors (unless ≥90-day washout)
14. Other medications (not indicated for lipid alteration):
    a. Tamoxifen, estrogens, progestins, thyroid hormone therapy, systemic corticosteroids (local, topical, inhalation, or nasal corticosteroids are allowed), HIV-protease inhibitors that have not been stable for ≥28 days prior to the qualifying lipid measurements (TG and LDL-C) during screening
    b. Cyclophosphamide or systemic retinoids during the screening period (unless ≥28-day washout) and/or plans for use during the treatment/follow-up period
15. Known AIDS (HIV-positive patients without AIDS are allowed)
16. Requirement for peritoneal dialysis or hemodialysis for renal insufficiency or creatinine clearance <30 mL/min
17. Unexplained elevated creatine kinase concentration >5 × ULN or elevation due to known muscle disease
18. Any condition or therapy which, in the opinion of the investigator, might pose a risk to

the patient or make participation in the study not in the patient's best interest

19. Drug or alcohol abuse within the past 6 months, and inability/unwillingness to abstain from drug abuse and excessive alcohol consumption during the study
20. Mental/psychological impairment or any other reason to expect patient difficulty in complying with the requirements of the study or understanding the goal and potential risks of participating in the study

AIDS denotes acquired immunodeficiency syndrome, CVD cardiovascular disease, DBP diastolic blood pressure, HIV human immunodeficiency virus, LDL-C low-density lipoprotein cholesterol, OM-3 omega-3, SBP systolic blood pressure, PCSK9 proprotein convertase subtilisin/kexin type 9, TG triglyceride, ULN upper limit of normal.

Supplementary Table 3. Select Prespecified Adjudicated Tertiary Endpoints – ITT Population.

Tertiary Endpoint	Icosapent Ethyl n/N (%)	Placebo n/N (%)	HR (95% CI)
Primary Endpoint in Patients with Diabetes at Baseline	433/2394 (18.1%)	536/2393 (22.4%)	0.77 (0.68, 0.87)
New Heart Failure	169/4089 (4.1%)	176/4090 (4.3%)	0.95 (0.77, 1.17)
New Heart Failure Requiring Hospitalization	141/4089 (3.4%)	144/4090 (3.5%)	0.97 (0.77, 1.22)
Transient Ischemic Attack	64/4089 (1.6%)	48/4090 (1.2%)	1.32 (0.91, 1.92)
Amputation for PVD	22/4089 (0.5%)	21/4090 (0.5%)	1.04 (0.57, 1.89)
Carotid Revascularization	31/4089 (0.8%)	26/4090 (0.6%)	1.18 (0.70, 1.98)
Coronary Revascularization	376/4089 (9.2%)	544/4090 (13.3%)	0.66 (0.58, 0.76)
Emergent Revascularization	41/4089 (1.0%)	65/4090 (1.6%)	0.62 (0.42, 0.92)
Urgent Revascularization	181/4089 (4.4%)	268/4090 (6.6%)	0.66 (0.54, 0.79)
Elective Revascularization	194/4089 (4.7%)	278/4090 (6.8%)	0.68 (0.57, 0.82)
Salvage Revascularization	0/4089 (0.0%)	2/4090 (0.0%)	0.00 (0.00, -)
Cardiac Arrhythmias Requiring Hospitalization of ≥ 24 Hours	188/4089 (4.6%)	154/4090 (3.8%)	1.21 (0.97, 1.49)
Cardiac Arrest	22/4089 (0.5%)	42/4090 (1.0%)	0.52 (0.31, 0.86)
Sudden Cardiac Death	61/4089 (1.5%)	87/4090 (2.1%)	0.69 (0.50, 0.96)
Ischemic Stroke	80/4089 (2.0%)	122/4090 (3.0%)	0.64 (0.49, 0.85)
Hemorrhagic Stroke	13/4089 (0.3%)	10/4090 (0.2%)	1.28 (0.56, 2.93)
New Onset of Diabetes[1]	65/1695 (3.8%)	63/1697 (3.7%)	1.04 (0.73, 1.47)

[1] Patients with with diabetes at baseline are excluded from this endpoint analysis.

PVD denotes peripheral vascular disease, n number of patients with events, N number of randomized patients for each endpoint analysis, HR hazard ratio, CI confidence interval.

Supplementary Table 4. Lipid, Lipoprotein, and Inflammatory Marker Data Over Time – ITT Population.

		Icosapent Ethyl (N=4089)				Placebo (N=4090)				Between Group Difference		
Biomarker	Visit	Median Observed Value	Median Absolute Change from Baseline	Median % Change from Baseline	Median % Change P-value[1]	Median Observed Value	Median Absolute Change from Baseline	Median % Change from Baseline	Median % Change P-value[1]	Median Absolute Change from Baseline[2]	Median % Change from Baseline[2]	Median % Change P value[3]
Triglycerides (mg/dL)	Baseline	216.5				216.0						
	Month 4	177.0	-37.5	-18.6	<0.001	221.0	5.5	2.7	<0.001	-45.5	-20.1	<0.001
	Year 1	175.0	-39.0	-18.3	<0.001	221.0	4.5	2.2	<0.001	-44.5	-19.7	<0.001
	Year 2	173.0	-38.5	-18.9	<0.001	220.0	4.3	2.1	<0.001	-43.8	-19.7	<0.001
	Year 3	167.0	-44.0	-21.7	<0.001	212.0	1.0	0.4	<0.001	-45.5	-20.3	<0.001
	Year 4	163.0	-42.5	-21.7	<0.001	200.0	-7.0	-3.7	>0.99	-38.0	-17.4	<0.001
	Year 5	158.0	-38.0	-20.0	<0.001	193.0	-3.0	-1.5	0.23	-33.5	-16.7	<0.001
	Last Visit	170.0	-45.0	-21.6	<0.001	202.0	-13.0	-6.5	<0.001	-32.0	-14.1	<0.001
Non-HDL-C (mg/dL)	Baseline	118.0				118.5						
	Month 4	113.0	-4.5	-4.0	<0.001	128.0	9.5	8.2	<0.001	-14.3	-12.2	<0.001
	Year 1	113.0	-4.0	-3.6	<0.001	130.0	12.0	10.4	<0.001	-15.5	-13.1	<0.001
	Year 2	113.0	-3.5	-3.1	0.002	129.0	11.5	9.8	<0.001	-14.5	-12.5	<0.001
	Year 3	112.0	-4.8	-4.2	<0.001	128.0	10.5	9.2	<0.001	-14.5	-12.4	<0.001
	Year 4	110.5	-5.0	-4.2	<0.001	126.0	9.5	8.1	<0.001	-14.0	-12.0	<0.001
	Year 5	109.0	-5.0	-4.4	0.004	123.0	7.0	6.1	<0.001	-11.0	-9.9	<0.001
	Last Visit	112.0	-5.0	-4.4	<0.001	124.0	6.0	5.1	<0.001	-10.0	-8.6	<0.001
LDL-C derived (mg/dL)[4]	Baseline	74.0				76.0						
	Year 1	77.0	2.0	3.1	<0.001	84.0	7.0	10.2	<0.001	-5.0	-6.6	<0.001
	Last Visit	77.0	2.0	3.1	<0.001	84.0	7.0	10.2	<0.001	-5.0	-6.6	<0.001
LDL-C Hopkins (mg/dL)	Baseline	85.8				86.7						
	Month 4	83.6	-1.6	-2.0	0.01	93.7	7.3	8.7	<0.001	-8.7	-10.3	<0.001
	Year 1	85.3	-1.1	-1.2	0.06	95.8	9.3	10.9	<0.001	-9.6	-11.4	<0.001
	Year 2	85.5	-0.1	-0.2	<0.001	96.1	9.5	11.4	<0.001	-9.4	-11.1	<0.001
	Year 3	84.6	-1.0	-1.2	0.01	95.7	9.0	10.5	<0.001	-8.7	-10.4	<0.001
	Year 4	83.6	-0.5	-0.6	0.07	94.7	8.8	10.1	<0.001	-8.9	-10.6	<0.001
	Year 5	82.2	-0.8	-0.7	0.23	91.6	6.2	6.9	<0.001	-6.6	-8.0	<0.001
	Last Visit	84.0	-1.0	-1.2	0.14	92.1	5.7	6.5	<0.001	-6.2	-7.4	<0.001
HDL-C (mg/dL)	Baseline	40.0				40.0						
	Month 4	39.0	-1.0	-2.8	<0.001	42.0	2.0	4.7	<0.001	-3.0	-7.2	<0.001
	Year 1	39.0	-1.0	-2.6	<0.001	42.0	1.5	3.8	<0.001	-2.5	-6.3	<0.001
	Year 2	40.0	0.0	0.0	0.21	42.0	1.5	4.2	<0.001	-2.0	-4.6	<0.001
	Year 3	40.0	0.0	0.0	0.006	42.0	1.5	4.0	<0.001	-1.5	-3.8	<0.001
	Year 4	40.5	0.5	1.0	<0.001	43.0	2.0	4.8	<0.001	-1.5	-3.9	<0.001
	Year 5	41.0	0.0	0.0	0.02	43.0	1.5	3.0	<0.001	-1.5	-3.0	<0.001
	Last Visit	41.0	1.0	2.5	<0.001	42.0	2.0	5.7	<0.001	-1.0	-3.0	<0.001
Apo B (mg/dL)	Baseline	82.0				83.0						
	Year 2	80.0	-2.0	-2.5	0.05	89.0	6.0	7.8	<0.001	-8.0	-9.7	<0.001
	Last Visit	80.0	-2.0	-2.5	0.06	86.0	4.0	4.5	<0.001	-5.0	-6.7	<0.001
hsCRP (mg/L)	Baseline	2.2				2.1						
	Year 2	1.8	-0.2	-13.9	0.04	2.8	0.5	32.3	<0.001	-0.9	-39.9	<0.001
	Last Visit	1.8	-0.2	-12.6	0.75	2.8	0.4	29.9	<0.001	-0.8	-37.6	<0.001
Log hsCRP (mg/L)	Baseline	0.8				0.8						
	Year 2	0.6	-0.1	-21.8	<.0001	1.0	0.3	0.0	0.9203	-0.4	-22.5	<.0001
	Last Visit	0.6	-0.1	-23.1	<.0001	1.0	0.3	-4.0	0.0481	-0.4	-21.2	<.0001
EPA (µg/mL)[5]	Baseline	26.1				26.1						
	Year 1	144.0	112.6	393.5	<0.001	23.3	-2.9	-12.8	<0.001	114.9	358.8	<0.001

[1] P value from Wilcoxon Signed-Rank test.
[2] Based on Hodges-Lehmann estimation.
[3] P Value from Wilcoxon rank-sum test.
[4] LDL-C value obtained via Preparative Ultracentrifugation was used. If the LDL-C Preparative Ultracentrifugation value was missing, then with prioritization, non-missing value obtained from LDL-C Direct measurements, followed by LDL-C value by the Friedewald calculation, and finally LDL-C value by the Hopkins calculation, was used.
[5] EPA was measured in serum samples at baseline and one year using a liquid chromatography-tandem mass spectrometry (LC-MS/MS) method as previously described.[14] Total EPA comprised of all EPA forms, including unesterified EPA as well as EPA incorporated into phospholipids, triacylglycerides, and cholesteryl esters.

Apo B denotes apolipoprotein B, EPA eicosapentaenoic acid, HDL-C high-density lipoprotein cholesterol, hsCRP high-sensitivity C-reactive protein, LDL-C low-density lipoprotein cholesterol.

Supplementary Table 5. Treatment-Emergent Adverse Events.

	Icosapent Ethyl (N=4089)	Placebo (N=4090)	P value[1]
Patients with at Least One TEAE,[2] n (%)	3343 (81.8%)	3326 (81.3%)	0.63
Serious TEAE	1252 (30.6%)	1254 (30.7%)	0.98
TEAE Leading to Withdrawal of Study Drug[3]	321 (7.9%)	335 (8.2%)	0.60
Serious TEAE Leading to Withdrawal of Study Drug[3]	88 (2.2%)	88 (2.2%)	1.00
Serious TEAE Leading to Death[4]	94 (2.3%)	102 (2.5%)	0.61

Note: A treatment-emergent adverse event (TEAE) is defined as an event that first occurs or worsens in severity on or after the date of dispensing study drug and within 30 days after the completion or withdrawal from study. Percentages are based on the number of patients randomized to each treatment group in the Safety population (N). Events that were positively adjudicated as clinical endpoints are not included.

[1] P value from Fisher's Exact test.

[2] All adverse events are coded using the Medical Dictionary for Regulatory Activities (MedDRA Version 20.1).

[3] Withdrawal of study drug excludes patients who were off drug in study (ODIS) for 30 days or more, and restarted study drug.

[4] The most common serious TEAEs leading to death by system organ class were neoplasms (1.1%); infections and infestations (0.4%); respiratory, thoracic, and mediastinal disorders (0.2%); cardiac disorders (0.2%); and vascular disorders (0.1%). No serious TEAEs leading to death by system organ class were statistically significant across treatment groups except for cardiac disorders, which occurred in 3 (0.1%) of icosapent ethyl patients and 15 (0.4%) of placebo patents (P=0.008).

Supplementary Table 6. Number (%) of Patients with Most Frequent Treatment-Emergent Adverse Events (≥5%) in Either Treatment Group by Preferred Term.

Preferred Term	Icosapent Ethyl (N=4089)	Placebo (N=4090)	P value [1]
Diarrhea	367 (9.0%)	453 (11.1%)	0.002
Back pain	335 (8.2%)	309 (7.6%)	0.29
Hypertension	320 (7.8%)	344 (8.4%)	0.35
Nasopharyngitis	314 (7.7%)	300 (7.3%)	0.56
Arthralgia	313 (7.7%)	310 (7.6%)	0.90
Upper respiratory tract infection	312 (7.6%)	320 (7.8%)	0.77
Bronchitis	306 (7.5%)	300 (7.3%)	0.80
Chest pain	273 (6.7%)	290 (7.1%)	0.48
Peripheral edema	267 (6.5%)	203 (5.0%)	0.002
Pneumonia	263 (6.4%)	277 (6.8%)	0.56
Influenza	263 (6.4%)	271 (6.6%)	0.75
Dyspnea	254 (6.2%)	240 (5.9%)	0.52
Urinary tract infection	253 (6.2%)	261 (6.4%)	0.75
Cough	241 (5.9%)	241 (5.9%)	1.00
Osteoarthritis	241 (5.9%)	218 (5.3%)	0.27
Dizziness	235 (5.7%)	246 (6.0%)	0.64
Pain in extremity	235 (5.7%)	241 (5.9%)	0.81
Cataract	233 (5.7%)	208 (5.1%)	0.22
Fatigue	228 (5.6%)	196 (4.8%)	0.11
Constipation	221 (5.4%)	149 (3.6%)	<0.001
Atrial fibrillation	215 (5.3%)	159 (3.9%)	0.003
Angina pectoris	200 (4.9%)	205 (5.0%)	0.84
Anemia	191 (4.7%)	236 (5.8%)	0.03

Note: A treatment-emergent adverse event (TEAE) is defined as an event that first occurs or worsens in severity on or after the date of dispensing study drug and within 30 days after the completion or withdrawal from study. Percentages are based on the number of patients randomized to each treatment group in the Safety population (N). Events that were positively adjudicated as clinical endpoints are not included.
All adverse events are coded using the Medical Dictionary for Regulatory Activities (MedDRA Version 20.1).
[1] P value from Fisher's Exact test.

Supplementary Table 7. Number (%) of Patients with Gastrointestinal Treatment-Emergent Adverse Events (≥3%) in Either Treatment Group by Preferred Term.

Primary System Organ Class Preferred Term	Icosapent Ethyl (N=4089)	Placebo (N=4090)	P value[1]
Gastrointestinal disorders	1350 (33.0%)	1437 (35.1%)	0.04
Diarrhea	367 (9.0%)	453 (11.1%)	0.002
Constipation	221 (5.4%)	149 (3.6%)	<0.001
Nausea	190 (4.6%)	197 (4.8%)	0.75
Gastroesophageal Reflux Disease	124 (3.0%)	118 (2.9%)	0.70

Note: A treatment-emergent adverse event (TEAE) is defined as an event that first occurs or worsens in severity on or after the date of dispensing study drug and within 30 days after the completion or withdrawal from study. Percentages are based on the number of patients randomized to each treatment group in the Safety population (N). Events that were positively adjudicated as clinical endpoints are not included.

All adverse events are coded using the Medical Dictionary for Regulatory Activities (MedDRA Version 20.1).

[1] P value from Fisher's Exact test.

Supplementary Table 8. Assessment of Serious Bleeding Treatment-Emergent Adverse Events by Category and by Preferred Term.

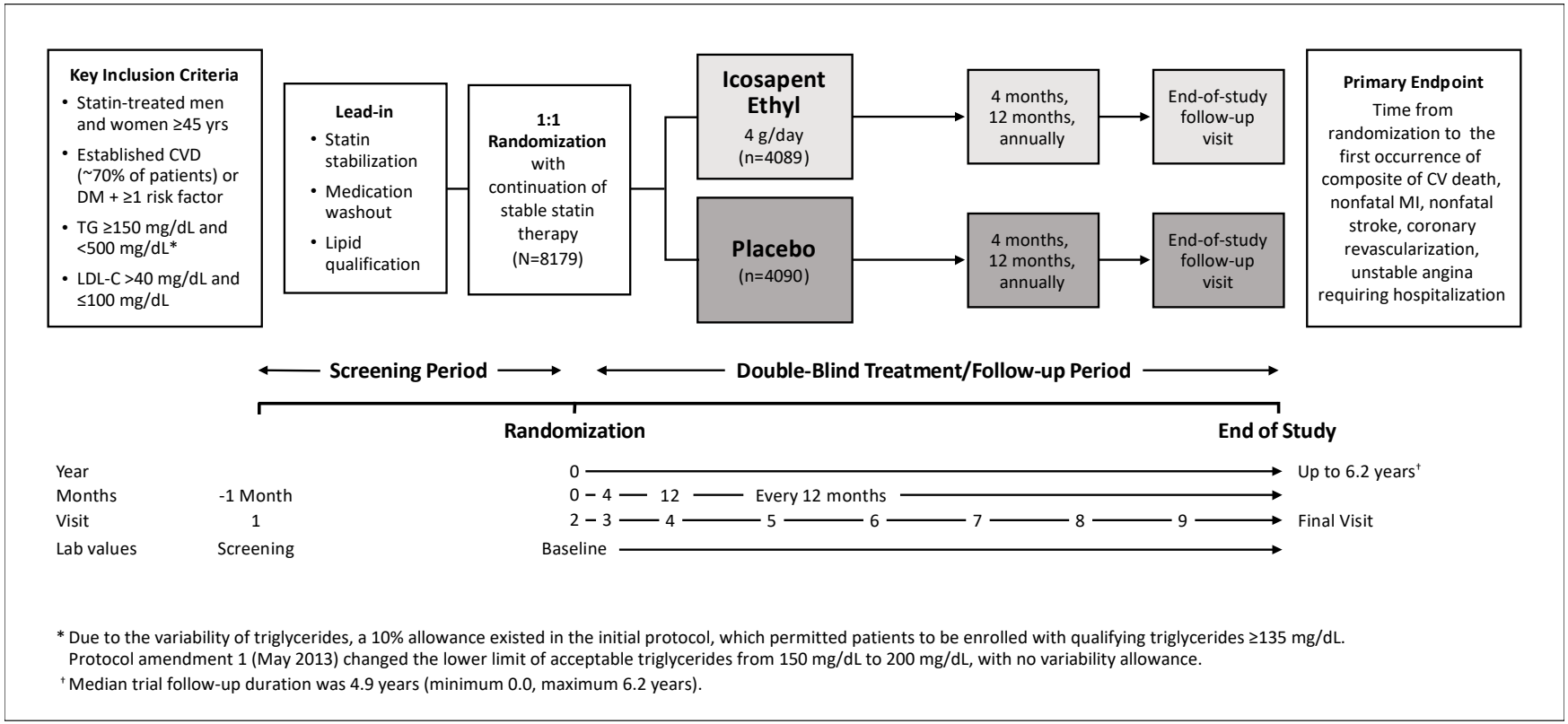
	Icosapent Ethyl (N=4089)	Placebo (N=4090)	P Value[1]
Patients with Bleeding-Related Disorders[2]	111 (2.7%)	85 (2.1%)	0.06
By Category			
Gastrointestinal Bleeding[3]	62 (1.5%)	47 (1.1%)	0.15
Central Nervous System Bleeding[4]	14 (0.3%)	10 (0.2%)	0.42
Other Bleeding[5]	41 (1.0%)	30 (0.7%)	0.19
By Preferred Term			
Gastrointestinal Hemorrhage	26 (0.6%)	20 (0.5%)	0.38
Rectal Hemorrhage	10 (0.2%)	6 (0.1%)	0.33
Subdural Hematoma	9 (0.2%)	5 (0.1%)	0.30
Hematuria	8 (0.2%)	4 (0.1%)	0.27
Epistaxis	7 (0.2%)	4 (0.1%)	0.39
Lower Gastrointestinal Hemorrhage	5 (0.1%)	4 (0.1%)	0.75
Post Procedural Hemorrhage	5 (0.1%)	3 (0.1%)	0.51
Hemorrhagic Anemia	4 (0.1%)	1 (0.0%)	0.22
Gastric Ulcer Hemorrhage	3 (0.1%)	1 (0.0%)	0.37
Hematemesis	3 (0.1%)	0 (0.0%)	0.12
Hemorrhoidal Hemorrhage	3 (0.1%)	1 (0.0%)	0.37
Melaena	3 (0.1%)	4 (0.1%)	>0.99
Upper Gastrointestinal Hemorrhage	3 (0.1%)	3 (0.1%)	>0.99
Diverticulum Intestinal Hemorrhagic	3 (0.1%)	3 (0.1%)	>0.99
Shock Hemorrhagic	2 (0.0%)	0 (0.0%)	0.25
Cystitis Hemorrhagic	2 (0.0%)	0 (0.0%)	0.25
Subarachnoid Hemorrhage	2 (0.0%)	1 (0.0%)	0.62
Subdural Hemorrhage	2 (0.0%)	1 (0.0%)	0.62
Traumatic Hematoma	2 (0.0%)	1 (0.0%)	0.62
Duodenal Ulcer Hemorrhage	2 (0.0%)	0 (0.0%)	0.25
Aortic Aneurysm Rupture	1 (0.0%)	1 (0.0%)	>0.99
Ecchymosis	1 (0.0%)	0 (0.0%)	0.50
Extravasation Blood	1 (0.0%)	0 (0.0%)	0.50
Gastric Hemorrhage	1 (0.0%)	3 (0.1%)	0.62
Gastrointestinal Angiodysplasia Hemorrhagic	1 (0.0%)	0 (0.0%)	0.50
Genital Hemorrhage	1 (0.0%)	0 (0.0%)	0.50
Hematochezia	1 (0.0%)	2 (0.0%)	>0.99
Hematoma	1 (0.0%)	1 (0.0%)	>0.99
Hemoptysis	1 (0.0%)	0 (0.0%)	0.50

	Icosapent Ethyl (N=4089)	Placebo (N=4090)	P Value[1]
Hemorrhagic Transformation Stroke	1 (0.0%)	0 (0.0%)	0.50
Hemothorax	1 (0.0%)	1 (0.0%)	>0.99
Intra-Abdominal Hemorrhage	1 (0.0%)	0 (0.0%)	0.50
Large Intestinal Hemorrhage	1 (0.0%)	1 (0.0%)	>0.99
Mallory-Weiss Syndrome	1 (0.0%)	0 (0.0%)	0.50
Menorrhagia	1 (0.0%)	0 (0.0%)	0.50
Pancreatitis Hemorrhagic	1 (0.0%)	0 (0.0%)	0.50
Peptic Ulcer Hemorrhage	1 (0.0%)	0 (0.0%)	0.50
Post Procedural Hematoma	1 (0.0%)	1 (0.0%)	>0.99
Retinal Hemorrhage	1 (0.0%)	1 (0.0%)	>0.99
Retroperitoneal Hemorrhage	1 (0.0%)	0 (0.0%)	0.50
Ulcer Hemorrhage	1 (0.0%)	0 (0.0%)	0.50
Urinary Bladder Hemorrhage	1 (0.0%)	1 (0.0%)	>0.99
Hemarthrosis	0 (0.0%)	1 (0.0%)	>0.99
Brain Contusion	0 (0.0%)	2 (0.0%)	0.50
Intracranial Hemorrhage	0 (0.0%)	1 (0.0%)	>0.99
Immune Thrombocytopenic Purpura	0 (0.0%)	1 (0.0%)	>0.99
Catheter Site Hemorrhage	0 (0.0%)	1 (0.0%)	>0.99
Mouth Hemorrhage	0 (0.0%)	1 (0.0%)	>0.99
Esophageal Hemorrhage	0 (0.0%)	1 (0.0%)	>0.99
Cerebral Hemorrhage	0 (0.0%)	2 (0.0%)	0.50
Pericardial Hemorrhage	0 (0.0%)	1 (0.0%)	>0.99
Post Procedural Hematuria	0 (0.0%)	1 (0.0%)	>0.99
Renal Hemorrhage	0 (0.0%)	1 (0.0%)	>0.99
Retroperitoneal Hematoma	0 (0.0%)	1 (0.0%)	>0.99
Traumatic Intracranial Hemorrhage	0 (0.0%)	1 (0.0%)	>0.99
Diverticulitis Intestinal Hemorrhagic	0 (0.0%)	1 (0.0%)	>0.99
Hemorrhagic Duodenitis	0 (0.0%)	1 (0.0%)	>0.99

Note: A treatment-emergent adverse event (TEAE) is defined as an event that first occurs or worsens in severity on or after the date of dispensing study drug and within 30 days after the completion or withdrawal from study. Percentages are based on the

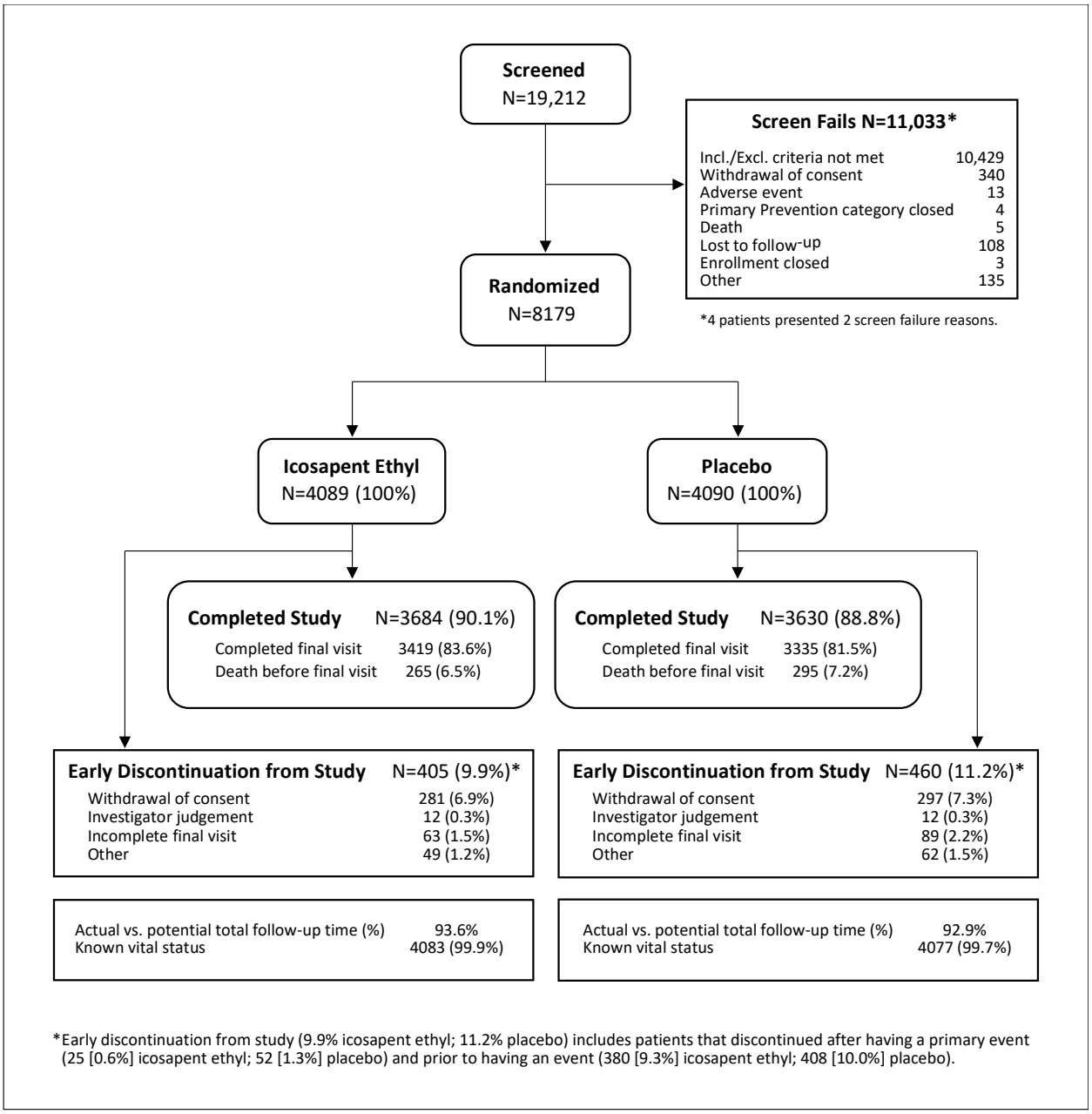
number of patients randomized to each treatment group in the Safety population (N). Events that were positively adjudicated as clinical endpoints are not included.
All adverse events are coded using the Medical Dictionary for Regulatory Activities (MedDRA Version 20.1).
[1] P value from Fisher's Exact test.
[2] Bleeding related events are identified using the Hemorrhage terms (excl laboratory terms), a Standard MedDRA Query (SMQ).
[3] Gastrointestinal (GI) related bleeding events are identified using the Gastrointestinal hemorrhage SMQ.
[4] Central nervous system (CNS) related bleeding events are identified using the Central Nervous System hemorrhages and cerebrovascular conditions SMQs.
[5] Other bleeding events are identified from the Hemorrhage terms (excl laboratory terms) SMQ excluding GI bleeding and CNS bleeding.

Supplementary Figure 1. Design of the REDUCE-IT Trial.[13]

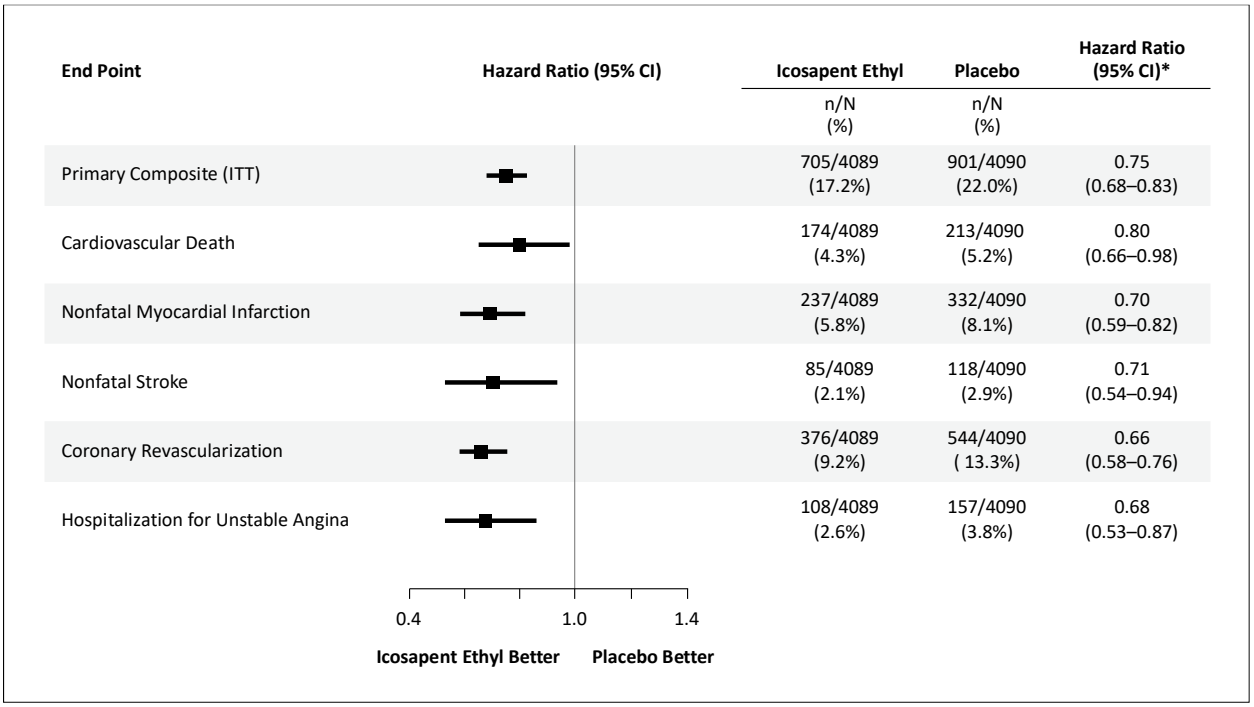


CVD denotes cardiovascular disease, DM diabetes mellitus, LDL-C low density lipoprotein cholesterol, MI myocardial infarction, TG triglyceride.

Supplementary Figure 2. CONSORT Diagram.



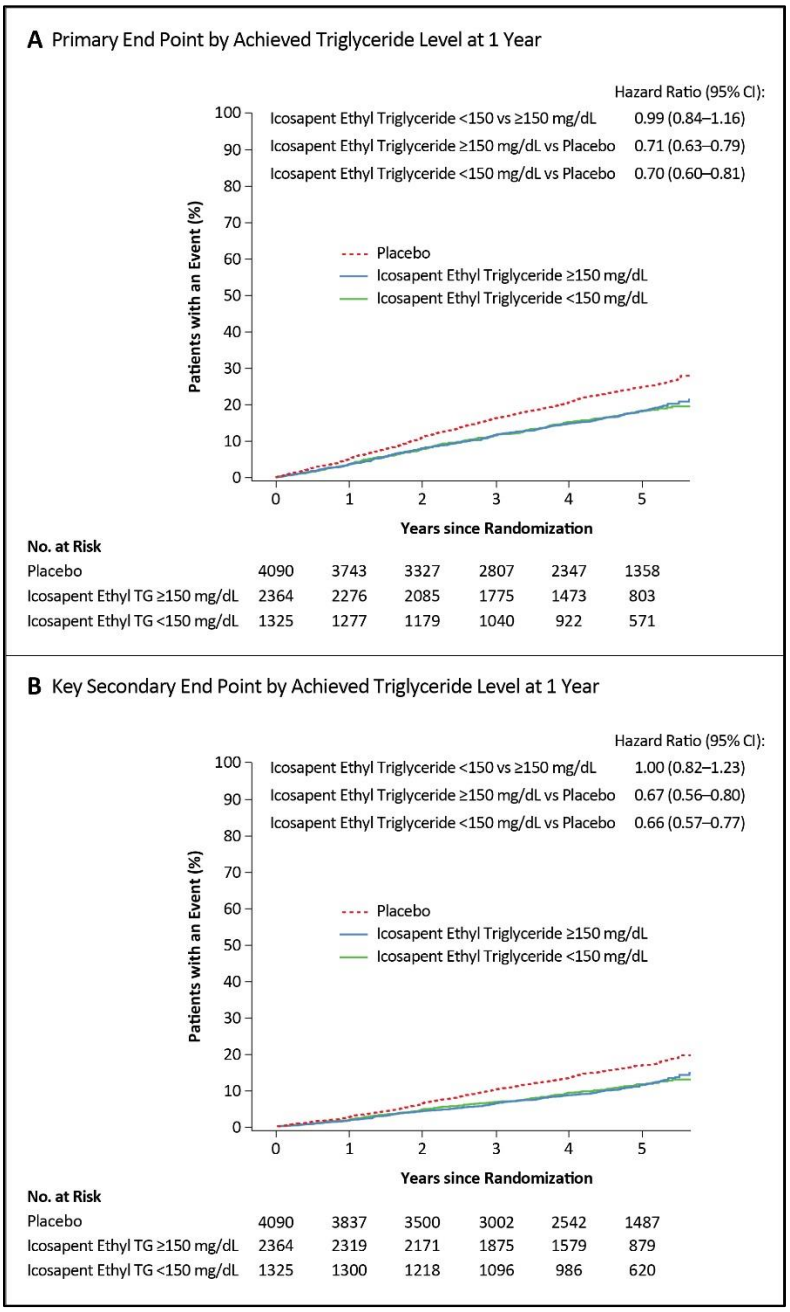
Supplementary Figure 3. Individual Components of the Primary Endpoint Analyzed as Time to First Event of Each Individual Endpoint. Shown first is the hazard ratio and 95% confidence interval for the primary composite endpoint event (time to first occurrence of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, coronary revascularization, or unstable angina). Shown separately beneath it are hazard ratios and 95% confidence intervals for time to first occurrence of each type of individual primary endpoint component event, irrespective of whether contributing to the primary composite endpoint event or not. Patients experiencing more than one event for any type of endpoint are counted for their first occurrence in each event type.



CI denotes confidence interval, ITT intent-to-treat.

*The confidence intervals have not been adjusted and inferences drawn from the intervals may not be reproducible

Supplementary Figure 4. Primary and Key Secondary End Points by Achieved Triglyceride Level (above or below 150 mg/dL) at 1 Year. Kaplan-Meier curves for time to first occurrence of the primary end point (cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, coronary revascularization, or unstable angina) and the key secondary end point (cardiovascular death, nonfatal myocardial infarction, nonfatal stroke) in the icosapent ethyl treatment group for patients with 1-year achieved triglycerides ≥150 mg/dL or <150 mg/dL, and the placebo group.



TG denotes triglyceride, CI confidence interval.

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