Supplementary Appendix

Supplement to: Lincoff AM, Bhasin S, Flevaris P, et al. Cardiovascular safety of testosterone-replacement therapy. N Engl J Med 2023;389:107-17. DOI: 10.1056/NEJMoa2215025

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

Table of Contents

TRAVERSE Site Investigators:

Number of patients enrolled in parentheses:

R. Helm, Investigative Clinical Research of Indiana, LLC, Elwood, IN (93); P. Trueba, Future Care Solution LLC, Miami, FL (91); S. Kester, Clinical Research Center of Florida, Pompano Beach, FL (84); S. Ansari, Longwood Research, Huntsville, AL (68); A. Makhlouf, Hillcroft Medical Clinic, Sugar Land, TX (60); V. Hoon, Advanced Biomedical Research of America Inc., Las Vegas, NV (57); S. Aslam, Northwest Houston Heart Center, Tomball, TX (51); K. Bender, DBC Research, Tamarac, FL (50); J. Cardona, Indago Research and Health Center, Inc., Hialeah, FL (47); A. Dinnerstein, Helix Biomedics, LLC, Boynton Beach, FL (47); B. Wieskopf, North Georgia Clinical Research, Woodstock, GA (47); R. Falcone, Amici Clinical Research, LLC - Raritan, Raritan, NJ (46); J. Mandry, West Orange Endocrinology, P.A., Ocoee, FL (46); E. Shapiro, Eclipse Clinical Research, Tucson, AZ (45); M. Darani, Marvel Clinical Research, LLC, Huntington Beach, CA (44); L. Pearlman, Synexus Clinical Research US, Inc. – Tempe, Chicago, IL (44); S. Nasir, Affinity Clinical Research Institute, Oak Brook, IL (43); R. Heller, Bayview Research Group LLC. Valley Village, CA (42); J. Miracle, Synexus Clinical Research US, Inc. – Tempe, Akron, OH (42); M. Digiovanna, DiGiovanna Family Care Center (DFCC), North Massapequa, NY (41); K. Lucas, Diabetes & Endocrinology Consultants, Morehead City, NC (41); N. Andrawis, Manassas Clinical Research Center, Manassas, VA (39); E. Davidson, New Phase Research & Development, LLC, Knoxville, TN (39); M. Doty, Care Research Center Inc., Miami, FL (39); D. Mishkin, InvesClinic Research Center, Fort Lauderdale, FL (38); C. Brinson, Austin Primary Care Physicians, Pflugerville, TX (37); N. Farris, The Research Group of Lexington, LLC, Lexington, KY (37); G. Kipp, Northwest Clinical Research Center, Bellevue, WA (37); A. Krishna, Diabetes and Endocrinology Associates of Stark County, Inc., Canton, OH (37); P. Moore, ClinRx Research, LLC, Plano, TX (37); G. Yeoman, Founders Research Corporation, Philadelphia, PA (37); M. Allaw, Clinical Research Advantage, Inc. Tempe, Evansville, IN (36); J. Bashour, Synexus – Dallas, Dallas, TX (35); R. Montgomery, Triad Clinical Trials, Greensboro, NC (35); A. Tan, West Coast Research, LLC, Dublin, CA (35); A. Ahmad, East Texas Cardiology, PA, Houston, TX (34); D. Levinson, Chicago Clinical Research Institute, Inc., Chicago, IL (34); G. Shockey, Desert Clinical Research, LLC, Mesa, AZ (34); K. Ayesu, Omega Research Consultants LLC, Orlando, FL (33); L. McGill, Clinical Neuroscience Solutions, Inc. (CNS Healthcare of Memphis), Memphis, TN (33); N. Secrist, Alliance for Multispecialty Research, LLC – Wichita, Wichita, KS (33); N. Gabra, Burke Internal Medicine & Research, Burke, VA (32); J. Kopp, Synexus Clinical Research US, Inc. – Tempe, Anderson, SC (32); L. McGill, Synexus Clinical Research US, Inc. / McGill Family Practice, Omaha, NE (32); N. Morrar, G & L Research, LLC, Foley, AL (32); R. Powell, Velocity Clinical Research - Cincinnati, Cincinnati, OH (32); R. Severance, East Valley Family Physicians, Chandler, AZ (32); P. Bravo, Bravo Health Care Center, North Bay Village, FL (31); R. Broughton, CB Flock Research Corporation, Mobile, AL (31); K. Cruz, Advanced Pharma CR, LLC, Miami, FL (31); S.

Gorrela, Spring Family Practice Associates, PA, Spring, TX (30); B. MacGillivray, Discovery Clinical Trials, San Antonio, TX (30); J. Loy, South Florida Wellness & Clinical Research Institute, Margate, FL (29); C. Lunn, Lynn Health Science Institute East, Oklahoma City, OK (29); T. Gilford, Associates in Medicine, PA, Houston, TX (27); P. Grossman, Masters of Clinical Research, Inc., Augusta, GA (27); T. Howard, Medical Affiliated Research Center, Huntsville, AL (27); A. Mendelson, Health Awareness, Inc. – Jupiter, Jupiter, FL (27); E. Riffer, Central Phoenix Medical Clinic, LLC, Phoenix, AZ (27); C. Calinescu, Synexus - Henderson DRS, Henderson, NV (26); P. Levins, Tatum Highlands Medical Associates, Glendale, AZ (26); R. Strzinek, Protenium Clinical Research, Hurst, TX (26); F. Velazquez, Pioneer Research Solutions, Inc., Houston, TX (26); M. Billings, Synexus – Greer, Greer, SC (25); G. Debs-Perez, Harmony Clinical Research, Inc., North Miami Beach, FL (25); K. Lee, Randolph Medical Associates, Asheboro, NC (25); I. Marar, West Broadway Clinic, Council Bluffs, IA (25); R. Toma, Simon-Williamson Clinic, Birmingham, AL (25); A. Adams, AB Clinical Trials, Las Vegas, NV (24); H. Audish, Encompass Clinical Research, Spring Valley, CA (24); M. Azizad, Valley Clinical Trials, Inc., Northridge, CA (24); C. Greiwe, Synexus Clinical Research US, Inc. – Columbus, OH (24); A.L. Lewy-Alterbaum, ALL Medical Research, LLC, Cooper City, FL (24); L. Akright, Northeast Endocrinology Associates, PA, Live Oak, TX (23); A. Al-Karadsheh, The Endocrine Center, Houston, TX (23); J. DeGrauw, Wasatch Peak Family Practice, Layton, UT (23); S. Dua, Valley Renal Medical Group, Northridge, CA (23); W. Jennings, Synexus Clinical Research US, Inc. - San Antonio, San Antonio, TX (23); L. Odekirk, Lynn Institute of Denver, Aurora, CO (23); M. Trevino, Innovative Research, Clearwater, FL (23); J. Venereo, Pharmax Research Clinic, Miami, FL (23); M. Agha, OnSite Clinical Solutions, LLC – Charlotte, Charlotte, NC (22); S. Benjamin, Universal Research Group, LLC, Tacoma, WA (22); M. Efros, Accumed Research Associates, Garden City, NY (22); J.C. Garza, Victorium Clinical Research, San Antonio, TX (22); V. Gold, FMC Science, LLC, Lampasas, TX (22); J. Kay, Clinical Research Advantage, Inc. - Council Bluffs, Omaha, NE (22); L. Rudolph, New Mexico Clinical Research & Osteoporosis Center, Inc., Albuquerque, NM (22); A. Fatakia, Tandem Clinical Research, LLC, Marrero, LA (21); M. Goisse, Frontier Clinical Research, LLC – Smithfield, Smithfield, PA (21); A. Hartman, Virginia Research Center, LLC, Midlothian, VA (21); K. Vora, Research Integrity, LLC, Owensboro, KY (21); A. Bhargava, Iowa Diabetes and Endocrinology Center (IDEC), West Des Moines, IA (20); L. Murray, Synexus Clinical Research US, Inc. - Pinellas Park, Pinellas Park, FL (20); T. Pluto, Frontier Clinical Research, LLC – Scottdale, Scottdale, PA (20); V. Fragoso, Texas Center for Drug Development, Inc., Houston, TX (19); S. Geller, Centennial Medical Group, Elkridge, MD (19); M. Lopez, Charlotte Heart & Vascular Institute, Port Charlotte, FL (19); R. Orr, Phoenix Medical Group, PC, Peoria, AZ (19); W. Patton, Quality of Life Medical & Research Center, Tuscon, AZ (19); B. Seidman, Seidman Clinical Trials, Delray Beach, FL (19); L. Thurman, IPS Research Company, Oklahoma City, OK (19); H. Tran, Texas Diabetes and Endocrinology - South Austin, Round Rock, TX (19); M. Winnie, Crossroads Clinical Research, LLC, Corpus Christi, TX (19); D. Allison, Hillcrest Clinics, Waco, TX (18); P. Nugent, Synexus Clinical Research US, Inc. – Cincinnati, Cincinnati, OH (18); L. Nunez, New Horizon Research Center, Miami, FL (18); M. Nunez, Synexus – Queens, Jamaica, NY (18); G. Quesada, Veritas Research, Corp., Miami Gardens, FL (18); J. Solis, Centex Studies, Inc. – McAllen, McAllen, TX (18); N. Wick, Meridien

Research Inc. – Tampa, Tampa, FL (18); J. Andersen, Meridien Research, Lakeland, FL (17); W. Bowman, Sensible Healthcare, Ocoee, FL (17); D. Butuk, Solaris Clinical Research, Meridian, ID (17); L. Connery, Intend Research, Norman, OK (17); G. Freeman, Health Research of Hampton Roads, Inc. (HRHR), Newport News, VA (17); M. Janik, Accellacare US Inc. of Wilmington, Wilmington, NC (17); R. Klein, Newport Native MD, Inc., Newport Beach, CA (17); R. Lending, Synexus Clinical Research US, Inc. – Tucson, Tucson, AZ (17); T. Lenzmeier, Lenzmeier Family Medicine, Glendale, AZ (17); J. Sandberg, Oakland Medical Research – Michigan, Troy, MI (17); P. Wylie, Preferred Research Partners, Little Rock, AR (17); N. Azad, Edward Hines Jr. VA Hospital, Hines, IL (16); A. Barber, OnSite Clinical Solutions, LLC – Charlotte; Hickory, NC (16); S. Bauer, OnSite Clinical Solutions, LLC – Charlotte, Charlotte, NC (16); H. Maheshwari, Midwest Endocrinology, Crystal Lake, IL (16); F. Munoz, Union Square Medical Associates, PC, Elizabeth, NJ (16); K. Soe, Veterans Affairs North Texas Health Care System (VANTHCS), Dallas, TX (16); E. Soroka, Eugene Soroka MD, Inc., Port Hueneme, CA (16); H. Upadhyay, Sandhill Research, LLC, St. Petersburg, FL (16); J. Agaiby, Clinical Investigation Specialists, Inc., Gurnee, IL (15); C. Bird, Colorado Springs Family Practice, Colorado Springs, CO (15); G. Disick, Imagine Research of Palm Beach County, Boynton Beach, FL (15); L. Duke, DMI Research (Decision Management International Health Care Group, Inc.), Pinellas Park, FL (15); T. Gaskin, Century Clinical Research, Inc., Daytona Beach, FL (15); N. Godbole, Summit Medical Group – Glendale, Glendale, AZ (15); R. Huling, Olive Branch Family Medical Center, Olive Branch, MS (15); D. Jack, Lone Peak Family Medicine, Draper, UT (15); W. Knapp, Med Research One, Florissant, MO (15); G. Ledesma, Arlington Family Health Pavilion, Arlington, TX (15); S. Makam, Mid Hudson Medical Research, PLLC, New Windsor, NY (15); S.A. Mujica Trenche, ALAS Science Clinical Research, Henderson, NV (15); J. Schmidt, North State Clinical Research, Lenoir, NC (15); L. Tharenos, Synexus Clinical Research US, Inc. - St. Louis, St. Louis, MO (15); S. Wilson, Ocean State Clinical Research Partners, LLC, Lincoln, RI (15); R. Anderson, VA Nebraska - Western Iowa Health Care System, Omaha, NE (14); K. Barbel-Johnson, Care Partners Clinical Research, Jacksonville, FL (14); P. Barnhill, Vineland Family Medicine, Whiteville, NC (14); J. Bashour, Synexus – Plano, Plano, TX (14); D. Bouda, Heartland Clinical Research, Omaha, NE (14); J. Daniel, Clinical Research Partners, LLC - Family Medicine / Internal Medicine, Richmond, VA (14); L. Feld, Horizon Clinical Research, LLC, Gilbert, AZ (14); T. Fiel, Fiel Family & Sports Medicine, Tempe, AZ (14); S. Grubb, Waterway Primary Care, LLC - Tabor City, Little River, SC (14); M. Hummel, Fountain Hills Family Practice PC, Fountain Hills, AZ (14); S. Koch, Koch Family Medicine, Morton, IL (14); M. Kramer, MB Clinical Research, Boca Raton, FL (14); J. Pouzar, Centex Studies, Inc. – Houston, Houston, TX (14); G. Trullenque, Floridian Research Institute LLC, Miami, FL (14); M. Welch, Consano Clinical Research, Shavano Park, TX (14); E. Armas, Well Pharma Medical Research, Miami, FL (13); J. Chang, Velocity Clinical Research, North Hollywood, North Hollywood, CA (13); R. Jordan, Center for Clinical Trials of Sacramento, Inc., Sacramento, CA (13); S. Leichter, Endocrine Consultants, PC – Columbus, Columbus, GA (13); R. Perry, Panax Clinical Research, Miami Lakes, FL (13); W. Randall, PriMed Clinical Research, Dayton, OH (13); R. Sastre, APF Research, LLC, Miami, FL (13); E. Bolster, Palmetto Clinical Research (PCR), Summerville, SC (12); A. Cohen, The Endocrine Clinic, PC, Memphis, TN (12); C.

Griffin, Lynn Health Science Institute (LHSI), Oklahoma City, OK (12); C. Herman, Quantum Clinical Trials, Miami Beach, FL (12); J. Jacqmein, Jacksonville Center for Clinical Research, Jacksonville, FL (12); B. Khan, Atlanta Vascular Research Foundation - Atlanta Clinical Research Centers, Atlanta, GA (12); I. Lieber, Texas Cardiology Associates of Houston, Kingwood, TX (12); C. Mbogua, Discovery MM Services, Inc. - Houston - Broadway St., Houston, TX (12); A. Murcia, DBC Research USA Corporation, Pembroke Pines, FL (12); R. Patel, Endocrine and Psychiatry Center, Houston, TC (12); H. Stamps, Collierville Medical Specialists, Collierville, TN (12); R. Swerdloff, Lundquist Institute for Biomedical Innovation at Harbor - UCLA Medical Center, Torrance, CA (12); J. Whatley, Centex Studies, Inc., Lake Charles, LA (12); M. Adams, Synexus Clinical Research US, Inc. - Salt Lake City, Murray, UT (11); J. Bailen, First Urology, Jeffersonville, IN (11); M. Bidair, San Diego Clinical Trials, La Mesa, CA (11); C. Breton, International Research Associates, LLC, Miami, FL (11); N. Daboul, Advanced Medical Research, LLC – Maumee, Maumee, OH (11); G. Flippo, Alabama Clinical Therapeutics, LLC, Birmingham, AL (11); M. Franco, Memorial Clinical Associates, PA, Houston, TX (11); G. Funk, Fundamental Research, Gulf Shores, AL (11); E. Gaddam, The Loretto Hospital, Chicago, IL (11); T. Hart, Terence T. Hart MD, Tuscumbia, AL (11); D. Headley, David M. Headley, MD, PA, Port Gibson, MS (11); D. James, The University Of Tennessee Health Science Center, Memphis, TN (11); D. Koontz, Palmetto Institute of Clinical Research, Inc., Pelzer, SC (11); D. McNeil, Optimed Research, LTD, Columbus, OH (11); M. Raikhel, Torrance Clinical Research Institute, Inc., Lomita, CA (11); M. Cornett, American Health Network of IN, LLC – Franklin, Franklin, IN (10); A. Daluga, American Health Network - Family Medicine and Specialty Care Services in Greenfield, Greenfield, IN (10); R. D'Anna, Applied Research Center of Arkansas, Little Rock, AR (10); A. Gosmanov, Albany Stratton VA Medical Center, Albany, NY (10); A. Iranmanesh, Salem VA Medical Center, Salem, VA (10); A. Qureshi, Pioneer Research Solutions, Inc., Beaumont, TX (10); H. Reyes, MediSphere Medical Research Center, Evansville, IN (10); S. Rosenberg, The Iowa Clinic, PC, West Des Moines, IA (10); D. Spiller, South Florida Research Solutions, LLC, Hollywood, FL (10); R. Estevez, Clinical Research of South Nevada, Las Vegas, NV (9); B. Green, B.G. Clinical Research Center, LLC, Little Rock, AR (9); E. Hanna, Internal Medicine Associates, Bridgeton, NJ (9); R. Kastelic, Richard M. Kastelic MD & Associates, PC, Johnstown, PA (9); M. Lawrence, Carteret Medical Group - Morehead City, Morehead City, NC (9); R. Manning, PMG Research of Knoxville, Knoxville, TN (9); K. Maynard, Investigators Research Group, LLC , Indianapolis, IN (9); C. Ng, Tower Urology, Los Angeles, CA (9); L. Phillips, Atlanta VA Medical Center, Decatur, GA (9); S. Plantholt, Maryland Cardiovascular Specialists, Baltimore, MD, (9); R. Powell, Meridien Research Inc. - Spring Hill, Spring Hill, FL (9); O. Ruffin, Trinity Clinical Research, LLC, Tullahoma, TN (9); J. Walsh, Richard L. Roudebush VA Medical Center, Indianapolis, IN (9); M. Woolman, Advanced Research Institute, Ogden, UT (9); S. Arora, Aventiv Research – Columbus, Columbus, OH (8); V. Awasty, Awasty Research Network, LLC, Marion, OH (8); T. Barker, PMG Research of Piedmont Healthcare, Mooresville, NC (8); S. Butman, Verde Valley Medical Center, Tucson, AZ (8); D. Cahn, Foothills Urology, Lakewood, CO (8); S. Dhindsa, Saint Louis University School of Medicine, St. Louis, MO (8); A. Doshi, PrimeCare Medical Group, Houston, TX (8); A. Drabick, Medication Management LLC, Raleigh, NC (8); R. Hood, Discover Research, Inc., Beaumont, TX

(8); M. Jardula, Desert Oasis Healthcare, Palm Springs, CA (8); J. Kovac, Urology of Indiana, Indianapolis, IN (8); D. McMullen, Discovery MM Services, Inc. - Missouri City, Missouri City, TX (8); W. Pharr, Medication Management LLC, Greensboro, NC (8); S. Phatak, Connecticut Clinical Research, LLC, Waterbury, CT (8); L. Quintero, International Research Associates, LLC – Hialeah, Hialeah, FL (8); A. Becker, Deaconess Clinic Downtown, Evansville, IN (7); B. Christine, Urology Centers of Alabama, P.C., Homewood, AL (7); W. Fitzgibbons, Skyline Medical Center, Elkhorn, NE (7); D. Fitz-Patrick, East-West Medical Research Institute, Honolulu, HI (7); N. Fraser, Troy Internal Medicine, P.C. - Research Division, Troy, MI (7); B. Gilbert, Office of Bruce R. Gilbert, MD, Great Neck, NY (7); I. Goldstein, San Diego Sexual Medicine, San Diego, CA (7); J. Haffizulla, Precision Clinical Research, LLC – Lauderdale Lakes, Lauderdale Lakes, FL (7); J. Lillo, Elite Clinical Studies, LLC, Phoenix, AZ (7); T. Nguyen, Solutions Through Advanced Research, Inc., Jacksonville, FL (7); E. Riley, Self Medical Group - Advanced Research Associates, Hodges, SC (7); D. Storey, American Health Network of IN, LLC – Avon, Avon, IN (7); S. Tebi, Care Access Research, Santa Clarita, CA (7); D. Uba, Rapha Institute for Clinical Research, Fayetteville, NC (7); J. Wayne, Clinical Trials Research, Lincoln, CA (7); D. Ajani, Discovery MM Services, Inc.– Katy, Houston, TX (6); E. Christofides, Endocrinology Research Associates, Columbus, OH (6); D. Francyk, Family Practice Specialists, Phoenix, AZ (6); D. Huffman, University Diabetes & Endocrine Consultants, Chattanooga, TN (6); S. Malempati, Tampa Bay Medical Research, Clearwater, FL (6); A. Odugbesan, Physicians Research Associates, LLC, Lawrenceville, GA (6); B. Pierpont, Advance Medical Research, Inc., St. Petersburg, FL (6); M. Rausch, Heartland Research Associates, LLC, El Dorado, KS (6); N. Razzaque, Synexus Clinical Research US, Inc. - West Florissant Internists, Bridgeton, MO (6); K. Rictor, SFM Clinical Trials, Scotland, PA (6); J. Stewart, Family Medicine Associates of Texas, PA, Carrollton, TX (6); D. Tripathy, South Texas Veterans Health Care System - Audie L. Murphy VA Hospital, San Antonio, TX (6); T. Briskin, Velocity Clinical Research - Cleveland, Cleveland, OH (5); K. Cohen, New West Physicians, PC, Golden, CO (5); A. Dang, Facey Medical Group, Mission Hills, CA (5); K. Fox, Family Medical Associates of Highland Park, LLC, Levittown, PA (5); S. Freedman, Sheldon J. Freedman, MD, Ltd., Las Vegas, NV (5); A. George, Seven Corners Medical Center, Falls Church, VA (5); E. Goldfischer, Premier Medical Group - Urology Division, Poughkeepsie, NY (5); R. Hollister, Lynn Institute of the Rockies, Colorado Springs, CO (5); R. Jacks, Hill Country Medical Associates, New Braunfels, TX (5); K. Kelley, Biofortis Clinical Research, Inc., Addison, IL (5); R. Mills, PMG Research of Charleston, Mt Pleasant, SC (5); R. Mohseni, Catalina Research Institute, LLC, Montclair, CA (5); F. Saba, Professional Health Care of Pinellas, Inc., St. Petersburg, FL (5); J. Sensenbrenner, PMG Research of Charlotte, Charlotte, NC (5); E. Sorial, Prima CARE, P.C., Fall River, MA (5); P. Wakefield, PMG Research of Knoxville, Knoxville, TN (5); L. Whitlock, Primary Care Group, LLC, Memphis, TN (5); M. Ampajwala, ACRC Trials, Frisco, TX (4); J. Borders, Drs. Borders, Hood, and Associates, Lexington, KY (4); P. Bradley, Meridian Clinical Research, LLC – Savannah, Savannah, GA (4); O.G. Brkic-Vukotic, Atlanta Center for Clinical Research, Roswell, GA (4); A. Brockmyre, Holston Medical Group, Bristol, TN (4); J. Chehade, University of Florida Health Endocrinology – Emerson, Jacksonville, FL (4); R. Harris, DeGarmo Institute of Medical Research, Greer, SC (4); N. Jaffrani, Alexandria Cardiology Clinic, Alexandria, LA (4); J.

Kaminetsky, Manhattan Medical Research, New York, NY (4); G. Ledger, Mercy Clinic Endocrinology, LLC, Springfield, MO (4); S. Lerman, The Center for Diabetes and Endocrine Care – Hollywood, Ft. Lauderdale, FL (4); A. Mabaquiao, TriWest Research Associates, El Cajon, CA (4); I.J. Madu, Diabetes Associates Medical Group, Orange, CA (4); R. Myers, "Clinic-LJ" Ltd, Ponte Vedra, FL (4); S. Nakhle, Palm Research Center, Inc., Las Vegas, NV(4); J. Perez, South Texas Cardiovascular Consultants, San Antonio, TX (4); W. Rust, Heritage Valley Medical Group, Beaver, PA (4); J. Serje, NY Total Medical Care, P.C., Brooklyn, NY (4); L. Smith, WVVA HealthCare Alliance, PC - Valley Medical Associates Inc., Lewisburg, WV (4); M. Tellez, Pacific Oaks Medical Group, Beverly Hills, CA (4); L. Belkoff, MidLantic Urology - Bala Cynwyd, Bala Cynwyd, PA (3); L. Berman, OnSite Clinical Solutions, LLC – Charlotte, Charlotte, NC (3); J. Cochran, Urology Clinics of North Texas, Dallas, TX (3); C. Cone, Montana Medical Research, Missoula, MT (3); K. Ellis, Clinical Research Associates of Tidewater, Norfolk, VA (3); S.M. Harman, Phoenix VA Health Care System, Phoenix, AZ (3); L. Herman, Herman Clinical Research, LLC, Suwanee, GA (3); J. Kirby, PMG Research of Knoxville, Jefferson City, TN (3); D. Liljenquist, Rocky Mountain Diabetes and Osteoporosis Center, Idaho Falls, ID (3); E. Morawski, Holston Medical Group, Kingsport, TN (3); N.C. Morcos, Syrentis Clinical Research, Santa Ana, CA (3); M. Patel, LaPorte County Institute for Clinical Research, Inc., Michigan City, IN (3); W. Penny, VA San Diego Healthcare System, San Diego, CA (3); E. Portnoy, Millennium Clinical Trials, Thousand Oaks, CA (3); M. Shanik, Endocrine Associates of Long Island, P.C., Smithtown, NY (3); H. Bagga, AGH Internal Medicine – Northside, Pittsburgh, PA (2); V. Bland, Bland Clinic, PA, Greensboro, NC (2); P. Bressler, North Texas Endocrine Center, Dallas, TX (2); J. Condit, American Health Network of Indiana – Muncie, Muncie, IN (2); A. Latorre, Applemed Research, Inc., Miami, FL (2); R. Leon, IMIC Inc., Palmetto Bay, FL (2); M. Marcelli, Michael E. DeBakey VA Medical Center, Houston, TX (2); M. Palatnik; Allied Clinical Research, LLC, Gold River; CA (2); B. Rizzardi, Velocity Clinical Research, Salt Lake City, West Jordan, UT (2); M. Vaughn, Cahaba Research, Inc., Birmingham, AL (2); J. Vazquez-Tanus, Research And Cardiovascular Corp., Ponce, PR (2); J. Willis, San Gabriel Clinical Research, Georgetown, TX (2); A. Alcantara, Centro de Endocrinologia Alcantara-Gonzalez, Bayamon, PR (1); K. Blaze, South Broward Research, LLC, Pembroke Pines, FL (1); W. Clark, Alaska Urological Institute, Anchorage, AK (1); G. Cortes-Maisonet, GCM Medical Group, PSC., San Juan, PR (1); T. Dixon, Tanner Clinic – Clinton, Clinton, UT (1); P. Greenberg, James J. Peters VA Medical Center, Bronx, NY (1); A. Gupta, Dayton VA Medical Center, Dayton , OH (1); C. Harper, Meridian Clinical Research, LLC – Norfolk, Norfolk, NE (1); H. Kerr, Cincinnati Veterans Affairs Medical Center, Cincinnati, OH (1); R. Leggett, Crossroads Clinical Research, LLC, Victoria, TX (1); E. Levin, VA Long Beach Healthcare System, Long Beach, CA (1); V. Mahabadi, Olive View - UCLA Medical Center, Sylmar, CA (1); B. Miranda, University of Miami - Miller School of Medicine, Miami, FL (1); J.H. Peniston, Thomas Jefferson University Hospital, Feasterville-Trevose, PA (1); A. Seftel, Cooper University Health Care, Camden, NJ (1); N. Sunkara, Optimum Clinical Research, Optimum Clinical Research, UT (1); A. Wokhlu, Malcom Randall VA Medical Center, Gainesville, FL (1); B. Wolf, Allied Clinical Research – Reno, Reno, NV (1); D. Wynn, Wright Clinical Research, Alabaster, AL (1); The following sites were also initiated to begin study activities: R. Adler, Hunter Holmes McGuire VA Medical

Center, Richmond, VA; A. Ahmad, Cardiovascular Association, PLLC, Humble, TX; O. Barnum, KAMP Medical Research, Inc., Natchitoches, LA; A. Clark, VA Pittsburgh Healthcare System, Pittsburgh, PA; D. Cohen-Neamie, Charter Research LLC, Winter Park, FL; A. Comulada Rivera, Advanced Clinical Research – Bayamon, Bayamon, PR; B. Cowan, Urology Associates of Colorado, Englewood, CO; M. Dawson, ACRC Trials, Austin, TX; A. Dobs, Johns Hopkins University School of Medicine, Baltimore, MD; J. Elsen, Pharmakon Inc., Evergreen Park, IL; J. Elsen, DuPage Medical Group - Downers Grove - 31st Street, Evergreen Park, IL; B. Essink, Meridian Clinical Research, LLC – Omaha, Omaha, NE; R. Farsad, Diagnamics, Encinitas, CA; B. First, Ritchken & First MDs, San Diego, CA; B. Frandsen, Sound Medical Research, Port Orchard, WA; A. Frisoli, Amici Clinical Research, LLC – Hoboken, Hoboken, NJ; N. Gabrail, Clinical Research Trials, LLC, Canton, OH; R. Garcia, Covenant Clinical Research, PA, San Antonio, TX; S. Georgeson, Medicor Cardiology, Bridgewater, NJ; J. Gilbert, St. Jude Hospital Yorba Linda, Fullerton, CA; L. Hernandez-Vazquez, Emanuelli Research and Development Center, Arecibo, PR; A. Hoffman, VA Palo Alto Health Care System, Palo Alto, CA; R. Hunter, ARA Arizona Research Associates, Tucson, AZ; D. Hurley, Family First Medical Care, LLC, Goose Creek, SC; L. Jenkins, The Ohio State University Wexner Medical Center - Department of Urology, Columbus, OH; A. Kabour, ID Clinical Research, Ltd., Toledo, OH; D. Kayne, The Medical Group of Encino, Encino, CA; Y. Kidokoro, Integrated Research Center, Inc., San Diego, CA; D. Lee, Irvine Center for Clinical Research, Irvine, CA; A. Matsumoto, VA Puget Sound Health Care System, Seattle, WA; A. Mills, Anthony Mills, MD, Inc., Los Angeles, CA; D. Mobley, Methodist Urology Associates, Houston, TX; S.P. Mokshagundam, University of Louisville, Louisville, KY; M. Pahor, University of Florida College of Medicine, Gainesville, FL; B. Purushottam, Monument Health Clinical Research, Rapid City, SD; O. Raheem, Tulane Medical Center, New Orleans, LA; S. Randhawa, S & W Clinical Research, Fort Lauderdale, FL; S. Shah, St. Joseph's Medical Associates, Inc., Stockton, CA; M. Syed, Endocrinology Associates of Armstrong – Indiana, Indiana, PA; S. Thomson, Veterans Affairs (VA) Health Care System – Tucson, Tucson, AZ; L. Torres, DeLeon Research, PLLC, Plano, TX

TRAVERSE Trial Leadership

Executive Steering Committee: Steven E. Nissen, MD (Chairman), Cleveland Clinic Coordinating Center for Clinical Research, Cleveland, OH; A. Michael Lincoff, MD (Co-Principal Investigator), Cleveland Clinic Coordinating Center for Clinical Research, Cleveland, OH; Shalender Bhasin, MBBS (Co-Principal Investigator), Harvard Medical School, Brigham and Women's Hospital, Boston, MA; Shehzad Basaria, MD, Harvard Medical School, Brigham and Women's Hospital, Boston, MA; William E. Boden, MD, VA Boston, MAVERIC Clinical Trials Network, Boston, MA; Glen R. Cunningham, MD, Baylor College of Medicine Medical Center, Houston, TX; Christopher B. Granger, MD, Duke Clinical Research Institute, Durham, NC; Mohit Khera, MD, MBA MPH, Baylor College of Medicine, Houston, TX; Ian M. Thompson, MD, CHRISTUS Santa Rosa Medical Center Hospital, San Antonio, TX

Cleveland Clinic Coordinating Center for Clinical Research (C5Research): Steven E. Nissen, MD (Executive Steering Committee Chairman), A. Michael Lincoff, MD (Co-Principal Investigator), Venu Menon, MD (Chairman, CEC Core Lab), Vidysagar Kalahasti, MD (Associate Chairman, CEC Core Lab), Lisa M. Mitchell, RN, BSN (Lead Project Manager), Kathy Wolski, MPH (Lead Statistician), Qiuqing Wang , MS (Primary Statistician for analysis), Deborah Davey, RN (Project Manager), Michelle Garcia, RN BSN (Project Manager), Kimberly J. Brown, BSN (CEC Manager), Robin Rodriguez, RN, MSN (CEC Lead Project Manager), Craig Balog, BS (System Analyst), Julie St. John, MS (Statistician), Tamera Gamble (Project Specialist)

AbbVie (Sponsor Leadership on behalf of the Testosterone Replacement Therapy (TRT) Manufacturer Consortium whose members include AbbVie, Acerus Pharmaceuticals Corporation, Endo Pharmaceuticals and Upsher-Smith Laboratories, LLC): Michael G. Miller, PharmD (Senior Director, Global Development Lead), Panagiotis Flevaris, MD, PhD (Medical Director, Clinical Lead), Michael C. Snabes, MD, PhD (Senior Medical Director), Anna Chan, PharmD (Scientific Director), Elena Dubcenco, MD, MS (Senior Medical Director), Xue Li, PhD (Associate Director, Statistics), Tingting Yi, PhD (Director Statistics), Biden Huang, PhD (Senior Director, Statistics), Teri Pannesi (Study Project Manager), Brage Garofalo (Program Lead), Rachel A. Preuss, MS (Study Management Associate III), Samantha J. Phillips, MPE, PMP (Study Management Associate III), Anne Shover (Statistical Analyst), Sheryn Bruso, BA (Senior Manager, Data Management), Tasneem Poonawala (Clinical Safety Analyst, Clinical Safety Management), Nader S. Khan, MD (Senior Medical Director), Fatima D. Khan, RN, CCRC (Senior Clinical Safety Analyst), Sandra Fukumoto, MBA (Study Project Manager II), Liangrui Sun (Senior Statistician, Statistical Science and Analytics, Data and Statistical Sciences), Thomas J. Korellis, BS (Study Management Associate III) and all AbbVie team members involved with TRAVERSE. The trial was funded by a consortium of testosterone manufacturers led by AbbVie, Inc. (North Chicago, IL) with additional financial support provided by Endo Pharmaceuticals (Malvern, PA), Acerus Pharmaceuticals Corporation (Ontario, Canada), Upsher-Smith Laboratories, LLC (Maple Grove, MN)

Advisory Committee: Culley Carson III, MD, University of North Carolina, Chapel Hill, NC; Adrian Dobs, MD, MHS, Johns Hopkins School of Medicine, Baltimore, MD; Alvin M. Matsumoto, MD, University of Washington, Seattle, WA; Peter Snyder, MD, Perelman School of Medicine, University of Pennsylvania, Division of Endocrinology, Diabetes and Metabolism, Philadelphia, PA; John R. Teerlink, MD, VA San Francisco/UCSF, San Francisco, CA

Data Monitoring Committee: John H. Alexander, MD, MHSc (Chairman), Duke Clinical Research Institute, Duke University, Durham, NC; William Bremner, MD, PhD, University of Washington, Seattle, WA; Eric Klein, MD, Cleveland Clinic, Cleveland, OH; Darren K. McGuire, MD MHSc, University of Texas Southwestern Medical Center, Dallas, TX; Janet Wittes, PhD, Wittes LLC, Washington, D.C.; Renato D. Lopes, MD, PhD (Observer, non-voting), Duke Clinical Research Institute, Durham, NC; Andrew Armstrong, MD, ScM (ad hoc consult), Duke University Medical Center, Duke Cancer Institute Center for Prostate and Urologic Cancers, Durham, NC
Independent Statistician for the Data Monitoring Committee*:* Kevin A. Buhr, PhD (non-voting Reporting Statistician), University of Wisconsin Statistical Data Analysis Center, Madison, WI

Clinical Events Committee: *Cardiovascular Committee:* Vidysagar Kalahasti, MD (Cardiovascular Neuro Chairman) Cleveland Clinic Coordinating Center for Clinical Research, Cleveland, OH; Cardiovascular Adjudicators at Cleveland Clinic, Cleveland, OH: Peter Hu, MD, David Nemer, MD, Divyang Patel, MD, Joshua Parker, MD, Nabil Sabbak, MD; Neurologist / Cardiovascular Adjudicator at Brookwood Baptist Health System Birmingham, AL: Jitendra Sharma, MD, MS; *Prostate Committee:* Michael P. O'Leary, MD, MPH (Chairman) Harvard Medical School, Brigham and Women's Hospital. Boston, MA; Prostate Adjudicators: Mark A. Preston, MD, Harvard Medical School, Boston MA; *Fracture Committee:* Douglas C. Bauer, MD, (Chairman), University of California, San Francisco, CA; Fracture Adjudicator at University of California, San Francisco, CA: Bo Fan, MD

Brigham and Women's Hospital, Harvard Medical School - Substudy Design and Substudy Committees Oversight: Shalender Bhasin, MB, BS (Co-Principal Investigator); Karol M. Pencina, PhD (Substudy Statistician); Thomas G. Travison, PhD (Substudy Statistician); Michael O'Leary (Chair, Prostate Events Adjudication Committee); Lauren Wilson (Substudy Project Manager)

Labcorp Contract Research Organization: Shein Nanji, BSc (Project Manager), Alicia Bush, RN, BSN (Adjudication Project Manager), Gopi Patel, MSc (Manager, Statistical Programming), Richa Chhibber, BDS, MS (Project Manager), Jennifer Potter, AS (Clinical Team Lead), S. Prem Sankar MSc (Associate Clinical Data Manager), Miriam Garduno Aguirre, MBA (Senior Clinical Data Specialist), Jamaal Ali, BS (Principal Clinical Data Manager), Sally Stephens, RN, BSN (Senior Clinical Trial Lead), Lindsey Sattler, RN, BSN (Associate Director), Diane Getsy Palmer, MD, PhD (Senior Medical Director), Renee Sullivan, MD, FACC (Senior Medical Director), Jamie Wantock, BSc (Senior Project Coordinator), Laura Gelpke, MA, PMP (Senior Director, Biopharma Global Project Delivery), Rosemary Molinari, PMP (Executive Director, Global Project Delivery), and all Labcorp team members involved with TRAVERSE

Eligibility Criteria

Inclusion Criteria
1. Men whose age is between 45 and 80 years, inclusive, at the time of Screening. 2. Meet the study definition of clinical hypogonadism as evidenced by: a) Two serum testosterone levels < 300 ng/dL collected between 5 AM and 11 AM local time. If Screening Visit (SV)1 level < 300 ng/dL, then proceed to SV2 or if needed, SV3: ● SV1 level < 300 ng/dL; and SV2 level < 300 ng/dL OR ● SV1 level < 300 ng/dL; and SV2 level between 300 ng/dL and 333 ng/dL; and with a SV3 level < 300 ng/dL ● If SV1 or SV2 level < 100 ng/dL, then additional SV3 confirmatory testosterone test is needed Note: Testosterone levels should be collected at least 48 hours apart. ***AND*** b) Presence of at least one sign or symptom that may be related to low testosterone values and is/are consistent with hypogonadism such as the following: ● Decreased sexual desire or libido ● Decreased spontaneous erections (e.g., morning erections) ● Decreased energy or fatigue/feeling tired ● Low mood or depressed mood ● Loss of body (axillary and pubic) hair or reduced shaving ● Hot flashes 3. Have pre-existing (historical) Cardiovascular (CV) disease as evidenced by at least one disease in Table OR at least three CV Risk Factors from Table .

Table A. Pre-Existing CV Disease

Coronary Artery Disease	• Acute Myocardial Infarction (MI) > 4 months before SV1 • Coronary Artery Disease (at least a 50% lesion in two of the major coronary artery distributions including their branches) as documented by angiogram • Coronary revascularization (coronary artery bypass grafting [CABG] or percutaneous coronary intervention [PCI]) > 4 months before SV1
Cerebrovascular Disease	• Stroke excluding hemorrhagic > 4 months before SV1 • Transient Ischemic Attack (TIA) that required treatment > 4 months before SV1 • Catheter-based or surgical revascularization of the carotid or middle cerebral arteries > 4 months before SV1 • Extracranial carotid artery stenosis > 50%, excluding intracranial vessels
Peripheral Arterial Disease	• Symptomatic peripheral arterial disease (i.e., lower extremity arterial disease documented by ankle/brachial index < 0.9 with claudication or resting limb ischemia obtained in the prior 12 months) • Peripheral arterial revascularization or amputation due to arterial obstructive disease > 4 months before SV1 • Peripheral arterial stenosis > 50% • Abdominal aortic aneurysm not due to connective tissue disorders

Table B. Cardiovascular Risk Factors

Risk Factor	Definition
Hypertension	- Hypertensive and taking prescription anti-hypertensive medication OR - Systolic blood pressure (SBP) > 140 or diastolic blood pressure (DBP) > 90 mmHg during Screening Period
Dyslipidemia	- Dyslipidemic and taking prescription anti-dyslipidemic medication OR - Low-density lipoprotein corrected (LDL-C) > 160 mg/dL or high-density lipoprotein cholesterol (HDL-C) < 40 mg/dL during Screening Period
Current Smoker	- Current daily cigarette/cigar smoker (e-cigarette smoking alone does not satisfy this criterion)
Stage 3 Chronic Kidney Disease (CKD) as defined by eGFR ranges	- Estimated Glomerular Filtration Rate (eGFR) > 30 and < 60 mL/min by Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) creatinine equation during Screening Period
Diabetes	-Diabetic and currently taking prescription anti-diabetic medication OR

	- Hemoglobin A1c (HbA1c) ≥ 6.5% or fasting glucose of ≥ 126 mg/dL during Screening Period
Elevated hsCRP	- History of high-sensitivity C-reactive protein (hsCRP) ≥ 2.0 mg/L (≥ 0.2 mg/dL) and confirmed at SV2
Documented Historical Agatston Coronary Calcium Score ≥ 75th percentile for age and race (supported by medical records)	- The Agatston coronary calcium score should not be obtained for the purposes of Screening (a link will be provided for calculation of the 75th percentile calcium score)
≥ 65 Years of Age	

4. Naïve to testosterone replacement, clomiphene, compounded or over-the-counter (OTC) androgenic steroid derivatives and dehydroepiandrosterone (DHEA), including investigational products that may affect the reproductive hormonal system within the past 6 months.
5. Willingness and the ability to apply topical testosterone gel as instructed by the study staff and comply with the requirements of this study protocol.
6. Intact skin surfaces on the upper arms and shoulders where the topical testosterone will be applied.

Exclusion Criteria

1. Congenital or acquired hypogonadism for whom long-term therapy with placebo would not be medically appropriate.
2. Two testosterone levels < 100 ng/dL during Screening.
3. Current or recurrent ulcer, erosion, lichenification, inflammation psoriasis, eczema or use of topical corticosteroids on the upper arms and shoulders. Tattoo application or removal in the region of study drug application within 6 months of Screening.
4. Known skin intolerance to alcohol or allergy to any of the ingredients of the study drug (see AndroGel 1.62% prescribing information).
5. History of treatment with growth hormone, anti-estrogen or estrogen treatment within 90 days prior to Screening.

6. Patients taking acute course (> 5 days) of opioids or systemic glucocorticoids > 7.5 mg prednisone equivalent per day (e.g., hydrocortisone 30 mg, methylprednisolone 6 mg, or dexamethasone 1.2 mg) for a recent acute condition (e.g., surgery, trauma, or illness) 1 week before SV1 through Day 1 (Note: Chronic daily therapy is allowable).
7. History of prostate (current or in the past) or breast cancer.
8. Severe lower urinary tract symptoms as indicated by an International Prostate Symptom Score (I-PSS) > 19.
9. Prostate nodule or induration as determined by the Investigator on screening Digital Rectal Examination (DRE). Men who have a documented normal DRE within 6 months of SV1 will not require a screening DRE. Prostate enlargement consistent with benign prostatic hyperplasia (BPH) is not an exclusion criterion. Prostate abnormalities where prostate cancer has been ruled out through previous negative biopsies are also not exclusionary.
10. Prostate-Specific Antigen (PSA) > 3.0 ng/mL; men treated with 5-alpha reductase inhibitors (e.g., dutasteride, finasteride) are eligible for participation as long as PSA levels are not > 1.5 ng/mL.
11. Seeking fertility currently or for the duration of the study.
12. History of untreated, severe obstructive sleep apnea.
13. Body Mass Index (BMI) > 50 kg/m^2.
14. Documented MI, coronary revascularization (CABG, PCI), unstable angina, stroke, transient ischemic attack (TIA) requiring treatment, catheter-based or surgical revascularization of the carotid or middle cerebral arteries or procedures to treat/current evidence of critical limb ischemia < 4 months of SV1 or during the Screening period.
15. New York Heart Association Class III or IV heart failure.
16. Sitting SBP > 180 mmHg or < 80 mmHg or sitting DBP > 110 mmHg or < 50 mmHg at any point during the Screening period.
17. HbA1c > 11% at Screening for diabetic patients.
18. History of unprovoked deep vein thrombosis (DVT), unprovoked pulmonary embolism (PE), or known thrombophilia.
19. Known history of polycythemia vera or secondary polycythemia, such as polycythemia due to untreated sleep apnea or severe chronic obstructive pulmonary disease (COPD).

20. History of major non-cardiovascular surgical procedure (e.g., major abdominal or thoracic procedure) within the 3 months prior to Screening and/or at the time of Screening, a major surgery is scheduled.

21. Any inpatient hospitalizations (duration of hospitalization > 24 hours) or major febrile illness (temperature > 101°F) within 4 weeks prior to Screening.

22. Active malignancy or diagnosed with or treated for cancer within the past 2 years. Patients with basal and squamous cell carcinoma of the skin that has been successfully treated will be allowed to participate.

23. A current condition, therapy, lab abnormality, history of clinically significant medical or psychiatric conditions or other circumstance or reasons which, in the opinion of the Investigator or the study staff, might pose a risk to the patient, make participation not in the patient's best interest, confound the results of the study (e.g., if patient cannot comply with requirements of the study), make the patient an unsuitable candidate to receive study drug, or interfere with the patient's participation for the full duration of the study.

24. History, suspicion, or evidence of significant drug or alcohol abuse or illicit steroid use within the previous 12 months prior to Screening (SV1), as determined by the Investigator.

25. Clinical laboratory analysis shows any of the following abnormal results:

    a. Hematocrit (Hct) > 50%.

    b. Alanine aminotransferase (ALT) or Aspartate aminotransferase (AST) > 3 × upper limit of normal (ULN).

26. Severe or end-stage CKD documented by eGFR < 30 mL/min.

27. Has been treated with any unapproved investigational drug within 30 days or five half-lives of the drug (whichever is longer) prior to the first dose of study drug. If the investigational product is known or thought to significantly affect the patient's CV risk profile, the washout period is 6 months prior to Screening (SV1).

28. Patient has a history of any of the following:

    - Major psychiatric disorder that is not controlled with a stable treatment regimen in the opinion of the Investigator.
    - Any suicide attempts within the past year or a response greater than 0 on Question 9 from Patient Health Questionnaire-9 (PHQ-9) at Screening.

29. Patients who have undergone female to male gender reassignment.

Titration of Testosterone Dose

The patients randomized to testosterone were started on 40.5 mg of study drug (2 actuations of the pump, each actuation delivering 20.25 mg testosterone) once daily; patients randomized to placebo group were started on 2 actuations of the pump delivering placebo on Study Day 1. The dose of the study drug was titrated based on the measurement of serum testosterone levels at the central laboratory (Labcorp) to achieve and maintain levels between 350 ng/dL and 750 ng/dL, as summarized in table below. The titration of testosterone dose occurred in patients receiving the active testosterone gel, while concurrent sham dose titrations occurred in patients receiving the placebo gel via the central Interactive Response Technology (IRT) system managed by the designated centrally located staff.

During study weeks 2, 4, 12, and 26 and months 12, 18, 24, 36 and 48, the study patients were asked to come to the clinical trial site for collection of a blood sample for serum testosterone measurement 24 hours (± 2 hours) after the last applied dose preferably in the morning. The titration of the study drug dose was guided by the on-treatment serum testosterone and hematocrit levels, according to the titration plan described below and the titration schedule shown in the table.

Dose Titration Schedule

Study Arm	**On-treatment serum testosterone concentrations 24 Hours (± 2 hours) after the last applied dose**	**Dose Titration**
Patients randomized to testosterone arm	Greater than 750 ng/dL	Decrease daily dose by 20.25 mg (one pump actuation)
	Between 350 ng/dL and 750 ng/dL, inclusive	No change: continue current dose
	Less than 350 ng/dL	Increase daily dose by 20.25 mg (one pump actuation)
Patients randomized to placebo arm	Irrespective of testosterone levels, patients received sham titrations.	Irrespective of testosterone levels, patients randomized to placebo received sham titrations

Titration instructions were communicated to the sites via the IRT system, while maintaining blinding of the trial site staff with respect to the intervention and the serum testosterone values. The patients randomized to the placebo arm of the trial also underwent sham dose titrations irrespective of their testosterone levels to maintain blinding.

If serum total testosterone concentration was greater than 750 ng/dL, the patient had his dose reduced by one study drug actuation (20.25 mg daily). The patient was then asked to return to the site for a repeat serum total testosterone measurement approximately 2 – 4 weeks after the dose reduction. If the repeat serum total testosterone level was still greater than 750 ng/dL,

the patient had his dose reduced by one study drug actuation followed by a repeat serum testosterone assessment approximately 2 weeks after the dose reduction. If serum testosterone level exceeded 750 ng/dL on the lowest dose (20.25 mg daily), the study medication was discontinued, and the patient was continued in the study in accordance with the intent-to-treat study design.

Hematocrit levels were also used to guide dose-titration as follows. Complete blood counts, including hematocrit levels, were obtained during months 6, 12, 18, 24, 36 and 48. If the hematocrit level was > 54%, the patient was asked to come back to the site for another blood draw approximately 2 weeks later to confirm result via the IRT system. Patients with confirmed hematocrit level > 54% were asked about secondary causes of elevated hematocrit (e.g., sleep apnea, severe dehydration) and had their dose reduced by two study drug actuations (40.45 mg daily). If the patient's dose could not be decreased by two actuations (e.g., in patients on 20.25 or 40.45 mg daily dose), then the dose was reduced by one actuation. The patient had a repeat hematocrit assessment approximately 30 to 45 days following the titration. If the repeat hematocrit level was > 54% even after dose titration to the lowest possible dose (20.25 mg daily), the study medication was stopped, and the patient was followed intent-to-treat.

Clinical Event Definitions

Primary Safety Endpoint: Time to Major Adverse Cardiovascular Events (MACE), is defined as time from randomization to the first component event occurrence of the composite MACE endpoint. MACE is defined as a composite endpoint consisting of any of the following:

- Nonfatal MI
- Nonfatal stroke
- Death due to CV causes

NON-FATAL MYOCARDIAL INFARCTION

The term myocardial infarction (MI) should be used when there is evidence of myocardial necrosis in a clinical setting consistent with myocardial ischemia. In general, the diagnosis of MI requires the combination of evidence of myocardial necrosis (either changes in cardiac biomarkers or post-mortem pathological findings); and supporting information derived from the clinical presentation, electrocardiographic changes, or the results of myocardial or coronary artery imaging. Note that silent MIs will not be adjudicated or counted toward the non-fatal MI endpoint during this study.

Criteria for Myocardial Infarction

a. Clinical Presentation- The clinical presentation should be consistent with diagnosis of myocardial ischemia and infarction.

b. Biomarker Elevations- For cardiac biomarkers, laboratories should report an upper reference limit (URL).

c. Electrocardiogram (ECG) Changes- Electrocardiogram changes can be used to support or confirm a MI. Supporting evidence may be ischemic changes and confirmatory information may be new Q waves.

***COVID-19 Positive Patients and Potential Coronary Ischemia Events**

Emerging evidence suggests that COVID-19 infection can cause myocarditis and pericarditis with associated elevations in cardiac enzymes and electrocardiographic changes. These events do not constitute endpoint MI. Thus, in patients who are COVID-19 positive, the Clinical Events Committee (CEC) must review the totality of evidence to help differentiate myocardial injury caused by COVID-19 from that caused by underlying CV disease/CV risk factors. Supporting information to be considered includes the results of myocardial and coronary imaging, including whether or not coronary revascularization is required or performed.

NON-FATAL STROKE

An acute episode of focal or global neurological dysfunction, caused by brain, spinal cord, or retinal vascular injury as a result of hemorrhage or infarction.

Ischemic

An acute episode of focal cerebral, spinal, or retinal dysfunction caused by infarction of central nervous system tissue. Note: Hemorrhage may be a consequence of ischemic stroke. In this situation, the stroke is an ischemic stroke with hemorrhagic transformation and not a hemorrhagic stroke.

Hemorrhagic
An acute episode of focal or global cerebral or spinal dysfunction caused by intra-parenchymal, intraventricular, or subarachnoid hemorrhage. Note: Subdural hematomas are intracranial hemorrhagic events and NOT strokes.

Undetermined
An acute episode of focal or global neurologic dysfunction caused by presumed brain, spinal cord, or retinal vascular injury as a result of hemorrhage or infarction but with insufficient information to allow categorization as either ischemic or hemorrhagic.

DEATH
All events with an outcome of death will be adjudicated to determine whether the death was related to a CV cause or a non-CV cause. The sites will additionally be allowed to enter an unknown cause of death. During adjudication, death will be classified into 1 or 2 categories: 1) cardiovascular death (which includes a subcategory of undetermined causes of death) and 2) non-cardiovascular death. Cardiovascular death includes death resulting from: an acute MI, sudden cardiac death, death due to heart failure (HF), death due to stroke, death due to cardiovascular (CV) procedures, death due to CV hemorrhage, and death due to other CV causes.

Non-Cardiovascular Death
When death is clearly due to a non-cardiovascular cause, a cardiovascular cause of death is excluded.

Secondary CV safety endpoints
Secondary CV safety endpoint, is defined as time from randomization to first component event occurrence of the composite endpoint consisting of any of the following:

- Nonfatal MI (note: silent MIs will not be adjudicated or counted toward the non-fatal MI endpoint during this study)
- Nonfatal stroke
- Death due to CV causes
- Coronary revascularization procedures/cardiac percutaneous coronary intervention (PCI) and coronary artery bypass graft (CABG) surgery. PCI is the placement of an angioplasty guide wire, balloon, or other device (e.g., stent, atherectomy, brachytherapy, or thrombectomy catheter) into a native coronary artery or CABG for the purpose of mechanical coronary revascularization. The assessment of coronary lesion severity by intravascular ultrasonography, coronary flow reserve, or fractional flow reserve is not considered a PCI procedure.

Tertiary Safety Endpoints

- All-cause mortality
- Heart failure (HF) events (hospitalization or urgent visit). Presentation of patient for an urgent, unscheduled hospital admission, with a primary diagnosis of HF, where the patient exhibits new or worsening symptoms of HF on presentation, has objective

evidence of new or worsening HF, and receives initiation or intensification of treatment specifically for HF. Objective evidence consists of at least 2 physical examination findings OR at least one physical examination finding and at least one laboratory criterion of new or worsening HF on presentation.

- Venous thromboembolic events include deep vein thrombosis, pulmonary artery embolism, and other peripheral venous thrombosis (excluding superficial thrombophlebitis).
- Peripheral arterial revascularization is a catheter-based or open surgical procedure designed to improve peripheral arterial blood flow or otherwise modify or revise vascular conduits. In general, the intention to perform percutaneous peripheral vascular intervention is denoted by the insertion of a guide wire into a peripheral artery. The target vessel(s) and the type of revascularization procedure (e.g., surgical bypass, thrombectomy, endarterectomy, percutaneous angioplasty, stent placement, thromboembolectomy, and thrombolysis) should be specified and recorded. This definition applies to the extracranial carotid artery and other non-cardiac arteries and excludes the intracranial vessels and lymphatics.

Restricted Mean Survival Time and Absolute Risk Difference Supportive Analyses in the Safety Set*

The absolute risk difference (RD) and restricted mean survival time (RMST) at 3-years were calculated and summarized as continuous measures. The RMST for this CV outcome trial may be described as the MACE-free expectancy over the restricted period between randomization and 3 years.

Assuming a background event rate of 1.5% for MACE in the Placebo arm, the decision threshold (non-inferiority margin) for RD and RMST at 3-years corresponding to a HR of 1.5 is set to be 2.14% and –12 days, respectively.

The RMST difference (Testosterone vs Placebo) at 3 years was 2.74 days with 95% CI (-7.00, 12.18). The absolute RD (Testosterone vs Placebo) at 3 years was -0.57% with 95% CI (-2.23%, 1.11%). Using the non-inferiority margin for RMST difference of -12 days and absolute RD of 2.14%, the P values for the non-inferiority of testosterone vs placebo with regard to the primary CV safety endpoint at 3 years were <0.001 (i.e., rejection of the null hypothesis that testosterone is inferior to placebo). These results support the non-inferiority test (Testosterone vs Placebo) for the HR margin of 1.5 (P<0.001) in terms of the primary MACE endpoint.

Primary MACE safety endpoint at 3 Years (Safety Set*)				
Estimate (SE) In Months	Testosterone	Placebo	RMST Difference (95% CI) in Months Testosterone – Placebo	RMST Difference (95% CI) in Days Testosterone – Placebo
RMST (Unadjusted[a)]	34.62 (0.11)	34.54 (0.12)	0.09 (-0.23, 0.40)	**2.74 (-7.00, 12.18)**
RMST (Adjusted[b])	34.26 (0.11)	34.21 (0.11)	0.05 (-0.26, 0.37)	1.52 (-7.91, 11.26)

RMST: Restricted Mean Survival Time; SE = Standard error

*The Safety Set is comprised of all randomized patients who received at least one dose of study drug (testosterone or placebo).

a. Unadjusted analysis results are obtained from Kaplan-Meier (KM) estimates using PROC LIFETEST procedure, where treatment group is included in the STRATA statement.

b. Adjusted analysis results are obtained from RMST regression model (PROC RMSTREG) with pre-existing CV disease and treatment group as covariates.

Primary MACE safety endpoint at 3 Years (Safety Set*)			
Estimate (%) (SE)	Testosterone	Placebo	Absolute RD (%) (95% CI) Testosterone – Placebo
Risk Estimate (Unadjusted[a)]	7.73 (0.59)	8.31 (0.61)	**-0.57 (-2.23, 1.11)**
Risk Estimate (Adjusted[b])	8.28 (0.61)	8.64 (0.62)	-0.36 (-2.01, 1.22)

RD: Risk Difference; SE = Standard error

*The Safety Set is comprised of all randomized patients who received at least one dose of study drug (testosterone or placebo).

a. Unadjusted analysis results (risk estimates along with their SEs and difference in risk estimates) are from Kaplan-Meier (KM) estimates using the PROC LIFETEST procedure, where treatment group is included in the STRATA statement. The 2-sided 95% CI of the difference in risk estimates are obtained by the bootstrap method with 5000 bootstrap samples.

b. Adjusted analysis results (risk estimates, difference in risk estimates) are from Cox proportional-hazards regression model (PROC PHREG) with prior CV disease status and treatment group as covariates. The SE of risk estimates and the 2-sided 95% CI of the difference in risk estimates are obtained by the bootstrap method with 5000 bootstrap samples.

Figure S1 – Flow of Patients Through the Trial

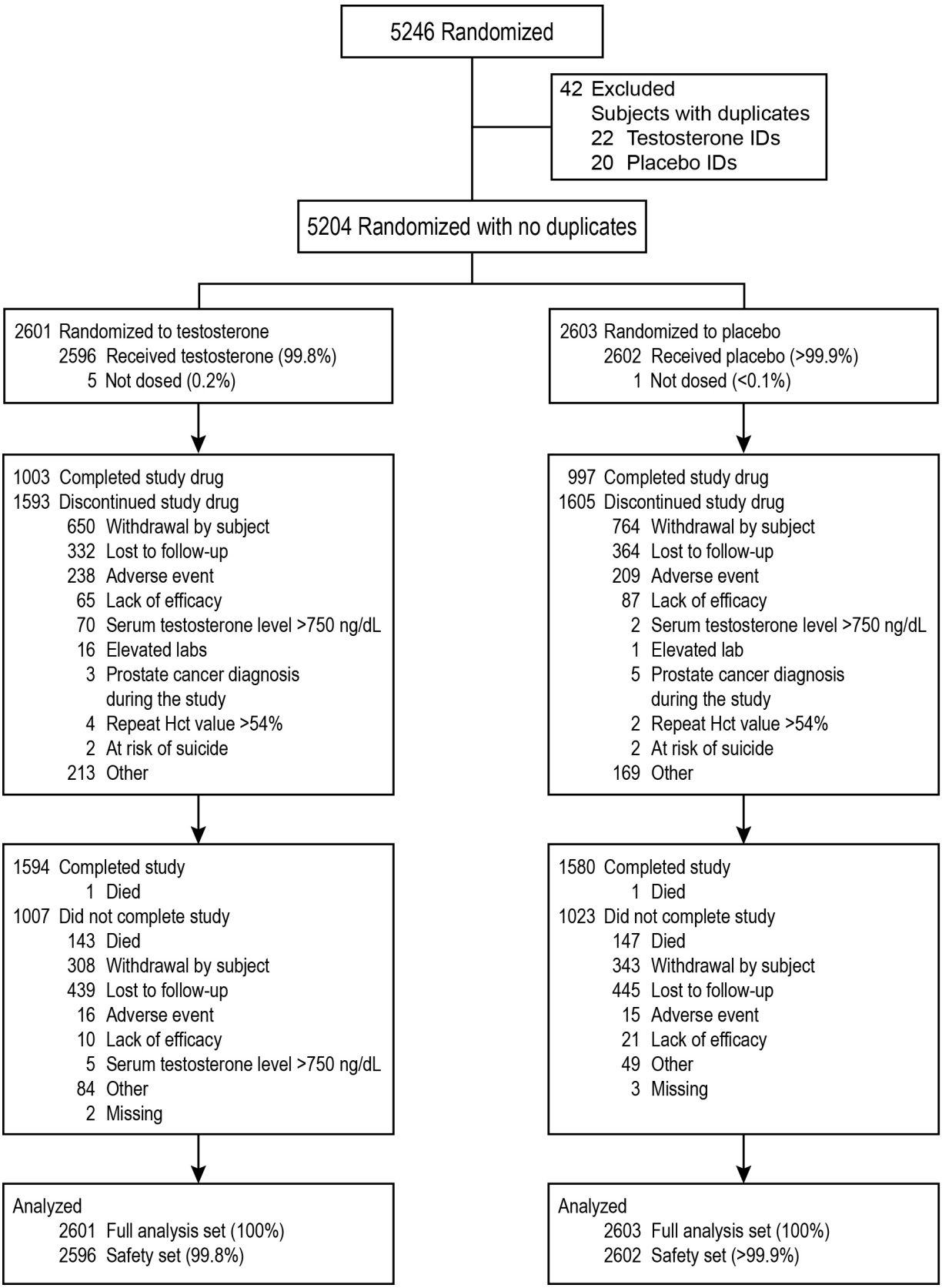
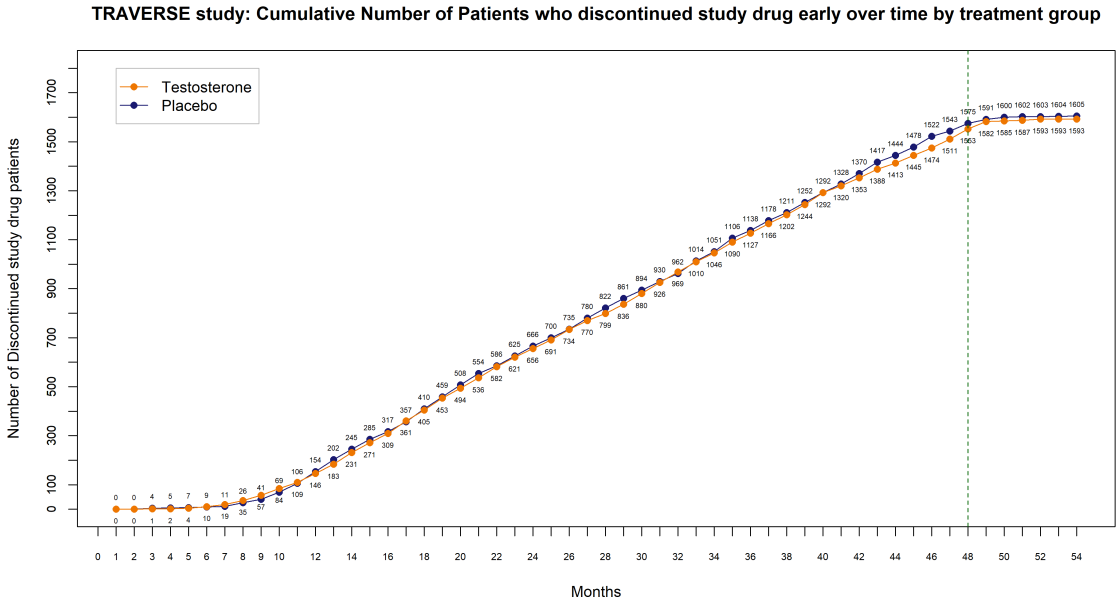
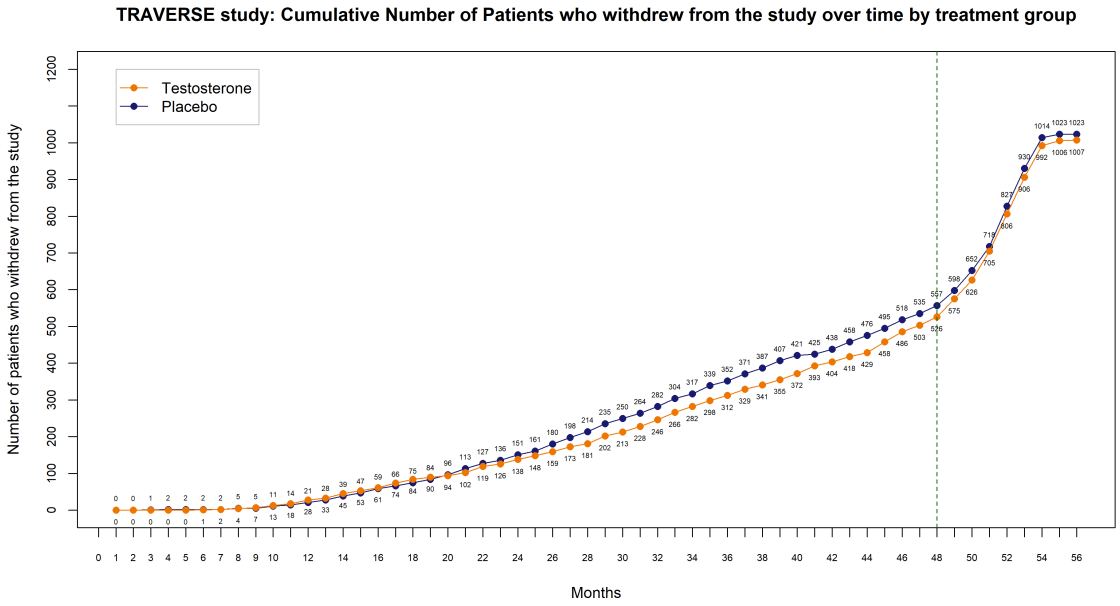


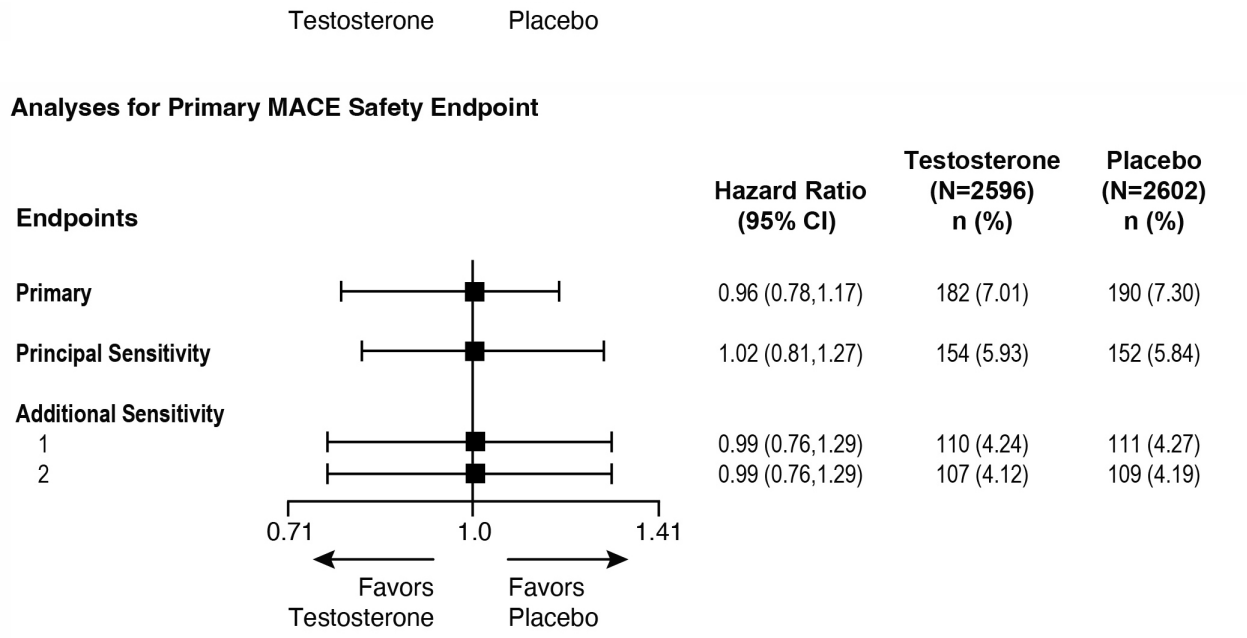
Figure S2 – Patients Who Discontinued Study Drug Early (Top Panel, Safety Set*) or Withdrew from the Study Early (Bottom Panel, Full Analysis Set*) During the Course of the Trial





Curves display cumulative number of patients who discontinued study drug early (top panel) or discontinued participation and study visits early (bottom panel) in the two treatment groups. The x-axis represents the months over the course of the trial, ranging from first patient enrollment (month 0 on the x-axis – May 23, 2018) through completion of the last patient end-of-study visit (month 56 on the x-axis – January 19, 2023). The dotted vertical line at month 48 represents the beginning of end-of-study visits after May 31, 2022. *The Safety Set excludes 6 patients that never received study drug. The Full Analysis Set is comprised of all randomized patients.

Figure S3 – Forest Plot of Primary and Sensitivity Analyses for the Primary MACE Safety Endpoint (Safety Set*)



Hazard ratios were calculated with the Cox proportional-hazards model, adjusted for pre-existing cardiovascular disease status.

*The Safety Set was comprised of all randomized patients who received at least one dose of study drug (testosterone or placebo). Patients with duplicate patient IDs were excluded.

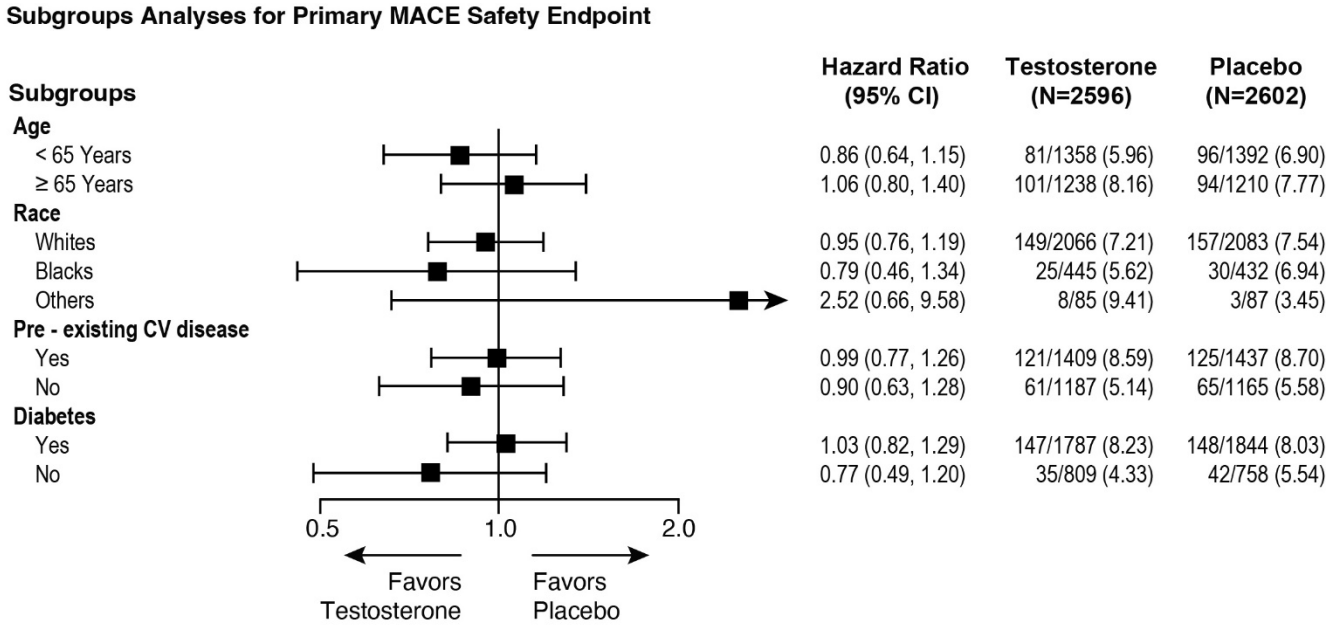
The primary analysis included all MACE (i.e., time to the first occurrence of MACE for each patient with an event) reported in the study.

The principal sensitivity analysis was performed based on “on-exposure” period. In this analysis, MACE that occurred during the period from randomization to 365 days post last dose were included. Events occurring after 365 days post last dose were censored.

Two additional sensitivity analyses were performed:

- Additional sensitivity analysis 1 - included MACE that occurred during the period from randomization to 30 days post last dose. Events occurring after 30 days post last dose were censored.
- Additional sensitivity analysis 2 – for patients with drug interruption(s) that was 3 months or longer, events occurring after 30 days post the start date of the first interruption of 3 months or longer were censored. For all other patients, events occurring after 30 days post last dose were censored.

Figure S4 – Forest Plot of Pre-Specified Subgroup Analyses for the Primary MACE Safety Endpoint by the Primary Analysis (Top Panel) and the Principal Sensitivity Analysis (Bottom Panel)



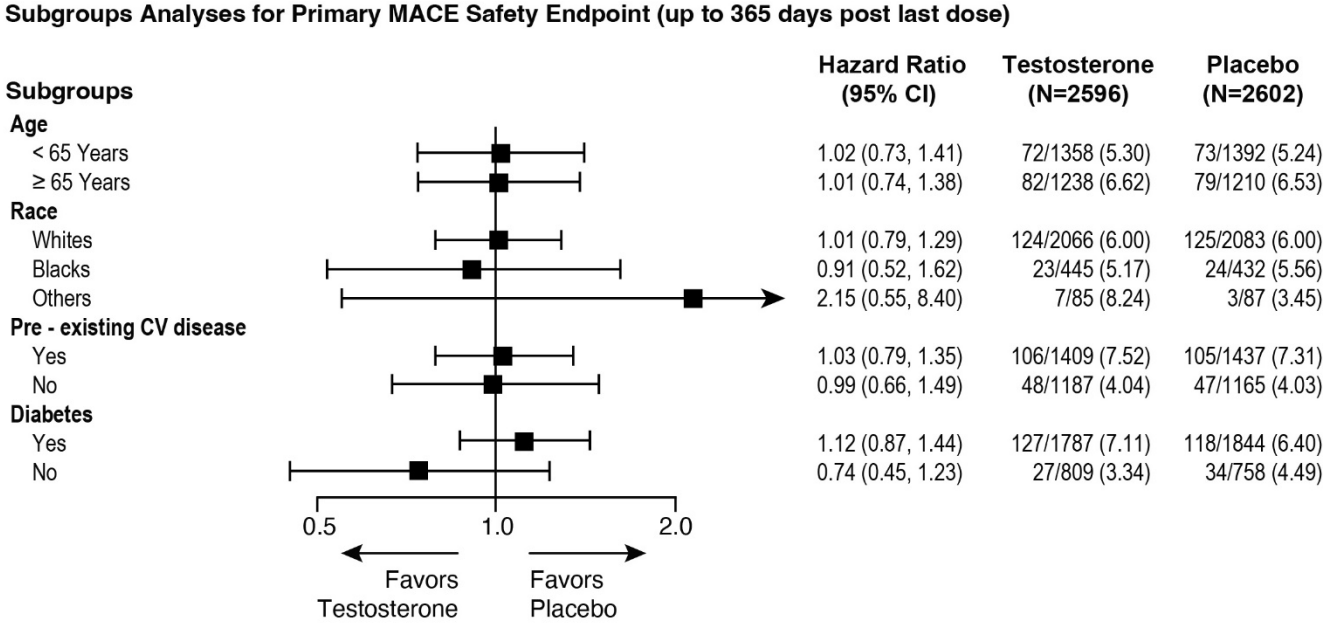


Table S1 – Study Outcomes: Primary, Secondary, and Tertiary Safety and Efficacy

Domain	Outcome	Population	Reported
Safety – Cardiovascular: Primary endpoint	MACE composite – death due to CV causes, non-fatal MI, non-fatal stroke	Safety Set	This paper
Safety – Cardiovascular: Secondary endpoints	Death due to CV causes	Safety Set	This paper
	Non-fatal MI	Safety Set	This paper
	Non-fatal stroke	Safety Set	This paper
	Cardiac revascularization	Safety Set	This paper
Safety – Cardiovascular: Tertiary endpoints	All-cause mortality	Safety Set	This paper
	Heart failure events	Safety Set	This paper
	Venous thromboembolic events	Safety Set	This paper
	Peripheral arterial revascularization	Safety Set	This paper
Safety – Prostate: Secondary endpoint	High grade prostate cancer (Gleason score of 4 + 3 or higher)	Safety Set	This paper
	Any prostate cancer	Safety Set	This paper
Safety – Prostate: Tertiary endpoints	Prostate biopsy	Safety Set	Future paper
	Acute urinary retention	Safety Set	Future paper
	Starting pharmacologic treatment for lower urinary tract symptoms	Safety Set	Future paper
	Invasive prostate surgical procedures for benign prostatic hyperplasia	Safety Set	Future paper
Efficacy – Sexual function	Change from baseline on overall sexual activity per PDQ Question 4	Randomized patients with low libido	Future paper
Efficacy – Low grade Persistent Depressive Disorder (PDD) (dysthymia)	Proportion of men whose PDD remits during intervention per remission definition	Randomized patients with late-onset, low grade PDD (dysthymia)	Future paper
Efficacy – Clinical bone fractures	Proportion of men with adjudicated clinical bone fractures	All randomized patients	Future paper
Efficacy – Diabetes	Proportion of men who had pre-diabetes at baseline who progress to diabetes	Randomized patients with pre-diabetes at baseline	Future paper
Efficacy – Anemia	Proportion of men with anemia whose anemia is corrected during the intervention period	Randomized patients with unexplained anemia at baseline	Future paper

Safety Set is comprised of all randomized patients who received at least one dose of study drug (testosterone or placebo).

PDD denotes Persistent Depressive Disorder and PDQ Psychosexual Daily Questionnaire.

Table S2 - The Representativeness of Study Patients

Category	
Disease, problem, or condition under investigation	Hypogonadism in middle-aged and older men.
Sex and gender	Male hypogonadism is a condition that affects only men. The issues of gender affirming hormone therapy in transgender and gender diverse people are distinct from those associated with testosterone replacement therapy in hypogonadal men. Testosterone treatment is not approved for use in women.
Age	Vast majority of testosterone prescriptions in the USA today are written for middle-aged and older men.[1,2] The issues of cardiovascular safety are particularly relevant to middle-aged and older men in this age range.
Race or ethnic group	There is no clear evidence of racial or ethnic differences either in the prevalence of hypogonadism in men or in men's response to testosterone treatment.
Geography	There are no data on geographic differences in the prevalence of hypogonadism in different regions of the US or in different countries.
Other considerations	The trial enrolled men who met the Endocrine Society's criteria for hypogonadism and who had evidence of cardiovascular disease or who were at increased risk of cardiovascular disease. Men with conditions in which testosterone replacement therapy might increase the risk of harm (e.g., previous history of prostate cancer, severe lower urinary tract symptoms, or venous thromboembolic event) were excluded.
Overall representativeness of this trial	The proportion of Black or African American and Hispanic or Latino men among the randomized patients was similar to that in the US population. Only people identifying as men were enrolled. Gender was not ascertained. The 316 trial sites were located across the United States and Puerto Rico. The enrolled patients had high prevalence of chronic conditions such as obesity, diabetes, hypertension, heart disease, and hyperlipidemia similar to that in men receiving a testosterone prescription in the US[1] or diagnosed with hypogonadism.[3,4] Because the trial enrolled men with hypogonadism who had evidence of cardiovascular disease or were at increased risk of cardiovascular disease, there was over-representation of men who had established cardiovascular disease, diabetes, obesity and other risk factors for cardiovascular disease compared to the general US population. We excluded men who had severe hypogonadism (two total testosterone levels < 100 ng/dL) because it was not deemed ethical to withhold testosterone replacement from these men.

Table S3 – Serum Testosterone Levels (ng/dL) at Scheduled Visits – Overall (top) and On-Treatment (bottom) Values (Safety Set*)

Visit	Testosterone Group N=2596			Placebo Group N=2602		
	n	Median (Q1, Q3)	Mean ± SD	n	Median (Q1, Q3)	Mean ± SD
Overall						
Baseline	2596	227 (189, 258)	220 ± 47	2602	227 (188, 258)	220 ± 48
Week 2	2412	326 (245, 448)	386 ± 256	2406	226 (181, 272)	231 ± 92
Month 1	2509	346 (262, 482)	415 ± 312	2508	227 (182, 271)	232 ± 87
Month 3	2376	351 (255, 493)	421 ± 322	2388	227 (183, 276)	235 ± 96
Month 6	2129	368 (266, 519)	436 ± 291	2146	231 (183, 278)	239 ± 102
Month 12	1683	371 (260, 525)	440 ± 312	1699	239 (186, 290)	249 ± 118
Month 18	1368	386 (253, 552)	455 ± 316	1333	235 (185, 291)	245 ± 98
Month 24	1125	360 (252, 514)	421 ± 255	1056	239 (186, 295)	252 ± 118
Month 36	731	358 (257, 506)	428 ± 292	724	247 (193, 311)	265 ± 131
On-Treatmentł						
Baseline	2596	227 (189, 258)	220 ± 47	2602	227 (188, 258)	220 ± 48
Week 2	2403	326 (246, 448)	387 ± 256	2396	225 (181, 272)	231 ± 92
Month 1	2487	347 (262, 483)	416 ± 313	2488	227 (182, 271)	232 ± 83
Month 3	2346	351 (256, 494)	421 ± 320	2350	227 (183, 276)	234 ± 90
Month 6	2040	369 (268, 520)	440 ± 293	2061	232 (182, 278)	238 ± 100
Month 12	1591	374 (261, 527)	441 ±300	1587	240 (186, 291)	249 ± 115
Month 18	1264	390 (257, 552)	459 ± 318	1219	234 (183, 291)	244 ± 97
Month 24	1012	370 (257, 525)	426 ± 252	954	239 (186, 296)	251 ± 115
Month 36	548	367 (259, 508)	432 ± 281	555	244 (191, 309)	264 ± 137

Blood samples were collected 24 hours (± 2 hours) after the last applied dose, preferably in the morning.

*The Safety Set is comprised of all randomized patients who received at least one dose of study drug (testosterone or placebo).

ł Excludes testosterone values after study drug discontinuation.

To convert serum total testosterone concentrations to SI units (nmol/L), divide testosterone concentration in ng/dL by 28.84.

Table S4 – Estradiol Levels (pg/mL) at Scheduled Visits – Overall (top) and On-Treatment (bottom) Values (Safety Set*)

Visit	Testosterone Group N=2596			Placebo Group N=2602		
	n	Median (Q1, Q3)	Mean ± SD	n	Median (Q1, Q3)	Mean ± SD
Overall						
Baseline	2470	20 (16, 25)	21 ± 8	2494	20 (15, 25)	21 ± 8
Month 12	1809	26 (18, 37)	31 ± 19	1786	19 (15, 24)	20 ± 9
Month 36	812	26 (19, 37)	31 ± 18	799	20 (16, 26)	22 ± 10
On-Treatmentł						
Baseline	2470	20 (16, 25)	21 ± 8	2494	20 (15, 25)	21 ± 8
Month 12	1623	26 (19, 38)	31 ± 19	1591	19 (15, 24)	20 ± 9
Month 36	547	27 (20, 38)	32 ± 19	548	20 (16, 26)	22 ± 10

*The Safety Set is comprised of all randomized patients who received at least one dose of study drug (testosterone or placebo).

ł Excludes estradiol values after study drug discontinuation.

To convert estradiol concentrations to SI units (pmol/L), divide the estradiol concentration in pg/mL by 0.272.

Table S5 – Supportive Analysis – Primary and Secondary Cardiovascular Outcomes in the Full Analysis Set Population

Outcome	Testosterone Group (N=2601)	Placebo Group (N=2603)	Hazard Ratio (95% CI)¶
	number of patients (percent)		
Primary safety endpoint (MACE§)	182 (7.0)	190 (7.3)	0.96 (0.78, 1.17)
Secondary CV safety endpoint‡	269 (10.3)	264 (10.1)	1.02 (0.86, 1.21)
Components of composite endpoints			
Death due to cardiovascular causes	87 (3.3)	103 (4.0)	0.84 (0.63, 1.12)
Nonfatal myocardial infarction	68 (2.6)	62 (2.4)	1.10 (0.78, 1.56)
Nonfatal stroke	36 (1.4)	38 (1.5)	0.94 (0.60, 1.49)
Coronary revascularization	144 (5.5)	121 (4.7)	1.20 (0.95, 1.53)

*The Full Analysis Set is comprised of all randomized patients.

¶ Hazard ratios, their two-sided 95% confidence intervals (CIs) and P values were estimated Hazard ratios were calculated with the Cox proportional-hazards model, adjusted for pre-existing cardiovascular disease status.

§ The composite outcome of major adverse cardiovascular events (MACE) in the primary analysis was the first occurrence of death due to cardiovascular causes, non-fatal myocardial infarction (MI), or non-fatal stroke.

‡ The secondary composite CV safety endpoint was the first occurrence of the components of the primary MACE safety outcome plus coronary revascularization procedures [percutaneous coronary intervention and coronary artery bypass graft surgery].

Table S6 – Blood Pressure (mmHg) at Scheduled Visits (Safety Set*)

Visit	Testosterone Group N=2596		Placebo Group N=2602	
	n	Mean ± SD	n	Mean ± SD
Systolic Blood Pressure				
Baseline	2596	132.8 ± 15.9	2602	132.5 ± 15.4
Week 2	2437	133.1 ± 15.6	2427	132.7 ± 15.9
Month 1	2523	133.0 ± 15.6	2533	132.0 ± 15.2
Month 3	2389	132.6 ± 15.6	2405	131.4 ± 15.9
Month 6	2147	133.0 ± 15.5	2161	131.0 ± 15.3
Month 12	1715	133.2 ± 16.3	1719	132.3 ± 16.1
Month 24	1200	133.5 ± 14.9	1143	132.0 ± 16.2
Month 36	743	133.8 ± 15.8	729	132.0 ± 15.2
Diastolic Blood Pressure				
Baseline	2596	79.1 ± 9.7	2602	79.3 ± 9.6
Week 2	2437	79.4 ± 9.7	2427	79.1 ± 9.9
Month 1	2523	79.1 ± 9.7	2533	78.8 ± 9.7
Month 3	2389	79.0 ± 9.8	2405	78.8 ± 9.9
Month 6	2147	79.2 ± 10.0	2161	78.5 ± 9.8
Month 12	1715	79.4 ± 10.5	1719	78.9 ± 9.7
Month 24	1200	78.9 ± 9.7	1143	78.7 ± 10.0
Month 36	743	78.7 ± 9.8	729	78.2 ± 9.8

*The Safety Set was comprised of all randomized patients who received at least one dose of study drug (testosterone or placebo).

References

1. Jasuja GK, Bhasin S, Reisman JI, et al. Who Gets Testosterone? Patient Characteristics Associated with Testosterone Prescribing in the Veteran Affairs System: a Cross-Sectional Study. J Gen Intern Med 2017;32(3):304-311. (In eng). DOI: 10.1007/s11606-016-3940-7.

2. Nguyen CP, Hirsch MS, Moeny D, Kaul S, Mohamoud M, Joffe HV. Testosterone and "Age-Related Hypogonadism"--FDA Concerns. N Engl J Med 2015;373(8):689-91. (In eng). DOI: 10.1056/NEJMp1506632.

3. Mulligan T, Frick MF, Zuraw QC, Stemhagen A, McWhirter C. Prevalence of hypogonadism in males aged at least 45 years: the HIM study. Int J Clin Pract 2006;60(7):762-9. (In eng). DOI: 10.1111/j.1742-1241.2006.00992.x.

4. Wu FC, Tajar A, Pye SR, et al. Hypothalamic-pituitary-testicular axis disruptions in older men are differentially linked to age and modifiable risk factors: the European Male Aging Study. The Journal of Clinical Endocrinology and Metabolism 2008;93(7):2737-45. (In eng). DOI: 10.1210/jc.2007-1972.