

Supplementary Appendix

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

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Cardiac Myosin Activation with Omecamtiv Mecarbil in Systolic Heart Failure.

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REFERENCES.....	55

EXECUTIVE COMMITTEE

John R. Teerlink, MD (Chair), San Francisco VA Medical Center and University of California San Francisco, San Francisco, CA, USA

Rafael Díaz, MD, ECLA (Estudios Clínicos Latinoamérica), Rosario, Santa Fe, Argentina

G. Michael Felker, MD, MHS, Duke University School of Medicine and Duke Clinical Research Institute, Durham, NC, USA

John J. V. McMurray, MD, British Heart Foundation, Cardiovascular Research Centre, University of Glasgow, Glasgow, UK

Marco Metra, MD, University of Brescia, Brescia, Italy

Scott D. Solomon, MD, Brigham & Women's Hospital, Boston, MA, USA

SPONSOR LEADERSHIP

Fady I. Malik, MD, PhD, Research and Development, Cytokinetics, South San Francisco, CA, USA

Christopher E. Kurtz, MD, Global Development, Amgen Inc., Thousand Oaks, CA, USA

Siddique Abbasi, MD, MSc, Global Development, Amgen Inc., Thousand Oaks, CA, USA

Beat Knusel, PhD, Global Development, Amgen Inc., Thousand Oaks, CA, USA

Thomas Hucko, MD, Global Development, Amgen Inc., Thousand Oaks, CA, USA

John Groarke, MBBCh, MPH, MSc, Global Development, Amgen Inc., Thousand Oaks, CA, USA

Narimon Honarpour, MD, PhD, Global Development, Amgen Inc., Thousand Oaks, CA, USA

Jason C. Legg, PhD, Global Biostatistics, Amgen Inc., Thousand Oaks, CA, USA

Lucie Sharpsten, PhD, Global Biostatistics, Amgen Inc., Thousand Oaks, CA, USA

Claire Varin, MD, Global Development, Servier, Suresnes, France

DATA MONITORING COMMITTEE

Marvin A. Konstam, MD (Chair), Tufts-New England Medical Center, Medford, MA, USA

Javed Butler, MD, MPH, University of Mississippi Medical Center, Jackson, MS, USA

Henry Dargie, MD, University of Glasgow, Glasgow, UK

Joseph Massaro, PhD, Boston University School of Public Health, Boston, MA, USA

Barry H. Greenberg, MD, University of California at San Diego, San Diego, CA, USA

James L. Januzzi, MD, Massachusetts General Hospital, Boston, MA, USA

Lawrence J. Lesko, PhD (Non-Voting Member), University of Florida, Gainesville, FL, USA

Jenica N. Upshaw, MD, MS (Non-Voting Member), Tufts New England Medical Center, Medford, MA, USA

CLINICAL EVENT ADJUDICATION COMMITTEE

G. Michael Felker, MD, MHS (Co-Chair), Duke University School of Medicine and Duke Clinical Research Institute, Durham, NC, USA

Renato Lopes MD, PhD (Co-Chair, Faculty Co-Director), Duke Clinical Research Institute, Durham, NC, USA

W. Schuyler Jones, MD (Faculty Co-Director), Duke University Medical Center, Durham, NC, USA

Karen P. Alexander, MD, Duke Clinical Research Institute, Durham, NC, USA

Sana M. Al-Khatib, MD, MHS, Duke Clinical Research Institute, Durham, NC, USA

Robert W. Harrison, MD, Duke University Medical Center, Durham, NC, USA

J. Dedrick Jordan, MD, PhD, University of North Carolina School of Medicine, Durham, NC, USA

David F. Kong, MD, Duke Clinical Research Institute, Durham, NC, USA

Robin Mathews, MD, Duke University Medical Center, Durham, NC, USA

Robert W. McGarrah, MD, Duke University Medical Center, Durham, NC, USA

Rajendra H. Metha, MD, MS, Duke Clinical Research Institute, Durham, NC, USA

Chiara Melloni, MD, MHS, Duke University Medical Center, Durham, NC, USA

Thomas J. Povsic, MD, PhD, Duke University Medical Center, Durham, NC, USA

Shreyansh Shah, MBBS, Duke University Medical Center, Durham, NC, USA

INDEPENDENT STATISTICIAN

Brian Claggett, PhD, Cardiovascular Division, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA

NATIONAL LEAD INVESTIGATORS

Kirkwood Adams, MD, University of North Carolina, Chapel Hill, NC, United States

Inder Anand, MD, PhD, University of Minnesota, Minneapolis, MN, United States

Alexandra Arias Mendoza, MD, Instituto Nacional de Cardiología, Mexico City, Mexico

Tor Biering-Sørensen, MD, University of Copenhagen, Aarhus N, Denmark

Michael Böhm, MD, Universitätsklinikum des Saarlandes, Homburg, Germany

Diana Bonderman, MD, Medical University of Vienna, Vienna, Austria

John Cleland, MD, National Heart and Lung Institute, Royal Brompton and Harefield Hospitals, Imperial College, London, Harefield, Middlesex, United Kingdom

Ramon Corbalan Herreros, MD, Catholic University, Santiago, Santiago, Chile

Marisa Crespo Leiro, MD, PhD, Universidad da Coruña, A Coruña, Galicia, Spain

Ulf Dahlstrom, MD, PhD, Linköping University Hospital, Linköping, Sweden

Rafael Diaz, MD, Estudios Clínicos Latino América (ECLA), Rosario, Argentina

Luis Eduardo Echeverria, MD, Fundacion Cardiovascular de Colombia, Floridablanca, Bucaramanga, Santander, Colombia

James Fang, MD, University of Utah, Salt Lake City, United States

Gerasimos Filippatos, MD, National and Kapodistrian University of Athens, Attikon University Hospital, Athens Greece

Candida Fonseca, MD, PhD, Universidade Nova de Lisboa, Lisbon, Portugal

Eva Goncalvesova, MD, PhD, Odd. Srdcovehozlyhavanja a Transplantacie, Bratislava, Slovakia

Assen Goudev, MD, PhD, Department of Cardiology, Queen Giovanna University Hospital and Medical University, Sofia, Bulgaria

Jonathan Howlett, MD, University of Calgary and Libin Cardiovascular Institute of Alberta, Calgary, AB, Canada

Lixin Jiang, MD, PhD, Fuwai Hospital, Beijing, China

David Lanfear, MD, MS, Heart and Vascular Institute, Henry Ford Hospital, Detroit, MI, United States

Jing Li, MD, National Clinical Research Center for Cardiovascular Diseases, NHC Key Laboratory of Clinical Research for Cardiovascular Medications, Fuwai Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China

Mayanna Lund, MD, Middlemore Hospital, Otahuhu, Auckland, New Zealand

Peter MacDonald, MD, PhD, St. Vincent's Hospital Sydney, Darlinghurst, NSW, Australia

Viacheslav Mareev, MD, PhD, Myasnikov Institute of Cardiology, Moscow, Russia

Marco Metra, MD, University of Brescia, Brescia, Italy

Shin-ichi Momomura, MD, Jichi Medical University Saitama Medical Center, Saitama, Japan

Eileen O'Meara, MD, Montreal Heart Institute, Montreal, QC, Canada

Alexander Parkhomenko, MD, PhD, Ukrainian Strazhesko Institute of Cardiology, Kiev, Ukraine

Piotr Ponikowski, MD, PhD, Wroclaw Medical University, Wroclaw, Poland

Felix Ramires, MD, PhD, Instituto do Coração (InCor), São Paulo, Brazil

Pranas Serpytis, MD, PhD, Vilnius University, Vilnius, Lithuania

Karen Sliwa, MD, PhD, University of Cape Town, Cape Town, South Africa

Jindrich Spinar, MD, PhD, Internal Cardiology Department, St. Ann Hospital and Masaryk
University Brno, Czech Republic

Thomas Suter, MD, Department of Cardiology, Inselspital, Bern University Hospital, University
of Bern, Switzerland

Janos Tomcsanyi, MD, PhD, St. John of God Hospital, Budapest, Hungary

Hans Vandekerckhove, MD, AZ Sint-Lucas, Ghent, Belgium

Dragos Vinereanu, MD, PhD, University of Medicine and Pharmacy Carol Davila, University and
Emergency Hospital, Bucharest, Romania

Adriaan Voors, MD, PhD, University of Groningen, Groningen, Netherlands

Mehmet Birhan Yilmaz, MD, Cumhuriyet University, Sivas, Turkey

Faiez Zannad, MD, PhD, Université de Lorraine, Nancy, France

LIST OF PRINCIPAL INVESTIGATORS BY COUNTRY

Participating Enrolling Centers: Displayed below are the investigators from the 945 enrolling centers in 35 participating countries. Countries are listed alphabetically and within each country, investigators are noted in order of enrollment contribution and then alphabetically.

Argentina: Diego Alejandro Besada, Claudio Rodolfo Majul, Marcos Raul Litvak Bruno, Sonia Sassone, Horacio Alberto Avaca, Mariela Rasmussen, Jorge Roberto Aiub, Miguel Angel

Hominal, Eduardo Perna, Ruben Omar Garcia Duran, Lilia Schiavi, Lilia Luz Lobo Marquez, Oscar Alberto Gomez Vilamajo, Ignacio Mackinnon, Ricardo Alfonso Leon de la Fuente, Oscar Romano Montana, Leonardo Novaretto, Rodolfo Andres Ahuad Guerrero, Daniela Garcia Brasca, Aldo Prado, Marcelo Alejandro Garrido, Hugo Luquez, Diego Felipe Martinez, Liliana Nicolosi, Maria Leonor Parody, Cesar Zaidman, Fernando Colombo Berra, Julio Ibañez, Gerardo Zapata, Marcos Amuchastegui, Alberto Caccavo, Roberto Colque, Mirta Diez, Carlos Poy, Oscar Alejandro Salomone, Daniel Vogel, Anselmo Paulino Bordonava, Alberto Fernandez.

Australia: John French, John Atherton, Andrew Hamilton, Alistair Begg, Walter Abhayaratna, Christopher Judkins, Peter Macdonald, Carmine De Pasquale, Scott McKenzie, John Amerena, Gregory Szto, Leighton Kearney, Hendrik Zimmet, Aaron Sverdlov, John Beltrame, Dariusz Korczyk, Andrew Sindone.

Austria: Deddo Moertl, Kurt Huber, Martin Huelsmann, Gabriele Jakl-Kotauschek, Klemens Ablasser, Friedrich Fruhwald, Christian Ebner, Peter Siostrzonek, Heinz Drexel, Gerhard Poelzl.

Belgium: Karl Dujardin, Matthias Dupont, Ian Buyschaert, Patrizio Lancellotti, Luc Pierard, Hans Vandekerckhove, Walter Droogne, Iman Chouchane.

Brazil: Fabio Silveira, Salvador Rassi, Gilmar Reis, Pedro Pimentel Filho, Marcus Vinicius Simoes, Joao Carlos Braga, Flavio Eduardo Giorgeto, Norberto Duda, Almir Ferraz, Cristiano Pederneiras Jaeger, Rafael Luiz Rech, Jose Francisco Saraiva, Alexandre Tognon, Juliano Cardoso, Oswaldo Greco, Maria Sanali Paiva, Bruno Paolino, Otavio Coelho Filho, Lilia Nigro Maia, Rodrigo da Silva, Manoel Canesin, Paulo Roberto Ferreira Rossi, Lidia Ana Zytynski Moura, Jose Augusto Ribas Fortes, Rodrigo Julio Cerci, Euler Roberto Fernandes Manenti, Paulo Ernesto Leaes, Luis Beck da Silva Neto, Weimar Kunz Barroso de Souza, Fernando Bacal, Renato Chaves, Felix Ramires, Maria Helena Vidotti, Flavio Brito, Pedro Gabriel Melo de Barros e Silva, Leopoldo Soares Piegas.

Bulgaria: Georgi Todorov, Maria Tzekova, Assen Goudev, Valentina Mincheva, Aleksandra Manolova, Ivaylo Vasilev, Snezhanka Tisheva- Gospodinova, Ivo Petrov, Arman Postadzhiyan, Chavdar Velikov, Bojidar Dimov.

Canada: Eileen O'Meara, Christian Constance, Denis-Carl Phaneuf, Lisa Mielniczuk, A Shekhar Pandey, Manohara Senaratne, Shelley Zieroth, Daniel Savard, Robert Stewart, Thao Huynh, Abdul Al-Hesayen, Nadia Giannetti, Gordon Moe, Ronald Bourgeois, Justin Ezekowitz, Michael Hartleib, Bruce Sussex, Mohan Babapulle, Raja Chehayeb, Daniel Gaudet, Robert McKelvie, Viviane Nguyen, Sherryn Roth, Milan Gupta, Yves Pesant, Dennis Rupka, Rakesh Bhargava, Atilio Costa-Vitali, Guy Proulx.

Chile: Mario Vega, Sergio Potthoff, Maria Cristina Schnettler Cid, Alex Mauricio Villablanca Sepulveda, Fernando Tomas Lanas Zanetti, Ramon Corbalan, Victor Areli Saavedra Gajardo, Carlos Conejeros Kindel, Christian Paolo Pincetti Jofre, Jorge Leonardo Cobos Segarra, Manuel Eduardo Rodriguez Venegas, Mario Yanez Hidalgo, Margarita Gertrudis Vejar Jalaf.

China: Weimin Li, Jinguo Zhang, Xin Fu, Xuelian Zhang, Dongye Li, Zhifang Wang, Yanling Qu, Zhe Zheng, Huifang Tang, Ping Yang, Yuhui Zhang, Yang Zheng, Yafei Mi, He Huang, Peili Bu, Guoqin Chen, Jiyan Chen, Yajun Han, Zhanquan Li, Shumei Ma, Xuming Yang, Zuyi Yuan, Yugang Dong, Zhaoping Li, Ailiman Mahemuti, Wentang Niu, Zhenyu Yang, Yuqing Zhang, Yuemin Sun, Weiheng Wu, Feng Liu, Jing Yan, Yinjun Li, Yi Wang, Shouyan Zhang, Changyong Zhou, Hanbin Cui, Jianjun Li, Tianfa Li, Qinghua Han, Yu Wei.

Colombia: Luis Eduardo Echeverria, Fernando Manzur Jattin, Jose Luis Accini Mendoza, Wilder Castaño Osorio, Gregorio Sanchez Vallejo, Carlos Alberto Luengas, Julian Alonso Coronel Arroyo, Miguel Alfredo Moncada Corredor, Clara Ines Saldarriaga Giraldo, Rodrigo Botero Lopez, Dora Ines Molina de Salazar, Miguel Urina Triana, Luis Horacio Atehortua Lopez, Pastor Olaya Rojas, Sebastian Velez Pelaez, Monica Lopez Pareja, Alberto Cadena Bonfanti.

Czech Republic: Rostislav Polasek, Zdenek Monhart, Karel Sochor, Zuzana Motovska, Jan Belohlavek, Ladislav Busak, Jiri Krupicka, Petr Tyl, Ondrej Jerabek, Ivo Podpera, Janka Skrobakova, Karel Peterka, Rudolf Spacek, Vladimir Cech, Ivana Kellnerova, Libor Nechvatal, Zbynek Pozdisek, Jindrich Spinar, Marek Houra, Radim Kryza, Vilma Machova, Tomas Brabec, Michal Cepelak, David Stepek, Kamil Zeman, Zdenek Klimsa, Pavel Koleckar, Alexandr Schee, Lenka Spinarova, Zdenek Coufal.

Denmark: Jorgen Jeppesen, Soren Vraa, Henrik Wiggers, Ole Nyvad, Tonny Nielsen, Niels Gadsboll, Peter Kaiser-Nielsen, Jacob Eifer Moller, Lars Videbaek.

France: Michel Galinier, Jean-Marie Lefebvre, Jean-Michel Tartiere, Guillaume De Geeter, Francois Roubille, Jean Etienne Ricci, Muriel Salvat, Jean-Pierre Gueffet, Eric Decoulx, Philippe Berdague, Guillaume Jondeau, Nathan Mewton, Michel Ovize, Pascal De Groote, Erwan Donal, Richard Isnard, Rémi Sabatier, Jean-Noel Trochu, Thibaud Damy, Jean-Louis Georges, Yann Rosamel, François Picard, Victor Aboyans, Thierry Laperche.

Germany: Veselin Mitrovic, Jens Taggeselle, Stefan Störk, Henning Ebelt, Sabine Genth-Zotz, Tienush Rassaf, Hans-Dirk Duengen, Marcus Mittag, Niels Menck, Stephan von Haehling, Uwe Zeymer, Michael Boehm, Lutz Frankenstein, Holger Killat, Hakima Bourhaial, Daniel Beug, Thomas Horacek, Roman Pfister, Marcus Sandri, Ralf Westenfeld, Christoph Kadel.

Greece: Haralambos Karvounis, Sotirios Patsilnakos, Ioannis Mantas, Apostolos Karavidas, Grigorios Giamouzis, Konstantinos Tsioufis, Katerina Naka, Dimitrios Tziakas, John Parissis, Ioannis Styliadis, Ioannis Barbetseas, Athanasios Manolis, George Kochiadakis, Fragkiskos Parthenakis.

Hungary: Bela Herczeg, Laszlo Nagy, Noemi Nyolczas, Kalman Toth, Bela Merkely, Janos Tomcsanyi, Zoltan Laszlo, Laszlo Mark, Imre Szakal, Andras Papp, Katalin Bezzegh, Eva Peterfai, Ferenc Lakatos, Erik Hajko, Aniko Papp, Tamas Forster, Geza Lupkovics, Attila Mohacsi, Csaba Salamon, Daniel Aradi, Peter Andreka, Gyula Szasz, Zsolt Zilahi, Rita Kazinczy.

Italy: Alberto Margonato, Piergiuseppe Agostoni, Alessandro Fucili, Marco Metra, Giancarlo Piovaccari, Michele Senni, Giuseppe Ambrosio, Erberto Carluccio, Claudio Bilato, Maria Frigerio, Ciro Indolfi, Gianfranco Sinagra, Natale Daniele Brunetti, Matteo Di Biase, Gianpiero Perna, Daniela Pini, Maurizio Volterrani, Gaetano Maria De Ferrari, Sergio Leonardi, Claudia Raineri, Felice Achilli, Domenico Bonaduce, Andrea Mortara, Giuseppe Musumeci, Hernan Emilio Francisco Polo Friz, Roberta Rossini, Carlo Gabriele Tocchetti, Antonella Vincenzi, Claudio Cavallini, Agata Marina Floresta, Valerio Zaca, Vittorio Giudici, Giovanni Quinto Villani.

Japan: Yorihiro Higashino, Shogo Oishi, Atsuyuki Wada, Yoshinori Yasaka, Shigeru Fukuzawa, Hiroyuki Kawata, Kenji Onoue, Yoshihiko Saito, Akihiro Koike, Tomomi Koizumi, Seigo Masuda, Hiroshi Meno, Kazuhisa Mitsuo, Kumiko Nakayama, Shuichi Taguchi, Natsuki Takahashi, Takashi Takenaka, Jun Tanabe, Hideyuki Tsuboi, Naoki Watanabe, Takeshi Yoshida, Tetsuya Amano, Masahiro Ishikawa, Keisuke Kida, Toru Kubota, Kentaro Nakamura, Tomohiro Sakamoto, Naoki Sato, Mitsuhiro Shimomura, Hiroki Uehara, Fumi Yamamoto, Masaru Yuge, Yutaka Akatsuka, Masayuki Doi, Hiroshi Domae, Mio Ebato, Kenshi Fujii, Wakaya Fujiwara, Seiichiro Gohara, Yoshiki Hata, Atsushi Hirayama, Hideo Izawa, Shuntaro Kagiya, Junji Kanda, Hiroaki Kitaoka, Hiroaki Kiyokawa, Kunihiko Makino, Takashi Matsumoto, Ichiro Michishita, Shinichiro Miura, Tetsuro Miyazaki, Makoto Nakahama, Akihiro Nakamura, Yuji Nakazato, Tomohiro Ogawa, Takahiro Okumura, Yasuo Okumura, Tetsuo Sakai, Keiji Saku, Yukihito Sato, Wataru Shimizu, Hiroshi Sugino, Masahiro Suzuki, Atsutoshi Takagi, Hiroshi Takaishi, Takahiro Tanaka, Toshiro Terasaki, Mitsuru Tsujimoto, Yasunori Ueda, Keiji Ujino, Makoto Usui, Mitsutaka Yamamoto, Masaki Yoshikawa, Masayoshi Ajioka, Kenji Ando, Masanori Asakura, Hiroshi Asano, Shigeru Fujii, Hisao Hara, Takayuki Inomata, Takaaki Isshiki, Toshiaki Kadokami, Hisashi Kai, Toshio Kasai, Katsunori Kawamitsu, Tomohiro Kawasaki, Tokushi Koga, Nobuyuki Komiyama, Yasuhiro Maejima, Mamoru Manita, Nobuhide Miyamoto, Kimiaki Nagase, Koichi Node, Kotaro Numaguchi, Yasushi Sakata, Takeshi Serikawa, Koichiro Sugimura, Noriaki Takama, Shunsuke Tatebe, Hideki Ueno, Yoshitoshi Urabe, Takayuki Hidaka, Shitoshi Hiroi, Harukazu Iseki, Hiroshi Ito, Kouji Kajinami, Hideo Kawakami, Yasuki Kihara, Yukihiko Momiyama, Masuki Mori, Yukiko Morita, Kaoru Okishige, Satoru Sakagami, Yasuchika Takeishi, Akihiro Terasawa, Noriaki Utsu.

Lithuania: Jolita Badariene, Jelena Celutkiene, Gintare Sakalyte, Rimvydas Slapikas, Pranas Serpytis, Dalia Jarasuniene.

Mexico: Armando Garcia Castillo, Manuel Odin De los Rios Ibarra, Gabriel Arturo Ramos Lopez, Edmundo Alfredo Bayram Llamas, Guillermo Antonio Llamas Esperon, Eduardo Salcido Vazquez, Ricardo Garcia Gonzalez, Jose Luis Arenas Leon, Salvador Leon Gonzalez, Maria Alexandra Arias Mendoza, Alicia Contreras Rodriguez, Gustavo Francisco Mendez Machado, Melchor Alpizar Salazar, Alberto Esteban Bazzoni Ruiz, Ana Maria De Leon Flores, Jose Alfredo Pagola Carrasco, Raul Reyes Araiza.

Netherlands: Tjeerd Römer, Johannes Remmen, Jacob Van Eck, Arif Elvan, Elvin Kedhi, Tom Smilde, Adriaan Voors, Ruud van de Wal, Dirk Lok, Jeroen Schaap, Aize van der Sluis, Gerardus Linssen, Michael Magro, Frank Willems, Dirk Schellings, Coenraad van der Zwaan, John van Hal, Driek Beelen, Dirk Boswijk, Walter Hermans, Pascalle van Huysduynen-Monraats, Henricus Van Kesteren.

New Zealand: Russell Scott, Hamish Hart, Mayanna Lund.

Poland: Marcin Szczyński, Tomasz Blicharski, Mariusz Kafara, Anna Stankiewicz, Grzegorz Skonieczny, Maciej Zabowka, Grzegorz Kania, Tomasz Borkowski, Jerzy Kopaczewski, Lidia Pawłowicz, Janusz Spyra, Aleksander Włodarczyk, Ryszard Sciborski, Paweł Balsam, Jarosław Drożdż, Bożena Sobkowicz, Małgorzata Konieczynska, Małgorzata Lelonek, Zbigniew Bednarkiewicz, Jarosław Trebacz, Piotr Jankowski, Mateusz Sidor, Piotr Berkowski, Zbigniew Chmielak, Lucyna Lenartowska, Jadwiga Nessler, Ewa Straburzynska-Migaj, Zbigniew Kalarus, Robert Kowalski, Ewa Kalecinska-Krystkiewicz, Zbigniew Gola, Zbigniew Pijanowski, Beata Wozakowska-Kapłon, Krzysztof Cymerman, Andrzej Rynkiewicz, Paweł Miekus.

Portugal: Pedro Monteiro, Pedro Morais Sarmiento, Filipa Almeida, Tatiana Duarte, Candida Fonseca, Luis Oliveira, Sara Soares Goncalves, Luis Santos, Dulce Brito.

Romania: Gabriela Stanciulescu, Dragos Vinereanu, Marilena Renata Spiridon, Constantin Militaru, Cristian Gheorghe Podoleanu, Dumitru Zdrengea, Mircea Ioachim Popescu, Cezar-Eugen Macarie, Alina Giuca, Florin Mitu, Olga-Cristina Voicu, Maria Dorobantu, Daniel Lighezan, Sorin Stamate.

Russia: Alexander Bykov, Zhanna Kobalava, Konstantin Zrazhevskiy, Irina Semenova, Alexander Vishnevsky, Elena Shutemova, Sergey Tereschenko, Yury Shvarts, Olga Barbarash, Yury Lukyanov, Mikhail Voevoda, Svetlana Dvogliss, Dmitry Dronov, Boris Goloshchekin, Maria Sitnikova, Marat Ezhov, Nikolay Tarasov, Mikhail Kotelnikov, Viktor Kostenko, Oleg Solovov, Sergey Boytsov, Ivan Goncharov, Roman Myasnikov, Svetlana Villevalde, Vladimir Rafalskiy, Vyacheslav Ryabov, Elena Kosmacheva, Igor Motylev, Vladimir Nosov, Irina Osipova, Vladimir Salukhov, Dmitriy Belenkiy, Olga Bolshakova, Leonid Pimenov, Nataliya Shilkina, Elena Kulibaba, Vyacheslav Mareev, Alexey Repin, Alexander Timofeev, Vladislav Mitrokhin, Valery Popov, Alexander Sherenkov, Georgy Arbolishvili.

Slovakia: Lubomir Antalík, Andrej Džupina, Peter Fulop, Eva Goncalvesova, Ivan Majercak, Jozef Gonsorcik, Daniela Vinanska, Egon Lenner, Jana Lukacova, Roman Margoczy, Rudolf Smik, Jan Stevlik, Rudolf Uhliar.

South Africa: Lesley Burgess, Aysha Badat, Eric Klug, Louis Van Zyl, Mark Abelson, Rajendran Moodley, Nqoba Tsabedze, Nyda Fourie.

Spain: Luis Almenar Bonet, Jose Maria Arizon del Prado, Manuel Martinez-Selles D Oliveira Soares, Julio Eduardo Nuñez Villota, Maria Generosa Crespo Leiro, Jose Ramon Gonzalez Juanatey, Domingo Andres Pascual Figal, Juan Luis Bonilla Palomas, Sonia Mirabet Perez, Juan Francisco Delgado Jimenez, Antonio Lara Padron, Andres Iñiguez Romo, Victor Alfonso Jimenez Diaz, Fernando Soto Loureiro, Javier Segovia Cubero, Antonio Juan Castro Fernandez, Vicente Eduardo Climent Paya, Alejandro Recio Mayoral, Luis de la Fuente Galan, Juan Jose Gomez Doblas, Ramon Bover Freire, Maria Teresa Blasco Peiro, Beatriz Diaz Molina, Laura Jordan Martinez, Jose Luis Lambert Rodriguez, Silvia Lopez Fernandez, Francisco Gonzalez Vilchez.

Sweden: Kurt Boman, Patric Karlstrom, Stefan Berglund, Barna Szabo, Magnus Peterson, Peter Wodlin, Carl-Johan Lindholm.

Switzerland: Tiziano Moccetti, Christian Mueller, Thomas Suter, Roger Hullin, Philippe Meyer, Georg Noll.

Turkey: Zerrin Yigit, Okan Onur Turgut, Mehmet Birhan Yilmaz, Lutfu Bekar, Tayfun Sahin, Zehra Lale Koldas, Ahmet Celik, Yuksel Cavusoglu, Mesut Demir, Ersel Onrat, Mehmet Duzenli, Kahraman Cosansu, Mustafa Vural, Ibrahim Haldun Muderrisoglu, Mustafa Tuncer, Ozer Badak, Sanem Nalbantgil, Cevat Kirma, Ertugrul Okuyan, Umit Guray.

Ukraine: Oleksandr Prokhorov, Oleksandr Karpenko, Igor Vakaliuk, Andriy Yagensky, Igor Kraiz, Mykola Stanislavchuk, Oleksii Kulynych, Mykola Rishko, Roman Stets, Vira Tseluyko, Larysa Mishchenko, Leonid Rudenko, Yevgeniya Svishchenko, Iurii Rudyk, Liudmyla Alieksieieva, Oleksii Korzh, Yuriy Mostovoy, Dmytro Reshotko, Oleksandr Parkhomenko, Lesya Rasputina, Leonid Voronkov, Georgiy Dzyak, Yurii Lymar, Larysa Vasilyeva.

United Kingdom: Philip Keeling, Craig Barr, Kenneth Wong, Dallas Price, Binoy Skaria, Andrew Clark, Badrinathan Chandrasekaran, Jasper Trevelyan, Brian Gordon, Patrick Donnelly, Jason Glover, Alisdair Ryding, Robin Weir, Chim Lang, Debashis Roy, Shaumik Adhya, Piers Clifford, Andrew Ludman, Elena Cowan, Paul Kalra, Mary Lynch, Shahid Mahmood, Abdallah Al Mohammad, Joshua Asubiaro, Balgit Chhokar, Patrick Davey, Einas Elmahi, Amal Muthumala, Justin Taylor.

United States: Dinesh Gupta, Venkatesh Nadar, David Henderson, Ronald Zolty, Andrew Sauer, Kirkwood Adams, Lokesh Chandra, Naseem Jaffrani, Gurinder Grewal, Donna Mancini, Dalton McLean, Javier Vasallo, Amarinder Bindra, Stephen Gottlieb, Susan Joseph, Rajat Barua, Mahazarin Ginwalla, Eiran Gorodeski, Assad Mouhaffel, Eugene Chung, Pratik Desai, Edward Portnay, Bhola Rama, Adrian Shandling, Llyod Stahl, Gregory Thomas, Karl Heilman, Binu Jacob, Juan Londono, Oswaldo Sandoval, Randall Starling, Omar Almousalli, Thomas Ashcom, Eugene Joseph Bauerlein, Sandra Chaparro, Charles Koo, Laurie Letarte, Frank McGrew, Navin Rajagopalan, Shawn Robinson, David Schultz, Mark Zucker, Larry Allen, Amrut Ambardekar, Ravi Bhagwat, John Boehmer, Manuel Bouza, Neil Farris, Scott Feitell, Jagadeesh Ganji, Edward Geltman, Julian Javier, John Andrew Morrow, Leonard Pianko, Frank Smart, Alexander Adler, Douglas Brinkley, Jose Cardona, Andrew Coletti, John Harris, Vernon Hunter, Mori Krantz, Christopher Lang, Daniel Lenihan, Charles Lovell, David Murray, Priya Pillutla, Amit Shah, Carlos Arrieta Garcia, Roberta Bogaev, Ira Dauber, Francesco Franchi, Richard Fremont, Philip Haines, Terence Hart, Brack Hattler, Matthew Janik, Wissam Khalife, Brenda Lemus, Sanjay Malhotra, Shafiq Mamdani, John Murray, William Nelson, Marisa Orgera, Aurelio Ortiz, Peter Rahko, Stephen Rennyson, Fabiana Rollini, Jooyoung Shin, Lana Tsao, Barry Uretsky, Faisal Wahid, Matt Wilkett, Aman Amanullah, Mathue Baker, Martin Berk, Fernando Boccalandro, Kimberly Cruz, Timothy Doyle, Scott Franczek, Lawrence Galitz, Giovanni Geronilla, Robert Gianfagna, Alonzo Jones, Anthony King, Steven Krueger, Norman Lepor, Melvin Martinez-Castrillon, Alan Meholick, Madhusudhan Pamganamamula, Michael Pham, Michael Radin, Joseph Radojevic, Kodangudi Ramanathan, Carsten Schmalfluss, Robert Schnitzler, Keyur Shah, Theodore Takata, Barry Bertolet, Brian Bostick, Andrew Civitello, John Collins, Cristina Danila, Nabil Dib, Stavros Drakos, James Fang, Richard Gilmore, Wayne Gray, Luanda Gazette, Tariq Haddad, Syed Hasni, Steven Hearne, Munir Janmohamed, Richard Katz, Navid Kazemi, David Lanfear, Sara Llerena, Nicole Lohr, George Marzouka, John Mignone, Arunima Misra, Henry Ooi, Gurusher Panjraht,

Anna Paszczuk, Christopher Pickett, Joseph Rahman, Gregory Sampognaro, Anays Santana Izquierdo, Douglas Sawyer, Steven Shayani, Inder Singh, Charles Treasure, Garth Vaz, Nampalli Vijay, James Watts, Celeste Williams, Gary Yeoman, Lily Zhang, Keith Aaronson, Wael Abo-Auda, Rami Alharethi, William Anderson, Mehrdad Ariani, Sourin Banerji, Paramdeep Baweja, Peter Carson, John Corbelli, Arthur Eberly III, James Elliott, Ronald Fernando, Daniel Fisher, Steven Forman, George Gabriel, Harinder Gogia, Craig Hametz, Glenn Hamroff, Brian Houston, Hassan Ibrahim, Farid Jadbabaie, Christos Kassiotis, Arun Krishnamoorthy, Michael Kwan, Steven Lupovitch, Leonardo Macias, Adnan Malik, Douglas Martel, Luis Martinez, Michael Miyamoto, Freny Mody, Vasilios Papademetriou, Devesh Patel, Daniel Pauly, Brenda Peart, Barbara Pisani, Mark Ramos, Mariel Rivero, Anil Shah, Mukesh Sharma, Rajesh Sharma, Tina Sichrovsky, Marc Simon, Deovrat Singh, Mark Smith, Julio Tallet, Christopher Vaccari, Mario Villoch, Bradley Weinberg, Matthew Wheeler, Amin Yehya, Kabir Yousuf, Rafik Abadier, Shuaib Abdullah, Raveen Arora, Shamaila Aslam, Andrew Boyle, Robert Buynak, David Chang, A Alan Chu, Johanna Contreras, Stephen Halpern, Michele Hamilton, Franklin Handel, John Heitner, William Herzog, Bruce Jackson, John Kao, Nicholas Kondo, Michael Koren, Martin LeWinter, Jeffrey Martindale, Joaquin Martinez-Arraras, Stephanie Olsen, Marek Piatek, Nandkishore Ranadive, William Randall, Sunder Rao, David Rawitscher, Gordon Reeves, James Rider, George Sokos, J Russell Strader, Nasir Sulemanjee, Naeem Tahirkheli, Vinay Thohan, Benjamin Trichon, Thomas Vanhecke, David Whellan, Mohammad Abuannadi, Gaurav Aggarwala, Saad Ahmad, Andre Artis, Jorge Cheirif, Jennifer Cook, Vladimir Cotarlan, Jeremy Cox, Charles Eaton, Viorel Florea, Theodore Frank, Keith Friedman, Vedampattu Ganeshram, Alan Gass, Anthony Gemignani, Chester Hedgepeth, William Herzog, Dipti Itchhaporia, Edo Kaluski, Amin Karim, Alan Kono, Ellis Lader, Batlagundu Lakshminarayanan, Neil Lewis, Vinay Malhotra, Nolan Mayer, Robert Mohapatra, Nandini Nair, Terrence O'Brien, Sunil Pauwaa, Florence Rothenberg, Christopher Rowan, Sanjeev Saxena, Arnold Seto, Nishant Shah, Pradeep Singh, Hal Skopicki, Marcus Stoddard, Nancy Sweitzer, Thomas Duythuc To.

INCLUSION AND EXCLUSION CRITERIA

Inclusion Criteria:

- Subject has provided informed consent
- Male or female, ≥ 18 to ≤ 85 years of age at signing of informed consent
- History of chronic HF (defined as requiring treatment for HF for a minimum of 30 days before randomization)
- LVEF $\leq 35\%$, per subject's most recent medical record, within 12 months prior to screening. The most recent qualifying LVEF must be at least 30 days after any of the following, if applicable: 1) an event likely to decrease EF (eg, myocardial infarction, sepsis); 2) an intervention likely to increase EF (eg, cardiac resynchronization therapy, coronary revascularization); or 3) the first ever presentation for HF.
- NYHA class II to IV at most recent screening assessment
- Managed with HF SoC therapies consistent with regional clinical practice guidelines according to investigator judgment of subject's clinical status. Oral SoC therapies for chronic HF (eg, beta blockers, renin-angiotensin-aldosterone system inhibitors) should be present, if not contraindicated. Subjects enrolled during either HF hospitalization or early after HF hospitalization discharge can be reinitiating or titrating oral SoC chronic HF therapies at the same time of randomization with the goal of achieving optimized therapy on study.
- Currently hospitalized with primary reason of HF OR one of the following events within 1 year to screening: 1) hospitalization with primary reason of HF; 2) urgent visit to ED with primary reason of HF
- B-type natriuretic peptide (BNP) level ≥ 125 pg/mL or an NT-proBNP level ≥ 400 pg/mL at most recent screening assessment (subjects receiving angiotensin receptor-neprilysin inhibitor [ARNi] must use NT-proBNP assessment; for subjects in atrial fibrillation/flutter at screening, the cut off levels are: BNP ≥ 375 pg/mL or NT-proBNP ≥ 1200 pg/mL)

Exclusion Criteria

- Currently receiving treatment in another investigational device or drug study, or < 30 days since ending treatment on another investigational device or drug study(ies). Other investigational procedures while participating in this study are excluded.
- Malignancy within 5 years prior to randomization with the following exceptions: localized basal or squamous cell carcinoma of the skin, cervical intraepithelial neoplasia, stage 1 prostate carcinoma, breast ductal carcinoma in situ.
- Subject has known sensitivity to any of the products or components to be administered during dosing.
- Factors expected to interfere with the subject's availability or ability to complete all protocol-required study visits or procedures, and/or to comply with all required study procedures to the best of the subject and investigator's knowledge (including ongoing substance abuse).

- Inability to swallow study medication tablet (eg, swallowing disorders, feeding tubes)
- Receiving mechanical hemodynamic support (eg, intra-aortic balloon pump counterpulsation), or invasive mechanical ventilation ≤ 7 days prior to randomization
- Receiving IV inotropes (eg, dobutamine, milrinone, levosimendan) or IV vasopressors (eg, epinephrine, norepinephrine, dopamine, or vasopressin) ≤ 3 days prior to randomization
- Receiving IV diuretics or IV vasodilators, supplemental oxygen therapy, or non-invasive mechanical ventilation (eg, bilevel positive airway pressure [BiPAP] or continuous positive airway pressure [CPAP] ≤ 12 hours prior to randomization (Note: the use of non-invasive ventilation for sleep disordered breathing is permitted)
- Acute coronary syndrome (ST-elevation myocardial infarction, non-ST-elevation myocardial infarction, unstable angina), stroke, or transient ischemic attack, major cardiac surgery or cardiac intervention (ie, implantation of cardiac closure devices, cardiac resynchronization therapy, or catheter ablation), percutaneous coronary intervention, or valvuloplasty/other cardiac valve repair or implantation within the 3 months prior to randomization
- Insertion of other cardiac devices (eg, implantable cardioverter defibrillator, permanent pacemaker, monitoring devices) within 30 days prior to randomization
- Severe uncorrected valvular heart disease, hypertrophic or infiltrative cardiomyopathy, active myocarditis, constrictive pericarditis, or clinically significant congenital heart disease
- Untreated severe ventricular arrhythmia (eg, ventricular tachycardia or ventricular fibrillation)
- Chronic antiarrhythmic therapy, with the exception of amiodarone. Note: for the purposes of this exclusion criterion, digoxin, calcium channel blocker, and beta-blocker therapy are not considered to be chronic antiarrhythmic therapies
- Symptomatic bradycardia or second or third degree heart block without a pacemaker
- Routinely scheduled outpatient intravenous infusions for HF (eg, inotropes, vasodilators [eg, nesiritide], diuretics) or routinely scheduled ultrafiltration
- Systolic blood pressure > 140 mmHg or < 85 mmHg, or diastolic blood pressure > 90 mmHg, or heart rate > 110 beats per minute, or < 50 beats per minute at screening
- Estimated glomerular filtration rate (eGFR) < 20 mL/min/1.73m² or receiving dialysis at screening
- Hepatic impairment defined by a total bilirubin (TBL) ≥ 2 times the upper limit of normal (ULN), or alanine aminotransferase (ALT) or aspartate aminotransferase (AST) ≥ 3 times ULN at screening
- Previously received omecamtiv mecarbil

- Severe, concomitant non-CV disease that is expected to reduce life expectancy to < 2 years
- Recipient of any major organ transplant (eg, lung, liver, heart, bone marrow, renal) or anticipated to receive chronic mechanical circulatory support or heart transplantation within 12 months from randomization
- Female subject of childbearing potential who is not willing to inform her partner of her participation in this clinical study and to use 2 acceptable methods of effective birth control or practice true sexual abstinence (the reliability of sexual abstinence must be evaluated by the investigator and be the preferred and usual lifestyle of the subject) during treatment with IP (OM or placebo) and for an additional 5 days after the last dose of IP. If the female subject or her sole male partner has had a surgical contraceptive method (bilateral tubal ligation/occlusion or vasectomy with medical assessment of surgical success), additional contraceptive methods are not required. Male subject with a female partner of childbearing potential and not willing to inform his partner of his participation in this clinical study.
- A female is considered of childbearing potential unless she has had a hysterectomy, bilateral oophorectomy, or bilateral salpingectomy or she is postmenopausal. Menopause is defined as ≥ 12 months of spontaneous and continuous amenorrhea in a female ≥ 55 years old; or no spontaneous menses for at least 2 years in a female < 55 years old; or age < 55 years and spontaneous menses within the past 1 year, but currently amenorrheic (eg, spontaneous or secondary to hysterectomy) and with follicle-stimulating hormone (FSH) levels > 40 IU/L, or postmenopausal estradiol levels (< 5 ng/dL), or according to the definition of “postmenopausal range” for the laboratory involved.
- Two acceptable methods of effective birth control include the following 2 options:
 - use of hormonal and barrier combination birth control methods (intrauterine device and barrier method with spermicide, intrauterine device and hormonal birth control method, hormonal birth control method and barrier method with spermicide),
 - 2 barrier methods (each partner must use 1 barrier method except a female condom) with at least 1 of the barrier methods including spermicide (a male and female condom may not be used together due to the risk of tearing)
- Hormonal methods of birth control include oral, intravaginal, transdermal, injectable, or implantable. Barrier methods of birth control include diaphragm with spermicide, cervical cap with spermicide, male or female condom with spermicide, and contraceptive sponge with spermicide. If spermicide is not commercially available in the local country/region a barrier method without spermicide is acceptable.

Note: If additional medications are given during treatment which may alter the contraceptive requirements (these additional medications may require an increase in the number of contraceptive methods and/or length of time that contraception is to be

utilized after the last dose of protocol-required therapies) the investigator is to discuss these changes with the study subject.

- Female subject is pregnant or breastfeeding or is planning to become pregnant or planning to breastfeed during treatment with IP (OM or placebo) or within 5 days after the end of treatment with IP.
- Planned to be discharged from the hospital to long term care facility (eg, skilled nursing facility) or hospice.
- History or evidence of any other clinically significant disorder (including cardiac arrhythmia), condition or disease (with the exception of those outlined above) that, in the opinion of the investigator or Amgen physician, if consulted, would pose a risk to subject safety or interfere with the study evaluation, procedures, or completion.

Randomization will be stratified by randomization setting (currently hospitalized for HF or recently and not currently hospitalized for HF) and region (5 strata: US and Canada; Latin America; Western Europe, South Africa, and Australasia; Eastern Europe including Russia; Asia). Approximately 25% or more of the total planned enrollment will include subjects who are hospitalized at randomization. Enrollment of subjects in atrial fibrillation/flutter at screening is limited to approximately 25%.¹

DOSE SELECTION IN GALACTIC-HF

The omecamtiv mecarbil dosing regimen selected for GALACTIC-HF is oral administration of 25 mg BID at the initiation of treatment. At study visit Week 2 (PK steady-state for initial dose), a predose PK sample will be collected. At Week 4, subjects with Week 2 OM predose plasma concentrations < 200 ng/mL will have their dose increased to 50 mg BID; subjects with Week 2 predose plasma concentrations \geq 200 and < 300 ng/mL will have their dose increased to 37.5 mg BID, subjects with Week 2 predose plasma concentrations \geq 300 ng/mL and < 1000 ng/mL will maintain a 25 mg BID dosing regimen, and subjects with plasma concentration \geq 1000 ng/mL will start administration of placebo BID. Similar to Study 20110151, PK-based dose adjustment in this study will be used to attain effective steady state concentrations for desired PD effect while maintaining OM plasma concentrations <1000 ng/mL.¹

ENDPOINTS / EVENT DEFINITIONS

Definitions are based on the recent ACC/AHA standards for endpoint definitions in cardiovascular clinical trials.^{2,3}

Death

Deaths will be classified as Cardiovascular, Non-cardiovascular, or Undetermined.

In addition, all deaths will be further sub-classified based on the specific cardiovascular (CV) or non-cardiovascular (Non-CV) categories defined below.

The cause of death will be determined by the principal condition that resulted in the death, not the immediate mode of death. For example, if a patient hospitalized and undergoing treatment for worsening heart failure dies of ventricular tachycardia, this would be classified as a heart failure death. CEC physicians will utilize all available information provided, along with clinical expertise, in their adjudication of the cause of death.

For every Death event where a protocol endpoint event is identified as the clear cause of death (MI, HF, complications from a CV procedure), the corresponding event will also be adjudicated as fatal. For example, if a death occurs due to an MI, there will be a corresponding MI event adjudicated as fatal, along with the Death event.

Similarly, for every event that is considered fatal (a fatal MI, for example), a corresponding Death event will also be adjudicated as such. For example, if a fatal MI occurs, there will be a corresponding Death event adjudicated as Death due to Acute MI.

Cardiovascular Death

- **Acute MI**

Death due to acute MI refers to a death by any CV mechanism (eg, arrhythmia, sudden death, heart failure, stroke, pulmonary embolus, peripheral arterial disease) **≤ 30 days after a MI related to the immediate consequences of the MI**, such as progressive heart failure or recalcitrant arrhythmia. We note there may be assessable mechanisms of CV death

during this time period, but for simplicity, if the CV death occurs ≤ 30 days of the MI, it will be considered a death due to MI.

Acute MI should be verified to the extent possible by the diagnostic criteria outlined for CV hospitalization for acute MI or by autopsy findings showing recent MI or recent coronary thrombosis.

Death resulting from a procedure to treat a MI, PCI, CABG, or to treat a complication resulting from MI should also be considered death due to acute MI.

If death occurs before biochemical confirmation of myocardial necrosis can be obtained, adjudication should be based on the clinical presentation and ECG evidence. Sudden cardiac death, if accompanied by symptoms suggestive of myocardial ischemia, new clinically significant ischemic ECG changes, or evidence of fresh thrombus by coronary angiography and/or at autopsy should be considered death resulting from an acute myocardial infarction, even if death occurs before blood samples or 12-lead electrocardiogram (ECG) could be obtained, or at a time before the appearance of cardiac biomarkers in the blood. Death resulting from a procedure to treat a myocardial infarction (eg, percutaneous coronary intervention (PCI), coronary artery bypass graft surgery (CABG), or to treat a complication resulting from myocardial infarction, should also be considered death due to acute MI.

? Sudden Cardiac Death

Sudden Cardiac Death refers to death that occurs unexpectedly and not following an acute MI, and includes the following deaths:

- Death witnessed and occurring without new or worsening symptoms.
- Death witnessed within 60 minutes of the onset of new or worsening cardiac symptoms, unless the symptoms suggest acute myocardial infarction.

- Death witnessed and attributed to an identified arrhythmia (eg, captured on an electrocardiographic (ECG) recording, witnessed on a monitor, or unwitnessed but found on implantable cardioverter-defibrillator (ICD) review).
- Death after unsuccessful resuscitation from cardiac arrest. (eg, ICD unresponsive sudden cardiac death, pulseless electrical activity arrest).
- Death after successful resuscitation from cardiac arrest and without identification of a specific cardiac or non-cardiac etiology.
- Unwitnessed death in a subject seen alive and clinically stable \leq 24-hours prior to being found dead without any evidence supporting a specific non-cardiovascular cause of death (information about the patient's clinical status preceding death should be provided, if available)

General Considerations

Unless additional information suggests an alternate specific cause of death (eg, Death due to Other Cardiovascular Causes), if a patient is seen alive \leq 24-hours of being found dead, **OR** circumstances suggest sudden death, sudden cardiac death should be recorded.

Typical scenarios include:

- Subject well the previous day but found dead in bed the next day.
- Subject found dead at home on the couch with the television on.

For patients who were not observed alive within 24-hours of death, undetermined cause of death should be recorded (eg, subject found dead in bed, but who had not been seen by family for several days).

Heart Failure

Death associated with clinically worsening symptoms and/or signs of HF, regardless of HF etiology. Deaths due to HF can have various etiologies, including single or recurrent myocardial infarctions, ischemic or non-ischemic cardiomyopathy, hypertension, or valvular disease.

Deaths that occur during a HF hospitalization will generally be attributed to heart failure, even if there is another immediate mode of death (eg, ventricular fibrillation). Deaths that occur in hospice or other similar palliative care setting for HF will generally be attributed to HF.

☐ **Stroke**

Death after a stroke that is either a direct consequence of the stroke or a complication of the stroke. Acute stroke should be verified to the extent possible. Deaths that occurred within 30 days of a stroke without a known cause will be considered death due to stroke.

☐ **Cardiovascular Procedure**

Death caused by the immediate complication(s) of a CV procedure.

☐ **Cardiovascular Hemorrhage**

Death related to hemorrhage, such as a non-stroke intracranial hemorrhage, (eg, subdural hematoma) non-procedural or non-traumatic vascular rupture (eg, aortic aneurysm), or hemorrhage causing cardiac tamponade.

☐ **Other Cardiovascular**

Death due to Other Cardiovascular Causes refers to a CV death not included in the above categories - but with a specific, known cause (e.g., pulmonary embolus or peripheral arterial disease).

Non-cardiovascular Death

☐ Pulmonary

Death attributable to disease of the lungs (excludes malignancy).

☐ Renal

Death attributable to renal failure.

☐ Gastrointestinal

Death attributable to disease of the esophagus, stomach, or intestines (excludes malignancy).

☐ Hepatobiliary

Death attributable to disease of the liver, gall bladder, or biliary ducts (excludes malignancy).

☐ Pancreatic

Death attributable to disease of the pancreas (excluded malignancy)

☐ Infection (including sepsis)

Death attributable to an infectious disease

☐ Inflammatory/Immune (including autoimmune)

Death attributable to an inflammatory or immune-mediated disease or process

Note: Includes SIRS, immunological, and autoimmune diseases and disorders. Includes anaphylaxis from environmental (eg, food) allergies.

☐ Hemorrhage

Death attributable to bleeding that is not considered CV hemorrhage or stroke.

☐ Non-CV procedure or surgery

Death caused by the immediate complications of a non-CV procedure/surgery.

☐ Trauma

Death attributable to trauma; includes homicide.

☐ Suicide

Death attributable to suicide.

☐ Non-prescription drug reaction or overdose

Death attributable to a non-prescription drug reaction or overdose.

❑ **Prescription drug reaction or overdose**

Death attributable to a prescription drug reaction or overdose (includes anaphylaxis).

❑ **Neurological**

Death attributable to disease of the nervous system (excludes malignancy).

Note: Excludes cardiovascular death from ischemic stroke, hemorrhagic stroke, or undetermined cause of stroke, or cardiovascular hemorrhage of central nervous system.

❑ **Malignancy**

Death attributable to leukemia, lymphoma, or other malignancy.

❑ **Other non-CV**

Death attributable to a cause other than those listed here (specify organ system, if applicable).

Undetermined Death

Death not attributable to one of the above categories of CV death or to a Non-CV cause. Inability to classify the cause of death may be due to lack of information (e.g., the only information received by the CEC is “patient died”) or when there is insufficiently supporting information or detail to assign the cause of death.

For patients who were not observed alive within 24-hours of death and with no additional information suggesting an alternate specific cause of death, undetermined cause of death will be recorded (e.g., a subject found dead in bed but who had not been seen by family members for > 24-hour prior to death). If seen alive \leq 24-hours before being found dead, sudden cardiac death will be recorded (see sudden cardiac death definition above).

Undetermined deaths will be further classified into 3 sub-categories:

❑ **Presumed Sudden Death**

Death occurred suddenly in an otherwise stable subject and the subject was last seen alive \geq 24 hours before.

❑ **Presumed Cardiovascular Death**

Death was likely from a cardiovascular cause but the data were insufficient to support a more specific cause.

❑ **Unknown Death**

Death with insufficient data available to make a reasonable differentiation between cardiovascular and non-cardiovascular causes.

In general, most deaths should be classified as CV or non-CV. The use of the undetermined category of death, therefore, should apply to few patients.

Heart Failure Event

Presentation of the patient for an urgent, unscheduled clinic/office/ED visit or 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.

Potential HF events will be further classified into one of the following categories:

- Hospitalization
- Urgent ER/ED Visit
- Urgent Office/Practice Visit

HF Hospitalization

A HF hospitalization is defined as an event that meets **ALL** of the following criteria:

- 1) The patient is admitted to the hospital with a primary diagnosis of HF.
- 2) The patient's length-of-stay in the hospital extends for at least 24-hours (or a change in calendar date if admission and discharge times are unavailable).
- 3) The patient exhibits documented new-or-worsening symptoms due to HF on presentation, to include **at least ONE** of the following:
 - Dyspnea (dyspnea with exertion, dyspnea at rest, orthopnea, paroxysmal nocturnal dyspnea)
 - Decreased exercise tolerance
 - Fatigue
 - Other symptoms of worsened end-organ perfusion or volume overload (eg, confusion, somnolence, swelling, etc.)

- 4) The patient has objective evidence of new or worsening HF; consisting of **EITHER:**

- **At least TWO** physical examination findings listed below,

OR

- **ONE** physical examination finding, **AND at least ONE** laboratory criterion listed below:

Physical examination findings considered to be due to HF, including new or worsened:

- Peripheral edema
- Increasing abdominal distention or ascites (in the absence of primary hepatic disease)
- Pulmonary rales/crackles/crepitation
- Increased jugular venous pressure and/or hepatojugular reflux
- S3 gallop
- Clinically significant or rapid weight gain thought to be related to fluid retention (usually more than 3-4 lbs in 3-4 days)

Laboratory evidence of new or worsening HF, if obtained within 24-hours of presentation:

- Increased BNP/NT-proBNP) concentrations consistent with decompensation of heart failure (such as BNP > 500 pg/mL or NT-proBNP > 2,000 pg/mL). In patients with chronically elevated natriuretic peptides, a significant increase should be noted above baseline.
- Radiological evidence of pulmonary congestion.
- **Non-invasive diagnostic evidence** of clinically significant elevated left- or right-sided ventricular filling pressure or low cardiac output. For example, echocardiographic criteria could include: E/e' > 15 or D-dominant pulmonary venous inflow pattern, plethoric inferior vena cava with minimal collapse on inspiration, or decreased left ventricular outflow tract (LVOT) minute stroke distance (time velocity integral (TVI)).

OR

- Invasive diagnostic evidence with right heart catheterization showing a pulmonary capillary wedge pressure (pulmonary artery occlusion pressure) \geq 18 mmHg, central venous pressure \geq 12 mmHg, or a cardiac index < 2.2 L/min/m².

- 5) The patient receives initiation or intensification of treatment specifically for HF, to include at least ONE of the following:

- Intravenous diuretic or vasoactive agent (e.g., inotrope, vasopressor or vasodilator).

- Mechanical or surgical intervention, including mechanical circulatory support (e.g., intra-aorta balloon pump, ventricular assist device, extracorporeal membrane oxygenation, total artificial heart).
- Mechanical fluid removal (e.g., ultrafiltration, hemofiltration, dialysis).

Urgent HF ER/ED Visit

An urgent HF visit is defined as an event that meets all the following criteria:

- 1) The patient has an urgent, unscheduled office/practice or emergency department visit for a primary diagnosis of HF, **but not meeting the criteria for a HF hospitalization.**
- 2) The patient exhibits documented new-or-worsening symptoms due to HF on presentation, to include **at least ONE** of the following:
 - Dyspnea (dyspnea with exertion, dyspnea at rest, orthopnea, paroxysmal nocturnal dyspnea)
 - Decreased exercise tolerance
 - Fatigue
 - Other symptoms of worsened end-organ perfusion or volume overload (e.g., confusion, somnolence, swelling)
- 3) The patient has objective evidence of new or worsening HF, consisting of **at least TWO** physical examination findings **OR ONE** physical examination finding **AND at least ONE** laboratory criterion listed below:

Physical examination findings considered to be due to heart failure, including new or worsened:

- Peripheral edema
- Increasing abdominal distention or ascites (in the absence of primary hepatic disease)
- Pulmonary rales/crackles/crepitation
- Increased jugular venous pressure and/or hepatojugular reflux
- S3 gallop
- Clinically significant or rapid weight gain thought to be related to fluid retention (usually more than 3-4 lbs. in 3-4 days)

Laboratory evidence of new or worsening HF, if obtained within 24-hours of presentation:

- Increased BNP/NT-pro BNP concentrations consistent with decompensation of heart failure (such as BNP > 500 pg/mL or NT-proBNP > 2,000 pg/mL). In patients with chronically elevated natriuretic peptides, a significant increase should be noted above baseline.
- Radiologic evidence of pulmonary congestion.

- Non-invasive diagnostic evidence of clinically significant elevated left- or right-sided ventricular filling pressure or low cardiac output. For example, echocardiographic criteria could include: $E/e' > 15$ or D-dominant pulmonary venous inflow pattern, plethoric inferior vena cava with minimal collapse on inspiration, or decreased left ventricular outflow tract (LVOT) minute stroke distance (time velocity integral (TVI)).

OR

- Invasive diagnostic evidence with right heart catheterization showing a pulmonary capillary wedge pressure (pulmonary artery occlusion pressure) ≥ 18 mmHg, central venous pressure ≥ 12 mmHg, or a cardiac index < 2.2 L/min/m²
- 4) The patient receives initiation or intensification of treatment specifically for HF, to include **at least ONE** of the following:
- Intravenous diuretic or vasoactive agent (e.g., inotrope, vasopressor or vasodilator).
 - Mechanical fluid removal (e.g., ultrafiltration, hemofiltration, dialysis).
 - Mechanical or surgical intervention, including mechanical circulatory support (e.g., intra-aorta balloon pump, ventricular assist device, extracorporeal membrane oxygenation, total artificial heart).

Urgent HF Office/Practice Visit

An urgent HF Office or Practice visit meets the exact same criteria, requirements, and specifications as the Urgent HF ER/ED Visit. The only difference, and when this option should be selected, is that the patient presents to an outpatient clinic rather than to an ER or ED.

Myocardial Infarction

Acute myocardial infarction will be adjudicated when a patient demonstrates the following biochemical indicator of myocardial necrosis:

- Detection of a rise and/or fall of cardiac biomarker values (preferably cTn) with **at least 1 value > 99th percentile of the URL**, with a typical pattern of rise-and-fall consistent with myocardial infarction, **AND at least ONE** of the two following criteria:
 - 1) Typical clinical presentation consistent with myocardial infarction defined as typical cardiac ischemic type pain/discomfort or dyspnea felt to be due to ischemia,

OR

2) Typical ECG changes consisting of any of the following:

- New (or presumed new) LBBB pattern.
- In the absence of LVH and LBBB pattern (or other confounder such as a paced rhythm) on ECG, either:
 - New (or presumed new) ST-elevation at the J-point in 2 contiguous leads with the following cut points: ≥ 0.1 mV in all leads other than leads V_2 to V_3 where the following cut points apply: ≥ 0.2 mV in men ≥ 40 y of age; ≥ 0.25 mV in men < 40 y of age, or ≥ 0.15 mV in women;

OR

- New (or presumed new) horizontal or downsloping ST-segment depression ≥ 0.05 mV in 2 contiguous leads and/or T inversion ≥ 0.1 mV in 2 contiguous leads with prominent R wave or R/S ratio > 1 .

OR

- 3) New pathologic Q-wave criteria for MI detected during routine ECG follow-up, or evidence of new MI by cardiac imaging, that cannot be directly attributed to a coronary revascularization procedure. New pathologic Q-waves need to be documented in 2 consecutive visits to exclude improper lead placement.

MI's will be further classified by subtype.⁴

Unstable Angina Hospitalization

The following criteria satisfy the diagnosis of hospitalization for unstable angina:

- Unscheduled admission to an inpatient unit or visit to an emergency department that results in at least a 24-hour stay or a change in calendar date if the hospital admission or discharge times are not available.

AND

- Documentation of worsening ischemic discomfort (angina or equivalent symptoms), usually of ≥ 10 minutes in duration, occurring at rest, or in an accelerating pattern with frequent episodes associated with progressively decreasing exercise capacity

AND

- Documentation of objective evidence of new or worsening coronary ischemia:
 - New or worsening new ST or T-wave changes on resting ECG (in absence of confounders, such as LBBB or LVH) defined as either:
 - 1) Transient ST-elevation (duration < 20 min): new ST-elevation at the J point of ≥ 0.1 in any two contiguous leads (other than V_2 - V_3). In V_2 - V_3 , the following cut-points apply: ≥ 0.2 mV in men ≥ 40 years, ≥ 0.25 mV in men < 40 years, and ≥ 0.15 mV in women.
 - 2) ST depression and T-wave changes: new horizontal or down-sloping ST depression ≥ 0.05 mV in two contiguous leads and/or net T-

inversion ≥ 0.03 mV in two contiguous leads with prominent R-wave or R/S ratio > 1 .

OR

- Inducible myocardial ischemia demonstrated by:
 - 1) An early positive stress test defined as ST elevation or ≥ 2 mm ST-depression prior to 5 METs.
 - 2) Reversible wall motion abnormality on stress echocardiography.
 - 3) Reversible perfusion defect on myocardial scintigraphy.
 - 4) MRI (myocardial perfusion deficit under pharmacologic stress).

OR

- Need for coronary revascularization procedure (PCI or CABG) for the presumed culprit lesion(s).

OR

- Angiographic evidence of new or worse $\geq 70\%$ lesion and/or thrombus in an epicardial coronary artery believed to be responsible for the myocardial ischemic signs/symptoms

AND

- Without rise-and-fall (negative confirmation) of biomarkers.

Coronary Revascularization

Percutaneous Coronary Intervention

Defined as the placement of an angioplasty guidewire, balloon, or other device (eg, stent, atherectomy, brachytherapy, or thrombectomy catheter) into a native coronary artery or CABG for the purpose of mechanical coronary revascularization.

The diagnostic assessment of coronary lesion severity by intravascular ultrasonography, coronary flow reserve, or fractional flow reserve is not considered a PCI procedure.

Surgical Procedures, Including Coronary Artery Bypass Graft (CABG)

CABG is defined as a procedure performed to bypass partially or completely occluded coronary arteries with veins and/or arteries harvested from elsewhere in the body, thereby improving the blood supply to the coronary circulation supplying the myocardium.

Classification of the urgency of a surgical procedure, based on the patient's clinical status before entering the operating room, is defined as:

- **Elective**

Patient cardiac status has been stable in the days or weeks before the operation. The procedure can be deferred without increased risk of compromised cardiac outcome.

- **Urgent**

Procedure required during the same hospitalization to minimize chances of clinical deterioration or adverse outcome. Clinical conditions include (but are not limited to) acute or worsening chest pain, acute or worsening HF, acute MI, critical coronary stenosis, IABP support, UA with intravenous nitroglycerin, and rest angina.

- **Emergency**

Procedure required because of ongoing, refractory (difficult, complicated, and/or unmanageable), unrelenting cardiac compromise, with or without hemodynamic instability, and not responsive to any form of therapy except cardiac surgery. An emergency operation is one in which there should be no delay in providing operative intervention.

- **Salvage**

The patient is undergoing CPR or is being managed with extracorporeal membrane oxygenation in route to the operating room or before induction of anesthesia. The clinical acuity of the patient is a dying state.

Stroke

A focal neurological deficit of central origin lasting more than 24 hours (except for death within 24hrs), with or without imaging confirmation of cerebral infarction or intracerebral hemorrhage;

OR

A focal neurological deficit of central origin lasting less than 24 hours with corresponding imaging evidence of cerebral infarction or intracerebral hemorrhage;

OR

A focal neurological deficit of central origin lasting less than 24 hours that was treated with thrombolytic therapy or directed percutaneous intervention;

OR

A non-focal encephalopathy lasting more than 24 hours (except for death within 24hrs) with imaging evidence of cerebral infarction or hemorrhage adequate to account for the clinical state.

OR

Retinal artery ischemia.

Sub-classifications:

- **Ischemic (Non-hemorrhagic) Stroke** – Stroke with imaging suggesting ischemic changes.
- **Ischemic (Non-hemorrhagic) Stroke with Hemorrhagic Conversion** - Stroke with evidence of hemorrhage on imaging, judged to be hemorrhagic transformation of a primary ischemic stroke.
- **Hemorrhagic Stroke** – Stroke with evidence on imaging of intracerebral hemorrhage not due to transformation of an ischemic stroke.
- **Unknown*** - When imaging is unavailable or inconclusive

*The deficit must be new, sudden in onset, and not attributable to any more likely alternative cause (e.g. tumor, trauma)

SAMPLE SIZE ASSESSMENT

A sample size of approximately 8,000 patients was chosen to provide 90% power to detect a hazard ratio of 0.8 for cardiovascular death assuming the following: a 10% annualized rate of cardiovascular death in the first year and 7% thereafter; a 24-month enrollment period; total study duration set to 48 months; a 3-month treatment lag with a treatment effect hazard ratio of 0.8 thereafter, 10% annual rate of study drug discontinuation, and 10% of subjects lost to endpoint determination either through non-cardiovascular death or study discontinuation over the course of the trial.¹

MULTIPLICITY ADJUSTMENT AND HEIRARCHICAL TESTING PROCEDURES

In order to preserve an overall type I error rate of 0.05 for the primary and secondary endpoints, the following multiplicity adjustment will be performed (see Figure S2): A total alpha of 0.001 (one-sided 0.0005) will be used for assessing superiority at the second interim analysis. If the study continues, a total alpha of 0.05 will be used for testing at the primary analysis triggered based on observing approximately 1590 CV deaths. Within an analysis, the total alpha will apply to all primary and secondary endpoint hypothesis tests. The primary endpoint will be tested first with the total alpha. If the primary endpoint reaches statistical significance, a Bonferroni split will be used where 0.96α is allocated to testing the time to CV death and 0.04α is allocated to testing change baseline in the KCCQ TSS. Alpha from a statistically significant result for these two endpoints after the split will propagate to the other endpoint with a small alpha (0.0001 fraction of the α used in the statistically significant test) propagating to testing time to first heart failure hospitalization.⁵ If statistical significance is achieved for both the time to CV death and change from baseline in the KCCQ TSS, time to first heart failure hospitalization will be tested at the full alpha. If time to first heart failure hospitalization is statistically significant, time to all-cause death will be tested with the same alpha as time to first heart failure hospitalization. Figure S2 illustrates the multiplicity testing propagation approach. Alpha will only propagate if the direction of the statistically significant effect favors omecamtiv mecarbil. Exploratory endpoints will be assessed using a nominal alpha level of 0.05 and not have multiplicity adjustments.

SENSITIVITY ANALYSES

Competing Risk Analysis

Competing risk subdistribution hazard ratios and associated 95% confidence intervals for treatment are computed for each time-to-event efficacy endpoint other than all-cause death.⁶ For each endpoint, deaths not included in the endpoint are considered as the competing risk. The same structure as for the primary analysis Cox models was used. (see Table S5)

Informative Censoring Analysis

A multivariate Cox model for the primary composite event was fit as a sensitivity analysis using baseline variables to potentially account for informative censoring.⁷ The approach used is that outlined in Van Lancker et al.⁸ following the general approach of Fang et al.⁹ Covariates considered are those used in the prespecified subgroups. Continuously collected covariates were retained as continuous in the multivariate Cox models unlike in the subgroup analyses. NT-proBNP was considered on the log scale. The stratification variables of randomization setting and region were those used at the time of randomization. Missing data for baseline NT-proBNP was substituted with the median for the respective randomization setting (inpatient or outpatient) and missing baseline weight was substituted with the median for the respective sex so all the data could be used. Interactions were not considered.

The approach follows these steps:

- 1) Fit an elastic net regularization Cox model including the treatment group and all the baseline covariates modeling the event times. For this model, the stratification variables were considered in the proportional hazard rather than baseline hazard. Ten-fold cross validation is used to select the regularization parameter, termed lambda, with the largest lambda such that the mean cross validation error is within 1 standard error of the error for the lambda that attains the minimum mean cross validation error. Covariates with non-zero parameter estimates for the selected lambda are retained.
- 2) Repeat step 1 except modeling the censoring times. Covariates with non-zero parameter estimates for the selected lambda are retained.
- 3) Fit a Cox model including the treatment group and baseline covariates selected in steps 1 and 2. For this model, the stratification variables are used in the baseline hazards. The sandwich variance estimator is used to construct confidence intervals.

From step 1, selected baseline covariates were ACEi use, diabetes mellitus, presence of an ICD, eGFR, heart rate, presence of a CRT, history of an MI, NT-proBNP, NYHA class, race, presence of atrial fibrillation/flutter at screening, randomization setting, region, systolic blood pressure, and weight.

From step 2, selected baseline covariates were ACEi use, MRA use, ARNi use, ethnicity, race, randomization setting, region, and weight.

The Cox model containing these parameters fit from step 3 has estimates in Table S6.

This sensitivity analysis has a small impact on the estimated treatment effect. Note that the treatment effect estimated with baseline covariates is the conditional hazard ratio rather than the marginal hazard ratio.

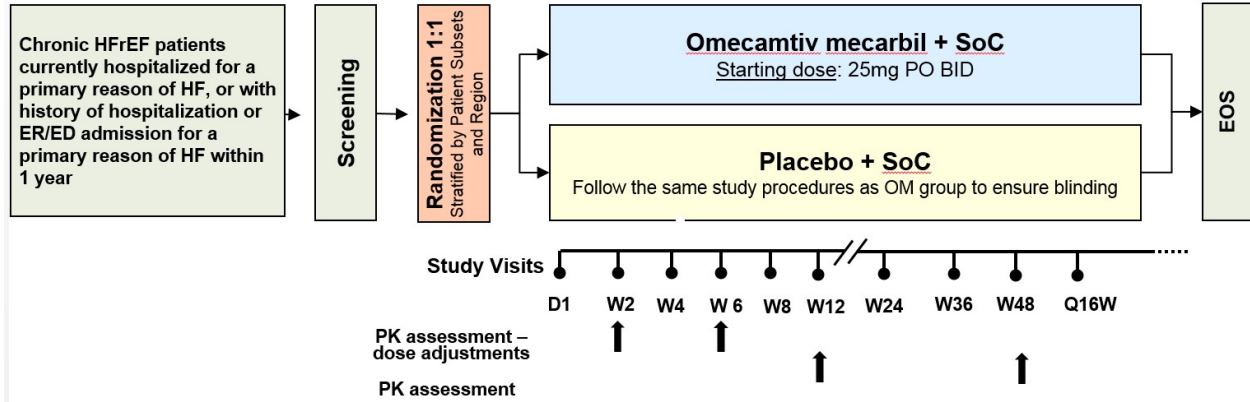
KCCQ Missing Data and Sensitivity Analysis

Reasons for missing Week 24 KCCQ TSS Endpoints are depicted in Table S7.

As a sensitivity for missing data due to death for the change from baseline to week 24 in the KCCQ TSS endpoint, a joint longitudinal and survival models were fit following the approach of Rizopoulos,¹⁰ as shown in Table S8. Models were fit within randomization setting using the observed values of the KCCQ TSS with random subject slopes and intercepts for the longitudinal models and included terms for baseline eGFR, region, and treatment by slope. The survival models were fit for all-cause death with baseline eGFR and treatment in the proportional hazard part of the models, the KCCQ TSS modeled values as the shared parameterization, and stratified by region with Weibull baseline functions. The treatment effect was estimated at Week 24 (Day 169) along with associated 95% confidence intervals.

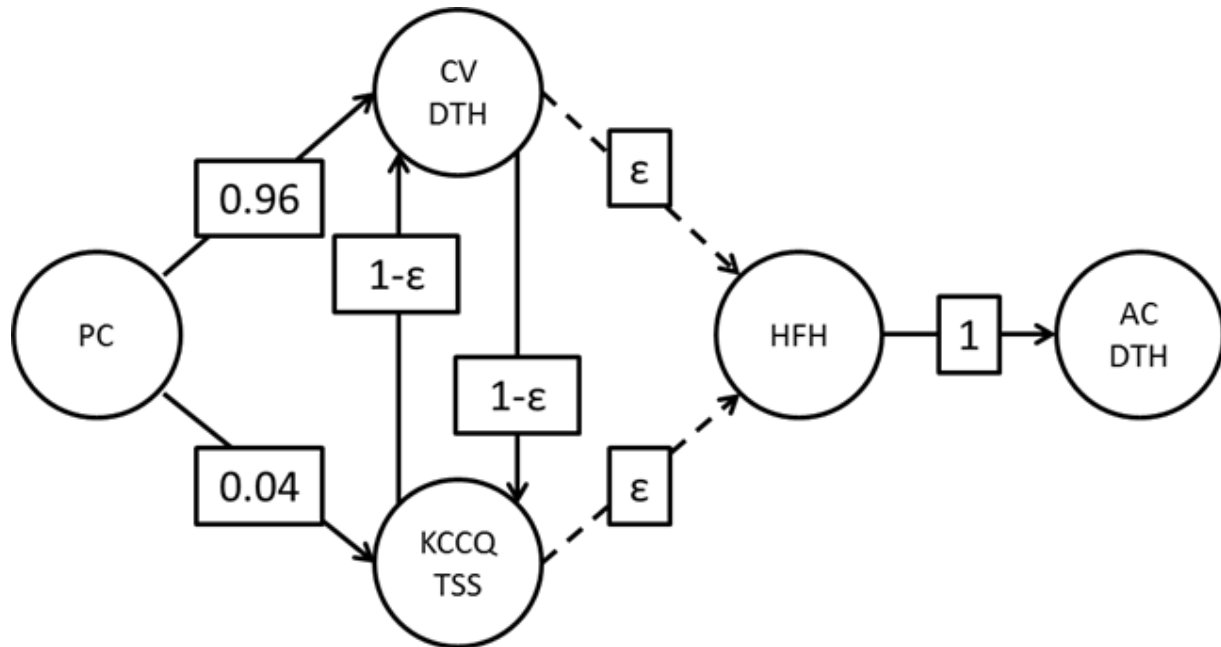
FIGURES

FIGURE S1: GALACTIC-HF Trial Design



BID = twice a day; ED = emergency department; EOS = end of study; ER = emergency room; HF = heart failure; HFrEF = heart failure with reduced ejection fraction; IP = investigational product; PK = pharmacokinetics; PO = by mouth; Q16W = every 16 weeks; SoC = standard of care.

FIGURE S2: GALACTIC-HF Hierarchical Testing Procedure



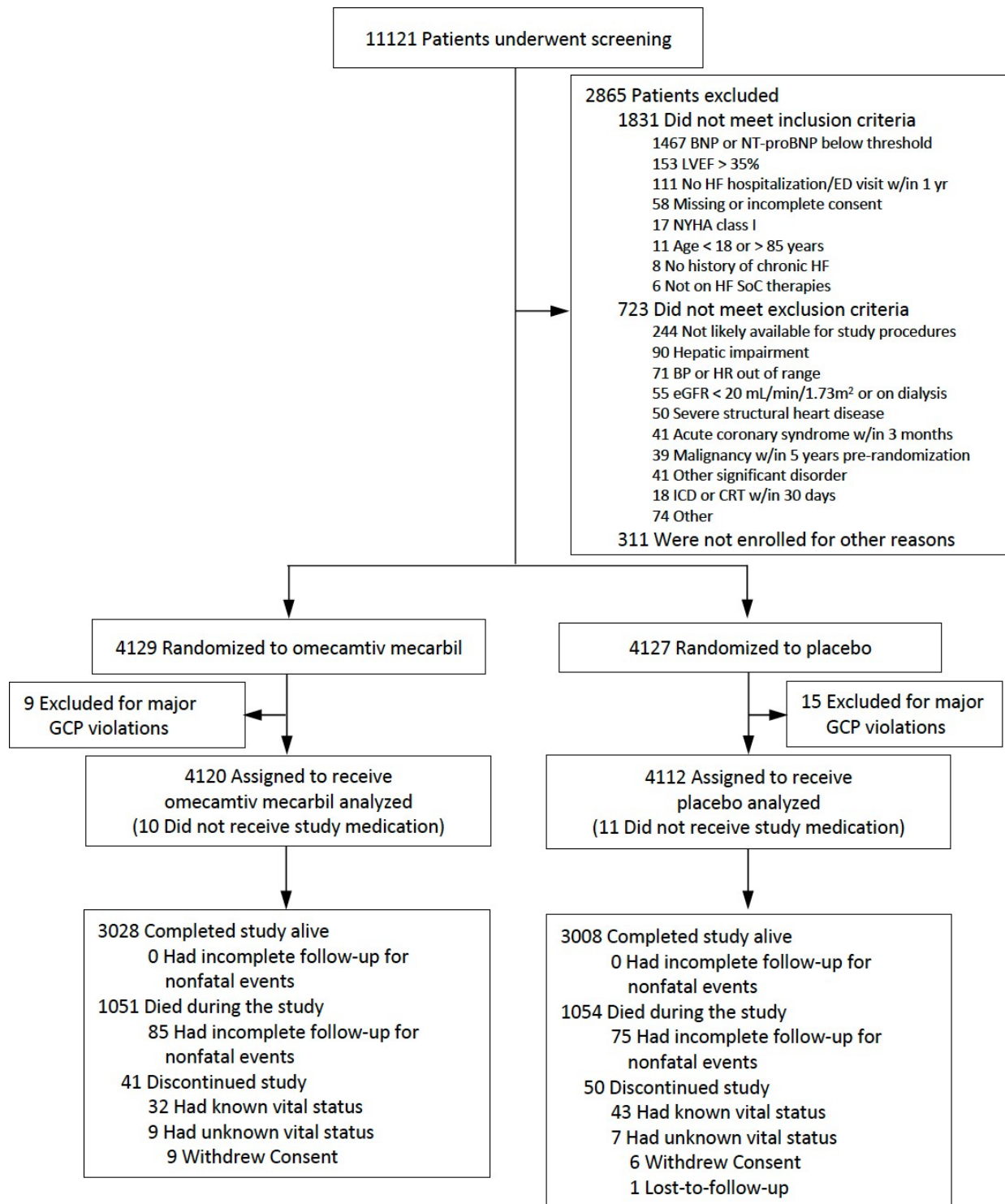
AC DTH = time to all-cause death; CV = cardiovascular death; CV DTH = time to CV death; HFH = time to first heart failure hospitalization; KCCQ TSS = Kansas City Cardiomyopathy Questionnaire Total Symptom Score; PC = primary composite endpoint

Each circle represents a hypothesis test. The values in boxes on the arrows indicate the fraction of α propagated in the direction of the arrow to the next hypothesis test(s). $\epsilon = 0.0001$, a small value to complete the graph while prioritizing the CV death and KCCQ TSS endpoints over the time to first heart failure hospitalization and all-cause death endpoints. Dashed arrows used to emphasize this prioritization.

No multiplicity adjustment will be made for exploratory or sensitivity analyses.

Overall alpha of 0.05 used for the primary analysis hypothesis testing.

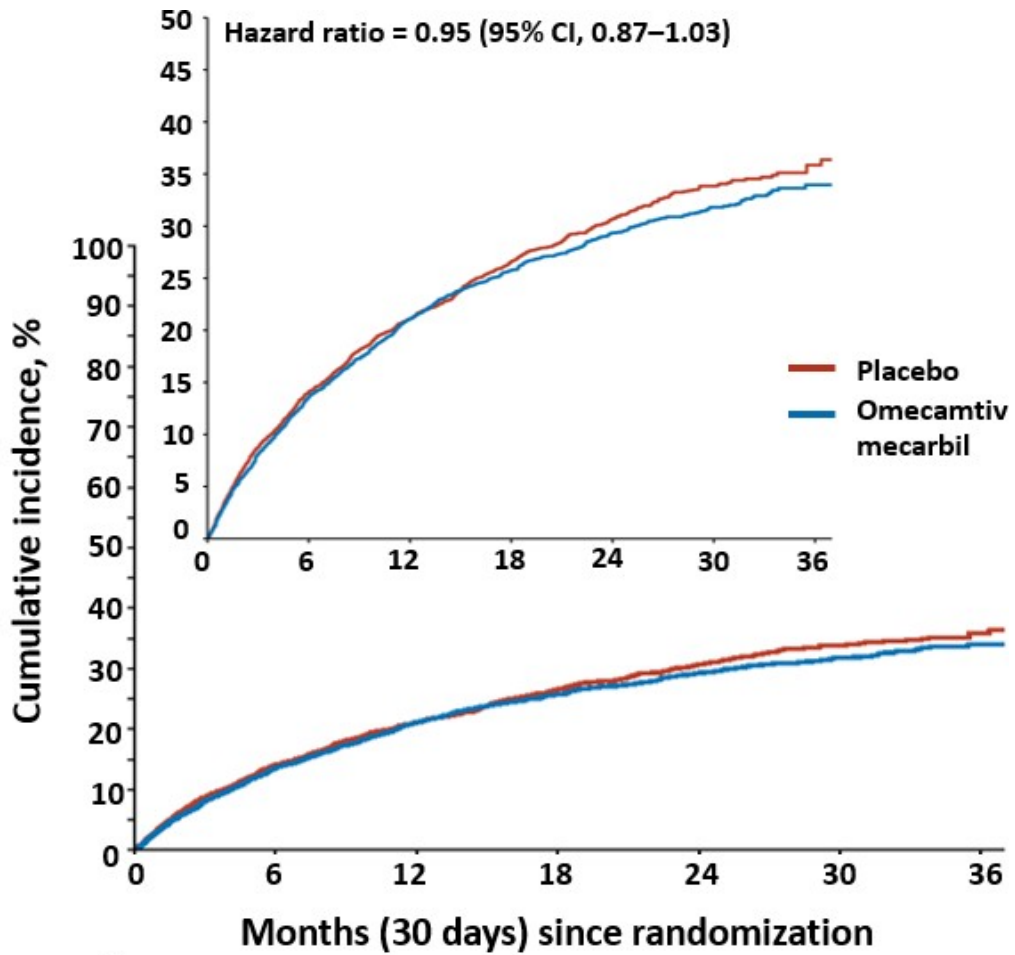
FIGURE S3: Enrollment and Follow-up



BNP, B-type natriuretic peptide; BP, blood pressure; CRT, cardiac resynchronization therapy; ED, emergency department; eGFR, estimated glomerular filtration rate; GCP, good clinical practice; HF, heart failure; HR, heart rate; ICD, implantable cardioverter-defibrillator; LVEF, left

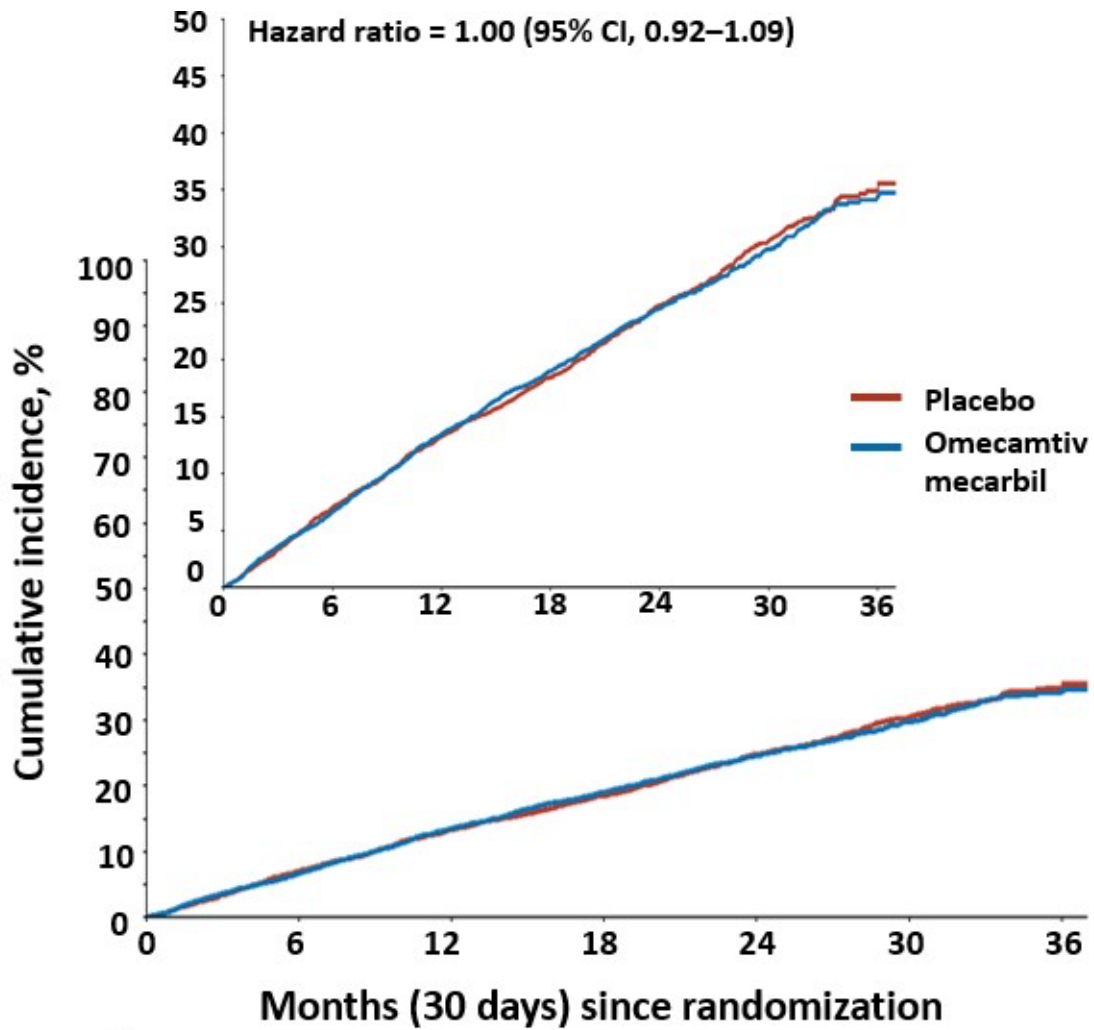
ventricular ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; SoC, standard of care; yr, year; w/in, within.

FIGURE S4: Time to First Heart Failure Hospitalization



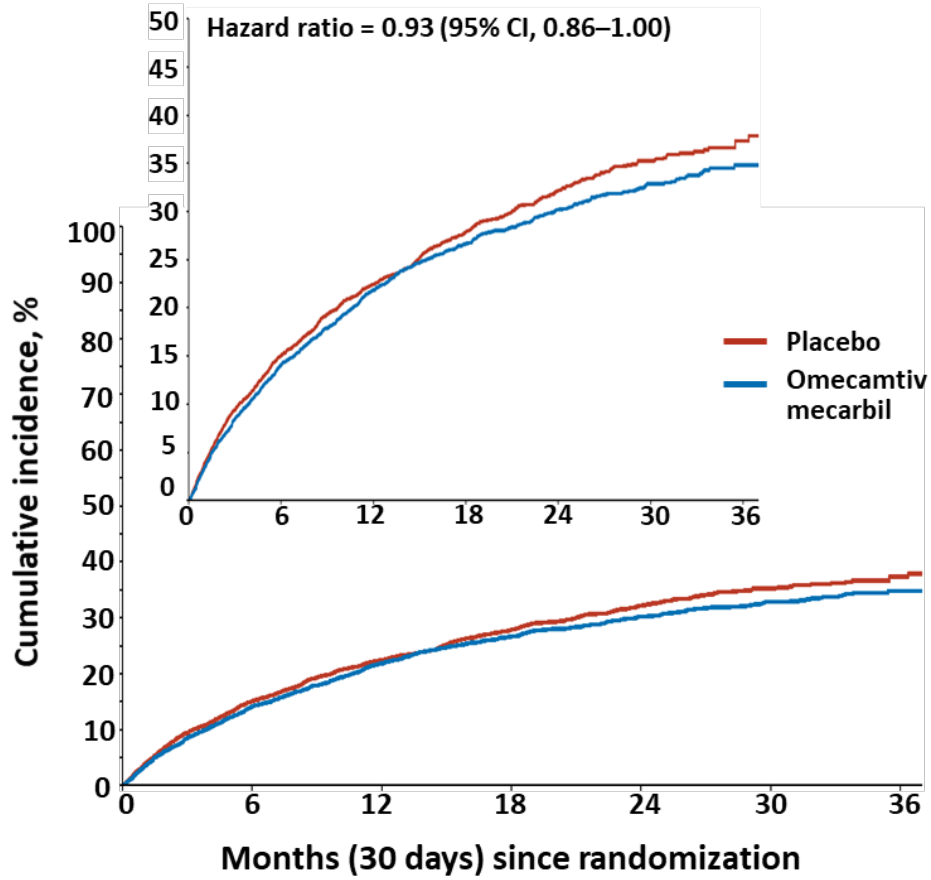
Patients at risk, n		0	6	12	18	24	30	36
Placebo	4112	3347	2937	2137	1370	658	142	
Omecamtiv mecarbil	4120	3410	2980	2182	1442	710	167	

FIGURE S5: Time to All-Cause Death



Patients at risk, n		0	6	12	18	24	30	36
Placebo	4112	3821	3560	2722	1788	885	201	
Omecamtiv mecarbil	4120	3838	3556	2710	1838	903	224	

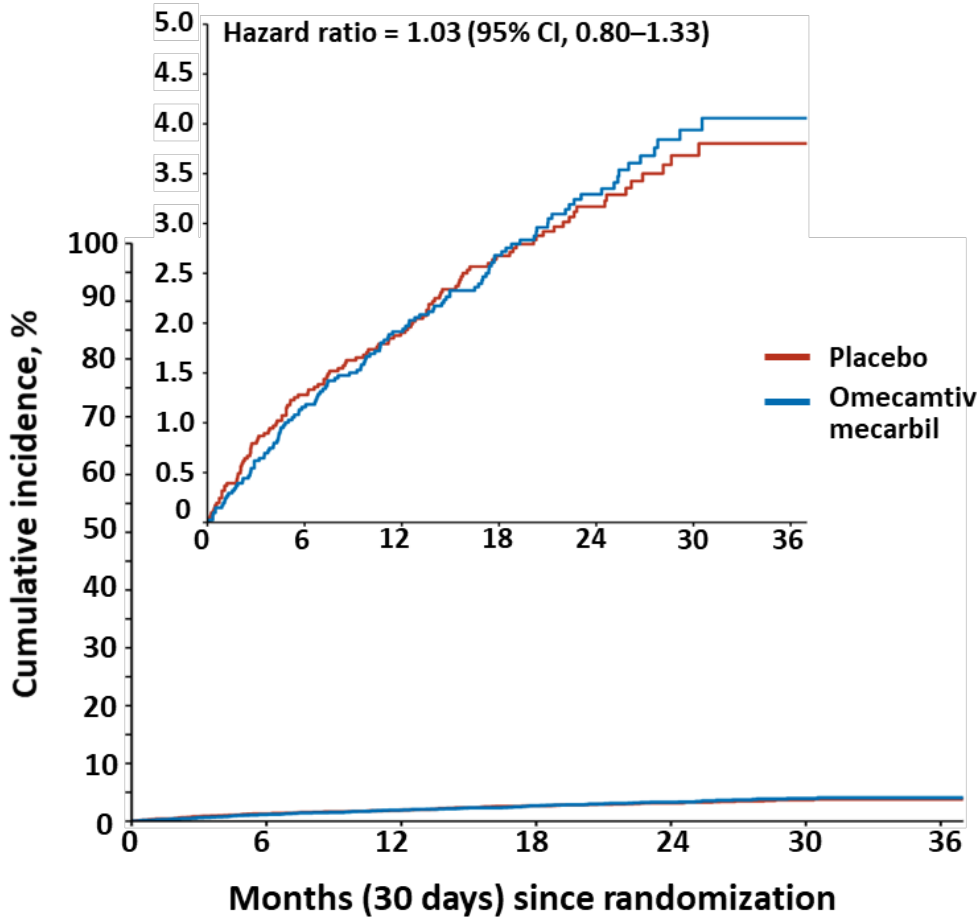
FIGURE S6: Time to First Heart Failure Event



Patients at risk, n

Placebo	4112	3309	2889	2102	1348	647	141
Omecamtiv mecarbil	4120	3391	2953	2156	1430	699	164

FIGURE S7: Time to First Positively Adjudicated Myocardial Infarction



Patients at risk, n

Placebo	4101	3762	3481	2639	1720	841	189
Omecamtiv mecarbil	4110	3788	3485	2634	1769	870	215

TABLES

TABLE S1: Roles of Sponsors and Executive Committee in GALACTIC-HF

	Amgen	Cytokinetics	Servier	Executive Committee
Design of the trial	X	X	X	X
Selection of participating centers	X	X	X	X
Supervision/monitoring of centers	X			
Collecting trial data	X			
Storing trial data	X			
Data analysis	X			Replicated by EC
Interpretation of trial results	X	X	X	X
Writing of the manuscript	X	X	X	First draft by JRT
Manuscript submission	X	X	X	X
Funding	X	X	X	

EC = Independent Statistician and Executive Committee; JRT = John R. Teerlink, MD

Regarding selection and enrollment of patients, and evaluation of patients during follow-up, both of these activities were the responsibility of investigators. Amgen monitored centers to ensure that these processes were done according to the requirements specified by protocol, and provided resources to sites when requested to facilitate these processes (e.g., public records search to determine vital status for patients lost to follow-up, where permitted by local laws and regulations), but no sponsor participated directly in selection or enrollment of patients or evaluation of patients during follow-up.

TABLE S2: Assessment Schedule

Timepoint/Frequency	Screen ^a	Rand D1	W2 ±3d	W4 ±3d	W6 ±3d	W8 ±3d	W12 ±3d	W24 ±7d	W36 ±7d	W48 ±7d	Q16W ^b ±7d	Q48W ±7d	EOS visit ^c
GENERAL PROCEDURES & SAFETY ASSESSMENTS													
Informed consent	X												
Medical/Surgical history	X												
Vital Signs (heart rate, blood pressure)	X	X	X	X	X	X	X	X	X	X	X	X	X
Weight	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events/serious adverse events/potential endpoints/disease-related events ^d	X	X	X	X	X	X	X	X	X	X	X	X	X
Instruction on IP administration		X		X		X	X	X	X	X	X	X	
Placebo run-in ^e	X												
Assessment of IP adherence ⁿ			X		X		X			X		X	
Concomitant therapy	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination/height ^m	X												X
ECG ^e	X	X								X		X	X
Randomization		X											
LOCAL LABORATORY^f													
Chemistry ^f	X ⁱ												
Screening BNP or NT-proBNP ^q	X ⁱ												
Serum pregnancy/FSH ^g	X ⁱ												
CENTRAL LABORATORY													
Chemistry ^h	X ^p	X								X		X	X
Hematology		X								X		X	X
Screening BNP or NT-proBNP ^q	X ^p												
Serum pregnancy/FSH ^g	X												
Urinalysis		X											X

Footnotes defined on the last page of the table

Timepoint/Frequency	Screen ^a	Rand D1	W2 ±3d	W4 ±3d	W6 ±3d	W8 ±3d	W12 ±3d	W24 ±7d	W36 ±7d	W48 ±7d	Q16W ^b ±7d	Q48W ±7d	EOS visit ^c
Abbreviated laboratory panel ⁱ							X	X	X				
NT-proBNP/Troponin I/CK-MB ^j		X	X		X			X		X		X	X
Biomarkers		X			X			X					X
PK samples			X ^k		X ^k		X			X		X	
PATIENT-REPORTED OUTCOMES AND TARGET SYMPTOMS ASSESSMENTS													
KCCQ/PGR-S/CGR-S		X					X	X	X	X		X	
EQ-5D		X					X	X	X	X		X	
NYHA Class	X	X	X	X	X	X	X	X	X	X	X	X	X
ACS signs and symptoms		X	X	X	X	X	X	X	X	X	X	X	X
INVESTIGATIONAL PRODUCT													
IP administration at site		X	X		X								
IP dispensation		X		X		X	X	X	X	X	X	X	
IP tablet count				X		X	X	X	X	X	X	X	X

ACS = acute coronary syndrome; ALP = alkaline phosphatase; ALT = alanine phosphatase; AST = aspartate aminotransferase; BNP = brain natriuretic peptide; CGR-S = Clinician Global Rating Severity; CK-MB = creatine kinase-MB; EOS = end of study; ECG = electrocardiogram; EQ-5D = EuroQOL 5 dimensions questionnaire; FSH = follicle-stimulating hormone; ICF = informed consent form; IP = investigational product; KCCQ = Kansas City Cardiomyopathy Questionnaire; NT-proBNP = n-terminal prohormone brain natriuretic peptide; NYHA = New York Heart Association; PGR-S = Patient Global Rating Severity; PK = pharmacokinetic; Q16W = every 16 weeks; Q48W = every 48 weeks; SGOT = serum glutamic oxaloacetic transaminase; SGPT = serum glutamic-pyruvic transaminase

^a The screening period can last up to 8 weeks after ICF signature.

^b After study visit Week 48 visits will be conducted every 16 weeks.

^c After the decision to end the study has been made, subjects will be scheduled for a final study visit.

^d Only adverse events possibly related to study procedures and serious adverse events are collected during the screening period.

^e Screening ECG to be performed and read locally for all sites. On study ECG to be performed and read locally, except on sites that have been provided with centralized ECG services equipment.

^f Chemistry panel for screening includes sodium, potassium, urea, creatinine, total bilirubin, direct bilirubin, CK, AST (SGOT), ALT (SGPT)

^g Serum pregnancy in females of childbearing potential; FSH only at screening if needed. Additional on-treatment pregnancy testing may be performed at the investigator's discretion if there is suspicion that a female subject is pregnant or per local laws and regulations.

^h Chemistry panel includes sodium, potassium, chloride, calcium, magnesium, phosphorus, urea, creatinine, total bilirubin, direct bilirubin, CK, ALP, LDH, AST (SGOT), ALT (SGPT), and HbA1c.

ⁱ Abbreviated laboratory panel includes sodium, potassium, urea, creatinine, AST, ALT, total bilirubin, direct bilirubin, and hemoglobin.

^j Central NT-proBNP, Troponin I, and CK-MB assessments after baseline will be blinded to subjects, investigators, and sponsor (Amgen).

TABLE S3: Baseline Characteristics of GALACTIC-HF Patients

Characteristic	Omecamtiv mecarbil (N = 4120)	Placebo (N = 4112)
Demographics		
Age — yr	64.5 ± 11.3	64.5 ± 11.4
Sex, female — no. (%)	875 (21.2)	874 (21.3)
Race — no. (%)*		
White	3196 (77.6)	3201 (77.8)
Asian	355 (8.6)	355 (8.6)
Black or African American	285 (6.9)	277 (6.7)
Other or Multiple Races	284 (6.9)	279 (6.8)
Ethnicity, Hispanic/Latino — no. (%)	886 (21.5)	885 (21.5)
Geographic Region — no. (%)		
Eastern Europe/ Russia	1344 (32.6)	1337 (32.5)
Western Europe/ South Africa/ Australasia	961 (23.3)	960 (23.3)
Latin America	787 (19.1)	787 (19.1)
US and Canada	693 (16.8)	693 (16.9)
Asia	335 (8.1)	335 (8.1)
Randomization Setting, Inpatient — no. (%)	1044 (25.3)	1040 (25.3)
Clinical Characteristics		
<i>Medical Conditions — no. (%)</i>		
Coronary artery disease	2568 (62.3)	2560 (62.3)
Myocardial infarction	1693 (41.1)	1742 (42.4)
Percutaneous coronary intervention	1232 (29.9)	1206 (29.3)
Coronary artery bypass grafting	639 (15.5)	678 (16.5)
Peripheral artery disease	418 (10.1)	429 (10.4)

Characteristic	Omecamtiv mecarbil (N = 4120)	Placebo (N = 4112)
Stroke	377 (9.2)	377 (9.2)
Atrial fibrillation or flutter at screening	1146 (27.8)	1099 (26.7)
Hypertension	2910 (70.6)	2874 (69.9)
Type 2 diabetes mellitus	1652 (40.1)	1657 (40.3)
Chronic kidney disease	1475 (35.8)	1519 (36.9)
Chronic Obstructive Pulmonary Disease	665 (16.1)	680 (16.5)
Asthma	218 (5.3)	222 (5.4)
<i>Heart Failure History</i>		
LVEF — %	26.6 ± 6.3	26.5 ± 6.3
MAGGIC Score	23.0 (19.0, 28.0)	23.0 (19.0, 28.0)
NYHA classification — no. (%)		
Class II	2195 (53.3)	2173 (52.8)
Class III	1801 (43.7)	1815 (44.1)
Class IV	124 (3.0)	124 (3.0)
Ischemic heart failure etiology — no. (%)	2193 (53.2)	2222 (54.0)
KCCQ Total Symptom Score	68.8 (49.0, 87.5)	68.8 (49.0, 87.5)
Outpatient	74.0 (54.2, 90.6)	75.0 (56.3, 91.7)
Inpatient	54.2 (34.4, 72.9)	52.1 (31.3, 69.8)
<i>Vitals and Laboratory Parameters</i>		
Body mass index — kg/m ²	28.5 (6.3)	28.4 (6.1)
SBP — mmHg	116.3 ± 15.4	116.6 ± 15.3
Heart rate — beats/min	72.4 ± 12.2	72.3 ± 12.1
NT-proBNP — pg/mL	1977 (980, 4061)	2025 (1000, 4105)
Troponin I — ng/L, median (Q3)	27 (52)	27 (52)

Characteristic	Omecamtiv mecarbil (N = 4120)	Placebo (N = 4112)
eGFR — mL/min/1.73m ²	58.8 (44.3, 74.3)	58.7 (43.8, 73.7)
G≤2: >60	1964 (47.7)	1947 (47.3)
G3: 30-59	1882 (45.7)	1912 (46.5)
G4: 15-29	270 (6.6)	252 (6.1)
G5: <15	4 (<0.1)	1 (<0.1)
Medications and Cardiac Devices — no. (%)		
ACEi, ARB or ARNi	3583 (87.0)	3576 (87.0)
ARNi	819 (19.9)	782 (19.0)
BB	3881 (94.2)	3883 (94.4)
MRA	3199 (77.6)	3198 (77.8)
(ACEi, ARB, or ARNi) + MRA + BB	2709 (65.8)	2716 (66.1)
Digitalis Glycosides	687 (16.7)	698 (17.0)
SGLT2 Inhibitors	104 (2.5)	114 (2.8)
Ivabradine	255 (6.2)	278 (6.8)
Cardiac Resynchronization Therapy	592 (14.4)	566 (13.8)
Implantable Cardioverter Defibrillator	1326 (32.2)	1288 (31.3)

Continuous variables were summarized as means ± standard deviations (SD) or medians and first and third quartiles (Q1, Q3), as appropriate. Categorical variables were summarized as counts and percentages. There were no significant differences between the two groups for any variable. Percentages may not total 100 due to rounding. ACEi indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNi, angiotensin receptor-neprilysin inhibitor; BB, beta blocker; CRT, cardiac resynchronization therapy; ED, emergency department; eGFR, estimated glomerular filtration rate; ICD, implantable cardioverter-defibrillator; KCCQ, Kansas City Cardiomyopathy Questionnaire; LVEF, left ventricular ejection fraction; MAGGIC, Meta-Analysis Global Group in Chronic HF; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; SBP, systolic blood pressure; SGLT2, sodium-glucose co-transporter 2.

*Race was reported by the patients, where Other includes American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, or Multiple self-identified races.

TABLE S4: Baseline Diuretic Use

Category Substance or Product	Omecamtiv mecarbil (N = 4120) n (%)	Placebo (N = 4112) n (%)	Total (N = 8232) n (%)
Diuretics other than MRAs	3692 (89.6)	3686 (89.6)	7378 (89.6)
Acetazolamide	9 (0.2)	10 (0.2)	19 (0.2)
Amiloride	2 (<0.1)	2 (<0.1)	4 (<0.1)
Azosemide	62 (1.5)	58 (1.4)	120 (1.5)
Bendroflumethiazide	6 (0.1)	6 (0.1)	12 (0.1)
Bumetanide	185 (4.5)	194 (4.7)	379 (4.6)
Chlorthalidone	18 (0.4)	18 (0.4)	36 (0.4)
Clopamide	8 (0.2)	6 (0.1)	14 (0.2)
Demeclocycline	0 (0.0)	1 (<0.1)	1 (<0.1)
Diuretic, Unspecified	3 (<0.1)	6 (0.1)	9 (0.1)
Etacrynic Acid	11 (0.3)	6 (0.1)	17 (0.2)
Furosemide	2819 (68.4)	2790 (67.9)	5609 (68.1)
Hydrochlorothiazide	186 (4.5)	189 (4.6)	375 (4.6)
Indapamide	48 (1.2)	59 (1.4)	107 (1.3)
Mannitol	1 (<0.1)	1 (<0.1)	2 (<0.1)
Metolazone	85 (2.1)	91 (2.2)	176 (2.1)
Tolvaptan	54 (1.3)	54 (1.3)	108 (1.3)
Torasemide	677 (16.4)	693 (16.9)	1370 (16.6)
Triamterene	3 (<0.1)	3 (<0.1)	6 (<0.1)
Trichlormethiazide	11 (0.3)	4 (<0.1)	15 (0.2)
Xipamide	14 (0.3)	10 (0.2)	24 (0.3)

TABLE S5: Competing Risk Analyses

Endpoint	Primary Analysis Model HR (95% CI)	Competing Risk Subdistribution HR (95% CI)
Primary composite	0.92 (0.86, 0.99)	0.92 (0.86, 0.99)
Cardiovascular death	1.01 (0.92, 1.11)	1.01 (0.92, 1.11)
Heart failure hospitalizations	0.95 (0.87, 1.03)	0.96 (0.88, 1.04)

TABLE S6: Adjusted Analyses to Account for Potential Informative Censoring

Covariate	Hazard ratio (95% CI)
Omecamtiv mecarbil (reference Placebo)	0.91 (0.84, 0.97)
ACEi use	0.89 (0.82, 0.97)
Diabetes mellitus	1.21 (1.12, 1.30)
Presence of an ICD	1.29 (1.18, 1.41)
eGFR (mL/min/1.73m ²)	0.99 (0.99, 1.00)
Heart rate (beats per minute)	1.00 (1.00, 1.01)
Presence of a CRT	1.11 (1.00, 1.24)
History of an MI	1.31 (1.21, 1.41)
Log NT-proBNP (log pg/mL)	1.56 (1.50, 1.63)
NYHA Class III (reference Class II)	1.26 (1.17, 1.36)
NYHA Class IV (reference Class II)	1.57 (1.29, 1.90)
Black or African American (reference Asian)	1.47 (0.89, 2.41)
Other race (reference Asian)	1.20 (0.72, 2.00)
White (reference Asian)	0.96 (0.59, 1.55)
Presence of atrial fibrillation/flutter at screening	1.19 (1.09, 1.29)
Systolic blood pressure (mmHg)	0.99 (0.99, 1.00)
Weight (kg)	1.00 (1.00, 1.01)
MRA use	1.00 (0.91, 1.09)
ARNi use	0.96 (0.86, 1.07)
Hispanic or Latino	0.94 (0.78, 1.13)

TABLE S7: Missing Data for KCCQ Total Symptom Scores

	Outpatient				Inpatient			
	Omecamtiv mecarbil		Placebo		Omecamtiv mecarbil		Placebo	
	n	%	n	%	n	%	n	%
Total	3076		3072		1044		1040	
Week 24 KCCQ TSS Collected	2715	88.3%	2704	88.0%	868	83.1%	835	80.3%
Missing Week 24 KCCQ TSS	361	11.7%	368	12.0%	176	16.9%	205	19.7%
Death prior to Week 24	172	5.6%	176	5.7%	96	9.2%	104	10.0%
Missing baseline KCCQ TSS	22	0.7%	23	0.7%	8	0.8%	8	0.8%
Missing and HF event within 30 days	14	0.5%	14	0.5%	10	1.0%	11	1.1%
Discontinued study prior to Week 24	9	0.3%	4	0.1%	6	0.6%	5	0.5%
Week 24 occurred but KCCQ TSS not collected	25	0.8%	21	0.7%	7	0.7%	12	1.2%
Week 24 visit missed	119	3.9%	130	4.2%	49	4.7%	65	6.3%

TABLE S8: Joint Model for KCCQ Total Symptom Score to Account for Missing Data Due to Death

Randomization setting	Primary analysis mixed model treatment effect (95% CI) [Omecamtiv mecarbil – placebo]	Joint model treatment effect (95% CI) [Omecamtiv mecarbil – placebo]
Outpatient	-0.46 (-1.40, 0.48)	-0.71 (-1.62, 0.20)
Inpatient	2.50 (0.54, 4.46)	2.31 (0.80, 3.82)

TABLE S9: Treatment-Emergent Serious Adverse Events by Preferred Term Reported by ≥ 1% of Subjects in Any Treatment Group (Safety Analysis Set)

Preferred Term	Omecamtiv Mecarbil (N = 4110) n (%)	Placebo (N = 4101) n (%)
Number of subjects reporting any treatment-emergent serious adverse events	2373 (57.7)	2435 (59.4)
Cardiac failure	988 (24.0)	1045 (25.5)
Cardiac failure acute	212 (5.2)	251 (6.1)
Pneumonia	171 (4.2)	179 (4.4)
Cardiac failure chronic	156 (3.8)	170 (4.1)
Cardiac failure congestive	147 (3.6)	154 (3.8)
Acute kidney injury	129 (3.1)	138 (3.4)
Ventricular tachycardia	106 (2.6)	129 (3.1)
Atrial fibrillation	94 (2.3)	113 (2.8)
Cardiogenic shock	75 (1.8)	68 (1.7)
Acute myocardial infarction	71 (1.7)	64 (1.6)
Death	65 (1.6)	49 (1.2)
Angina unstable	63 (1.5)	49 (1.2)
Chronic obstructive pulmonary disease	63 (1.5)	38 (0.9)
Sudden death	52 (1.3)	58 (1.4)
Sepsis	51 (1.2)	60 (1.5)
Cardiac arrest	50 (1.2)	64 (1.6)
Hypotension	49 (1.2)	37 (0.9)
Syncope	42 (1.0)	46 (1.1)
Angina pectoris	41 (1.0)	40 (1.0)
Myocardial infarction	36 (0.9)	54 (1.3)
Ventricular fibrillation	30 (0.7)	49 (1.2)

TABLE S10: Adverse Events Occurring in $\geq 5.0\%$ of Patients in Either Treatment Group (Safety Analysis Set)

Adverse Event	Omecamtiv Mecarbil	Placebo
	(N = 4110) n (%)	(N = 4101) n (%)
Cardiac failure	1132 (27.5)	1203 (29.3)
Hypotension	309 (7.5)	271 (6.6)
Dyspnea	273 (6.6)	277 (6.8)
Pneumonia	259 (6.3)	292 (7.1)
Dizziness	237 (5.8)	189 (4.6)
Atrial fibrillation	236 (5.7)	263 (6.4)
Acute kidney injury	230 (5.6)	225 (5.5)
Cardiac failure, acute	221 (5.4)	263 (6.4)
Hyperkalemia	216 (5.3)	230 (5.6)
Cardiac failure, chronic	204 (5.0)	210 (5.1)
Hypertension	198 (4.8)	229 (5.6)

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