SUPPLEMENTAL DIGITAL CONTENT

- Supplemental Digital Content 1. Table that lists the names of the Institutional Review Boards. docx
- Supplemental Digital Content 2. Table that summarizes the deaths occurring during the study period. docx

Supplemental Digital Content 1. Institutional Review Boards.

Location	Institutional Review Board
Australia	Hunter New England Research Ethics Committee Research Ethics and Governance Unit, District Headquarters Administration Building Lookout Road New Lambton, NSW 2305 Australia Royal Adelaide Hospital Research Ethics Committee Royal Adelaide Hospital North Terrace Adelaide SA 5000 Australia Bellberry HREC 129 Glen Osmond Road

	Eastwood, SA 5063 Australia
Belgium	Commissie Medische Ethiek van Universitaire Ziekenhuizen KULeuven – Campus Gasthuisberg Herestraat 49 Leuven 3000 Belgium
Denmark	Den Videnskabsetiske Komite for Region Syddanmark Regionshuset Damhaven 12 Vejle 7100 Denmark
Estonia	Tallinn Medical Research Ethics Committee Hiiu str. 42 Tallinn Harjumaa 11619 Estonia
France	CPP TOURS – Region Centre – Ouest 1 Hopital Bretonneau – CHRU

	TOURS – Batiment B1A 2, Boulevard Tonnelle TOURS Cedax 9 37044 France
Germany	Ethikkommission der Landesarztekammer Thuringen Im Semmicht 33 Jena Thuringen 07751 Germany
Hungary	Egeszsegugyi Tudomanyos Tanacs Klinikai Farmakologiai Etkai Bizottsaga Arany Janos u. 6-8 Budapest H-1051 Hungary
Poland	Komisja Bioetyczna przy Slaskiej Izbie Lekarskiej w Katowicach ul. Grazynskiego 49a Katowice 40-126 Poland
South Africa	University of the Witwatersrand Human Research Ethics Committee 8 Blackwood Avenue

	Parktown Johannesburg Gauteng 2193 South Africa
Spain	CEIC Hospital Universitari de Girona Doctor Josep Trueta Avinguda de Franca s/n Girona 17007 Spain CEIC – Consorci Sanitari Integral Hospital General De l-Hospitalet AV Joseph Molins, 29-41 L'Hospitalet de Llobregat Barcelona 08906 Spain
Sweden	Regionala Etikprovningsnamnden i Stockholm Karolinska Institutet/Solna Nobels vag 9, plan D3 Stockholm 171 Sweden
United Kingdom	NRES Committee North West – Liverpool East North West Centre of Research

	Ethics Committees 3rd Floor, Barlow House 4 Minshull Street Manchester M1 3DZ United Kingdom
United States	Schulman Associates Institutional Review Board 4445 Lake Forest Drive Suite 300 Cincinnati, OH 45242 United States

Supplemental Digital Content 2. Summary of all deaths during the study period (safety population).

Treatment	Sex	Age, years	Race	BMI, kg/m^2	Day of Death*	TEAE†	Cause of Death
Naldemedine	Female	53	White	22.6	350	No	Cerebrovascular accident
	Female	58	White	37.3	162	No	Acute exacerbation of COPD
	Female	52	White	35.8	169	No	Stage IV pulmonary adenocarcinoma
	Male	49	White	27.7	350	Yes	Myocardial infarction related to diabetes
Placebo	Male	52	Black	28.1	50	No	Accidental overdose‡
	Male	64	White	28.8	28	Yes	Cardiac arrest

	Female	49	White	37.1	31	Yes	Complications of arteriosclerotic CVD
	Female	78	White	38.1	179	Yes	Cerebrovascular accident

*Day of death since the start of treatment with the study drug.

†A death was not considered a TEAE if the patient died >14 days after their last visit and the bottles of pills were never returned for accountability.

‡Accidental overdose was of a noninvestigational product.

BMI, body mass index; COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease; TEAE, treatment-emergent adverse event.