Supplemental Online Content

Dulhunty JM, Brett SJ, De Waele, et al; BLING III Study Investigators; Australian and New Zealand Intensive Care Society Clinical Trials Group. Continuous vs intermittent β-lactam antibiotic infusions in critically ill patients with sepsis: the BLING III randomized clinical trial. *JAMA*. doi:10.1001/jama.2024.9779

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

BLING III STUDY INVESTIGATORS

Australia

Austin Hospital: Rinaldo Bellomo, Glenn Eastwood, Leah Peck, Helen Young.

Bankstown Hospital: Andrew Cheng, Luke Lau, Magdalena Luciuk, Margaret Muteitha, Manoj Saxena.

Bendigo Hospital: Catherine Boschert, Timothy Chimunda, Cameron Knott, Julie Smith.

Blacktown Hospital: Treena Sara, Charudatt Shirwadkar, Kiran Nand.

Box Hill Hospital: Peter Chan, Graeme Duke, John Dyett, Kym Gellie, Stephanie Hunter, Melissa Kaufman, Owen Roodenburg, Joseph Vetro.

Caboolture Hospital: Julia Affleck, Mahesh Ramanan, Megan Ratcliffe, Alexis Tabah, Timothy Warhurst.

Gold Coast University Hospital: Maimoonbe Gough, Maree Houbert, Julie Pitman, Mandy Tallott, James Winearls.

Gosford Hospital: Shelley Donovan, Katrina Ellis, Atul Gaur, Mary Keehan, Amy Kelty, Elisha Turner.

John Hunter Hospital: Cynthia Bierl, Gail Brinkerhoff, Dustin Bush, Joshua Davis, Amber-Louise Poulter, Krishna Sunkara.

Logan Hospital: Melanie Cooper, Lynette Morrison, Sunil Sane, Joanne Sutton, Hayden White.

Lyell McEwin Hospital: Vishwanath Biradar, Milind Sanap, Natalie Soar.

Princess Alexandra Hospital: Megan Davis, Meg Harward, Cassie Jones, Josie Mackay, Niki McGuinness, Jason Meyer, Emma Saylor, Adam Suliman, Alexis Tabah, Ellen Venz, James Walsham, Krista Wetzig.

The Queen Elizabeth Hospital: Catherine Kurenda, Sandra Peake, Patricia Williams

Redcliffe Hospital: Stuart Baker, Maree Duroux, Kylie Jacobs, Hamish Pollock, Megan Ratcliffe, Sam Shone, Alexis Tabah, Tim Warhurst.

Royal Brisbane and Women's Hospital: Jenie Butler, Cheryl Fourie, Marianne Kirrane, Melissa Lassig-Smith, Daisy Lindsay, Jeffrey Lipman, Amelia Livermore, Bree-Yana McConnochie, Lynn Murray, Georgina Peacock, Therese Starr, Janine Stuart.

Royal Darwin Hospital: Sidharth Agarwal, Margaret Phillips, Kirsty Smyth.

Royal Hobart Hospital: David Cooper, Rick McAllister.

Royal Melbourne Hospital: Yasmine Ali Abdelhamid, Deborah Barge, Kathleen Byrne, Adam Deane, Sarah Doherty, Simon Iles, Brie Jelbart, Thomas Rechnitzer.

Royal North Shore Hospital: Angela Ashelford, Frances Bass, Celia Bradford, Anthony Delaney, Simon Finfer, Jonathan Gatward, Naomi Hammond, Roger Harris, Pierre Janin, Richard Lee, Elizabeth Limbrey, Sharon Mar, Naomi Pallas, Julia Pilowsky, Melanie Ross, Wade Stedman, Miyuki Tokumitsu, Elizabeth Yarad.

Royal Prince Alfred Hospital: Maryam Alborzi, Heidi Buhr, Jennifer Coles, David Gattas.

St George Hospital: Andrew Cheng, Deborah Inskip, Asako Ito, Jennene Miller.

St Vincent's Hospital: Claire Reynolds, Sam Rudham.

University Hospital Geelong: Alison Bone, Claire Cattigan, Tania Elderkin*, Tania Salerno.

The Wesley Hospital: Jeremy Cohen, Amanda Davie, Amy Owens, Roslyn Purcell, Balasubramanian Venkatesh.

Westmead Hospital: David Bowen, Peter Clark, Mohammad Hamidi, Jenyfer Joy, Jing Kong, Vineet Nayyar.

Belgium

Antwerp University Hospital: Kaatje Cruysberghs, Philippe Jorens, Petra Vertongen.

Brussels University Hospital: Marc Diltoer, Marie Claire Van Malderen.

Civil Hospital Marie Curie: Anne Joosten, Maxime Van Cutsem.

Erasmus Hospital: Caroline Abbenhuijs, Dominique Durand, Nancy Matumikina, Fabio Taccone.

Ghent University Hospital: Stephanie Bracke, Lesley De Coster, Luc De Crop, Anouska De Smeytere, Jan De Waele, Jolien Van Hecke, Daisy Vermeiren.

Maria Middelares Hospital: Jan Heerman, Steffi Ryckaert, Annelies Van Damme.

Saint-Pierre Ottignies Clinic: Nicolas De Schryver, Anne Thirifays.

Stuivenberg Hospital: Els Fannes, Niels Van Regenmortel.

France

Brabois Hospital Nancy: Corentine Alauzet, Thibaut Belveyre, Jessica Breistroff, Aurélie Gutehrle, Emmanuel Novy, Maximilien Saint Gilles.

Henri Duffaut Hospital Centre: Marie Bonnefoy, Audrey Clavier, Pierre Ducq, Antoine Frouin, Sébastien Moschietto, Marion Touzet.

Poitiers University Hospital: Claire Dahyot-Fizelier, Angéline Jamet, Angela Kostencovska, Quentin Saint Genis.

Salon de Provence Hospital: Sami Alaya, Ali Mofredj.

University Hospital of Nîmes: Caroline Boutin, Loubna Elotmani, Martin Mahul, Laurent Muller, Nicolas Perin, Claire Roger.

Malaysia

Hospital University Sains Malaysia: Sanihah Che Omar, Suki Ismet, Noor Iellieya Maisarah Jamaludin, Md Fadhil Mat Armin, Mohd Zulfakar Mazlan, Husna Mohd Nor, Nabila Mohd Sukri, Nurul Amira Nizar, Mahamarowi Omar, Era Nabilah Roslan, Zeti Norfidiyati

Salmuna, Tuan Zulfadli Syazwan Tuan Mohd Adnan, W Mohd Nazarudin W Hassan, Halimatun Arwa Yakuub.

University Malaya Medical Centre: Mohd Shahnaz Hasan, Marhainie Mohamad, Mohamad Irfan Othman Jailani, Helmi Sulaiman.

New Zealand

Auckland City Hospital (Cardiothoracic and Vascular Intensive Care Unit): Farisha Ali, Magdalena Butler, Keri-Anne Cowdrey, Eileen Gilder, Jane Hallion, Immanuel Hennessy, Shay McGuinness, Philippa Neal, Karina O'Connor, Rachael Parke, Samantha Ryan, Melissa Woollett (Robertson).

Auckland City Hospital (Department of Critical Care Medicine): Yan Chen, Colin McArthur, Rachael McConnochie, Caroline O'Connor, Catherine Simmonds.

Christchurch Hospital: Brandon Burke, Tara Doyle, Jan Mehrtens, Stacey Morgan, Anna Morris, Kym Van Der Heyden.

Middlemore Hospital: Dinu Girijadevi, Vivian Lai, Rima Song, Tony Williams.

Waikato Hospital: Amelia Butler, Caitriona Fiske, Annette Forrest, Erin Furborough, Robert Martynoga, Renesh Nair, Sarah Rogers, Livia Schischka, Kara Trask.

Wellington Hospital: April Aguilar**,** Colin Barnes, Ben Barry, Niña Beehre, Kirsha Delaney, Dick Dinsdale, Kim Grayson, Deb Hendry, Anna Hunt, April Jane, Harriet Judd, Charlotte Latimer-Bell, Cassie Lawrence, Eden Lesona, Rosie Martin, Agnes Mckay-Vucago, Alex Millington, James Moore, Leanlove Navarra, Shaanti Olatunji, Alex Psirides, Yve Robertson, Chelsea Robertson, Hannah Smellie, Rhoze Sol Cruz, Raulle Sol Cuz, Shawn Sturland, Kate Tiejens, Bob Ure, Lawrence Walker, Jason Wright.

Sweden

Helsingborg Hospital: Sara Andertun, Martin Annborn, Maria Nelderup.

Skåne University Hospital, Lund: Lisa Boström, Susann Schrey.

Skåne University Hospital, Malmö: Marina Larsson, Fredrik Sjövall.

United Kingdom

Basingstoke & North Hampshire Hospital: Maria Alvarez Corral, Anthony Ashton, Nicolas J Cortes, Denise Griffin, Nycola Muchenje, McDonald Mupudzi, Dawn Trodd.

Blackpool Victoria Hospital: Leonie Benham, Zena Bradshaw, Gemma Brown, Janette Brown, Jason Cupitt, Lisa Elawamy, Alan Fahey, James Glen, Shamina Hankinson, Gareth Hardy, Jazmine McCooey, Sam Remnant, Ella Riedel, Emma Stoddard, Bhagawathi Suryanarayanan, Lauren Thornborough, Emma Ward, Scott Warden, Conor Wilkinson.

Bristol Royal Infirmary: Jeremy Bewley, Anna Chillingworth, Georgia Efford, Zoe Garland, Lisa Grimmer, Rebekah Johnson, Katie Sweet, Denise Webster, Kim Wright.

Broomfield Hospital: Mandy Austin, Vallish Bhardwaj, Stacey Cotterell, Fiona McNeela, Victoria Mead, Lauren Perkins, Jayachanan Radhakrishnan, Susan Smolen, Christopher Westall.

Charing Cross Hospital: David Antcliffe, Ziortza Fernandez, Eleanor Jepson, Roceld Rojo, Anita Tamang Gurung, Maie Templeton.

Countess of Chester Hospital: Dolores Beach, Melanie Colegrove, Maria Faulkner, Laura McKay, Jos Wickett, Lawrence Wilson.

Darent Valley Hospital: Zakaulla Belagodu, Ryan Coe, Katy Collins, Charlotte Kamundi, Naomi Oakley, Carmel Stuart.

Derriford Hospital: Nikitas Nikitas, Ana Sanchez-Rodriguez, Kayleigh Spencer, Liana Stapleton, Bethan Stowe, Colin Wells.

Dorset Country Hospital: Sarah Doyle, Stephanie Dukes, Sarah Horton, James Rees, Mark Shortland, Ruth Thomas, Sophie Webber, Trish Williams.

Freeman Hospital: Lauren Butler, Leigh Dunn, Arti Gulati, Jonathan Shelton.

Frimley Park Hospital: Yvonne Bland, Lianne Chapman, Rozzie Dolman, George Evetts, Danni Greener, Istvan Kajtor, Stephen Lewis, Cat Lumby, Helen Rayner.

Glasgow Royal Infirmary: Susanne Cathcart, Pamela MacTavish, Kathryn Puxty.

Golden Jubilee National Hospital: Christine Aitken, Elizabeth Boyd, Julie Buckley, Charlene Hamilton, Ilkin Kasmani, Thomas Keast, Phil McCall, Ruth McLaren, Ben Shelley.

Hammersmith Hospital: Stephen Brett, Sonia Sousa Arias, Jenny Wong.

Hereford County Hospital: Susan Anderson, Eleanor Andrews, Janine Birch, Emma Collins, Mark Forrest, Surpreet Grewal, Kate Hammerton, Andrew Holland, Robin Jootun, Ryan O'Leary, Kyaw Pyae Soan, Carl Stevenson, Samantha Summers, Laura Troth.

Hull Royal Infirmary: Louise Foster, Andrew Gratrix, Matthew Hines, Victoria Martinson, Vanessa Rivers, Elizabeth Stones.

Ipswich Hospital: Sarah Bartholomew, Stephanie Bell, Kate Turner, Karen Winter.

James Cook University Hospital: Uwe Franke, Evie Headlam, Keith Hugill, Jessica Jones, Abigail List, Joanne Morley, Tracy Ruddick, Amy Thompson.

King's College Hospital: Nikkita Adams, Emma Clarey, Maeve Cockrell, Ele Corcoran, Maria Depante, Clare Finney, Aparna George, Philip Hopkins, Nauman Hussain, Reena Mehta, Kevin O'Reilly, Mandeep K Phull, John Smith.

King's Mill Hospital: Mandy Gill, Jill Kirk, Pulak Paul, Sarah Shelton.

Kingston Hospital: Hanan Abdullise, Samantha Bacciarelli, Julia Balcioglu, Isabel Bradley, Sabrina Carta, Rebecca Crowe, Marion Gillespie, Margaret Grout, Rosaleen Herdman-Grant, Olumayowa Ogunwemimo, Nicole Richard, Kathryn Sollesta, Andrew Swain, Joan Willis.

Maidstone Hospital: Miriam Davey, Rebecca Seaman, James Wood.

Medway Maritime Hospital: Iram Ahmed, Rebecca Collins, Tessa Glazebrook, Paul Hayden, Thyra Khyere Diaborr, Robert Musalagani, Linda Ofori, Vonganyi Ogbeide, Sana Sowah, Rebecca Squires.

Milton Keynes University Hospital: Louise Mew, James Pocock, Richard Stewart, Sara-Beth Sutherland.

Ninewells Hospital: Pauline Austin, Louise Cabrelli, Matthew Casey, Susan Chapman.

Northumbria Specialist Emergency Care Hospital: Hayley McKie, Jessica Reynolds, Tracy Smith, Gail Waddell, Jack Wilkinson, Bryan Yates.

Pinderfields Hospital: Ali Alayan, Andrew Ashcroft, Sarah Buckley, Elizabeth Denis, Lucy Gurr, Amy Major, Alex Metcalfe, Alice Poole, Alistair Rose, Brendan Sloan, Sharwend Supermanian, Nicola Thompson, Katie Wilson.

Poole Hospital: Julie Camsooksai, Yasmin De'Ath, Sarah Jenkins, Emma Langridge, Rebecca Miln, Sarah Patch, Magda Pomichowska, Henrik Reschreiter, Suzanne Roffe, Sarah Savage.

Princess Royal Hospital: Nikkita Adams, Emma Clarey, Maeve Cockrell, Ele Corcoran, Maria Depante, Clare Finney, Aparna George, Nauman Hussain, Reena Mehta, Kevin O'Reilly, Mandeep K Phull, John Smith.

Queen Alexandra Hospital: Helen Claridge, Aimi Collins, Zoe Daly, Dovy Domingo, James McNicholas, Angie Nown, Steve Rose.

Queen Elizabeth Hospital Birmingham: Mansoor Bangash, Colin Bergin, Ronald Carrera, Amy Clark, Lauren Cooper, Natalie Dooley, Karen Ellis, Emma Fellows, Stephanie Gouny, Samantha Harkett, Saffron King, Tracy Mason, Aoife Neal, Alex Newtown-Cox, Dhruv Parekh, Jaimin Patel, Christopher Sheridan, Hazel Smith, Elaine Spruce.

Queen's Hospital: Nikkita Adams, Sam Bosompem, Parveen Dugh, Aparna George, Nauman Hussain, Mariha Khalid, Lace Paulyn Rosaroso, Mandeep K Phull, Tatiana Pogreban.

Queen's Medical Centre, Nottingham: Saima Ashraf, Marc Chikhani, Amy Clark, Louise Conner, Martin Dent, Daniel Harvey, Treesa Joseph, Megan Meredith, Lucy Morris, Cecilia Peters, Lucy Ryan, Julia Sampson, Anju Thomas, Catherine Walton.

Royal Berkshire Hospital: Shauna Bartley, Parminder Bhuie, Sabi Gurung Rai, Nicola Jacques, Andrew Walden.

Royal Bolton Hospital: Hugo Buckley, Madhu Balasubramaniam, Scott Latham.

Royal Hampshire County Hospital: Emily Bevan, Arthur Goldsmith, Irina Grecu, Jane Martin, Dawn Trodd, Simon Williams, Caroline Wrey Brown.

Royal London Hospital: Amaia Arrieta, Maria Fernandez, Aelx Fowler, Ryan Haines, Mareena Joseph, Tim Martin, Filipa Santos, Fatima Seidu, Ruzena Uddin, Parjam Zolfaghari.

Royal Marsden Hospital: Claudio Addari, Sekina Bakare, Lauren Barraclough, Thomas Bemand, Ethel Black, Matt Clayton, Arnold Dela Rosa, Luke Edwards, Hugh Furness, Richard Gordon-Williams, Nicole Greenshields, Natalie Hester, Francesca Holden, Emma Hunt, Aatif Husain, Ryan Howle, Sultan Iqbal, Venkateswaran Jambunathan, Shaman Jhanji, Ahalya Kadirvelarasan, Harriet Kemp, Suzannah Lant, Sarah Loftus, Sam Maese, Laura Matthews, Olivia Morley, Kshiteeja Naik, Isabel Norris, Nicola Ocean, Luke Parker, Amee Patel, Shivali Patel, Rvishankar Raobaikady, Martin Shao Foong Chong, William Sherwood, Sam Smith, Prakhar Srilastava, Sharjeel Tahir, Shamil Tanna, Kate Tatham, Benjamin Thomas, Pete Thomas, Shree Voralia, Kritchai Vutipongsatorn, Zoszka Webb, Tanith Westerman, Alasdair Wills.

Royal Surrey County Hospital: Hafsana Ali, Michele Bossy, Naomi Boyer, Letitia Bullman, Dorota Burda, Paula Carveli, Sana Chmielewska, Daniel Cottam, Nichlaus Dawson,

Jeanny Del Socorro, Lui Forni, John Hilton, Sherin John, Justin Kirk Bayley, Donna May Sanga, Kathryn Mcintosh, Jame McKinley, Rugaia Montaser, Tahir Nasser, Razan Nour, Elizabeth Porter, Stephanie Rouse, Amorel Salberg, Joe Tooley, Emma Tyson, Jerik Verula, Eva Wilson, Waldtraud Wutte.

Royal Victoria Infirmary: Lauren Butler, Leigh Dunn, Arti Gulati, Jonathan Shelton.

Salford Royal Hospital: Emma Boxall, Kathryn Cawley, Joy Dearden, Reece Doonan, John MacDonald, Danielle McLaughlan.

Southampton General Hospital: Alice Baker, Clare Bolger, Rachel Burnish, Michael Carter, Rebecca Cusack, Susan Jackson, Karen Salmon.

St George's Hospital: Lijun Ding, Sarah Farnell Ward, Helen Farrah, Geraldine Gray, Pamela Kabungo, Susannah Leaver, Romina Pepermans Saluzzio, Christine Sicat, Maria Thanasi, Vince Ventura, Nikki Yun.

St Mary's Hospital: Dorota Banach, Anthony Gordon, Amal Mohammed.

St Thomas' Hospital: Ehsan Ahmadnia**,** Mike Barker, Aneta Bociek, Lynda Cameron, Fabiola D'Amato, Fraser Hanks, Sarah Khorshid, Rosario Lim, Shelley Lorah, Kyma Morera, Marlies Ostermann, Gill Radcliffe, Chris Remmington, Natasha Thaladi, Duncan Wyncoll.

Stoke Mandeville Hospital: Judith Abrams, Oliver Dare, Geraldine Hambrook, Katarina Manso, Elizabeth McKerrow, Pradeep Shanmugasundaram.

Sunderland Royal Hospital: Sarah Cornell, Alistair Roy, Lindsey Woods.

Tunbridge Wells Hospital: Rebecca Collins, Hayley Dolan, Paul Hayden.

University Hospital Coventry: Thomas Billyward, Pamela Bremmer, Carl Hawkins, Sophie Jackson, Geraldine Ward.

University Hospital of North Tees: Michele Clark, Vijay Jagannathan, Sarah Purvis, Pam Race, Thomas Robb, Simon Sinclair.

University Hospital of Wales: Jenny Brooks, Jade Cole, Rhys Davies, Helen Hill, Matt Morgan, Craig Spencer, Angharad Williams, Emma Thomas.

Watford General Hospital: Chiara Ellis, Elvira Hoxha, Valerie Page, Xiaobei Zhao.

Whittington Hospital: Nick Ivin, Rachel Johnston, Louise Ma, Anezka Pratley, Aine Ruttledge, Kathryn Simpson.

Whiston Hospital: Greg Barton, Anthony Cochrane, Clare Harrop, Chelcie Jewitt, Charlotte Preston, Karen Shuker.

**Deceased*

The collaborating investigators for the BLING II trial are also listed in Supplement 4.

BLING III STUDY MANAGEMENT COMMITTEE

Jeffrey Lipman (Chair), Stephen J. Brett, Jan J. De Waele, Menino O. Cotta, Joshua S. Davis, Joel M. Dulhunty, Simon Finfer, Naomi E. Hammond, Serena Knowles, Shay McGuinness, John A. Myburgh, David L. Paterson, Sandra Peake, Dorrilyn Rajbhandari, Andrew Rhodes, Jason A. Roberts, Claire Roger, Charudatt Shirwadkar, Therese Starr and Colman Taylor.

The Writing Committee comprised the BLING III Study Management Committee, Laurent Billot, lead statistician, and biostatisticians, Xiaoqiu Liu and Jayanthi Mysore.

BLING III STUDY INDEPENDENT DATA SAFETY AND MONITORING COMMITTEE

J. Duncan Young (Chair)[1], John Marshall[2,3], Thomas Van der Poll[3]

Affiliations:

1. University of Oxford, Oxford, United Kingdom.

2. Critical Care Medicine, St. Michael's Hospital, Toronto, Canada.
3. University of Toronto, Toronto, Canada.
4. Department of Medicine, Amsterdam University Medical Centers, Amsterdam, Netherlands.

THE GEORGE INSTITUTE FOR GLOBAL HEALTH, SYDNEY, AUSTRALIA

Senior Project Manager: Dorrilyn Rajbhandari.

Critical Care Division, Academics: Simon Finfer, Naomi Hammond, John Myburgh.

Critical Care Division, Operations: Marwa Abdel-All, Mohd Hafiz Abdul-Aziz (Malaysia), Rebecca Anderson, Fatima Butt, Hayley Clark, Benjamin Finfer, Fiona Goodman, Miranda Hardie, Serena Knowles, Carolyn Koch, Sharon Micallef, Dijlah Moungatonga, Conrad Nangla, Fiona Osbourne, Julia Pilowsky, Tina Schneider, Isabella Scholer, Anna Tippett.

Data Management: Mirza Ahmad Baig, Manuela Armenis, Mahesh Basavaraj, Dominic Byrne, Marouane Daki, Amrutha Nagarajaiah, GanaVani Puttashetty, Carlyn Quek, Tummapudi Ravikumar, Ravinder Singh.

Biostatistics and Data Science Division: Laurent Billot, Gian Luca Di Tanna, Qiang Li, Xiaoqiu Liu, Jayanthi Mysore.

Legal Office: Legal Counsel team.

THE UNIVERSITY OF QUEENSLAND, BRISBANE, AUSTRALIA

Project Support: Mohd Hafiz Abdul-Aziz, Sia Athanasas, Luminita Vlad.

REGIONAL COORDINATION

Australia Coordination: Jeffrey Lipman, Dorrilyn Rajbhandari.

Australian Monitors (The George Institute for Health): Rebecca Anderson, Fiona Goodman, Miranda Hardie, Serena Knowles, Carolyn Koch, Sharon Micallef, Conrad Nangla, Fiona Osbourne, Julia Pilowsky, Tina Schneider, Anna Tippett.

Belgium and Europe Coordination: Jan De Waele, Daisy Vermeiren.

Belgian Monitors (Ghent University Hospital): Daisy Vermeiren, Charlotte Clauwaert.

France Coordination: Claire Roger, Loubna Elotmani.

French Monitor (University Hospital of Nîmes): Alice Dubois.

Malaysia Coordination: Mohd Hafiz Abdul-Aziz.

Malaysian Monitor: Mohd Hafiz Abdul-Aziz.

New Zealand Coordination: Shay McGuinness, Sally Hurford.

New Zealand Monitors (Medical Research Institute of New Zealand): Sally Hurford, Shaanti Olatunji.

Sweden Coordination: Fredrik Sjövall.

Swedish Monitor (Skåne University Hospital, Malmö): Liz Jergle.

United Kingdom Coordination: Stephen Brett, Farah Al-Beidh, Janis Best-Lane.

United Kingdom Monitors (Imperial College London): Janis Best-Lane, Ravinder Kaur Dhaliwal, Elizabeth Fagbodun, Lucy Stronach.

EMETHODS

Inclusion and Exclusion Criteria

Table 1. Inclusion and Exclusion Criteria

Inclusion criteria:

- The patient has a documented site of infection or strong suspicion of infection
- The patient is expected to be in the Intensive Care Unit the day after tomorrow
- The patient has been commenced on piperacillin-tazobactam or meropenem to treat the episode of infection
- Giving piperacillin-tazobactam or meropenem by intermittent infusion or continuous infusion is considered equally appropriate for the patient
- One or more organ dysfunction criteria in the previous 24 hours:
    - Mean Arterial Pressure < 60 mmHg for at least 1 hour
    - Vasopressors required for > 4 hours
    - Respiratory support using supplemental high flow nasal prongs, continuous positive airway pressure, bilevel positive airway pressure or invasive mechanical ventilation for at least 1 hour
    - Serum creatinine concentration > 220 µmol/L or > 2.49 mg/dL

Exclusion criteria:

- The patient’s age is less than 18 years
- The patient has received piperacillin-tazobactam or meropenem for more than 24 hours during current infectious episode
- The patient is known or suspected to be pregnant
- The patient has a known allergy to piperacillin-tazobactam, meropenem or penicillin
- The patient is requiring renal replacement therapy at the time of randomization, including renal replacement therapy for chronic renal failure
- The attending clinician or patient or surrogate legal decision maker is not committed to advanced life-support, including mechanical ventilation, dialysis and vasopressor administration, for at least the next 48 hours

Exclusion criteria (continued):

- The patient's death is deemed imminent and inevitable
- The patient has previously been enrolled in the BLING III study

---

Definition of Clinical Cure

Clinical cure was defined as the completion of the β-lactam antibiotic treatment course (on or prior to Day 14) without recommencement of antibiotic therapy within 48 hours of cessation. For the purposes of evaluating clinical cure, a change of antibiotic therapy (either escalation or de-escalation) for the same indication for which the β-lactam antibiotic was commenced was considered part of the antibiotic treatment course. Participants discharged from hospital within 14 days following randomization were considered to meet the definition of clinical cure. However, if a participant was readmitted within 14 days of randomization, then the participant was assessed against the definition of clinical cure as above, using information available at readmission (i.e., if a participant was readmitted and commenced on antibiotic therapy for the same indication within 48 hours of cessation, then clinical cure was coded as "No").

Participants who deceased while receiving the antibiotic treatment course or where antibiotic therapy was ceased in the setting of death being deemed imminent and inevitable, were assessed as not meeting the criteria for clinical cure. Participants who did not receive any β-lactam antibiotic treatment after randomization were coded as not meeting the definition of clinical cure.

Consent

Informed consent was obtained in accordance with legal and Human Research Ethics Committee or Institutional Review Board requirements in each jurisdiction as outlined in section 10.3 of the study protocol (Supplement 1). This included a hierarchy of consent or a framework for providing treatment to patients who were unable to consent for themselves.

Consent could be refused or revoked without any reason for any, or all, of the following study procedures:

- Further administration of the β-lactam antibiotic via the study assigned administration method. The participant would continue to receive the β-lactam antibiotic via the standard method of administration at the site if still prescribed.
- Data collected prior to refusal/revocation. In this case, all data collected prior to date and time of consent refusal/revocation was deleted and not used.
- Data collection after refusal/revocation, including data collection and follow-up that did not involve contact with the patient/substitute decision maker. In this case, no data was collected or used after consent refusal/revocation. Vital status could not be obtained either by direct contact with the patient/substitute decision maker, by review of the patient record, or any other method.
- Vital status at Day 90 determined by direct contact with the patient/substitute decision maker. If vital status at 90 days could not be obtained by direct contact with the patient/substitute decision maker, in certain cases it could be ascertained from the patient record with consent. For example, if the patient was still in the hospital, or attended outpatient appointments, or if the patient had died, and this was documented in the patient record.

Australia

In Australia, written consent prior to randomization was obtained from the patient or the substitute decision maker, where possible to do so, as outlined in section 10.3.1 of the study protocol (Supplement 1). When it was not possible for the patient or the substitute decision maker to provide written consent in a timely manner, the patient was enrolled into the study under a waiver of consent and written consent to continue participation was obtained from the patient or the substitute decision maker as soon as possible. If the patient died or didn't regain capacity, and there was no substitute decision maker available, the ethics committee gave approval for use of data in accordance with relevant legislation.

Belgium

Deferred informed consent was approved by the ethics committee. Where possible, informed consent was obtained from the patient and/or legal representative prior to randomization. The substitute decision maker was identified as the legal representative in Belgium. An information brochure was left in the family waiting room, along with an information poster. If the patient was unable to give consent themselves and no substitute decision maker was present at the time the antibiotics were prescribed, the patient was randomized and consent to continue in the study was obtained as soon as possible.

France

The ethics committee approved obtaining written informed consent and/or a declaration from a substitute decision maker in a hierarchical approach as outlined above and in section 10.3 of the study protocol (Supplement 1).

New Zealand

In New Zealand, only the patient could provide consent to participate in the clinical trial. When prior patient consent was not possible, steps were taken to ascertain the views of the patient from persons interested in their welfare as outlined in section 10.3.2 of the study protocol (Supplement 1). Consent to continue participation was obtained from the patient when their condition allowed. If written consent was not able to be obtained, verbal consent was allowed as per the ethics committee approval. If the patient died or didn't regain capacity, the ethics committee gave approval for use of data as per the views of the patient from persons interested in their welfare.

Malaysia

In Malaysia, written consent was required from the patient or substitute decision maker prior to randomization.

United Kingdom

The ethics committee for England, Scotland and Wales approved obtaining written informed consent and/or a declaration from a consultee in a hierarchical approach as outlined in section 10.3.3 of the study protocol (Supplement 1).

Sweden

In Sweden, written informed consent was sought from eligible patients. If the patient was deemed incapable of expressing consent due to their acute illness, the patient's next of kin was informed about the study and could decline participation. Written informed consent was sought as soon as possible in patients who regained mental capacity.

Changes to Informed Consent due to the COVID-19 Pandemic

From March 2020, regulations put in place to minimize the impact of the SARS-CoV-2 (COVID-19) pandemic placed significant limitations on processes allowed for obtaining written informed consent from patients or their substitute decision maker. These included the majority of Intensive Care Units (ICU) limiting or stopping visitor access due to social distancing laws, and limitations on the use of paper consent forms in clinical areas. Consequently, some participating sites suspended recruitment due to the difficulties in obtaining written consent.

Australia and France

A temporary change to the informed consent process was approved by the relevant ethics committees in Australia and France allowing sites to obtain verbal consent for the duration of the COVID-19 pandemic. This reduced risk to patients, substitute decision makers and staff, and allowed participating sites to continue to recruit patients.

As part of the verbal consent process, sites were required to do the following:

- Clearly document the verbal consent process in the patient record, including the date and time of the consent conversation, name of the clinician who obtained consent, name of the person who provided consent and any questions asked/answered.
- After verbal consent was obtained, provide the patient or substitute decision maker with the Patient Information Sheet/Consent Form by post or email, so that they had the option to withdraw from the study at any time. To minimize the infection risk to all concerned, the patient or substitute decision maker did not return the Patient Information Sheet/Consent Form if verbal consent had been obtained.

Documentation of all written and verbal consents was reviewed by study monitors at monitoring visits.

Belgium

During the COVID-19 pandemic, the ethics committee approved consent to be obtained verbally with the following process. There was no change to the Patient Information Sheet/Consent Form or the Legal Representative Consent Form. If the patient was not competent to provide consent and the legal representative was not able to attend the hospital, the legal representative was contacted by the site investigator or designee by telephone. Upon consent for participation, the site investigator or designee signed and dated the Legal Representative Consent Form and the form was given or sent via email to the legal representative. The following information was documented in the patient record: the consent form version number, the name of the site investigator or designee obtaining the consent, the name of the legal representative from whom consent was obtained, their relationship to the patient, the date and time consent was obtained, an indication that adequate time was provided to consider participation, whether a copy of the consent form had been sent to the legal representative and the name of the study staff to be contacted in case of questions.

New Zealand

Verbal consent was part of the original ethics committee approval; therefore, no further changes were required during the COVID-19 pandemic.

Malaysia

There was no change in the process of obtaining consent due to the COVID-19 pandemic.

Written consent was required from the patient or the substitute decision maker prior to enrolment.

United Kingdom

The Institutional Review Board approved verbal consent during the COVID-19 pandemic with the following process. In instances where the patient was not competent to provide consent the personal or nominated consultee would be contacted by telephone to seek assent to commence or continue the study. The site investigator or designee would complete the verbal assent via telephone, which was witnessed by an independent member of staff. A Telephone Agreement Form was then signed by both the site investigator or designee and the witness. The form included date and time, who provided assent, their relationship to the patient, the site investigator or designee, the staff witness, the discussion and any questions discussed. The verbal consent process was documented in the patient record.

Sweden

There were no changes to the consent process due to the COVID-19 pandemic.

Sites of Infection

The primary site of infection was determined by the attending clinician based on a documented site of infection or strong suspicion of infection. Second and third sites of infection were recorded where there were further documented sites of infection or a strong suspicion of infection in additional sites as identified by the attending clinician. A documented site of infection was indicated by either: (1) an organism grown in blood or a sterile site, or (2) an abscess or volume of infected tissue (e.g. pneumonia, peritonitis, soft tissue etc.). A strong suspicion of infection was based on clinical signs of infection, e.g. white

blood cells in a normally sterile fluid (e.g. urine or cerebrospinal fluid), evidence of a perforated viscus (e.g. free air on abdominal X-ray or computed tomography scan or acute peritonitis) or an abnormal chest X-ray consistent with pneumonia.

Infective Organisms

Infective organisms were bacteria, identified from microbiological culture of samples taken up to 72 hours prior to randomization. If multiple organisms were identified from the same site of infection, all clinically significant organisms, as determined by the attending clinician, were recorded. Viruses, fungi and protozoa were not reported as infective organisms.

Length of Stay

ICU and hospital length of stay variables were calculated from the date of randomization and censored at Day 90. In the case of multiple ICU and hospital admissions, the period that participants were out of the ICU and hospital were excluded from the ICU and hospital length of stay calculations, respectively.

Time to discharge from the index ICU admission refers to the duration in days from randomization to the index ICU discharge. Index ICU discharge was defined as the date of first discharge from the ICU. For participants who died in the ICU, the discharge date was the date of death. If a participant was transferred directly to another ICU, date of discharge was the date of discharge from the subsequent ICU (not the date of transfer).

Time to discharge from the index hospital admission refers to the duration in days from randomization to the index hospital discharge. Index hospital discharge was the date of first discharge from the hospital. For participants who died in hospital, the discharge date was the

date of death. If a participant was transferred to another acute hospital, date of discharge was the date of discharge from the subsequent hospital (not the date of transfer). If a participant was transferred from an acute hospital to a non-acute hospital, nursing home or rehabilitation unit, date of transfer from the acute hospital was the date of discharge.

Study Days

Day 1 was from the time of randomization until the end of the calendar day. Subsequent study days were a full calendar day from 00:00 hours until 23:59 hours.

Study Drug Administration

The choice of β-lactam antibiotic, either piperacillin-tazobactam or meropenem, and the dose and dosing interval (i.e. the amount of study drug the participant received in 24 hours) was determined by the attending clinician prior to randomization. The amount of β-lactam antibiotic prescribed reflected the patient body size and estimated drug clearance as per standard prescribing practices. Therapeutic drug monitoring of the study drug (piperacillin-tazobactam or meropenem) was not permitted while the participant was receiving randomized treatment due to a potential differential impact on dosing practices between treatment groups. During the study period, the attending clinician could modify the β-lactam antibiotic dose in response to clinical changes of the patient.

If following randomization, the attending clinician decided to change from piperacillin-tazobactam to meropenem or vice versa, the new prescription continued to be administered in the allocated method (continuous or intermittent infusion over 30 minutes). Participants in the continuous infusion group received a loading dose prior to commencement of the new

prescription by continuous infusion. If the participant was still prescribed the β-lactam antibiotic following Intensive Care Unit (ICU) discharge or after Day 14, the standard administration method at the site was used. If the participant was readmitted to the ICU prior to the end of Day 14, the study assigned administration method was followed. If the β-lactam antibiotic prescription was stopped and the participant recommenced on a β-lactam antibiotic (piperacillin-tazobactam or meropenem) prior to Day 14, the study assigned administration method was followed whilst in the ICU.

Study Drug Supply and Handling

The β-lactam antibiotics were supplied by the hospital/institution. Handling and storage of the β-lactam antibiotic followed local site policy and regulatory requirements. The manufacturer's instructions regarding storage were followed. The β-lactam antibiotic was reconstituted with a compatible diluent as per the manufacturer's instructions and according to local policy. The stability of the reconstituted β-lactam antibiotic was considered in preparing the continuous infusion.

Study Drug Stability

The two β-lactam antibiotics have different stability durations when reconstituted, which was taken into consideration when preparing a continuous infusion.[1] Piperacillin-tazobactam has sufficient stability at room temperature to allow for preparation of one infusion bag to be administered over 24 hours.[2-4] Therefore, the maximum piperacillin-tazobactam dose prepared in an infusion bag/syringe was a 24-hour dose given over 24 hours. Meropenem, when diluted with 0.9% sodium chloride, has sufficient stability at room temperature for 8 hours.[5-7] Therefore, the maximum meropenem dose prepared in an infusion bag/syringe was an 8-hour dose given over 8 hours (i.e., three infusion bags/syringes over 24 hours). In the

United Kingdom, further analyses for drug stability were conducted and meropenem was deemed to have sufficient stability at room temperature for administration over 12 hours (Greg Barton, personal communication). Therefore, the maximum dose prepared in an infusion bag/syringe in the United Kingdom was a 12-hour dose given over 12 hours (i.e., two infusion bags/syringes over 24 hours).

Regardless of the β-lactam antibiotic prescribed, each infusion bag or syringe was prepared just prior to commencement of the infusion. Infusion bags or syringes for continuous infusion were prepared according to local policy with consideration of stability and product information. For example, if normal practice at the site was to prepare syringes with 6-hour doses, then these were infused over 6 hours with a new bag/syringe every 6 hours.

Intermittent Infusions and Loading Doses

Intermittent infusions were given over 30 minutes at the scheduled dosing intervals evenly spaced over a 24-hour period. The intermittent infusion dose of the β-lactam antibiotic was reconstituted in a compatible fluid of at least 20 mL volume as per standard site policy and prepared just prior to administration.

A loading dose, comprising a single dose of the β-lactam antibiotic, was given prior to commencement of the continuous infusion. An intermittent or extended infusion dose given prior to randomization could qualify as the loading dose.

Timing of Study Drug Administration

Instructions for commencement of the study assigned administration method are described in Table 2. Commencement of a continuous infusion following standard administration by intermittent infusion or extended infusion was made with reference to half the standard dosing interval (Figure 1).

Instructions following a pause or delay in the study assigned administration method are described in Table 3. A pause or delay of greater than 1 hour was recorded as a Protocol Deviation. Figure 2 summarizes recommencement of a continuous infusion following a pause.

Instructions for continuation of the study assigned administration method after a change of the β-lactam antibiotic are summarized in Table 4. Instructions for reverting back to the standard administration method are summarized in Table 5.

Table 2. Commencement of the Study Assigned Administration Method

Randomization allocation	Administration method prior to randomization	Instructions
Intermittent infusion	Intermittent infusion	• Continue with intermittent infusion at prescribed dosing interval. • Give intermittent infusion doses over 30 minutes.
	Extended infusion	• **IF** extended infusion is running at time of randomization, ensure all dose of extended infusion is given. • Start intermittent infusion at the next dosing interval. • Give intermittent infusion doses over 30 minutes.
	Continuous infusion	• **STOP** continuous infusion and start first dose of intermittent infusion immediately. • **IF** bolus dose was given prior to commencing continuous infusion **AND** randomization is within the first intermittent dosing interval, **THEN** wait a full dosing interval from the time of the bolus dose before commencing the intermittent infusion. • Give intermittent infusion doses over 30 minutes.
Continuous infusion	Continuous infusion	• Continue with continuous infusion.
	Intermittent infusion	**Randomization prior to half the dosing interval (& up to 1 hour after half the dosing interval)** • Start continuous infusion at a time that is equivalent to half the intermittent dosing interval. **Randomization after half the dosing interval** • **WAIT** until next intermittent dose due and give intermittent infusion dose, **THEN** start the continuous

Randomization allocation	Administration method prior to randomization	Instructions
		infusion at a time that is equivalent to half the intermittent dosing interval.
	Extended infusion	**Randomization prior to half the dosing interval (& up to 1 hour after half the dosing interval)** • Start continuous infusion at a time that is equivalent to half the intermittent dosing interval. **Randomization after half the dosing interval** • **WAIT** until the next extended infusion dose is due and give bolus dose, **THEN** start continuous infusion at a time that is equivalent to half the intermittent dosing interval.

Table 3. Instructions Following a Pause in Study Drug Administration

Randomization allocation	Pause duration	Instructions
Intermittent infusion	Delay up to half the dosing interval past the scheduled dosing time	• Give intermittent infusion dose as soon as possible over 30 minutes. • Continue at the prescribed dosing intervals for further doses. • This is a Protocol Deviation if the delay is > 1hr.
	Delay greater than half the dosing interval past the scheduled dosing time	• Give intermittent infusion dose as soon as possible over 30 minutes. • Reset the prescribed dosing intervals for further doses to align with time delayed intermittent dose given. • This is a Protocol Deviation.
Continuous infusion	Pause < 1hr	• Restart the continuous infusion at the usual rate. • This is not a Protocol Deviation.
	Pause > 1hr, but less than half the dosing interval	• **GIVE** the remaining part of bag/syringe at a faster rate to complete the continuous infusion at the usual time. • Start the next continuous infusion bag/syringe at the prescribed time. • This is a Protocol Deviation.
	Pause > 1hr and greater than half the dosing interval	• **GIVE** a bolus dose that is equivalent to half the standard intermittent dose, **THEN** restart the continuous infusion immediately. • This is a Protocol Deviation.
	Planned pause > 1hr	• **GIVE** a bolus dose that is equivalent to half the standard intermittent dose at the time of stopping the continuous infusion • For each time that is equivalent to half the intermittent dosing interval that the continuous infusion is stopped,

Randomization allocation	Pause duration	Instructions
		GIVE a bolus dose that is equivalent to half the standard intermittent dose • Restart the continuous infusion as soon as possible. • This is a Protocol Deviation.

Table 4. Instructions for Changing the β-Lactam Antibiotic

Randomization allocation	Instructions
Intermittent infusion	• Continue with intermittent infusion at prescribed dosing interval. Only give the new β-lactam antibiotic earlier than the prescribed dosing interval if there is a clinical reason to start the new β-lactam antibiotic sooner. • Give intermittent infusion doses over 30 minutes.
Continuous infusion	• **STOP** continuous infusion of the old β-lactam antibiotic prescription and give a bolus dose of the new prescription β-lactam antibiotic immediately. • Start continuous infusion of the new prescription β-lactam antibiotic at half the intermittent dosing interval.

Table 5. Instructions for Reverting Back to the Standard Administration Method

Randomization allocation	Standard administration method at site	Instructions
Intermittent infusion	Intermittent	• **Continue** with intermittent doses at prescribed dosing interval.
	Extended infusion	• **Start** extended infusion at the next scheduled dosing interval.
	Continuous infusion	• **Start** continuous infusion at a time equivalent to half the dosing interval after the last intermittent infusion dose.
Continuous infusion	Continuous infusion	• **Continue** with continuous infusion.
	Intermittent infusion	• **Start** intermittent dose at half the intermittent dosing interval from the time the continuous infusion is stopped.
	Extended infusion	• **Start** extended infusion at half the intermittent dosing interval from the time the continuous infusion is stopped.

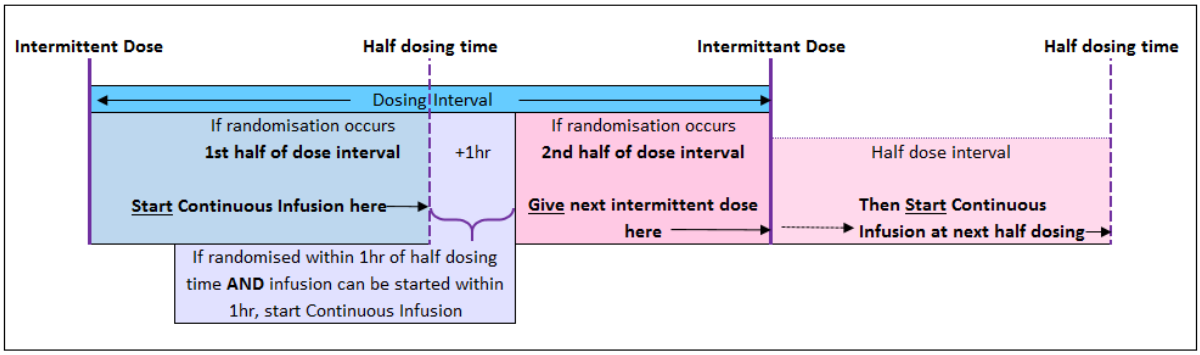


Figure 1. Commencement of a Continuous Infusion from Intermittent Infusion

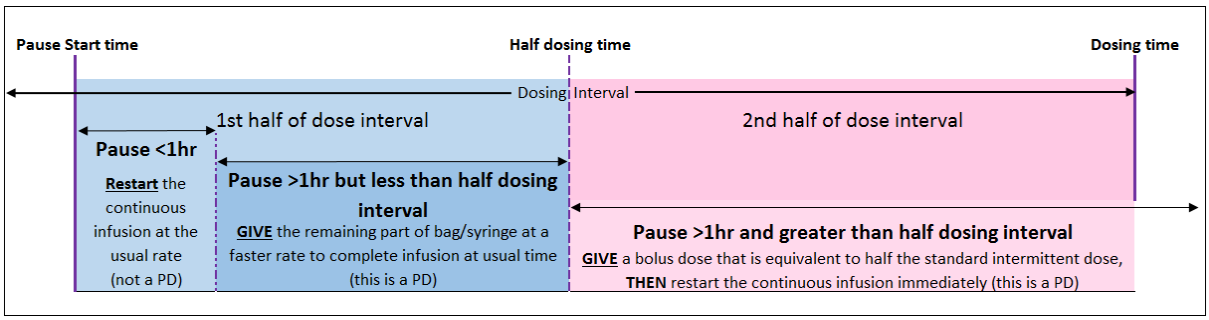


Figure 2. Recommencement of the Continuous Infusion Following a Pause

Source Data Verification and Monitoring

Source data verification (SDV) and monitoring activities were performed at each site by a Study Monitor or Project Manager. Complete (100%) SDV was performed on all participants for the following:

- Written informed consent obtained in accordance with the Human Research Ethics Committee or Institutional Review Board approved documents and verbal consent documentation when approved during the COVID-19 pandemic.
- Primary outcome measure, i.e., Day 90 vital status and date of death (if applicable).
- Length of stay in the Intensive Care Unit and hospital.

Complete (100%) SDV was performed for the first 2 participants enrolled at each site. Complete (100%) SDV was also performed for at least one participant if a new study staff began collecting study data at a site. Additional SDV was performed if error rates were of concern or more than 10%.

After this, if the Study Monitor and Project Manager were confident of site staff competence, a reduced partial SDV plan was used for the 10% of randomly selected remaining participants at each site. This was then reduced to 5% of randomly selected remaining participants if the Project Manager considered error rates acceptable. Partial SDV included:

- Eligibility criteria
- β-lactam antibiotic prescription and dosing administration
- Secondary outcome measures
- Study treatment compliance
- Protocol deviations
- Adverse drug reactions

In collaboration with data management, pre-defined sets of edit checks were run to ensure consistency and valid range checks in an attempt to validate data.

Changes to Source Data Verification and Monitoring due to the COVID-19 Pandemic

From March 2020 until July 2022, monitoring activities were significantly affected by the COVID-19 pandemic. This was due to pandemic planning in participating Intensive Care Units, including redeployment of research staff to clinical roles, travel restrictions, infection control measures, and visitor restrictions. By this time, complete (100%) SDV had been performed for the first 2 participants at all participating sites, therefore the following adjustments were made to the SDV:

- Prioritized review of written informed consent or verbal consent documentation and primary outcome measures for all participants.
- Sites with acceptable error rates (<5%) had significantly reduced or no further SDV (decision made by the Senior Project Manager on a site-by-site basis).
- Remote monitoring was increased to include a review of all data entry forms for obvious errors.
- If on-site visits could not be conducted before the study was completed, data were reviewed by other methods, for example via video call and review of scanned/de-identified medical records.

Protocol Deviations

Protocol deviations were captured in the case report form as follows:

- Randomization of an ineligible patient
- Failure to comply with the study assigned administration method

    - Administration method for a β-lactam antibiotic dose did not occur as per the study assigned method of administration
    - All non-administered doses, e.g. failure to give an intermittent or continuous dose
    - A delay in a dose via intermittent infusion of greater than 1 hour
    - A pause in the continuous infusion of greater than 1 hour
    - Failure to give a bolus (loading) dose prior to starting continuous infusion, or after a delay of greater than half the dosing interval, or on restarting a continuous infusion or changing the type of β-lactam antibiotic
- Follow-up assessment not completed correctly
    - For an alive participant, Day 90 follow-up occurred on or before the Day 90 date
    - Quality of life assessment (in Australia) for all alive participants not conducted within 14 days of Day 90
- Other reason for a protocol deviation.

Protocol deviations were reviewed and classified into four categories for reporting purposes: (1) randomization of an eligible patient, (2) administration or dosing related, (3) follow-up assessment not done correctly, and (4) other (i.e. not fitting into one of the previous categories).

SUPPLEMENTARY RESULTS

Tables

eTable 1. Enrolment by Country and Site

Country / Site[a]	Continuous Infusion (n = 3498)	Intermittent Infusion (n = 3533)
Australia (no. of sites = 25)	n = 1087	n = 1086
Austin Hospital	21	19
Bankstown Hospital	12	13
Bendigo Hospital	50	49
Blacktown Hospital	34	38
Box Hill Hospital	12	12
Caboolture Hospital	20	21
Gold Coast University Hospital	66	68
Gosford Hospital	33	31
John Hunter Hospital	24	20
Logan Hospital	30	31
Lyell McEwin Hospital	11	11
Princess Alexandra Hospital	131	130
The Queen Elizabeth Hospital	25	25
Redcliffe Hospital	30	28
Royal Brisbane and Women's Hospital	121	118
Royal Darwin Hospital	26	23
Royal Hobart Hospital	32	33
Royal Melbourne Hospital	56	59
Royal North Shore Hospital	94	97
Royal Prince Alfred Hospital	40	39
St George Hospital	29	28
St Vincent's Hospital	47	46

Country / Site[a]	Continuous Infusion (n = 3498)	Intermittent Infusion (n = 3533)
University Hospital Geelong	17	17
The Wesley Hospital	28	32
Westmead Hospital	98	98
Belgium (no. of sites = 8)	n = 228	n = 231
Antwerp University Hospital	6	6
Brussels University Hospital	33	35
Civil Hospital Marie Curie	7	9
Erasmus Hospital	15	14
Ghent University Hospital	102	101
Maria Middelares Hospital	7	7
Saint-Pierre Ottignies Clinic	30	32
Stuivenberg Hospital	28	27
France (no. of sites = 5)	n = 218	n = 215
Brabois Hospital Nancy	19	20
Henri Duffaut Hospital Centre	54	54
Poitiers University Hospital	26	27
Salon de Provence Hospital	10	10
University Hospital of Nîmes	109	104
Malaysia (no. of sites = 2)	n = 174	n = 179
Hospital University Sains Malaysia	94	95
University Malaya Medical Centre	80	84
New Zealand (no. of sites = 6)	n = 291	n = 286
Auckland City Hospital (Cardiothoracic and Vascular Intensive Care Unit)	54	54
Auckland City Hospital (Department of Critical Care Medicine)	27	25
Christchurch Hospital	79	77

Country / Site[a]	Continuous Infusion (n = 3498)	Intermittent Infusion (n = 3533)
Middlemore Hospital	13	14
Waikato Hospital	38	38
Wellington Hospital	80	78
Sweden (no. of sites = 3)	n = 64	n = 72
Helsingborg Hospital	13	15
Skåne University Hospital, Lund	5	5
Skåne University Hospital, Malmö	46	52
United Kingdom (no. of sites = 54)	n = 1436	n = 1464
Basingstoke & North Hampshire Hospital	24	23
Blackpool Victoria Hospital	21	20
Bristol Royal Infirmary	31	32
Broomfield Hospital	8	7
Charing Cross Hospital	72	73
Countess of Chester Hospital	10	12
Darent Valley Hospital	15	18
Derriford Hospital	53	55
Dorset County Hospital	19	21
Freeman Hospital	6	5
Frimley Park Hospital	13	13
Glasgow Royal Infirmary	15	14
Golden Jubilee National Hospital	9	9
Hammersmith Hospital	42	44
Hereford County Hospital	7	8
Hull Royal Infirmary	33	35
Ipswich Hospital	21	22
James Cook Hospital	124	124
King’s College Hospital	117	116

Country / Site[a]	Continuous Infusion (n = 3498)	Intermittent Infusion (n = 3533)
King’s Mill Hospital	3	5
Kingston Hospital	5	5
Maidstone Hospital	5	6
Medway Maritime Hospital	27	29
Milton Keynes University Hospital	17	18
Ninewells Hospital	10	11
Northumbria Specialist Emergency Care Hospital	6	8
Pinderfields Hospital	13	14
Poole Hospital	27	32
Princess Royal Hospital	1	0
Queen Alexandra Hospital	28	30
Queen Elizabeth Hospital Birmingham	26	25
Queen's Hospital	12	12
Queen’s Medical Centre, Nottingham	41	38
Royal Berkshire Hospital	22	22
Royal Bolton Hospital	5	4
Royal Hampshire County Hospital	11	14
Royal London Hospital	9	9
Royal Marsden Hospital	22	23
Royal Surrey County Hospital	28	29
Royal Victoria Infirmary	14	13
Salford Royal Hospital	29	29
Southampton General Hospital	25	25
St George's Hospital	51	52
St Mary's Hospital	74	74
St Thomas’ Hospital	33	33
Stoke Mandeville Hospital	8	9

Country / Site[a]	Continuous Infusion (n = 3498)	Intermittent Infusion (n = 3533)
Sunderland Royal Hospital	8	10
Tunbridge Wells Hospital	48	46
University Hospital Coventry	65	64
University Hospital of North Tees	23	24
University Hospital of Wales	23	24
Watford General Hospital	21	22
Whittington Hospital	1	2
Whiston Hospital	55	52

[a]Countries and sites are listed alphabetically.

eTable 2. APACHE III Diagnoses

Diagnoses	Continuous infusion (n = 3498)[a]	Intermittent infusion (n = 3533)[a]
Non-operative diagnoses	2509 (71.8)	2547 (72.1)
Respiratory	814 (23.3)	878 (24.9)
Sepsis	599 (17.1)	594 (16.8)
Trauma	269 (7.7)	251 (7.1)
Neurological	251 (7.2)	239 (6.8)
Cardiovascular	252 (7.2)	231 (6.5)
Gastrointestinal	183 (5.2)	180 (5.1)
Metabolic	66 (1.9)	69 (2.0)
Musculoskeletal/skin	28 (0.8)	36 (1.0)
Hematological	13 (0.4)	15 (0.4)
Renal/genitourinary	11 (0.3)	13 (0.4)
Other	23 (0.7)	41 (1.2)
Operative diagnoses	985 (28.2)	985 (27.9)
Gastrointestinal	418 (12.0)	407 (11.5)
Cardiovascular	163 (4.7)	164 (4.6)
Neurological	123 (3.5)	122 (3.5)
Trauma	97 (2.8)	113 (3.2)
Musculoskeletal/skin	88 (2.5)	82 (2.3)
Respiratory	54 (1.5)	54 (1.5)
Renal/genitourinary	32 (0.9)	34 (1.0)
Gynecological	7 (0.2)	5 (0.1)
Hematological	2 (0.1)	2 (0.1)
Metabolic	1 (0.0)	2 (0.1)

Abbreviation: APACHE, Acute Physiology and Chronic Health Evaluation.

[a]The denominator are those with any baseline APACHE III diagnosis data available; there are 4 participants and 1 participant with missing data in the continuous and intermittent infusion groups, respectively.

eTable 3. Infective Organisms Identified from the Primary Site of Infection

Organism	Continuous infusion (n = 3498)[a]	Intermittent infusion (n = 3533)[a]
Organism/s identified in primary site of infection	1432 (40.9)[b]	1435 (40.6)[b]
Gram positive bacteria	435 (30.4)	441 (30.7)
Methicillin-sensitive *Staphylococcus aureus*	149 (10.4)	182 (12.7)
Streptococcus pneumoniae (or Pneumococcus)	56 (3.9)	61 (4.3)
Enterococcus	43 (3.0)	44 (3.1)
β-hemolytic streptococci (group A, B, C or G)	50 (3.5)	31 (2.2)
Coagulase negative staphylococci	39 (2.7)	34 (2.4)
Methicillin-resistant *Staphylococcus aureus*	31 (2.2)	27 (1.9)
Viridans group streptococci	17 (1.2)	7 (0.5)
Gram positive cocci (not otherwise specified)	6 (0.4)	14 (1.0)
Corynebacterium species	3 (0.2)	5 (0.3)
Clostridioides difficile	1 (0.1)	5 (0.3)
Clostridium species	2 (0.1)	4 (0.3)
Bacillus species	3 (0.2)	2 (0.1)
Cutibacterium species	3 (0.2)	2 (0.1)
Other Gram positive organisms	8 (0.6)	8 (0.6)
Gram negative bacteria	991 (69.2)	982 (68.4)
Escherichia species	252 (17.6)	259 (18.0)
Klebsiella species	171 (11.9)	182 (12.7)
Pseudomonas species	161 (11.2)	151 (10.5)
Enterobacter species	96 (6.7)	104 (7.2)
Haemophilus species	85 (5.9)	80 (5.6)
Serratia species	49 (3.4)	54 (3.8)
Citrobacter species	41 (2.9)	27 (1.9)
Proteus species	28 (2.0)	25 (1.7)

Organism	Continuous infusion (n = 3498)[a]	Intermittent infusion (n = 3533)[a]
Acinetobacter species	23 (1.6)	22 (1.5)
Stenotrophamonas species	15 (1.0)	8 (0.6)
Gram negative rods (not otherwise specified)	10 (0.7)	11 (0.8)
Coliform bacteria (genus not specified)	11 (0.8)	7 (0.5)
Morganella species	9 (0.6)	9 (0.6)
Bacteroides species	5 (0.3)	8 (0.6)
Moraxella catarrhalis	6 (0.4)	5 (0.3)
Burkholderia species	3 (0.2)	7 (0.5)
Raoultella species	4 (0.3)	6 (0.4)
Legionella species	6 (0.4)	2 (0.1)
Hafnia alvei	3 (0.2)	4 (0.3)
Pantoea species	2 (0.1)	3 (0.2)
Other Gram negative organisms	19 (1.3)	19 (1.3)
Other	18 (1.3)	22 (1.5)
Mixed anaerobes	16 (1.1)	21 (1.5)
Mycobacterium tuberculosis	2 (0.1)	0
Unknown	0	2 (0.1)

[a]As there may be more than 1 infective organism per participant, organism totals and percentages do not add up to 100%.

[b]Column percentages in the first row refer to the number of participants with an identified organism in the primary site of infection by treatment group. Column percentages in subsequent rows refer to organism percentages in participants with an identified organism in the primary site of infection by treatment group.

eTable 4. Secondary and Tertiary Sites of Infection

Site of infection	Continuous Infusion	Intermittent Infusion
Second site	(n = 929)[a]	(n = 946)[a]
Pulmonary	327 (35.2)	333 (35.2)
Blood	244 (26.3)	227 (24.0)
Urinary	97 (10.4)	113 (11.9)
Intra-abdominal	95 (10.2)	91 (9.6)
Skin	72 (7.8)	75 (7.9)
Intravenous catheter	18 (1.9)	27 (2.9)
Gut	17 (1.8)	21 (2.2)
Central nervous system	19 (2.0)	16 (1.7)
Endocarditis	7 (0.8)	5 (0.5)
Other[b]	33 (3.6)	38 (4.0)
Third site	(n = 263)[a]	(n = 273)[a]
Pulmonary	75 (28.5)	79 (28.9)
Blood	64 (24.3)	57 (20.9)
Urinary	32 (12.2)	46 (16.8)
Intra-abdominal	35 (13.3)	38 (13.9)
Skin	37 (14.1)	31 (11.4)
Gut	5 (1.9)	5 (2.2)
Intravenous catheter	2 (0.8)	6 (2.2)
Central nervous system	6 (2.3)	0
Other[c]	7 (2.7)	11 (4.0)

[a]Column percentages refer to the site of infection percentage in participants with a secondary or tertiary site of infection by treatment group.

[b]Other includes oro-nasopharyngeal, 10 (1.1%) vs 11 (1.2%); intrathoracic, 7 (0.8%) vs 3 (0.3%); soft tissue, 2 (0.2%) vs 7 (0.7%); musculoskeletal, 2 (0.2%) vs 6 (0.6%); gynecological, 2 (0.2%) vs 3 (0.3%); infected graft/hardware, 3 (0.3%) vs 2 (0.2%); ear/eye infection, 2 (0.2) vs 0; unknown, 5 (0.5%) vs 6 (0.6%); for continuous and intermittent infusion, respectively.

[c]Other includes oro-nasopharyngeal, 1 (0.4%) vs 5 (1.8%); intrathoracic, 2 (0.8%) vs 1 (0.4%); musculoskeletal, 0 vs 3 (1.1%); soft tissue, 1 (0.4%) vs 1 (0.4%); gynecological, 0 vs 1 (0.4%); unknown, 3 (1.1%) vs 0; for continuous and intermittent infusion, respectively.

eTable 5. Infective Organisms Identified from Second Site of Infection

Organism	Continuous infusion (n = 929)[a]	Intermittent infusion (n = 946)[a]
Organism/s identified in secondary site of infection	n = 659 (70.9)[b]	n = 674 (71.2)[b]
Gram positive bacteria	234 (35.5)	238 (35.3)
Methicillin-sensitive *Staphylococcus aureus*	57 (8.6)	50 (7.4)
Enterococcus	41 (6.2)	54 (8.0)
Coagulase negative staphylococci	39 (5.9)	31 (4.6)
Methicillin-resistant *Staphylococcus aureus*	19 (2.9)	25 (3.7)
Streptococcus pneumoniae (or Pneumococcus)	21 (3.2)	19 (2.8)
Viridans group streptococci	14 (2.1)	25 (3.7)
β-hemolytic streptococci (group A, B, C or G)	17 (2.6)	14 (2.1)
Gram positive cocci (not otherwise specified)	7 (1.1)	6 (0.9)
Corynebacterium species	3 (0.5)	4 (0.6)
Cutibacterium species	2 (0.3)	3 (0.4)
Other Gram positive organisms	14 (2.1)	8 (1.2)
Gram negative bacteria	419 (63.6)	432 (64.1)
Escherichia species	116 (17.6)	121 (18.0)
Klebsiella species	88 (13.4)	87 (12.9)
Pseudomonas species	55 (8.3)	53 (7.9)
Enterobacter species	38 (5.8)	51 (7.6)
Haemophilus species	19 (2.9)	20 (3.0)
Acinetobacter species	15 (2.3)	13 (1.9)
Citrobacter species	19 (2.9)	9 (1.3)
Proteus species	15 (2.3)	13 (1.9)
Serratia species	12 (1.8)	15 (2.2)
Bacteroides species	7 (1.1)	8 (1.2)
Morganella species	6 (0.9)	4 (0.6)

Organism	Continuous infusion (n = 929)[a]	Intermittent infusion (n = 946)[a]
Gram negative rods (not otherwise specified)	2 (0.3)	6 (0.9)
Coliform bacteria (genus not specified)	4 (0.6)	3 (0.4)
Moraxella catarrhalis	5 (0.8)	2 (0.3)
Stenotrophamonas species	2 (0.3)	4 (0.6)
Burkholderia species	2 (0.3)	3 (0.4)
Fusobacterium species	1 (0.2)	4 (0.6)
Other Gram negative organisms	15 (2.3)	16 (2.4)
Other	6 (0.9)	5 (0.7)
Mixed anaerobes	5 (0.8)	4 (0.6)
Bacterial vaginosis	0	1 (0.1)
Mycobacterium tuberculosis	1 (0.2)	0

[a]As there may be more than 1 infective organism per participant, organism totals and percentages do not add up to 100%.

[b]Column percentages in the first row refer to the number of participants with an identified organism in the secondary site of infection by treatment group. Column percentages in subsequent rows refer to organism percentages in participants with an identified organism in the secondary site of infection by treatment group.

eTable 6. Infective Organisms Identified from Third Site of Infection

Organism	Continuous infusion (n = 263)[a]	Intermittent infusion (n = 273)[a]
Organism/s identified in secondary site of infection	n = 219 (83.3)[b]	n = 218 (79.9)[b]
Gram positive bacteria	96 (43.8)	81 (37.2)
Methicillin-sensitive *Staphylococcus aureus*	28 (12.8)	18 (8.3)
Enterococcus	21 (9.6)	24 (11.0)
Viridans group streptococci	10 (4.6)	7 (3.2)
Coagulase negative staphylococci	9 (4.1)	7 (3.2)
Methicillin-resistant *Staphylococcus aureus*	9 (4.1)	6 (2.8)
Streptococcus pneumoniae (or Pneumococcus)	4 (1.8)	4 (1.8)
β-hemolytic streptococci (group A, B, C or G)	5 (2.3)	2 (0.9)
Clostridium species	2 (0.9)	3 (1.4)
Other Gram positive organisms	8 (3.7)	10 (4.6)
Gram negative bacteria	120 (54.8)	136 (62.4)
Escherichia species	19 (8.7)	37 (17.0)
Klebsiella species	20 (9.1)	24 (11.0)
Pseudomonas species	23 (10.5)	15 (6.9)
Enterobacter species	12 (5.5)	13 (6.0)
Proteus species	10 (4.6)	8 (3.7)
Haemophilus species	8 (3.7)	7 (3.2)
Bacteroides species	5 (2.3)	4 (1.8)
Citrobacter species	4 (1.8)	5 (2.3)
Morganella species	2 (0.9)	7 (3.2)
Serratia species	6 (2.7)	3 (1.4)
Acinetobacter species	4 (1.8)	2 (0.9)
Other Gram negative organisms	7 (3.2)	11 (5.0)

Organism	Continuous infusion (n = 263)[a]	Intermittent infusion (n = 273)[a]
Other	4 (1.8)	1 (0.5)
Mixed anaerobes	3 (1.4)	1 (0.5)
Mycobacterium tuberculosis	1 (0.5)	0

[a]As there may be more than 1 infective organism per participant, organism totals and percentages do not add up to 100%.

[b]Column percentages in the first row refer to the number of participants with an identified organism in the third site of infection by treatment group. Column percentages in subsequent rows refer to organism percentages in participants with an identified organism in the third site of infection by treatment group.

eTable 7. β-Lactam Antibiotic Administration Details

Administration details	Continuous infusion	Intermittent infusion
Antibiotic	(n = 3498)	(n = 3533)
	Antibiotic administered, n (%), or dose prepared (g)[a]	Antibiotic administered, n (%) or dose prepared (g)[a]
Prior to randomization		
Piperacillin-tazobactam	2804/3498 (80.2)	2815/3533 (79.7)
Mean (SD)	10.8 (6.3)	10.5 (6.0)
Median (IQR)	9.0 (4.5, 13.5)	9.0 (4.5, 13.5)
min max	2.3 117.0	2.3 108.0
Meropenem	656/3498 (18.8)	655/3533 (18.5)
Mean (SD)	2.7 (1.7)	2.6 (1.7)
Median (IQR)	2.0 (1.0, 3.0)	2.0 (1.0, 3.0)
min max	0.5 8.0	0.5 13.0
Prescribed for eligibility		
Piperacillin-tazobactam	2739/3498 (78.3)	2766/3533 (78.3)
Mean (SD)	15.0 (2.8)	14.9 (2.5)
Median (IQR)	13.5 (13.5, 18.0)	13.5 (13.5, 18.0)
min max	4.5 66.0	4.5 22.5
Meropenem	637/3498 (18.2)	639/3533 (18.1)
Mean (SD)	3.5 (1.4)	3.6 (1.6)
Median (IQR)	3.0 (3.0, 3.0)	3.0 (3.0, 3.0)
min max	0.5 9.0	1.0 18.0
Method of administration	n = 3415	n = 3445
Intermittent infusion	2658 (77.8)	2809 (81.5)
Extended infusion	307 (9.0)	287 (8.3)
Continuous infusion	450 (13.2)	349 (10.1)
Cumulative dose of antibiotics		
received, g[b]		
Piperacillin-tazobactam		

Administration details	Continuous infusion	Intermittent infusion
Antibiotic	(n = 3498)	(n = 3533)
	Antibiotic administered, n (%), or dose prepared (g)[a]	Antibiotic administered, n (%) or dose prepared (g)[a]
n	2866	2869
Mean (SD)	79.3 (53.1)	78.0 (52.0)
Median (IQR)	72.0 (40.5, 108.0)	70.8 (40.5, 103.5)
min max	2.0 346.0	5.0 351.0
Meropenem		
n	1285	1311
Mean (SD)	20.9 (16.7)	20.1 (16.7)
Median (IQR)	17.0 (9.0, 29.0)	16.0 (8.0, 28.0)
min max	0.0 103.0	0.0 108.0
Time from randomization to first study drug infusion (hours)		
n	3468	3485
Mean (SD)	2.9 (9.8)	4.2 (10.0)
Median (IQR)	2.0 (0.8, 3.3)	3.4 (1.3, 5.6)
min max	-9.3[c] 357.8	-5.2[c] 264.3
Time on study treatment (days)[d]		
Overall		
n	3468	3485
Mean (SD)	6.9 (4.6)	6.8 (4.7)
Median (IQR)	5.8 (3.1, 10.2)	5.7 (3.1, 10.3)
min max	0.0 16.4	0.0 15.9
Piperacillin-tazobactam		
n	2866	2869
Mean (SD)	5.5 (4.0)	5.5 (4.0)
Median (IQR)	4.8 (2.5, 7.1)	4.7 (2.5, 7.2)
min max	0.0 16.4	0.0 15.8

Administration details	Continuous infusion	Intermittent infusion
Antibiotic	(n = 3498)	(n = 3533)
	Antibiotic administered, n (%), or dose prepared (g)[a]	Antibiotic administered, n (%) or dose prepared (g)[a]
Meropenem		
n	1285	1311
Mean (SD)	6.0 (4.2)	5.8 (4.2)
Median (IQR)	5.3 (2.6, 8.7)	5.0 (2.1, 8.4)
min max	0.0 16.0	0.0 15.6
Day 1[e]		
Piperacillin-tazobactam	2689/3498 (76.9)	2613/3533 (74.0)
Mean (SD)	6.8 (3.5)	7.3 (2.8)
Median (IQR)	6.6 (4.5, 8.4)	9.0 (4.5, 9.0)
min max	0.1 30.3	0.2 22.5
Meropenem	711 (20.3)	660 (18.7)
Mean (SD)	1.6 (0.9)	1.8 (1.0)
Median (IQR)	1.5 (1.0, 2.0)	2.0 (1.0, 2.0)
min max	0.0 7.5	0.1 6.0
Day 2		
Piperacillin-tazobactam	2698/3483 (77.5)	2690/3515 (76.5)
Mean (SD)	14.8 (4.1)	14.1 (3.5)
Median (IQR)	14.0 (13.3, 18.0)	13.5 (13.5, 18.0)
min max	0.6 38.1	4.5 24.3
Meropenem	803/3483 (23.1)	801/3515 (22.8)
Mean (SD)	3.2 (1.5)	3.2 (1.5)
Median (IQR)	3.0 (2.3, 3.5)	3.0 (2.0, 3.0)
min max	0.0 8.3	0.0 8.0
Day 3		
Piperacillin-tazobactam	2393/3434 (69.7)	2379/3472 (68.5)
Mean (SD)	14.4 (4.2)	13.9 (3.7)

Administration details	Continuous infusion	Intermittent infusion
Antibiotic	(n = 3498)	(n = 3533)
	Antibiotic administered, n (%), or dose prepared (g)[a]	Antibiotic administered, n (%) or dose prepared (g)[a]
Median (IQR)	13.8 (13.3, 17.9)	13.5 (13.5, 18.0)
min max	0.1 40.6	2.8 27.0
Meropenem	763/3434 (22.2)	763/3472 (22.0)
Mean (SD)	3.3 (1.5)	3.1 (1.5)
Median (IQR)	3.0 (2.3, 3.5)	3.0 (2.0, 3.0)
min max	0.0 9.2	0.5 10.0
Day 4		
Piperacillin-tazobactam	2086/3390 (61.5)	2101/3423 (61.4)
Mean (SD)	14.3 (4.4)	13.8 (3.8)
Median (IQR)	13.7 (13.2, 18.0)	13.5 (13.5, 18.0)
min max	0.2 40.6	0.9 28.8
Meropenem	717/3390 (21.2)	707/3423 (20.7)
Mean (SD)	3.3 (1.5)	3.2 (1.5)
Median (IQR)	3.0 (2.3, 3.6)	3.0 (2.0, 3.0)
min max	0.3 9.9	0.5 10.0
Day 5		
Piperacillin-tazobactam	1782/3347 (53.2)	1812/3381 (53.6)
Mean (SD)	14.0 (4.5)	13.4 (3.9)
Median (IQR)	13.5 (12.5, 18.0)	13.5 (13.5, 18.0)
min max	0.7 40.6	1.5 27.0
Meropenem	703/3347 (21.0)	691/3381 (20.4)
Mean (SD)	3.2 (1.6)	3.1 (1.4)
Median (IQR)	3.0 (2.1, 3.5)	3.0 (2.0, 3.0)
min max	0.2 9.0	0.2 8.0
Day 6		
Piperacillin-tazobactam	1414/3295 (42.9)	1451/3337 (43.5)

Administration details	Continuous infusion	Intermittent infusion
Antibiotic	(n = 3498)	(n = 3533)
	Antibiotic administered, n (%), or dose prepared (g)[a]	Antibiotic administered, n (%) or dose prepared (g)[a]
Mean (SD)	13.7 (4.4)	13.0 (4.3)
Median (IQR)	13.5 (11.3, 17.7)	13.5 (9.0, 17.1)
min max	0.3 36.0	0.9 23.4
Meropenem	664/3295 (20.2)	645/3337 (19.3)
Mean (SD)	3.3 (1.5)	3.2 (1.4)
Median (IQR)	3.0 (2.3, 3.4)	3.0 (2.8, 3.0)
min max	0.0 9.0	0.1 8.0
Day 7		
Piperacillin-tazobactam	1070/3255 (32.9)	1117/3302 (33.8)
Mean (SD)	13.3 (4.5)	12.4 (4.5)
Median (IQR)	13.5 (10.3, 17.4)	13.5 (9.0, 13.5)
min max	1.5 44.3	0.9 27.0
Meropenem	638/3255 (19.6)	618/3302 (18.7)
Mean (SD)	3.2 (1.5)	3.1 (1.5)
Median (IQR)	3.0 (2.2, 3.5)	3.0 (2.0, 3.0)
min max	0.1 9.3	0.5 10.0
Day 8		
Piperacillin-tazobactam	804/3214 (25.0)	780/3252 (24.0)
Mean (SD)	12.9 (4.8)	12.4 (4.7)
Median (IQR)	13.5 (9.0, 17.3)	13.5 (9.0, 15.9)
min max	0.2 34.9	0.7 27.0
Meropenem	577/3214 (18.0)	566/3252 (17.4)
Mean (SD)	3.2 (1.5)	3.1 (1.5)
Median (IQR)	3.0 (2.2, 3.3)	3.0 (2.0, 3.0)
min max	0.1 9.2	0.5 8.0
Day 9		

Administration details	Continuous infusion	Intermittent infusion
Antibiotic	(n = 3498)	(n = 3533)
	Antibiotic administered, n (%), or dose prepared (g)[a]	Antibiotic administered, n (%) or dose prepared (g)[a]
Piperacillin-tazobactam	561/3175 (17.7)	590/3214 (18.4)
Mean (SD)	13.1 (4.5)	12.5 (4.7)
Median (IQR)	13.5 (9.4, 17.2)	13.5 (9.0, 14.4)
min max	0.2 27.0	0.1 27.0
Meropenem	526/3175 (16.6)	518/3214 (16.1)
Mean (SD)	3.3 (1.6)	3.2 (1.5)
Median (IQR)	3.0 (2.4, 3.4)	3.0 (2.0, 3.0)
min max	0.2 14.0	0.5 10.0
Day 10		
Piperacillin-tazobactam	462/3140 (14.7)	482/3167 (15.2)
Mean (SD)	13.1 (4.7)	12.8 (4.4)
Median (IQR)	13.5 (9.0, 17.3)	13.5 (9.0, 16.0)
min max	0.1 29.6	0.3 27.0
Meropenem	480/3140 (15.3)	475/3167 (15.0)
Mean (SD)	3.3 (1.6)	3.2 (1.6)
Median (IQR)	3.0 (2.6, 3.4)	3.0 (2.0, 3.0)
min max	0.2 16.3	0.1 15.0
Day 11		
Piperacillin-tazobactam	381/3106 (12.3)	423/3131 (13.5)
Mean (SD)	13.3 (4.5)	12.9 (4.7)
Median (IQR)	13.5 (10.2, 17.1)	13.5 (9.0, 17.1)
min max	0.1 26.7	2.3 27.0
Meropenem	429/3106 (13.8)	445/3131 (14.2)
Mean (SD)	3.4 (1.6)	3.2 (1.5)
Median (IQR)	3.0 (2.8, 3.3)	3.0 (2.0, 3.0)
min max	0.2 17.3	0.1 12.0

Administration details	Continuous infusion	Intermittent infusion
Antibiotic	(n = 3498)	(n = 3533)
	Antibiotic administered, n (%), or dose prepared (g)[a]	Antibiotic administered, n (%) or dose prepared (g)[a]
Day 12		
Piperacillin-tazobactam	345/3086 (11.2)	370/3098 (11.9)
Mean (SD)	13.2 (5.0)	12.9 (4.7)
Median (IQR)	13.5 (9.0, 17.6)	13.5 (9.0, 17.1)
min max	0.6 36.5	2.7 41.4
Meropenem	397/3086 (12.9)	428/3098 (13.8)
Mean (SD)	3.3 (1.5)	3.2 (1.5)
Median (IQR)	3.0 (2.7, 3.4)	3.0 (2.0, 3.6)
min max	0.1 12.7	0.0 8.4
Day 13		
Piperacillin-tazobactam	309/3059 (10.1)	324/3065 (10.6)
Mean (SD)	13.2 (4.6)	13.5 (4.2)
Median (IQR)	13.5 (9.0, 17.8)	13.5 (13.5, 18.0)
min max	2.5 31.7	3.6 27.0
Meropenem	369/3059 (12.1)	399/3065 (13.0)
Mean (SD)	3.2 (1.5)	3.2 (1.5)
Median (IQR)	3.0 (2.5, 3.3)	3.0 (2.0, 3.2)
min max	0.5 9.0	0.5 10.0
Day 14		
Piperacillin-tazobactam	276/3035 (9.1)	293/3045 (9.6)
Mean (SD)	13.1 (4.5)	13.5 (4.4)
Median (IQR)	13.5 (9.1, 17.2)	13.5 (13.5, 18.0)
min max	0.5 26.4	2.3 27.0
Meropenem	339/3035 (11.2)	356/3045 (11.7)
Mean (SD)	3.1 (1.4)	3.1 (1.5)
Median (IQR)	3.0 (2.1, 3.2)	3.0 (2.0, 3.0)

Administration details	Continuous infusion	Intermittent infusion
Antibiotic	(n = 3498)	(n = 3533)
	Antibiotic administered, n (%), or dose prepared (g)[a]	Antibiotic administered, n (%) or dose prepared (g)[a]
min max	0.1 9.0	0.6 9.6
Day 15		
Piperacillin-tazobactam	227/3013 (7.5)	257/3025 (8.5)
Mean (SD)	12.9 (4.9)	12.9 (4.5)
Median (IQR)	13.5 (9.0, 17.8)	13.5 (9.0, 17.1)
min max	0.2 26.6	4.1 27.0
Meropenem	285/3013 (9.5)	318/3025 (10.5)
Mean (SD)	3.1 (1.4)	3.0 (1.5)
Median (IQR)	3.0 (2.4, 3.2)	3.0 (2.0, 3.0)
min max	0.2 9.0	0.5 7.6
Day 16		
Piperacillin-tazobactam	180/2995 (6.0)	213/2999 (7.1)
Mean (SD)	12.4 (5.0)	13.1 (4.3)
Median (IQR)	13.5 (9.0, 14.7)	13.5 (9.0, 17.1)
min max	0.8 26.6	4.5 27.0
Meropenem	240/2995 (8.0)	265/2999 (8.8)
Mean (SD)	3.0 (1.5)	3.1 (1.5)
Median (IQR)	3.0 (2.0, 3.1)	3.0 (2.0, 3.0)
min max	0.1 10.5	0.4 8.0

Abbreviations: IQR, inter-quartile range; SD, standard deviation.

[a]For β-lactam antibiotics prior to randomization, all doses administered are reported. For the "eligibility prescription", the dose prescription at the time of randomization is reported. For the antibiotic surveillance period (Days 1-16), the 24-hour dose administered in both treatment groups is reported by antibiotic.

[b]Cumulative dose of β-lactam antibiotic (piperacillin-tazobactam and/or meropenem) received (mg) up to Day 16.

[c]Negative values refer to a loading dose given prior to randomization.

[d]Time on study treatment is defined as the number of days between the first and last day of piperacillin-tazobactam and/or meropenem administration (up to Day 16).

[e]Dose post-randomization on Day 1.

eTable 8. Reasons for Cessation of β-Lactam Antibiotic

Reason	Continuous infusion (n = 3415)[a]	Intermittent infusion (n = 3448)[a]
Change in antimicrobial therapy	2645 (77.5)	1984 (57.5)
Treatment course completed	576 (16.9)	1115 (32.3)
Discharge from Intensive Care Unit	140 (4.1)	212 (6.1)
Treatment focus changed to palliation	48 (1.4)	120 (3.5)
Adverse event or contraindication to β-lactam antibiotic	6 (0.2)	17 (0.5)

[a]Descriptive statistics are reported for all participants with available data by group.

eTable 9. Other Antibiotics Administered

Antibiotic[a]	Continuous infusion (n = 3498)[b]	Intermittent infusion (n = 3533)[b]
Another antibiotic	n = 2916 (83.4)	n = 3005 (85.1)
Amoxicillin-clavulanic acid	899 (25.7)	945 (26.7)
Vancomycin	861 (24.6)	889 (25.2)
Gentamicin	592 (16.9)	627 (17.7)
Metronidazole	537 (15.4)	554 (15.7)
Ceftriaxone	447 (12.8)	461 (13.0)
Amikacin	309 (8.8)	335 (9.5)
Amoxicillin/Ampicillin	275 (7.9)	262 (7.4)
Azithromycin	231 (6.6)	255 (7.2)
Trimethoprim-sulfamethoxazole	234 (6.7)	247 (7.0)
Cefazolin	221 (6.3)	222 (6.3)
Ciprofloxacin	225 (6.4)	217 (6.1)
Flucloxacillin	220 (6.3)	213 (6.0)
Clarithromycin	181 (5.2)	220 (6.2)
Erythromycin	158 (4.5)	187 (5.3)
Clindamycin	157 (4.5)	168 (4.8)
Linezolid	169 (4.8)	137 (3.9)
Cefuroxime	127 (3.6)	112 (3.2)
Penicillin (Penicillin G or Benzylpenicillin)	108 (3.1)	105 (3.0)
Cefotaxime	80 (2.3)	111 (3.1)
Teicoplanin	93 (2.7)	92 (2.7)
Doxycycline	78 (2.2)	96 (2.7)
Ceftazidime	66 (1.9)	94 (2.7)
Cefepime	73 (2.1)	65 (1.8)
Levofloxacin	69 (2.0)	62 (1.8)
Tobramycin	44 (1.3)	41 (1.2)

Antibiotic[a]	Continuous infusion (n = 3498)[b]	Intermittent infusion (n = 3533)[b]
Rifampicin	24 (0.7)	25 (0.7)
Amoxicillin/Ampicillin-sulbactam	25 (0.7)	23 (0.7)
Cephalexin	31 (0.9)	15 (0.4)
Cloxacillin	23 (0.7)	23 (0.7)
Lincomycin	26 (0.7)	19 (0.5)
Daptomycin	18 (0.5)	24 (0.7)
Spiramycin	18 (0.5)	22 (0.6)
Moxifloxacin	16 (0.5)	19 (0.5)
Polymyxin B	17 (0.5)	18 (0.5)
Aztreonam	14 (0.4)	20 (0.6)
Rifaximin	14 (0.4)	15 (0.4)
Imipenem-cilastatin	16 (0.5)	12 (0.3)
Temocillin	13 (0.4)	14 (0.4)
Ertapenem	10 (0.3)	9 (0.3)
Isoniazid	9 (0.3)	8 (0.2)
Phenoxymethylpenicillin	8 (0.2)	9 (0.3)
Tigecycline	5 (0.1)	10 (0.3)
Cefoperazone	6 (0.2)	8 (0.2)
Fidaxomicin	3 (0.1)	9 (0.3)
Ofloxacin	5 (0.1)	6 (0.2)
Pyrazinamide	4 (0.1)	5 (0.1)
Colistin	3 (0.1)	5 (0.1)
Chloramphenicol	5 (0.1)	2 (0.1)
Dicloxacillin	3 (0.1)	3 (0.1)
Ethambutol	4 (0.1)	2 (0.1)
Nitrofurantoin	2 (0.1)	4 (0.1)
Other	21 (0.6)	23 (0.7)

[a]Includes all antibiotics (apart from the study drugs) administered in the 24 hours before randomization up to Day 16.

[b]Column percentages refer to percentages of other antibiotics in all participants by treatment group.

eTable 10. Place and Cause of Death

Place/cause of death	Continuous infusion (n = 3468)	Intermittent infusion (n = 3485)
Place of death	n = 850	n = 924
ICU (including intensivist supervised HDU)	569 (66.9)	620 (67.1)
Ward (including HDU if not supervised by intensivist)	213 (25.1)	234 (25.3)
Other	44 (5.2)	41 (4.4)
Home	24 (2.8)	29 (3.1)
Proximate cause of death[a]	n = 847	n = 912
Hypoxic respiratory failure	212 (25.0)	225 (24.7)
Distributive (septic) shock	170 (20.1)	204 (22.4)
Neurological (no TBI) without brain death	69 (8.1)	61 (6.7)
Cardiogenic shock	27 (3.2)	39 (4.3)
Neurological TBI without brain death	27 (3.2)	21 (2.3)
Neurological (no TBI) with brain death	19 (2.2)	23 (2.5)
Arrhythmia	27 (3.2)	14 (1.5)
Metabolic	17 (2.0)	23 (2.5)
Neurological TBI with brain death	10 (1.2)	14 (1.5)
Hypovolemic shock	13 (1.5)	10 (1.1)
Other	256 (30.2)	278 (30.5)
Underlying cause of death[a]	n = 846	n = 909
Respiratory cause	493 (58.3)	544 (59.8)
Pneumonia	204 (24.1)	206 (22.7)
Cancer	104 (12.3)	115 (12.7)
Other respiratory condition	68 (8.0)	82 (9.0)
Chronic obstructive pulmonary disease	35 (4.1)	50 (5.5)
Acute Respiratory Distress Syndrome (pulmonary)	39 (4.6)	36 (4.0)
Aspiration pneumonitis	22 (2.6)	30 (3.3)
Pulmonary fibrosis	14 (1.7)	16 (1.8)

Place/cause of death	Continuous infusion (n = 3468)	Intermittent infusion (n = 3485)
Pulmonary hemorrhage	4 (0.5)	4 (0.4)
Asthma	3 (0.4)	4 (0.4)
Acute Respiratory Distress Syndrome (non-pulmonary)	0	1 (0.1)
Cardiovascular cause	429 (50.7)	478 (52.6)
Sepsis with multi-organ failure	187 (22.1)	205 (22.6)
Other cardiovascular condition	97 (11.5)	127 (14.0)
Hepatic failure	42 (5.0)	52 (5.7)
Acute myocardial infarction	38 (4.5)	32 (3.5)
Hemorrhage not due to trauma	21 (2.5)	20 (2.2)
Pancreatitis	18 (2.1)	8 (0.9)
Aortic valvular disease	11 (1.3)	8 (0.9)
Massive pulmonary thromboembolism	9 (1.1)	9 (1.0)
Mitral valve disease	2 (0.2)	7 (0.8)
Ruptured or leaking abdominal aortic aneurysm	4 (0.5)	4 (0.4)
Hemorrhage due to trauma	0	3 (0.3)
Pericardial tamponade	0	2 (0.2)
Myocarditis	0	1 (0.1)
Neurological cause	172 (20.3)	203 (22.3)
Hypoxic brain injury	41 (4.8)	40 (4.4)
Other neurological condition	28 (3.3)	33 (3.6)
Ischemic stroke	22 (2.6)	33 (3.6)
Hemorrhagic stroke	18 (2.1)	30 (3.3)
TBI (unsurvivable primary injury)	20 (2.4)	19 (2.1)
Aneurysmal SAH	17 (2.0)	22 (2.4)
Meningoencephalitis	8 (0.9)	8 (0.9)
Metabolic encephalopathy	8 (0.9)	7 (0.8)
Status epilepticus	7 (0.8)	6 (0.7)

Place/cause of death	Continuous infusion (n = 3468)	Intermittent infusion (n = 3485)
TBI (refractory intracranial hypertension)	3 (0.4)	4 (0.4)
Cerebral abscess	0	1 (0.1)
Metabolic cause	108 (12.8)	108 (11.9)
Renal failure	57 (6.7)	62 (6.8)
Diabetes	29 (3.4)	37 (4.1)
Hepatitis	8 (0.9)	2 (0.2)
Anorexia/cachexia	4 (0.5)	3 (0.3)
Drug induced	6 (0.7)	1 (0.1)
Vasculitis	2 (0.2)	2 (0.2)
Drug overdose	2 (0.2)	1 (0.1)
Other cause (not listed)	194 (22.9)	220 (24.2)

Abbreviations: HDU, high dependency unit; ICU, intensive care unit; SAH, subarachnoid hemorrhage; TBI, traumatic brain injury.

[a]Each participant had only one proximate cause of death, but up to six underlying causes of death.

eTable 11. Summary of Adverse Events

	Continuous infusion (n = 3468)	Intermittent infusion (n = 3485)
Any adverse event	10# 10 (0.3)[a]	6# 6 (0.2)[a]
Rash	4# 4 (0.1)	1# 1 (0.0)
Elevated liver enzyme/s	1# 1 (0.0)	1# 1 (0.0)
Fever	2# 2 (0.1)	0
Elevated bilirubin	1# 1 (0.0)	0
Encephalopathy	1# 1 (0.0)	0
Hypertension/hypotension	0	1# 1 (0.0)
Post-operative bleeding	0	1# 1 (0.0)
Rash, tachycardia, hypotension	0	1# 1 (0.0)
Redness/pain at intravenous insertion site	0	1# 1 (0.0)
Study drug error with increased monitoring (no specific adverse event)	1# 1 (0.0)	0
Any serious adverse event	1# 1 (0.0)	0
Life-threatening	1# 1 (0.0)[b]	0
Relationship to study treatment		
Possibly related	8# 8 (0.2)	5# 5 (0.1)
Probably related	2# 2 (0.1)	1# 1 (0.0)
Definitely related	0	0

Adverse events are summarized as the total number of events reported (#) followed by the number and percentage of patients having at least one event.

[a]*P* value = 0.33.

[b]The event was severe encephalopathy resulting in aspiration pneumonia, cardiac arrest and death and assessed as possibly related to the intervention (continuous infusion of meropenem).

eTable 12. Summary of Protocol Deviations

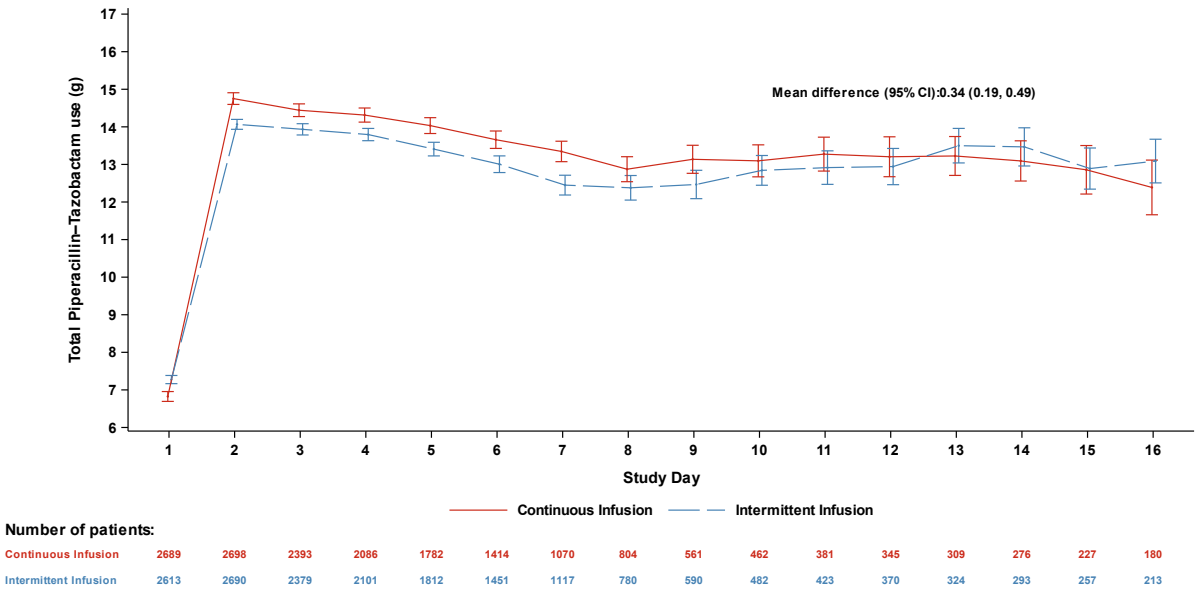
	Continuous infusion (n = 3468)	Intermittent infusion (n = 3485)
Any protocol deviation	2889# 1105 (31.9)[a]	2645# 1187 (34.1)[a]
Randomization of ineligible patient	197# 197 (5.5)	204# 204 (5.9)
No dose prior to randomization	95# 95 (2.7)	116# 116 (3.3)
On β-lactam antibiotic >24 h	58# 58 (1.7)	58# 58 (1.7)
Allergy	10# 10 (0.3)	13# 13 (0.4)
Not ineligible	10# 10 (0.3)	6# 6 (0.2)
Other	24# 24 (0.7)	20# 20 (0.6)
Administration or dosing related	2607# 929 (26.8)[b]	2358# 996 (28.6)[b]
Incorrect study assigned administration method used	1298# 282 (8.1)	790# 169 (4.8)
Pause or delay >1 h	769# 529 (15.3)	1234# 786 (22.6)
Intermittent dose not given as 30 min infusion	44# 9 (0.3)	228# 66 (1.9)
Clinician decision to not give via study assigned administration method	132# 17 (0.5)	9# 6 (0.2)
Missed dose	50# 44 (1.3)	68# 56 (1.6)
No bolus / loading dose	115# 106 (3.1)	1# 1 (0.0)
Drug given / started early	61# 60 (1.7)	3# 3 (0.1)
Not given via study assigned administration method (other reason)	50# 19 (0.8)	8# 6 (0.2)
Delayed start	30# 29 (0.8)	3# 3 (0.1)
Dose preparation incorrect (wrong solution)	24# 23 (0.7)	0
Meropenem infusion administration >8 h	23# 16 (0.5)	0
Over-dosed	4# 4 (0.1)	14# 3 (0.1)
Under-dosed	7# 6 (0.2)	0
Follow-up assessment not done correctly	55# 52 (1.5)	51# 48 (1.4)
Other	30# 30 (0.9)	23# 23 (0.7)

Protocol deviations are summarized as the total number of events reported (#) followed by the number and percentage of patients having at least one event.

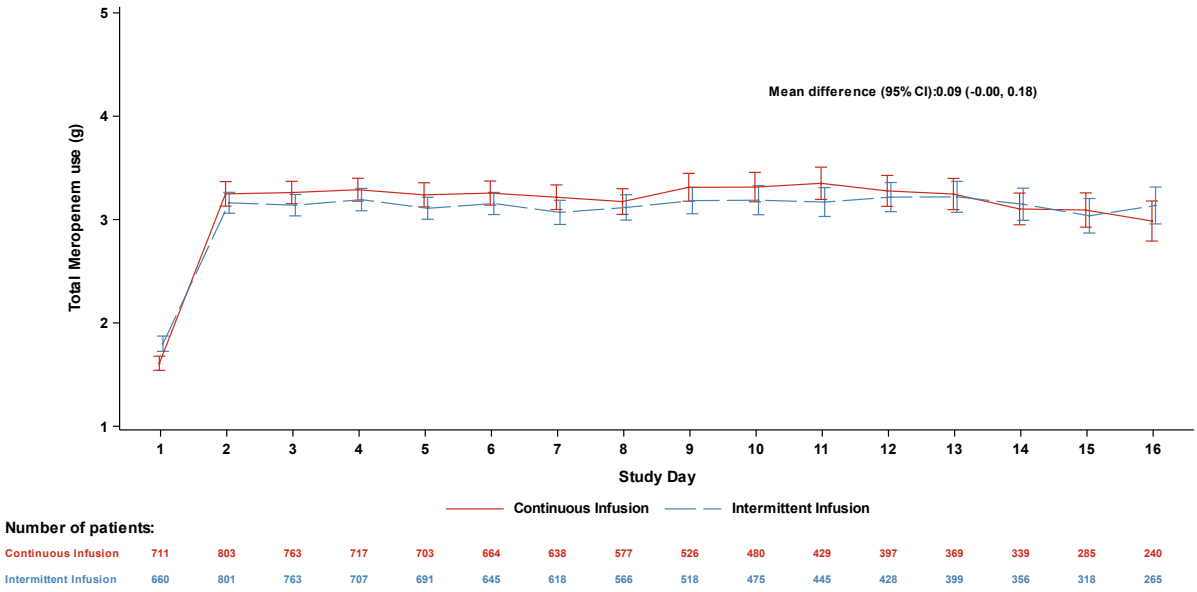
[a]*P* value = 0.05.

[b]The number of events as a percentage of the total number of doses (given and missed) was 5.5% (2607/47327) and 4.0% (2358/58931) for the continuous and intermittent infusion groups, respectively.

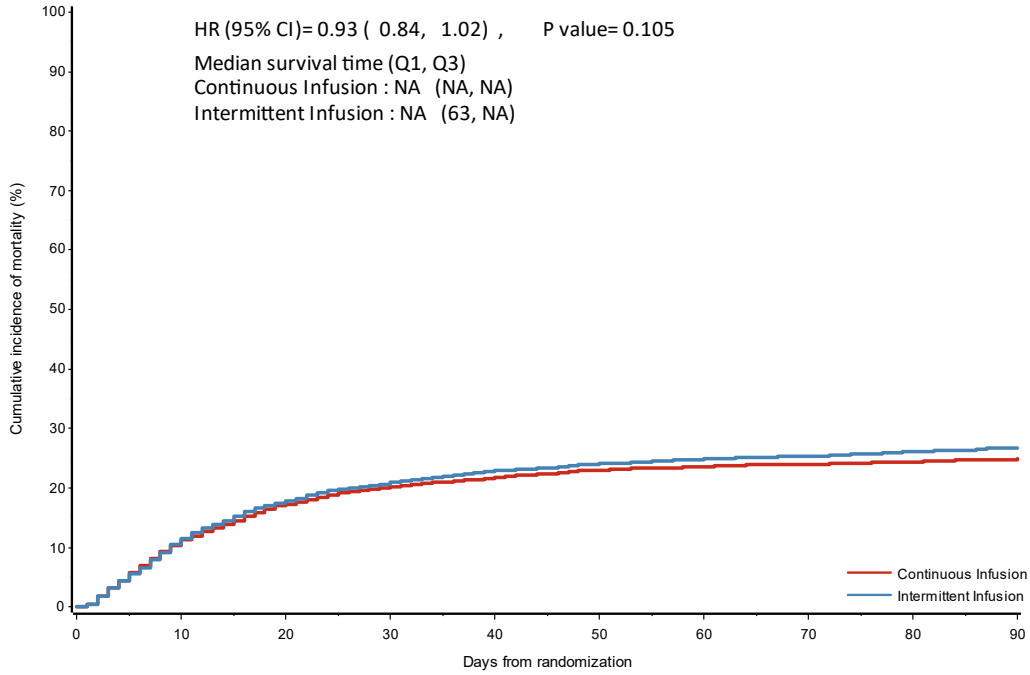
Figures



eFigure 1. Longitudinal Mean Plot of the Daily Dose of Piperacillin-Tazobactam



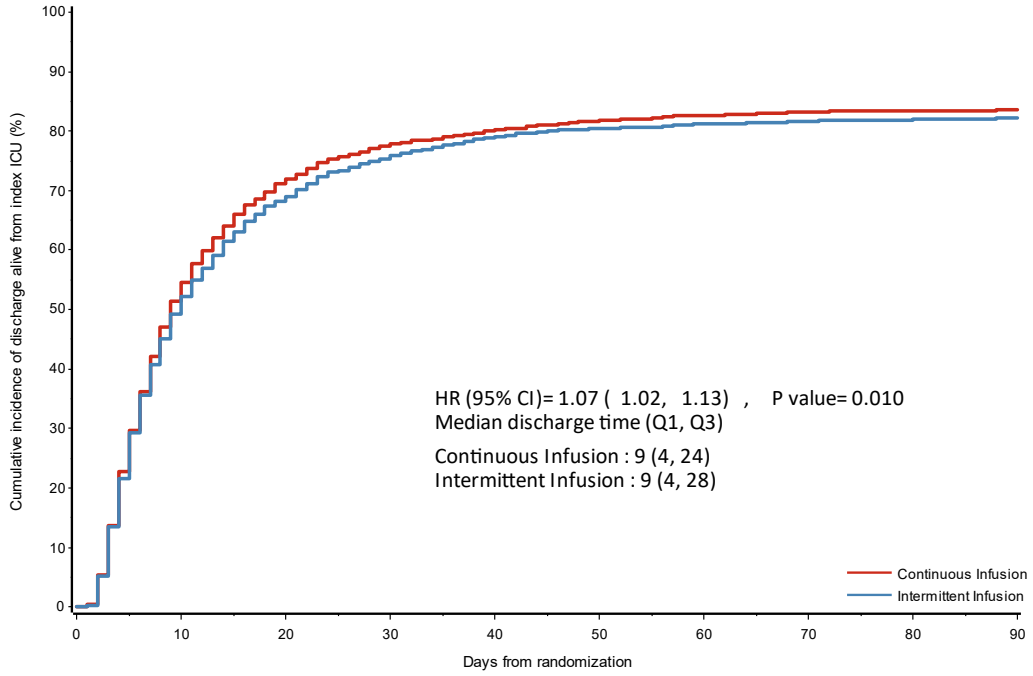
eFigure 2. Longitudinal Mean Plot of the Daily Dose of Meropenem



No. at Risk										
Continuous Infusion	3474	3116	2885	2778	2726	2676	2657	2642	2627	2613
Intermittent Infusion	3507	3141	2895	2783	2709	2667	2637	2619	2591	2568

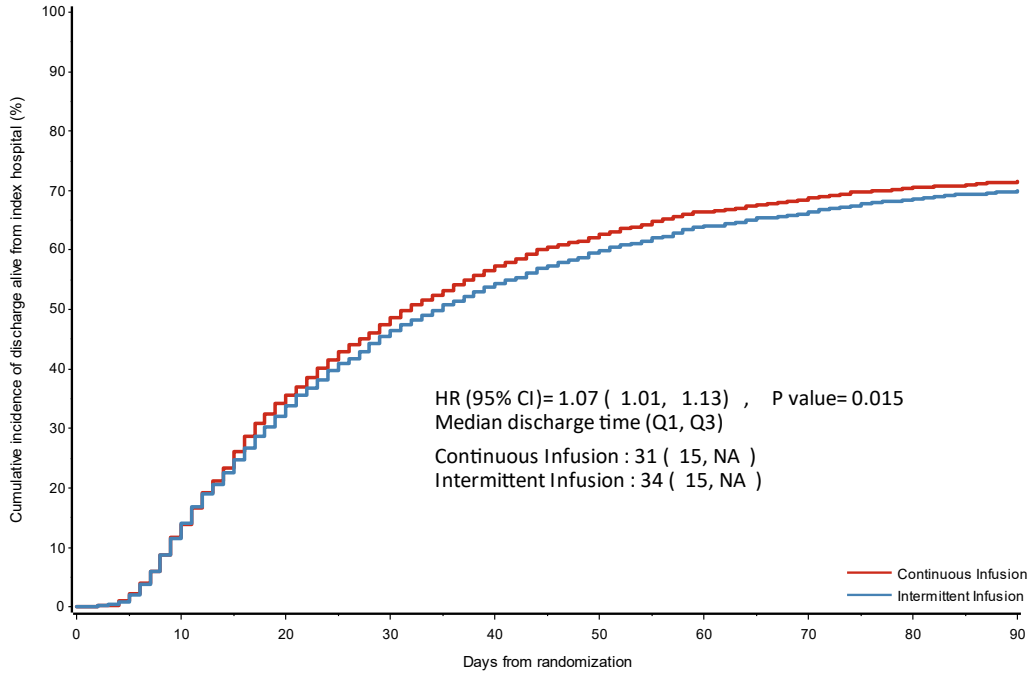
Post-hoc adjusted analysis: HR (95% CI) = 0.91 (0.83-1.00), *P* value = 0.05

eFigure 3. Cumulative Incidence Function of Time to Death



No. at Risk										
Continuous Infusion	3481	1375	556	280	164	95	58	37	28	23
Intermittent Infusion	3516	1454	629	327	168	109	76	55	42	31

eFigure 4. Cumulative Incidence Function of Time to Alive Discharge from Index ICU Admission



No. at Risk										
Continuous Infusion	3476	2713	1714	1159	804	570	409	331	256	216
Intermittent Infusion	3515	2746	1789	1215	859	631	462	372	275	224

eFigure 5. Cumulative Incidence Function of Time to Alive Discharge from Index Hospital Admission

CO-ENROLMENT LIST

Co-enrolment between the BLING III trial and other clinical trials was encouraged but was subject to a formal review process. The BLING III Study Management Committee and the relevant management committee for other clinical trials reviewed each other's trial protocols, and if both committees agreed that there were no scientific, ethical or procedural impediments to co-enrolment, then co-enrolment was allowed.

A co-enrolment table for the BLING III trial was kept up-to-date and available on the trial website. The following clinical trials were approved for co-enrolment by the BLING III Study Management Committee:

Trial Acronym	Full Trial Name	Trial Registration No.
65 Study	Evaluating the clinical and cost-effectiveness of permissive hypotension in critically ill patients aged 65 years or over with vasodilatory hypotension	ISRCTN10580502
A2B	Alpha 2 agonists for sedation to produce better outcomes from critical illness (A2B Trial)	NCT03653832
ADAPT-Sepsis	Multicentre randomised controlled trial in critical care patients using biomarker-guided duration of antibiotic treatment for sepsis: the ADAPT-Sepsis trial	ISRCTN47473244
AdrenOSS-2	A double-blind, placebo-controlled, randomized, multicenter, proof of concept and dose-finding phase II clinical trial to investigate the safety, tolerability and efficacy	NCT03085758

Trial Acronym	Full Trial Name	Trial Registration No.
	of ADRECIZUMAB in patients with septic shock and elevated adrenomedullin	
AID-ICU	Agents Intervening against Delirium in Intensive Care Unit (AID-ICU): a randomized, blinded, placebo-controlled trial	NCT03392376
ARISE FLUIDS	Australasian Resuscitation In Sepsis Evaluation: FLUid or vasopressors in emergency Department Sepsis (ARISE FLUIDS)	NCT04569942
ARREST	A randomised trial of expedited transfer to a cardiac arrest centre for non-ST elevation out-of-hospital cardiac arrest	NCT03872960
A-STOP	Rapid diagnostic tests and treatment opportunities for fungal infection in critically ill patients	ISRCTN43895480
BALANCE	Bacteremia Antibiotic Length Actually Needed for Clinical Effectiveness: randomized controlled trial	NCT03005145
BLENDER	Blend to Limit oxygEN in ECMO: a ranDomised controllEd Registry trial (the BLENDER trial) – a phase II multicentre randomised controlled trial	NCT03841084
CLASSIC	The Conservative vs. Liberal Approach to fluid therapy of Septic Shock in Intensive Care trial	NCT03668236
COMICS	Conventional versus Minimally Invasive extra-corporeal circulation in patients undergoing Cardiac Surgery: a randomised controlled trial	ISRCTN92590475
CONFIDENT	A multicenter randomized trial to assess the efficacy of CONvalescent plasma therapy in	NCT04558476

Trial Acronym	Full Trial Name	Trial Registration No.
	patients with Invasive COVID-19 and acute respiratory failure treated with mechanical ventilation: the CONFIDENT trial	
CRYOSTAT-2	CRYOSTAT-2: a multi-centre, randomised controlled trial evaluating the effects of early high-dose cryoprecipitate in adult patients with major trauma haemorrhage requiring major haemorrhage protocol (MHP) activation	ISRCTN14998314
CT-CSF	A prospective pharmacokinetic evaluation of the plasma and cerebrospinal fluid concentrations of a single dose ceftolozane/tazobactam in infected critically ill patients with an indwelling external ventricular drain	NCT03309657
EFFORT	The effect of higher protein dosing in critically ill patients: a multicenter registry-based randomized trial	NCT03160547
EMPRESS	EMPRESS: A feasibility study of early mobilisation programmes in critical care	NCT03771014
EPO-TRAUMA	A randomised, double-blind, placebo-controlled trial of erythropoietin alfa versus placebo in mechanically ventilated critically ill patients following traumatic injury	NCT04588311
EVADE	A phase 2 proof-of-concept study to evaluate the efficacy and safety of MEDI3902 in mechanically ventilated patients for the prevention of nosocomial pneumonia caused by *Pseudomonas aeruginosa*	NCT02696902

Trial Acronym	Full Trial Name	Trial Registration No.
FluDReSS	A phase II open label randomised controlled clinical trial of different dosing regimens of fludrocortisone in septic shock with assessment of temporal changes in hormonal, inflammatory, and genetic markers of vascular responsiveness	NCT04494789
Glycine	The effect of enteral glycine on plasma glycine and muscle histopathology, structure and function in the critically ill	ACTRN12618000409279
HEAL-COVID	HElping Alleviate the Longer-term consequences of COVID-19 (HEAL-COVID): a national platform trial	NCT04801940
HEMOTION	HEMOglobin Transfusion threshold in traumatic brain Injury OptimizatioN: the HEMOTION trial	NCT03260478
HOT-ICU	Handling Oxygenation Targets in adults with acute hypoxaemic respiratory failure in the Intensive Care Unit: a randomised clinical trial of a lower versus a higher oxygenation target	NCT03174002
INTACT	INTACT: a randomised feasibility study of INtravenous iron versus usual care to Treat Anaemia in CriTical care survivors	ISRCTN13721808
INTENT	Intensive Nutrition Therapy comparEd to usual care iN criTically ill adults: a randomised pilot trial	NCT03292237
LOVIT	Lessening Organ Dysfunction with VITamin C (LOVIT)	NCT03680274
LUCID	Liberal glUcose Control in critically Ill patients with pre-existing type 2 Diabetes (LUCID): a	ACTRN12616001135404

Trial Acronym	Full Trial Name	Trial Registration No.
	phase II multicentre randomised controlled trial to evaluate the prevalence and effect of hypoglycaemia	
MARCH	A 2x2 factorial, randomised, controlled, open-label, Phase III, pragmatic, clinical and cost-effectiveness trial with an internal pilot, to determine whether mucoactives (carbocisteine and hypertonic saline) in critically ill patients with acute respiratory failure reduce the duration of mechanical ventilation	ISRCTN17683568
MAST	Pharmacological management of seizures post traumatic brain injury (MAST trial)	ISRCTN13200656
Mega-ROX	A randomised, registry-embedded, single blinded clinical trial comparing conservative oxygen therapy to liberal oxygen therapy in mechanically ventilated adults in the intensive care unit	ACTRN12620000391976
MOSAICC	Evaluating the clinical and cost-effectiveness of sodium bicarbonate administration for critically ill patients with acute kidney injury and metabolic acidosis	ISRCTN14027629
PATCH	A multi-centre randomised, double-blinded, placebo-controlled trial of pre-hospital treatment with tranexamic acid for severely injured patients at risk of acute traumatic coagulopathy	NCT02187120
PEPTIC	A multi-centre, cluster randomised, crossover, registry trial comparing the safety and efficacy	ACTRN12616000481471

Trial Acronym	Full Trial Name	Trial Registration No.
	of proton pump inhibitors with histamine-2 receptor blockers for ulcer prophylaxis in intensive care patients requiring invasive mechanical intervention	
PHIND	Clinical evaluation of a POC assay to identify PHenotypes IN the Acute Respiratory Distress Syndrome	NCT04009330
PLUS	Comparison of Plasma-Lyte 148® and saline for fluid resuscitation and intravenous fluid therapy in critically ill adults	NCT02721654
PRISM	Prevention of Respiratory Insufficiency after Surgical Management (PRISM) Trial: a pragmatic randomised controlled trial of continuous positive airway pressure (CPAP) to prevent respiratory complications and improve survival following major abdominal surgery	ISRCTN56012545
Pro-MEDIC	Pro-phylactic administration of Melatonin for the prevention of Delirium in Intensive Care units – a randomized placebo controlled trial (Pro-MEDIC study)	ACTRN12616000436471
REALIST	Repair of Acute Respiratory Distress Syndrome by Stromal Cell Administration (REALIST): an open label dose escalation phase 1 trial followed by a randomised, double-blind, allocation concealed, placebo-controlled trial	NCT03042143
RECOVERY	Randomised Evaluation of COVID-19 Therapy	NCT04381936

Trial Acronym	Full Trial Name	Trial Registration No.
RECOVERY-RS	In adult patients with known or suspected COVID-19, does the use of Continuous Positive Airway Pressure (CPAP) or high-flow nasal oxygen (HFNO), compared with standard care reduce mortality or need for tracheal intubation?	ISRCTN16912075
REDCARB	REDuced CARBohydrate enteral formula compared to standard care to improve glycaemic control in critically ill tube fed patients – a randomised controlled phase II trial	ACTRN12621000859886
RE-ENERGIZE	Effects of enteral glutamine supplementation on mortality and infectious morbidity in severely burned patients: a multi-center pilot trial	NCT00985205
REMAP-CAP	Randomized, Embedded, Multifactorial Adaptive Platform trial for Community-Acquired Pneumonia	NCT02735707
RePHILL	A multicentre randomised controlled trial of pre-hospital blood product administration versus standard care for traumatic haemorrhage	ISRCTN62326938
REST	pRotective vEntilation With veno-venouS lung assisT in respiratory failure	NCT02654327
REVISE	Re-EValuating the Inhibition of Stress Erosions: prophylaxis against gastrointestinal bleeding in the critically ill (the REVISE) trial	NCT03374800
REVIVAL	A DB, placebo-controlled, two-arm parallel-group, phase 3 RCT to investigate the efficacy	NCT04411472

Trial Acronym	Full Trial Name	Trial Registration No.
	and safety of recombinant human alkaline phosphatase for treatment of patients with SA-AKI	
RISCIS	A multi-center, randomized, placebo controlled, double-blinded, trial of efficacy and safety of riluzole in acute spinal cord injury	NCT01597518
ROWTATE	Multicentre research programme to enhance return to work after trauma (ROWTATE) – feasibility of providing a vocational rehabilitation and psychological intervention to adults with moderate to severe traumatic injury	ISRCTN74668529
SA-AKI	Phase 3 randomized, double-blind study to evaluate the safety and efficacy of Reltecimod as compared to placebo in addition to standard of care in patients with sepsis-associated acute kidney injury (SA-AKI)	NCT03403751
SAHaRA	Aneurysmal SubArachnoid Hemorrhage - Red blood cell transfusion And outcome (SAHaRA): a randomized controlled trial	NCT03309579
SEAL	Safety and efficacy of inhaled pegylated adrenomedullin (PEG-ADM) in patients suffering from Acute Respiratory Distress Syndrome (ARDS): a double-blind, randomized, placebo-controlled, multicenter phase 2a/b clinical trial	NCT04417036
SEPCELL	A phase Ib/IIa, randomised, double blind, parallel group, placebo controlled, multicentre study to assess the safety and efficacy of	NCT03158727

Trial Acronym	Full Trial Name	Trial Registration No.
	expanded Cx611 allogeneic adipose-derived stem cells (eASCs) for the intravenous treatment of adult patients with severe community-acquired bacterial pneumonia and admitted to the intensive care unit	
SIFTI-2	A multi-centre, prospective study to examine the relationship between neutrophil function and sepsis in adults and children with severe thermal injuries	NCT04693442
SOFTER	Effect of denosumab and zoledronic acid on bone turnover markers in critically ill women – a safety and feasibility, randomised, placebo controlled trial	ACTRN12617000545369
SOS	Sugar or Salt (SOS) trial: hyperosmolar therapy in traumatic brain injury	ISRCTN16075091
SPICE III	Early goal-directed sedation compared with standard care in mechanically ventilated critically ill patients: a prospective multicentre randomised controlled trial	NCT01728558
STARRT-AKI	STandard versus Accelerated initiation of Renal Replacement Therapy in Acute Kidney Injury (STARRT-AKI): a multi-centre, randomized, controlled trial (principal trial)	NCT02568722
STRESS-L	STudy into the REversal of Septic Shock with Landiolol (Beta Blockade)	ISRCTN12600919
SuDDICU	A crossover, cluster randomised controlled trial of Selective Decontamination of the Digestive tract in Intensive Care Unit patients (SuDDICU)	NCT02389036

Trial Acronym	Full Trial Name	Trial Registration No.
SUNRRISE	Single Use Negative pRessure dressing for Reduction In Surgical site infection following Emergency laparotomy	ISRCTN17599457
TAME	TAME Cardiac Arrest Trial: targeted therapeutic mild hypercapnia after resuscitated cardiac arrest: a phase III multi-centre randomised controlled trial	NCT03114033
TARGET	The Augmented versus Routine approach to Giving Energy Trial (TARGET): a feasibility trial in the critically ill	ACTRN12611000793910
TARGET Protein	TARGET Protein Feasibility Study: a prospective, blinded, parallel group, randomised controlled trial to assess the feasibility of conducting a phase III trial of protein targets in critically ill adults	ACTRN12618001829202
TGC-Fast	Impact of tight blood glucose control within normal fasting ranges with insulin titration prescribed by the Leuven algorithm in adult critically ill patients	NCT03665207
THIAMINE 4 HYPOPHOS-PHATEMIA	Effect of exogenous vitamin B1 (thiamine) administration on blood lactate concentrations in enterally-fed, critically ill patients with hypophosphatemia	ACTRN12619000121167
TIGHT K	Prevention of dysrhythmias on the cardiac intensive care unit – does maintenance of high-normal serum potassium levels matter?	NCT04053816
TRAIN	TRansfusion strategies in Acute brain INjured patients. A prospective multicenter randomized study	NCT02968654

Trial Acronym	Full Trial Name	Trial Registration No.
TTM2	Targeted hypothermia versus targeted normothermia after out-of-hospital cardiac arrest. A randomised clinical trial	NCT02908308
UK-REBOA	A randomised controlled trial of the effectiveness, and cost-effectiveness, of Resuscitative Endovascular Balloon Occlusion of the Aorta (REBOA) for trauma	ISRCTN16184981
UK-ROX	Evaluating the clinical and cost-effectiveness of a conservative approach to oxygen therapy for invasively ventilated adults in intensive care	ISRCTN13384956
Urine Alkalinisation in COVID-19	Urine alkalinisation to prevent Acute Kidney Injury in COVID-19	NCT04655716
VACIRiSS	Pneumococcal vaccination to accelerate immune recovery in sepsis survivors	NCT03565159
Vitamin C in septic shock	Vitamin C administration in severe sepsis: a pilot randomised controlled trial of vasopressor requirements	ACTRN12617001184369
VITAMINS	The VitamIn C, HydrocorTisone and ThiAMINe in patients with Septic shock trial (VITAMINS Trial) - a prospective, feasibility, pilot, multi-centre, randomised, open-label controlled trial	NCT03333278
VITDALIZE UK	Effect of high-dose vitamin D3 on 28-day mortality in adult critically ill patients with severe vitamin D deficiency: the UK arm of an international multi-centre, placebo-controlled, phase III double-blind trial	ISRCTN44822292

In some instances (5), non-interventional studies were reviewed and approved for co-enrolment by the BLING III Study Management Committee, however, these studies are not listed in the above table.

AMENDMENTS TO PROTOCOL

Version	Date	Amendment
1.0	27/03/2017	*Not applicable*
2.0	20/09/2017	Secondary and tertiary outcomes listed separately and additional tertiary outcomes included; outcomes associated with the economic evaluation moved to “Pre-specified sub-studies” (section 14); pharmacokinetic-pharmacodynamic and economic evaluation sub-study details added; wording amendments for clarity and typographical corrections. *See Supplement 6 for full details.*
3.0	07/12/2017	Duration of assessment amended for 2 secondary and tertiary outcomes; rewording of inclusion and exclusion criteria for clarity and pragmatism; update to schedule of assessments; wording amended to include United Kingdom and European regulations and terminology. *See Supplement 6 for full details.*
4.0	12/02/2018	Administrative changes, including addition of coordinating center details in the United Kingdom and Europe; clarification of patient and public involvement; additional information on randomization process; additional information on the consent process in the United Kingdom and other regions; clarification of processes and responsibilities for the site and regional or central coordinating center; expanded details on the statistical analysis plan; wording amendments for clarity. *See Supplement 6 for full details.*
5.0	21/06/2018	Additional exclusion criteria added for “known allergy to piperacillin-tazobactam, meropenem or penicillin”; addition of multi-drug resistant Pseudomonas to the definition of a multi-resistant organism, including how this is defined; wording amendments for clarity. *See Supplement 6 for full details.*
6.0	01/04/2022	Amendment to the sample size to enable the study to extend beyond 7000 patients for the pharmacokinetic-pharmacodynamic sub-study. *See Supplement 6 for full details.*

AMENDMENTS TO STATISTICAL ANALYSIS PLAN

Version	Date	Amendment
1.0[a]	06/09/2021	*Not applicable*
Corridendum[b]	24/05/2023	Typographical corrections: trial registration number, APACHE III score to APACHE II score and author affiliation.

Abbreviation: APACHE, Acute Physiology and Chronic Health Evaluation.

[a]Reference: Billot L, Lipman J, Brett SJ, et al. Statistical analysis plan for the BLING III study: a phase 3 multicentre randomised controlled trial of continuous versus intermittent β-lactam antibiotic infusion in critically ill patients with sepsis. *Crit Care Resusc.* 2021;23(3):273-284.

[b]Reference: Billot L, Lipman J, Brett SJ, et al. Corrigendum to "Statistical analysis plan for the BLING III study: a phase 3 multicentre randomised controlled trial of continuous versus intermittent β-lactam antibiotic infusion in critically ill patients with sepsis." *Crit Care Resusc.* 2023;25(1):60.

EREFERENCES

1. Mouton JW, Vinks AA. Continuous infusion of beta-lactams. *Curr Opin Crit Care.* 2007;13(5):598-606.
2. Viaene E, Chanteux H, Servais H, Mingeot-Leclercq MP, Tulkens PM. Comparative stability studies of antipseudomonal beta-lactams for potential administration through portable elastomeric pumps (home therapy for cystic fibrosis patients) and motor-operated syringes (intensive care units). *Antimicrob Agents Chemother.* 2002;46(8):2327-32.
3. Arlicot N, Rochefort GY, Schlecht D, Lamoureux F, Marchand S, Antier D. Stability of antibiotics in portable pumps used for bronchial superinfection: guidelines for prescribers. *Pediatrics.* 2007;120(6):1255-9.
4. Zhang Y, Trissel LA. Stability of piperacillin and ticarcillin in AutoDose infusion system bags. *Ann Pharmacother.* 2001;35(11):1360-3.
5. Smith DL, Bauer SM, Nicolau DP. Stability of meropenem in polyvinyl chloride bags and an elastomeric infusion device. *Am J Health Syst Pharm.* 2004;61(16):1682-1685.
6. Patel PR, Cook SE. Stability of meropenem in intravenous solutions. *Am J Health Syst Pharm.* 1997;54(4):412-21.
7. Berthoin K, Le Duff CS, Marchand-Brynaert J, Carryn S, Tulkens PM. Stability of meropenem and doripenem solutions for administration by continuous infusion. *J Antimicrob Chemother.* 2010;65(5):1073-5.