THE LANCET
Haematology

Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: Male C, Lensing AWA, Palumbo JS, et al. Rivaroxaban compared with standard anticoagulants for the treatment of acute venous thromboembolism in children: a randomised, controlled, phase 3 trial. *Lancet Haematol* 2019; published online Nov 4. https://doi.org/10.1016/S2352-3026(19)30219-4.

Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work. Supplement to: Male C, et al. Rivaroxaban for the treatment of acute venous thromboembolism in children. XXX

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List of investigators by country and number of randomized children	
ARGENTINA	Juan Chain, Hospital del Niño Jesus, San Miguel de Tucumán (3)
AUSTRALIA	Paul Monagle, Royal Children's Hospital Melbourne, Parkville (8); Jeremy Robertson, Lady Cilento Children's Hospital, South Brisbane (2)
AUSTRIA	Christoph Male, Katharina Thom, Universitätsklinik für Kinder- und Jugendheilkunde, Medizinische Universität Wien (8); Werner Streif, Landeskrankenhaus - Universitätskliniken Innsbruck, Innsbruck (3); Rudolf Schwarz, Kepler Universitätsklinikum, Linz (1); Klaus Schmitt, Kepler Universitätsklinikum, Linz (2), Gernot Grangl, Medizinische Universität Graz, Granz (1)
BELGIUM	An Van Damme, CU Saint-Luc/UZ St-Luc, Brüssels (3); Philip Maes, UZ Antwerpen, Edegem (3); Veerle Labarque, UZ Leuven Gasthuisberg, Leuven (4)
BRAZIL	Antônio Petrilli, UNIFESP/EPM, São Paulo (3); Sandra Loggeto, Fundação José Luiz Egydio Setúbal -Hosp.Infantil Sabará, São Paulo (1); Estela Azeka, Hospital das Clínicas da Faculdade de Medicina da USP, São Paulo (1)
CANADA	Anthony Chan, McMaster Children's Hospital, Hamilton (11); Leonardo Brandao, Hospital for Sick Children, Toronto (4); Doan Le, Alberta Children's Hospital, Calgary (1); Christine Sabapathy, Montreal Children's Hospital-MUHC, Montreal (1); Patricia Massicotte, University of Alberta Hospital, Edmonton (7)
CHINA	Runhui Wu, Beijing Children's Hospital, Capital Medical University, Beijing (1); Jie Ding, Peking University First Hospital, Beijing (4); Wenyan Huang, Children's Hospital of Shanghai, Shangai (2); Jianhua Mao, The Children's Hospital Zhengjiang University School of Medicine, Hangzhou (2)
FINLAND	Päivi Lähteenmäki, Turun yliopistollinen keskussairaala, kantasairaala, Turku (1)
FRANCE	Pascal Amedro, Hôpital Arnaud de Villeneuve – Montpellier, Montpellier (8); Damien Bonnet, Hopital Necker les enfants malades – Paris; Paris (16); Stéphane Decramer, Hôpital des Enfants, Toulouse, (2)
GERMANY	Jan Beyer-Westendorf, Universitätsklinikum Carl Gustav Carus Dresden, Dresden (7); Susanne Holzhauer, Charité Campus Virchow-Klinikum (CVK), Berlin (9); Toralf Bernig, Med. Fakultät der Martin-Luther-Universität Halle-Wittenberg, Halle (5); Martin Chada, Universitätsklinikum Erlangen, Erlangen (1)
HONG KONG	Godfrey Chan, Queen Mary Hospital, Hong Kong (1)

HUNGARY	Krisztian Kally, DPCKh Orszagos Hematologiai es Infektologiai Intezet, Budapest (7)
IRELAND	Beatrice Nolan, Our Lady's Hospital For Sick Children, Crumlin (2)
ISRAEL	Gili Kenet, Chaim Sheba Medical Center, Ramat Gan (10); Shoshana Revel Vilk, Hadassah Hebrew University Hospital Ein Kerem, Jerusalem (2); Hannah Tamary, Schneider Children's Medical Center of Israel, Petach Tikva (2); Carina Levin, Haemek Medical Center, Afula (1)
ITALY	Daniela Tormene, A.O. di Padua, Padua (8); Maria Abbattista, Andrea Artoni, Fondazione IRCCS Ca Granda Ospedale Maggiore Policlinico, Milano (7); Paola Saracco, A.O.U. Città della Salute e della Scienza di Torino, Torino (7)
JAPAN	Takanari Ikeyama, Aichi Children's Health and Medical Center, Obu (3); Ryo Inuzuka, The University of Tokyo Hospital, Bunkyo-ku (1); Satoshi Yasukochi, Nagano Children's Hospital, Azumino (2)
MEXICO	Michelle Morales Soto, Antiguo Hospital Civil de Guadalajara Fray Antonio Alcalde, Guadalajara (3); Karina Anastacia Solis Labastida, UMAE Hospital de Pediatria Dr Silvestre Frenk CMN Siglo XXI, Ciudad de Mexico (2)
NETHERLANDS	Monique H. Suijker, Academisch Medisch Centrum, Amsterdam (7); Marike Bartels, University Medical Center Utrecht, Utrecht (3); Rienk Y.J. Tamminga, Universitair Medisch Centrum Groningen, Groningen (12); C. Heleen van Ommen, Erasmus Medisch Centrum, Rotterdam (6); D.M.W.M te Loo, Universitair Medisch Centrum St. Radboud, Nijmegen (3)
PORTUGAL	Rui Anjos, Centro Hospitalar de Lisboa Ocidental, EPE - H.Santa Cruz, Carnaxide (1)
RUSSIA	Lyudmila Zubarovskaya, Institute of Children's Oncology, Hematology and Transplantation, St. Petersburg (1); Natalia Popova, Regional Clinical Oncology Dispensary #1, Volgograd (1); Elena Samochatova, Center of Children's Hematology, Oncology and Immunology, Moscow (4); Margarita Belogurova, City Hospital #31, St. Petersburg (1); Pavel Svirin, Morozov Children's City Clinical Hospital, Moscow (1); Tatiana Shutova, Nizhniy Novgorod Regional Children's Clinical Hospital, Nizhny Novgorod (1); Vladimir Lebedev, Children's Regional Clinical Hospital, Krasnodar (6), Olga Lvova, Ural State Medical University, Yekaterinburg (8), Olga Barbarash, Sci-Res. Institute of Complex Cardiovascular Disorders, Kemerovo (3); Ildar Nurmeev, Kazan State Medical University, Kazan (20)
SINGAPORE	Pei Lin Koh, National University Hospital, Singapore (2); Joyce Ching Mei, KK Women's and Children's Hospital, Singapore (3)
SLOVAKIA	Ludmila Podracka, Narodny ustav detskych chorob, Bratislava (2)

SPAIN	Rubén Berrueco, Hospital Sant Joan de Déu, Esplugues de Llobregat (2); Amparo Santamaría Ortiz, Ciutat Sanitària i Universitaria de la Vall d Hebron, Barcelona (9); María Fernanda López Fernández, Hospital Teresa Herrera (2)
SWEDEN	Tony Frisk, Astrid Lindgrens Barnsjukhus, Solna (1)
SWITZERLAND	Sebastian Grunt, Inselspital Universitätsspital Bern, Bern (4); Johannes Rischewski, Kinderspital Luzern, Luzern (1); Manuela Albisetti Pedroni, Universitätskinderspital Zürich, Zürich (2)
TURKEY	Ali Antmen, Acibadem Adana Hastanesi, Adana (2); Huseyin Tokgoz, Necmettin Erbakan Universitesi Meram Tip Fakultesi Hastanesi, Konya (1); Zeynep Karakas, Istanbul Universitesi İstanbul Tip Fakultesi, Istanbul (5)
UNITED KINGDOM	Tina Biss, Royal Victoria Infirmary, NewCastle Upon Tyne (7); Elizabeth Chalmers, Royal Hospital for Children, Glasgow (8); Jayashree Motwani, Birmingham Children's Hospital, Birmingham (3); Michael Williams, Birmingham Children's Hospital, Birmingham (1); John Grainger, Royal Manchester Children's Hospital, Manchester (3); Philip Connor, University Hospital of Wales, Cardiff (13), Jeanette Payne, Sheffield Children´s NHS Foundation Trust, Sheffield (6); Mike Richards, Leeds General Infirmary, Leeds (2); Susan Baird, Royal Hospital for Sick Children, Edinburgh (5); Neha Bhatnagar, John Radcliffe Hospital, Oxford (2); Angela Aramburo, Royal Brompton Hospital, London (1)
UNITED STATES OF AMERICA	Shelley Crary, Arkansas Children's Hospital, Little Rock (4); Tung Wynn, University of Florida-Gainesville, Gainesville (3); Shannon Carpenter, Children's Mercy Hospital & Clinics, Kansas City (4); Kerry Hege, Riley Hospital for Children, Indianapolis (18); Marcela Torres, Cook Children's Medical Center, Fort Worth (12); Sanjay Ahuja, University Hospitals Cleveland Medical Center, Cleveland (6); Neil Goldenberg, All Children's Hospital John Hopkins Medicine, St. Petersburg (2); Gary Woods, Children's Healthcare of Atlanta, Atlanta (4); Kamar Godder, Miami Children's Hospital, Miami (5); Ajovi Scott-Emuakpor; Michigan State University, Lansing (3); Joseph Palumbo, Cincinnati Children's Hospital and Medical Center, Cincinnati (28), Gavin Roach, Mattel Children's Hospital – UCLA Health, Los Angeles (1), Rukhmi Bhat, Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago (8); Riten Kumar, Nationwide Children's Hospital, Columbus (20); Leslie Raffini, Children's Hospital of Philadelphia, Philadelphia (2); Guy Young, Children's Hospital of Los Angeles, Los Angeles (6); Donald Yee, Texas Children's Hospital, Houston (8); Nirmish Shah, Duke Children's Hospital & Health Center, Durham (1); Sanjay Shah, Phoenix Children's Hospital, Phoenix (4); Courtney Thornburg, Rady Children's Hospital San Diego, San Diego (5); Cynthia Gauger, Nemours Children's Clinic – Jacksonville, Jacksonville (7); Ayesha Zia, University of Texas Southwestern Medical Center, Dallas (2); Roger Berkow, Nemour's Children's Clinic – Pensacola, Pensacola (1)

Study committees: list of collaborators	
Steering committee	
Paul Monagle	Royal Children's Hospital, University of Melbourne, Australia;
Christoph Male	Medical University of Vienna, Austria
Guy Young	University of Southern California Keck School of Medicine, Los Angeles, USA
Angelo C. Molinari	Giannina Gaslini Children's Hospital, Genova, Italy
Patricia M. Massicotte,	Hospital for Sick Children and The University of Toronto, Canada.
Ulrike Nowak Göttl	Thrombosis and Hemostasis Treatment Center, Kiel, Germany
Gili Kenet	Tel Aviv University, and Sheba Medical Center, Tel Hashomer, Israel
Anthony K.C. Chan	McMaster Children's Hospital, Hamilton, Canada
Anthonie W.A. Lensing	Bayer AG, Wuppertal, Germany
Dagmar Kubitza	Bayer AG, Wuppertal, Germany
Central independent adjudication committee	
Martin H. Prins	University of Maastricht, Maastricht, the Netherlands
Hugo ten Cate	University of Maastricht, Maastricht, the Netherlands
Jonathan Coutinho	Academic Medical Center, Amsterdam, the Netherlands
Harry Buller	Academic Medical Center, Amsterdam, the Netherlands
Data safety and monitoring board	
Mark Crowther	McMaster University, Hamilton, Canada
Stefan Schmidt	University of Florida, Orlando, USA
Vicki Price	IWK Health Centre, Halifax, Canada

Bayer study organization: list of collaborators	
Study team	Ivet Adalbo, Hazel Wohlfahrt, Imma López Muñoz, Amy Mason, Pablo Iveli, Melanie Goth, Hi-Gung Bae, Nicola Cirillo, Madhurima Majumder, Frank Czekalla, Donatella D'Urso, Veronica Torres Barthelemy, Antonella Serra, Nicole Wächter, Suvi Rajamaki, Walther Seiler, Stefanie Augsburg, Ying Cheng, Xinyu Xu, Matthew Gale, Lisa Morch, Natalia Tkhinvaleli, Arif Syed, Stefanie Kraff, Almut Guenzel, Marta Ozog, Jennifer Wiley, Angelika Zweigart, Paula Batalha.
Country lead monitors	Paula Giuliani, Duncan Hui, Heike Winter, Evy Bouthez, Christian Vera, Michelle Lee-Scott, Shu Qi, Hanna Heikkila, Alexandra Dekeyser, Andrea Kühn, Ann Tam, Balazs Vagovits, Tanya Godfrey, Nitzan Noyman, Gloria Sbarra, Yumi Kagawa, Maria Pineda, Sanne Meijer, Lukasz Wincza, Anna Malysheva, Berta Sicilia Fernández, Pauline Koch, Camilla Carlsson, Tanya Godfrey, Carrie Gittelson, Meltem Akyurek, Sofia Lima Resende, Olga Babelova, Helen Seok Yin Chew, George Constantin, Christine Mugo.

Elrohe, Academic Research Organization: list of collaborators	
Project director	Petro van Bergen
Adjudication office	Sanne Koopmans, Frank Raedts

Table S1. Eligibility criteria of the EINSTEIN-Jr. study.	
Inclusion	
1	Children aged birth to <18 years with confirmed venous thromboembolism who receive initial treatment with therapeutic dosages of UFH, LMWH or fondaparinux and require anticoagulant therapy for at least 90 days. However, children aged birth to < 2 years with catheter-related thrombosis require anticoagulant therapy for at least 30 days
2	Informed consent provided and, if applicable, child assent provided
3	For children younger than 6 months: - Gestational age at birth of at least 37 weeks - Oral feeding/nasogastric/gastric feeding for at least 10 days - Body weight ≥2600 g
Exclusion	
1	Active bleeding or bleeding risk contraindicating anticoagulant therapy
2	An estimated glomerular filtration rate <30 mL/min/1.73 m^2 (in children younger than 1 year, serum creatinine results above 97.5th percentile excludes participation
3	Hepatic disease which is associated with either: coagulopathy leading to a clinically relevant bleeding risk, or alanine aminotransferase > 5x upper level of normal (ULN) or total bilirubin > 2x ULN with direct bilirubin > 20% of the total
4	Platelet count < 50 x 10^9/L
5	Sustained uncontrolled hypertension defined as systolic and/or diastolic blood pressure > 95th age percentile
6	Life expectancy < 3 months
7	Concomitant use of strong inhibitors of both cytochrome P450 isoenzyme 3A4 (CYP3A4) and P-glycoprotein, including but not limited to all human immunodeficiency virus protease inhibitors and the following azole-antimycotics agents: ketoconazole, itraconazole, voriconazole, posaconazole, if used systemically (fluconazole allowed)
8	Concomitant use of strong inducers of CYP3A4, including but not limited to rifampicin, rifabutin, phenobarbital, phenytoin and carbamazepine
9	Childbearing potential without proper contraceptive measures, pregnancy or breast feeding
10	Hypersensitivity or any other contraindication listed in the local labeling for the comparator treatment or experimental treatment
11	Inability to cooperate with the study procedures
12	Previous assignment to treatment during this study
13	Participation in a study with an investigational drug or medical device within 30 days prior to randomization

Table S2. Body weight-adjusted rivaroxaban regimens in a 20 mg equivalent dose.

Body weight (kg)		od dose	bid dose	tid dose	Total daily dose
Min	Max				
2.6	<3			0.8 mg	2.4 mg
3	<4			0.9 mg	2.7 mg
4	<5			1.4 mg	4.2 mg
5	<7			1.6 mg	4.8 mg
7	<8			1.8 mg	5.4 mg
8	<9			2.4 mg	7.2 mg
9	<10			2.8 mg	8.4 mg
10	<12			3.0 mg	9 mg
12	<30		5 mg		10 mg
30	<50	15 mg			15 mg
≥ 50		20 mg			20 mg

OD denotes once daily, BID twice daily, and TID thrice daily.

Table S3. Definitions of major bleeding and clinically relevant non-major bleeding events.	
Major bleeding	
	overt bleeding and:
	associated with a fall in hemoglobin of 2 g/dL or more, or
	leading to a transfusion of the equivalent of 2 or more units of packed red blood cells or whole blood in adults, or
	occurring in a critical site, e.g. intracranial, intraspinal, intraocular, pericardial, intra-articular, intramuscular with compartment syndrome, retroperitoneal, or
	contributing to death
Clinically relevant non-major bleeding	
	overt bleeding not meeting the criteria for major bleeding, but associated with:
	medical intervention, or
	unscheduled contact (visit or telephone call) with a physician, or
	(temporary) cessation of study treatment, or
	discomfort for the child such as pain, or
	impairment of activities of daily life (such as loss of school days or hospitalization

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Table S4. Algorithm for the classification of outcomes of repeat imaging

Repeat imaging	Status of anticoagulant therapy	Adjudication outcome	Total n=500
Performed in time window*	Not applicable	Accept adjudication outcome	392 (78.4%)
Performed before time window*	If any anticoagulation** stopped within 7 days after imaging	Accept adjudication outcome	6 (1.2%)
Performed before time window*	If any anticoagulation continued for >7 days after imaging	Classify outcome as "uncertain"	34 (6.8%)
Performed after time window*	Not applicable	Classify as "uncertain"	23 (4.6%)
Not performed or not evaluable	If any anticoagulation stopped before study treatment time window[&]	Classify as "uncertain"	15 (3.0%)
Not performed or not evaluable	If any anticoagulation stopped during study treatment time window[&]	Classify as "improved"	8 (1.6%)
Not performed or not evaluable	If any anticoagulation is continued after study treatment time window[&]	Classify as "uncertain"	13 (2.6%)
Confirmed primary efficacy outcome[+]	Not applicable	Classify as "deteriorated"	9 (1.8%)

VTE denotes venous thromboembolism.
*Time window for repeat imaging relative to randomization: Day 90±21 (or Day 30±7 for children with catheter-related VTE younger than 2 years).
**Any anticoagulation defined as anticoagulant therapy with either study medication or non-study medication with either direct factor Xa inhibitors, direct thrombin inhibitors, unfractionated or low molecular weight heparin, fondaparinux, or a vitamin K antagonist. Non-study anticoagulant therapy counted if started within 3 days after stop of study medication with a duration of at least 3 days. [&]Time window for stop of anticoagulation relative to randomisation: Day 83-97 (or Day 23-37 for children with catheter-related venous thromboembolism younger than 2 years). [+]Regardless of availability of repeat imaging up to the upper limit of the end of main treatment time window.

Table S5. Recurrent VTE, major bleeding, and mortality in relation to clinical characteristics*

Site of index event	Age	Weight (kg)	Risk factor profile	Day of event**	Presentation of event	Treatment at time of event
Rivaroxaban group						
Recurrent VTE						
Lung	13	53	Persistent/ transient	5	Lung	LMWH
Upper extremity	14	63	Unprovoked	28	Upper extremity	Rivaroxaban tablet
Lower extremity	16	58	Persistent/ transient	22	Lower extremity, stent	LMWH, thrombectomy, stent
Lower extremity	16	110	Persistent	6	Lower extremity	Rivaroxaban suspension
Mortality						
Lungs	17	52	Persistent	34	Cancer-progression	Rivaroxaban tablet
Comparator group						
Recurrent VTE						
Lungs	3	16	Persistent	5	Lungs	LMWH
Brain	6	23	Transient	30	Brain	VKA
Lower extremity	16	55	Persistent/ transient	6	Lower extremity	VKA
Lower extremity	16	70	Unprovoked	12	Lower extremity	LMWH
Lungs	17	101	Transient	6	Lower extremity	LMWH
Major bleeding						
Brain	0.5	7	Transient	14	Intracranial bleed	Enoxaparin
Upper extremity	16	57	Unprovoked	24	Hemothorax	Enoxaparin

*All index events of children with recurrent VTE, major bleeding or mortality were not related to the use of central venous catheters, **relative to randomization. LMWH denotes low molecular weight heparin, VTE venous thromboembolism and VKA vitamin K antagonist therapy.

Table S6. Adverse events during the main study treatment period (full version).

	Rivaroxaban N=329			Standard anticoagulation N=162		
System Organ Class **Preferred Term**	**Grade 1-2**	**Grade 3**	**Grade 4**	**Grade 1-2**	**Grade 3**	**Grade 4**
Any event	231 (70.2)	39 (11.9)	4 (1.2)	100 (61.7)	23 (14.2)	1 (0.6)
Blood and lymphatic system disorders	29 (8.8)	8 (2.4)	1 (0.3)	12 (7.4)	4 (2.5)	0
Anaemia	10 (3.0)	1 (0.3)	0	4 (2.5)	0	0
Bone marrow failure	2 (0.6)	0	1 (0.3)	0	0	0
Febrile neutropenia	3 (0.9)	7 (2.1)	0	0	1 (0.6)	0
Leukopenia	3 (0.9)	2 (0.6)	0	1 (0.6)	0	0
Lymphopenia	0	1 (0.3)	0	0	0	0
Neutropenia	5 (1.5)	1 (0.3)	0	3 (1.9)	1 (0.6)	0
Pancytopenia	1 (0.3)	0	0	1 (0.6)	2 (1.2)	0
Thrombocytopenia	10 (3.0)	4 (1.2)	0	2 (1.2)	0	0
Thrombocytosis	2 (0.6)	0	0	0	1 (0.6)	0
Cardiac disorders	8 (2.4)	1 (0.3)	1 (0.3)	4 (2.5)	2 (1.2)	0
Atrial tachycardia	1 (0.3)	0	0	0	1 (0.6)	0
Cardiac failure	0	1 (0.3)	0	0	0	0
Low cardiac output syndrome	0	0	1 (0.3)	0	0	0
Pericardial haemorrhage	0	0	1 (0.3)	0	0	0
Supraventricular tachycardia	0	0	0	0	1 (0.6)	0
Congenital, familial and genetic disorders	3 (0.9)	0	0	0	1 (0.6)	0
Muscular dystrophy	0	0	0	0	1 (0.6)	0
Eye disorders	18 (5.5)	0	0	7 (4.3)	0	0
Gastrointestinal disorders	101 (30.7)	9 (2.7)	0	44 (27.2)	1 (0.6)	0
Abdominal pain	17 (5.2)	2 (0.6)	0	8 (4.9)	1 (0.6)	0
Constipation	10 (3.0)	0	0	12 (7.4)	0	0
Diarrhoea	22 (6.7)	2 (0.6)	0	9 (5.6)	0	0
Faecaloma	0	1 (0.3)	0	1 (0.6)	0	0
Gingival bleeding	12 (3.6)	1 (0.3)	0	1 (0.6)	0	0
Haematochezia	0	1 (0.3)	0	1 (0.6)	0	0
Intestinal dilatation	0	1 (0.3)	0	0	0	0
Nausea	21 (6.4)	0	0	7 (4.3)	0	0
Small intestinal obstruction	0	1 (0.3)	0	1 (0.6)	0	0
Vomiting	31 (9.4)	4 (1.2)	0	13 (8.0)	0	0
General disorders and administration site conditions	74 (22.5)	7 (2.1)	0	51 (31.5)	1 (0.6)	0
Catheter site haematoma	0	1 (0.3)	0	0	0	0
Catheter site rash	0	0	0	0	1 (0.6)	0
Chest pain	14 (4.3)	1 (0.3)	0	6 (3.7)	0	0
Fatigue	18 (5.5)	2 (0.6)	0	6 (3.7)	0	0
Mucosal inflammation	3 (0.9)	1 (0.3)	0	0	0	0
Pain	3 (0.9)	1 (0.3)	0	0	0	0

Peripheral swelling	4 (1.2)	1 (0.3)	0	2 (1.2)	0	0
Pyrexia	35 (10.6)	0	0	13 (8.0)	0	0
Hepatobiliary disorders	5 (1.5)	2 (0.6)	0	3 (1.9)	0	0
Cholecystitis	0	1 (0.3)	0	0	0	0
Drug-induced liver injury	0	1 (0.3)	0	0	0	0
Hepatic function abnormal	1 (0.3)	1 (0.3)	0	0	0	0
Immune system disorders	8 (2.4)	0	0	0	1 (0.6)	0
Anaphylactic reaction	0	0	0	0	1 (0.6)	0
Infections and infestations	110 (33.4)	5 (1.5)	1 (0.3)	44 (27.2)	5 (3.1)	0
Bacteraemia	0	1 (0.3)	0	0	0	0
Bacterial sepsis	0	0	0	0	1 (0.6)	0
Bronchiolitis	1 (0.3)	1 (0.3)	0	0	0	0
Candida infection	1 (0.3)	1 (0.3)	0	0	0	0
Gastroenteritis viral	2 (0.6)	1 (0.3)	0	0	0	0
Infected dermal cyst	0	0	0	0	1 (0.6)	0
Nasopharyngitis	25 (7.6)	0	0	8 (4.9)	0	0
Oral herpes	4 (1.2)	1 (0.3)	0	0	0	0
Osteomyelitis	2 (0.6)	1 (0.3)	0	0	0	0
Peritonitis	0	0	0	0	1 (0.6)	0
Pneumonia	0	1 (0.3)	0	1 (0.6)	0	0
Pneumonia viral	0	0	0	0	1 (0.6)	0
Sepsis	0	0	1 (0.3)	0	0	0
Tonsillitis streptococcal	0	0	0	0	1 (0.6)	0
Injury, poisoning and procedural complications	74 (22.5)	4 (1.2)	0	27 (16.7)	3 (1.9)	1 (0.6)
Contusion	14 (4.3)	0	0	10 (6.2)	0	0
Joint dislocation	0	1 (0.3)	0	0	0	0
Post lumbar puncture syndrome	0	1 (0.3)	0	0	0	0
Postoperative thoracic procedure complication	0	0	0	0	1 (0.6)	0
Procedural haemorrhage	1 (0.3)	1 (0.3)	0	0	0	0
Skin abrasion	3 (0.9)	1 (0.3)	0	1 (0.6)	0	0
Stoma site erythema	0	1 (0.3)	0	0	0	0
Subdural haemorrhage	0	0	0	0	0	1 (0.6)
Toxicity to various agents	0	1 (0.3)	0	0	0	0
Transfusion reaction	2 (0.6)	0	0	0	1 (0.6)	0
Traumatic haemothorax	0	0	0	0	1 (0.6)	0
Investigations	27 (8.2)	9 (2.7)	1 (0.3)	17 (10.5)	5 (3.1)	0
Alanine aminotransferase increased	4 (1.2)	3 (0.9)	0	4 (2.5)	3 (1.9)	0
Aspartate aminotransferase increased	5 (1.5)	1 (0.3)	0	2 (1.2)	0	0
Blood bilirubin increased	5 (1.5)	1 (0.3)	0	1 (0.6)	0	0
C-reactive protein increased	1 (0.3)	1 (0.3)	0	0	0	0
Full blood count abnormal	0	0	0	0	1 (0.6)	0
Gastrointestinal stoma output decreased	0	1 (0.3)	0	0	0	0
Hepatic enzyme increased	2 (0.6)	1 (0.3)	1 (0.3)	0	0	0

Oxygen saturation decreased	0	0	0	1 (0.6)	1 (0.6)	0
Platelet count decreased	6 (1.8)	3 (0.9)	0	2 (1.2)	0	0
Transaminases increased	0	1 (0.3)	0	1 (0.6)	0	0
Metabolism and nutrition disorders	26 (7.9)	1 (0.3)	0	7 (4.3)	0	0
Acidosis	0	1 (0.3)	0	0	0	0
Musculoskeletal and connective tissue disorders	52 (15.8)	4 (1.2)	0	19 (11.7)	0	0
Back pain	10 (3.0)	2 (0.6)	0	2 (1.2)	0	0
Costochondritis	0	1 (0.3)	0	2 (1.2)	0	0
Pain in extremity	22 (6.7)	2 (0.6)	0	8 (4.9)	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (0.3)	0	0	1 (0.6)	2 (1.2)	0
Craniopharyngioma	0	0	0	0	1 (0.6)	0
Lymphangioma	0	0	0	0	1 (0.6)	0
Nervous system disorders	78 (23.7)	5 (1.5)	0	34 (21.0)	4 (2.5)	0
Encephalitis autoimmune	0	0	0	0	1 (0.6)	0
Epilepsy	0	1 (0.3)	0	0	0	0
Headache	56 (17.0)	1 (0.3)	0	22 (13.6)	2 (1.2)	0
Intercostal neuralgia	0	0	0	0	1 (0.6)	0
Migraine	1 (0.3)	1 (0.3)	0	0	0	0
Neuralgia	0	1 (0.3)	0	0	0	0
Sciatic nerve neuropathy	0	1 (0.3)	0	0	0	0
Product issues	3 (0.9)	0	0	1 (0.6)	1 (0.6)	0
Device leakage	0	0	0	0	1 (0.6)	0
Renal and urinary disorders	13 (4.0)	6 (1.8)	0	5 (3.1)	0	0
Acute kidney injury	2 (0.6)	1 (0.3)	0	1 (0.6)	0	0
IgA nephropathy	0	1 (0.3)	0	0	0	0
Nephrotic syndrome	0	1 (0.3)	0	0	0	0
Renal impairment	0	1 (0.3)	0	0	0	0
Urinary bladder haemorrhage	2 (0.6)	1 (0.3)	0	0	0	0
Urinary retention	1 (0.3)	1 (0.3)	0	0	0	0
Reproductive system and breast disorders	27 (8.2)	2 (0.6)	0	13 (8.0)	0	0
Menorrhagia	23 (7.0)	0	0	5 (3.1)	0	0
Ovarian cyst	0	1 (0.3)	0	0	0	0
Vaginal haemorrhage	3 (0.9)	1 (0.3)	0	2 (1.2)	0	0
Respiratory, thoracic and mediastinal disorders	78 (23.7)	2 (0.6)	1 (0.3)	33 (20.4)	1 (0.6)	0
Bronchopneumopathy	0	1 (0.3)	0	0	0	0
Cough	16 (4.9)	0	0	10 (6.2)	0	0
Epistaxis	38 (11.6)	0	0	18 (11.1)	0	0
Pleural effusion	1 (0.3)	1 (0.3)	0	0	1 (0.6)	0
Respiratory failure	0	0	1 (0.3)	0	0	0
Skin and subcutaneous tissue disorders	61 (18.5)	0	0	25 (15.4)	1 (0.6)	0
Rash	14 (4.3)	0	0	3 (1.9)	1 (0.6)	0
Surgical and medical procedures	10 (3.0)	1 (0.3)	0	4 (2.5)	1 (0.6)	0

Colostomy	0	1 (0.3)	0	0	1 (0.6)	0
Faecal disimpaction	0	1 (0.3)	0	0	0	0
Vascular disorders	12 (3.6)	2 (0.6)	0	4 (2.5)	0	0
Haemorrhage	0	1 (0.3)	0	0	0	0
Post thrombotic syndrome	1 (0.3)	1 (0.3)	0	0	0	0

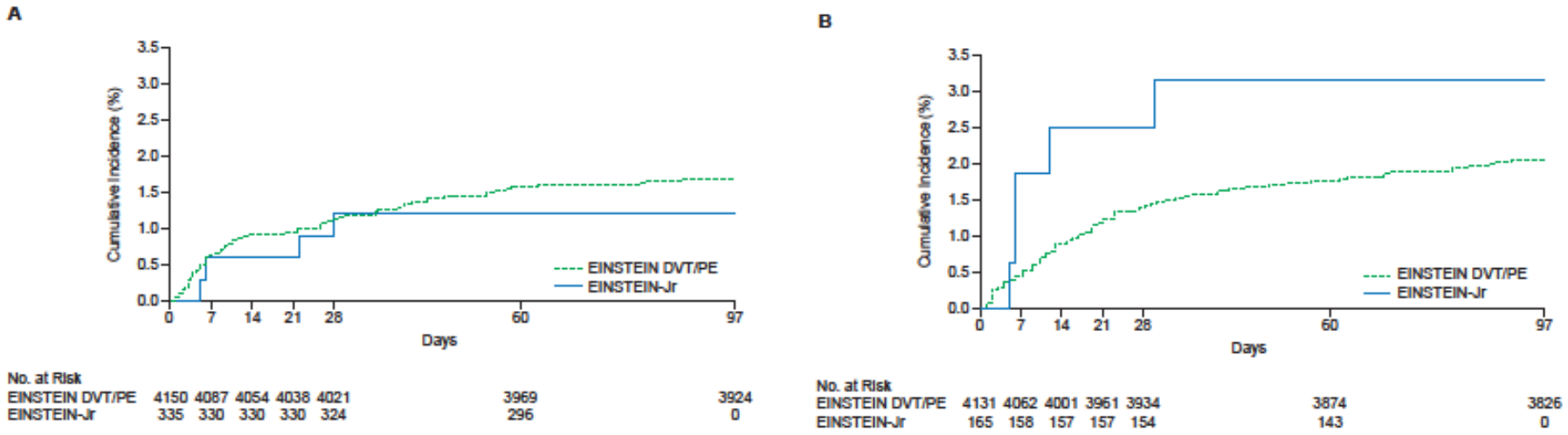
Data are n (%) of events (as defined by the Medical Dictionary for Regulatory Activities). Data shown for all randomized patients who received at least one dose of treatment. All grade 3 or worse events are shown, but grade 1–2 events are only shown if there were grade 3 or worse events. Grade 1–2 events would also have been shown had they occurred in at least 5% of children. A single grade 5 event occurred (i.e., myxofibrosarcoma in the rivaroxaban group).

Table S7. Recurrent VTE, major bleeding and mortality at 3 months in EINSTEIN-Jr. (children) compared to the pooled EINSTEIN-DVT and EINSTEIN-PE results (adults).[1-3]

	Rivaroxaban		Comparator		Absolute risk difference		Hazard ratio	
	n/N	% (95% CI)	n/N	% (95% CI)	%	(95% CI)		(95% CI)
Recurrent VTE								
EINSTEIN-Jr.	4/335	1.2 (0.4 - 3.0)	5/165	3.0 (1.2 – 6.6)	-1.8	(-6.0 - 0.6)	0.40	(0.11 - 1.41)
EINSTEIN DVT/PE	69/4150	1.7 (1.3 - 2.1)	82/4131	2.0 (1.6 - 2.5)	-0.3	(-0.9 - 0.3)	0.82	(0.60 - 1.13)
Major bleeding								
EINSTEIN-Jr.	0/328	0.0 (0.0 - 1.1)	2/164	1.2 (0.1 - 4.3)	-1.2	(-2.9 - 0.5)	-	
EINSTEIN DVT/PE	28/4130	0.7 (0.5 - 1.0)	49/4116	1.2 (0.9 - 1.6)	-0.5	(-0.9 - -0.1)	0.55	(0.35 - 0.88)
Major or CRNM bleeding								
EINSTEIN-Jr.	10/329	3.0 (1.6 - 5.5)	3/162	1.9 (0.5 – 5.3)	1.2	(-2.8 - 4.0)	1.58	(0.51 - 6.27)
EINSTEIN DVT/PE	286/4130	6.9 (6.2 - 7.7)	287/4116	7.0 (6.2 - 7.8)	0.0	(-1.1 - 1.0)	0.98	(0.83 - 1.16)
Net clinical benefit*								
EINSTEIN-Jr.	4/335	1.2 (0.4 - 3.0)	7/165	4.2 (2.0 - 8.4)	-3.0	(-7.5- 0.3)	0.30	(0.08 - 0.93)
EINSTEIN DVT/PE	100/4150	2.4 (2.0 - 2.9)	131/4131	3.2 (2.7 - 3.8)	-0.8	(-1.5 - -0.1)	0.74	(0.57 - 0.96)
Mortality								
EINSTEIN-Jr.	1/335**	0.3 (0.1 - 2.2)	0/165	0.0 (0.0 - 2.2)	0.3			
EINSTEIN DVT/PE	53/4150	1.3 (1.0 - 1.7)	61/4131	1.5 (1.1 - 1.9)	-0.2	(-0.7 - 0.3)	0.81	(0.56 - 1.17)

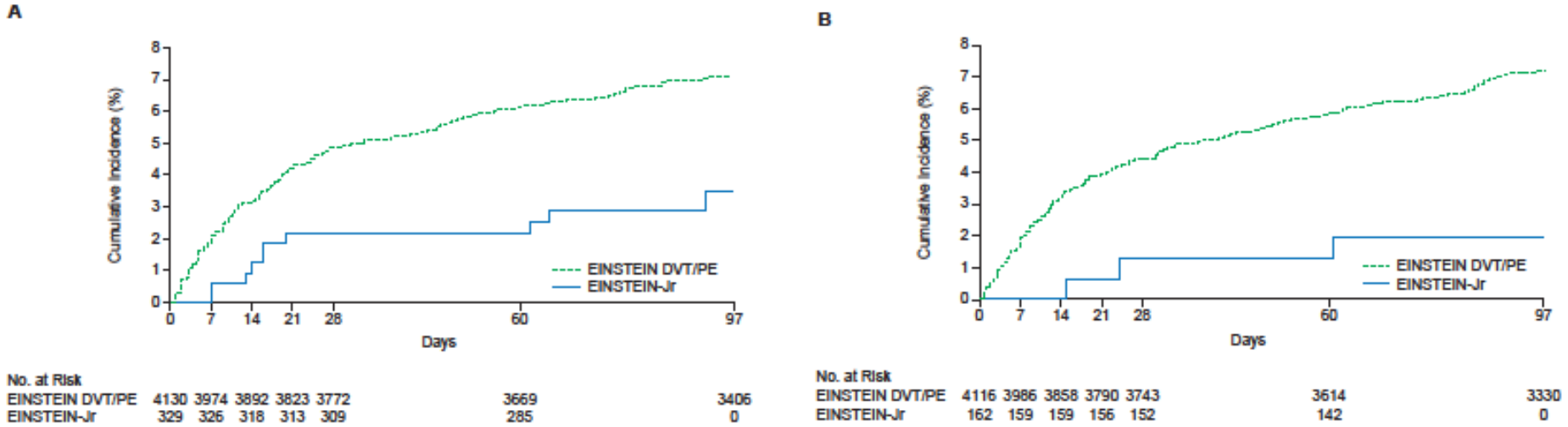
VTE denotes venous thromboembolism, DVT deep vein thrombosis, PE pulmonary embolism, CRNM clinically relevant nonmajor. *composite of recurrent VTE and major bleeding. **Death related to progression of cancer.

Figure S1. Kaplan–Meier Rates of Recurrent Venous Thromboembolism with Rivaroxaban and Standard Anticoagulation in EINSTEIN-Jr. in children as compared with those observed in the EINSTEIN DVT/PE Program in Adults.



Kaplan–Meier curves are shown for the first event of recurrent venous thromboembolism in EINSTEIN-Jr. during the 3-month main study treatment period (or the 1-month main study treatment period in children younger than 2 years who presented with catheter-related VTE). Results are compared with those observed in the EINSTEIN DVT and PE program in adults.[1-3] Results are presented separately for rivaroxaban (Panel A) and for standard anticoagulation (Panel B).

Figure S2. Kaplan–Meier Rates of Major or Clinically relevant Nonmajor bleeding with Rivaroxaban and Standard Anticoagulation in EINSTEIN-Jr. as compared with those observed in the EINSTEIN DVT/PE Program in Adults.



Kaplan–Meier curves are shown for the first episode of major or clinically relevant nonmajor bleeding in EINSTEIN-Jr. during the 3-month main study treatment period (or the 1-month main study treatment period in children younger than 2 years who presented with catheter-related VTE) in the safety population (i.e. between the administration of the first dose of study drug and 48 hours after the administration of the last dose). Rates are compared with those observed in the EINSTEIN DVT/PE program in adults.[1-3] Results are presented separately for rivaroxaban (Panel A) and for standard anticoagulation (Panel B).

References

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3. Prins MH, Lensing AW, Bauersachs R, et al. Oral rivaroxaban versus standard therapy for the treatment of symptomatic venous thromboembolism: a pooled analysis of the EINSTEIN-DVT and PE randomized studies. Thromb J 2013;11:21.

Data Sharing Statement

Male C, et al. Rivaroxaban for the treatment of acute venous thromboembolism in children. DOI: xxxx.

Question	Authors' Response
Will the data collected for your study be made available to others?	Yes
Would you like to offer context for your decision?	Data will be shared with academic researchers upon reasonable request
Which data?	Individual participant data that underlie the results reported in the main manuscript, after de-identification (main text, main tables, main figure).
Additional information about data	Data points reported in the main manuscript will be made available.
How or where can the data be obtained?	Anthonie.lensing@bayer.com
When will data availability begin?	Once all planned analyses have been completed and published or presented (if not planned to be published).
When will data availability end?	3 years from the date of publication.
Will any supporting documents be available?	—
Which supporting documents?	Analytic/Statistical code.
Additional information about supporting documents	—
How or where can supporting documents be obtained?	Anthonie.lensing@bayer.com
When will supporting documents availability begin?	Once all planned analyses have been completed and published or presented (if not planned to be published).
When will supporting documents availability end?	3 years from the date of publication.
To whom will data be available?	Proposed study is to be submitted to Anthonie Lensing for consideration by the relevant custodian.
For what type of analysis or purpose?	—
By what mechanism?	Requester will be required to enter into a Data Sharing Agreement with Bayer AG which meets Bayer's data sharing requirements.
Any other restrictions?	N/A
Additional information	—