Rivaroxaban for the treatment of acute venous thromboembolism in children

Male C *et al*, Presented at ISTH 2019; Oral presentation LB 01.5

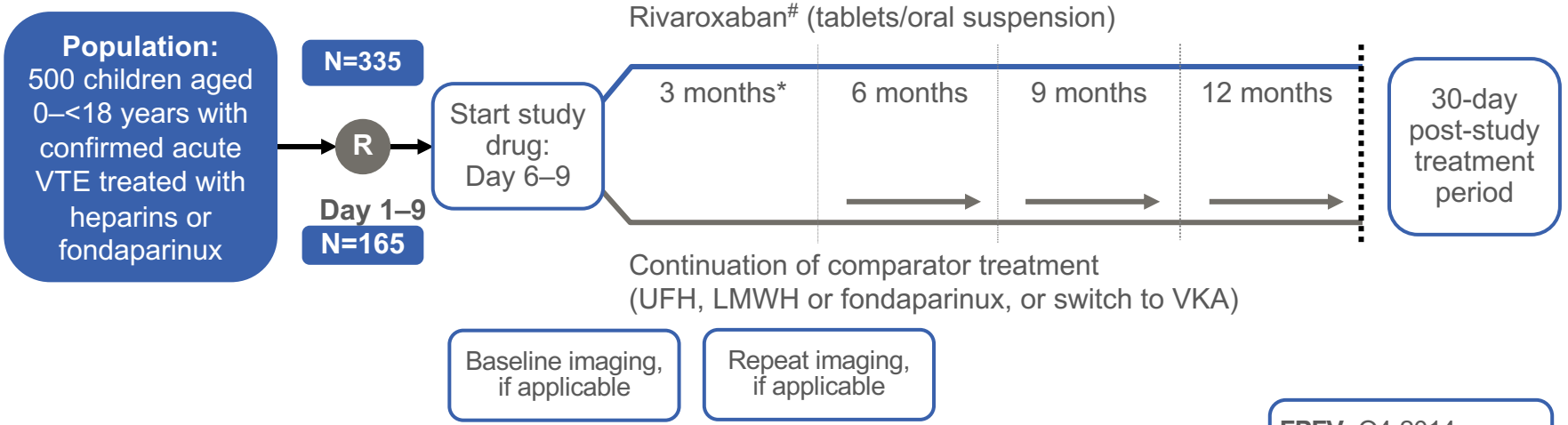
Rationale

- In children, an oral anticoagulant treatment that does not require daily subcutaneous/intravenous injections and regular blood sampling for coagulation monitoring is desirable
- In the absence of dedicated phase III clinical studies, current paediatric dosing recommendations have been developed from adult guidelines based on a Grade 2 level of evidence[1]
- There is a medical need for additional clinical studies that address the efficacy and safety of anticoagulant treatment in children
- In adults, rivaroxaban demonstrated a favourable benefit–risk profile compared with enoxaparin/VKA in the phase III EINSTEIN DVT and EINSTEIN PE studies[2]

1. Monagle P *et al*, *Chest* 2012;141:e737S–e801S; 2. Prins MH *et al*, *Thromb J* 2013;11:21

EINSTEIN JUNIOR Phase III: study design

Objective: Open-label, randomized (2:1) trial to assess the efficacy and safety of bodyweight-adjusted rivaroxaban in a 20 mg-equivalent dose compared with the standard of care in children with acute VTE



FPFV: Q4-2014
LPLV: Q1-2019

*Children aged <2 years with catheter-related VTE: extension with maximum two blocks of 1 month, decision to stop or continue treatment made after each 3- or 1-month period; #bodyweight-adjusted rivaroxaban dose equivalent to 20 mg od adult dose

Lensing AWA *et al*, *Thromb J* 2018;16:34; www.clinicaltrials.gov/ct2/show/NCT02234843

EINSTEIN JUNIOR

Rivaroxaban Dose Regimens for Children*

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

Body weight (kg)		Formulation	Regimen			Total daily dose
Min.	Max.		od	bid	tid	
2.6	<3	Oral suspension			0.8 mg	2.4 mg
3	<4	Oral suspension			0.9 mg	2.7 mg
4	<5	Oral suspension			1.4 mg	4.2 mg
5	<6	Oral suspension			1.6 mg	4.8 mg
6	<7	Oral suspension			1.6 mg	4.8 mg
7	<8	Oral suspension			1.8 mg	5.4 mg
8	<9	Oral suspension			2.4 mg	7.2 mg
9	<10	Oral suspension			2.8 mg	8.4 mg
10	<12	Oral suspension			3.0 mg	9 mg
12	<30	Oral suspension		5 mg		10 mg
30	<50	Tablet/oral suspension	15 mg			15 mg
≥50		Tablet/oral suspension	20 mg			20 mg

OD denotes once daily, BID twice daily, and TID thrice daily. *Based on clinical data from phase I/II and modelling

Male C, et al. Lancet Haematol. 2020 Jan;7(1):e18-e27.

EINSTEIN JUNIOR Phase III: Study Details

Study outcomes

- **Primary efficacy outcome:** Fatal or symptomatic non-fatal recurrent VTE
- **Principal safety outcome:** Major or clinically relevant non-major bleeding
- **Other predefined outcomes:**
  - Composite of symptomatic recurrent VTE and asymptomatic deterioration on repeat imaging (secondary efficacy outcome)

Inclusion criteria*

- Children aged 0–<18 years
- Confirmed VTE
- Started initial treatment with therapeutic doses of UFH, LMWH or fondaparinux

Main exclusion criteria#

- High risk for bleeding
- Severe renal impairment
- Hepatic disease associated with coagulopathy
- Platelet count <50×10^9/l
- Systolic/diastolic blood pressure >95th age percentile
- Life expectancy <3 months

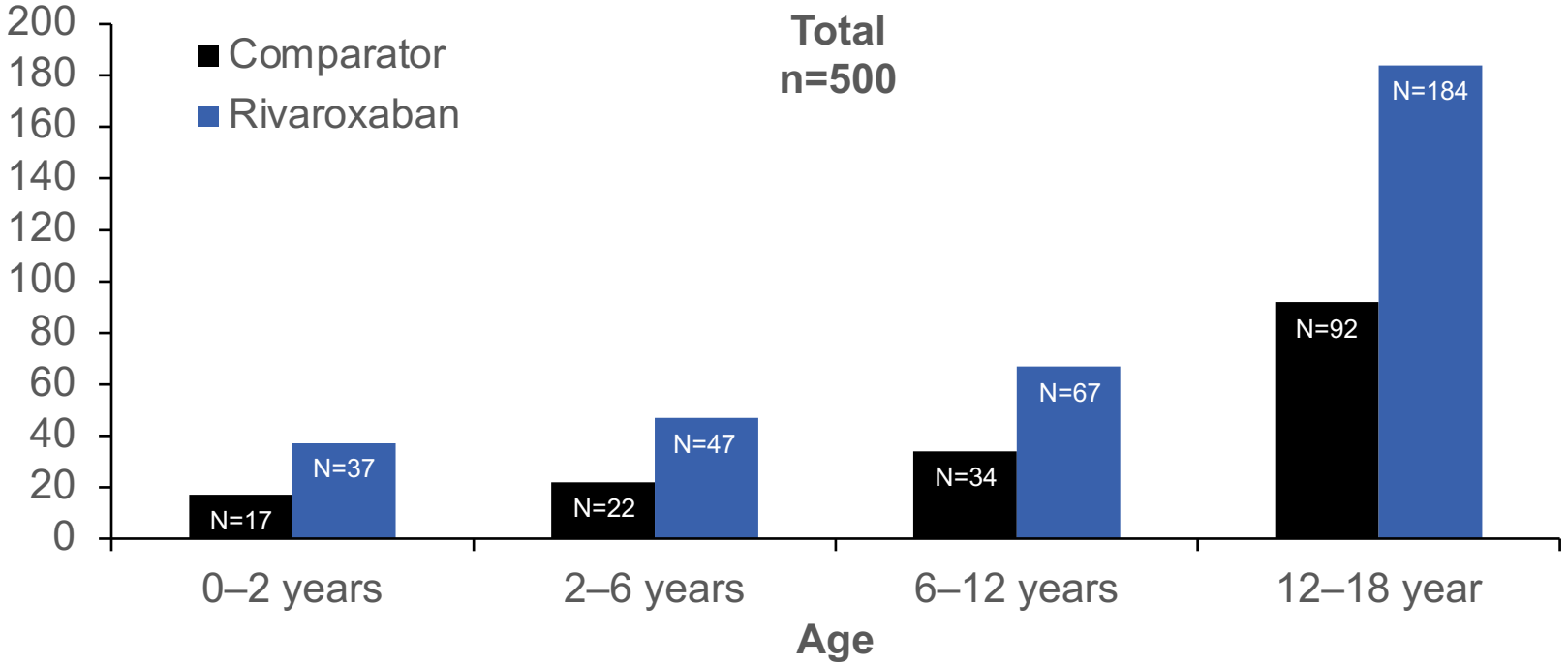
*Including but not limited to; #any other exclusion criteria in conjunction with hypersensitivity or any other contraindication listed in the local labeling for the comparator or rivaroxaban

Lensing AWA *et al*, *Thromb J* 2018;16:34; Male C *et al*, Presented at ISTH 2019; Oral presentation LB 01.5

EINSTEIN JUNIOR

EINSTEIN JUNIOR Phase III Included Children From 0-18 Years Old With Venous Thromboembolism

Patient Distribution According to Age



Male C, et al. Lancet Haematol. 2020 Jan;7(1):e18-e27.

EINSTEIN JUNIOR Phase III Patients Clinical Characteristics and Venous Thromboembolism Risk Factor Profiles

	Rivaroxaban N=335	Comparator N=165
Male sex – n (%)	175 (52)	80 (48)
Bodyweight – range (kg)	2.7 - 135	3.0 - 160
Index VTE location, n (%)		
Cerebral vein or sinus thrombosis	74 (22)	43 (26)
Catheter related VTE	90 (27)	37 (22)
Non-catheter-related VTE	171 (51)	85 (52)
Symptomatic VTE, n (%)	271 (81)	136 (82)
Cause of index VTE, n (%)		
Persistent risk factor	62 (19)	25 (15)
Transient risk factor	151 (45)	85 (52)
Persistent and transient risk factor	90 (27)	25 (15)
Unprovoked	31 (9)	25 (15)
Risk factor, n (%)		
Active cancer	40 (12)	16 (10)
Major organ disease	63 (19)	20 (12)
Major surgery or trauma	78 (23)	42 (25)
Major infectious disease	96 (29)	46 (28)
Use of estrogens or progestins	53 (16)	24 (15)

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EINSTEIN JUNIOR Phase III: Efficacy And Safety Results

Efficacy And Safety Study Outcomes

	Rivaroxaban n (%)	Comparator n (%)	Hazard ratio	95% CI
Intention-to-treat population	*335*	*165*		
Symptomatic recurrent VTE, n (%)	4 (1)	5 (3)	0.40	0.11–1.41
Symptomatic recurrent VTE or deterioration on repeat imaging, n (%)	5 (1)	6 (4)	0.41	0.12–1.36
Net clinical benefit[#], n (%)	4 (1)	7 (4)	0.30	0.08–0.93
Mortality*, n (%)	1 (<1)	0 (0)	–	
Safety population	*329*	*162*		
Major bleeding, n (%)	0 (0)	2 (1)	–	
Major or CRNM bleeding, n (%)	10 (3)	3 (2)	1.58	0.51–6.27

[#]first occurrence of recurrent VTE or major bleeding; *only cancer-related occurred
CRNM, clinically relevant non-major bleeding

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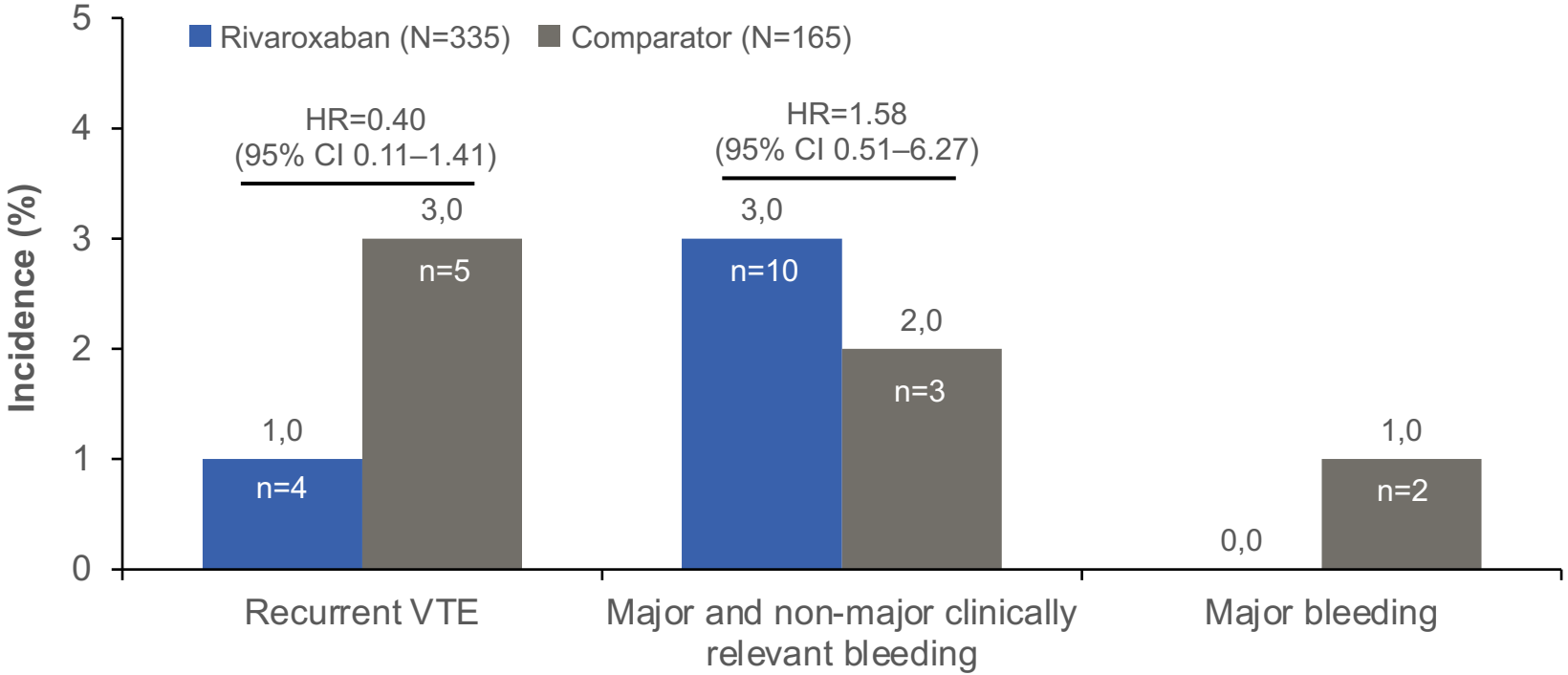
EINSTEIN JUNIOR Phase III: Efficacy And Safety Results



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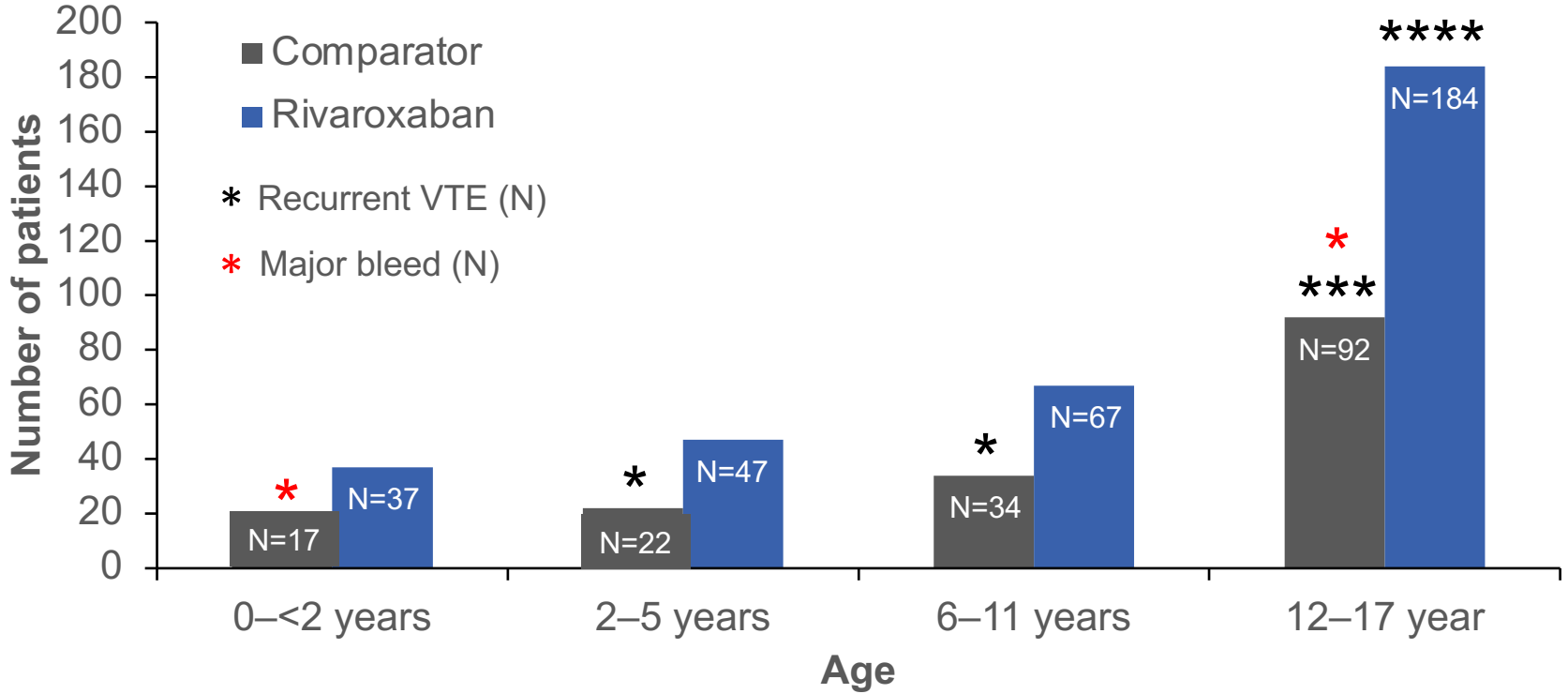
EINSTEIN JUNIOR Phase III: Recurrent VTE and Major Bleeding in Children With VTE in Relation to Age



Male C *et al, Lancet Haematol* 2020;7(1):e18-e27

EINSTEIN JUNIOR Phase III: Change in Thrombotic Burden on Repeat Imaging Compared to the Index Event

	Rivaroxaban N=335	Comparator N=165
Normalized	128 (38%)	43 (26%)
Improved	129 (39%)	75 (45%)
Uncertain	57 (17%)	28 (17%)
No relevant change	16 (5%)	13 (8%)
Deteriorated	1 (<1%)	1 (<1%)
Symptomatic recurrent VTE	4 (1%)	5 (3%)

- van Elteren test for comparison of ordered categories: p=0.012
- Odds ratio for normalization: 1.71 (95% CI 1.12–2.59)

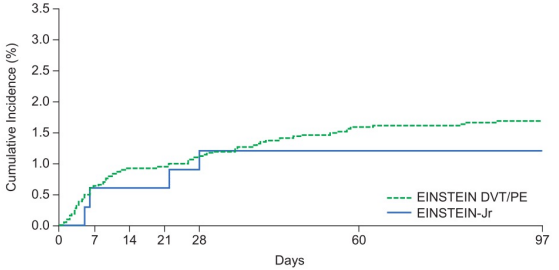
Male C, et al. Lancet Haematol. 2020 Jan;7(1):e18-e27.

Rivaroxaban Demonstrated Consistent Efficacy and Safety Results in Children and Adults

Rivaroxaban

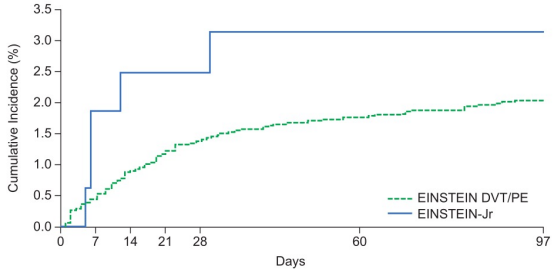
Comparator

Recurrent VTE



No. at Risk

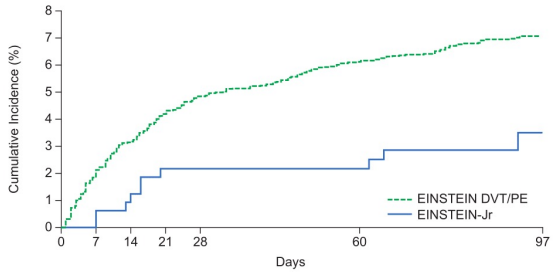
EINSTEIN DVT/PE	4150	4087	4054	4038	4021	3969	3924
EINSTEIN-Jr	335	330	330	330	324	296	0



No. at Risk

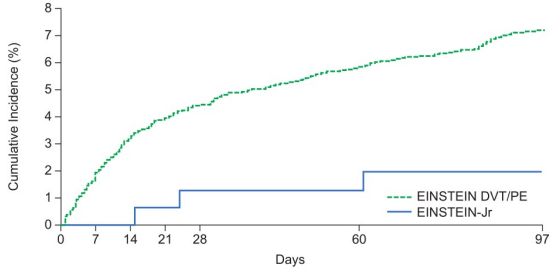
EINSTEIN DVT/PE	4131	4062	4001	3961	3934	3874	3826
EINSTEIN-Jr	165	158	157	157	154	143	0

Major or clinically relevant non-major bleeding



No. at Risk

EINSTEIN DVT/PE	4130	3974	3892	3823	3772	3669	3406
EINSTEIN-Jr	329	326	318	313	309	285	0



No. at Risk

EINSTEIN DVT/PE	4116	3986	3858	3790	3743	3614	3330
EINSTEIN-Jr	162	159	159	156	152	142	0

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EINSTEIN JUNIOR Phase III - Summary

- EINSTEIN JUNIOR assessed the efficacy and safety of bodyweight-adjusted rivaroxaban in a 20 mg-equivalent dose compared with the standard of care in children with acute VTE[1]
  - Symptomatic recurrent venous thromboembolism rates were low with rivaroxaban and numerically lower vs standard of care
  - Clinically relevant bleedings were infrequent in both arms and no major bleeding event was observed in the rivaroxaban group

- The results of EINSTEIN JUNIOR were comparable with previous trials in adults and further confirm the benefit–risk profile of rivaroxaban for the treatment of VTE in challenging patient populations[1–4]

1. Male C *et al*, Presented at ISTH 2019; Oral presentation LB 01.5; 2. Prins MH *et al*, *Thromb J* 2013;11:21;
3. Bauersachs RM *et al*, *Thromb J* 2014;12; 4. Prins MH *et al*, *Lancet Haematol* 2014;1:e37–e46

EINSTEIN JUNIOR Phase III - Conclusions

Goals achieved for EINSTEIN-Jr. phase III

- Reconfirm pediatric exposure is in the adult target exposure range
  - Tablets ✓
  - Oral suspension ✓
- Confirm clinical course of VTE is comparable in children and adults treated with rivaroxaban
  - Incidence rates recurrent VTE ✓
  - Major bleeding ✓
  - Net clinical benefit ✓
  - Mortality ✓
- Confirm relative efficacy/safety is comparable to those observed in adults
  - Efficacy ✓
  - Safety ✓
- Additional efficacy confirmation: reduced clot burden on repeat imaging ✓

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