CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

Clinical Studies

NDA #:	215859
Supplement #:	0001
Drug Name:	Xarelto (Rivaroxaban)
Indication(s):	1) Venous thromboembolism (VTE) treatment and reduction of risk of VTE recurrence in pediatric patients (<18y) 2) Thromboprophylaxis in pediatric patients (2y to 8y) with congenital heart disease after the Fontan procedure
Applicant:	Janssen Pharmaceuticals Inc.
Receipt Date:	Jun 22, 2021
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Biometrics Division:	Division of Biometrics IX
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EDR Location:	\\CDSESUB1\evsprod\NDA215859\0001

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1. EXECUTIVE SUMMARY

Janssen Research & Development, LLC (JRD), on behalf of Janssen Pharmaceuticals, Inc., submitted a new drug application (NDA) for Xarelto (rivaroxaban) oral suspension to support inclusion of the proposed new indications in the prescribing information. Xarelto was initially approved for the treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE) in patients undergoing hip or knee replacement surgery on July 1, 2011, and it was approved for the prophylaxis of venous thromboembolism (VTE) in adult patients on October 11, 2019. The current submission is for an oral suspension dosage form with two new indications for pediatric patients in responding to the FDA's comments to the Sponsor's exclusivity request: (1) for treatment of VTE and reduction in the risk of recurrent VTE in pediatric patients from birth to less than 18 years, and (2) for thromboprophylaxis in pediatric patients two years and older with congenital heart disease (CHD) after the Fontan procedure.

This NDA includes two phase III clinical studies: Study 14372 (EINSTEIN Jr) and Study CHD3001 (UNIVERSE). EINSTEIN Jr was an open-label, active-controlled, randomized multicenter, multinational study in pediatric subjects (birth to <18 years) with acute VTE to evaluate the efficacy and safety of rivaroxaban compared to standard of care (SoC). A total of 520 children were screened in 109 study centers in 28 countries and the study was conducted from November 13, 2014 to January 30, 2019. UNIVERSE was a prospective, open-label, active-controlled, multicenter, multinational study in pediatric subjects (2-8 years) with single-ventricle physiology who had completed the Fontan procedure within 4 months prior to enrollment to evaluate the PK and PK/PD profiles, safety and efficacy of rivaroxaban compared to Aspirin. A total of 112 subjects were enrolled in this study in 10 countries including the US and the study was conducted from November 17, 2016 to July 16, 2020.

Although the two studies were not powered adequately for achieving statistical significance, the rivaroxaban has been shown with promising efficacy findings as a treatment for VTE and CHD thromboprophylaxis.

In the EINSTEIN Jr study, the primary efficacy outcome (VTE recurrence) had a lower incidence rate in the rivaroxaban group (1.2%) than in the comparator group (3.0%) with a risk difference of -1.8% (95% CI: -6%, 0.64%) during the main treatment period. In the UNIVERSE study, the primary efficacy outcome (any thrombotic events) had a lower incidence rate in the rivaroxaban group (1.6%) than in the Aspirin group (8.8%) with a risk difference of -7.3% (95% CI: -22%, 1.1%). For safety outcomes, results of both studies were in general comparable between treatment groups. In the EINSTEIN Jr study, the principal safety outcome (composite of overt major and clinically relevant non-major bleeding) had an incidence rate of 3.0% in the rivaroxaban group and an incidence rate of 1.9% in the comparator group (risk difference = 1.2%; 95% CI: -2.8%, 4.0%). In the UNIVERSE study, the primary safety outcome of major bleeding had an incidence rate of 1.6% in the rivaroxaban Part B group and 0% in the Aspirin group (risk difference = 1.6%; 95% CI: -9.9%, 8.4%).

2. REGULATORY BACKGROUND

This NDA (NDA 215859) serves as the Sponsor's response to a Written Request (WR) for pediatric studies of rivaroxaban (Xarelto) for the purpose of pediatric exclusivity determination, and to fulfill the Pediatric Research Equity Act (PREA) Post-marketing Requirements (PMRs) under NDA 022406.

On 30 August 2012, the VTE treatment and reduction in recurrence of VTE program, consisting of 6 studies (PMRs 1966-1, 1966-2, 1966-3, 1966-4, 1966-5, and 1966-6), was initially proposed as basis for requesting a WR.

On 29 May 2015, at FDA's request, the proposed pediatric study request was updated to include a thromboprophylaxis program in pediatric subjects with CHD post-Fontan procedure.

On 04 August 2016, a Type C Meeting was held in which FDA agreed with the proposed use of granules for oral suspension formulation in the Phase 3 clinical studies in the VTE treatment and thromboprophylaxis program, and bridging strategy to support the introduction of the granules for oral suspension in the Phase 3 studies.

On 08 June 2017, WR for Pediatric Studies was issued by FDA. The WR included all PREA PMR studies [PMR 1966-2 (WR study 1), 1966-3 (WR study 2), 1966-4 & 1966-5 (WR study 4), and 1966-6 (WR study 3), UNIVERSE study (WR study 5) and excludes PMR 1966-1 (study report was submitted prior to obtaining the WR)].

On 29 November 2017, a Type C Meeting was held in which FDA agreed on the alignment of pediatric clinical development studies between WR and PREA PMRs.

On 23 March 2018, the WR Amendment 1 was issued by FDA to reflect the alignment of changes between WR and PREA PMR studies per agreement reached at the 29 November 2017 Type C meeting.

3. DATA SOURCES AND SUBMISSION LINKS

Data were provided electronically in standard data format. The data submitted were considered acceptable by the FDA. SAS programs used to create key efficacy and safety outputs for the two studies were submitted along with the data.

The links to the data of the two studies are listed below.

EINSTEIN Jr	\\CDSESUB1\evsprod\NDA215859\0001\m5\datasets\14372
UNIVERSE	\\CDSESUB1\evsprod\NDA215859\0001\m5\datasets\39039090chd3001

On 3 August 2021, the FDA sent an Information Request (IR) regarding the interpretation of the benefit-risk forest plot for the EINSTEIN Jr study. The content of the IR and the response of the Sponsor can be found at: \\CDSESUB1\evsprod\NDA215859\0005\m1\us

On 23 November 2021, the FDA sent an IR to the Sponsor regarding the discrepancy in the calculation for the confidence intervals of the risk differences for the UNIVERSE study. The content of the IR and the response of the Sponsor can be found at: \\CDSESUB1\evsprod\NDA215859\0036\m1\us

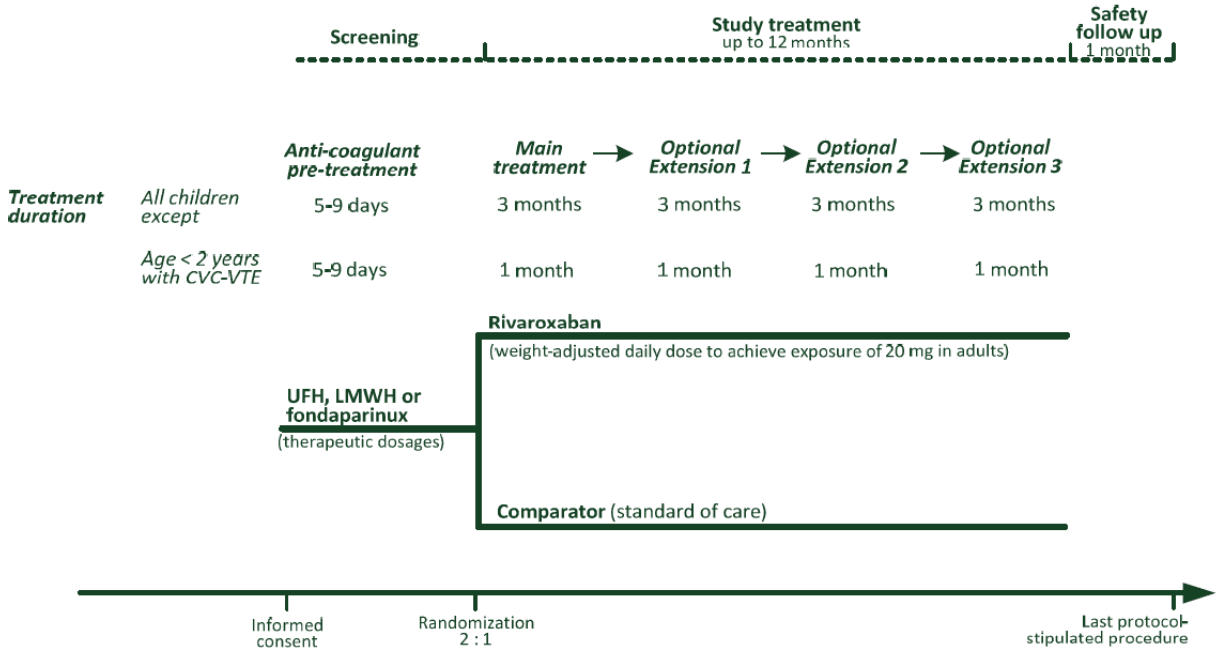
4. STATISTICAL EVALUATION

4.1 Phase III 14372 (EINSTEIN Jr) Study

4.1.1 Study Design

EINSTEIN Jr Phase 3 was an open-label, active-controlled, randomized multicenter, multinational study in pediatric subjects (birth to <18 years) with acute VTE to evaluate the efficacy and safety of a body weight-adjusted rivaroxaban regimen administered either as tablets or granules for oral suspension, compared to SoC in pediatric subjects. The design overview is depicted in Figure 1 below. Enrollment was staggered by consecutive age cohorts: cohort 1 (12 to <18 years), cohort 2 (6 to <12 years), cohort 3 (2 to <6 years), and cohort 4 (birth to <2 years). Eligible subjects with confirmed acute VTE were randomized (2:1) to receive either rivaroxaban (body weight-adjusted dose targeting the exposure range obtained in adults who received 20 mg once daily for the treatment of DVT) or SoC, i.e., unfractionated heparin (UFH), low-molecular-weight heparin (LMWH), fondaparinux with or without vitamin K antagonist (VKA).

Figure 1: Design overview (EINSTEIN Jr Study)



Note: CVC = central vein catheter; LMWH = low-molecular-weight heparin; UFH = unfractionated heparin; VTE = venous thromboembolism.
Source: Section 7.1 of the CSR (PH-40166)

Subjects received either rivaroxaban or comparator for the main study treatment period of 3 months (1 month for subjects with central venous catheter venous thromboembolism (CVC-VTE) aged <2 years). Diagnostic imaging was obtained at baseline and at the end of the main study treatment period if clinically feasible. After the completion of the main treatment period, study treatment could be continued for additional 3, 6, or 9 months (1 or 2 months for subjects <2 years with CVC-VTE) at the discretion of the investigator.

Regardless of the duration of study treatment, an additional 30-day post-treatment observational safety follow-up period was to be completed for all children in the study. Subjects were required to be treated with UFH, LMWH, or fondaparinux for at least 5 days prior to start of study drug. Rivaroxaban was administered either as oral tablet or granules for oral suspension.

4.1.2 Endpoints and Statistical Methodologies

Analysis Sets:

- Full analysis set (FAS): This analysis set includes all randomized children.
- Safety analysis set (SAF): This analysis set includes all randomized children who received at least one dose of study medication.
- Per-protocol set (PPS): This analysis set excludes children with major protocol deviations.
- Listing-only set: This analysis set includes all screening failures.

Efficacy Outcomes:

- Primary efficacy outcome: Composite of symptomatic recurrent VTE
- Secondary efficacy outcome: Composite of symptomatic recurrent VTE and asymptomatic deterioration in thrombotic burden on repeat imaging at the end of the main treatment period
- Further efficacy outcomes:
    - Composite of symptomatic recurrent VTE and major bleeding
    - Composite of symptomatic recurrent VTE and asymptomatic deterioration and no change in thrombotic burden assessment on repeat imaging at the end of the main treatment period
    - Composite of symptomatic recurrent VTE and thrombotic burden assessment at repeated imaging at the end of the main treatment period (symptomatic recurrent VTE, asymptomatic deterioration, no relevant change, uncertain, improved, normalized).
    - Normalization of thrombotic burden assessment on repeat imaging at the end of the main treatment period without confirmed symptomatic recurrent VTE
    - Fatal or non-fatal pulmonary embolism
    - Composite of symptomatic recurrent VTE and other clinically significant thrombosis

Efficacy Analyses:

All efficacy analyses were performed on the full analysis set population based on the outcomes confirmed by the central independent adjudication committee (CIAC).

The study was not designed to test a hypothesis regarding comparing incidences of outcomes between rivaroxaban versus comparator with standard of care. Incidence rates and cumulative incidences (time to first event; Kaplan-Meier [1]) were calculated for the efficacy outcomes by treatment group at 3 months for pooled data. In addition, incidence rates were calculated for each age stratum at 3 months and by baseline presentation of venous thrombosis. Incidence rates were calculated for the primary outcomes by treatment group and overall at 6, 9 and 12 months. Denominators were the number of patients at risk at the start of the respective period.

Two-sided 95% confidence intervals for the frequency efficacy outcomes were calculated by applying the method of Blyth-Still-Casella [2, 3]. For time-to-event analyses, the censoring mechanism was assumed to be non-informative.

Stratified (strata: cerebral vein and sinus thrombosis (CVST), CVC-VTE, non-CVC-VTE) Cox proportional hazards model was fitted for the primary efficacy outcome as exploratory analysis. Firth's penalized maximum likelihood estimation was used to reduce bias in the parameter estimates. Point estimates for the hazard ratio, confidence interval (obtained with profile-likelihood function) and p-value for the treatment effect were obtained.
Risk differences (differences in incidence rates) for the efficacy outcomes for the main treatment period were calculated between rivaroxaban and comparator overall with two-sided 95% confidence intervals by applying the method of Agresti-Min [4] as exploratory analysis.

Safety Outcomes:

- Principal safety outcome: Composite of overt major and clinically relevant non-major bleeding.
- Further safety outcomes:
    - Death
    - Other vascular events (arterial thrombotic complications i.e., myocardial infarction, ischemic stroke, cerebrovascular accident, non-CNS systemic embolism)
    - Major bleeding
    - Clinically relevant non-major bleeding
    - Trivial bleeding

Safety Analyses:
For comparing incidences of outcomes between rivaroxaban versus comparator, stratified (strata: CVST, CVC-VTE+Unconfirmed/Unknown, non-CVC-VTE) Cox proportional hazards model was fitted for the time to principal safety outcome as an exploratory analysis. Firth's penalized maximum likelihood estimation was used to reduce bias in the parameter estimates. Point estimates for the hazard ratio, confidence interval (obtained with profile-likelihood function) and p-value for the treatment effect were obtained.

Risk differences (differences in incidence rates) for the safety outcomes for the main treatment period were calculated between rivaroxaban and comparator. Two-sided 95% confidence intervals were obtained by applying the method of Agresti-Min [4].

Sample Size Planning:
There was no formal sample size calculation due to the low incidence of VTE in children, and the lack of well-documented information on recurrence rate and treatment effect with standard of care in children. There were at least 170 children to be enrolled in the study, with at least:

- 20 children aged birth to 2 year, with at least 12 aged birth to <0.5 year,
- 20 children aged 2 to <6 years,
- 30 children aged 6 to <12 years, and
- 80 children aged 12 to <18 years.

Interim Analysis:
No interim analysis was performed for this study.

Multiplicity Adjustment:
No multiplicity adjustment was applied because none of the analyses were intended for hypothesis testing.

4.1.3 Patient Disposition

A total of 520 children were screened in 109 study centers in 28 countries. 500 children passed the screening, were randomized (335 rivaroxaban, 165 comparator) and were valid for FAS. 491 children (329 rivaroxaban, 162 comparator) took at least one dose of study medication, and were valid for SAF.

A total of 487[1] children completed the main treatment period (Table 1), 218 (43.6%) entered and 179 (82.1%) completed the first block of extended treatment, 91 (18.2%) entered and 84 (92.3%) completed the second block of extended treatment, and 48 (9.6%) entered and all (100%) completed the third block of extended treatment.

[1]The number was manually corrected for database errors: 3 more children than given in the clinical database completed the main treatment period. For details see the corresponding CSR (PH-40166).

Table 1: Treatment Disposition – FAS (EINSTEIN Jr Study)

			Treatment Group					
			Rivaroxaban		**Comparator**		**Total**	
Completed Main Treatment Period	**Took Study Medication**	**Reason for Non-Completion**	**n**	**%**	**n**	**%**	**n**	**%**
Y			325	97.01	159	96.36	484	96.8
N	Y	Death	1	0.30	0	0.00	1	0.2
		Efficacy outcome reached	2	0.60	0	0.00	2	0.4
		Lost to follow-up	0	0.00	1	0.61	1	0.2
		Physician decision	1	0.30	0	0.00	1	0.2
		Protocol violation	1	0.30	0	0.00	1	0.2
		Withdrawal by subject	2	0.60	2	1.21	4	0.8
		Total	7	2.09	3	1.82	10	2.0
	N	Withdrawal by subject	3	0.90	3	1.82	6	1.2
		Total	3	0.90	3	1.82	6	1.2
Total			335	100.0	165	100.0	500	100.0

Source: FDA analysis

A total of 469/500 (93.8%) children completed the 30-day post-study treatment follow up period. The main reasons for not completing the 30-day follow-up period were “withdrawal by subject” (5 rivaroxaban, 5 comparator) and “lost to follow-up” (4 rivaroxaban, 4 comparator).

4.1.4 Baseline Demographic Characteristics

Of the 500 randomized subjects, 49.0% were female, 79.0% were white, 5.0% were black, and 5.6% were Asian. The mean age of subjects was 11.1 years (median 13.2 years), average weight was 46.4 kg (median 48.3 km), and average height was 141 cm (median 156 cm).

Comparisons of patients’ baseline demographic characteristics data between the treatment groups overall and across the 5 age groups are shown in Table 2. In general, baseline demographic characteristics were balanced between the treatment groups.

Table 2: Baseline Demographic Characteristics – FAS (EINSTEIN Jr Study)

	< 6 months		*0.5 - <2 years*		*2 - <6 years*	
	Rivaroxaban (N=16)	**Comparator (N=8)**	**Rivaroxaban (N=21)**	**Comparator (N=9)**	**Rivaroxaban (N=47)**	**Comparator (N=22)**
Age in Years						
Mean (SD)	0.19 (± 0.16)	0.08 (± 0.05)	1.07 (± 0.48)	1.31 (± 0.47)	3.91 (± 1.18)	4.12 (± 1.24)
Sex						
F	5 (31.3%)	1 (12.5%)	10 (47.6%)	5 (55.6%)	24 (51.1%)	9 (40.9%)
M	11 (68.8%)	7 (87.5%)	11 (52.4%)	4 (44.4%)	23 (48.9%)	13 (59.1%)
Race						
WHITE	10 (62.5%)	4 (50.0%)	12 (57.1%)	7 (77.8%)	40 (85.1%)	17 (77.3%)
BLACK OR AFRICAN AMERICAN	1 (6.3%)	0 (0%)	2 (9.5%)	0 (0%)	1 (2.1%)	0 (0%)
ASIAN	2 (12.5%)	2 (25.0%)	4 (19.0%)	1 (11.1%)	2 (4.3%)	2 (9.1%)
AMERICAN INDIAN OR ALASKA NATIVE	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
NATIVE HAWAIIAN OR OTHER PACIFIC ISLANDER	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (2.1%)	0 (0%)
NOT REPORTED	3 (18.8%)	2 (25.0%)	3 (14.3%)	0 (0%)	3 (6.4%)	3 (13.6%)
MULTIPLE	0 (0%)	0 (0%)	0 (0%)	1 (11.1%)	0 (0%)	0 (0%)
Baseline Weight (kg)						
Mean (SD)	3.94 (± 0.92)	3.60 (± 0.85)	9.40 (± 2.37)	9.99 (± 2.69)	15.88 (± 3.39)	16.32 (± 3.24)
Baseline Height (cm)						
Mean (SD)	53.81 (± 4.51)	51.29 (± 4.81)	72.99 (± 7.99)	77.41 (± 6.58)	101.18 (±10.13)	102.73 (± 9.41)
Baseline Body Mass Index (kg/m^2)						
Mean (SD)	13.43 (± 1.46)	13.41 (± 2.41)	16.93 (± 2.62)	16.42 (± 2.39)	15.48 (± 1.97)	15.36 (± 1.59)

Source: FDA analysis

Table 2: Baseline Demographic Characteristics – FAS (EINSTEIN Jr Study) (*continued*)

	6 - <12 years		*12 - <18 years*		*Overall*	
	Rivaroxaban (N=67)	**Comparator (N=34)**	**Rivaroxaban (N=184)**	**Comparator (N=92)**	**Rivaroxaban (N=335)**	**Comparator (N=165)**
Age in Years						
Mean (SD)	8.90 (± 1.75)	9.04 (± 1.71)	15.73 (± 1.48)	15.74 (± 1.62)	11.04 (± 5.84)	11.27 (± 5.74)
Sex						
F	24 (35.8%)	15 (44.1%)	97 (52.7%)	55 (59.8%)	160 (47.8%)	85 (51.5%)
M	43 (64.2%)	19 (55.9%)	87 (47.3%)	37 (40.2%)	175 (52.2%)	80 (48.5%)
Race						
WHITE	51 (76.1%)	23 (67.6%)	158 (85.9%)	73 (79.3%)	271 (80.9%)	124 (75.2%)
BLACK OR AFRICAN AMERICAN	2 (3.0%)	4 (11.8%)	7 (3.8%)	8 (8.7%)	13 (3.9%)	12 (7.3%)
ASIAN	9 (13.4%)	1 (2.9%)	3 (1.6%)	2 (2.2%)	20 (6.0%)	8 (4.8%)
AMERICAN INDIAN OR ALASKA NATIVE	0 (0%)	1 (2.9%)	0 (0%)	1 (1.1%)	0 (0%)	2 (1.2%)
NATIVE HAWAIIAN OR OTHER PACIFIC ISLANDER	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0.3%)	0 (0%)
NOT REPORTED	5 (7.5%)	5 (14.7%)	13 (7.1%)	8 (8.7%)	27 (8.1%)	18 (10.9%)
MULTIPLE	0 (0%)	0 (0%)	3 (1.6%)	0 (0%)	3 (0.9%)	1 (0.6%)
Baseline Weight (kg)						
Mean (SD)	30.67 (± 10.91)	33.11 (± 11.40)	68.38 (± 19.46)	64.45 (± 18.59)	46.70 (± 29.19)	45.66 (± 26.87
Baseline Height (cm)						
Mean (SD)	133.17 (±12.55)	132.07 (±12.91)	168.04 (±11.09)	167.92 (± 9.62)	140.71 (±37.43)	141.37 (±36.16)
Baseline Body Mass Index (kg/m^2)						
Mean (SD)	16.97 (± 3.33)	18.35 (± 4.07)	24.15 (± 6.51)	22.57 (± 5.81)	20.57 (± 6.58)	19.96 (± 5.72)

Source: FDA analysis

4.1.5 Efficacy Results

Composite of symptomatic recurrent VTE (primary efficacy outcome) occurred in 4 of 335 (1.2%; 95% CI: 0.4%, 3.0%) in the rivaroxaban group and 5 of 165 (3.0%; 95% CI: 1.2%, 6.6%) in the comparator group. The risk difference of the primary efficacy outcome between the rivaroxaban and comparator groups is -1.8% (95% CI: -6%, 0.64%).

Reviewer's comment: The primary method of CIs of all risk differences in Study EINSTEIN Jr is Agresti-Min method. FDA's CIs were calculated by StatXact 11 and gamma = 0.000001, where gamma is the parameter for the restriction method proposed by Berger and Boos [5] to reduce the conservativeness caused by the unlikely values of the nuisance parameter. However, the Sponsor's values were obtained by StatXact 10, although both results are very similar.

The hazard ratio of the primary efficacy outcome between the rivaroxaban and comparator groups is 0.40 (95% CI: 0.11, 1.41) with a p-value of 0.15 (Table 3).

Table 3: Results from the stratified Cox proportional hazard model: Primary efficacy outcome up to the end of main treatment period – FAS (EINSTEIN Jr Study)

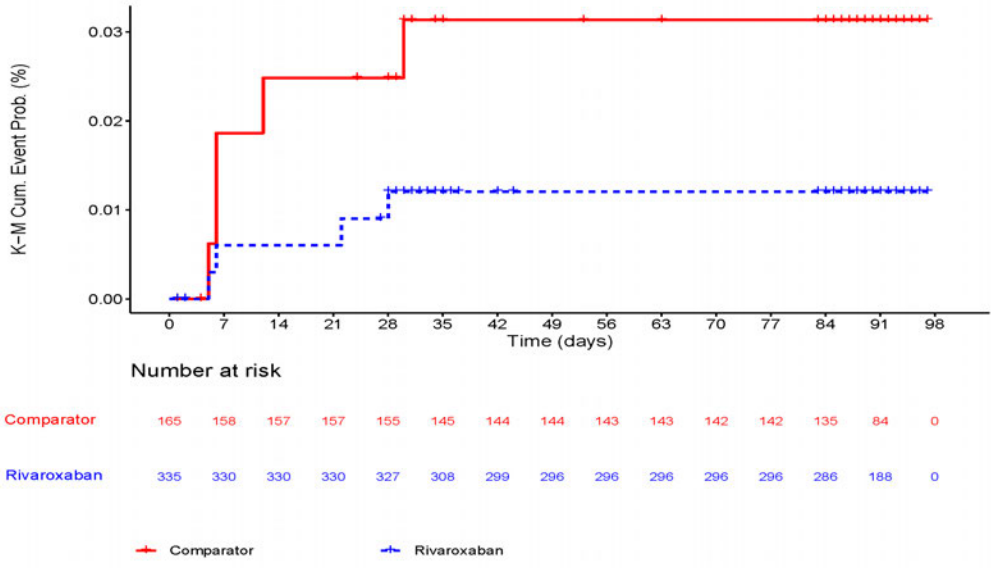
Outcome	*Rivaroxaban* Incidence Rate	*Comparator* Incidence Rate	Hazard Ratio between Rivaroxaban and Comparator (95% CI)	p-value
Composite of symptomatic recurrent VTE (Primary efficacy outcome)	1.2% (4 / 335)	3.0% (5 / 165)	0.40 (0.11,1.41)	0.15

Notes: Estimates were based on stratified (strata: CVST, CVC-VTE, non-CVC-VTE) proportional hazard model. Notes: Firth's penalized maximum likelihood estimation was used to obtain parameter estimates and profile-likelihood confidence intervals.
Source: FDA analysis

In the clinical study report for PH-40166, the Sponsor conducted a sensitivity analysis to evaluate the potential influence of dropouts on the incidence of the primary efficacy outcome for the main treatment period. In this analysis subjects with premature termination before the end of intended main treatment period were assumed as having hazard of recurrence of VTE 1.5 times and twice as high as the hazard calculated including all patients within each treatment group assuming informative censoring. The results of the sensitivity analysis showed that even if one assumed that dropouts in the rivaroxaban group were more likely (1.5 and 2.0 times more likely applying the respective informative missingness hazard ratio) to have a primary efficacy outcome than those in the comparator group, the observed point estimates of the comparisons between rivaroxaban and comparator were similar.

The Kaplan-Meier cumulative incidences of the primary efficacy outcome in the rivaroxaban and comparator groups during the main study treatment period on the full analysis are shown in Figure 2 below. The observed cumulative incidence rate was lower in the rivaroxaban group than in the comparator group.

Figure 2: Kaplan-Meier cumulative incidence of the primary efficacy outcome during the main treatment period – FAS (EINSTEIN Jr Study)



Source: FDA analysis

A summary of the incidence rates for efficacy outcomes in the rivaroxaban and comparator groups and risk differences between the two treatment groups is provided in Table 4 below.

Table 4: Treatment group comparison for efficacy outcomes at the end of main treatment period – FAS (EINSTEIN Jr Study)

	Rivaroxaban		*Comparator*		
Outcome	**Incidence Rate**	**(95% CI[a])**	**Incidence Rate**	**(95% CI[a])**	**Risk Difference between Rivaroxaban and Comparator (95% CI[b])**
Composite of symptomatic recurrent VTE (Primary efficacy outcome)	1.2% (4 / 335)	(0.4%, 3.0%)	3.0% (5 / 165)	(1.2%, 6.6%)	−1.8% (−6%, 0.64%)
Composite of Symptomatic recurrent VTE and asymptomatic deterioration in thrombotic burden on repeat imaging (Secondary efficacy outcome)	1.5% (5 / 335)	(0.6%, 3.4%)	3.6% (6 / 165)	(1.6%, 7.6%)	−2.1% (−6.5%, 0.57%)
Composite of symptomatic recurrent VTE and major bleeding	1.2% (4 / 335)	(0.4%, 3.0%)	4.2% (7 / 165)	(2.0%, 8.4%)	−3% (−7.5%, −0.28%)
Composite of symptomatic recurrent VTE and asymptomatic deterioration and no change in thrombotic burden assessment on repeat imaging at the end of the main treatment period	6.3% (21 / 335)	(4.0%, 9.2%)	11.5% (19 / 165)	(7.3%, 17.4%)	−5.2% (−11%, −0.16%)
Not normalization of thrombotic burden assessment on repeat imaging at the end of the main treatment period without confirmed symptomatic recurrent VTE	61.8% (207 / 335)	(56.5%, 67.0%)	73.9% (122 / 165)	(67.0%, 80.2%)	−12% (−20%, −3.4%)
Fatal or non-fatal pulmonary embolism	0.3% (1 / 335)	(0.0%, 1.6%)	0.6% (1 / 165)	(0.0%, 3.1%)	−0.31% (−3.2%, 1.1%)
Composite of symptomatic recurrent VTE and other clinically significant thrombosis	1.5% (5 / 335)	(0.6%, 3.4%)	3.6% (6 / 165)	(1.6%, 7.6%)	−2.1% (−6.5%, 0.57%)

[a]CIs for incidence rates were calculated by applying the Blyth-Still-Casella method.
[b]CIs for risk differences were calculated by applying the Agresti-Min method.
Note: Subjects were counted only once for any given event.
Source: FDA analysis

4.1.6 Safety Results

Composite of overt major and clinically relevant non-major bleeding (principal safety outcome) occurred in 10 of 329 (3.0%; 95% CI: 1.6%, 5.5%) in the rivaroxaban group and 3 of 162 (1.9%; 95% CI: 0.5%, 5.3%) in the comparator group. The risk difference of the primary efficacy outcome between the rivaroxaban and comparator groups is 1.2% (95% CI: -2.8%, 4.0%). The hazard ratio of the primary efficacy outcome between the rivaroxaban and comparator groups is 1.55 (95% CI: 0.50, 6.16) with a p-value of 0.46 (Table 5).

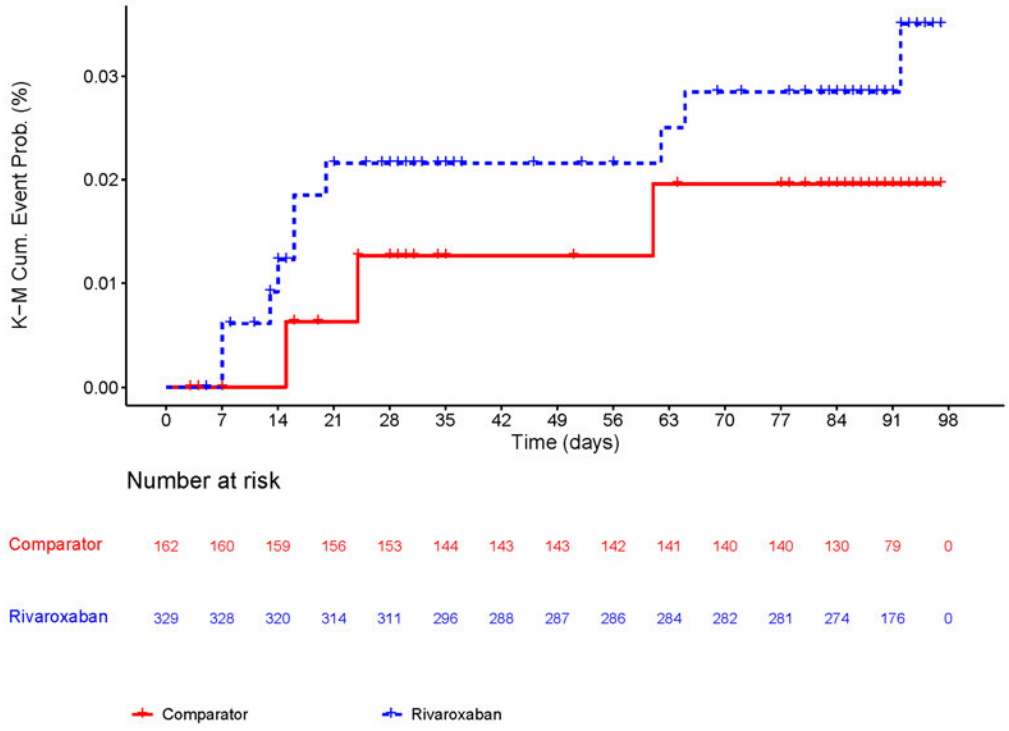
Table 5: Results from the stratified Cox proportional hazard model: Treatment-Emergent Principal safety outcome up to the end of main treatment period – SAF (EINSTEIN Jr Study)

Outcome	*Rivaroxaban* Incidence Rate	*Comparator* Incidence Rate	Hazard Ratio between Rivaroxaban and Comparator (95% CI)	P-value
Composite of overt major and clinically relevant non-major bleeding (Principal safety outcome)	3.0% (10 / 329)	1.9% (3 / 162)	1.55 (0.50,6.16)	0.46

Notes: Estimates were based on stratified (strata: CVST, CVC-VTE, non-CVC-VTE) proportional hazard model.
Notes: Firth's penalized maximum likelihood estimation was used to obtain parameter estimates and profile-likelihood confidence intervals.
Source: FDA analysis

The Kaplan-Meier cumulative incidences of the principal safety outcome in the rivaroxaban and comparator groups during the main study treatment period on the safety analysis are shown in Figure 3 below. The cumulative incidence rate was higher in the rivaroxaban group than in the comparator group.

Figure 3: Kaplan-Meier cumulative incidence of the principal safety outcome during the main treatment period – SAF (EINSTEIN Jr Study)



Source: FDA analysis

A summary of incidence rates for safety outcomes in the rivaroxaban and comparator groups and risk differences between the two treatment groups is provided in Table 6 below.

Table 6: Treatment group comparison for treatment-emergent safety outcomes at the end of main treatment period – SAF (EINSTEIN Jr Study)

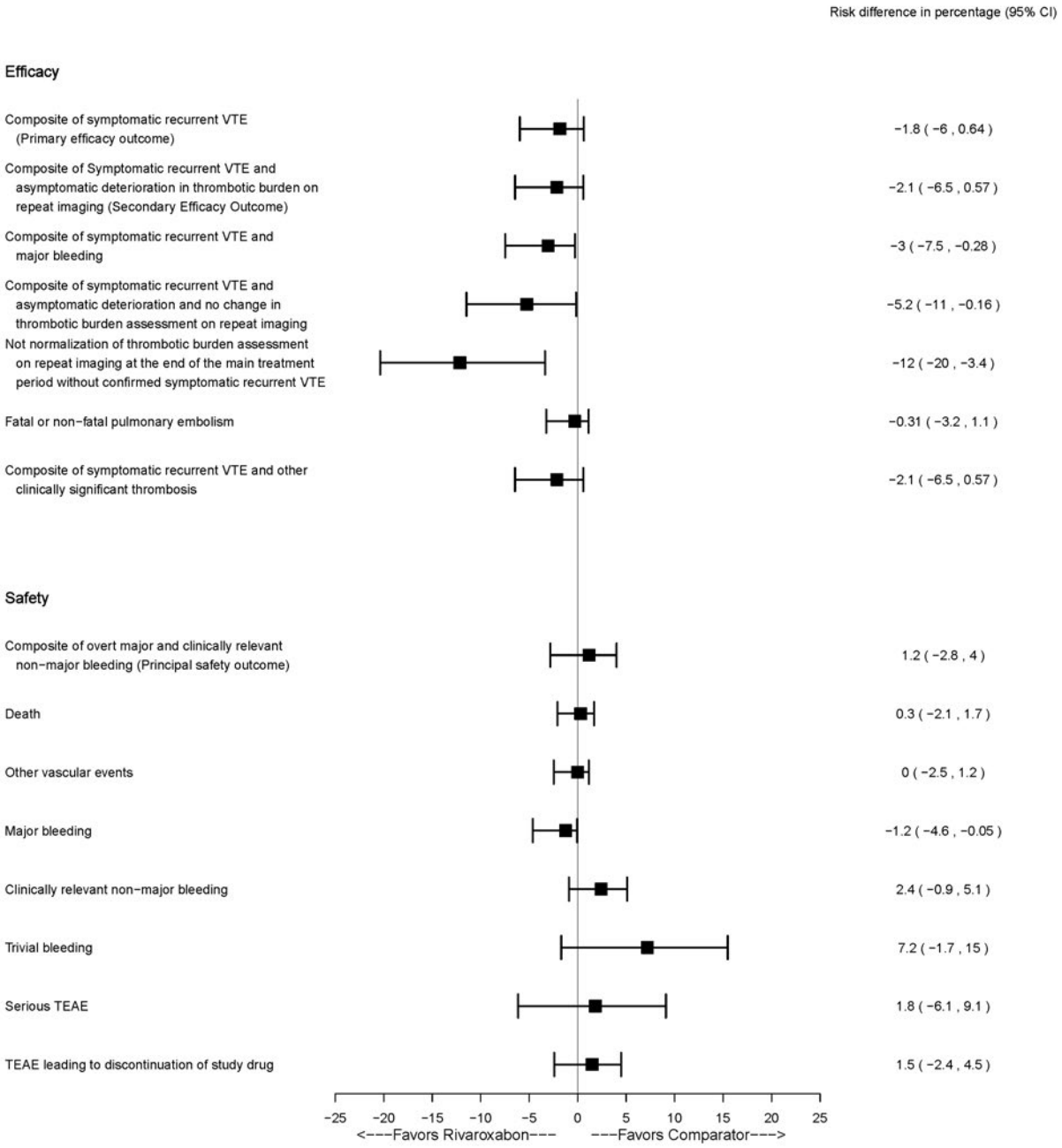
	Rivaroxaban		***Comparator***		
Outcome	**Incidence Rate**	**(95% CI[a])**	**Incidence Rate**	**(95% CI[a])**	**Risk Difference between Rivaroxaban and Comparator (95% CI[b])**
Composite of overt major and clinically relevant non-major bleeding (Principal safety outcome)	3.0% (10 / 329)	(1.6%, 5.5%)	1.9% (3 / 162)	(0.5%, 5.3%)	1.2% (−2.8%, 4.0%)
Death	0.3% (1 / 329)	(0.0%, 1.6%)	0.0% (0 / 162)	(0.0%, 2.2%)	0.3% (−2.1%, 1.7%)
Other vascular events (arterial thrombotic complications i.e., myocardial infarction, ischemic stroke, cerebrovascular accident, non-CNS systemic embolism)	0.0% (0 / 329)	(0.0%, 1.1%)	0.0% (0 / 162)	(0.0%, 2.2%)	0.0% (−2.5%, 1.2%)
Major bleeding	0.0% (0 / 329)	(0.0%, 1.1%)	1.2% (2 / 162)	(0.2%, 4.3%)	−1.2% (−4.6%, −0.05%)
Clinically relevant non-major bleeding	3.0% (10 / 329)	(1.6%, 5.5%)	0.6% (1 / 162)	(0.0%, 3.1%)	2.4% (−0.9%, 5.1%)
Trivial bleeding	34.3% (113 / 329)	(29.2%, 39.5%)	27.2% (44 / 162)	(20.5%, 34.3%)	7.2% (−1.7%, 15%)
Serious TEAE	21.6% (71 / 329)	(17.4%, 26.3%)	19.8% (32 / 162)	(13.9%, 26.7%)	1.8% (−6.1%, 9.1%)
TEAE leading to discontinuation of study drug	3.3% (11 / 329)	(1.7%, 5.7%)	1.9% (3 / 162)	(0.5%, 5.3%)	1.5% (−2.4%, 4.5%)

[a]CIs for incidence rates were calculated by applying the Blyth-Still-Casella method.
[b]CIs for risk differences were calculated by applying the Agresti-Min method.
Note: Subjects were counted only once for any given event.
Source: FDA analysis

4.1.7 Benefit-Risk Assessment

The benefit-risk assessment compared rivaroxaban with comparator for efficacy and safety outcomes. The comparison of rivaroxaban against comparator was evaluated based on the risk difference, i.e., the difference in incidence rates. A forest plot based on the risk difference results (Tables 4 and 6) was used to visualize the comparison between two treatment groups (Figure 4). The assessment was considered exploratory without any hypothesis testing.

Figure 4: Forest plot for treatment group comparison of efficacy outcomes (FAS) and treatment-emergent safety outcomes (SAF) at the end of main treatment period (EINSTEIN Jr Study)



Note: The forest plot was based on risk difference results in Tables 4 and 6.
Note: CIs for risk differences were calculated by applying the Agresti-Min method.
Source: FDA analysis

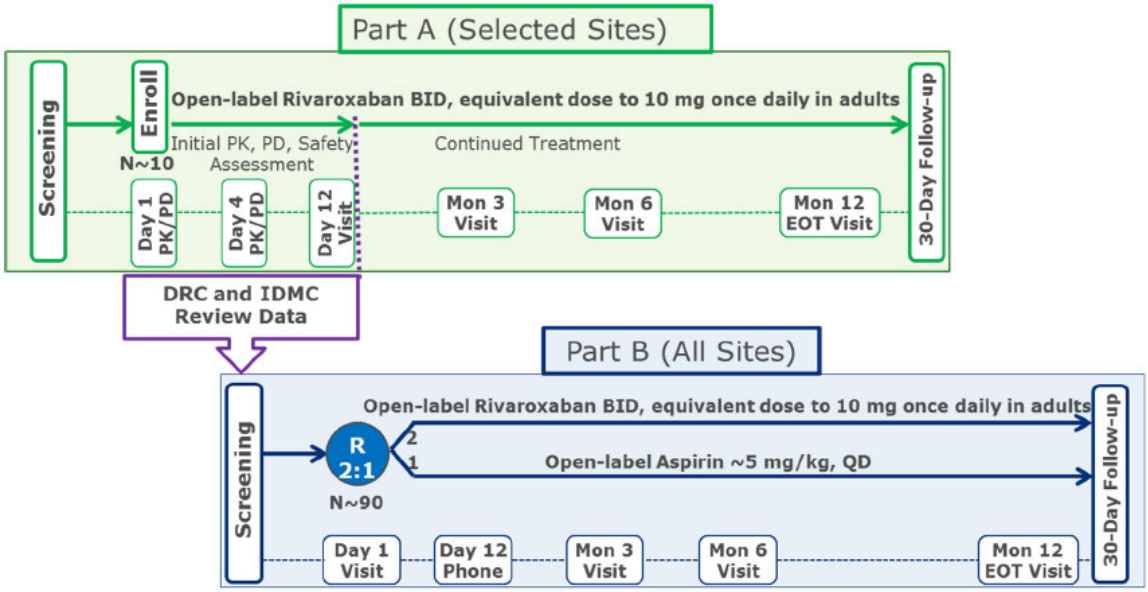
In Figure 4, the results to the left of the vertical line favor the rivaroxaban over the comparator. The risk differences for all efficacy outcomes have shifted to the left. For safety outcomes, the risk difference for major bleeding has shifted to the left, while the risk differences for the other safety outcomes are in the middle or have shifted to the right.

4.2 Phase III CHD3001 (UNIVERSE) Study

4.2.1 Study Design

UNIVERSE was a Phase 3, prospective, open-label, active-controlled, multicenter, multinational study in pediatric subjects (2-8 years) with single-ventricle physiology who had completed the Fontan procedure within 4 months prior to enrollment to evaluate the PK and PK/PD profiles, safety and efficacy of rivaroxaban, administered twice daily (exposure matched to rivaroxaban 10 mg once daily in adults) compared to Aspirin, given once daily (approximately 5 mg/kg) for thromboprophylaxis. The design overview is depicted in Figure 5 below.

Figure 5: Design overview (UNIVERSE Study)



BID=twice daily, DRC= Data Review Committee, EOT=end of treatment; IDMC=Independent Data Monitoring Committee, Mon=month; PD= pharmacodynamics, PK= pharmacokinetic(s); QD=once daily; R=randomization.
Note: An internal DRC assessed by Day 12 the PK, PD, and the safety data from each subject, prior to the continuing subject in the study to complete the planned 12 months of open-label rivaroxaban therapy. Enrollment in Part A ended, and enrollment in Part B was started, once the cumulative data from all subjects in the Initial PK, PD, and Safety Assessment Period of Part A were deemed acceptable by the IDMC.
Source: Section 3.1.1 of CSR (CHD3001)

The study consisted of Part A, the 12-month, open-label rivaroxaban, single-arm part of the study, which included a 12-day initial PK, PD, and safety assessment period, and Part B, the 2-arm, randomized, open-label, active-controlled part of the study that evaluated the safety and

efficacy of rivaroxaban compared to Aspirin for thromboprophylaxis for 12 months. Subjects randomized to rivaroxaban also had PK and PD assessments.

4.2.2 Endpoints and Statistical Methodologies

Analysis sets:

- Full Analysis Set: This analysis set consists of all subjects in Part A who received at least 1 dose of study drug and all subjects in Part B who are randomized and received at least 1 dose of study drug.
- Safety Analysis Set: This is the same as Full Analysis Set.
- Per-protocol Set: The per-protocol set excludes subjects with key protocol deviations from full analysis set.

Efficacy Outcomes:

The primary efficacy outcome is any thrombotic event (venous or arterial), defined as:

- The appearance of a new thrombotic burden within the cardiovascular system on either routine surveillance or clinically indicated imaging, or
- The occurrence of a clinical event known to be strongly associated with thrombus (such as cardioembolic stroke, pulmonary embolism).

Subjects who developed either a symptomatic or asymptomatic thrombotic event during the study discontinued the study drug. After cessation of study treatment, it was at the investigator's discretion to continue with other antithrombotic therapy. All available imaging results, e.g., transthoracic or transesophageal echocardiograms, or MRIs, relevant to a suspected thrombotic event were sent to the CIAC for event adjudication, blinded to assigned treatment. Thrombotic events were not reported as adverse events or serious adverse events, as they were reported as efficacy outcomes.

Efficacy Analyses:

The main efficacy description was based on Full Analysis Set during the On-treatment period. No formal hypothesis testing was performed. Incidence rates (number of subjects with efficacy event during the period divided by number of subjects at risk at the beginning of the period) by treatment group, risk differences between treatment groups, and the respective 95% CIs were calculated for the efficacy outcomes.

Safety Outcomes:

The primary safety outcome is the major bleeding events, defined as 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: intracranial, intraspinal, intraocular, pericardial, intraarticular, intramuscular with compartment syndrome, retroperitoneal; or
- Contributing to death.

The secondary safety outcomes are clinically relevant non-major bleeding events and trivial (minimal) bleeding. The clinically relevant non-major bleeding events is defined as 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 subject such as pain, or
- Impairment of activities of daily life (such as loss of school days or hospitalization).

Trivial (minimal) bleeding is defined as any other overt bleeding event that does not meet criteria for clinically relevant non major bleeding.

Safety Analyses:
The main safety description was based on Safety Analysis Set during the On-treatment period (bleeding events confirmed by the CIAC). No formal hypothesis testing was performed. Incidence rates (number of subjects with bleeding event during the period divided by the number of subjects at risk at the beginning of the period) by treatment group, risk differences between treatment groups, and the respective 95% CIs were calculated.

Sample Size Calculation:
A total of at least 100 pediatric subjects overall were planned to be enrolled in this study. Due to the limited availability of the study population and the expected low event rates, this study was not powered to test formal hypothesis for efficacy. The total expected sample size was based on regulatory feedback to obtain sufficient safety data in this pediatric population.

The sample size of approximately 10 subjects for Part A was considered adequate for the initial PK assessment of rivaroxaban in the studied pediatric subjects. Approximately 90 subjects were planned to be enrolled into Part B of the study.

Interim Analysis:
No interim analysis was performed for this study.

Multiplicity Adjustment:
No multiplicity adjustment was applied because none of the analyses were intended for hypothesis testing.

4.2.3 Patient Disposition

A total of 129 subjects with single ventricle physiology were screened at 36 sites in 10 countries (Argentina, Belgium, Brazil, Canada, Japan, Malaysia, Mexico, the Netherlands, Spain, and the United States of America). Of the screened children, 112 (86.8%) subjects passed screening and were enrolled in this study. Of these 112 subjects, 12 were in the rivaroxaban Part A group and 100 were in the Part B group (66 in the rivaroxaban group and 34 in the Aspirin group).

Of the 112 subjects enrolled, 99 (88.4%) subjects completed the study treatment (10 [83.3%] subjects in the rivaroxaban Part A group; 59 [89.4%] in the rivaroxaban Part B group; 30

[88.2%] in the Aspirin Part B group (Table 7). The most frequent reason for not completing study treatment was thrombosis for 3 subjects (1 in the rivaroxaban Part B group and 2 in the Aspirin Part B group) followed by not treated (2 subjects in the rivaroxaban group) and withdrawal by parent or guardian (2 subjects in the rivaroxaban group).

Table 7: Treatment Disposition – All Enrolled Subjects (UNIVERSE Study)

	Rivaroxaban		***Aspirin***	**Total**
	Part A	Part B	Part B	
Enrolled	12 (100%)	66 (100%)	34 (100%)	112 (100%)
Completed study treatment	10 (83.3%)	59 (89.4%)	30 (88.2%)	99 (88.4%)
Did not complete study Treatment	2 (16.7%)	7 (10.6%)	4 (11.8%)	13 (11.6%)
Reason for not completing study treatment				
- Not treated	0	2 (3.0%)	0	2 (1.8%)
- Bleeding event		1 (1.5%)		1 (0.9%)
- Non-bleeding adverse event	0	1 (1.5%)	0	1 (0.9%)
- Ischemic stroke	0	0	1 (2.9%)	1 (0.9%)
- Thrombosis	0	1 (1.5%)	2 (5.9%)	3 (2.7%)
- DRC decision	2 (16.7%)	0	0	2 (1.8%)
- Lost to follow-up	0	0	1 (2.9%)	1 (0.9%)
- Withdrawal by parent/guardian	0	2 (3.0%)	0	2 (1.8%)

Note: DRC = Data Review Committee
Note: Percentages calculated with the number of enrolled subjects in each group as denominator
Source: FDA analysis

4.2.4 Baseline Demographic Characteristics

Among the enrolled 112 subjects, 46 (41.1%) subjects were female, and 68 (60.7%) subjects were white. The mean age was 3.9 years (standard deviation:1.74; median: 4 years; range: 2 to 8 years).

The demographic and baseline characteristics were generally balanced between the rivaroxaban and the Aspirin groups (Table 8). However, among the enrolled 112 subjects, the proportion of males was lower in the rivaroxaban Part B group (36 [54.5%]) than in the Aspirin Part B group (23 [67.6%]). The number of males in the rivaroxaban Part A group was 7 (58.3%). In addition, in the rivaroxaban Part B a total of 36 (54.5%) subjects did not have a Fontan-fenestration whereas only 13 (38.2%) were not fenestrated in the Aspirin group. In rivaroxaban Part A 9 subjects (75%) did not have a Fontan-fenestration.

Table 8: Baseline Demographic Characteristics – Full Analysis Set (UNIVERSE Study)

	Rivaroxaban (Part A) (N=12)	*Rivaroxaban (Part B) (N=66)*	*Aspirin (Part B) (N=34)*	*Overall (N=112)*
Age				
Mean (SD)	2.50 (± 0.67)	4.06 (± 1.74)	4.18 (± 1.80)	3.93 (± 1.74)
Sex				
F	5 (42 %)	30 (45 %)	11 (32 %)	46 (41 %)
M	7 (58 %)	36 (55 %)	23 (68 %)	66 (59 %)
race				
Asian	0 (0 %)	14 (21 %)	7 (21 %)	21 (19 %)
Black or African American	3 (25 %)	8 (12 %)	1 (3 %)	12 (11 %)
White	8 (67 %)	40 (61 %)	20 (59 %)	68 (61 %)
Other	1 (8 %)	2 (3 %)	3 (9 %)	6 (5 %)
Not reported	0 (0 %)	2 (3 %)	3 (9 %)	5 (4 %)
Ethnicity				
Hispanic or Latino	1 (8 %)	22 (33 %)	11 (32 %)	34 (30 %)
Not Hispanic or Latino	11 (92 %)	42 (64 %)	19 (56 %)	72 (64 %)
Not reported	0 (0 %)	2 (3 %)	4 (12 %)	6 (5 %)
Baseline Weight (kg)				
Mean (SD)	13.83 (± 2.37)	15.81 (± 3.66)	15.69 (± 3.14)	15.56 (± 3.42)
Baseline Height (cm)				
Mean (SD)	90.38 (± 7.12)	100.96 (± 12.53)	102.98 (± 11.98)	100.44 (± 12.36)
Heart Rate (Beats/min)				
Mean (SD)	110.67 (± 13.38)	108.95 (± 16.40)	106.59 (± 15.47)	108.42 (± 15.75)
Systolic Blood Pressure (mmHg)				
Mean (SD)	108.67 (± 8.76)	99.32 (± 12.76)	102.29 (± 10.56)	101.22 (± 12.03)
Diastolic Blood Pressure (mmHg)				
Mean (SD)	62.75 (± 11.16)	59.17 (± 11.11)	62.85 (± 9.01)	60.68 (± 10.58)
Duration, Fontan Proc. to 1st Dose (Days)				
Mean (SD)	11.58 (± 16.77)	45.28 (± 41.21)	36.74 (± 34.52)	38.96 (± 38.45)
<=30	11 (92 %)	31 (47 %)	19 (56 %)	61 (54 %)
>30	1 (8 %)	33 (50 %)	15 (44 %)	49 (44 %)
Fenestration				
Y	3 (25 %)	30 (45 %)	21 (62 %)	54 (48 %)
N	9 (75 %)	36 (55 %)	13 (38 %)	58 (52 %)

Source: FDA analysis

4.2.5 Efficacy Results

Thrombotic events (primary efficacy outcome) occurred in 1 of 64 (1.6%; 95% CI: 0.1%, 7.8%) in the rivaroxaban Part B group and 3 of 34 (8.8%; 95% CI: 2.4%, 22.2%) in the Aspirin group. The risk difference of thrombotic event between rivaroxaban Part B group and Aspirin group is -7.3% (95% CI: -22%, 1.1%).

The 1 thrombotic event in the rivaroxaban Part B group was adjudicated as pulmonary embolism and the 3 thrombotic events in the Aspirin Part B group were adjudicated as: 2 (5.9%) venous thrombotic events and 1 (2.9%) ischemic stroke. Further details of the incidence rates for efficacy outcomes in Part B treatment groups and risk differences between Part B treatment groups are provided in Table 9 below.

Table 9: Part B Treatment group comparison for efficacy outcomes at the end of main treatment period – Full Analysis Set (UNIVERSE Study)

	Part B: Rivaroxaban		***Part B: Aspirin***			
Outcome	**Incidence Rate**	**(95% CI[a])**	**Incidence Rate**	**(95% CI[a])**	**Part B: Risk Difference between Rivaroxaban and Aspirin (95% CI[b])**	
					FDA's	**Sponsor's**
Any thrombotic event (Primary efficacy outcome)	1.6% (1 / 64)	(0.1%, 7.8%)	8.8% (3 / 34)	(2.4%, 22.2%)	−7.3% (−21.7%, 1.1%)	-7.3% (-21.8%, 1.2%)
Venous thromboembolism	1.6% (1 / 64)	(0.1%, 7.8%)	5.9% (2 / 34)	(1.1%, 18.8%)	−4.3% (−18.6%, 3.5%)	
- Venous thrombosis	0.0% (0 / 64)	(0.0%, 5.6%)	5.9% (2 / 34)	(1.1%, 18.8%)	−5.9% (−20.6%, −0.1%)	-5.9% (-20.6%, 0.1%)
- Pulmonary embolism	1.6% (1 / 64)	(0.1%, 7.8%)	0.0% (0 / 34)	(0.0%, 9.0%)	1.6% (−9.9%, 8.4%)	1.6% (-8.9%, 8.4%)
Arterial/intracardiac thrombosis	0.0% (0 / 64)	(0.0%, 5.6%)	0.0% (0 / 34)	(0.0%, 9.0%)	0.0% (−11.8%, 5.9%)	
Ischemic stroke	0.0% (0 / 64)	(0.0%, 5.6%)	2.9% (1 / 34)	(0.2%, 15.1%)	−2.9% (−16.2%, 2.9%)	-2.9% (-16.2%, 3.0%)
All-cause death[c]	0.0% (0 / 64)	(0.0%, 5.6%)	0.0% (0 / 34)	(0.0%, 9.0%)	0.0% (−11.8%, 5.9%)	

[a]CIs for incidence rates were calculated by applying the Blyth-Still-Casella method.
[b]CIs for risk differences were calculated by applying the Agresti-Min method.
[c]All-cause deaths were counted as thrombotic events.
Source: FDA analysis

Review's comment: For the UNIVERSE study, the Sponsor used Wald method with continuity correction to calculate CIs of risk differences instead of Agresti-Min method when the CIs were provided in the clinical study report. The FDA suggested the Sponsor provide the CIs for all the major risk differences by using the Agresi-Min method. FDA's CIs were calculated by StatXact 11 and gamma = 0.000001, where gamma is the parameter for the restriction method proposed by Berger and Boos [5] to reduce the conservativeness caused by the unlikely values of the nuisance parameter, whereas the Sponsor's values were obtained from SAS FREQ procedure. As seen from Table 9, the Sponsor's CIs and FDA's CIs are not exactly the same, but conclusions are the same. The results of FDA's CIs are described in the label.

4.2.6 Safety Results

Major bleeding (primary safety outcome) occurred in 1 of 64 (1.6%; 95% CI: 0.1%, 7.8%) in the rivaroxaban Part B group and 0 of 34 (0.0%; 95% CI: 0.0%, 9.0%) in the Aspirin group. The risk difference of major bleeding between rivaroxaban Part B group and Aspirin group is 1.6% (95% CI: -9.9%, 8.4%).

Clinically relevant non-major bleeding (secondary safety outcome) occurred in 4 of 64 (6.3%; 95% CI: 2.2%, 15.0%) in the rivaroxaban Part B group and 3 of 34 (8.8%; 95% CI: 2.4%, 22.2%) in the Aspirin group. The risk difference of clinically relevant non-major bleeding between rivaroxaban Part B group and Aspirin group is -2.6% (95% CI: -18%, 8.0%).

Trivial bleeding (secondary safety outcome) occurred in 21 of 64 (32.8%; 95% CI: 22.2%, 44.8%) in the rivaroxaban Part B group and 12 of 34 (35.3%; 95% CI: 20.0%, 53.5%) in the Aspirin group. The risk difference of trivial bleeding between rivaroxaban Part B group and Aspirin group is -2.5% (95% CI: -23%, 17%).

Table 10 below summarizes the incidence rates for safety outcomes in Part B treatment groups and risk differences between Part B treatment groups.

Table 10: Part B Treatment group comparison for safety outcomes at the end of main treatment period – Safety Analysis Set (UNIVERSE Study)

	Part B: Rivaroxaban		***Part B: Aspirin***		
Outcome	**Incidence Rate**	**(95% CI[a])**	**Incidence Rate**	**(95% CI[a])**	**Part B: Risk Difference between Rivaroxaban and Aspirin (95% CI[b])**
Major bleeding (Primary safety outcome)	1.6% (1 / 64)	(0.1%, 7.8%)	0.0% (0 / 34)	(0.0%, 9.0%)	1.6% (−9.9%, 8.4%)
- Fatal or critical site bleeding	0.0% (0 / 64)	(0.0%, 5.6%)	0.0% (0 / 34)	(0.0%, 9.0%)	0.0% (−12%, 5.9%)
- Fall in hemoglobin ≥ 2 g/dL or transfusion of the equivalent ≥ 2 units of packed red blood cell (RBC) or whole blood (WB) in adults	1.6% (1 / 64)	(0.1%, 7.8%)	0.0% (0 / 34)	(0.0%, 9.0%)	1.6% (−9.9%, 8.4%)
Clinically relevant non-major bleeding (Secondary safety outcome)	6.3% (4 / 64)	(2.2%, 15.0%)	8.8% (3 / 34)	(2.4%, 22.2%)	−2.6% (−18%, 8.0%)
Major and clinically relevant non-major bleeding	7.8% (5 / 64)	(3.1%, 16.4%)	8.8% (3 / 34)	(2.4%, 22.2%)	−1% (−17%, 10%)
Trivial bleeding (Secondary safety outcome)	32.8% (21 / 64)	(22.2%, 44.8%)	35.3% (12 / 34)	(20.0%, 53.5%)	−2.5% (−23%, 17%)
SAEs	28.1% (18 / 64)	(18.2%, 40.2%)	23.5% (8 / 34)	(11.3%, 40.7%)	4.6% (−15%, 22%)

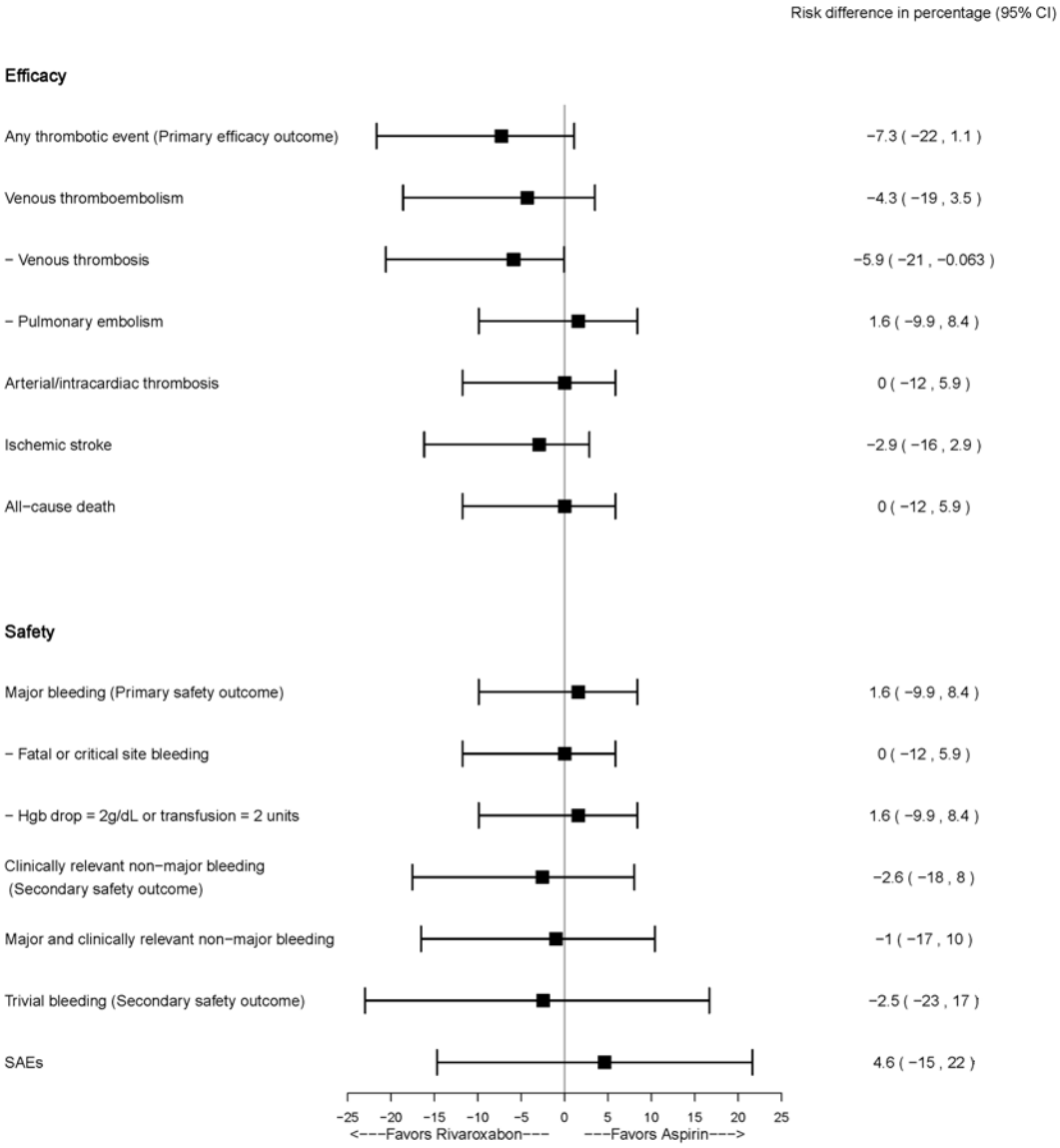
[a]CIs for incidence rates were calculated by applying the Blyth-Still-Casella method.
[b]CIs for risk differences were calculated by applying the Agresti-Min method.
Source: FDA analysis

4.2.7 Benefit-Risk Assessment

The efficacy and safety outcomes were summarized for Benefit-Risk evaluation. The efficacy evaluation included any thrombotic events, whereas safety evaluation included primarily all bleeding events (adjudicated by the CIAC using the International Society on Thrombosis and Hemostasis (ISTH) recommendations) and serious adverse events (SAEs).

The incident proportions of efficacy and safety outcomes and the corresponding 95% CIs were summarized for each treatment group and shown in Tables 9 and 10. The difference in incident proportions between Part B treatment groups (i.e., risk difference) and the corresponding 95% CIs were also summarized. A forest plot based on the risk differences for efficacy and safety outcomes was used to visualize the comparison (Figure 6). Note that none of the Benefit-Risk analyses were conducted for formal hypothesis testing.

Figure 6: Forest plot for Part B treatment group comparison of efficacy outcomes (Full Analysis Set) and safety outcomes (Safety Analysis Set) at the end of main treatment period (UNIVERSE Study)



Note: The forest plot was based on risk difference results in Tables 9 and 10.
Note: All-cause deaths were counted as thrombotic events.
Note: CIs for risk differences were calculated by applying the Agresti-Min method.
Source: FDA analysis

As seen in Figure 6, the risk difference between the rivaroxaban and Aspirin for the primary efficacy outcome (any thrombotic event) has shifted to the left, also for the component efficacy outcomes which have generally shifted to the left or in the middle. The risk differences of safety outcomes are in general in the middle.

5. STATISTICAL ISSUES

The Sponsor had successfully addressed most items listed in the FDA WR, including summarizing descriptive statistics by treatment groups, describing primary safety and efficacy analyses by using cumulative incidences and incidence rates. The following items are suggested by the review team to further enhance trial clarity.

EINSTEIN Jr Study:

- When evaluating the benefit-risk profile, the Sponsor focused on the "Composite of Symptomatic Recurrent VTE and Major Bleeding" (b) (4)

UNIVERSE Study:

- In the clinical study report, the Sponsor used the normal approximation methods (Wald method with continuity correction) to compute the CIs for incidence rates and risk differences. The methods requiring normality are not suitable for a small sized study with rare events. As a result, many CIs were listed as "NA" in the CSR because their values were invalid (e.g., the bounds of CIs for the incidence rates were not between 0 and 1). By using Blyth-Still-Casella [2,3] and Agresti-Min methods [4], this reviewer computed the exact 95% CIs for incidence rates and risk differences for the efficacy and safety outcomes (Tables 9 and 10).

- In the clinical study report, the Sponsor concluded that (b) (4)

6. CONCLUSIONS

The sponsor submitted two phase III studies (EINSTEIN Jr and UNIVERSE) for both efficacy and safety of rivaroxaban to support inclusion of the proposed new indications (i.e., VTE treatment and CHD thromboprophylaxis) in the prescribing information. The sample sizes of these studies were small and did not provide adequate statistical power for confirmatory analyses. As a result, the two studies were determined to be exploratory only, and thus no formal statistical tests can be performed and results should be interpreted with caution.

Despite the small size, the results from the EINSTEIN Jr study were not inconsistent with rivaroxaban being efficacious in the treatment of VTE in children, as indicated by the fact that all efficacy outcomes trended in the direction favoring rivaroxaban (Figure 4). In particular, the

incidence rate of VTE recurrence (primary efficacy outcome) in the rivaroxaban group during the main treatment period (1.2%; 95% CI: 0.4%, 3.0%) was lower than that in the comparator group (3.0%; 95% CI: 1.2%, 6.6%) with a risk difference of -1.8% (95% CI: -6%, 0.64%). The results from the UNIVERSE study also did not contradict the product's thromboprophylaxis effect in pediatric patients with CHD after the Fontan procedure: during the main treatment period, the thrombotic events (primary efficacy outcome) occurred less frequently in the rivaroxaban group (1.6%; 95% CI: 0.1%, 7.8%) than in the Aspirin group (8.8%; 95% CI: 2.4%, 22.2%), with a risk difference of -7.3% (95% CI: -22%, 1.1%).

In both studies, the pattern of safety outcomes was in general comparable between the rivaroxaban and comparator/Aspirin groups (Figures 4 and 6). A noteworthy observation was that, in EINSTEIN Jr study, several safety outcomes showed a slight trend towards the direction favoring the comparator group. E.g., the incidence rate of clinically relevant non-major bleeding during the main treatment period was 3.0% in the rivaroxaban group and 0.6% in the comparator group (risk difference = 2.4%; 95% CI: -0.9%, 5.1%); the incidence rate of trivial bleeding during the main treatment period was 34.3% in the rivaroxaban group and 27.2% in the comparator group (risk difference = 7.2%; 95% CI: -1.7%, 15%). However, the risk differences for those safety outcomes were not statistically significant between treatment groups. For detailed analyses of safety, please refer to the clinical review.

7. LABELING RECOMMENDATIONS

EINSTEIN Jr Study:

- For the EINSTEIN Jr Study, the FDA recommended the sponsor provide in the label risk differences and the corresponding 95% CIs (using Agresti-Min method) for the primary and secondary efficacy outcomes in the table of efficacy results and indicate the method in the footnote of the table. The Sponsor accepted the FDA's recommendation and added the CI results (calculated using StatXact) from the clinical study report.

- The Sponsor referred to the (b) (4) and claimed that the (b) (4). The FDA recommended the Sponsor not (b) (4) The Sponsor accepted the FDA's recommendation.

UNIVERSE Study:

- For the UNIVERSE Study, the FDA recommended the sponsor provide in the label the 95% CIs (using Blyth-Still-Casella method) for incidence rates for the efficacy outcomes in the

table of efficacy results and indicate the method in the footnote of the table. The Sponsor accepted the Agency's recommendation and added the required CIs.

- The FDA recommended the sponsor provide in the label risk differences and the corresponding 95% CIs (using Agresti-Min method) for the efficacy outcomes in the table of efficacy results with the detailed statistical method noted under the footnote of the table. The Sponsor accepted the Agency's recommendation and added the required CIs.

8. REFERNCES

1. Kalbfleisch JD, Prentice RL. The Statistical Analysis of Failure Time Data. John Wiley & Sons; 2002 Sep 9.

2. Blyth CR, Still HA. Binomial Confidence Limits. Journal of the American Statistical Association. 1983;78:108-16.

3. Casella G. Refining binomial confidence intervals. Canadian Journal of Statistics. 1986 Jun;14(2):113-29.

4. Agresti A, Min Y. On small-sample confidence intervals for parameters in discrete distributions. Biometrics. 2001 Sep;57(3):963-71.

5. Berger RL, Boos DD. P values maximized over a confidence set for the nuisance parameter. Journal of the American Statistical Association. 1994 Sep 1;89(427):1012-6.

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