CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

215859Orig1s000

CLINICAL REVIEW(S)

CLINICAL REVIEW

Application Type	505b2 NDA for a new formulation and two indications
Application Number(s)	NDA 215859
Priority or Standard	Priority review containing a response to a Written Request
Submit Date(s)	06/22/21
Received Date(s)	06/22/21
PDUFA Goal Date	12/22/2021
Division/Office	DNH/OCHEN
Reviewer Name(s)	Carrie Diamond, MD Ann T. Farrell, MD (this also serves as the DD and CDTL review)
Review Completion Date	12/20/2021
Established/Proper Name	XARELTO
(Proposed) Trade Name	rivaroxaban
Applicant	Janssen
Dosage Form(s)	Currently marketed – tablets; proposed formulation – oral solution
Applicant Proposed Dosing Regimen(s)	Age and weight-based algorithm ranging from 1 to 3 times a day
Applicant Proposed Indication(s)/Population(s)	1) Treatment of Venous Thromboembolism and Reduction in Risk of Recurrent Venous Thromboembolism in Pediatric Patients XARELTO is indicated for the treatment of venous thromboembolism (VTE) and the reduction in the risk of recurrent VTE in pediatric patients from birth to less than 18 years after at least 5 days of initial parenteral anticoagulant treatment. 2) Thromboprophylaxis in Pediatric Patients with Congenital Heart Disease after the Fontan Procedure XARELTO is indicated for thromboprophylaxis in pediatric patients aged 2 years and older with congenital heart disease who have undergone the Fontan procedure.
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	1) Treatment of Venous Thromboembolism and Reduction in Risk of Recurrent Venous Thromboembolism in Pediatric Patients XARELTO is indicated for the treatment of venous thromboembolism (VTE) and the reduction in the risk of

	recurrent VTE in pediatric patients from birth to less than 18 years after at least 5 days of initial parenteral anticoagulant treatment. 2) Thromboprophylaxis in Pediatric Patients with Congenital Heart Disease after the Fontan Procedure XARELTO is indicated for thromboprophylaxis in pediatric patients aged 2 years and older with congenital heart disease who have undergone the Fontan procedure.

Table of Contents

Glossary 11

1. Executive Summary 14
   1.1. Product Introduction 14
   1.2. Conclusions on the Substantial Evidence of Effectiveness 15
   1.3. Benefit-Risk Assessment 17
   1.4. Patient Experience Data 26

2. Therapeutic Context 26
   2.1. Analysis of Condition 26
   2.2. Analysis of Current Treatment Options 29

3. Regulatory Background 32
   3.1. U.S. Regulatory Actions and Marketing History 32
   3.2. Summary of Presubmission/Submission Regulatory Activity 33
   3.3. Foreign Regulatory Actions and Marketing History 33

4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety 33
   4.1. Office of Scientific Investigations (OSI) 33
   4.2. Product Quality 33
   4.3. Clinical Microbiology 34
   4.4. Nonclinical Pharmacology/Toxicology 34
   4.5. Clinical Pharmacology 34
   4.6. Devices and Companion Diagnostic Issues 34
   4.7. Consumer Study Reviews 34

5. Sources of Clinical Data and Review Strategy 34
   5.1. Table of Clinical Studies 34
   5.2. Review Strategy 47

6. Review of Relevant Individual Trials Used to Support Efficacy 48
   6.1. EINSTEIN JR 48
      6.1.1. Study Design 48

6.1.2. Study Results 52
6.2. UNIVERSE 66
6.2.1. Study Design 66
6.2.2. Study Results 70
6.3. Study 14373 82
6.3.1. Study Design 82
6.3.2. Study Results 84
6.4. Study 14374 88
6.4.1. Study Design 88
6.4.2. Study Results 91
6.5. Study 17618 96
6.5.1. Study Design 96
6.5.2. Study Results 99
6.6. Study 17992 103
6.6.1. Study Design 103
6.6.2. Study Results 105
6.7. Study 12892 109
6.7.1. Study Design 109
6.7.2. Study Results 111

7. Integrated Review of Effectiveness 114
7.1. Integrated Assessment of Effectiveness 115

8. Review of Safety 116
8.1. Safety Review Approach 117
8.2. Review of the Safety Database 118
8.2.1. Overall Exposure 118
8.2.2. Relevant characteristics of the safety population: 120
8.2.3. Adequacy of the safety database: 120
8.3. Adequacy of Applicant's Clinical Safety Assessments 121
8.3.1. Issues Regarding Data Integrity and Submission Quality 121
8.3.2. Categorization of Adverse Events 121

8.3.3. Routine Clinical Tests....122
8.4. Safety Results....123
8.4.1. Deaths....123
8.4.2. Serious Adverse Events....124
8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects....133
8.4.4. Significant Adverse Events....136
8.4.5. Treatment Emergent Adverse Events and Adverse Reactions....140
8.4.6. Laboratory Findings....149
8.4.7. Vital Signs....153
8.4.8. Electrocardiograms (ECGs)....153
8.4.9. QT....153
8.4.10. Immunogenicity....153
8.5. Analysis of Submission-Specific Safety Issues....154
8.5.1. Bleeding....154
8.5.2. Drug Induced Liver Injury....158
8.5.3. Pleural Effusion....160
8.5.4. Thrombocytopenia....161
8.5.5. Vomiting....164
8.6. Safety Analyses by Demographic Subgroups....166
8.7. Specific Safety Studies/Clinical Trials....166
8.8. Additional Safety Explorations....170
8.8.1. Human Carcinogenicity or Tumor Development....170
8.8.2. Human Reproduction and Pregnancy....170
8.8.3. Pediatrics and Assessment of Effects on Growth....170
8.8.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound....170
8.9. Safety in the Postmarket Setting....170
8.9.1. Safety Concerns Identified Through Postmarket Experience....170
8.9.2. Expectations on Safety in the Postmarket Setting....171
8.9.3. Additional Safety Issues From Other Disciplines....172
8.10. Integrated Assessment of Safety....172

9. Advisory Committee Meeting and Other External Consultations 174

10. Labeling Recommendations 174

10.1. Prescription Drug Labeling 174

10.2. Nonprescription Drug Labeling.....174

11. Risk Evaluation and Mitigation Strategies (REMS) 175

12. Postmarketing Requirements and Commitments.....175

13. Appendices.....175

13.1. References.....175

13.2. Financial Disclosure 177

Table of Tables

Table 1: Summary of Treatment Armamentarium Relevant to Proposed Indications 29
Table 2 Listing of Clinical Trials Relevant to this NDA/BLA 35
Table 3 Patient Disposition, Trial 14372 54
Table 4 Disposition with Respect to Entry into Extension Treatment, Trial 14372 55
Table 5 Baseline Demographic and Clinical Characteristics, Safety Population, Trial 14372 56
Table 6. Medical History (>10% of Patients), Safety Population, Trial 14372.....58
Table 7. VTE risk factors, Trial 14372.....59
Table 8 Body Weight-Adjusted Rivaroxaban Dosing Schedule for Children for Trial 14372 60
Table 9 Patients Having Imaging Classified as Uncertain by CIAC, Trial 14372 62
Table 10. Composite of Recurrent VTE and Asymptomatic Deterioration During the Main Treatment Period, Trial 14372.....63
Table 11. Thrombotic Burden Assessment at the End of the Main Treatment Period, Trial 14372 64
Table 12 Duration of Exposure, Safety Population, Trial 14372 65
Table 13 Patient Disposition for Trial 3001 72
Table 14: Demographic characteristics of the patients enrolled in 3001 74
Table 15 Duration between Fontan Procedure and First Dose of Study Agent, in days for Trial 3001.....75
Table 16 Underlying Congenital Cardiac, Familial and Genetic Disorders for Trial 3001 76
Table 17. Surgical and Medical Procedures for Trial 3001 77
Table 18 Dosing for rivaroxaban administration in 3001 (oral suspension) 78
Table 19 CIAC Adjudicated Primary Efficacy Outcome to End of Treatment (Month 12 or End of Study Medication) using Full Analysis Set for Trial 3001 80
Table 20 - Duration of Exposure, Safety Population, Trial CHD3001 81
Table 21: Demographic Characteristics of the Pediatric Patients Enrolled and Treated in Trial 14373.....86
Table 22: Demographic Characteristics of the Pediatric Patients Enrolled and Treated on Trial 14374.....94
Table 23: Demographic Characteristics of the Pediatric Patients Enrolled and Treated in Trial 17618.....100
Table 24: Demographic Characteristics of Pediatric Patients Enrolled in Trial 17992.....106
Table 25: Demographic Characteristics of Pediatric Patients Enrolled in Trial 12892 112
Table 26. Duration of Exposure (Main Treatment Period and Extended), Safety Population, Trial 14372.....118
Table 27. Duration of Exposure in Main Treatment Period for Pediatric patients with CVST, non-CVC-VTE or CVC-VTE > 2 years, Safety Population, Trial 14372.....118
Table 28. Duration of Exposure in Main Treatment Period for Pediatric patients with CVC-VTE < 2 years, Safety Population, Trial 14372 119
Table 29. Duration of Exposure, Safety Population, Trial CHD3001 119

Table 30. Patient Age in Main Treatment Period, Safety Population, Trial 14372 120
Table 31 Serious Adverse Events by System Organ Class and Preferred Term, Safety Population, Trial 14372 124
Table 32 Serious Adverse Events by System Organ Class and FDA Medical Query (Narrow), Safety Population, Trial 14372 128
Table 33 Serious Adverse Events by System Organ Class and Preferred Term, Safety Population, Trial CHD3001 130
Table 34 Serious Adverse Events by System Organ Class and FDA Medical Query (Narrow), Safety Population, Trial CHD3001 132
Table 35. Adverse Events Leading to Discontinuation by System Organ Class and Preferred Term, Safety Population, Trial 14372 133
Table 36 Adverse Events Leading to Discontinuation by System Organ Class and FDA Medical Query (Narrow), Safety Population, Trial 14372 134
Table 37. Adverse Events Leading to Discontinuation by System Organ Class and Preferred Term, Safety Population, Trial CHD3001 135
Table 38. Adverse Event Frequency Leading to Dose Modification, Safety Population, Trial 14372 136
Table 39. Adverse Events Leading to Dose Interruption, Safety Population, Trial 14372 137
Table 40. Adverse Events Frequency Leading to Dose Modification, Safety Population, Trial CHD3001 137
Table 41. Adverse Events Leading to Dose Interruption, Safety Population, Trial CHD3001 138
Table 42. Severity of Adverse Events, Safety Population, Trial 14372 139
Table 43. Severity of Adverse Events, Safety Population, Trial CHD3001 139
Table 44 Adverse Events by System Organ Class, Safety Population, Trial 14372 140
Table 45 Common Adverse Events, Safety Population in >1% of Rivaroxaban Treatment Group, Trial 14372 141
Table 46. Adverse Events by System Organ Class and FDA Medical Query (Narrow), Safety Population, Trial 14372 143
Table 48 Common Adverse Events Occurring in >2% of Patients in the Rivaroxaban Group, Safety Population, Trial CHD3001 146
Table 49 Adverse Events by System Organ Class and FDA Medical Query (Narrow), Safety Population, Trial CHD3001 147
Table 51 Patients with One or More Liver Biochemistry Analyte Values Outside Specified Levels, Safety Population, Trial 14372 150
Table 52 Patients with One or More Liver Biochemistry Analyte Values Outside Specified Levels, Safety Population, Trial CHD3001 151
Table 53 Potential DILI, Safety Population, Trial CHD3001 153
Table 54. Trial 14372- Bleeding Events: Major, Clinically Relevant non-Major Bleeding and Trivial Bleeding in the Main Treatment Period 154
Table 55. Trial 14372 - Severity of Bleeding by Site by Treatment 154

Table 56. Trial 14372 Bleeding Events by Age Group 155
Table 57. Trial 14372- Bleeding Events: Major, Clinically Relevant non-Major Bleeding and Trivial Bleeding Any Time After Randomization 156
Table 58. Trial 3001 - Bleeding Events: Major, Clinically Relevant non-Major Bleeding and Trivial Bleeding 157
Table 59 Trial 3001 - Severity of Bleeding by Site by Treatment 158
Table 60. Adverse Events of Special Interest, Safety Population, Trial 14372 159
Table 61. Subjects with Treatment-Emergent Pleural Effusion, CHD3001 160
Table 62. List of Platelet Count Values ≥Level 2 Criteria (<125,000cells/uL), Safety Population, Trial 14372 163
Table 63. Adverse Events by Gastrointestinal Disorders System Organ Class and FDA Medical Query (Narrow), Safety Population, Trial 14372 165
Table 64. Adverse Events by System Organ Class and FDA Medical Query (Narrow), Safety Population, Trial CHD3001 166

Table of Figures

Figure 1 Drug-Induced Liver Injury Case Screening Plot, Safety Population, Trial CHD3001.....151
Figure 2. Summary of Bleeding Events from Postmarketing Sources.....170

Glossary

AC	advisory committee
AE	adverse event
ALT	alanine transaminase
aPTT	activated partial thromboplastin time
AR	adverse reaction
ASA	aspirin
PBPK	physiological based pharmacokinetic
BID or b.i.d.	twice a day
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CAD	coronary artery disease
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDS	Clinical Data Scientist
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CIAC	central and independent adjudication committee
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRNM	clinically relevant non-major (in reference to bleeding)
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
CVAD	central venous access device
CVC	Central venous catheter
CVST	Cerebral vein and venous sinus
DMC	data monitoring committee
DVT	deep venous thrombosis
ECG	electrocardiogram
eCTD	electronic common technical document
ESMD	early study medication discontinuation
ETASU	elements to assure safe use
FDA	Food and Drug Administration

FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
FMQ	FDA Medical Queries
GCP	good clinical practice
GRMP	good review management practice
Hb	hemoglobin
HIT	heparin induced thrombocytopenia
HITT	heparin induced thrombocytopenia and thrombosis
ICH	International Council for Harmonization
IND	Investigational New Drug Application
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
LMWH	low molecular weight heparin
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
o.i.d	once daily
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PAD	peripheral artery disease
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PE	pulmonary embolism
PI	prescribing information or package insert
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
PT	prothrombin time
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan

SCS	summary of clinical safety
SD	standard deviation
SGE	special government employee
SOC	standard of care
TE	thromboembolism
TEAE	treatment emergent adverse event
TID or t.i.d.	three times a day
UFH	unfractionated heparin
ULN	upper limit of normal
UPSI	United States Prescribing Information
VKA	vitamin K antagonist
VTE	venous thromboembolism

1. Executive Summary

1.1. Product Introduction

Proprietary Name Xarelto®
Established Name- rivaroxaban
Dosage Forms - Tablets: 2.5 mg, 10 mg, 15 mg, and 20 mg
Granules for oral solution: 1 mg/ml after reconstitution-pending
Chemical Class- Small molecule
Pharmacologic Class- Factor Xa inhibitor
Mechanism of Action - Factor Xa inhibitor and inhibitor of prothrombinase activity

Rivaroxaban is an oral anticoagulant approved since 2011 for the following indications for use in adult patients:

- Reduction of Risk of Stroke and Systemic Embolism in Nonvalvular Atrial Fibrillation
- Treatment of Deep Vein Thrombosis
- Treatment of Pulmonary Embolism
- Reduction in the Risk of Recurrence of Deep Vein Thrombosis and/or Pulmonary Embolism
- Prophylaxis of Deep Vein Thrombosis Following Hip or Knee Replacement Surgery
- Prophylaxis of Venous Thromboembolism in Acutely Ill Medical Patients at Risk for Thromboembolic Complications Not at High Risk of Bleeding
- To Reduce the Risk of Major Cardiovascular Events in Patients with Coronary Artery Disease (CAD)
- To Reduce the Risk of Major Thrombotic Vascular Events in Patients with Peripheral Artery Disease (PAD), Including Patients after Recent Lower Extremity Revascularization Due to Symptomatic PAD

Rivaroxaban is not approved for any pediatric indication. This submission contains data to fulfill a Written Request and support two indications for use of rivaroxaban in the pediatric population. The Applicant's proposed indications are proposed below:

#1- Treatment of Venous Thromboembolism and Reduction in Risk of Recurrent Venous Thromboembolism in Pediatric Patients

XARELTO is indicated for the treatment of venous thromboembolism (VTE) and the reduction in the risk of recurrent VTE in pediatric patients from birth to less than 18 years after at least 5 days of initial parenteral anticoagulant treatment.

#2- Thromboprophylaxis in Pediatric Patients with Congenital Heart Disease after the Fontan Procedure

XARELTO is indicated for thromboprophylaxis in pediatric patients aged 2 years and older with congenital heart disease who have undergone the Fontan procedure.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The Applicant has provided substantial evidence of effectiveness for the following indications:

#1: Treatment of Venous Thromboembolism and Reduction in Risk of Recurrent Venous Thromboembolism in Pediatric Patients

#2. Thromboprophylaxis in Pediatric Patients with Congenital Heart Disease after the Fontan Procedure

Indication #1

Evidence of effectiveness for the first indication was based on results of the EINSTEIN Jr study, a phase 3, randomized, open-label, active-controlled, multicenter, international study in which 500 pediatric patients from birth to <18 years of age with acute VTE who received at least five days of parenteral anticoagulation were randomized to rivaroxaban or standard of care comparator (2:1) for the treatment and prevention of reoccurrence of VTE. The recommended rivaroxaban dose was exposure matched to 20 mg daily in adults, this was determined via a physiological based pharmacokinetic (PBPK) model, in addition to phase 1 and phase 2 studies.

Efficacy was demonstrated by the incidence of symptomatic recurrent VTE in the rivaroxaban and comparator groups. During the main treatment period, 4 out of 355 patients (1.2%, 95% CI 0.4%, 3%) who received rivaroxaban had a recurrent VTE, compared to 5 out of 165 patients (3%, 95% CI 1.2%, 6.6%) in the comparator group with a risk difference of -1.8% (95% CI: -6%, 0.87%). Efficacy was further supported by a higher proportion of patients in the rivaroxaban group had improvement in thrombotic burden. Complete resolution of thrombus on repeat imaging without recurrent VTE occurred in 128 out of 335 patients (38.2%, 95% CI 33.0%, 43.5%) in the rivaroxaban group and 43 out of 165 patients (26.1%, 95% CI 19.8%, 33.0%) in the comparator group. Lastly, the composite of recurrent VTE and asymptomatic deterioration occurred in 5 out of 335 patients (1.5%, 95% CI 0.6%, 3.4%) patients in the rivaroxaban group and in 6 out of 165 (3.6%, 95% CI 1.6%, 7.6%) patients in the comparator group. An acceptable benefit-risk profile was demonstrated by a lower proportion patients with the composite of recurrent VTE or major bleeding in the rivaroxaban group compared to the comparator group. Symptomatic recurrent VTE or major bleeding events occurred in 4 out of 335 patients (1.2%, 95% CI 0.4%, 3.0%) in the rivaroxaban group and 7 out of 165 patients (4.2%, 95% CI 2.0%,

8.4%) in the comparator group.

The EINSTEIN Jr study is an adequate and well controlled trial. When considering the rarity of VTE, EINSTEIN Jr included a sufficient number of pediatric patients of all age groups, birth to <18 years old to conclude substantial evidence of effectiveness. Overall, demographics, baseline characteristics, and risk factors are representative of the pediatric VTE population. Therefore, the study results are applicable to pediatric patients with VTE in clinical practice.

The study was not designed to show a difference in effectiveness, as this would not be feasible given the rarity of thromboembolism in pediatric patients and the challenges with enrolling a large number of pediatric patients in clinical trials. Rivaroxaban was previously FDA approved for the following adult indications; treatment of deep vein thrombosis (DVT), treatment of pulmonary embolism (PE), and reduction in the risk of recurrence of DVT or PE. While risk factors and hemostatic differences are important considerations, given the pathophysiology and clinical outcomes of VTE are similar to adults, it is reasonable to partially extrapolate efficacy and PK/PD data. Therefore, the prior determination of effectiveness of rivaroxaban for the treatment of DVT, PE and prevention of recurrent DVT and PE in adults is further evidence of effectiveness applicable to pediatric patients. In addition, supportive studies 14373, 14374, and 17618 also suggested the benefit of rivaroxaban as there were no VTE events in clinical trials.

In summary, the results of EINSTEIN Jr indicates that the use of rivaroxaban weight-based dosing (suspension or tablets), demonstrates benefit in terms of low incidence of symptomatic recurrent VTE that occurred at a lower rate compared to standard of care in pediatric patients with an acute VTE from birth <18 years old. The EINSTEIN Jr study is the largest completed trial to date evaluating the effectiveness of an anticoagulant for pediatric patients with acute VTE. The toxicity profile is manageable, as demonstrated with no patients in the rivaroxaban group having a major bleeding event and a low incidence of clinically relevant non-major bleeding. Approval based on a single adequate and well controlled phase 3 study with 500 pediatric patients, along with supportive phase 1 and 2 studies, in addition to partial extrapolation of efficacy and PK/PD from adult studies, is appropriate given the rarity and seriousness of VTE in pediatric patients and the unmet need for new oral anticoagulants in pediatric patients, including very young infants down to birth.

Indication #2

Evidence of effectiveness for the second indication was based on the UNIVERSE study, a phase 3, randomized, open-label, multicenter, international, 2-part study, which included 110 pediatric patients between 2 to 8 years of age with a recent Fontan operation for single ventricle physiology. Part A was a single-arm part to characterize PK and PD and initial safety profile of rivaroxaban, this included 12 patients. Part B was the randomized, active-controlled part in which 98 patients were randomized 2:1 to rivaroxaban or aspirin to demonstrate efficacy and safety of rivaroxaban for thromboprophylaxis. The rivaroxaban dose was exposure

matched to 10 mg daily in adults. The study clearly demonstrated rivaroxaban suspension as an effective therapy for thromboprophylaxis in pediatric patients following Fontan procedure, by demonstrating a low incidence of thromboembolism (TE) in the rivaroxaban group, which occurred in a lower percentage of patients in the rivaroxaban group compared to aspirin. In total, 1 patient (8.3%) in rivaroxaban group Part A had a TE and 1 patient (1.6%) in rivaroxaban Part B had TE, compared to 3 patients (8.8%) in the aspirin group Part B.

Overall, demographics and baseline characteristics were similar in the rivaroxaban group and the aspirin group. The time between start of prophylactic treatment after the Fontan operation was longer in the rivaroxaban group compared to aspirin group (34 days vs 24 days, respectively). There is no consensus on when to initiate thromboprophylaxis, therefore this important information will be included in the USPI. The patient population included in the UNIVERSE study is well representative of pediatric patients who would be candidates for thromboprophylaxis post-Fontan.

The study was not powered to show a difference in effectiveness between rivaroxaban and aspirin, as this would not be feasible given the rarity of congenital heart disease with single ventricle physiology and the Fontan procedure. Rivaroxaban was previously FDA approved for thromboprophylaxis in adults following orthopedic surgery and for acutely medically ill adults. Given the pathophysiology of formation of thromboembolism and clinical outcomes are similar to adults, it is reasonable to partially extrapolate efficacy and PK/PD data. Therefore, the prior determination of effectiveness of rivaroxaban for thromboprophylaxis in adults is further evidence of effectiveness applicable to pediatric patients.

In summary, the randomized, active-controlled, multicenter study results of UNIVERSE indicate that rivaroxaban weight-based dosing, demonstrates substantial benefit in terms of prevention of TE, as evidenced by a low proportion of pediatric patients over the age of 2 years who experienced TE (venous or arterial) in the rivaroxaban group, which occurred at a lower rate than the aspirin group. The safety profile is manageable, with low rates of major and CRNM bleeding. Approval based on a single adequate and well controlled phase 3 study with 110 pediatric patients, along with supportive partial extrapolation from adult studies is appropriate given the rarity and seriousness of TE in pediatric patients two years and older following Fontan procedure for congenital heart disease and the unmet need for oral anticoagulants in pediatric patients.

1.3. Benefit-Risk Assessment

Benefit-Risk Integrated Assessment

Indication #1
The benefit-risk assessment supports regular approval of rivaroxaban for the treatment venous thromboembolism and reduction in risk of recurrent venous thromboembolism in pediatric patients from birth to <18-year-old.

The assessment of benefit-risk was mainly based on the EINSTEIN Jr study, a phase 3, randomized, active-controlled, open-label, international study in which pediatric patients from birth to less than 18 years old with an acute VTE were randomized to weight-based dose of rivaroxaban (suspension or tablet) or comparator (UFH, LMWH, or fondaparinux with or without VKA) after at least 5 days of parenteral anticoagulation. An oral weight-based formulation was used that matched exposure of rivaroxaban 20mg daily in adults based on PBPK approach.

The determination of efficacy was primarily based on the EINSTEIN Jr study. The trial randomized a total of 500 patients, of which 335 patients were randomized to rivaroxaban and 165 patients were randomized to the comparator group. Pediatric patients were included from birth to <18 years of age (276 children aged 12 to <18 years, 101 children aged 6 to <12 years, 69 children aged 2 to <6 years, and 54 children aged <2 years). All age groups were well represented when considering the rarity of VTE in pediatric patients and allowed for an adequate analysis of efficacy. While the trial was not powered to demonstrate a difference between treatment groups, fewer patients in the rivaroxaban group had symptomatic recurrent VTE compared to standard of care. During the main treatment period, 4 patients (1.2%) who received rivaroxaban had a symptomatic recurrent VTE, compared to 5 patients (3%) in the comparator group with a risk difference of -1.8% (95% CI: -6%, 0.87%). Evidence of benefit is further supported by a higher proportion of patients in the rivaroxaban group achieving improvement in thrombotic burden. Complete resolution of thrombus on repeat imaging without recurrent VTE occurred in 128 patients (38.2%) in the rivaroxaban group and 43 patients (26.1%) in the comparator group. Also, a smaller proportion of patients in the rivaroxaban group had recurrent VTE and asymptomatic deterioration compared to standard of care. The composite of recurrent VTE and asymptomatic deterioration occurred in 5 patients (1.5%) in the rivaroxaban group and in 6 patients (3.6%) in the comparator group. Supportive studies 14373, 14374, and 17618 further demonstrated the benefit of rivaroxaban by showing no patient who received rivaroxaban developed VTE.

The safety database primarily consisted of 491 pediatric patients (birth to <18 years old) who received at least one dose of study drug from the EINSTEIN Jr study. The majority of the safety review was based on the main treatment period, which was 3 months, except for patients <2 years age and a CVC-VTE in which patients received 1 month of treatment. The sample size was sufficient to adequately assess the risk of rivaroxaban

in pediatric patients from birth to < 18 years old. Overall the safety profile was manageable and tolerable. There were no patient deaths related to rivaroxaban. Bleeding is a significant adverse reaction (AR) that can occur with rivaroxaban, previously identified through adult studies. While bleeding overall occurred in a higher proportion of patients in the rivaroxaban group compared to the comparator group (36.2% vs 27.8%, respectively), most bleeding events were trivial. There were no major bleeding events in the rivaroxaban group compared to two patients (1.2%) with major bleeding events in the comparator group. The number of patients who experienced a CRNMB was low, this occurred in 10 patients (3%) in the rivaroxaban group and 1 patient (0.6%) in the comparator group. Overall the most common bleeding sites were nasal, skin and genital. When examining the age groups, bleeding did occur at a higher incidence in the rivaroxaban group in the youngest age group, birth to 2 years (36.1% in the rivaroxaban group vs 17.6% in the comparator) although, most bleeding events were trivial. In patients from birth to <2 years old, 2 patients (5.6%) had CRNMB in the rivaroxaban group compared to none in the comparator. In female patients who experienced menarche between the ages of 12 to <18 years of age, menorrhagia occurred at a higher incidence in the rivaroxaban group compared to the comparator (27% vs 10%, respectively). This is an important consideration for providers prescribing rivaroxaban to female patients who have experienced menarche. Drug discontinuation due to bleeding occurred in 1.5% of patients in the rivaroxaban group and 1.9% in the comparator. The low discontinuation rates supports the tolerability of rivaroxaban in pediatric patients. The safety profile of non-bleeding treatment-emergent adverse events (TEAEs) was acceptable. The most common TEAEs, occurring in over 10% of the pediatric patients included headache, nasopharyngitis, pyrexia and vomiting. Non-bleeding adverse reactions reported in ≥5% in the rivaroxaban arm with a relative risk >1.5 for rivaroxaban vs comparator group included pain in extremity and fatigue and will be included in the USPI. While vomiting did not meet this threshold it was considered an important AR by the clinical review team and will be noted as an AR in the USPI. The safety findings in clinical trials 17992, 17618, 12892, 14374 and 14373 did not alter the safety profile of rivaroxaban.

Overall, the benefit-risk profile is favorable of rivaroxaban in pediatric patients (birth to <18 years old) for the treatment and prevention of reoccurrence of acute VTE. The totality of efficacy and safety data was considered. The EINSTEIN Jr study was an adequate and well controlled trial and provided sufficient data to establish weight-based dosing of rivaroxaban (tablets or suspension) as an effective treatment for acute VTE and prevention of reoccurrence of VTE, as demonstrated by a lower incidence of symptomatic recurrent VTE in the rivaroxaban group compared to standard of care. In addition, EINSTEIN Jr demonstrated a tolerable safety profile, in which the risks associated with rivaroxaban, in particular bleeding events across all age groups is manageable and can be addressed in labeling. The positive benefit-risk profile was further demonstrated in the secondary endpoint of the composite of symptomatic recurrent VTE or major bleeding. Symptomatic recurrent VTE or major bleeding events occurred in 4 patients (1.2%, 95% CI 0.4%, 3.0%) in the rivaroxaban group and 7 patients (4.2%, 95% CI 2.0%, 8.4%) in the comparator group. While not designed to show a difference between rivaroxaban and the comparator, this clearly demonstrates that rivaroxaban was well tolerated and had low recurrent VTE rates. Rivaroxaban also has

the added benefit of availability as an oral solution, so it can be administered to the youngest age groups. No other oral anticoagulant is approved all the way down to birth. In addition, rivaroxaban does not require frequent blood monitoring for levels, this is an advantage in a pediatric population in which frequent venipuncture can be quite challenging.

Indication #2
The benefit-risk assessment supports the regular approval of rivaroxaban in pediatric patients over the age of two years for thromboprophylaxis following the Fontan procedure for congenital heart disease. The assessment of benefit-risk was primarily based off of the UNIVERSE study, a phase 3, open-label, randomized, multicenter study, in which pediatric patients between 2 to 8 years of age with a recent Fontan operation for single ventricle physiology were randomized to weight-based rivaroxaban (granules for oral suspension) or aspirin for thromboprophylaxis (2:1). The dose of rivaroxaban was exposure matched to 10mg daily in adults.

The study results clearly demonstrated rivaroxaban as an effective therapy for prevention of TE in pediatric patients following Fontan procedure. The trial included 110 patients between the age of 2 to 8 years, 76 patients received rivaroxaban (Part A = 12 patients, Part B= 64 patients) and 34 patients received aspirin. The sample size was sufficient to establish efficacy of rivaroxaban for thromboprophylaxis in pediatric patients post-Fontan. In total, 1 patient (8.3%) in rivaroxaban group Part A had a TE and 1 patient (1.6%) in rivaroxaban Part B had TE, compared to 3 patients (8.8%) in the aspirin group in Part B. The study was not designed to show a difference in effectiveness between rivaroxaban and aspirin, but the lower incidence of TE in the rivaroxaban group compared to aspirin is demonstration that rivaroxaban is effective at preventing TE.

The safety of rivaroxaban in patients post-Fontan was primarily assessed in 110 patients from ages 2 to 8 years old in the UNIVERSE study. The median duration of therapy was 51.3 weeks in both study arms. The sample size and duration of therapy was adequate to assess safety given the rarity of pediatric patients who have had a Fontan procedure. The safety profile was acceptable, and risks can be managed with labeling. There were no deaths on study. In total, there was one major bleeding event of epistaxis in the study, this occurred in one patient (1.3%) in the rivaroxaban group. No patient in the aspirin group had a major bleeding event. The incidence of CRNMB was low. CRNMB occurred in 1 patient (8.3%) in the rivaroxaban group Part A, 4 patients (6.2%) in rivaroxaban group Part B, and 3 patients (8.8%) in the aspirin group. The majority of bleeding events were trivial. Overall, bleeding occurred in a lower proportion of patients in the rivaroxaban group compared to the aspirin group (33.3% in rivaroxaban Part A and 35.9% in rivaroxaban Part B vs 41.2% in the aspirin group Part B.). SAEs were higher in the rivaroxaban group compared to the aspirin group (50% in rivaroxaban group Part A and 28.1% in rivaroxaban Part B vs 23.5% in aspirin group Part B.). The

most common SAE was pleural effusion, occurring in 2 patients (16.7%) in rivaroxaban group Part A and 9 patients (14.1%) in the rivaroxaban group Part B compared to 2 patients (5.9%) in the aspirin group Part B. Pleural effusion was not considered an AR as this was most likely related to the Fontan procedure and not rivaroxaban. The most common TEAEs (occurring in >10% of patients in the rivaroxaban group Parts A and B) were nasopharyngitis, pyrexia, cough, upper respiratory tract infection, and vomiting. Non-bleeding ARs reported ≥5% in the rivaroxaban arm with a relative risk >1.5 for rivaroxaban group Part B vs aspirin group included cough, vomiting, rash, and gastroenteritis this will be included in the USPI. In total, 2 patients (3.1%)in rivaroxaban group Part B discontinued rivaroxaban prematurely due TEAEs, one event was bleeding related. Overall, the low discontinuation rates supports the tolerability of rivaroxaban in pediatric patients following Fontan procedure.

The benefit-risk profile supports the approval of rivaroxaban for thromboprophylaxis in pediatric patients (over 2 years of age) following Fontan procedure for single ventricle physiology. The UNIVERSE study provided sufficient data to establish weight-based dosing of rivaroxaban as an effective therapy for thromboprophylaxis in pediatric patients following the Fontan operation. This was demonstrated by the lower incidence of TE events in the rivaroxaban group compared to the aspirin group. The safety profile is manageable, and overall there was low rates of major and CRNM bleeding. In addition, bleeding overall occurred at a lower incidence in the rivaroxaban group compared to the aspirin group. Rivaroxaban also has the added benefit of availability as an oral solution so it can be administered to the youngest age groups. In addition, rivaroxaban does not require frequent blood monitoring for levels, this is an advantage in a pediatric population in which frequent venipuncture can be quite challenging. While the study was limited to patients between the ages of 2 to 8 years, it is expected that rivaroxaban would have the same effect in pediatric patients over 8 years old. Although the protocol provided for dosing recommendations for patients with a weight of 7kg to 8kg, no patients were enrolled below 8kg. However the literature notes that patients under 8 kg do receive a Fontan procedure, therefore, the USPI will provide dosing recommendations for patients with weight of 7kg and higher. Patients with low weight for age are at increased risk for poor outcomes and TE events in this population can have devastating consequences, therefore there is an unmet need for thromboprophylaxis. The effect is expected to same in pediatric patients of lower weight based on TE pathophysiology, TE outcomes and exposure matching data.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	Indication #1 • The incidence of VTE in the pediatric population has been estimated to be between 0.07 to 0.14 per 10000 children per year. • VTE rates have been increasing in hospitalized children. • There are many risk factors that can contribute to the development of VTE. Most risk factors are provoking risk factors, the most common being CVC. • VTE may result in significant morbidity such as extremity pain and/or swelling, postthrombotic syndrome, organ dysfunction, pulmonary embolism, stroke, infection, prolonged hospitalization, loss of catheter function and death. Indication #2 • Congenital heart disease (CHD) affects about 40,000 births per year. • The Fontan procedure is the final palliative surgery in patients with single ventricle physiology and is one of the most common procedures performed for patients with congenital heart disease after the age of 2 years. • Thromboembolism is a significant complication following the Fontan procedure, with an estimated prevalence up to 33% and thromboembolism associated mortality of 25% in pediatrics.	Indication #1 VTE in pediatric patients is a rare and serious condition that is associated with significant morbidity and mortality. Indication #2 Thromboembolic events are a serious complication which can occur following the Fontan procedure in pediatric patients with congenital heart disease.
Current Treatment Options	Indication #1 • Most treatment guidelines and/or recommendations for the treatment of VTE in children are based off of adult experience. • The most commonly used anticoagulants in children are unfractionated heparin (UFH), low molecular weight heparin (LMWH),	Indication #1 There is an unmet need for an effective therapy for the treatment and prevention of recurrent VTE in pediatric patients. Specifically, there is a need for oral anticoagulants in

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	fondaparinux and vitamin K antagonists (VKA). • The formulation of available anticoagulants may not be suitable for all ages, younger patients may not be able to swallow pills and receiving injections and/or venipuncture for monitoring can be challenging. • There are two FDA approved anticoagulants. (1) Dalteparin (LMWH) for the treatment of symptomatic venous thromboembolism (VTE) to reduce the recurrence in pediatric patients 1 month of age and older. (2) Dabigatran (oral direct thrombin inhibitor) for the treatment and reduction of risk of recurrence of VTE in pediatric patients ages 3 months to less than 18 years. Indication #2 • There are no approved anticoagulants for post-Fontan thromboprophylaxis. • Current guidelines recommend thromboprophylaxis following Fontan procedure, but there is no consensus regarding the type of thromboprophylaxis and optimal duration. • Warfarin and aspirin are commonly used in pediatric patients following the Fontan procedure to prevent TE.	pediatric patients including very young children down to birth. Indication #2 There is a clear unmet need for an effective therapy to prevent thromboembolism following Fontan procedure in children.
Benefit	Indication #1 • During the main treatment period of EINSTEIN Jr, 4 out of 355 patients (1.2%, 95% CI 0.4%, 3%) who received rivaroxaban had a recurrent VTE, compared to 5 out of 165 patients (3%, 95% 1.2%, 6.6%) in the comparator group with a risk difference of -1.8% (95% CI: -6%, 0.6%). • Complete resolution of thrombus on repeat imaging without	Indication #1 While the EINSTEIN Jr trial was not powered to demonstrate a difference between treatment groups, a lower proportion of patients in the rivaroxaban group had a symptomatic recurrent VTE compared to the comparator group. In addition, complete resolution of the

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	recurrent VTE occurred in 128 out of 335 patients (38.2%, 95% CI 33.0, 43.5%) in the rivaroxaban group and 43 out of 165 patients (26.1%, 95% CI 19.8, 33.0%) in the comparator group. • The composite of recurrent VTE and asymptomatic deterioration occurred in 5 out of 335 patients (1.5%, 95% CI 0.6, 3.4%) patients in the rivaroxaban group and in 6 out of 165 (3.6%, 95% CI 1.6%, 7.6%) patients in the comparator group with a risk difference of -2.1% (95% CI -6.5%, 0.6%). • Symptomatic recurrent VTE or major bleeding events occurred in 4 out of 335 patients (1.2%, 95% CI 0.4%, 3.0%) in the rivaroxaban group and 7 out of 165 patients (4.2%, 95% CI 2.0%, 8.4%) in the comparator group. Indication #2 • There was 1 patient (8.3%, 95% CI 0.4%, 34.9%) with a venous thrombosis in rivaroxaban Part A, 1 patient (1.6%, 95% CI 0.1%, 7.8%) with a pulmonary embolism in rivaroxaban Part B, and 3 patients (8.8%, 95% CI 2.4%, 22.2%) with thrombotic events (2 patients with venous thrombosis and 1 patient with ischemic stroke) in aspirin Part B group.	thrombus on repeat imaging was higher in the rivaroxaban group. This clearly demonstrates substantial evidence of effectiveness for the treatment and prevention of recurrent VTE in pediatric patients. Indication #2 While the UNIVERSE trial was not powered to demonstrate a difference between treatment groups, the lower incidence of thromboembolic events in the rivaroxaban group compared to the aspirin group demonstrates that rivaroxaban is an effective therapy for thromboprophylaxis in pediatric patients with congenital heart disease following the Fontan operation.
Risk and Risk Management	Indication #1 • The most common TEAEs occurring in ≥10% of patients in the rivaroxaban group were headache, nasopharyngitis, pyrexia and vomiting. • Non-bleeding adverse reactions reported ≥5% in the rivaroxaban arm	Indication #1 Overall, the safety profile of rivaroxaban is acceptable for pediatric patients from birth to less than 18 years of age for the treatment and prevention recurrent VTE.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	with a relative risk >1.5 for rivaroxaban vs comparator group included pain in extremity and fatigue. • No major bleeding events occurred in the rivaroxaban group. CRNM bleeding occurred in higher proportion of patients in the rivaroxaban group compared to the comparator group (3% vs 0.6%, respectively). • Any bleeding occurred at a higher proportion of patients in the rivaroxaban group compared to the comparator group (36.2% vs 28.7, respectively). • Drug discontinuation due to bleeding occurred in 1.5% of patients in the rivaroxaban group and 1.9% in the comparator during the main treatment period. • In female patients who experienced menarche, ages 12 to <18 years of age, menorrhagia occurred at a higher rate in the rivaroxaban group compared to the comparator (27% vs 10%, respectively). Indication #2 • The most common TEAEs (occurring in >10% of patients in the rivaroxaban groups Part A and B) were nasopharyngitis, pyrexia, cough, upper respiratory tract infection, and vomiting. • Non-bleeding adverse reactions reported ≥5% in the rivaroxaban arm with a relative risk >1.5 for rivaroxaban group Part B vs comparator group included vomiting, cough, gastroenteritis and rash. • Major bleeding event of epistaxis occurred in one (1.6%) patient in the rivaroxaban group Part B and none in aspirin group. CRNMB occurred at a lower rate in the rivaroxaban group Part B compared to the aspirin Part B (6.3% vs 8.8%, respectively).	Risks of rivaroxaban, including bleeding, can be sufficiently addressed in the United States Prescribing Information (USPI). Indication #2: Overall, the safety profile of rivaroxaban is acceptable for thromboprophylaxis in pediatric patients with congenital heart disease after the Fontan procedure. Risks of rivaroxaban, including bleeding, can be sufficiently addressed in the United States Prescribing Information (USPI).

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• Discontinuation due to bleeding events occurred in 1 (1.6%) in the rivaroxaban group Part B.	

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

□	The patient experience data that was submitted as part of the application include:	Section where discussed, if applicable
	□ Clinical outcome assessment (COA) data, such as	[e.g., Sec 6.1 Study endpoints]
	□ Patient reported outcome (PRO)	
	□ Observer reported outcome (ObsRO)	
	□ Clinician reported outcome (ClinRO)	
	□ Performance outcome (PerfO)	
	□ Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)	
	□ Patient-focused drug development or other stakeholder meeting summary reports	[e.g., Sec 2.1 Analysis of Condition]
	□ Observational survey studies designed to capture patient experience data	
	□ Natural history studies	
	□ Patient preference studies (e.g., submitted studies or scientific publications)	
	□ Other: (Please specify)	
□	Patient experience data that were not submitted in the application, but were considered in this review:	
	□ Input informed from participation in meetings with patient stakeholders	
	□ Patient-focused drug development or other stakeholder meeting summary reports	[e.g., Current Treatment Options]
	□ Observational survey studies designed to capture patient experience data	
	□ Other: (Please specify)	
X	Patient experience data was not submitted as part of this application.	

2. Therapeutic Context

2.1. Analysis of Condition

Venous thromboembolism (VTE)

The CDC estimates that the precise number of people affected by DVT/PE is unknown, although as many as 900,000 people could be affected (1 to 2 per 1,000) each year in the United States with millions more internationally. The VTE incidence in pediatric population has been estimated between 0.07 to 0.14 per 10000 children per year [1]. VTE rates have been increasing in hospitalized children, from 5.3 events per 10,000 pediatric hospital admissions in the early 1990s to 30-58 events per 10,000 hospital admissions currently[2]. Many more adult patients than pediatric patients developed VTEs; thus, there are many more adult patients who could potentially participate in clinical trials for VTE prophylaxis and treatment.

There are differences in the etiology of VTE in pediatrics compared to the adults, in particular in younger children. Genetic, anatomic and acquired risk factors may impact the risk of developing VTE. Neonates and adolescents are at the highest risk for VTE[1]. Unlike adults, in which a significant number of VTE events are spontaneous, the vast majority of VTEs occurring in children are provoked[3]. The most common provoking risk factor is the presence of central venous catheter (CVC) which attributes to >90% of VTEs in neonates and >60% in older children[1]. Other risk factors include cancer, sickle cell disease, congenital heart disease, trauma, thrombophilia, nephrotic syndrome, obesity, infection, inflammatory bowel disease, illness, medications, and inflammatory states[3]. Also, similar to adults, immobility, oral contraceptive use and surgery are risk factors as well. Unprovoked VTEs do occur but are much less common. Often, pediatric patients have comorbidities, such as serious illness.

Similar to adults, VTE can lead to significant morbidity and mortality. VTE may result in postthrombotic syndrome, pain and/or swelling at the affected site, organ dysfunction, pulmonary embolism (PE), stroke, infection, prolonged hospitalization, loss of catheter function and even death[2].

Treatment guidelines recommend anticoagulation for the initial treatment of symptomatic VTE in both adults and children. The goal of therapy is to prevent clot extension, embolism and reoccurrence. The benefits of anticoagulation must be carefully weighed against the risk, most importantly the risk of bleeding[2]. Due to a lack of adequate and well controlled pediatric trials and overall paucity of data from pediatric studies, treatment recommendations are often based on the adult experience or observation. But, there are important considerations unique to pediatric patients this includes; developmental hemostasis, increased frequency of illness or comorbidities, vascular access issues, and heterogeneity within the pediatric population (i.e. age, weight, and risk factors)[2]. In addition, the formulation of anticoagulants may not be suitable for all ages, as younger patients will not be able to swallow pills and receiving injections can be challenging. As VTE rates are increasing, with many patients with

complex medical conditions, there is a significant unmet need for safe and effective oral anticoagulant for pediatric patients.

Thromboprophylaxis Post-Fontan

According to the CDC, in the United States congenital heart disease (CHD) affects about 40,000 births per year. The prevalence of CHD is approximately 12 cases per 1000 children [4]. The incidence of infants born with single ventricle physiology ranges from ~3.1–4.9 per 10,000 live birth[5]. The Fontan procedure is the final palliative surgery in patients with single ventricle physiology and is increasingly being performed. This procedure diverts systemic venous return directly into the pulmonary arteries, without the need of a right ventricle[6]. The Fontan operation has become the most common procedure performed for congenital heart disease after the age of 2 years[7]. It has been estimated that approximately 1000 Fontan procedures are performed each year in the United States[8]. The Fontan surgery is typically completed in childhood, between 18 months to 4 years of age, and most commonly around the age of 2 years[9, 10]. The Fontan operation has been performed in children as young as 7 months, there are conflicting reports if morbidity is increased in patients <10kg[11]. Although, low weight for age is associated with poor outcomes[11]. As surgical techniques have improved, patients are living longer, but thromboembolism (TE) has continued to be identified as a significant complication.

Thrombosis is a major complication post-Fontan procedure and a significant cause of morbidity and mortality, patients are at risk for stroke, myocardial infarction, pulmonary embolism and death[12]. The risk of TE is highest within the first 6 months to a year after Fontan surgery and again after 10 years[13, 14]. Thrombosis can be venous or arterial, and can occur at a variety of sites including; intracardiac, intravascular, cerebrovascular, or other embolism[6]. The frequency of thromboembolism post-Fontan is not known, intracardiac thrombosis has a reported prevalence of up to 33%, venous and stroke incidence has ranged between 3-19% of patients[6]. Mortality in pediatric patients from thrombosis after Fontan surgery has been reported to be as high as 25%[6].

The cause of thrombosis is related to many factors including hypercoagulability, turbulent blood flow, areas of stasis, presence of prosthetic material, and arrhythmias[14, 15]. Multiple risk factor have been identified for TE post-Fontan, including pulmonary artery distortion, pulmonary atresia with intact ventricular septum, prolonged use of central lines, conduit-related factors, right to left shunting and pulmonary artery banding[12, 14]. In addition, alterations in pro and anti-coagulant factors have been described[12].

Thromboprophylaxis is often indicated following the Fontan procedure[12]. The National Heart, Lung and Blood Institute convened a Working Group in 2012 and identified patients with single ventricle physiology both before and after Fontan as a top research priority, noting that there is no consensus on the type and duration of thromboprophylaxis and neither currently used therapy (aspirin or warfarin) are optimal[16].

2.2. Analysis of Current Treatment Options

Indication #1
The most commonly used anticoagulants in children are unfractionated heparin (UFH), low molecular weight heparin (LMWH), fondaparinux and vitamin K antagonists (VKA)[1]. Currently, there are two FDA approved anticoagulants in children. First, dalteparin is a low molecular weight heparin (LMWH), given subcutaneously, approved in 2019 for the treatment of symptomatic VTE to reduce the recurrence in pediatric patients 1 month of age and older. The second was dabigatran, an oral direct thrombin inhibitor, approved in 2021 for the treatment and reduction of risk of recurrence of VTE in pediatric patients ages 3 months to less than 18 years. While UFH does not have a pediatric indication, pediatric dosing is described in the USPI. A summary of the commonly used anticoagulants in pediatrics is summarized in Table 1.

The American Society of Hematology recently published guidelines in 2018 for the treatment of pediatric venous thromboembolism. The guidelines recommend <3 months of treatment for provoked DVT or PE, and possibly longer if the causative risk factor persists. For unprovoked DVT or PE treatment was recommended for 6 to 12 months. Anticoagulation was also recommended for CVST. The ASH guidelines suggests using LMWH or VKA for anticoagulation in patients with symptomatic DVT or PE. A recommendation on the use of direct oral anticoagulants (DOACs) were not made due to lack of available data from clinical trials[1]. For CVC-related VTE the 2012 American College of Chest Physicians Evidence-Based Clinical Practice Guidelines recommend that children should be treated with LMWH or UFH between 6 weeks and 3 months[17].

There is a clear unmet need for oral anticoagulants in pediatric patients. Heparins and LMWHs require frequent monitoring and injections. VKAs are given orally, but also require frequent monitoring with venipuncture, in addition there is no approved liquid formulation, and INR levels are impacted by diet and concomitant medications.

Table 1 Summary of Treatment Armamentarium Relevant to Proposed Indications

Product (s) Name	Relevant Indication	Year of	Route and Frequency of	Efficacy Information	Important Safety and Tolerability	Other Comments

		Approval	Administration		Issues	(e.g., subpopulation not addressed
FDA Approved Treatments [Combine by Pharmacologic Class, if relevant]						
Dabigatran capsules and oral pellets	1) For the treatment of venous thromboembolic events (VTE) in pediatric patients aged 3 months to less than 18 years of age who have been treated with a parenteral anticoagulant for at least 5 days 2) To reduce the risk of recurrence of VTE in pediatric patients aged 3 months to less than 18 years of age who have been previously treated	2021	Oral twice daily, weight based	Based on extrapolation from adult trials and pediatric clinical trials	In pediatric trials the major safety issue was bleeding Gastrointestinal adverse reactions Alopecia	Approval does not cover the entire pediatric age range
Dalteparin injection (LMWH)	Treatment of symptomatic venous thromboembolism (VTE) to reduce the recurrence in pediatric patients 1 month of age and older	2019	Subcutaneous Injection twice daily, based on age	Based on extrapolation from adult trials and pediatric clinical trials	In pediatric trials the major safety issue was bleeding Heparin induced thrombocytopenia (HIT) or heparin induced thrombocytopenia and thrombosis (HITT) Hypersensitivity	Approval does not cover the entire pediatric age range
Other Treatments – Not FDA approved for pediatric patients						
Heparin (Unfractionated heparin)			Intravenous Initial Dose 75 to 100	Target aPTT of 60-85 secs assuming this reflects	Bleeding risk HIT and HITT	Dosing for pediatric patients is described in

			units/kg IV bolus over 10 minutes Maintenance dose: Infants: 25-30 units/kg/hour Children: >1 year of age: 18 to 20 units/kg/hour	an anti-Factor Xa level of 0.35 to 0.70	Hypersensitivity Antidote-protamine	the UPSI Use preservative-free heparin sodium injection in neonates and infants

Indication #2

There are no products approved for thromboprophylaxis treatment of pediatric patients post Fontan surgery. Rivaroxaban is approved for the prophylactic treatment of adult patients following hip and knee surgery.

Multiple studies have demonstrated that thromboprophylaxis post-Fontan procedure decreases the risk of TE[12, 18]. Practice guidelines recommend aspirin or therapeutic UFH followed by VKAs over no therapy in children post-Fontan[19]. A meta-analysis of 1200 patients post-Fontan who received thromboprophylaxis with either aspirin or warfarin showed a statically significant reduction in thromboembolism compared to placebo. The overall incidence of TE was 18.6% in patients not receiving thromboprophylaxis, 8.6% for those who received aspirin and 9% for those who received warfarin[18]. There is no drug or anticoagulant approved for thromboprophylaxis post-Fontan and there is no consensus on which therapy is best for patients or duration of treatment[20]. Warfarin and aspirin are often used for thromboprophylaxis, but thrombosis still occurs and there is no difference in incidence of early or late TE when comparing aspirin and warfarin[18, 21].

Warfarin is an oral vitamin K antagonist and is the most common oral anticoagulant used in pediatrics off-label. While warfarin is commonly used it poses many challenges in children. First, it requires frequent venipuncture for monitoring of INR levels due to the narrow therapeutic window. This can be very difficult for small children. Also, response to warfarin may differ based on genetic factors[20]. In addition, diet and concomitant medications can impact INR. Supratherapeutic levels increase risk of bleeding while subtherapeutic levels may increase risk of thrombosis. It has also been suggested that patients have a lower compliance rate in the warfarin group compared to aspirin[12]. Patients who continue warfarin long-term may be at increased risk for low bone marrow density[22].

Aspirin inhibits platelet aggregation by suppressing thromboxane A2 production by irreversible inactivation of cyclooxygenase[23]. Aspirin has the advantage of not needing frequent

monitoring. One disadvantage of aspirin is there is a subpopulation that is resistant to aspirin[22]. In addition, the optimal dose of aspirin therapy is not known. Aspirin has been recommended for long-term prophylaxis following the Fontan procedure, although it may not be sufficient for high-risk patients[21].

In summary, there is an unmet need for thromboprophylaxis for pediatric patients following the Fontan operation as there is no approved therapy for this indication and neither commonly used thromboprophylaxis regimen is optimal.

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

As noted above in 1.1, rivaroxaban has been approved since 2011 for multiple prophylactic and treatment indications for adult patients. Rivaroxaban is not approved for pediatric patients.

The Agency has not reviewed previously the main clinical studies supporting the proposed indications and the proposed pediatric granules for oral formulation.

3.2. Summary of Presubmission/Submission Regulatory Activity

This submission contains the response to a Pediatric Written Request issued on 08 June 2017 and subsequently amended on 23 March 2018 (Amendment 1). The pediatric written request was the subject of more than 12 industry meetings.

3.3. Foreign Regulatory Actions and Marketing History

The following countries have approved rivaroxaban in 2021 to treat pediatric patients for prophylaxis or treatment of venous thromboembolism:
Canada
European Union/European Medicines Agency
Japan
Nicaragua
Panama
Switzerland
United Kingdom

The Applicant has indicated [redacted] (b) (4)

4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

From the Office of Scientific Investigations review

Based on these inspections, the conduct of the above studies appears to be adequate. The study data derived from these clinical investigator sites are considered reliable: Riten Kumar, M.D., and Joseph Palumbo, M.D. for Study 14372, and Biagio Pietra, M.D. and Andrew van Bergen, M.D. for Study 39039039CHD3001. The study data submitted to the Agency for assessment appear acceptable in support of the proposed indication.

4.2. Product Quality

From the Office of Product Quality review

OPQ recommends approval of NDA 215859 for marketing of XARELTO (rivaroxaban) for oral suspension 1 mg/mL. The applicant provided adequate information to ensure the identity, strength, purity, and quality of the proposed product. All facilities are in good standing.

4.3. Clinical Microbiology

None

4.4. Nonclinical Pharmacology/Toxicology

From the Nonclinical Pharmacology/Toxicology review by Bo Yeon Lee, Ph.D.
"The nonclinical program reviewed under reference NDAs 202439 and 022406 concluded that rivaroxaban was approvable for the indications listed above in adult patient population. The reference NDAs include nonclinical studies in juvenile, adolescent and adult rats, and the overall nonclinical assessment remains unchanged. In addition, the Sponsor submitted additional PK studies of pediatric protein binding and of substrate characteristics towards a fetal CYP isoform, which showed that the unbound fraction in pediatric plasma was higher than in adult plasma and that rivaroxaban is a poor substrate for the fetal isoform CYP3A7.

Therefore, there are no safety concerns from the nonclinical perspective and rivaroxaban is approvable to be used in pediatric populations for the proposed indications based on the nonclinical assessment of the new PK studies and reviews by nonclinical reviewers of reference NDAs."

4.5. Clinical Pharmacology

From the Clinical Pharmacology review submitted by Harisudhan Thanukrishnan, Ph.D.

The Office of Clinical Pharmacology (OCP)/ Division of Cardiometabolic and Endocrine Pharmacology and Division of Pharmacometrics have reviewed the information contained in NDA 215859. The OCP review team recommends approval of NDA 215859, rivaroxaban granules for oral suspension and tablets, for use in pediatric patients from birth (at-term) to <18 years of age for the VTE treatment and reduction of risk of VTE recurrence and pediatric patients aged 2 years or older after the Fontan procedure for thromboprophylaxis.

Clinical pharmacology information demonstrated similar exposure- response relationships for clotting time variables (PT, aPTT and anti-factor Xa) between pediatric and adult patients with VTE and pediatric patients with CHD after the Fontan procedure. In addition, the proposed doses in pediatric patients are expected to result in a similar range of steady-state rivaroxaban trough concentrations, as observed in adults.

The proposed body weight-based dosing regimens are appropriate for the treatment or reduction in recurrence of VTE in pediatric patients from at-term birth (weighing ≥ 2.6 kg) to <18 years and for thromboprophylaxis in patients 2 years or older with CHD after the Fontan procedure based on clinical PK, efficacy and safety data from Studies EINSTEIN Jr and UNIVERSE, as well as population PK/PD and PBPK modeling and simulation analyses.

The clinical pharmacology team provided recommendations regarding dosing instructions with food, missed doses, renal impairment, and concomitant medications.

4.6. Devices and Companion Diagnostic Issues

None

4.7. Consumer Study Reviews

None

5. Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

Appears this way on original

Table 2 Listing of Clinical Trials Relevant to this NDA/BLA

Trial Identity	NCT no.	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population
		Controlled Studies to Support Efficacy and Safety					
INDICATION #1							
PH-40166/14372 (EINSTEIN Jr)		Phase: 3 Randomized, open-label, active-controlled, 2-arm, multicenter study	Rivaroxaban: suspension or tablet (Oral) Standard of care (either LMWH, fondaparinux, UFH, and VKA) at the discretion of the attending physician (Oral or SC or IV) Body weight-adjusted rivaroxaban to achieve a similar exposure as that observed in adults treated for VTE with 20 mg rivaroxaban QD. Rivaroxaban treated: 329 12 to <18 years: 180 6 to <12 years: 67 2 to <6 years: 46	1) To access the Incidence of symptomatic recurrent VTE; 2) to access the incidence of symptomatic recurrent VTE and asymptomatic deterioration on repeat imaging; 3) to assess the incidence of overt major and clinically relevant non-major bleeding	3-month main study treatment period which could be extended with 3 blocks of 3 months each; subjects with catheter-related VTE aged <2 years the main treatment period was 1 month which could be extended with 2 blocks of 1 month each	500	Pediatric subjects aged between birth and <18 years with confirmed VTE who receiv initial treatment with therapeutic dosages of UF LMWH or fondaparinux ar required anticoagulant the for at least 90 days; Subje with catheter-related VTE <2 years were required to anticoagulant therapy for least 30 days

			0.5 to <2 years: 21 <0.5 years: 15 Comparators were administered as per standard of care. Comparator treated: 162 12 to <18 years: 89 6 to <12 years: 34 2 to <6 years: 22 0.5 to <2 years: 9 <0.5 years: 8				
INDICATION #2							
39039039CHD 3001/ 18226 (UNIVERSE)		Phase: 3 Prospective, open-label, multinational, multicenter study with single-arm Part A and 2-arm, randomized, active- controlled Part B Pediatric subjects between 2 to 8 years of age, who	Rivaroxaban: 0.1% (1 mg/mL) suspension ASA: 81 or 100 mg tablet (Oral) Parts A and B: 12 months each	Part A: To characterize the single- and multiple-dose PK and PK/PD profiles after oral rivaroxaban therapy administered to pediatric subjects 2 to 8 years of age with single ventricle physiology	Parts A and B: 12 months each	112	Pediatric subjects betwee 8 years of age, who had Fo procedure within 4 month prior to enrollment

		had Fontan procedure within 4 months prior to enrollment Part A: To characterize the single- and multiple-dose PK and PK/PD profiles after oral rivaroxaban therapy administered to pediatric subjects 2 to 8 years of age with single ventricle physiology Part B: To evaluate the safety and efficacy of rivaroxaban, administered BID (exposure matched to rivaroxaban 10 mg QD in adults) compared to		Part B: To evaluate the safety and efficacy of rivaroxaban, administered BID (exposure matched to rivaroxaban 10 mg QD in adults) compared toASA, given QD (approximately 5 mg/kg) for thromboprophylaxis in pediatric subjects 2 to 8 years of age with single ventricle physiology			

-							
		Studies to Support Safety					
PH-38995/14373		Phase: 2 Open-label, multinational, multicenter study	Rivaroxaban: suspension or tablet (Oral) Standard of care (either LMWH, fondaparinux or VKA) at the discretion of the attending physician (Oral or SC or IV) Age- and body weight-adjusted dosing of rivaroxaban to achieve a similar exposure as that observed in adults treated for VTE with 20 mg rivaroxaban once daily.	To assess the incidence of major bleeding and clinically relevant non-major bleeding	30 days	64	Pediatric subjects betwee and <18 years of age with documented symptomatic asymptomatic venous thrombosis treated for at 2 months or, in case of cat related thrombosis, treate at least 6 weeks with LMW fondaparinux and/or VKA
PH-39333/14374		Phase: 2 Open-label, single arm, multicenter study	Rivaroxaban: 0.1% ready to use suspension (Oral) Locally used anticoagulant at the discretion of the attending physician	To assess the incidence of major bleeding and clinically relevant non-major bleeding	30 days	46	Pediatric subjects aged 6 months to <6 years with documented symptomatic asymptomatic venous thrombosis treated for at 2 months or, in case of catheter- related thrombo treated for at least 6 week with LMWH, fondaparinux and/or VKA

			(Oral or SC or IV) 30 days Age- and body weight-adjusted dosing of rivaroxaban to achieve a similar exposure as that observed in adults treated for VTE with 20 mg				
PH-39733/17618		Phase 1/2 Multinational, multicenter study Pediatric subjects from birth to less than 6 months with documented symptomatic or asymptomatic venous or arterial thrombosis, who have been treated with anticoagulant therapy for at least 5 days or 2 weeks To characterize the PK/PD	Rivaroxaban: 0.1% ready to use suspension (Oral)	To characterize the PK/PD profile of a 7-day treatment with oral rivaroxaban	7 days	10	Pediatric subjects from bir less than 6 months with documented symptomatic asymptomatic venous or arterial thrombosis, who have bee treated with anticoagulan therapy for at least 5 days 2 weeks To characterize the PK/PD profile of a 7-day treatme with oral rivaroxaban

		profile of a 7-day treatment with oral rivaroxaban					
-							
		Other studies pertinent to the review of efficacy or safety (e.g., clinical pharmacological studies)					
PH-38629/17769		Phase: 1 Randomized, open-label, 4-way crossover, non-placebo-controlled, single-dose, single- center study	Rivaroxaban: suspension and IR tablet (Oral) 4 single dose administrations separated by washout period of 7 days Treatment A: 10 mg rivaroxaban dry powder oral suspension fasted; Treatment B: 20 mg rivaroxaban dry powder oral suspension fed; Treatment C: 10 mg rivaroxaban ready-to-use oral suspension fasted; Treatment D: 10 mg rivaroxaban immediate release tablets fasted.	To characterize AUC, AUC/D, Cmax, and Cmax/D of the dry powder oral suspension in comparison to the ready-to-use oral suspension; To characterize AUC, AUC/D, Cmax, and Cmax/D of the dry powder oral suspension in comparison to an IR tablet	1 day	18	Healthy men, aged 18-55 y (inclusive)
PH-38690/17861		Phase: 1 Randomized, open-label, 5-way crossover,	Rivaroxaban: suspension (Oral) 5 single dose	To characterize the influence of different amounts of	35 days	16	Healthy men, aged 18-55 y (inclusive)

		non-placebo-controlled, single-dose, single-center study	administrations separated by washout period of 7 days	water on the PK with the particular focus on the absorption phase of the ready-to-use oral suspension of rivaroxaban			
PH-36262/14022		Phase: 1 Open-label, randomized, non-placebo controlled, 4-way crossover, single-dose, single-center study	Rivaroxaban suspension and tablets (Oral)	To characterize the PK of 10 and 20 mg of rivaroxaban administered as an oral suspension in comparison to a 10 mg immediate release tablet. The potential for a food effect was investigated for 20 mg oral suspension.	4 months	17	Healthy men, age 18 to 55 years
PH-40127/19365		Phase 1	Rivaroxaban Suspension, granules and tablets (Oral) Single oral dose of a 10 mg	To establish bioequivalence with respect to AUC, AUC(0-tlast) and Cmax		30	Healthy men, aged 18-55 y (inclusive)

			tablet rivaroxaban, administered under fasting conditions; Single oral dose of 10 mg rivaroxaban, granules for oral suspension administered under fasting conditions.	of 10 mg granules for oral suspension versus 10 mg tablets rivaroxaban when administered as single oral dose under fasting conditions			
PH-40136/19366		Phase:1 Randomized, open-label, 2-waycrossover, non- placebo-controlled, single-dose, single- center study	Rivaroxaban: suspension and tablet (Oral) Two single dose administrations separated by washout period of 7 days	To establish bioequivalence with respect to AUC, AUC(0-tlast) and Cmax of 20 mg granules for oral suspension versus 20 mg tablets rivaroxaban when administered as single oral dose under fed conditions		30	Healthy men, aged 18-55 y (inclusive)
PH-37535/16886		Phase: 1 Randomized,	Rivaroxaban: suspension and IR tablet (Oral)	To characterize the PK of 10 and 20 mg of		14	Healthy men, aged 18-55 y (inclusive)

		open-label, 4-way crossover, non-placebo-controlled, single-dose, single- center study		rivaroxaban administered as an oral suspension in comparison to a 10 mg IR tablet. The potential for a food effect was investigated for the 20 mg oral suspension			
PH-38996/17992		Phase: 1 Open-label, 3-cohort, single-dose, multicenter study Groups A and B: Children with an age between 6 months and <12 years who have completed anticoagulant treatment at least 10 days prior to the planned study drug	Planned: Group A and B: 6 to 24 each group; Group C: 3 to 10 Actual: 47 Rivaroxaban: suspension (Oral) Single dose Administration Rivaroxaban: 1.25, 2.5, 5, 7.5, 10, 15, and 20 mg film coated IR tablet; 1 mg/mL oral suspension. (Oral)	To characterize the single dose PK profile of rivaroxaban administered as granules for oral suspension formulation		47	Children > or = 2 months t 12 years who have recent completed anticoagulant treatment Body weight-adjusted sing doses administered as granules for oral suspension according three dosing regimens: Group A (n=22): Dosing as low dose in Phase 1 study 12892; Group B (n=23): Dosing as ready to use suspension d in Phase 2 studies 14373 a 14374; Group C (n=2): Dosing of

		administration; Group C: Children with an age ≥2 months and weight between3 kg and <12 kg, who have completed anticoagulant treatment at least 10 days prior to the planned study drug administration, and have gestational age at birth of at least 37 weeks, and oral feeding/nasogastric/gastric feeding for at least 10 days To characterize the PK profile of rivaroxaban administered as granules for oral suspension	Single dose administration				0.4 mg/kg body weight for children weighing 3 to <12 kg.

		formulation 3 kg and <12 kg, who have completed anticoagulant treatment at least 10 days prior to the planned study drug administration, and have gestational age at birth of at least 37 weeks, and oral feeding/nasogastric/gastric feeding for at least 10 days To characterize the PK profile of rivaroxaban administered as granules for oral suspension formulation					
PH-38444/12892		Phase: 1 Single-dose, open-label,	Rivaroxaban: 1.25, 2.5, 5, 7.5, 10, 15, and 20 mg film coated IR tablet; 1 mg/mL	To investigate PK and PD of single oral doses of rivaroxaban		59	Rivaroxaban doses (tablet oral suspension) administe based on individual age and body w

		noncontrolled, multinational, multicenter study Pediatric subjects ≥6 months and <18 years of age To investigate PK and PD of single oral doses of rivaroxaban in pediatric subjects in order to obtain weight adjusted doses with equivalent exposure compared to 10 mg and 20 mg doses in adults	oral suspension. (Oral) Single dose administration	in pediatric subjects in order to obtain weight adjusted doses with equivalent exposure compared to 10 mg and 20 mg doses in adults			A high dose group and a lo dose group, equivalent to 20 mg and the 10 mg dose adults, respectively. Subje between age of ≥6 months to <6 years with b weight between 2 to 14 kg received oral suspension o to 5 mg in high dose group 0.4 to 2.5 mg in low dose group; Subjects between a 6 year to <18 years with body weigh between 14 to 50 kg received oral suspension o 10 mg in high dose group 2.5 to 5 mg in low dose gr and/or received tablet of 5 15 mg in high dose group 2.5 to 7 mg in low dose gr Subjects with body weight comparable to adult (50 to ≥100 kg) received tablet o mg in high dose group and mg in low dose group. 12 to <18 years: 9 6 to <12 years: 24 2 to <6 years: 16 6 months to <2 years: 10

Reviewer's Comment: The Applicant's program was very clearly devised and comprehensive.

5.2. Review Strategy

The clinical data package included both healthy volunteer studies involving formulation and trials enrolling pediatric patients. All trials involving pediatric patients were reviewed for PK, PD efficacy and safety including single dose studies. All healthy volunteer studies were reviewed.

The Office of Scientific Investigations was consulted to provide their input on reliability of data for the two major trials (EINSTEIN Jr and UNIVERSE).

The primary clinical review was conducted by Ann Farrell and Carrie Diamond. The primary statistical review was conducted by Huan Wang and Yeh-Fong Chen. The safety analysis was supported by clinical data scientists, Adam Horin and Qunshu Zhang.

Table 2 lists the pivotal clinical trials evaluating the efficacy and safety of rivaroxaban in the pediatric population, early phase clinical pharmacology trials evaluating PK/PD and safety, and healthy volunteer studies in adult men.

The two main trials for review are EINSTEIN JR which was an adequate and well-controlled trial that provided sufficient efficacy and safety data for review of rivaroxaban in the pediatric population for indication #1 and UNIVERSE an adequate and well-controlled trial that provided sufficient data (mostly safety data) for indication #2. These trials were not pooled because of differences in trial design.

For indication #1, the Applicant's development program consisted of 4 studies supporting efficacy: Phase 3 study, 14372 (EINSTEIN Jr Phase 3), two Phase 2 studies: Study 14373 and Study 14374, and the Phase 1/2 study, Study 17618.

For indication #2, the Applicant had a single Phase 3 study, CHD3001 (UNIVERSE) study.

For both indications, there were 2 additional supportive Phase 1 studies, Study 12892 and Study 17992, that helped to establish the pediatric dosing recommendations.

All trials were reviewed separately because of differences in design, populations, treatment duration and intent. The trials employed similar endpoints.

The statistical and clinical review of safety and efficacy included the following:

- Current literature on VTE in the pediatric population, epidemiology and treatment along with the Applicant's background materials.
- Current literature on Fontan Surgery and post-op recovery
- Review of phase 2 and 3 trials to support the indication, including the clinical study report (CSR), protocol, protocol amendments, case reports forms and narratives,

statistical analysis plan (SAP) and SAP amendments
- Review datasets and sent queries for unstandardized and missing data entries
- Performed data analyses using datasets submitted as SAS transport files
- Review of the OSI and BIMO inspection reports- Review and evaluation of proposed labeling.

Careful consideration of use of extrapolation from adult experience to pediatric data to support approval for the indications due to the rarity of the condition.

6. Review of Relevant Individual Trials Used to Support Efficacy

6.1. EINSTEIN JR

6.1.1. Study Design

Overview and Objective

The trial had a number of objectives:

For efficacy
Assess the incidence of symptomatic recurrent venous thromboembolism
Assess the incidence of symptomatic recurrent venous thromboembolism and asymptomatic deterioration on repeat imaging.
For safety
Assess the incidence of overt major and clinically relevant non-major bleeding.
Additional objective to characterize the pharmacokinetic/pharmacodynamic profile of rivaroxaban.

The trial hypothesis was that body weight-adjusted rivaroxaban administered as oral tablets or oral suspension which achieved a similar exposure as that observed in adults treated for venous thromboembolism (VTE) with 20 mg rivaroxaban once daily would be effective treatment.

Reviewer's Comment: These objectives are appropriate for the development of a dosing strategy for prophylaxis/treatment of thromboembolism.

Trial Design

Multicenter, open-label, active-controlled, randomized study to evaluate the efficacy and safety of an age-and body weight adjusted rivaroxaban regimen compared to standard of care in pediatric patients with acute venous thromboembolism

Standard of care for this trial was defined as subcutaneous low molecular weight heparin (LMWH), subcutaneous fondaparinux, intravenous unfractionated heparin (UFH) and/or oral vitamin K antagonist (VKA).

Reviewer Comment: This trial is the largest performed to date evaluating the effectiveness of an anticoagulant treatment for pediatric patients with a VTE.

The main inclusion criteria were:

- Pediatric patients aged between birth and <18 years with confirmed VTE who received initial treatment with therapeutic dosages of UFH, LMWH or fondaparinux and required anticoagulant therapy for at least 90 days.
- Pediatric patients with catheter-related VTE aged < 2 years were required to have anticoagulant therapy for at least 30 days.
- For pediatric patients younger than 6 months:
    - o Gestational age at birth of at least 37 weeks.
    - o Oral feeding/nasogastric/gastric feeding for at least 10 days.
- Body weight ≥2600 g

The main exclusion criteria were:

- Bleeding risk contraindicating anticoagulant therapy
- eGFR <30 mL/min/1.73 m2 (in those younger than 1 year, serum creatinine results above 97.5th percentile excludes participation)
- Hepatic disease: with coagulopathy leading to a clinically relevant bleeding risk, or ALT >5x ULN, or total bilirubin >2x ULN with direct bilirubin >20% of the total.
- Platelet count <50 x 109/L.
- Sustained uncontrolled hypertension defined as systolic and/or diastolic blood pressure >95th age percentile.
- Life expectancy <3 months.
- Concomitant use of strong inhibitors of both CYP3A4 and P-gp
- Concomitant use of strong inducers of CYP3A4
- Childbearing potential without proper contraceptive measures, pregnancy or breast feeding.
- Hypersensitivity or any other contraindication listed in the local labeling for the comparator treatment or experimental treatment.

Patients received body weight-adjusted rivaroxaban in a once daily, twice-daily, or thrice-daily regimen. Those randomized to comparator received standard of care anticoagulation.

The main study treatment period was 3 months, which could be extended with 3 blocks of 3 months each, followed by an observational period of another 30 days.

For pediatric patients with catheter-related VTE aged < 2 years the main study treatment period was 1 month, which could be extended with 2 blocks of 1 month each, followed by an observational period of 30 days.

All suspected clinical study outcomes and baseline and repeat thrombosis imaging tests were assessed by a central independent adjudication committee (CIAC).

An independent data monitoring committee monitored the children's safety and gave recommendations to the steering committee.

Study Endpoints

Primary efficacy endpoint- symptomatic recurrent VTE

Secondary efficacy endpoint - composite of symptomatic recurrent VTE and asymptomatic deterioration in thrombotic burden on repeat imaging

Additional secondary endpoints

- 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.

Safety endpoint- composite of overt major and clinically relevant non-major bleeding (CRNMB).

Other: The variables for pharmacodynamics were PT, aPTT, and antifactor Xa. Pharmacokinetic variables were AUC(0-24),ss, Cmax,ss and Ctrough,ss were analyzed as a function of body weight and age and in comparison, to adult exposure levels.

A Taste-and-Texture questionnaire was also used in this study to determine the acceptance of the oral suspension in children aged ≥4 years.

Statistical Analysis Plan

Per the Applicant - The study was not powered to test a hypothesis regarding comparison of incidences of outcomes with rivaroxaban versus SoC, exploratory stratified (strata: CVST, CVC-VTE, non-CVC-VTE) Cox proportional hazards models were fitted for the time to event variables primary efficacy outcome (symptomatic recurrent VTE), the composite of all symptomatic recurrent VTE and major bleeding, and the treatment-emergent principal safety outcome up to the end of main treatment period.

Firth's penalized maximum likelihood estimation was used to reduce bias in the parameter estimates. Confidence intervals were obtained using profile-likelihood functions and p-values for the treatment effect were calculated using likelihood ratio tests.

The ordered categorical outcome of composite of symptomatic recurrent VTE and change in thrombus burden categories at the end of main treatment period were compared between treatment groups with the nonparametric test by van Elteren for stratified ordinal response data and by fitting proportional odds model.

The frequencies of the composite of symptomatic recurrent VTE and asymptomatic deterioration in thrombus burden, the composite of symptomatic recurrent VTE and asymptomatic deterioration and no change in thrombus burden, the normalization of thrombus burden were compared between treatment group using logistic regression models. Confidence intervals and p-values were calculated from the logistic regression models and from the proportional odds models with covariates treatment group and index event categories.

Two-sided 95% confidence intervals for the frequency of efficacy and principal safety outcomes were calculated by applying the exact method of Blyth-Still-Casella.
Confidence intervals for the differences in frequencies of the efficacy and principal safety outcomes up to the end of the main treatment period were calculated with unstratified exact method using the standardized test statistic and inverting a two-sided test.

Reviewer's Comment: Given the rarity of the condition, to conduct a study enrolling only pediatric patients powered to demonstrate efficacy and safety with statistical significance would have required many years. Therefore, the Applicant's statistical analysis plan is acceptable. See statistical review for further details.

Protocol Amendments

Major Amendments were

4 (07/21/15)

- Implementation of dosing regimen for pediatric patients aged between 6 to <12 years based on data obtained from the phase II study (14373).
- Menstruation intensity assessments to reflect that the intensity of menstruation has to be assessed from visit 2 to visit 7.
-Recommendations were provided on body weight adjusted treatment in patients who turned 2, 6, 12 and 18.
Heparins flushes were added to maintain catheter patency.
- Rivaroxaban administration guidelines with an o.d. and b.i.d. regimen for patients aged between 6 and <12 years were added.
- Instructions for handling of missed doses for o.d. and bid dosing in children aged between 6 and <12 years.

#8 (09/20/16)

- The timeframe in which randomization can be done was extended from day 1-5 to day 1-9 of the initial treatment.
- Information was added for switch from VKA to rivaroxaban.
- Exclusion criterion 1 updated to read: “bleeding risk contraindicating anticoagulant therapy”.
- Clarification of exclusion criterion 5 regarding pediatric patients with sustained uncontrolled hypertension
- Collection of body weight was added for Visits 2 and 3.
- The assessment of the incidence of post-thrombotic syndrome was added for children of ≥12 years with lower or upper extremity DVT at Visit 4, 5, 6 and 7.
- Enrollment of patients aged between 0.5 to <6 years was opened, and the structure of age cohort specific dosing and regiment instructions was resolved and replaced by a consistent description applicable for patients aged between 0.5 and <18 years.
- The suspension formulation could be used by any pediatric patient.

#10 (01/11/17)

- The dosing table was revised to include dosing information for children with body weight of 6 kg to 12 kg. Patients with body weight between 6 and <12 kg were to be treated according to a t.i.d. schedule.

#12 (09/27/17)

- New dosing information for pediatric patients with body weight between 2.6 and <6 kg, and also aged between birth and 0.5 year.

Reviewer’s Comment: For added safety a stepped down approach to enrolling pediatric patients by age was conducted. Protocol amendments did not impact the integrity of the clinical trial.

6.1.2. Study Results

Compliance with Good Clinical Practices

The Applicant stated that the study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and the International Council for Harmonisation (ICH) guideline E6: Good Clinical Practice (GCP) and the ethical standards of Directive 2001/20/EC.

The study used informed consent processes. After the parents/guardian/legally authorized representative voluntarily signed, the pediatric patient if able to understand was provided the opportunity.

The study had Central Laboratory determinations for pharmacokinetics and pharmacodynamics were performed by 3 sponsor central laboratories:

1. For PK: (b) (4)
2. For PT and aPTT: Bayer AG, (b) (4)
3. For anti-Xa: Bayer AG, (b) (4)

The study employed the following committees:

-Steering Committee (SC): to provide an overall academic leadership

-Independent Data Monitoring Committee (IDMC/DMC): to evaluate all study data to ensure subjects safety throughout the study.

-Central Independent Adjudication Committee (CIAC): to review independently specified safety and all efficacy outcomes in the study in compliance with the charter, and to adjudicate and classify the events, including the confirmation of the documented index thrombotic event before first study treatment administration.

Financial Disclosure

There were 796 investigators (including sub investigators) and 107 principal investigators. Of the 107, six had disclosable interest.

The Applicant's comment regarding these investigators was to provide information regarding the number of patients that they personally enrolled in the study. The percentage contribution

to the total enrolled was less than 4% per site.

Reviewer Comment: I agree that the disclosable financial payments were unlikely to have influenced the trial results for multiple reasons including the trial had a central adjudication committee for the main outcome of interest. I agree that the company performed due diligence to obtain the required financial disclosure.

Patient Disposition

Five hundred and twenty pediatric patients were screened with twenty who were not able to be enrolled (13 did not meet inclusion/exclusion criteria, 1 patient convenience, 4 withdrawal, and 2 other).

Table 3 below lists patient disposition for the 500 enrolled and treated.

Table 3 Patient Disposition, Trial 14372

Disposition Outcome	Rivaroxaban N=329 n (%)	Comparator N=162 n (%)
Patients randomized	335	165
Patients not treated	6	3
Patients randomized and treated	329	162
Per-protocol population	327	158
Safety population	329	162
Discontinued study	32 (9.7)	15 (9.3)
Adverse event	11 (3.3)	2 (1.2)
Death	1 (0.3)	0 (0)
Efficacy outcome reached	2 (0.6)	2 (1.2)
Lost to follow-up	1 (0.3)	1 (0.6)
Non-compliance with study drug	1 (0.3)	2 (1.2)
Other	3 (0.9)	2 (1.2)
Patient convenience	2 (0.6)	1 (0.6)
Physician decision	5 (1.5)	1 (0.6)
Protocol violation	1 (0.3)	0 (0)
Recovery	1 (0.3)	0 (0)
Withdrawal by subject	4 (1.2)	4 (2.5)

Source: CSR and ds.xpt, adsl.xpt; Software: R
Abbreviations: N, number of patients in treatment arm; n, number of patients in specified population or group; NA, not applicable

Reviewer Comment: The discontinuation rate was approximately 9.5%. The reasons for discontinuation were fairly balanced between the treatment arms except for discontinuation because of an adverse event which was higher in the rivaroxaban arm.

The study also allowed treatment extension for those patients requiring longer anticoagulation for their specific medical condition. After main treatment period completion, study treatment could be continued three times with blocks of 3 months each except for pediatric patients with CVC-VTE aged <2 years, whose study treatment could be continued two times with blocks of 1 month each (maximum study treatment duration, 3 months). See table below.

Of the 500 randomized children, 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. Although some children with CVC-VTE aged <2 years were included before Amendment 12 (and therefore had a main study treatment period of 3 months rather than 1 month), the main treatment duration was considered to be 1 month for all of these children.

Table 4 Disposition with Respect to Entry into Extension Treatment, Trial 14372

Disposition Outcome	Rivaroxaban N=335 n (%)	Comparator N=165 n (%)	Total N=500 n (%)
Randomized	335 (100%)	165 (100%)	500 (100%)
Treated	329 (98.2%)	162 (98.2%)	491 (98.2%)
Premature Treatment Discontinuation (withdrawal)	1 (0.3%)	3 (1.8%)	4 (0.8%)
Completed Main Treatment Period	328 (97.9%)	159 (96.4%)	487 (97.4%)
No extension	179 (53.4%)	90 (54.5%)	269 (53.8%)
Started Extension 1	149 (44.5%)	69 (41.8%)	218 (43.6%)
Did Not Complete Extension 1	26 (7.8%)	13 (7.8%)	39 (7.8%)
Adverse Event	4 (1.2%)	0	4 (0.8%)
Non-compliance	2 (0.6%)	0	2 (0.4%)
Other	2 (0.6%)	3 (1.8%)	5 (1%)
Physician Decision	16 (4.8%)	8 (4.8%)	24 (4.8%)
Protocol Deviation	1 (0.3%)	0	1 (0.2%)
Recovery	1 (0.3%)	0	1 (0.2%)
Withdrawal	0 (0.3%)	2 (1.2%)	2 (0.4%)
Completed Extension 1	123 (36.7%)	56 (33.9%)	179 (35.8%)
No extension 2	61 (18.2%)	27 (16.4%)	88 (17.6%)

Started Extension 2	62 (18.5%)	29 (17.6%)	91 (18.2%)
Did Not Complete Extension 2	5 (1.5%)	2 (1.2%)	7 (1.4%)
Adverse Event	1 (0.3%)	0	1 (0.2%)
Lost to Follow Up	1 (0.3%)	1 (0.6%)	2 (0.4%)
Physician Decision	3 (0.8%)	1 (0.6%)	4 (0.8%)
Completed Extension 2	57 (17%)	27 (16.4%)	84 (16.8%)
No extension 3	26 (7.8%)	10 (6.1%)	36 (7.2%)
Started Extension 3	31 (9.3%)	17 (10.3%)	48 (9.6%)
Did Not Complete Extension 3	0	0	0
Completed Extension 3	31 (9.3%)	17 (10.3%)	48 (9.6%)

Source: Clinical reviewer and CSR

Clinical reviewer comment: The proportion of patients that continued on to complete extension 2 and 3 were similar between the two treatment groups.

Protocol Violations/Deviations

Major protocol deviations were reported for 29 (5.8%) of the pediatric patients: 22 (6.6%) in the rivaroxaban group and 7 (4.2%) in the comparator group; 22 had major protocol deviations related to PK/PD (rivaroxaban group only), 9 treatment deviations – did not take study drug, and 6 other protocol deviations – CIAC could not confirm the index event.

Minor protocol deviations were reported for 345 (69.0%) of the 500 pediatric patients: 72.2% in the rivaroxaban group and 62.4% in the comparator group.

Clinical reviewer comment: Major protocol deviations to not appear to impact the integrity of the study and occurred at a similar rate in the rivaroxaban and comparator group.

Table of Demographic Characteristics

Table 5 Baseline Demographic and Clinical Characteristics, Safety Population, Trial 14372

Characteristic	**Rivaroxaban N=329**	**Comparator N=162**
Sex, (n%)		
Female	159 (48.3)	82 (50.6)
Male	170 (51.7)	80 (49.4)
Age, years		
Mean (SD)	11 (5.8)	11.2 (5.8)
Median (min, max)	13.3 (0, 18)	13.1 (0, 18)
Age group, years, (n%)		
<0.5 years	15 (4.6)	8 (4.9)
0.5 - <2 years	21 (6.4)	9 (5.6))
2 - <6 years	46 (14.0)	22 (13.6)
6 - <12 years	67 (20.4)	34 (21.0)

Characteristic	Rivaroxaban N=329	Comparator N=162
12 - <18 years	180 (54.7)	89 (54.9)
Ethnicity, (n%)		
Hispanic or Latino	17 (5.2)	11 (6.8)
Not Hispanic or Latino	286 (86.9)	136 (84.0)
Not Reported[1]	26 (7.9)	15 (9.3)
Race, (n%)		
American Indian or Alaska Native	0 (0)	2 (1.2)
Asian	20 (6.1)	8 (4.9)
Black or African American	12 (3.6)	12 (7.4)
Native Hawaiian or Other Pacific Islander	1 (0.3)	0 (0)
White	267 (81.2)	121 (74.7)
Multiple	3 (0.9)	1 (0.6)
Not Reported[1]	26 (7.9)	18 (11.1)
Country of participation, (n%)		
Argentina	3 (0.9)	0 (0)
Australia	9 (2.7)	1 (0.6)
Austria	8 (2.4)	4 (2.5)
Belgium	8 (2.4)	2 (1.2)
Brazil	4 (1.2)	1 (0.6)
Canada	17 (5.2)	7 (4.3)
Switzerland	5 (1.5)	2 (1.2)
China	8 (2.4)	1 (0.6)
Germany	18 (5.5)	4 (2.5)
Spain	7 (2.1)	6 (3.7)
Finland	1 (0.3)	0 (0)
France	15 (4.6)	11 (6.8)
Great Britain	32 (9.7)	17 (10.5)
Hong Kong	0 (0)	1 (0.6)
Hungary	5 (1.5)	2 (1.2)
Ireland	1 (0.3)	1 (0.6)
Israel	11 (3.3)	4 (2.5)
Italy	14 (4.3)	8 (4.9)
Japan	4 (1.2)	2 (1.2)
Mexico	2 (0.6)	3 (1.9)
Netherlands	22 (6.7)	8 (4.9)
Portugal	1 (0.3)	0 (0)
Russia	29 (8.8)	17 (10.5)
Singapore	3 (0.9)	2 (1.2)
Slovakia	1 (0.3)	1 (0.6)
Sweden	1 (0.3)	0 (0)
Turkey	4 (1.2)	4 (2.5)
United States	96 (29.2)	53 (32.7)

Source: adsl.xpt; Software: R
Abbreviations: N, number of patients in treatment group; n, number of patients with given characteristic; SD, standard deviation

1 Data on race and ethnicity were nor reported in per local regulations/country laws.

Clinical reviewer comment: Patient demographics were well balanced between the rivaroxaban and comparator arm. Most patients were adolescents. The youngest age group, ages 0-2 years of age had the smallest proportion of patients (11% in the rivaroxaban group and 10.3% in the

comparator group). This is reasonable given the difficulty of enrolling very young children in clinical trials and the rarity of VTE. The youngest patient enrolled in the clinical trial was 5 days old.

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

About 97% had significant medical history findings (Table 6). The most common medical histories of these patients were congenital abnormalities (29%), cardiac (15%), neoplasm (13%), hematologic (20%), surgery (42%) and infectious disease (50%). Most children had normal kidney function with less than one percent having a creatinine clearance under 50 ml/min.

Table 6 Medical History (>10% of Patients), Safety Population, Trial 14372 Primary System Organ Class	Rivaroxaban N=329 n (%)	Comparator N=162 n (%)	Total N=491 n(%)
Blood and lymphatic system disorders	66 (20.1)	31 (19.1)	97 (19.8)
Cardiac disorders	52 (15.8)	20 (12.3)	72 (14.7)
Congenital familial and genetic disorders	94 (28.6)	47 (29)	141 (28.7)
Gastrointestinal disorders	106 (32.2)	48 (29.6)	154 (31.4)
Constipation	38 (11.6)	26 (16)	64 (13)
General disorders and administration site conditions	91 (27.7)	36 (22.2)	127 (25.9)
Pyrexia	37 (11.2)	15 (9.3)	52 (10.6)
Immune system disorders	42 (12.8)	14 (8.6)	56 (11.4)
Infections and infestations	167 (50.8)	79 (48.8)	246 (50.1)
Mastoiditis	35 (10.6)	15 (9.3)	50 (10.2)
Injury, poisoning and procedural complications	52 (15.8)	26 (16)	78 (15.9)
Investigations	78 (23.7)	24 (14.8)	102 (20.8)
Metabolism and nutrition disorders	63 (19.1)	27 (16.7)	90 (18.3)
Musculoskeletal and connective tissue disorders	67 (20.4)	36 (22.2)	103 (21)
Neoplasm	46 (14)	19 (11.7)	65 (13.2)
Nervous system disorders	98 (29.8)	46 (28.4)	144 (29.3)
Headache	39 (11.9)	20 (12.3)	59 (12)
Psychiatric disorders	48 (14.6)	29 (17.9)	77 (15.7)
Respiratory, thoracic and mediastinal disorders	99 (30.1)	38 (23.5)	137 (27.9)
Skin and subcutaneous tissue disorders	63 (19.1)	18 (11.1)	81 (16.5)
Surgical and medical procedures	145 (44.1)	59 (36.4)	204 (41.5)

Central venous catheterization	37 (11.2)	15 (9.3)	52 (10.6)
Vascular disorders	48 (14.6)	18 (11.1)	66 (13.4

Source: Adapted from CSR

CIAC confirmed an index VTE in 99.7% of pediatric patients in the rivaroxaban arm and 97.6% in the comparator arm. Most events were lower extremity VTE (33.4% - rivaroxaban, 32.1% - comparator) and followed by CVST (22.1% - rivaroxaban, 26.1% -comparator) and followed by PE (14.6% - rivaroxaban, 18.8% -comparator). CVC-VTE was found in 90/335, 26.9% in rivaroxaban group and 37/165, 22.4% in comparator group.

VTE was unprovoked in 56 (11.2%), provoked by persistent risk factors in 87 (17.4%), provoked by transient risk factors in 236 (47.2%), and by both transient and persistent risk factors in 115 (23.0%) pediatric patients. The most common persistent risk factors were major organ disease (16.6%) especially cardiac (9.8%) and active cancer (11.2%), mostly hematologic malignancy (7.2%) and solid tumor (4%). Most common transient risk factors were major infectious disease (28.4%) and use of central venous catheter (25.2%). An acquired thrombophilia was seen in 2%, family history of venous thrombosis in 1.4%, and known inherited thrombophilia in 6.4%. Morbid obesity was a risk factor for 3.6%.

Table 7. VTE risk factors, Trial 14372

Risk factor	Rivaroxaban N=335 n(%)	Comparator N=165 n(%)	Total N=500 n(%)
Unprovoked	31 (9.3)	25(15.2)	56 (11.2)
Provoked	303 (90.4)	135 (81.8)	438 (87.6)
Transient risk factor only	151 (45.1)	85 (51.5)	236 (47.2)
Persistent risk factor only	62 (18.5)	25 (15.2)	87 (17.4)
Persistent and transient risk factor	90 (26.9)	25 (15.2)	115 (23)
Unknown	1 (0.3)	5 (3)	6 (1.2)

Source: Adapted from CSR

Clinical reviewer comment: Overall, baseline characteristics including medical history and location of the index event were well balanced between treatment arms. There were slightly more patients with a provoking risk factors in the rivaroxaban arm and a higher proportion of patients had an unprovoked risk factor in the comparator. The significance of these differences is not clear given the small patient numbers. Overall, 25% of patients had a CVC-VTE, as this is typically the most common reason for VTE in paediatrics, this is lower than what would be expected.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

These patients were on multiple other medications besides those taken for the thromboembolism, most patients (95.1%) received at least one concomitant medication. However, for the purposes of this review, I will focus on the anticoagulant therapies. The Applicant based the dosing on exposure matching to 20 mg daily in adults.

Table 8 Body Weight-Adjusted Rivaroxaban Dosing Schedule for Children for Trial 14372

Patient Body Weight (kg)	Single daily dose	Twice a day dosing	Three times a day dosing	Total dose per day
2.6 < 3			0.8 mg[a]	2.4 mg
3 < 4			0.9 mg[a]	2.7 mg
4 < 5			1.4 mg[a]	4.2 mg
5 <7			1.6 mg[a]	4.8 mg
7 <8			1.8 mg[a]	5.4 mg
8 <9			2.4 mg[a]	7.2 mg
9 <10			2.8 mg[a]	8.4 mg
10 <12			3.0 mg[a]	9 mg
12 <20		5 mg[a]		10 mg
20 <30		5 mg[a,b]		10 mg
30 <50	15 mg [a,b]			15 mg
≥ 50	20 mg[a,b,c]			20 mg

[a]Suspension
[b]Tablets
[C] in Japan 15 mg

For switching from unfractionated heparin (UFH), low molecular weight heparin (LMWH), or fondaparinux to rivaroxaban, the first rivaroxaban dose was planned 4 hours after stopping the infusion of UFH, 12 hours after the last injection of LMWH with a twice-daily regimen, or 24 hours after the last injection of fondaparinux or LMWH with a once-daily regimen. Also UFH, LMWH, or fondaparinux treatment were not continued after the start of rivaroxaban treatment.

Less than 5% of pediatric patients received a thrombolytic prior to study medication. More than 95% of pediatric patients received UFH or LMWH prior to study medication. The mean and median duration of anticoagulant treatment prior to start of study treatment was 7 days. Approximately 97% of patients received parenteral anticoagulant duration of at least 5 days.

Children randomized to the comparator group continued with UFH, LMWH or

fondaparinux or switched to VKA therapy. VKA dosages were adjusted to maintain the INR within the therapeutic range (target 2.5, range 2.0 - 3.0). UFH, LMWH or fondaparinux could be discontinued once the INR was above 2.0 on two separate occasions, 24 hours apart.

Treatment compliance for rivaroxaban

Twenty-five out of 329 patients did not return their dispensed medication thus an understanding of their compliance was not possible. Of the remaining, 304 patients, none had treatment compliance less than 50%, 6 had treatment compliance between 50% and 80% with all others having greater than 80%.

Treatment compliance for comparator

Treatment compliance was only available for France, Italy, Poland, Belgium, Spain, Japan, Austrian, Russia, and Turkey. Of the 91 patients with available compliance data, 1 patient had a compliance less than 50%, 4 had compliance between 50% and 80% with all others having greater than 80%.

Clinical reviewer comment: Almost all patients received parental anticoagulation for at least 5 days prior to initiating study drug. Overall, compliance rate was high in both rivaroxaban and the comparator for the patients in which compliance data was available.

Efficacy Results – Primary Endpoint

Because repeat imaging studies can be difficult to obtain, the Agency and Applicant agreed that at the end of the main treatment period, repeat thrombosis imaging was performed (provided no additional ionizing radiation or general anesthesia was required). The repeat imaging studies were compared to baseline imaging studies.

The CIAC classified the results as normalized, improved (ie, thrombus still present but partly recanalized or involving less venous segments), no relevant change (ie, not recanalized and similar in extent) or deteriorated (ie, new venous segment involved). Repeat imaging outcomes were not performed for children who had developed a symptomatic recurrent venous thromboembolic complication during the main treatment period. Also, if repeat imaging could not be adequately evaluated, the outcome was considered “uncertain”. These process and procedure were based on an algorithm for the classification of outcomes of repeat imaging in the SAP.

Imaging time window was defined as Day 90 ± 21 days (or Day 30 ± 7 for patients less than 2

years of age with a CVC-VTE).

Out of 459 patients with repeat imaging, 370 had the imaging performed within the time window. Four patients had imaging performed before time window and had their study medication stopped within 7 days of imaging. Nine patients had a scan which confirmed the primary outcome and were classified as deteriorated (Table 9).

Table 9 Patients Having Imaging Classified as Uncertain by CIAC, Trial 14372

Repeat Imaging	Status of Study Anticoagulation	Adjudication Outcome	Number of Patients
Performed Before time Window	Treatment continued for more than 7 days after imaging	Uncertain	30
Performed After time Window	Not applicable	Uncertain	22
Not performed or unevaluable	If any anticoagulation stopped before study treatment time window	Uncertain	8
Not performed or unevaluable	If any anticoagulation stopped during study treatment time window	Improved	7
Not performed or unevaluable	If any anticoagulation continued after study treatment time window	Uncertain	9

Source: Clinical reviewer

Reviewer's Comment: These steps taken by the Applicant are reasonable and appropriate as this is a pediatric population.

Primary Endpoint- Main Treatment Period

During the main treatment period, four patients of 335 (1.2%) who received rivaroxaban had a recurrent VTE. Five patients out of 165 (3%) in the comparator group had a recurrent VTE (HR of 0.40; 95% CI: 0.11 to 1.41). In the rivaroxaban group, all 4 recurrences occurred in the non-CVC-VTE group and presented in the same anatomical location as the index event: upper extremity in one patient, lungs in one patient and lower extremity in two patients. Recurrent

VTE occurred during initial heparinization in 1 patient, during rivaroxaban treatment in 2 patients (1 tablet, 1 suspension), and in 1 patient while temporarily off rivaroxaban and receiving heparin during placement of a venous stent. Two patients had transient and persistent risk factors, one patient had a persistent risk factor, and one patient had an unprovoked VTE. All events occurred during the first month of treatment (range: 5-28 days).

In the comparator group, 4 out of 5 recurrences occurred in the non-CVC-VTE group and presented in the same anatomical location as the index event in 3 of these 4 children. An additional pediatric patient in the comparator group had a recurrent CVST. Location of index events included lower extremity in 3 patients, CVST in one patient, and lung in one patient. At the time of the recurrent VTE, two patients were receiving vitamin K antagonist (VKA), one tinzaparin, one enoxaparin and one dalteparin. Transient risk factors were present in two patients, persistent risk factor in one patient, transient and persistent risk factor in one patient and unprovoked in one patient. All events occurred during the first month of treatment (range: 5-30 days).

Extended Treatment

During the extended treatment period, one out of 38 patients (2.6%) in the rivaroxaban arm (during extension period 2) and two patients in the comparator had a recurrent VTE (one out of 46 patients (2.2%) during extension period 1 and one out of 19 patients (5.3%) during extension period 2). This occurred only in children aged 12 to <18 years with non-CVC-VTE as index event.

Reviewer's Comment: The trial was not powered to demonstrate a difference between treatment groups. The Applicant performed several subgroup analyses reviewing the primary results by original site of clot, age, weight and formulation. However, these subgroup analyses like the primary efficacy analyses have small numbers so it is not possible to make substantial conclusions. Overall, there was a lower incidence of symptomatic recurrent VTE in the rivaroxaban group vs comparator group.

See the Clinical Pharmacology and Statistical reviews for their analyses

Data Quality and Integrity

No issues of data integrity arose during the trial.

Reviewer's Comment: Although the trial was open-label, the CIAC were blinded to treatment assignment.

Efficacy Results – Secondary and other relevant endpoints

During the main study treatment period, the secondary efficacy outcome (composite of recurrent VTE and asymptomatic deterioration) occurred in 5 out of 335 patients (1.5%, 95% CI

0.6,3.4%) in the rivaroxaban group and in 6 out of 165 patients (3.6%, 95% CI 1.6%, 7.6%) in the comparator group (Table 10).

Table 10. Composite of Recurrent VTE and Asymptomatic Deterioration During the Main Treatment Period, Trial 14372

Outcome	Rivaroxaban N=335 n (%)	Comparator N=165 n (%)
Composite of recurrent VTE and asymptomatic deterioration	5 (1.5%)	6 (3.6)
Recurrent VTE	4 (1.2)	5 (3)
Asymptomatic deterioration	1 (0.3)	1 (0.6)

The composite outcome of symptomatic recurrent VTE or bleeding events occurred in 4 out of 335 patients (1.2%, 95% CI 0.4%, 3.0%) in the rivaroxaban group and 7 out of 165 patients (4.2%, 95% CI 2.0%, 8.4%) in the comparator group.

Complete resolution of thrombus on repeat imaging without recurrent VTE occurred in 128 out of 335 patients (38.2%, 95% CI 33.0, 43.5%) in the rivaroxaban group and 43 out of 165 patients (26.1%, 95% CI 19.8, 33.0%) in the comparator group. Overall, repeat imaging showed improved clot resolution with rivaroxaban compared with the comparator (Table 11). Not all patients were candidates for repeat imaging.

Table 11. Thrombotic Burden Assessment at the End of the Main Treatment Period, Trial 14372

Outcome	Rivaroxaban N=335 n (%)	Comparator N=165 n (%)
Normalized	128 (38.2%)	43 (26.1%)
Improved	129 (38.5%)	75 (45.5%)
Uncertain	57 (17%)	28 (17%)
No relevant change	16 (4.8%)	13 (7.9%)
Deterioration	1 (0.3%)	1 (0.6%)

Source: Adapted from CSR

The composite outcome of recurrent VTE, asymptomatic deterioration and no change on repeat imaging occurred in 21 out of 335 patients (6.3%) in the rivaroxaban group and 19 out of 165 patients (11.5%) in the comparator group.

Non-fatal pulmonary embolism occurred in 1 out of 335 patients (0.3%) in the rivaroxaban group and 1 out of 165 patient (0.6%) in the comparator group.

Reviewer's Comment: The trial was not powered to demonstrate a difference between treatment groups, therefore secondary endpoints are descriptive and exploratory. When considering the rarity and the seriousness of VTE in pediatric patients, the secondary endpoints are informative and highlight the benefit-risk profile of rivaroxaban in pediatric patients, in particular when combining efficacy and safety endpoints. See statistical review for further analysis.

Dose/Dose Response

Table 12 displays exposure in patients who received at least one dose of study drug.

Table 12 Duration of Exposure, Safety Population, Trial 14372

Variable	Rivaroxaban N=329 n (%)	Comparator Group N=162 n (%)
Duration of exposure, weeks		
Mean (SD)	20.1 (13.1)	19.9 (13.6)
Median (Q1, Q3)	13.4 (12.4, 25.6)	13.6 (12.5, 25.5)
Min, Max	0.1, 55	0.1, 53.9
Total exposure (person years)	127	62
Patients treated, by duration, n (%)		
<12 weeks	54 (16.4)	27 (16.7)
≥12 to <26 weeks	199 (60.5)	99 (61.1)
≥26 to <50 weeks	48 (14.6)	19 (11.7)
≥50 to <100 weeks	28 (8.5)	17 (10.5)
≥100 weeks	0	0

Source: adex.xpt; Software: R
Abbreviations: N, number of subjects in treatment arm; n, number of subjects with given treatment duration; SD, standard deviation; Q1, first quartile; Q3, third quartile

Durability of Response

Reviewer's Comment: Given the need for continued treatment, the effect appears durable.

Persistence of Effect

Reviewer's Comment: Not applicable as patients were treated for as long as they were at risk for

a recurrent clot. Overall there were low numbers of symptomatic recurrent VTE in the main treatment period and extension period.

Additional Analyses Conducted on the Individual Trial

No additional analyses were performed by this reviewer.

6.2. UNIVERSE

6.2.1. Study Design

Overview and Objective

UNIVERSE Study was an international, prospective, open-label, multicenter study in two parts enrolling pediatric patients between 2 to 8 years of age who have had the Fontan surgical procedure for single ventricle physiology within the 4 months prior to enrollment. The study evaluated the efficacy, safety and tolerability of rivaroxaban treatment.

Trial Design

The study had two parts enrolling pediatric patients who have undergone the Fontan surgical procedure.

Part A was a single-arm part designed to characterize the single- and multiple-dose PK and PK/PD profiles after oral rivaroxaban therapy.

Part B was the randomized, active- controlled part which evaluated the safety and efficacy of rivaroxaban, administered twice daily compared to aspirin (ASA) given once daily. The rivaroxaban dose was exposure matched to 10 mg daily in adults. The ASA dose was approximately 5mg/kg daily.

Inclusion/Exclusion criteria (major)

Inclusion

1. Boys or girls 2 to 8 years of age with single ventricle physiology and who have completed the initial Fontan procedure within 4 months prior to enrollment
2. Considered to be clinically stable by the investigator and able to tolerate oral or enteral administration of a suspension formulation and oral/enteral feedings
3. Satisfactory initial post-Fontan transthoracic echocardiographic screening as defined in the

Post-Fontan Echocardiographic Examination Research Protocol
4. Parent/legally acceptable representative must sign an informed consent form (ICF) and child assent will also be provided, if applicable, according to local requirements.

Exclusion

1. Evidence of thrombosis, including those that are asymptomatic confirmed by post- Fontan procedure transthoracic echocardiogram, or other imaging techniques, during the screening period of the study
2. History of gastrointestinal disease or surgery associated with clinically relevant impaired absorption
3. History of or signs/symptoms suggestive of protein-losing enteropathy
4. Active bleeding or high risk for bleeding contraindicating antiplatelet or anticoagulant therapy, including a history of intracranial bleeding
5. Criterion modified per Amendment INT-2
    5.1. Indication for anticoagulant or antiplatelet therapy other than current study, However:
    A subject who has received VKA after the Fontan procedure may be eligible provided that the subject has discontinued VKA before the screening visit.
    Baseline laboratory samples must be obtained at least 7 days after the last dose of VKA.
    A subject who is receiving ASA at the time of the screening visit may be eligible and may continue on ASA provided the last dose is taken at least 24 hours prior to the first dose of study drug.
    A subject who is receiving heparin or LMWH after the Fontan procedure may be eligible and may continue receiving either of these anticoagulants during the screening period provided the study drug (rivaroxaban or ASA) is started 0 to 2 hours prior to the next scheduled administration of either of these anticoagulants and omit their administration thereafter.
    6. Chronic use of NSAIDs
    7. Platelet count <50 x 109/L at screening
    8. Criterion modified per Amendment INT-2
        8.1. Estimated glomerular filtration rate (eGFR) <30 mL/min/1.73m2 (Attachment 3)
    9. Known clinically significant liver disease (eg, cirrhosis, acute hepatitis, chronic active hepatitis, or alanine aminotransferase (ALT) >3x upper limit of normal (ULN) with concurrent total bilirubin >1.5x ULN with direct bilirubin >20% of the total at screening)
    10. Criterion modified per Amendment INT-2
        10.1. Known contraindication to ASA, or has or is recovering from chicken pox or flulike symptoms (subjects participating in Part B only)

11. Criterion modified per Amendment INT-2
    11.1. Known allergies, hypersensitivity, or intolerance to rivaroxaban, ASA or its excipients (Investigator's Brochure)
12. Inability to cooperate with study procedures
13. Combined P-gp and strong CYP3A4 inhibitors (such as but not limited to ketoconazole,
telithromycin, or protease inhibitors) use within 4 days before enrollment, or planned use during the study. Itraconazole use within 7 days before enrollment or planned use during the study
14. Combined P-gp and strong CYP3A4 inducers (such as but not limited to rifampin/rifampicin, rifabutin, rifapentine, phenytoin, phenobarbital, carbamazepine, or St. John's Wort) use within 2 weeks before enrollment, or planned use during the study
15. Planned use of drugs that are moderate CYP3A4 inhibitors (such as erythromycin) during the Initial PK, PD, and Safety Assessment Period of Part A only
16. Participation in a clinical study with an investigational drug or medical device in the previous 30 days prior to enrollment
17. Any condition for which, in the opinion of the investigator, participation would not be in the best interest of the subject (e.g., compromise the well-being) or that could prevent, limit, or confound the protocol-specified assessments

Study Endpoints

Part A – single and multiple dose PK and PD and safety and tolerability of rivaroxaban treatment

Part B - To evaluate the safety, efficacy and PK/PD of rivaroxaban, administered twice daily compared to ASA, given once daily for thromboprophylaxis in same population as Part A.

Clinical reviewer comment: These endpoints are appropriate for the development of a dosing strategy for prophylaxis of thromboembolism post-Fontan procedure.

Statistical Analysis Plan (SAP)

Original SAP November 15th, 2016 – no formal hypothesis testing – the descriptive statistical methods will be used to present the data. Per the plan, summaries by treatment group using appropriate descriptive statistics will be provided for study variables. Descriptive statistics such as mean, median, standard deviation, 95% CIs (when applicable), minimum, and maximum will be used to summarize continuous variables; Counts and percentages will be used to summarize categorical variables. The Kaplan-Meier (KM) method will be used to summarize time-to-event data. Graphical data displays may also be used to summarize the data. All adjudicated efficacy and bleeding outcomes will be used in the final analyses.

Amendment 1 May 16th, 2019 - Amendment 1 - clarifies the definition of the categories and terms of key protocol deviations considered for the Per protocol Set. Also, PK/PD analysis plan in Section 6 was updated to include Part B data.

Sample Size - At least 100 pediatric subjects – However, because of the limited availability of the study population and the expected low event rates, this study is not powered to test formal hypothesis for efficacy. The sample size of approximately 10 subjects for Part A is considered adequate for the initial PK assessment with an additional 90 patients enrolled into Part B.

No interim analysis planned.

Data Review Committee, consisted of Sponsor members not directly involved in the conduct of the study, evaluated the PK and safety of each patient in Part A.

Independent Data Monitoring Committee (IDMC), consisted of an independent expert advisory group external to the Sponsor, evaluated PK, PD, safety and efficacy data to ensure patient safety throughout the study. The IDMC operated for both Part A and Part B.

Central Independent Adjudication Committee (CIAC), comprised of specialty physicians who do not directly enroll subjects in the study, are not involved in the study monitoring, and do not have direct operational responsibilities for the conduct of the study. This committee reviewed all safety and efficacy outcomes that occur post- enrollment as they become available and adjudicated and classified the following events in a consistent and unbiased manner according to definitions in the CIAC charter while blinded to treatment assignment: Safety and efficacy outcomes including bleeding events, any thrombotic event (venous or arterial), other vascular events, and deaths that occur during the study and the 30-day post-study treatment period. Bleeding events will be adjudicated by the CIAC using the International Society on Thrombosis and Hemostasis (ISTH) recommendations (Buller 2007, Schulman 2005).

Full Analysis Set: All subjects in Part A who receive at least 1 dose of study drug and all subjects in Part B who are randomized and receive 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 will exclude subjects with key protocol deviations from full analysis set.

The main efficacy description will be based on Full Analysis Set, excluding subjects who start on study drug but are discontinued if central reading by the core laboratory reports thrombosis on the Screening transthoracic echocardiogram. In terms of presentation, thrombotic events might be summarized, but not limited to, as the following: venous thromboembolism, venous thrombosis, pulmonary embolism, arterial/intracardiac thrombosis, ischemic stroke and all-cause death.

Reviewer's Comment: Given the rarity of the condition, to conduct a study enrolling only pediatric patients powered to demonstrate efficacy and safety with statistical significance would have required many years. Therefore, the Applicant's statistical analysis plan is acceptable. See the statistical review for further comments.

Protocol Amendments

INT-1 and INT-2

INT-1

The purpose of the amendment was to clarify that collection of blood samples and heparin flushes were allowed except before PK/PD samples were drawn, and study conduct was simplified to enhance enrollment and data collection.

INT-2

The purpose of the amendment was to provide clarification for subjects participating in Part B, the list of committees commissioned, and exclusion criteria were revised. Other minor edits included revisions in selected time points, study procedures, current anticoagulant use in children, concomitant medication and prohibited medications, instructions on vomiting, bleeding event, and electronic serious adverse event reporting.

Clinical reviewer comment: Protocol amendments did not impact the integrity of the trial.

6.2.2. Study Results

Compliance with Good Clinical Practices

This study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with Good Clinical Practices and applicable regulatory requirements.

The company had several committees concerned with patient welfare, endpoints, and study conduct.

Executive Committee (EC)
The EC provided overall academic leadership for the study; oversaw the conduct of the study and the publication of the results. In addition, the EC was to receive recommendations from the IDMC regarding modifications to the study and decide whether to accept the recommendations.

Independent Data Monitoring Committee (IDMC)
The IDMC evaluated PK, PD, safety, and efficacy data to ensure subject safety throughout the study. The IDMC was an independent expert advisory group external to the sponsor and study. For Part A only, the IDMC reviewed the cumulative data from the Initial PK, PD, and Safety Assessment Period and provided the recommendation to the EC and Sponsor Committee to cease enrollment in Part A and to start enrollment directly into Part B. The decision tree of rivaroxaban exposure acceptability criteria was described in the IDMC charter. The IDMC was to operate for both Part A and Part B.

Data Review Committee
The DRC was an internal committee that consisted of members from the sponsor not directly involved in the conduct of the study, who evaluated the PK and safety of each subject in Part A, and who evaluated that information relative to the PBPK model predictions. The DRC assessed before the subject returned for Day 12 Visit the PK, PD, and the safety data available from each subject, prior to the subject continuing in the study to complete the planned 12 months of open label rivaroxaban therapy. The DRC only operated during Part A.

Central Independent Adjudication Committee (CIAC)
The CIAC was comprised of specialty physicians. Committee members did not directly enroll subjects in the study, were not involved in the study monitoring, and did not have direct operational responsibilities for the conduct of the study. Members reviewed all safety and efficacy outcomes that occurred post-enrollment as they became available and adjudicated and classified the events in a consistent and unbiased manner according to definitions in the CIAC charter while blinded to treatment assignment.

Steering Committee
The SC advised and assisted the EC with regard to the scientific and operational aspects of the study in their regions. Details of the composition, roles, and responsibilities were documented in the EC/SC charter.

Sponsor Committee
The Sponsor Committee communicated the IDMC recommendations within the Sponsor and identified appropriate actions based on the recommendations of the IDMC.

Financial Disclosure – no issues see appendix

Patient Disposition

The number of patients screened was 129 with 17 screen failures with 112 enrolled. Of the 112 patients enrolled, 2 patients were discontinued before they received rivaroxaban. All patients who were screen failures did not meet the necessary eligibility criteria.

Part A enrolled 12 patients who received rivaroxaban with 10 completing treatment and 11 completing the study. The DRC made the decision to discontinue patients from part A.

Part B enrolled 100 patients randomizing 66 patients to rivaroxaban and 34 to ASA. Two patients in the rivaroxaban arm did not receive treatment. Part B randomized 66 patients to rivaroxaban with 59 completing treatment and 63 completing the study. Part B randomized 34 patients to ASA with 30 completing treatment and 33 completing the study.

In part B two pediatric patients randomized to rivaroxaban but not treated were withdrawn by parent or guardian.

The table below gives the disposition of the trial.

Table 13 Patient Disposition for Trial 3001

Disposition Outcome	Rivaroxaban (Part A) N=12 n (%)	Rivaroxaban (Part B) N=64 n (%)	Total Rivaroxaban N=76 n (%)	Aspirin (Part B) N=34 n (%)
Patients randomized	12	64	76	34
Per-protocol population	12	62	74	34
Safety population	12	64	76	34
Discontinued study drug	2 (16.7)	5 (7.8)	7 (9.2)	4 (11.8)
Adverse event-bleeding event	0	1 (1.6)	1 (1.3)	0
Adverse event - other than bleeding event	0	1 (1.6)	1(1.3)	0
Doctor's decision	2 (16.7)	0	2 (2.6)	0

Disposition Outcome	Rivaroxaban (Part A) N=12 n (%)	Rivaroxaban (Part B) N=64 n (%)	Total Rivaroxaban N=76 n (%)	Aspirin (Part B) N=34 n (%)
Lost to follow-up	0	0	0	1 (2.9)
Other	0	0	0	1 (2.9)
Thrombosis non screening	0	1 (1.6)	1 (1.3)	2 (5.9)
Withdrawal by parent/guardian	0	2 (3.1)	2 (2.6)	0

Source: ds.xpt, adsl.xpt; Software: R

Abbreviations: N, number of patients in treatment arm; n, number of patients in specified population or group; NA, not applicable

The Full Analysis Set is all patients enrolled in Part A and Part B who received one dose of study treatment. The Per-protocol Analysis Set is all patients in the Full Analysis Set who do not have major violations.

Clinical reviewer comment: The discontinuation rate was similar between treatment groups.

Protocol Violations/Deviations

Five patients had major protocol deviations, and all were in Part B rivaroxaban arm. Two received disallowed concomitant treatment: one received combined P-Gp and strong CYP-3A inhibitor (clarithromycin) and one received clopidogrel. Two received incorrect dose and one received rivaroxaban from a dosing pipette that was beyond the recommended timing for the suspension administration.

Clinical reviewer comment: The reviewer does not anticipate the protocol deviations would impact efficacy results.

Table of Demographic Characteristics

Demographic characteristics are displayed in the table below.

Table 14: Demographic characteristics of the patients enrolled in 3001

Demographic Parameters	Aspirin Group (N= 34) n (%)	Treatment Group	
		Rivaroxaban Part A (N=12) n (%)	Rivaroxaban B (N=66) n (%)
Sex			
Female	11 (32.4%)	5 (41.7%)	30 (45.5%)
Male	23 (67.6%)	7 (58.3%)	36 (54.5%)
Age			
Mean years (SD)	4.2 (1.80)	2.5 (0.67)	4.1 (1.74)
Median (years)	4	2	4
Min, max (years)	(2,8)	(2,4)	(2,8)
Race			
White	20 (58.8%)	8 (66.7%)	40 (60.6%)
Black or African American	1 (2.9%)	3 (25%)	8 (12.1%)
Asian	7 (20.6%)	0	14 (21.1%)
American Indian or Alaska Native	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0
Other – not further elaborated	3 (8.8%)	1 (8.3%)	2 (3%)
Other[1]	3 (8.8%)	0	2 (3%)
Ethnicity			
Hispanic or Latino	11 (32.4%)	1 (8.3%)	22 (33.3%)
Not Hispanic or Latino	19 (55.9%)	11 (91.7%)	42 (63.6%)
Not Reported	4 (11.8%)	0	2 (3.0%)
Region (all enrolled)			
United States	8 (23.5%)	7 (58.3%)	25 (37.9%)
Rest of the World			
Canada	3 (8.8%)	0	3 (4.5%)
South America	13 (38.2%)	0	18 (27.3%)
Europe	4 (11.8%)	5 (41.7%)	7 (10.6%)
Asia	6 (17.6%)	0	13 (19.7%)
Africa	0	0	0
Country of participation, (n%)			
Argentina	1 (2.9%)	0 (0)	5 (7.8%)
Belgium	4 (11.8%)	0 (0)	5 (7.8%)
Brazil	10 (29.4%)	0 (0)	7 (10.9%)
Canada	3 (8.8%)	0 (0)	2 (3.1%)

Spain	0 (0)	5 (41.7%)	1 (1.6%)
Japan	1 (2.9%)	0 (0)	8 (12.5%)
Mexico	2 (5.9%)	0 (0)	6 (9.4%)
Malaysia	5 (14.7%)	0 (0)	5 (7.8%)
Netherlands	0 (0)	0 (0)	1 (1.6%)
United States	8 (23.5%)	7 (58.3%)	24 (37.5%)

[1] Data on race and/or ethnicity were not collected in several countries because of local regulations.

Source: adsl.xpt; Software: R
Abbreviations: N, number of patients in treatment group; n, number of patients with given characteristic; SD, standard deviation

Clinical reviewer comment: Overall baseline demographic characteristics were well balanced between rivaroxaban and aspirin groups. Although, more patients were enrolled in the ASA from Brazil compared to rivaroxaban, in which more patients were enrolled in the US. It is not anticipated that differences in clinical practices would greatly impact thrombosis risk.

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

Table 15 Duration between Fontan Procedure and First Dose of Study Agent, in days for Trial 3001

Treatment Arm	Part A (rivaroxaban) N=12	Part B (rivaroxaban) N=64	Part B (aspirin) N=34
Mean (SD)	11.6 (16.77)	45.3 (41.21)	36.7 (34.52)
Median	4	34	24
Range	(2, 61)	(2, 124)	(2, 117)
Less or equal to 30 days	11 (91.7%)	31 (48.4%)	19 (55.9%)
Greater than 30 days	1 (8.3%)	33 (51.6%)	15 (44.1%)

Source: Clinical reviewer

Abbreviations: N, number of patients in treatment group; SD, standard deviation

Clinical reviewer comment: The median duration from Fontan procedure to initiating study drug was 34 days in the rivaroxaban group compared to 24 days in the comparator group. There is no consensus on when thromboprophylaxis should be initiated following Fontan procedure, and risk of bleeding must be considered.

The table below lists the congenital, familial, and genetic disorders.

Table 16 Underlying Congenital Cardiac, Familial and Genetic Disorders for Trial 3001

Treatment Arm	Part A (rivaroxaban) N=12 n(%)	Part B (rivaroxaban) N=66 n(%)	Part B (aspirin) N=34 n(%)
N	12	66	34
Congenital tricuspid valve atresia	1 (8.3%)	28 (42.4%)	13 (38.2%)
Hypoplastic left heart syndrome	5 (41.7%)	20 (30.3%)	8 (23.5%)
Congenital pulmonary valve atresia	2 (16.7%)	12 (18.2%)	8 (23.5%)
Double outlet right ventricle	3 (25.0%)	13 (19.7%)	4 (11.8%)
Multiple cardiac defects	3 (25.0%)	9 (13.6%)	2 (5.9%)
Hypoplastic right heart syndrome	0	10 (15.2%)	3 (8.8%)
Mitral valve atresia	3 (25.0%)	7 (10.6%)	3 (8.8%)

Atrioventricular septal defect	3 (25.0%)	5 (7.6%)	3 (8.8%)
Double inlet left ventricle	0	5 (7.6%)	4 (11.8%)
Heterotaxia	3 (25.0%)	5 (7.6%)	0
Atrial septal defect	0	3 (4.5%)	3 (8.8%)

Source: Clinical reviewer

The most frequently reported procedure was cardiac catheterization (88.4%).

Table 17. Surgical and Medical Procedures for Trial 3001

Treatment Arm	Part A (rivaroxaban) N=12 n(%)	Part B (rivaroxaban) N=66 n(%)	Part B (aspirin) N=34 n(%)
Cavopulmonary anastomosis	5 (41.7%)	57 (86.4%)	30 (88.2%)
Norwood procedure	5 (41.7%)	45 (68.2%)	19 (55.9%)
Systemic-pulmonary artery shunt	6 (50.0%)	16 (24.2%)	9 (26.5%)
Pulmonary artery banding	3 (25.0%)	7 (10.6%)	5 (14.7%)

Aorta coarctation repair	2 (16.7%)	7 (10.6%)	5 (14.7%)
Atrial septal defect repair	0	4 (6.1%)	3 (8.8%)
Cardiac Catheterizations	11 (91.7%)	60 (90.9%)	28 (82.4%)

Source: Clinical reviewer

Most patients underwent the Fontan procedure using an extracardiac conduit: 11 [91.7%] in Part A and 61 [92.4%] in Part B groups who received rivaroxaban and 29 [85.3%] in ASA part B group. Also, GORE-TEX was the most common baffle or conduit used: 11 [91.7%] in Part A and 53 [80.3%] in Part B groups who received rivaroxaban, and 23 [67.6%] in ASA part B group. Fenestration was performed for 3 [25.0%] in Part A and 30 [45.5%] in Part B groups who received rivaroxaban and 21 [61.8%] in ASA part B group).

Clinical reviewer comment: Overall baseline characteristics were well balanced between rivaroxaban and aspirin, except for fenestration, this occurred more in the rivaroxaban group compared to aspirin (43% compared to 62%, respectively). Fenestration is not known to impact thrombosis risk[12, 20].

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

The Applicant based the dosing on exposure matching to 10 mg daily in adults.

Table 18 Dosing for rivaroxaban administration in 3001 (oral suspension)

Patient Body Weight (kg)	Twice daily dose (mg or mL)	Total Daily Dose (mg)
7 < 8	1.1	2.2
8<10	1.6	3.2
10<12	1.7	3.4
12<20	2	4
20< 30	2.5	5

Source: Clinical reviewer

Clinical reviewer comment: No patient received rivaroxaban in the 7 < 8 kg weight group. While not common, there are patients with congenital heart disease who undergo the Fontan procedure under the age or 2 years and/or weight under 8kg[24, 25]. These patients may be at increased risk for significant morbidity or mortality, in particular patients who have low weight for age Z score -2[11]. As it is possible patients in the 7 <8kg weight group will need

thromboprophylaxis post-Fontan, the rivaroxaban USPI will still address this weight group despite lack of clinical experience in the UNIVERSE clinical trial.

The following concomitant medications were prohibited for all patients in the Study:
1. The use of any other antiplatelet, anticoagulant (other than study drug) taken concomitantly with study drug.
2. Chronic NSAID therapy during the study.
3. Modification of an effective preexisting therapy for the explicit purpose of entering a subject into the study.

The following concomitant medications were prohibited for Subjects Receiving Rivaroxaban only:
1. Combined P-gp and strong CYP3A4 inhibitors (such as but not limited to ketoconazole, telithromycin, or protease inhibitors) use within 4 days before enrollment, or during the study. Itraconazole use within 7 days before enrollment or during the study.
2. Combined P-gp and strong CYP3A4 inducers (such as but not limited to rifampin/rifampicin, rifabutin, rifapentine, phenytoin, phenobarbital, carbamazepine, or St. John's Wort) use within 2 weeks before enrollment, or planned use during the study.
3. Planned use of drugs that are moderate CYP3A4 inhibitors (such as erythromycin or fluconazole) were not allowed during the Initial PK, PD, and Safety Assessment Period of Part A only. However, they were allowed during the 12-month Open-Label Treatment Periods of Part A and Part B.

Compliance

In total, 103 patients (94%) had a compliance rate of ≥90%. A total of 4 patients (6.3%) in the rivaroxaban Part B group and 1 patient (2.9%) in the aspirin Part B group had compliance less than 60%. Two patients (16.7%) in the rivaroxaban Part A group also had compliance less than 60%.

Clinical reviewer comment: Both treatment groups had high compliance rates.

Efficacy Results – Primary Endpoint

Primary efficacy outcome - any thrombotic event (venous or arterial), defined as: appearance of a new thrombotic burden within the cardiovascular system on either routine surveillance or clinically indicated imaging, or occurrence of a clinical event known to be strongly associated with thrombus (such as cardioembolic stroke, pulmonary embolism)

The main efficacy description will be based on Full Analysis Set with exclusions as noted above. Thrombotic events might be summarized, but not limited to, as the following: venous thromboembolism, venous thrombosis, pulmonary embolism, arterial/intracardiac thrombosis, ischemic stroke and all-cause death.

Transthoracic Echocardiograms will be obtained at screening, at Month 6 and Month 12 for the assessment of thrombotic events and for any pediatric patients who prematurely discontinue study drug for any reason (except when the child is enrolled because the local reader reviews the screening echo as without thrombosis and later on the central reviewer reports the presence of a thrombus), the final echocardiogram will be performed as soon as possible after discontinuation.

Reviewer- The primary endpoint definitions for efficacy and safety are reasonable.

Below is the table for the Primary Efficacy Outcome for all treated patients. Note this table does not include those who were not dosed with either rivaroxaban or aspirin and those who were screen failures. All available imaging results relevant to a suspected thrombotic event were adjudicated by the CIAC which was blinded to treatment assignment.

Table 19 CIAC Adjudicated Primary Efficacy Outcome to End of Treatment (Month 12 or End of Study Medication) using Full Analysis Set for Trial 3001

Treatment Part-Group/Outcome	Rivaroxaban Part A (N=12) n(%)	Rivaroxaban Part B (N=64) n(%)	ASA Part B (N=34) n(%)
Primary Efficacy Outcome	1 (8.3%)	1 (1.6%)	3 (8.8%)
Ischemic Stroke	0	0	1 (2.9%)
Pulmonary Embolism	0	1 (1.6%)	0
Venous Thrombosis	1 (8.3%)	0	2 (5.9%)

Source: Clinical reviewer

In total, three patients had venous thrombosis events. One patient in rivaroxaban group Part A had a left supra hepatic vein thrombosis. Two patients in the aspirin Part B group had a venous thrombosis, this included thrombotic events in the superior vena cava and extra cardiac Fontan conduit.

Per CIAC determination, no intracardiac thromboses were observed. Local investigator and CIAC did not agree on two readings. One investigator reading was arterial/intracardiac thrombosis that was read by the CIAC as pulmonary embolism. A second investigator reported an other thrombosis which was read as a venous thrombosis by CIAC. Otherwise, there was agreement between local reading and CIAC.

All patients who completed treatment had scanning at month 12 except for 1 patient in the ASA Part B group. A total of 11 patients discontinued their study treatment early – all but 1 in the ASA Part B group had end of study medication scanning.

Reviewer's Comment: This trial was not powered for a statistical comparison. Overall, there were a low number of thromboembolisms in the rivaroxaban group, and this was lower than the aspirin group. See statistical review for further analysis.

Data Quality and Integrity – no data integrity issues were uncovered during the review

The CIAC was blinded to treatment which decreased the potential for bias with the efficacy and bleeding evaluations.

Efficacy Results – Secondary and other relevant endpoints – see safety and clinical pharmacology analyses including PK/PD.

Dose/Dose Response

The trial used twice daily administration and pediatric weight-based dosing. The rivaroxaban concentrations in pediatric patients were similar to those observed in adults dosed with 5 mg twice daily or 10 mg once daily rivaroxaban administration. Exposure metrics revealed a slightly lower steady state C_{max} and slightly higher steady state C_{trough}.

Durability of Response –

The table below outlines the time of exposure on the trial.

Table 20 - Duration of Exposure, Safety Population, Trial CHD3001

Variable	Rivaroxaban (Part A) N=12 n (%)	Rivaroxaban (Part B) N=64 n (%)	Total Rivaroxaban N=76 n (%)	Aspirin (Part B) N=34 n (%)
Duration of exposure, weeks				
Mean (SD)	43.1 (19.3)	48.2 (11.7)	47.4 (13.2)	48.1 (9.8)
Median (Q1, Q3)	51.3 (50.8, 51.6)	51.3 (50.6, 52)	51.3 (50.7, 52)	51.3 (50.6, 52)
Min, Max	1.4, 52.1	1, 54.4	1, 54.4	13, 55
Total exposure (person years)	10	59	69	31
Patients treated, by duration, n (%)				
<12 weeks	2 (16.7)	3 (4.7)	5 (6.6)	0
≥12 to <26 weeks	0	2 (3.1)	2 (2.6)	3 (8.8)
≥26 to <50 weeks	0	2 (3.1)	2 (2.6)	1 (2.9)
≥50 to <100 weeks	10 (83.3)	57 (89.1)	67 (88.2)	30 (88.2)
≥100 weeks	0	0	0	0

Source: adex.xpt; Software: R
Abbreviations: N, number of subjects in treatment arm; n, number of subjects with given treatment duration; SD, standard deviation; Q1, first quartile; Q3, third quartile

Most pediatric patients (86% - rivaroxaban and 82% -ASA) received more than 353 days of exposure. The trial participation ended with 12 months of treatment.

Reviewer Comment: Because few patients developed the outcome of interest the data suggests the anticoagulant effect was durable.

Persistence of Effect

Reviewer Comment: The on-treatment development of thrombosis was very low (2/76 or 2.6%) suggesting maintenance of anticoagulant treatment effect.

Additional Analyses Conducted on the Individual Trial

No further analysis was conducted by the clinical reviewer.

6.3. Study 14373

6.3.1. Study Design

Overview and Objective

30-day, single-arm study of the safety, efficacy and the pharmacokinetic and pharmacodynamic properties of oral rivaroxaban in children with various manifestations of venous thrombosis. Initially this study was proposed as a comparative trial with randomization to rivaroxaban or standard of care. After amendment 6, all patients received rivaroxaban.

The primary objective was:
to assess the incidence of major bleeding and clinically relevant non-major bleeding

The secondary objectives were:
to assess the incidence of recurrent venous thromboembolism
to assess asymptomatic deterioration in the thrombotic burden on repeat imaging
to characterize the pharmacokinetic/ pharmacodynamic profile of a 30-day treatment with oral rivaroxaban

Trial Design

Initially this study was proposed as a randomized comparative trial with randomization to rivaroxaban or standard of care. After amendment 6, all patients received rivaroxaban.

Major enrolled population – pediatric patients aged 6 to < 18 years with documented symptomatic or asymptomatic venous thrombosis treated for at least 2 months or, in case of catheter related thrombosis, treated for at least 6 weeks with LMWH, fondaparinux and/or vitamin K antagonist (VKA).

The imaging of the index thrombotic event was confirmed by the central independent adjudication committee (CIAC).

Study Endpoints

The efficacy outcome was symptomatic recurrence of venous thrombosis or asymptomatic deterioration.

Clinical pharmacology: The primary variables for pharmacodynamics were PT, aPTT, and anti-Factor Xa. Rivaroxaban plasma concentrations were used to assess the pharmacokinetics of rivaroxaban.

Safety: Composite of major and clinically relevant non-major bleeding, adverse events, vital signs, physical examination (including body weight and height), urine pregnancy test, laboratory

Other: A taste and texture questionnaire in the form of a 3-point scale was used to determine the acceptance of the oral suspension in children aged from 6 to <12 years.

Statistical Analysis Plan

For the demography and baseline characteristics, summary statistics (arithmetic mean, standard deviation, median, minimum and maximum for quantitative variables) were presented by treatment and age group. Frequency tables for qualitative data were provided.

Medical history findings were summarized using Medical Dictionary for Regulatory Activities (MedDRA) terms.
All efficacy analyses were performed on the full analysis set population. The occurrence of recurrent venous thromboembolism and asymptomatic deterioration in thrombotic burden were to be summarized by age group

All safety analyses were performed on the SAS population. The analysis primarily focused on

bleeding that occurred during or within 2 days after stop of study treatment. Bleeding events observed later were described separately. Individual listings of major and clinically relevant non-major bleeding were provided. The incidence of bleeding was summarized descriptively. For PD analyses, quantitative data were described by the summary statistics mentioned above, and presented descriptively for the original data as well as for the difference, respectively, ratio to baseline.

Protocol Amendments (major ones)

Amendment 2

Thrombotic burden assessment was added as a secondary objective.
Lab tests for bilirubin and ALT were added in the inclusion and exclusion criteria.
Added that subjects with concomitant therapy with other anticoagulants or fibrinolytic during the study treatment were to be prematurely discontinued from study treatment.

Amendment 6

The comparator arm was removed. Furthermore, due to the comparator arm removal the total subject number was reduced.
Inclusion criterion 1 was changed to enable enrollment of children who are on long-term anticoagulant treatment.
Additionally, instructions on how to safely handle the switch from heparin, fondaparinux, and VKA to rivaroxaban and vice versa were made available in the protocol
The platelet count threshold for exclusion of children was adjusted from <100x109/L to <50x109/L.

6.3.2. Study Results

Compliance with Good Clinical Practices

The study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and the International Council on Harmonization (ICH) guideline E6: Good Clinical Practice (GCP).

The study employed the following committees:

-Steering Committee (SC): to provide an overall academic leadership
-Independent Data Monitoring Committee (IDMC/DMC): to evaluate all study data to ensure subjects safety throughout the study.
-Central Independent Adjudication Committee (CIAC): to review independently specified safety and all efficacy outcomes in the study in compliance with the charter, and to

adjudicate and classify the events, including the confirmation of the documented index thrombotic event before first study treatment administration.

Financial Disclosure - not necessary per Agency agreement

Patient Disposition

Sixty-eight pediatric patients were screened with 4 patients who were considered screen failures and did not receive treatment.

Sixty-four patients were assigned treatment and one did not receive treatment and constituted the Full Analysis Set (assigned to treatment), of whom one child was not treated.
Sixty-three were actually treated and included in the Safety Analysis Set:

- 11 children aged 12-18 years received rivaroxaban o.d. as tablets
- 13 children aged 12-18 years received comparator
- 13 children aged 6-12 years received rivaroxaban o.d. as tablets
- 19 children aged 6-12 years were administered rivaroxaban b.i.d. as oral suspension
- 7 children aged 6-12 years received comparator

42 children were valid for the PK and PD analyses.

Children in the comparator groups continued with the anticoagulant treatment that had been used prior to study randomization.

During the treatment phase, 1 child, treated in the rivaroxaban tablet 6-12 years group, withdrew study treatment after a treatment duration of 16 days but completed the 30-day post study treatment visit. For this child no PK and PD samples are available. A reason for withdrawal was not given.

In total, 63/68 children completed the study have actually completed the 30-day post study treatment period

Protocol Violations/Deviations

There were no major protocol deviations.

Table of Demographic Characteristics

Table 21: Demographic Characteristics of the Pediatric Patients Enrolled and Treated in Trial 14373

Demographic Parameters	Control Group (N=20) n (%)	Treatment Group	
		All rivaroxaban cohorts (N=43)[1] n (%)	Total (N=64) n (%)
Sex			
Male	10 (50%)	24 (55.8%)	34 (54%)
Female	10 (50%)	19 (44.2%)	29 (46%)
Age			
Mean years (SD)	12.8 (3.2)	10.2 (3.6)	11
Median (years)	14.5	10	
Min, max (years)	(6,16)	(6,17)	(6,17)
Age Group			
< 17 years	20	44	64
Race			
White	16 (80%)	37 (86%)	53 (84%)
Black or African American	1 (5%)	2 (4.7%)	3 (5%)
Asian	0	2 (4.7%)	2 (3%)
American Indian or Alaska Native	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0
Multiple races	1 (5%)	0	1 (2%)
Other[2]	2 (10%)	2 (4.7%)	4 (6%)
Ethnicity			
Hispanic or Latino	0	4 (10%)	4 (6%)
Not Hispanic or Latino	19 (95%)	37 (86%)	56 (89%)
Not reported	1 (5%)	2 (5%)	3 (4.8%)
Region			
United States			15 (23%)
Rest of the World			8 (12.5%)
Canada			3 (4.7%)
South America			0
Europe			38 (59%)
Asia			0
Africa			0

[1] One patient did not take treatment but completed study – some demographic information available.

[2] Data on race and/or ethnicity were not collected in XX country because of local regulations.

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

All pediatric patients had a history of a venous thromboembolism and all were on anticoagulant treatment at trial entry. Most had a history of infections (57%).

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

All pediatric patients in the comparator group were 100% compliant. Approximately 95% of pediatric patients in the rivaroxaban group were greater than 80% compliant. One pediatric patient was categorized as complaint between 50 to 80% of the time.

Efficacy Results – Primary Endpoint

The primary endpoint was assessed by repeat imaging for most patients. None of the patients treated with study medication had a confirmed symptomatic recurrent VTE during the treatment period and during the 30-day post treatment period. Forty-two pediatric patients had repeat imaging and three patients' scans were not evaluable. Thus 39 patients had repeat imaging which did not demonstrate asymptomatic deterioration of the thrombus. Twenty pediatric patients did not have repeat imaging (which was not a requirement when they enrolled in the study). Therefore, of those enrolled after the amendment for repeat imaging was added to the protocol 42/44 (95.5%) had repeat imaging.

In the 32 patients treated with rivaroxaban who had evaluable repeat imaging, the thrombus burden was adjudicated as normalized (9/32; 28.1%), improved (21/32; 65.6%) or unchanged (2/32; 10.5%).

In the 7 patients treated with comparator who had repeat imaging, the thrombosis burden was adjudicated as normalized (3/7; 42.9%), improved (4/7; 57.1%) and no relevant change (0/7; 0%).

Reviewer Comment: Because of the limited and small sample size, no comparison can be made between treatments received and outcome.

Data Quality and Integrity

Central adjudication of imaging results decreased the potential for biased results.

Efficacy Results – Secondary and other relevant endpoints

See clinical pharmacology review.

Dose/Dose Response

See clinical pharmacology review.

Durability of Response- demonstrated

Persistence of Effect- demonstrated

6.4. Study 14374

6.4.1. Study Design

Overview and Objective

The final version of the study is as a 30-day, single-arm study of the safety, efficacy and the pharmacokinetic and pharmacodynamic properties of oral rivaroxaban in pediatric patients aged 6 months to less than 6 years with various manifestations of venous thrombosis.

Initially this study was proposed as a comparative trial with randomization to rivaroxaban or standard of care. After amendment 4, all patients received rivaroxaban.

The primary objective was:

to assess the incidence of major bleeding and clinically relevant non-major bleeding

The secondary objectives were:

to assess the incidence of recurrent symptomatic venous thromboembolism
to assess asymptomatic deterioration in the thrombotic burden on repeat imaging
to characterize the pharmacokinetic/pharmacodynamic profile of a 30-day treatment with oral rivaroxaban.

Trial Design

Initially this study was proposed as a randomized comparative trial with randomization to rivaroxaban or standard of care. After amendment 4, all patients received rivaroxaban.

The study tested the proposed age- and body weight-adjusted dosing of rivaroxaban to achieve a similar exposure as that observed in adults treated for venous thromboembolism (VTE) with 20 mg rivaroxaban once daily.

Children received rivaroxaban according to an age- and body weight-adjusted regimen.
The study treatment period was for a total of 30 days followed by an observational period of another 30 days.

All suspected clinical study outcomes and baseline and repeat thrombosis imaging tests were assessed by a CIAC.

An independent data monitoring committee (DMC) monitored the children's safety and gave recommendations to the steering committee.

Major enrolled population – pediatric patients aged 6 months to < 6 years with documented symptomatic or asymptomatic venous thrombosis treated for at least 2 months or, in case of catheter related thrombosis, treated for at least 6 weeks with LMWH, fondaparinux and/or vitamin K antagonist (VKA).

The imaging of the index thrombotic event was confirmed by the central independent adjudication committee (CIAC).

Inclusion and exclusion criteria

Inclusion criteria
1.Children aged between 6 months to < 6 years who had been treated for at least 2 months or, in case of catheter related thrombosis, for at least 6 weeks with LMWH, fondaparinux and/or VKA for documented symptomatic or asymptomatic venous thrombosis
2. Hemoglobin, platelets, creatinine and alanine aminotransferase (ALT) and bilirubin evaluated within 10 days prior to Visit 2
3. Informed consent provided.

Exclusion
1. Active bleeding or high risk for bleeding contraindicating anticoagulant therapy
2. Symptomatic progression of venous thrombosis during preceding anticoagulant treatment
3. Planned invasive procedures, including lumbar puncture and removal of nonperipherally placed central lines during study treatment.
4. An estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73 m2
5. Hepatic disease which was associated with: coagulopathy leading to a clinically relevant bleeding risk, or ALT > 5x upper level of normal (ULN), or total bilirubin > 2x ULN with direct bilirubin > 20% of the total.
6. Platelet count < 50 x 109/L
7. Hypertension defined as > 95th age percentile
8. Life expectancy < 3 months
9. Concomitant use of strong inhibitors of both CYP3A4 and P-gp, i.e. all human immunodeficiency virus protease inhibitors and the following azole-antimycotics agents:

ketoconazole, itraconazole, voriconazole, posaconazole, if used systemically (fluconazole was allowed)
10. Concomitant use of strong inducers of CYP3A4, i.e. rifampicin, rifabutin, phenobarbital, phenytoin and carbamazepine
11. Hypersensitivity or any other contraindication listed in the local labeling for the experimental treatment
12. Inability to cooperate with the study procedures
13. Previous participation in this study
14. Participation in a study with an investigational drug or medical device within 30 days prior to Visit 2.

Reviewer Comment: These inclusion/exclusion criteria are reasonable and appropriate for the study's objectives.

Allocation to treatment (1:1 - rivaroxaban: standard of care) was done centrally by an interactive voice/web response system (IxRS). Allocation was stratified by baseline presentation of venous thrombosis.

Study Endpoints

Efficacy - The secondary outcome was symptomatic recurrence of venous thrombosis or asymptomatic deterioration.

Clinical Pharmacology - The variables for pharmacodynamics were PT, aPTT, and antifactory Xa (secondary outcome). Rivaroxaban plasma concentrations were used to assess the pharmacokinetics of rivaroxaban (secondary outcome).

Safety: The primary outcome was composite of major and clinically relevant non-major bleeding . Other safety outcomes were adverse events, vital signs, physical examination (including bodyweight and height), and laboratory measures.

Other: A taste and texture questionnaire in the form of a 3-point scale was used to determine the acceptance of the oral suspension in children aged ≥ 4 years.

Statistical Analysis Plan

For the demography and baseline characteristics, summary statistics (arithmetic mean, standard deviation, median, minimum and maximum for quantitative variables) were presented by treatment and age group. Frequency tables for qualitative data were provided. Medical history findings were summarized using Medical Dictionary for Regulatory Activities (MedDRA) terms.

All efficacy analyses were performed on the full analysis set population. The occurrence of

recurrent venous thromboembolism and asymptomatic deterioration in thrombotic burden were summarized by age group. None of these events occurred in the study.

All safety analyses were performed on the SAS population. The analysis primarily focused on bleeding that occurred during or within 2 days after stop of study treatment. Bleeding events observed later were described separately. Individual listings of major and clinically relevant non-major bleeding were provided.

The incidence of bleeding was summarized descriptively.

For PD analyses, quantitative data were described by the summary statistics mentioned above, and presented descriptively for the original data as well as for the difference, respectively, ratio to baseline. PK/PD modeling, using population approaches, was used to describe the pharmacokinetics of rivaroxaban, including potential influence of relevant co-variables, and to relate anticoagulant parameters of rivaroxaban with plasma concentrations.

Protocol Amendments (major)

Amendment 1 included:

Erroneous dosing information was corrected.
The suspension information was adjusted and summary of oral suspension preparation was provided.

Amendment 4 included:

The comparator arm was removed. Furthermore, due to the comparator arm removal, the total subject number was reduced.
Inclusion criterion 1 was changed to enable enrollment of children who are on long-term anticoagulant treatment.
Additionally, instructions on how to safely handle the switch from heparin, fondaparinux, and VKA to rivaroxaban and vice versa were made available in the protocol.
The platelet count threshold for exclusion of children was adjusted from <100x109/L to <50x109/L.

6.4.2. Study Results

Compliance with Good Clinical Practices

The study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and the International Council on Harmonization (ICH) guideline E6: Good Clinical Practice (GCP).

Central Laboratory determinations for pharmacokinetics and pharmacodynamics were

performed by 3 sponsor central laboratories:

For PK: Swiss (b) (4)

For PT and aPTT: (b) (6), Bayer AG, (b) (4)

For anti-Xa: (b) (6) Bayer AG, (b) (4)

The study employed the following committees:
-Independent Data Monitoring Committee (IDMC/DMC): to evaluate all study data to ensure subjects safety throughout the study.
-Central Independent Adjudication Committee (CIAC): to review independently specified safety and all efficacy outcomes in the study in compliance with the charter, and to adjudicate and classify the events, including the confirmation of the documented index thrombotic event before first study treatment administration.

Financial Disclosure- not necessary per Agency agreement

Patient Disposition

Fifty-one pediatric patients were screened; however, 46 were assigned to study treatment and received at least one dose of study medication. Most were not dosed because of withdrawal by parent/guardian.

For the age range of ≥2-6 years:

25 children received diluted rivaroxaban ready-to-use suspension b.i.d.
6 children received comparator

For the age range of 6 months- ≤ 2 years: 15 children received diluted rivaroxaban ready-to-use suspension b.i.d.

One child in 2-6 years group was assigned to anticoagulant comparator treatment, but mistakenly received rivaroxaban. The child completed the study as planned and is included in the rivaroxaban group.

Two children on rivaroxaban (1 in age group of 2-6 years and 1 in age group of 6 months-2 years) withdrew consent.

Additionally, one child on rivaroxaban discontinued the study treatment due to the need for a series of lumbar punctures and completed the study.

Forty-four patients entered the 30 day post study treatment follow-up and completed the

study.

Protocol Violations/Deviations

One pediatric patient in the 6 months to 2 years group was considered to have a major protocol violation because the PD samples were either not taken or results were invalid. Minor protocol violations were noted for 36 pediatric patients.

Table of Demographic Characteristics

Table 22: Demographic Characteristics of the Pediatric Patients Enrolled and Treated on Trial 14374

Demographic Parameters	Control Group (2-6 years) (N=6) n (%)	Treatment Group		
		Rivaroxaban (2-6 years) (N=25) n (%)	Rivaroxaban (less than 2 years) (N=15) n (%)	Total (N=46) n (%)
Sex				
Male	3(50%)	13 (52%)	6 (40%)	22 (48%)
Female	3(50%)	12 (48%)	9 (60%)	24 (52%)
Age				
Mean years (SD)	3.67 (0.68)	3.77 (1.03)	1.26 (0.45)	2.9
Median (years)	3.5	4	1.33	3
Min, max (years)	(3,5)	(2,5)	(0.5, 1.9)	(0.5, 5)
Age Group				
< 17 years	6 (100%)	25 (100%)	15 (100%)	46 (100%)
≥ 17 - < 65 years	0	0	0	0
≥ 65 years	0	0	0	0
> 65 - < 75 years	0	0	0	0
≥ 75 years	0	0	0	0
Race				
White	6 (100.0%)	23 (92.0%)	10 (66.7%)	39 (85%)
Black or African American	0	1 (4.0%)	2 (13.3%)	3 (7%)
Asian	0	0	1 (6.7%)	1 (22%)
American Indian or Alaska Native	0	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0	0
Multiple	0	0	1 (6.7%)	1 (22%)
Other[1]	0	1 (4.0%)	1 (6.7%)	2 (4.3%)
Ethnicity				
Hispanic or Latino	0	2 (8.0%)	2 (13.3%)	4 (9%)
Not Hispanic or Latino	6 (100.0%)	23 (92.0%)	12 (80%)	41 (89%)
Not reported	0	0	1 (6.7%)	1 (2.2%)
Region				
United States	0	5(20%)	3(20%)	8 (17%)
Rest of the World				
Canada	0	0	1 (6.7%)	1 (2.2%)
South America	0	1 (4%)	2 (13.3%)	3 (7%)
Europe	4 (67%)	13 (52%)	6 (40%	6 (13%)
Asia	2 (33%)	6 (24%)	3 (20%)	3 (7%)
Africa	0	0	0	0

[1] Data on race and/or ethnicity were not collected in XX country because of local regulations.

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

All pediatric patients had thromboses and the majority had thromboses involving the cerebral vein, sinus or jugular vein.

In addition, 30 or 65% had infections, 21 or 46% had surgical procedures, 8 or 17% had acute leukemia.

Reviewer comment: These pediatric patients were significantly impacted by other diseases.

The Applicant reported that prior to trial entry, most children (45/46, 97.8%) were treated with LMWH/heparin. Vitamin K-antagonists, fondaparinux and enzymes (thrombolytic therapy) were reported for 4/46 (8.7%), 1/46 (2.2%) and 1/46 (2.2%) children, respectively.

The Applicant reported that the median for treatment duration for thrombosis prior to treatment assignment in this study was 65.5 days (range: 27-973 days).

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Two pediatric patients had compliance categorized as being between 50 to less than 80% with the other 44 being categorized as having at least 80% or more compliance with the medication.

Efficacy Results – Primary Endpoint – see safety section

Data Quality and Integrity – no apparent issues

Efficacy Results – Secondary and other relevant endpoints

None of the 46 pediatric patients had a confirmed symptomatic recurrent VTE (composite of DVT or fatal of non-fatal PE) during the treatment period or during the 30-day post treatment period.

Repeat imaging was available for 38/46 (82.6%) pediatric patients. Of the 8 patients with missing repeat imaging at visit 4, 2 children withdrew consent, 1 child had repeat imaging at later time point and 5 children did not undergo repeat imaging.

Of the 33 children in rivaroxaban groups, who had repeat imaging, the thrombus burden was normalized in 10/33 (30.3%) children, improved in 19/33 (57%) children, and unchanged in 4/33 (12.1%) children. Of the 5 children in comparator group, who had repeat imaging, the thrombus burden was normalized in 1/5 (20%) child, improved in 3/5 (60%) children, and

unchanged in 1/5 (20%) child.
One pediatric patient in the aged 6 months-2 years group had a suspected recurrent venous thrombosis in the lower extremity as reported by the investigator but the event was not confirmed by the CIAC.

Repeat imaging was available for 35 pediatric patients - 31/40 (77.5%) pediatric patients who received rivaroxaban and 4/6 (66.7%) pediatric patients who received heparin.

The outcome of adjudicated thrombotic burden was reported as “normalized” or improved” in 6/22 (27.3%) and 15/22 (68.2%) of patients in the rivaroxaban 2-6 years group with “no relevant change” reported in 1/22 (4.5%).

Thrombotic burden outcomes in comparator 2-6 years group were “normalized” in 1/5 (20.0%) child, “improved” in 3/5 (60.0%) children and “no relevant change” in 1/5 (20.0%) pediatric patient.

No “deteriorated” or “not evaluable” outcomes were reported in pediatric patients aged 6 months to 2 years and aged 2-6 years. However, for one child with an upper extremity DVT a day 30 scan was categorized as improved and an unscheduled one was categorized as deteriorated.

Dose/Dose Response

See clinical pharmacology review.

Durability of Response- demonstrated

Persistence of Effect - demonstrated

Additional Analyses Conducted on the Individual Trial

6.5. Study 17618

6.5.1. Study Design

Overview and Objective

Seven-day study of the safety, efficacy and the pharmacokinetic and pharmacodynamic properties of oral rivaroxaban in children from birth to less than 6 months with arterial or venous thrombosis

Primary objective is to characterize the pharmacokinetic/pharmacodynamic profile of a 7-day treatment with oral rivaroxaban in pediatric patients less than 6 months of age.
Secondary objectives are:

- to assess the incidence of major bleeding and clinically relevant non-major bleeding
- to assess the incidence of symptomatic recurrent thromboembolism and
- to assess asymptomatic deterioration in the thrombotic burden on repeat imaging

Trial Design-

An international, multicenter study evaluating the safety, efficacy and pharmacokinetic/pharmacodynamic (PK/PD) profile of a 7-day treatment with age- and body weight-adjusted oral rivaroxaban in children younger than 6 months with symptomatic or asymptomatic arterial or venous thrombosis.

Study Endpoints

Clinical Pharmacology - results of pharmacokinetics (PK) / pharmacodynamics (PD) - (prothrombin time, activated partial thromboplastin time and antifactory Xa activity)

Efficacy - Composite of all symptomatic recurrent thromboembolism and asymptomatic deterioration in thrombotic burden on repeat imaging.

Safety: Secondary outcome was composite of major and clinically relevant non-major bleeding.

Statistical Analysis Plan

For the demography and baseline characteristics, summary statistics (arithmetic mean, standard deviation, median, minimum and maximum for quantitative variables) were to be presented by treatment group. Frequency tables for qualitative data were provided. Medical history findings were summarized using Medical Dictionary for Regulatory Activities (MedDRA) terms.

For PD analyses, quantitative data were to be described by the summary statistics mentioned above, and presented descriptively for the original data as well as for the difference, respectively, ratio to baseline. PK/PD modeling, using population approaches, was used to describe the pharmacokinetics of rivaroxaban, including potential influence of relevant co-

variables, and to relate anticoagulant parameters of rivaroxaban with plasma concentrations.

All efficacy analyses were to be performed on the full analysis set population. The occurrence of recurrent venous thromboembolism and asymptomatic deterioration in thrombotic burden were summarized.
All safety analyses were performed on the safety analysis set (SAS). The analysis primarily focused on bleeding that occurred during or within 2 days after stop of study treatment.

Protocol Amendments

Amendment 1 included

- A minimum body weight of 2600g was added to inclusion criteria 6 to ensure that the total volume of blood collected in the course of the study did not exceed the total volume allowed by respective guidelines.
- Blood pressure measurement was added at screening.
- The international normalized ratio (INR) measurement was added at Visit 2 in the study flow charts and the visit description at screening.
  Rivaroxaban could be started only if the INR was below 2.5. Therefore, the INR had to be collected before rivaroxaban was started.
- A body weight-adjusted dosing Table for rivaroxaban oral suspension was added.
- The text of visit 2 was changed in order to enroll children without prior CIAC confirmation if they met the inclusion criteria and did not meet any of the exclusion criteria.

Amendment 4

- The study population was extended by removing the requirement of having a "catheter-related" arterial or venous thrombosis.
- Inclusion criterion 1 was changed. The minimum time of initial heparinization before start of rivaroxaban treatment was reduced from at least 2 weeks to at least 5 days.
- In exclusion criterion 6, the word "uncontrolled" was added. Children with antihypertensive therapy leading to normal blood pressure values (i.e. < 95th percentile) were allowed to be enrolled in the study.
- In exclusion criterion 12, it was clarified that children should not have an indication for continued antiplatelet or non-steroid anti-inflammatory drug (NSAID) therapy. However, incidental use is allowed.
- The rivaroxaban formulation was changed from "ready-to-use" suspension to "granules for oral suspension".
- The process for assessment of the index event by the CIAC was clarified. The CIAC assessed the index event; however, inclusion of child into the study did not depend on the outcome of the assessment.
- At visit 3 (day 3) drug accountability and compliance were not to be assessed. It was decided to measure the volume only after completion of treatment.

- Timing of rivaroxaban administration in relation to feeding was defined. Rivaroxaban should be administered immediately before or (early) during feeding.

Amendment 5

- The dosing regimen was modified from twice daily schedule to three times daily administration of the same individual dose previously used with the twice daily schedule.
- Provision of additional imaging tests for adjudication was added. Investigators were asked to also submit diagnostic tests other than ultrasound for evaluation of repeat imaging by the Central Independent Adjudication Committee, if available.

6.5.2. Study Results

Compliance with Good Clinical Practices

The study employed local IEC/IRB at each study site. The study was conducted in accordance with ethical principles as outlined in the Declaration of Helsinki and the International Council on Harmonization (ICH) guideline E6: Good Clinical Practice (GCP). Informed Consent process was used to obtain consent from the parent or guardian depending upon the circumstances.

The study employed the following committees:

-Steering Committee (SC): to provide an overall academic leadership

-Independent Data Monitoring Committee (IDMC/DMC): to evaluate all study data to ensure subjects safety throughout the study.

-Central Independent Adjudication Committee (CIAC): to review independently specified safety and all efficacy outcomes in the study in compliance with the charter, and to adjudicate and classify the events, including the confirmation of the documented index thrombotic event before first study treatment administration.

Financial Disclosure- not reported as per agreement with the Agency for a phase 1/2 study

The study was conducted at 9 study centers in 7 countries. Central Laboratory determinations for pharmacokinetics and pharmacodynamics were performed by 3 sponsor central laboratories:

-For PK: (b) (4)

-For PT and aPTT: (b) (4), Bayer AG, (b) (4)

-For anti-Xa: (b) (4), Bayer AG, (b) (4)

Patient Disposition

Eleven children were enrolled and 1 parent/guardian withdrew informed consent. Ten children were valid for both: full PK/PD analysis set and safety analysis set. Ten completed screening and treatment.

Protocol Violations/Deviations

No major protocol deviations were reported.

Table of Demographic Characteristics

Table 23: Demographic Characteristics of the Pediatric Patients Enrolled and Treated in Trial 17618

Demographic Parameters	Treatment Group		
	Rivaroxaban BID (N=5) n (%)	Rivaroxaban TID (N=5) n (%)	Total (N=10) n (%)
Sex			N/A
Male	4 (80%)	1 (20%)	5 (50%)
Female	1 (20%)	4(80%)	5 (50%)
Age			
Mean months (SD)	1.81 (2.24)	1.12 (0.60)	1.47
Median (months)	1.02	1.02	1.02
Min, max (months)	(0.5,5.8)	(0.5, 2.1)	(0.5,5.8)
Age Group			
< 17 years	5 (100%)	5 (100%)	10 (100%)
Race			
White	3 (60%)	5 (100%)	8 (80%)
Black or African American	1 (20%)	0	1 (10%)
Asian	0	0	0
American Indian or Alaska Native	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0
Other[1]	1 (20%)	0	1 (10%)

Ethnicity			
Hispanic or Latino	1 (20%)	1 (20%)	2 (20%)
Not Hispanic or Latino	3 (60%)	4 (80%)	7 (70%)
Not reported	1 (20%)	0	1 (10%)
Region			
United States	0	0	0
Rest of the World			
Canada	0	0	0
South America	0	0	0
Europe	5 (100%)	5 (100%)	10 (100%)
Asia	0	0	0
Africa	0	0	0

[1] Data on race and/or ethnicity were not collected because of local regulations.

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

All pediatric patients had a venous thrombosis with catheter-related thrombosis the most frequent. In addition, 5 or 50% had congenital, familial or genetic disorders and cardiac disorders 3 or 30%, surgical and medical procedures 2 (20%) with ventricular septal defect repair 2 (20%), and vascular disorders 4 (40%).

Only one pediatric patient weighed more than 6 kg and that patient was assigned to b.i.d. dosing group. All others in the b.i.d. dosing group weighed less than 6 kg. All pediatric patients enrolled on the t.i.d. dosing weighed less than 6 kg.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Children received rivaroxaban according to a body weight adjusted regimen.
The study treatment period was for a total of 7 days followed by an observational period of another 30 days. There was 100% compliance. However, for both arms the categorized treatment compliance of 80% or greater was 80% for both arms. With one patient in either arm, having between 50 to 80% clearance.
All suspected clinical study outcomes and baseline and repeat thrombosis imaging tests were to be assessed by a CIAC. An independent data monitoring committee (DMC) monitored the children's safety.

Efficacy Results – Primary Endpoint

For clinical pharmacology, see the clinical pharmacology review.

No occurrence of recurrent venous thromboembolism or asymptomatic deterioration in thrombotic burden were observed.

Because this was a seven-day study the thrombotic burden at the time of the index event was compared to the thrombotic burden at the time of repeat imaging. Repeat imaging was available for 5/5 (100%) pediatric patients in the rivaroxaban b.i.d. group and for 4/5 (80%) pediatric patients in the rivaroxaban t.i.d. group as one parent withdrew their child in the t.i.d. dosing. All imaging results were reviewed by a central committee.

In the rivaroxaban b.i.d. group, repeat imaging was adjudicated as normalized in 4/5 (80%) and improved in 1/5 (20%).

In the rivaroxaban t.i.d. group, repeat imaging was adjudicated as normalized, improved or no relevant change in 1/4 (25%), 2/4 (50%), 1/4 (25%), respectively.

Only two patients in the rivaroxaban group had an evaluable scan. One scan was read as

improved and the other scan was read as no relevant change.

Data Quality and Integrity

No apparent issues.

Efficacy Results – Secondary and other relevant endpoints

Not applicable

Dose/Dose Response

Children received rivaroxaban according to a body weight adjusted regimen either twice a day or three times a day.

Durability of Response

Study only lasted for seven days.

Persistence of Effect

Not applicable

Additional Analyses Conducted on the Individual Trial

6.6. Study 17992

6.6.1. Study Design

Overview and Objective

Single dose pharmacokinetic (PK) study of rivaroxaban granules for oral suspension in pediatric patients aged 2 months to 12 years

Primary objective - To characterize the pharmacokinetic profile of rivaroxaban administered as granules for oral suspension formulation
Secondary objective- To document safety and tolerability in terms of adverse events (AEs) observed after administration of a single dose of the rivaroxaban granules for oral suspension formulation

Trial Design

Multicenter, single-dose, open-label, cohort study

Major Inclusion/Exclusion Criteria

For Groups A and B:

Children with an age between 6 months and <12 years who have completed anticoagulant treatment at least 10 days prior to the planned study drug administration

For Group C:

Children with an age ≥ 2 months and weight between 3 kg and <12 kg, who have completed anticoagulant treatment at least 10 days prior to the planned study drug administration, and have

• Gestational age at birth of at least 37 weeks, and

• Oral feeding/ nasogastric/ gastric feeding for at least 10 days

Body weight-adjusted single doses administered as granules for oral suspension according to three dosing regimens:

Group A: Dosing as low dose in phase 1 study 12892.

Group B: Dosing as ready to use suspension dose in phase 2 studies 14373 and 14374.

Group C: Dosing of 0.4 mg/kg body weight for children weighing 3 to < 12 kg

Study Endpoints

Results of pharmacokinetics (PK) / PD (PT, aPTT and anti-Factor Xa activity)

Safety: - composite of major bleeding and clinically relevant non major bleeding. Other safety outcomes included all deaths and other vascular events (myocardial infarction, cerebrovascular accident, non-central nervous system systemic embolism).

Other: A taste and texture questionnaire in the form of a 3-point scale was used to determine the acceptance of the oral suspension in children aged ≥ 4 years.

Statistical Analysis Plan

For demographic and other baseline characteristics, summary statistics (arithmetic mean, standard deviation, median, minimum and maximum for quantitative variables) were used by treatment group. Frequency tables for qualitative data were provided. Medical history findings were summarized using MedDRA (Medical Dictionary for Regulatory Activities) terms.

For PK analyses, see the clinical pharmacology review for details.

For safety, quantitative data (hematology, blood chemistry, pulse rate) was described by the following summary statistics: arithmetic mean, standard deviation, median, minimum and maximum. These summary statistics were presented for the original data, as well as for the difference to baseline. Frequency tables were provided for qualitative data. Laboratory data outside the reference range were listed and flagged with 'L' for low and 'H' for high. Additional tables with all abnormal values were presented.

Protocol Amendments

One minor and two major amendments

Second amendment – 2016
1) added a new dose cohort for evaluation of the PK/PD of the granules for suspension based on the oral suspension dosing used in two phase 2 studies (14373 and 14374).
2) Revised the formula for eGFR (estimated glomerular filtration rate) to Schwartz formula which is more appropriate for eGFR calculation in children.
3) Increased the number of pediatric patients
4) The study procedures were updated to clarify that heparin use within 24 hours of PD sampling should be avoided.

Third Amendment- 2017
1) Revised the age range of the study population was extended from 6 months to < 12 years to ≥2 months to include children with body weight from 3 to < 12 kg into Group C
2) Added an additional dose group was added for dosing according to a fixed per body weight dose of 0.4 mg/kg body weight
3) Revised to extend hospital stay from 5 to 8 hours on Day 1 as the children had to stay until the last PK sample was taken

6.6.2. Study Results

Compliance with Good Clinical Practices

The study employed local IEC/IRB at each study site. The study was conducted in accordance with ethical principles as outlined in the Declaration of Helsinki and the International Council on Harmonization (ICH) guideline E6: Good Clinical Practice (GCP). Informed Consent process was used to obtain consent from either the parent or guardian or child depending upon the circumstances.

Financial Disclosure – not reported as per agreement with the Agency for a phase 1/2 study

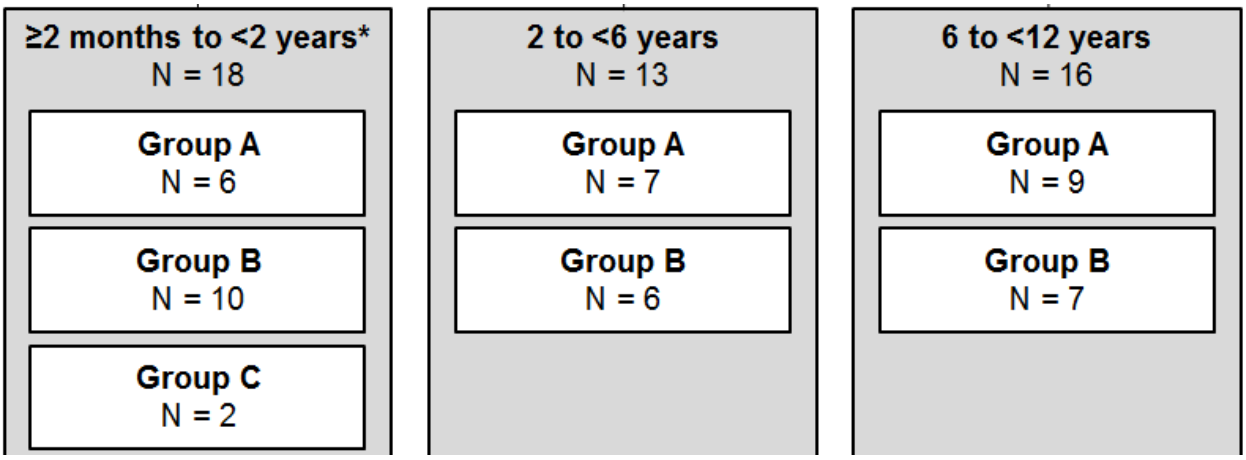
The study was conducted at 21 centers. Central Laboratory determinations for pharmacokinetics

and pharmacodynamics were performed by 3 sponsor central laboratories: For PK: (b) (4) , for PT and aPTT: Bayer AG, (b) (4) and for anti-Xa: Bayer AG, (b) (4)

Patient Disposition

Before amendment 2, all children were assigned to group A. After amendment 2 was instituted and before amendment 3 was instituted all children were assigned to group B. After amendment 3 was instituted, all children were assigned to group C.

Fifty-six pediatric patients were screened and forty-seven pediatric patients were treated. The diagram below shows the enrollment into the various groups.



All 47 patients who were treated completed the trial.

Protocol Violations/Deviations

There were two major protocol and 30 minor protocol deviations. The two major protocol deviations were inability to obtain or use a blood sample for testing in group B. All 22 pediatric patients in group A and 21 of 23 pediatric patients in group B were available for the PD analysis; all pediatric patients enrolled save for those two pediatric patients with problems with sampling were available for the PK analysis.

Table of Demographic Characteristics

Table 24: Demographic Characteristics of Pediatric Patients Enrolled in Trial 17992

Demographic Parameters	Rivaroxaban
	Treatment (N=47) n (%)
Sex	
Male	29 (61.7%)
Female	18 (38.3%)
Age	
Mean years (SD)	5.03 (3.95)
Median (years)	4.75
Min, max (years)	(0.3,12.0)
Age Group	
< 17 years	47 (100%)
Race	
White	37 (78.7%)
Black or African American	2 (4.3%)
Asian	0
American Indian or Alaska Native	1 (2.1%)
Native Hawaiian or Other Pacific Islander	0
Other[1]	3 (6.4%)
Multiple Races	4 (8.5%)
Ethnicity	
Hispanic or Latino	3 (6.4%)
Not Hispanic or Latino	41 (87.2%)
Not Reported	3 (6.4%)
Region (based on screening)	
United States	5 (10.6%)
Rest of the World	
Canada	14 (29.8%)
South America	0
Europe	28 (59.6%)
Asia	0
Africa	0

[1] Data on race and/or ethnicity were not available for two in Canada and one in Finland.

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

The pediatric patients enrolled in these trials had complex pertinent medical histories. The majority of pediatric patients had vascular disorders 23 (48.9%), with cerebral venous thrombosis 11 (23.4%), the most common preferred term; infections were 19 (40.4%); congenital, familial and genetic disorders 16 (34.0%) including atrial septal defect 3 (6.4%), ventricular septal defect 3 (6.4%), and transposition of the great vessels 3 (6.4%); surgical and medical procedures 16 (34.0%) including arterial switch operation 4 (8.5%); respiratory, thoracic and mediastinal disorders 10 (21.3%); neoplasms, benign, malignant and unspecified (incl. cysts and polyps) 8 (17.0%); cardiac disorders 7 (14.9%) including atrial thrombosis 4 (8.5%); and general disorders and administration site conditions 6 (12.8%) including device related thrombosis 5 (10.6%).

Seven patients (14.9%) were on an antithrombotic.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

There was 100% compliance with the single dose administration.

Pediatric patients were on concomitant medication, but the medication did not interfere with assays for required trial data collection.

Efficacy Results – Primary Endpoint

See the clinical pharmacology review.

Data Quality and Integrity

See the clinical pharmacology review.

Efficacy Results – Secondary and other relevant endpoints

See the clinical pharmacology review.

Dose/Dose Response

See the clinical pharmacology review.

Durability of Response

See the clinical pharmacology review.

Persistence of Effect

See the clinical pharmacology review.

6.7. Study 12892

6.7.1. Study Design

Overview and Objective

Single dose pilot study of rivaroxaban in pediatric patients with venous thromboembolism Rivaroxaban was administered as tablet or liquid formulation adapted to the individual per kg body weight class.

Primary objective - To investigate pharmacokinetics and pharmacodynamics of single oral doses of rivaroxaban in pediatric subjects in order to obtain weight adjusted doses with equivalent exposure compared to 10 mg and 20 mg doses in adults.

Secondary objective- To document safety and tolerability

Trial Design

International, multicenter, single-dose, open-label, non-controlled study

Route of administration: Oral administration as tablet (children aged 6 years and older) or as oral suspension (children aged younger than 12 years)

Age groups were > 12-18 years, > 6-12 years, 2-6 years and 6 months to < 2 years. Within those age groups, patients were furthered divided by low dose and high dose to match the equivalent adult exposures for the 10 mg and 20 mg doses.

Major Inclusions/Exclusion criteria

Inclusion criteria

Children ≥6 months and <18 years of age at the time of administration of study drug who completed treatment of VTE, but were considered to have a risk for recurrence and who could take oral medication

Written informed consent (and age-appropriate assent) as per local requirements

Clinically stable children who could be treated on an ambulatory basis

Exclusion criteria

Any condition requiring ongoing anticoagulation

Known bleeding disorder

Any major or clinically relevant bleed during the previous VTE treatment

Abnormal coagulation test results within 10 days prior to study drug administration

Planned invasive procedures (including removal of central lines) 24 hours before and after single dose

Participation in a therapeutic study with a new investigational drug within 30 days prior to study drug administration (Visit 2)

Severe renal impairment, e.g. calculated creatinine clearance <30 mL/min for children > 12 years (for Cockcroft-Gault see Section 14.5 in the study protocol,

Hepatic disease which was associated with either: coagulopathy leading to a clinically relevant bleeding risk, or ALT >5x upper limit of normal (ULN) or total bilirubin >2xULN with direct bilirubin >20% of the total

Known bacterial endocarditis

Life expectancy <3 months

Platelet count <150 x 109/L

Hypertension (as defined by >95th percentile for age)

Concomitant use of strong CYP3A4 inhibitors

Pregnancy or lactation in menstruating girls

Medical disorder, condition, or history of such that would impair the child's ability to participate or complete this study in the opinion of the investigator or the sponsor

History of gastrointestinal disease (e.g. Crohn's disease) which could result in impaired absorption of the study drug

Any other disease or condition which may influence the physiological metabolic turnover (e.g.

endocrine diseases, febrile condition, severe infections)

Febrile illness within 7 days prior to study drug administration (Visit 2)

Reviewer's Comment: The inclusion/exclusion criteria were appropriate for the single dose study.

Study Endpoints

PK/PD of rivaroxaban in children ≥ 6 months and <18 years of age at the time of administration of study drug who completed treatment of VTE

The primary variables for pharmacokinetics were standard PK parameters for exposure such as AUC and Cmax. They were calculated and compared with PBPK-based predictions and previous Phase I adult data.

The primary variables for pharmacodynamics were PT, aPTT, and anti-Factor Xa. Due to limitations on blood volumes for sampling PK/PD - Emax and Etrough were determined for each parameter.

Safety: Adverse events, vital signs (systolic / diastolic blood pressure and heart rate), physical examination (including body weight and height), urine pregnancy test, laboratory

Other: A taste and texture questionnaire in the form of a visual analog scale was used to determine the acceptance of the oral suspension in children aged from 4 to <12 years.

Statistical Analysis Plan

Summary statistics were applied for pharmacokinetic and pharmacodynamic parameters.

Protocol Amendments

No substantial amendments were made to version 3 of the protocol which was used at the start of the study except for extending the time for the study because of slow accrual.

6.7.2. Study Results

Compliance with Good Clinical Practices

The study was conducted in accordance with the ethical principles that have their origin in the

Declaration of Helsinki and the International Conference on Harmonization (ICH) guideline E6: Good Clinical Practice (GCP).

Financial Disclosure- not applicable per agreement with the Agency

Central laboratory determinations for pharmacokinetics and pharmacodynamics (PT, activated or adjusted partial thromboplastin time [aPTT], anti-Xa) of rivaroxaban were performed by 3 sponsor central laboratories:

For PK:

(b) (4) Bayer Pharma AG, (b) (4)

For PT and aPTT:

(b) (4) Bayer Pharma AG, (b) (4)

For anti-Xa:

(b) (4) Bayer Pharma AG, (b) (4)

Patient Disposition – Seventy-two were screened with 13 patients whose medical issues and history failed screening thus 59 were dosed. Of the 72 patients, 3 withdrew consent, 1 patient refused a blood test so could not confirm eligibility, 5 had protocol violations making them ineligible for the study, and 4 had technical problems.

Protocol Violations/Deviations

Of the 59 pediatric patients who were dosed; 17 received tablets and 42 received oral suspension.

No major protocol violations occurred among the 59 pediatric patients. Eleven pediatric patients had 12 minor protocol violations. No pediatric patients were excluded from the analyses.

Table of Demographic Characteristics

Table 25: Demographic Characteristics of Pediatric Patients Enrolled in Trial 12892

Demographic Parameters	Rivaroxaban
	Total (N=59) n (%)

Sex	
Male	33 (56%)
Female	26 (44%)
Age	
Mean years (SD)	6.8 (4.9)
Median (years)	6
Min, max (years)	(0,17)
Age Group	
< 17 years	59 (100%)
≥ 17 - < 65 years	0
≥ 65 years	0
> 65 - < 75 years	0
≥ 75 years	0
Race	
White (may include Hispanic/Latino reported below)	44 (75%)
Black or African American	1 (2%)
Asian	3 (5%)
American Indian or Alaska Native	0
Native Hawaiian or Other Pacific Islander	0
Other[1]	4 (7%)
Ethnicity	
Hispanic or Latino	7 (12%)
Not Hispanic or Latino	Not reported
Region	
United States	14 (23.7%)
Rest of the World	11 (18.6%)
Canada	14 (23.7%)
South America	0
Europe	20 (33.9%)
Asia	0
Africa	0

[1] Data on race and/or ethnicity were not collected in France because of local regulations.

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

Sixty-nine percent had a history of vascular disorders such as venous thromboembolism and 20% had a history of cerebrovascular and sinus thrombosis.

Eight percent had a history of warfarin sodium use and seven percent had a history of enoxaparin use.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

All 59 pediatric patients were dosed.

Efficacy Results – Primary Endpoint

See the clinical pharmacology review.

Data Quality and Integrity

See the clinical pharmacology review.

Efficacy Results – Secondary and other relevant endpoints

See the clinical pharmacology review.

Dose/Dose Response- not applicable a single dose study

Durability of Response- not applicable a single dose study

Persistence of Effect- not applicable a single dose study

Additional Analyses Conducted on the Individual Trial – none

7. Integrated Review of Effectiveness

7.1. Integrated Assessment of Effectiveness

There were two phase 3 studies that were adequate and well controlled trials; EINSTEIN Jr (Trial 14372) and UNIVERSE (Trial 3001). Given differences in clinical trial design, indication for treatment/prophylaxis, patient population, and length of therapy, clinical trials were evaluated independently for effectiveness.

Indication #1
Einstein Jr was a phase 3, randomized, open-label, active-controlled, multicenter, international trial which demonstrated a weight based dosing regimen of rivaroxaban is an effective therapy for the treatment and prevention of recurrent VTE. The rivaroxaban dose was exposure matched to 20 mg daily in adults.

The trial randomized a total of 500 patients, of which 335 patients were randomized to rivaroxaban and 165 patients were randomized to the comparator. The majority of patients received at least 5 days of parenteral therapy prior to study drug. Pediatric patients were included from birth to <18 years of age (276 children aged 12 to <18 years, 101 children aged 6 to <12 years, 69 children aged 2 to <6 years, and 54 children aged <2 years). All age groups were well represented and allowed for an adequate analysis of efficacy. Demographics and baseline characteristics were well balanced between treatment arms. It is notable that 25% of patients had a CVC-VTE. This is lower than expected. CVC is the most common risk factor for VTE and has been estimated to be the cause in >50% of cases and even higher in neonates[26]. Despite this, study results remain applicable to the majority of pediatric patients with VTE as a variety of risk factors for VTE were well represented and a variety of VTE index locations.

The primary endpoint was the incidence of symptomatic recurrent VTE. During the main treatment period, four patients of 335 (1.2%) who received rivaroxaban had a recurrent VTE. Five patients out of 165 (3%) in the comparator group had a recurrent VTE. The trial was not powered to demonstrate a difference between treatment groups, although the lower rate of recurrent VTE in the rivaroxaban group is evidence of benefit.

There were multiple secondary endpoints, rivaroxaban was favorable or comparable to the comparator group in all secondary endpoints. Complete resolution of thrombus on repeat imaging without recurrent VTE occurred in 128 of 335 patients (38.2%) in the rivaroxaban group and 43 of 165 patients (26.1%) in the comparator group. The composite of recurrent VTE and asymptomatic deterioration occurred in 5 out of 335 patients (1.5%)in the rivaroxaban group and in 6 out of 165 patients (3.6%) in the comparator group. The composite outcome of recurrent VTE and major bleeding occurred in 4 out of 335 patients (1.2%) in the rivaroxaban group and 7 out of 165 patients (4.2%) in the comparator group.

In studies 14373, 14374, and 17618 no patient had a recurrent VTE, this further supports the clinical benefit of rivaroxaban.

In summary, symptomatic recurrent VTE occurred in a lower percentage of patients in the rivaroxaban group compared to the standard of care group. This, along with a greater improvement in thrombotic burden in the rivaroxaban group and a smaller incidence of the composite of recurrent VTE and asymptomatic deterioration, is clear evidence of substantial effectiveness. Therefore, the clinical review team recommends approval for rivaroxaban for pediatric patients birth to <18 years old for the treatment and prevention of recurrent VTE.

Indication #2
UNIVERSE Study was an international, prospective, open-label, randomized, multicenter, 2 part study, which included pediatric patients between 2 to 8 years of age with a recent Fontan operation for single ventricle physiology. Part A was a single-arm part to characterize PK and PD of rivaroxaban, this included 12 patients. Part B was the randomized, active-controlled part in which patients were randomized 2:1 to rivaroxaban or ASA. The rivaroxaban dose was exposure matched to 10 mg daily in adults. The study clearly demonstrated rivaroxaban as an effective therapy for prevention of thrombosis in pediatric patients following Fontan procedure.

The trial included 110 patients, 76 received rivaroxaban (Part A = 12 patients, Part B= 64 patients) and 34 patients received aspirin. Patients ages 2 to 8 years of age were included in the study, with a median age of 4. Overall, demographics and baseline characteristics were similar between treatment groups, with the exception of more patients in the aspirin arm were from South America and more patients in the rivaroxaban arm were from the United States, this unlikely impacted efficacy results as many regions were well represented including; Canada, United States, South America, Europe and Asia. It was notable that the duration between Fontan operation was longer in the rivaroxaban group compared to aspirin group (34 day vs 24 days, respectively). There is no consensus on when to initiate thromboprophylaxis. While some reports suggest early initiation of thromboprophylaxis may decrease the risk of thrombosis[27] its unlikely that the 10 day difference in initiation of study drug had a substantial effect on thrombosis risk. It will be important for prescribers to be aware of when thromboprophylaxis was initiated in this study, this will be included in the USPI.

In total, 1 (8.3%) of patient in rivaroxaban group part A had a thromboembolism (TE) and 1 (1.6%) patient in rivaroxaban part B had TE, compared to 3 (8.8%) of patients in the aspirin group in part B. The study was not designed to show a difference in effectiveness between rivaroxaban and aspirin, but the lower TE incidence in the rivaroxaban group is demonstration that rivaroxaban is an effective and preventing TE in pediatric patients over the age of 2 years following a Fontan operation.

8. Review of Safety

8.1. Safety Review Approach

The focus of the safety review was based on the two Phase 3 studies: Study 14372 (EINSTEIN Jr) for indication #1 and Study CHD3001 (UNIVERSE) for indication #2. The EINSTEIN Jr safety assessment was focused on the main treatment period (randomization and first dose of study drug to 3 months of treatment or 1 month for patients <2 years with CVC-VTE). There were no pooled analysis of safety data from the two Phase 3 studies. Additional safety data was included from an additional 5 supportive Phase 1 or 2 studies: Studies 14272, 14274, 17618, 12892, 17992. Table 2 includes a summary of each study.

Review of safety was based upon:

- Clinical Study Reports (CSR) for studies
- Protocol for studies
- Data sets for the populations described above
- Summary of clinical safety (SCS)
- Patient narratives
- Case report forms

Case report forms and narratives were provided and reviewed for adverse events (AE) of interest, serious adverse events (SAEs), and deaths that occurred in safety populations.

Particular emphasis was focused on bleeding adverse events. TEAEs of special interest (identified by the Applicant) in EINSTEIN Jr consisted of liver injury, low platelet counts and allergic skin reactions. TEAEs of special interest in UNIVERSE were toxic effects on the bone marrow (severe thrombocytopenia, severe neutropenia, pancytopenia, aplastic anemia), severe hypersensitivity reactions, skin reactions such as stevens-johnson syndrome and suspected severe liver injury.

Analysis by the clinical reviewer were performed using JMP 14 (SAS, Inc. Cary. N.C.). No major issues were identified with respect to recording, coding, and categorizing AEs. Adverse events were analyzed by MedDRA preferred terms. Similar preferred terms were grouped by standardized groupings of related preferred terms through FDA Medical Queries (FMQs). Additional analyses were provided by the Clinical Data Scientist (CDS) support team.

Clinical comment: The clinical review team agreed that the phase 3 studies should not be pooled given differences in patient population, dosing regimen, and study design. The clinical review team did not identify any major data quality or integrity issues that precluded performing a safety review.

8.2. Review of the Safety Database

8.2.1. Overall Exposure

EINSTEIN Jr

In total, 491 patients were exposed to either rivaroxaban (329 patients) or a comparator (162 patients) for a main treatment period of 3 months (1 month for patients < 2 years with CVC-VTE) with the option of extending treatment. In the entire treatment period (main and extended), the mean duration of rivaroxaban exposure was 20.1 weeks, which was similar to comparator group exposure of 19.9 weeks (Table 26). Exposure by age group during the main treatment period is described in Table 27 and Table 28.

Table 26. Duration of Exposure (Main Treatment Period and Extended), Safety Population, Trial 14372

Variable	Rivaroxaban N=329 n (%)	Comparator Group N=162 n (%)
Duration of exposure, weeks		
Mean (SD)	20.1 (13.1)	19.9 (13.6)
Median (Q1, Q3)	13.4 (12.4, 25.6)	13.6 (12.5, 25.5)
Min, Max	0.1, 55	0.1, 53.9
Total exposure (person years)	127	62
Patients treated, by duration, n (%)		
<12 weeks	54 (16.4)	27 (16.7)
≥12 to <26 weeks	199 (60.5)	99 (61.1)
≥26 to <50 weeks	48 (14.6)	19 (11.7)
≥50 to <100 weeks	28 (8.5)	17 (10.5)
≥100 weeks	0	0

Source: Clinical data analyst, adex.xpt; Software: R
Abbreviations: N, number of subjects in treatment arm; n, number of subjects with given treatment duration; SD, standard deviation; Q1, first quartile; Q3, third quartile

Table 27. Duration of Exposure in Main Treatment Period for Pediatric patients with CVST, non-CVC-VTE or CVC-VTE ≥ 2 years, Safety Population, Trial 14372

Variable	Rivaroxaban N=304 n (%)	Comparator Group N=154 n (%)
Duration of exposure, days		
Mean (SD)	88 (15.3)	86.7 (17.7)
Median	91	91
Min, Max	6, 97	1, 97

Source: Adapted from Clinical Summary of Safety
Abbreviations: N, number of subjects in treatment arm; n, number of subjects with given treatment duration; SD, standard deviation

Table 28. Duration of Exposure in Main Treatment Period for Pediatric patients with CVC-VTE ≤ 2 years, Safety Population, Trial 14372

Variable	Rivaroxaban N=26 n (%)	Comparator Group N=11 n (%)
Duration of exposure, days		
Mean (SD)	29.8 (8)	29.5 (3.4)
Median	32	29
Min, Max	3, 37	24,35

Source: Adapted from Clinical Summary of Safety
Abbreviations: N, number of subjects in treatment arm; n, number of subjects with given treatment duration; SD, standard deviation;

Clinical reviewer comment: The duration of exposure was similar in the rivaroxaban group and comparator group. There is adequate exposure to rivaroxaban to inform safety in EINSTEIN Jr study.

UNIVERSE

A total of 110 patients received study drug, this included 12 patients in rivaroxaban Part A group, 64 patients in rivaroxaban Part B, and 34 patients in aspirin Part B. The mean duration of rivaroxaban exposure in Part B was 48.2 weeks, this was similar to the aspirin group of 48.1 weeks (Table 29). Most patients (>88%) in both the rivaroxaban group and aspirin group were exposed to for over 50 weeks.

Table 29. Duration of Exposure, Safety Population, Trial CHD3001

Variable	Rivaroxaban (Part A) N=12 n (%)	Rivaroxaban (Part B) N=64 n (%)	Total Rivaroxaban N=76 n (%)	Aspirin (Part B) N=34 n (%)
Duration of exposure, weeks				
Mean (SD)	43.1 (19.3)	48.2 (11.7)	47.4 (13.2)	48.1 (9.8)
Median (Q1, Q3)	51.3 (50.8, 51.6)	51.3 (50.6, 52)	51.3 (50.7, 52)	51.3 (50.6, 52)
Min, Max	1.4, 52.1	1, 54.4	1, 54.4	13, 55
Total exposure (person years)	10	59	69	31
Patients treated, by duration, n (%)				
<12 weeks	2 (16.7)	3 (4.7)	5 (6.6)	0
≥12 to <26 weeks	0	2 (3.1)	2 (2.6)	3 (8.8)
≥26 to <50 weeks	0	2 (3.1)	2 (2.6)	1 (2.9)
≥50 to <100 weeks	10 (83.3)	57 (89.1)	67 (88.2)	30 (88.2)
≥100 weeks	0	0	0	0

Source: Clinical data analyst, adex.xpt; Software: R
Abbreviations: N, number of subjects in treatment arm; n, number of subjects with given treatment duration; SD, standard deviation; Q1, first quartile; Q3, third quartile

Clinical reviewer comment: The duration of exposure was similar in the rivaroxaban group and

comparator group. There is adequate exposure to rivaroxaban to inform safety in UNIVERSE study.

8.2.2. Relevant characteristics of the safety population:

EINSTEIN Jr

There was a similar proportion of males and females in the rivaroxaban and comparator group. The median age was about 13 years in both groups. Most patients were between the age of 12 to <18 years old in both groups, although patients were included from birth to <18 years (Table 30). Most patients were not Hispanic or latino in both groups. Baseline demographic data is shown in Table 5 in section 6 of the review.

Table 30. Patient Age in Main Treatment Period, Safety Population, Trial 14372

Age Group	Rivaroxaban N=329 n(%)	Comparator N=162 n(%)
<0.5 years	15 (4.6)	8 (4.9)
0.5 - <2 years	21 (6.4)	9 (5.6))
2 - <6 years	46 (14.0)	22 (13.6)
6 - <12 years	67 (20.4)	34 (21.0)
12 - <18 years	180 (54.7)	89 (54.9)

Clinical reviewer comment: Overall the demographic characteristics were well balanced between the two groups. All age groups are well represented. See further comments in section 6.1.2 of efficacy.

UNIVERSE

More patients were male in both the rivaroxaban group and comparator group (67.6% and 56.6%, respectively). The median age was 4 years of age in both groups, with a range from 2 to 8 years. Most patients were from the United States in the rivaroxaban group (40.8% in the rivaroxaban group vs 23.5% in the aspirin group). In the aspirin group more patients were from South America. Baseline demographic data is shown in Table 14 in section 6 of the review.

Clinical reviewer comment: Overall the demographic characteristics were well balanced between the two groups. Of note, most patients (40.8%) were from the United States in the rivaroxaban group, compared to the aspirin group in which most patients were from Brazil. Further analysis of demographic characteristics can be found in section 6.2.2.

8.2.3. Adequacy of the safety database:

EINSTEIN Jr
The safety database of EINSTEIN Jr consisted of 491 pediatric patients (age <18 years) who were exposed to either rivaroxaban or a comparator.

Clinical reviewer comment: While the safety database of EINSTEIN Jr is small, the population is an adequate representation of patients at risk for recurrent venous thromboembolism. The safety database allows for an adequate safety evaluation.

UNIVERSE
The safety database of UNIVERSE consists of 110 pediatric patients (age 2-8 years) who were exposed to either rivaroxaban or aspirin.

Clinical reviewer comment: While the safety database of UNIVERSE is small, the population is an adequate representation of patients following Fontan procedure for which thromboprophylaxis would be indicated. The safety database allows for an adequate safety evaluation.

8.3. Adequacy of Applicant's Clinical Safety Assessments

8.3.1. Issues Regarding Data Integrity and Submission Quality

There were no concerns regarding the quality and integrity of this submission.

8.3.2. Categorization of Adverse Events

Adverse events were coded using Medical Dictionary for Regulatory Activities (MedDRA) Version 18.0 for Study 12892, Version 19.0 for Study 14373, Version 20.0 for Study 14374, Version 20.1 for Study 17618, Version 21.0 for Study 17992, Version 21.1 for EINSTEIN Jr, and Version 23.0 for UNIVERSE, and were categorized by primary system organ class (SOC) according to the MedDRA Preferred Term.

In EINSTEIN Jr, the start date for a TEAE was the day from randomization, except for bleeding events which occurred on day of randomization were only considered treatment-emergent if the investigator stated it was related to the study drug.

In UNIVERSE, all AEs were defined as treatment-emergent and all bleeding events were defined as on-treatment. Treatment-emergent and on-treatment refer to the period from the first dose until 2 days after the last dose of study drug.

The primary safety outcome is major bleeding events.

Clinically relevant non-major bleeding events and trivial (minimal) bleeding will be secondary

safety outcomes.

Bleeding events will be adjudicated by the CIAC using the International Society on Thrombosis and Hemostasis (ISTH) recommendations (Buller 2007, Schulman 2005).

Major bleeding is 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.

Clinically relevant non-major bleeding 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.

The main description will be based on Safety Analysis Set during the On-treatment period (bleeding events confirmed by the CIAC).

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) and the respective 95% CIs will be calculated for the major and clinically relevant non major bleedings by treatment group. Cumulative incidence rates (time to first event; Kaplan-Meier) will be calculated for the major bleeding and clinically relevant non-major bleeding.

In addition, listing for all bleedings will be provided, including those that are reported more than 2 days after stop of study medication.

8.3.3. Routine Clinical Tests

EINSTEIN Jr

Laboratory parameters for hemoglobin (Hb), platelets, alanine transaminase (ALT), creatinine, total/direct bilirubin were collected at screening and, with the exception of serum creatinine, at Visit 4 (Visit 2 for subjects with CVC-VTE). Body length, height, and blood pressure were collected at screening only. Body weight was collected at screening and at additional visits.

UNIVERSE
Laboratory parameters were collected at screening, at month 12, and/or early study medication discontinuation (ESMD) visit for hematology and serum chemistry. In Part A, prothrombin time (PT) and activated partial thromboplastin time (aPTT) could be performed at local laboratories during screening only. Additionally, for patients participating in Part A, blood samples for serum chemistry were collected at the Month 3 visit. Body weight, height, blood pressure, heart rate, and physical examinations were performed at the screening visit. Body weight and height were also measured at Day 1, Month 6, Month 12, and/or ESMD visits. Physical exams were repeated at Day 12 (Part A only), Month 12, and ESMD visit

8.4. Safety Results

8.4.1. Deaths

EINSTEIN Jr Trial
Two deaths occurred on the trial.

One death occurred in a 17-year-old male patient with recurrent myxofibrosarcoma who was originally diagnosed in (b) (6). In (b) (6), he presented with a pulmonary embolism. Following initial enoxaparin therapy, he was enrolled and randomized to the rivaroxaban treatment arm. Thirty-one days after enrollment in trial, the patient was noted to have progressive cancer and three days later he died.

Second death was in a 13-year-old female patient with a history of Hodgkin Lymphoma diagnosed in (b) (6). In (b) (6) she was diagnosed with a catheter-related thrombosis with upper extremity deep vein thrombosis and treated initially with enoxaparin. She was then enrolled in the trial and randomized to rivaroxaban treatment. She received treatment and repeat ultrasound suggested improvement. She completed the main treatment portion of the study and began the extension phase. In (b) (6) she was hospitalized due to worsening respiratory status, sepsis, and progressive disease. She began palliative care and subsequently died.

UNIVERSE Trial
No deaths occurred.

Study 14373, Study 14374, Study 12892, Study 17992, Study 17618
No deaths occurred in any of the other trials enrolling pediatric patients.

Adult Healthy Male Volunteer PK/PD studies – no deaths occurred in any of these studies.

Clinical Comment: In clinical trials there were 2 deaths in pediatric patients. The two described patient deaths do not appear to be related to rivaroxaban, both patients died of progressive underlying disease unrelated to rivaroxaban.

8.4.2. Serious Adverse Events

EINSTEIN Jr

In the main treatment period, the incidence of SAEs in the rivaroxaban group was 71 out of 329 (21.6%) patients compared to the comparator group in which 32 out of 162 (19.8%) patients. All treatment-emergent SAEs are shown in Table 31. The most commonly affected SOCs based on preferred term in the rivaroxaban group were 'blood and lymphatic system disorders' and 'gastrointestinal disorders' (3.0% each vs 1.9% each in the comparator group). The breakdown of SAEs based on FMQ analysis is described in Table 32Table 32. The most common SAEs occurring in over 1.5% of patients in the rivaroxaban group that are not bleeding related are pyrexia (3.3% vs 1.9% in the comparator), leukopenia (2.1% vs 1.2% in the comparator), and vomiting (1.8% vs 0% in the comparator).

In the main treatment period, 11 (3.3%) of patients in the rivaroxaban group had a serious bleeding event, compared to 2 (1.2%) of patients in the comparator group. Bleeding SAEs in the rivaroxaban group included; urinary bladder hemorrhage, retinal hemorrhage, procedural hemorrhage, gastric hemorrhage, menorrhagia, enterocolitis hemorrhagic, laryngeal hemorrhage, urethral hemorrhage, hemorrhage, and hematuria. Bleeding SAEs in the comparator group included subdural hemorrhage and traumatic hemothorax.

Table 31 Serious Adverse Events by System Organ Class and Preferred Term, Safety Population, Trial 14372

System Organ Class Preferred Term	Rivaroxaban N=329 n (%)	Comparator Group N=162 n (%)
Blood and lymphatic system disorders (SOC)	10 (3.0)	3 (1.9)
Febrile neutropenia	7 (2.1)	1 (0.6)
Thrombocytopenia	2 (0.6)	0
Bone marrow failure	1 (0.3)	0
Lymphadenopathy	1 (0.3)	0
Pancytopenia	0	1 (0.6)
Sickle cell anaemia with crisis	0	1 (0.6)

System Organ Class Preferred Term	Rivaroxaban N=329 n (%)	Comparator Group N=162 n (%)
Cardiac disorders (SOC)	4 (1.2)	1 (0.6)
Cardiac failure	1 (0.3)	0
Low cardiac output syndrome	1 (0.3)	0
Pericardial effusion	1 (0.3)	0
Postural orthostatic tachycardia syndrome	1 (0.3)	0
Atrial tachycardia	0	1 (0.6)
Congenital, familial and genetic disorders (SOC)	0	1 (0.6)
Muscular dystrophy	0	1 (0.6)
Ear and labyrinth disorders (SOC)	0	1 (0.6)
Vertigo	0	1 (0.6)
Eye disorders (SOC)	2 (0.6)	0
Papilloedema	1 (0.3)	0
Retinal haemorrhage	1 (0.3)	0
Gastrointestinal disorders (SOC)	10 (3.0)	3 (1.9)
Vomiting	6 (1.8)	0
Enterocolitis haemorrhagic	1 (0.3)	0
Faecaloma	1 (0.3)	0
Gastric haemorrhage	1 (0.3)	0
Intestinal dilatation	1 (0.3)	0
Abdominal pain	2 (0.6)	1 (0.6)
Small intestinal obstruction	1 (0.3)	1 (0.6)
Pancreatitis	0	1 (0.6)
General disorders and administration site conditions (SOC)	6 (1.8)	3 (1.9)
Peripheral swelling	1 (0.3)	0
Pyrexia	4 (1.2)	2 (1.2)
Chest pain	1 (0.3)	1 (0.6)
Hepatobiliary disorders (SOC)	1 (0.3)	0
Drug-induced liver injury	1 (0.3)	0
Immune system disorders (SOC)	1 (0.3)	0
Autoimmune disorder	1 (0.3)	0

System Organ Class Preferred Term	Rivaroxaban N=329 n (%)	Comparator Group N=162 n (%)
Infections and infestations (SOC)	16 (4.9)	10 (6.2)
Osteomyelitis	2 (0.6)	0
Bacteraemia	1 (0.3)	0
Bronchiolitis	1 (0.3)	0
Candida infection	1 (0.3)	0
Device related infection	1 (0.3)	0
Eczema herpeticum	1 (0.3)	0
Gastritis viral	1 (0.3)	0
Gastroenteritis rotavirus	1 (0.3)	0
Herpes zoster	1 (0.3)	0
Influenza	1 (0.3)	0
Meningitis bacterial	1 (0.3)	0
Parainfluenzae virus infection	1 (0.3)	0
Urinary tract infection	1 (0.3)	0
Viral infection	1 (0.3)	0
Wound infection	1 (0.3)	0
Gastroenteritis	1 (0.3)	1 (0.6)
Bacterial sepsis	0	1 (0.6)
Implant site infection	0	1 (0.6)
Infected dermal cyst	0	1 (0.6)
Meningitis	0	1 (0.6)
Nasopharyngitis	0	1 (0.6)
Peritonitis	0	1 (0.6)
Pneumonia viral	0	1 (0.6)
Tonsillitis streptococcal	0	1 (0.6)
Varicella	0	1 (0.6)
Injury, poisoning and procedural complications (SOC)	5 (1.5)	3 (1.9)
Procedural haemorrhage	2 (0.6)	0
Accidental underdose	1 (0.3)	0
Post lumbar puncture syndrome	1 (0.3)	0
Procedural pain	1 (0.3)	0
Toxicity to various agents	1 (0.3)	0
Accidental overdose	0	1 (0.6)
Subdural haemorrhage	0	1 (0.6)
Traumatic haemothorax	0	1 (0.6)
Investigations (SOC)	3 (0.9)	2 (1.2)
Alanine aminotransferase increased	2 (0.6)	0
Aspartate aminotransferase increased	1 (0.3)	0
Blood bilirubin increased	1 (0.3)	0
Gastrointestinal stoma output decreased	1 (0.3)	0
Drug clearance decreased	0	1 (0.6)
Oxygen saturation decreased	0	1 (0.6)

System Organ Class Preferred Term	Rivaroxaban N=329 n (%)	Comparator Group N=162 n (%)
Metabolism and nutrition disorders (SOC)	5 (1.5)	0
Acidosis	1 (0.3)	0
Dehydration	1 (0.3)	0
Fluid overload	1 (0.3)	0
Hyponatraemia	1 (0.3)	0
Metabolic acidosis	1 (0.3)	0
Musculoskeletal and connective tissue disorders (SOC)	6 (1.8)	0
Pain in extremity	3 (0.9)	0
Back pain	2 (0.6)	0
Joint range of motion decreased	1 (0.3)	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps) (SOC)	1 (0.3)	1 (0.6)
Myxofibrosarcoma	1 (0.3)	0
Craniopharyngioma	0	1 (0.6)
Nervous system disorders (SOC)	9 (2.7)	9 (5.6)
Dysaesthesia	1 (0.3)	0
Epilepsy	1 (0.3)	0
Hemiparaesthesia	1 (0.3)	0
Hemiparesis	1 (0.3)	0
Intracranial pressure increased	1 (0.3)	0
Neuralgia	1 (0.3)	0
Sciatic nerve neuropathy	1 (0.3)	0
Cerebral infarction	0	1 (0.6)
Encephalitis autoimmune	0	1 (0.6)
Hemianaesthesia	0	1 (0.6)
Syncope	0	1 (0.6)
Headache	3 (0.9)	3 (1.9)
Seizure	1 (0.3)	2 (1.2)
Product issues (SOC)	1 (0.3)	0
Device malfunction	1 (0.3)	0
Psychiatric disorders (SOC)	2 (0.6)	0
Confusional state	1 (0.3)	0
Drug abuse	1 (0.3)	0
Renal and urinary disorders (SOC)	8 (2.4)	1 (0.6)
Acute kidney injury	1 (0.3)	0
Haematuria	1 (0.3)	0
IgA nephropathy	1 (0.3)	0
Nephrotic syndrome	1 (0.3)	0
Renal impairment	1 (0.3)	0
Urethral haemorrhage	1 (0.3)	0
Urinary bladder haemorrhage	1 (0.3)	0
Urinary retention	1 (0.3)	0
Nephrolithiasis	1 (0.3)	1 (0.6)
Reproductive system and breast disorders (SOC)	1 (0.3)	0
Menorrhagia	1 (0.3)	0

System Organ Class Preferred Term	Rivaroxaban N=329 n (%)	Comparator Group N=162 n (%)
Respiratory, thoracic and mediastinal disorders (SOC)	3 (0.9)	2 (1.2)
Bronchopneumopathy	1 (0.3)	0
Laryngeal haemorrhage	1 (0.3)	0
Respiratory failure	1 (0.3)	0
Pleural effusion	1 (0.3)	1 (0.6)
Pneumonitis	0	1 (0.6)
Skin and subcutaneous tissue disorders (SOC)	0	1 (0.6)
Rash	0	1 (0.6)
Surgical and medical procedures (SOC)	2 (0.6)	2 (1.2)
Faecal disimpaction	1 (0.3)	0
Lumboperitoneal shunt	1 (0.3)	0
Colostomy	1 (0.3)	1 (0.6)
Sclerotherapy	0	1 (0.6)
Vascular disorders (SOC)	1 (0.3)	0
Haemorrhage	1 (0.3)	0

Source: Clinical data analyst, adae.xpt; Software: R
Treatment-emergent adverse events defined as AEs occurring between randomization and up to 2 days after the last dose. Duration is 90 days (main treatment period).
Abbreviations: CI, confidence interval; N, number of patients in treatment arm; n, number of patients with adverse event; SOC, system organ class

Table 32 Serious Adverse Events by System Organ Class and FDA Medical Query (Narrow), Safety Population, Trial 14372

System Organ Class FMQ (Narrow)	Rivaroxaban N=329 n (%)	Comparator Group N=162 n (%)
Blood and lymphatic system disorders (SOC)		
Leukopenia*	7 (2.1)	2 (1.2)
Thrombocytopenia*	2 (0.6)	1 (0.6)
Anaemia*	0	2 (1.2)
Cardiac disorders (SOC)		
Arrhythmia	0	1 (0.6)
Tachycardia	0	1 (0.6)
Ear and labyrinth disorders (SOC)		
Vertigo	0	1 (0.6)
Gastrointestinal disorders (SOC)		
Vomiting	6 (1.8)	0
Abdominal pain	2 (0.6)	1 (0.6)
Pancreatitis	0	1 (0.6)

System Organ Class FMQ (Narrow)	Rivaroxaban N=329 n (%)	Comparator Group N=162 n (%)
General disorders and administration site conditions (SOC)		
Pyrexia*	11 (3.3)	3 (1.9)
Peripheral oedema	1 (0.3)	0
Hepatobiliary disorders (SOC)		
Hepatic injury*	2 (0.6)	0
Infections and infestations (SOC)		
Nasopharyngitis	0	1 (0.6)
Pneumonia	0	1 (0.6)
Musculoskeletal and connective tissue disorders (SOC)		
Back pain	2 (0.6)	0
Nervous system disorders (SOC)		
Confusional state	1 (0.3)	0
Paraesthesia*	1 (0.3)	0
Dizziness	0	1 (0.6)
Headache*	4 (1.2)	3 (1.9)
Seizure*	2 (0.6)	2 (1.2)
Syncope	0	1 (0.6)
Renal and urinary disorders (SOC)		
Acute kidney injury	1 (0.3)	0
Urinary retention	1 (0.3)	0
Reproductive system and breast disorders (SOC)		
Excessive menstrual bleeding	1 (0.3)	0
Respiratory, thoracic and mediastinal disorders (SOC)		
Pneumonitis*	1 (0.3)	1 (0.6)
Skin and subcutaneous tissue disorders (SOC)		
Rash	0	1 (0.6)
Vascular disorders (SOC)		
Haemorrhage*	9 (2.7)	0

Source: Clinical data analyst, adae.xpt; Software: R
Treatment-emergent adverse events defined as AEs occurring between randomization and up to 2 days after the last dose.
Duration is 90 days (main treatment period).
Risk difference column shows difference (with 95% confidence interval) between total treatment and comparator.
Abbreviations: CI, confidence interval; FMQ, FDA medical query; N, number of patients in treatment arm; n, number of patients with adverse event; SOC, system organ class

The following preferred terms were combined:
Anemia: pancytopenia, sickle cell crisis with anemia
Headache: headache, post lumbar puncture syndrome
Hemorrhage: procedural hemorrhage, enterocolitis hemorrhagic, gastric hemorrhage, hematuria, hemorrhage, laryngeal hemorrhage, menorrhagia, retinal hemorrhage
Hepatic injury: Alanine aminotransferase increased, Aspartate aminotransferase increased, Drug-induced liver injury

Leukopenia: febrile neutropenia, pancytopenia
Paraesthesia: dysesthesia, hemiparaesthesia
Pneumonitis: bronchopneumopathy, pneumonitis
Pyrexia: febrile neutropenia, pyrexia
Thrombocytopenia: thrombocytopenia, pancytopenia

Reviewer's Comment: There were no major differences in AE patterns and frequency between treatment groups. As noted above in the efficacy section there were a number of patients with other concurrent illnesses (cancer undergoing chemotherapy treatment, sickle cell crises, thalassemia, etc.). For many of the AEs noted above the concurrent illness is a confounder to making a definitive attribution and in some cases is the more likely cause of the AE.

UNIVERSE

In total, the incidence of SAEs was higher in the rivaroxaban group occurring in 24 out of 76 patients (31.6%) (50% of patients in Part A and 28.1% of patients in Part B) compared aspirin in which 8 out of 34 patients (23.5%) had a treatment-emergent SAE. All treatment-emergent SAEs are shown in Table 33 and Table 34. The most common SAE was pleural effusion, occurring in 11 (14.5%) of patient in the rivaroxaban group compared to 2 (5.9%) of patients in the aspirin group.

There was one serious bleeding event that (hemorrhagic shock) which occurred in one patient in the rivaroxaban Part B group. This was the only SAE that was considered by the investigator to be study drug related.

Table 33 Serious Adverse Events by System Organ Class and Preferred Term, Safety Population, Trial CHD3001

System Organ Class Preferred Term	Rivaroxaban (Part A) N=12 n (%)	Rivaroxaban (Part B) N=64 n (%)	Total Rivaroxaban N=76 n (%)	Aspirin (Part B) N=34 n (%)
Cardiac disorders (SOC)	0	2 (3.1)	2 (2.6)	0
Cardiac failure congestive	0	1 (1.6)	1 (1.3)	0
Supraventricular tachycardia	0	1 (1.6)	1 (1.3)	0
Eye disorders (SOC)	0	1 (1.6)	1 (1.3)	0
Periorbital oedema	0	1 (1.6)	1 (1.3)	0
General disorders and administration site conditions (SOC)	1 (8.3)	0	1 (1.3)	1 (2.9)
Pyrexia	1 (8.3)	0	1 (1.3)	0
Swelling face	0	0	0	1 (2.9)

System Organ Class Preferred Term	Rivaroxaban (Part A) N=12 n (%)	Rivaroxaban (Part B) N=64 n (%)	Total Rivaroxaban N=76 n (%)	Aspirin (Part B) N=34 n (%)
Infections and infestations (SOC)	3 (25.0)	5 (7.8)	8 (10.5)	4 (11.8)
Gastroenteritis viral	0	1 (1.6)	1 (1.3)	0
Laryngitis	1 (8.3)	1 (1.6)	2 (2.6)	0
Stoma site cellulitis	0	1 (1.6)	1 (1.3)	0
Vaccination site abscess	0	1 (1.6)	1 (1.3)	0
Bronchitis	1 (8.3)	0	1 (1.3)	0
Viral infection	1 (8.3)	0	1 (1.3)	0
Pneumonia	1 (8.3)	1 (1.6)	2 (2.6)	1 (2.9)
Influenza	0	0	0	1 (2.9)
Viral upper respiratory tract infection	0	0	0	1 (2.9)
Wound abscess	0	0	0	1 (2.9)
Injury, poisoning and procedural complications (SOC)	0	1 (1.6)	1 (1.3)	0
Stoma site pain	0	1 (1.6)	1 (1.3)	0
Investigations (SOC)	0	2 (3.1)	2 (2.6)	0
Investigation	0	1 (1.6)	1 (1.3)	0
Weight decreased	0	1 (1.6)	1 (1.3)	0
Nervous system disorders (SOC)	0	2 (3.1)	2 (2.6)	2 (5.9)
Partial seizures with secondary generalisation	0	1 (1.6)	1 (1.3)	0
Seizure	0	1 (1.6)	1 (1.3)	1 (2.9)
Syncope	0	0	0	1 (2.9)
Respiratory, thoracic and mediastinal disorders (SOC)	2 (16.7)	9 (14.1)	11 (14.5)	3 (8.8)
Pleural effusion	2 (16.7)	9 (14.1)	11 (14.5)	2 (5.9)
Chylothorax	0	1 (1.6)	1 (1.3)	0
Bronchospasm	0	0	0	1 (2.9)
Vascular disorders (SOC)	0	1 (1.6)	1 (1.3)	0
Shock haemorrhagic	0	1 (1.6)	1 (1.3)	0

Source: Clinical data scientist, adae.xpt; Software: R
Treatment-emergent adverse events defined as those AEs that started on or after the first dose of study drug and up to 2 days after the last dose of study drug.
Duration is 12 months.
Abbreviations: CI, confidence interval; N, number of patients in treatment arm; n, number of patients with adverse event; SOC, system organ class

Table 34 Serious Adverse Events by System Organ Class and FDA Medical Query (Narrow), Safety Population, Trial CHD3001

System Organ Class FMQ (Narrow)	Rivaroxaban (Part A) N=12 n (%)	Rivaroxaban (Part B) N=64 n (%)	Total Rivaroxaban N=76 n (%)	Aspirin (Part B) N=34 n (%)
Cardiac disorders (SOC)				
Arrhythmia	0	1 (1.6)	1 (1.3)	0
Tachycardia	0	1 (1.6)	1 (1.3)	0
General disorders and administration site conditions (SOC)				
Pyrexia	1 (8.3)	0	1 (1.3)	0
Infections and infestations (SOC)				
Pneumonia	1 (8.3)	1 (1.6)	2 (2.6)	1 (2.9)
Nervous system disorders (SOC)				
Seizure*	0	2 (3.1)	2 (2.6)	1 (2.9)
Syncope	0	0	0	1 (2.9)
Respiratory, thoracic and mediastinal disorders (SOC)				
Bronchospasm	0	0	0	1 (2.9)
Vascular disorders (SOC)				
Haemorrhage	0	1 (1.6)	1 (1.3)	0

Source: adae.xpt; Software: R
Treatment-emergent adverse events defined as those AEs that started on or after the first dose of study drug and up to 2 days after the last dose of study drug.
Duration is 12 months.
For specific preferred terms under each FMQ, see the table "Serious Adverse Events by System Organ Class, FDA Medical Query (Narrow) and Preferred Term…"
Abbreviations: CI, confidence interval; FMQ, FDA medical query; N, number of patients in treatment arm; n, number of patients with adverse event; SOC, system organ class

*The following preferred terms were combined:
Seizure: partial seizures with secondary generalization, seizure

Reviewer's Comment: While a higher proportion of patients treated with rivaroxaban had an SAE, the majority of SAEs were likely not related to rivaroxaban. In particular, more patients treated with rivaroxaban developed a pleural effusion. The Applicant describes this finding as related to differences in the surgical procedures performed. The clinical review team agreed

with the Applicant that pleural effusion is not an adverse reaction. This is discussed further in section 8.5.3 of the safety review. There are no other major differences for SAEs between treatment groups.

8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

EINSTEIN Jr

In the main treatment period, 11 out of 329 patients (3.3%) in the rivaroxaban group and 3 out of 162 patients (1.9%) in the comparator group discontinued study drug due to an AE. A list of all the TEAEs leading to drug discontinuation is shown in
Table 35 and Table 36. The most frequent TEAEs associated with drug discontinuation were bleeding events for which, 5 patients (1.5%) discontinued due to bleeding in the rivaroxaban group vs 3 patients (1.9%) in the comparator group. The second most common TEAE leading to drug discontinuation was vomiting, with 2 (0.6%) patients discontinuing in the rivaroxaban group and none for the comparator.

Table 35. Adverse Events Leading to Discontinuation by System Organ Class and Preferred Term, Safety Population, Trial 14372

System Organ Class Preferred Term	Rivaroxaban N=329 n (%)	Comparator Group N=162 n (%)
Blood and lymphatic system disorders (SOC)	1 (0.3)	0
Thrombocytopenia	1 (0.3)	0
Cardiac disorders (SOC)	1 (0.3)	0
Low cardiac output syndrome	1 (0.3)	0
Gastrointestinal disorders (SOC)	3 (0.9)	0
Vomiting	2 (0.6)	0
Large intestinal hemorrhage	1 (0.3)	0
General disorders and administration site conditions (SOC)	0	1 (0.6)
Injection site hematoma	0	1 (0.6)
Hepatobiliary disorders (SOC)	1 (0.3)	0
Hepatic function abnormal	1 (0.3)	0
Injury, poisoning and procedural complications (SOC)	1 (0.3)	2 (1.2)
Procedural hemorrhage	1 (0.3)	0
Subcutaneous hematoma	0	1 (0.6)
Subdural hemorrhage	0	1 (0.6)

System Organ Class Preferred Term	Rivaroxaban N=329 n (%)	Comparator Group N=162 n (%)
Musculoskeletal and connective tissue disorders (SOC)	1 (0.3)	0
Pain in extremity	1 (0.3)	0
Nervous system disorders (SOC)	2 (0.6)	0
Epilepsy	1 (0.3)	0
Headache	1 (0.3)	0
Renal and urinary disorders (SOC)	3 (0.9)	0
Hematuria	1 (0.3)	0
Urinary bladder hemorrhage	1 (0.3)	0
Urinary retention	1 (0.3)	0
Reproductive system and breast disorders (SOC)	0	1 (0.6)
Menorrhagia	0	1 (0.6)
Respiratory, thoracic and mediastinal disorders (SOC)	1 (0.3)	0
Pulmonary hemorrhage	1 (0.3)	0
Vascular disorders (SOC)	1 (0.3)	0
Hemorrhage	1 (0.3)	0

Source: Clinical data scientist, adae.xpt; Software: R
Treatment-emergent adverse events defined as AEs occurring between randomization and up to 2 days after the last dose. Duration is 90 days (main treatment period).
Risk difference column shows difference (with 95% confidence interval) between total treatment and comparator.
Abbreviations: CI, confidence interval; N, number of patients in treatment arm; n, number of patients with adverse event; SOC, system organ class

Table 36 Adverse Events Leading to Discontinuation by System Organ Class and FDA Medical Query (Narrow), Safety Population, Trial 14372

System Organ Class FMQ (Narrow)	Rivaroxaban N=329 n (%)	Comparator Group N=162 n (%)
Blood and lymphatic system disorders (SOC)		
Thrombocytopenia	1 (0.3)	0
Gastrointestinal disorders (SOC)		
Vomiting	2 (0.6)	0
General disorders and administration site conditions (SOC)		
Local administration reactions	0	1 (0.6)
Hepatobiliary disorders (SOC)		
Hepatic injury	1 (0.3)	0

System Organ Class FMQ (Narrow)	Rivaroxaban N=329 n (%)	Comparator Group N=162 n (%)
Nervous system disorders (SOC)		
Headache	1 (0.3)	0
Seizure	1 (0.3)	0
Renal and urinary disorders (SOC)		
Urinary retention	1 (0.3)	0
Reproductive system and breast disorders (SOC)		
Abnormal uterine bleeding	0	1 (0.6)
Excessive menstrual bleeding	0	1 (0.6)
Vascular disorders (SOC)		
Haemorrhage*	5 (1.5)	2 (1.2)

Source: Clinical data scientist, adae.xpt; Software: R
Treatment-emergent adverse events defined as AEs occurring between randomization and up to 2 days after the last dose. Duration is 90 days (main treatment period).
For specific preferred terms under each FMQ, see the table "Adverse Events Leading to Discontinuation by System Organ Class, FDA Medical Query (Narrow) and Preferred Term…"
Abbreviations: CI, confidence interval; FMQ, FDA medical query; N, number of patients in treatment arm; n, number of patients with adverse event; SOC, system organ class

*The following preferred terms were combined:
Hemorrhage: hematuria, hemorrhage, large intestinal hemorrhage, procedural hemorrhage, pulmonary hemorrhage, injection site hemorrhage, menorrhagia, subcutaneous hematoma

Reviewer's Comment: The frequency of AEs leading to discontinuation for rivaroxaban were similar to those for the comparator group. Bleeding and vomiting were the most common TEAE that led to study drug discontinuation in the rivaroxaban group. Both bleeding and vomiting will be listed as adverse reactions in the USPI. Bleeding rates that led to drug discontinuation will be noted in the USPI. The low rates of discontinuations supports the tolerability of rivaroxaban in pediatric patients.

UNIVERSE

A total of 2 patients (3.1%) in the rivaroxaban Part B group and none in the aspirin Part B group had an AE resulting in permanent discontinuation of study drug. All TEAEs leading to drug discontinuation are listed in Table 37.

Table 37. Adverse Events Leading to Discontinuation by System Organ Class and Preferred Term, Safety Population, Trial CHD3001

System Organ Class Preferred Term	Rivaroxaban (Part A) N=12 n (%)	Rivaroxaban (Part B) N=64 n (%)	Total Rivaroxaban N=76 n (%)	Aspirin (Part B) N=34 n (%)
Psychiatric disorders (SOC)	0	1 (1.6)	1 (1.3)	0
Mood altered	0	1 (1.6)	1 (1.3)	0
Vascular disorders (SOC)	0	1 (1.6)	1 (1.3)	0
Shock hemorrhagic	0	1 (1.6)	1 (1.3)	0

Source: Clinical data scientist, adae.xpt; Software: R
Treatment-emergent adverse events defined as those AEs that started on or after the first dose of study drug and up to 2 days after the last dose of study drug.
Duration is 12 months.
Risk difference column shows difference (with 95% confidence interval) between total treatment and comparator.
Abbreviations: CI, confidence interval; N, number of patients in treatment arm; n, number of patients with adverse event; SOC, system organ class

Reviewer's Comment: The clinical team reviewed the case of the patient who developed mood alteration and it is not clear that the AE was related to study drug administration. The bleeding event leading to drug discontinuation occurred in the rivaroxaban group and will be described in the USPI. Low rates of drug discontinuation support the tolerability of rivaroxaban as thromboprophylaxis in post-Fontan pediatric patients.

8.4.4. Significant Adverse Events

Adverse Events Leading to Dose Modification
EINSTEIN Jr

In the tables below, the frequency and type of adverse events are described leading to dose interruption. A higher proportion of patients in the rivaroxaban group compared to the comparator group had a drug interruption due to an adverse event (14.9% vs 8.6%, respectively). The most common reasons for drug interruption in the rivaroxaban group were vomiting (1.8%) and thrombocytopenia (1.2%) (Table 38).

Table 38. Adverse Event Frequency Leading to Dose Modification, Safety Population, Trial 14372

Event Category	Rivaroxaban N=329 n (%)	Comparator Group N=162 n (%)
AE leading to dose modification of study drug	52 (15.8)	18 (11.1)
AE leading to interruption of study drug	49 (14.9)	14 (8.6)
AE leading to reduction of study drug	4 (1.2)	5 (3.1)
AE leading to dose delay of study drug	0	0
Other	0	0

Source: Clinical data analyst, adae.xpt; Software: R
Treatment-emergent adverse events defined as AEs occurring between randomization and up to 2 days after the last dose. Duration is 90 days (main treatment period).
Risk difference column shows difference (with 95% confidence interval) between total treatment and comparator.
Abbreviations: AE, adverse event; N, number of patients in treatment arm; n, number of patients with at least one event

Table 39. Adverse Events Leading to Dose Interruption, Safety Population, Trial 14372

Adverse Event	Rivaroxaban N=329 n (%)	Comparator Group N=162 n (%)
Vomiting	6 (1.8)	0
Thrombocytopenia	5 (1.5)	2 (1.2)
Accidental overdose	3 (0.9)	1 (0.6)
Accidental underdose	3 (0.9)	0
Central venous catheterization	3 (0.9)	0
Haematuria	3 (0.9)	0
Gastric haemorrhage	2 (0.6)	0
Menorrhagia	2 (0.6)	0
Tooth extraction	2 (0.6)	0
Urinary bladder haemorrhage	2 (0.6)	0

Source: Clinical reviewer

Clinical reviewer comment: A higher proportion of patients in the rivaroxaban group had a TEAE leading to drug interruption. The most common reason for drug interruption was vomiting and thrombocytopenia.

UNIVERSE
In the table below, the frequency of adverse events leading to dose interruption or reduction are described.

Table 40. Adverse Events Frequency Leading to Dose Modification**, Safety Population, Trial CHD3001**

Event Category	Rivaroxaban (Part A) N=12 n (%)	Rivaroxaban (Part B) N=64 n (%)	Total Rivaroxaban N=76 n (%)	Aspirin (Part B) N=34 n (%)
AE leading to dose modification of study drug	2 (16.7)	8 (12.5)	10 (13.2)	3 (8.8)
AE leading to interruption of study drug	2 (16.7)	8 (12.5)	10 (13.2)	3 (8.8)
AE leading to reduction of study drug	0	0	0	0
AE leading to dose delay of study drug	0	0	0	0
Other	0	0	0	0

Source: adae.xpt; Software: R
Treatment-emergent adverse events defined as those AEs that started on or after the first dose of study drug and up to 2 days after the last dose of study drug.
Duration is 12 months.
Risk difference column shows difference (with 95% confidence interval) between total treatment and comparator.
Abbreviations: AE, adverse event; N, number of patients in treatment arm; n, number of patients with at least one event;

Table 41. Adverse Events Leading to Dose Interruption, **Safety Population, Trial CHD3001**

Adverse Event	Rivaroxaban (Part A) N=12 n (%)	Rivaroxaban (Part B) N=64 n (%)	Total Rivaroxaban N=76 n (%)	Aspirin (Part B) N=34 n (%)
Product dispensing error	0	2 (3.1%)	2 (2.6%)	0
Epistaxis	0	1 (1.6%)	1 (1.3%)	0
Gastroenteritis	0	1 (1.6%)	1 (1.3%)	0
Pleural effusion	0	1 (1.6%)	1 (1.3%)	0
Procedural hemorrhage	0	1 (1.6%)	1 (1.3%)	0
Prothrombin time prolonged	0	1 (1.6%)	1 (1.3%)	0
Seizure	0	1 (1.6%)	1 (1.3%)	0
Stoma site cellulitis	0	1 (1.6%)	1 (1.3%)	0
Stoma site pain	0	1 (1.6%)	1 (1.3%)	0
Tooth injury	0	1 (1.6%)	1 (1.3%)	0
Hematoma	1 (8.3%)	0	1 (1.3%)	1 (2.9%)
Skin laceration	1 (8.3%)	0	1 (1.3%)	0
Wound hemorrhage	1 (8.3%)	0	1 (1.3%)	0
Constipation	0	0	0	1 (2.9%0
Tooth development disorder	0	0	-	1 (2.9%)

Source: Clinical reviewer

Clinical reviewer comment: Slightly more patients in the rivaroxaban group had a TEAE leading to drug interruption. Reasons for drug interruption were variable, product dispensing error was the only TEAE that occurred more than once in the UNIVERSE study.

Severity of Adverse Events
EINSTEIN Jr

In the main treatment period, a higher proportion of patients in the rivaroxaban group had a TEAE. In total, 83% of patients in the rivaroxaban group had a TEAE compared to 75% of patients in the comparator group. Most TEAEs were mild to moderate in severity in both treatment groups. The severity of TEAEs are described in Table 42.

Table 42. **Severity of Adverse Events, Safety Population, Trial 14372**

Event Category	Rivaroxaban N=329 n (%)	Comparator Group N=162 n (%)
TEAE	274 (83.3)	122 (75.3)
Death	1 (0.3)	0
Life-threatening	0	0
Severe	41 (12.5)	23 (14.2)
Moderate	102 (31.0)	44 (27.2)
Mild	130 (39.5)	55 (34.0)

Source: adae.xpt; Software: R
Treatment-emergent adverse events defined as AEs occurring between randomization and up to 2 days after the last dose. Duration is 90 days (main treatment period).
Risk difference column shows difference (with 95% confidence interval) between total treatment and comparator.
Abbreviations: AE, adverse event;; N, number of patients in treatment arm; n, number of patients with at least one event;

Clinical reviewer comment: More patients in the rivaroxaban group experienced TEAEs, most of these events were mild to moderate in intensity. Severity of TEAEs were similar between rivaroxaban and the comparator group.

UNIVERSE

TEAEs occurred in most patients in both treatment groups (87% of patients in rivaroxaban group and 85% in aspirin group). In both treatment groups, the most common TEAE was mild in severity. The severity of TEAEs are described in Table 43.

Table 43. Severity of Adverse Events, Safety Population, Trial CHD3001

Event Category	Rivaroxaban (Part A) N=12 n (%)	Rivaroxaban (Part B) N=64 n (%)	Total Rivaroxaban N=76 n (%)	Aspirin (Part B) N=34 n (%)
AE	11 (91.7)	55 (85.9)	66 (86.8)	29 (85.3)
Death	0	0	0	0
Life-threatening	0	0	0	0
Severe	0	8 (12.5)	8 (10.5)	3 (8.8)
Moderate	5 (41.7)	10 (15.6)	15 (19.7)	6 (17.6)
Mild	6 (50.0)	37 (57.8)	43 (56.6)	20 (58.8)

Source: adae.xpt; Software: R
Treatment-emergent adverse events defined as those AEs that started on or after the first dose of study drug and up to 2 days after the last dose of study drug.
Duration is 12 months.
Risk difference column shows difference (with 95% confidence interval) between total treatment and comparator.
Abbreviations: AE, adverse event; N, number of patients in treatment arm; n, number of patients with at least one event;

Clinical reviewer comment: The frequency and severity of TEAEs were balanced between treatment groups. Most TEAEs were mild to moderate in intensity.

8.4.5. Treatment Emergent Adverse Events and Adverse Reactions

EINSTEIN Jr

The tables below describe the most common TEAEs in the safety population during the main treatment period. The most common TEAE (occurring in >10% of patients in the rivaroxaban group) were headache, nasopharyngitis, pyrexia and vomiting.

Table 44 Adverse Events by System Organ Class, Safety Population, Trial 14372

	Rivaroxaban N=329 n (%)	Comparator Group N=162 n (%)
Musculoskeletal and connective tissue disorders	55 (16.7)	17 (10.5)
Gastrointestinal disorders	106 (32.2)	43 (26.5)
Infections and infestations	114 (34.7)	47 (29.0)
Injury, poisoning and procedural complications	77 (23.4)	30 (18.5)
Metabolism and nutrition disorders	25 (7.6)	7 (4.3)
Respiratory, thoracic and mediastinal disorders	79 (24.0)	34 (21.0)
Nervous system disorders	82 (24.9)	36 (22.2)
Renal and urinary disorders	17 (5.2)	4 (2.5)
Skin and subcutaneous tissue disorders	60 (18.2)	26 (16.0)
Immune system disorders	8 (2.4)	1 (0.6)
Eye disorders	17 (5.2)	6 (3.7)
Vascular disorders	13 (4.0)	4 (2.5)
Ear and labyrinth disorders	9 (2.7)	3 (1.9)
Blood and lymphatic system disorders	35 (10.6)	16 (9.9)
Reproductive system and breast disorders	29 (8.8)	13 (8.0)
Cardiac disorders	10 (3.0)	4 (2.5)
Surgical and medical procedures	11 (3.3)	5 (3.1)
Congenital, familial and genetic disorders	2 (0.6)	1 (0.6)
Hepatobiliary disorders	6 (1.8)	3 (1.9)
Product issues	3 (0.9)	2 (1.2)
Psychiatric disorders	9 (2.7)	5 (3.1)
Endocrine disorders	0	1 (0.6)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2 (0.6)	3 (1.9)
Investigations	34 (10.3)	22 (13.6)
General disorders and administration site conditions	79 (24.0)	51 (31.5)

Reviewer's Comment: Musculoskeletal and Connective Tissue Disorders, Gastrointestinal disorders are more frequently reported and at greater than 5% for the rivaroxaban treatment group.

Table 45 Common Adverse Events, Safety Population in >1% of Rivaroxaban Treatment Group, Trial 14372

Preferred Term	Rivaroxaban N=329 n (%)	Comparator Group N=162 n (%)
Any AE	274 (83.3)	122 (75.3)

Preferred Term	Rivaroxaban N=329 n (%)	Comparator Group N=162 n (%)
Menorrhagia	23 (7.0)	5 (3.1)
Gingival bleeding	12 (3.6)	1 (0.6)
Nasopharyngitis	25 (7.6)	8 (4.9)
Pain in extremity	23 (7.0)	7 (4.3)
Rhinorrhoea	11 (3.3)	1 (0.6)
Vomiting	35 (10.6)	13 (8.0)
Accidental underdose	8 (2.4)	0
Back pain	12 (3.6)	2 (1.2)
Fatigue	20 (6.1)	6 (3.7)
Hypokalaemia	8 (2.4)	0
Pyrexia	34 (10.3)	13 (8.0)
Headache	56 (17.0)	24 (14.8)
Nausea	21 (6.4)	7 (4.3)
Thrombocytopenia	11 (3.3)	2 (1.2)
Wound haemorrhage	11 (3.3)	2 (1.2)
Febrile neutropenia	8 (2.4)	1 (0.6)
Gastroenteritis	8 (2.4)	1 (0.6)
Rash	14 (4.3)	4 (2.5)
Accidental overdose	7 (2.1)	1 (0.6)
Groin pain	5 (1.5)	0
Mouth haemorrhage	5 (1.5)	0
Platelet count decreased	9 (2.7)	2 (1.2)
Pruritus	7 (2.1)	1 (0.6)
Rectal haemorrhage	7 (2.1)	1 (0.6)
Rhinitis	11 (3.3)	3 (1.9)
Tachycardia	5 (1.5)	0
Diarrhoea	23 (7.0)	9 (5.6)
Abdominal pain upper	10 (3.0)	3 (1.9)
Arthralgia	10 (3.0)	3 (1.9)
Dyspnoea	6 (1.8)	1 (0.6)
Ear pain	4 (1.2)	0
Erythema	6 (1.8)	1 (0.6)
Mucosal inflammation	4 (1.2)	0
Neck pain	6 (1.8)	1 (0.6)
Oral candidiasis	6 (1.8)	1 (0.6)
Oral herpes	4 (1.2)	0
Pain	4 (1.2)	0
Skin haemorrhage	4 (1.2)	0
Stomatitis	4 (1.2)	0
Subcutaneous haematoma	12 (3.6)	4 (2.5)
Blood bilirubin increased	5 (1.5)	1 (0.6)
Chest pain	15 (4.6)	6 (3.7)
Dizziness	9 (2.7)	3 (1.9)
Haematuria	5 (1.5)	1 (0.6)
Leukopenia	5 (1.5)	1 (0.6)
Nasal congestion	7 (2.1)	2 (1.2)
Anaemia	10 (3.0)	4 (2.5)
Aspartate aminotransferase increased	6 (1.8)	2 (1.2)

Preferred Term	Rivaroxaban N=329 n (%)	Comparator Group N=162 n (%)
Decreased appetite	4 (1.2)	1 (0.6)
Myalgia	4 (1.2)	1 (0.6)
Nephrolithiasis	4 (1.2)	1 (0.6)
Oedema peripheral	4 (1.2)	1 (0.6)
Paraesthesia	6 (1.8)	2 (1.2)
Procedural pain	6 (1.8)	2 (1.2)
Skin abrasion	4 (1.2)	1 (0.6)
Vaginal haemorrhage	4 (1.2)	1 (0.6)
Fall	5 (1.5)	2 (1.2)
Oropharyngeal pain	7 (2.1)	3 (1.9)
Peripheral swelling	5 (1.5)	2 (1.2)
Epistaxis	37 (11.2)	18 (11.1)
Upper respiratory tract infection	8 (2.4)	4 (2.5)
Urinary tract infection	4 (1.2)	2 (1.2)
Abdominal pain	18 (5.5)	9 (5.6)
Influenza	5 (1.5)	3 (1.9)
Neutropenia	6 (1.8)	4 (2.5)
Papilloedema	4 (1.2)	3 (1.9)
Tonsillitis	5 (1.5)	4 (2.5)
Alopecia	7 (2.1)	5 (3.1)
Contusion	14 (4.3)	9 (5.6)
Cough	16 (4.9)	10 (6.2)
Alanine aminotransferase increased	7 (2.1)	7 (4.3)
Constipation	8 (2.4)	11 (6.8)

Table 46. Adverse Events by System Organ Class and FDA Medical Query (Narrow), Safety Population, Trial 14372

System Organ Class FMQ (Narrow)	Rivaroxaban N=329 n (%)	Comparator Group N=162 n (%)
Blood and lymphatic system disorders (SOC)		
Thrombocytopenia	17 (5.2)	6 (3.7)
Anemia	14 (4.3)	7 (4.3)
Leukopenia	15 (4.6)	8 (4.9)
Cardiac disorders (SOC)		
Palpitations	1 (0.3)	0
Systemic hypertension	2 (0.6)	1 (0.6)
Tachycardia	6 (1.8)	3 (1.9)
Arrhythmia	6 (1.8)	4 (2.5)
Ear and labyrinth disorders (SOC)		
Vertigo	0	1 (0.6)
Endocrine disorders (SOC)		
Hypoglycemia	0	1 (0.6)

System Organ Class FMQ (Narrow)	Rivaroxaban N=329 n (%)	Comparator Group N=162 n (%)
Gastrointestinal disorders (SOC)		
Vomiting	35 (10.6)	13 (8.0)
Nausea	21 (6.4)	7 (4.3)
Diarrhoea	24 (7.3)	9 (5.6)
Dyspepsia	11 (3.3)	3 (1.9)
Dry mouth	1 (0.3)	0
Abdominal pain	26 (7.9)	13 (8.0)
Pancreatitis	0	1 (0.6)
Constipation	8 (2.4)	11 (6.8)
General disorders and administration site conditions (SOC)		
Pyrexia	40 (12.2)	13 (8.0)
Fatigue	24 (7.3)	9 (5.6)
Peripheral oedema	9 (2.7)	3 (1.9)
Decreased appetite	4 (1.2)	1 (0.6)
Local administration reactions	3 (0.9)	16 (9.9)
Hepatobiliary disorders (SOC)		
Hepatic injury	12 (3.6)	7 (4.3)
Immune system disorders (SOC)		
Anaphylactic reaction	0	2 (1.2)
Infections and infestations (SOC)		
Nasopharyngitis	38 (11.6)	14 (8.6)
Pneumonia	1 (0.3)	3 (1.9)
Musculoskeletal and connective tissue disorders (SOC)		
Back pain	12 (3.6)	3 (1.9)
Arthralgia	10 (3.0)	3 (1.9)
Myalgia	5 (1.5)	1 (0.6)
Nervous system disorders (SOC)		
Headache	58 (17.6)	25 (15.4)
Dizziness	13 (4.0)	4 (2.5)
Paraesthesia	8 (2.4)	3 (1.9)
Somnolence	1 (0.3)	0
Confusional state	1 (0.3)	1 (0.6)
Syncope	2 (0.6)	2 (1.2)
Seizure	4 (1.2)	4 (2.5)
Psychiatric disorders (SOC)		
Depression	4 (1.2)	1 (0.6)
Insomnia	1 (0.3)	0
Irritability	1 (0.3)	0
Parasomnia	1 (0.3)	0
Anxiety	4 (1.2)	2 (1.2)

System Organ Class FMQ (Narrow)	Rivaroxaban N=329 n (%)	Comparator Group N=162 n (%)
Renal and urinary disorders (SOC)		
Urinary retention	1 (0.3)	0
Acute kidney injury	2 (0.6)	1 (0.6)
Reproductive system and breast disorders (SOC)		
Excessive menstrual bleeding	23 (7.0)	5 (3.1)
Abnormal uterine bleeding	25 (7.6)	8 (4.9)
Respiratory, thoracic and mediastinal disorders (SOC)		
Dyspnoea	8 (2.4)	2 (1.2)
Bronchospasm	1 (0.3)	0
Pneumonitis	1 (0.3)	1 (0.6)
Cough	17 (5.2)	10 (6.2)
Skin and subcutaneous tissue disorders (SOC)		
Erythema	11 (3.3)	2 (1.2)
Pruritus	8 (2.4)	3 (1.9)
Urticaria	2 (0.6)	1 (0.6)
Alopecia	8 (2.4)	5 (3.1)
Rash	24 (7.3)	13 (8.0)
Vascular disorders (SOC)		
Haemorrhage	119 (36.2)	51 (31.5)
Hypotension	2 (0.6)	0

Source: adae.xpt; Software: R
Treatment-emergent adverse events defined as AEs occurring between randomization and up to 2 days after the last dose. Duration is 90 days (main treatment period).
Risk difference column shows difference (with 95% confidence interval) between total treatment and comparator.
For specific preferred terms under each FMQ, see the table "Adverse Events by System Organ Class, FDA Medical Query (Narrow) and Preferred Term…"
Abbreviations: CI, confidence interval; FMQ, FDA medical query; N, number of patients in treatment arm; n, number of patients with adverse event; SOC, system organ class

Clinical reviewer comment: The clinical review team carefully analyzed TEAEs. Causality of the majority of TEAEs were difficult to determine given the complexity of patient population. The Applicant proposed to include ARs in the USPI that occurred in >5% of patients and had a relative risk of >1.5, this strategy had been used previously in the XARELTO USPI. This included the ARs pain in extremity and fatigue. The clinical review team agreed with this approach considering the small patient numbers. The clinical review team also noted vomiting as a common AR, although not meeting the threshold of relative risk >1.5, and recommended including in the USPI. This is discussed further in section 8.5.5.

UNIVERSE

The tables below describe the most common TEAEs in the safety population in UNIVERSE. The most common TEAE (occurring in >10% of patients in the rivaroxaban group) were nasopharyngitis, pyrexia, cough, upper respiratory tract infection, and vomiting.

Table 47 Common Adverse Events Occurring in >2% of Patients in the Rivaroxaban Group, Safety Population, Trial CHD3001

Preferred Term	Rivaroxaban (Part A) N=12 n (%)	Rivaroxaban (Part B) N=64 n (%)	Total Rivaroxaban N=76 n (%)	Aspirin (Part B) N=34 n (%)
Any AE	11 (91.7)	55 (85.9)	66 (86.8)	29 (85.3)
Pleural effusion	3 (25.0)	12 (18.8)	15 (19.7)	2 (5.9)
Gastroenteritis	0	5 (7.8)	5 (6.6)	0
Cough	0	10 (15.6)	10 (13.2)	3 (8.8)
Vomiting	3 (25.0)	9 (14.1)	12 (15.8)	3 (8.8)
Pharyngitis	0	5 (7.8)	5 (6.6)	1 (2.9)
Bronchitis	2 (16.7)	3 (4.7)	5 (6.6)	0
Eczema	0	3 (4.7)	3 (3.9)	0
Nasal congestion	0	3 (4.7)	3 (3.9)	0
Pain in extremity	0	3 (4.7)	3 (3.9)	0
Nasopharyngitis	1 (8.3)	14 (21.9)	15 (19.7)	6 (17.6)
Skin abrasion	0	4 (6.2)	4 (5.3)	1 (2.9)
Chylothorax	1 (8.3)	2 (3.1)	3 (3.9)	0
Gingival bleeding	1 (8.3)	2 (3.1)	3 (3.9)	0
Impetigo	0	2 (3.1)	2 (2.6)	0
Laryngitis	1 (8.3)	2 (3.1)	3 (3.9)	0
Otitis media acute	0	2 (3.1)	2 (2.6)	0
Periorbital haemorrhage	0	2 (3.1)	2 (2.6)	0
Petechiae	0	2 (3.1)	2 (2.6)	0
Product dispensing error	0	2 (3.1)	2 (2.6)	0
Purpura	0	2 (3.1)	2 (2.6)	0
Rash maculo-papular	0	2 (3.1)	2 (2.6)	0
Thermal burn	0	2 (3.1)	2 (2.6)	0
Pyrexia	1 (8.3)	15 (23.4)	16 (21.1)	7 (20.6)
Sinusitis	0	5 (7.8)	5 (6.6)	2 (5.9)
Contusion	0	3 (4.7)	3 (3.9)	1 (2.9)
Gastroenteritis viral	1 (8.3)	3 (4.7)	4 (5.3)	1 (2.9)
Subcutaneous haematoma	0	3 (4.7)	3 (3.9)	1 (2.9)
Varicella	0	3 (4.7)	3 (3.9)	1 (2.9)
Catarrh	1 (8.3)	1 (1.6)	2 (2.6)	0
Urinary tract infection	1 (8.3)	1 (1.6)	2 (2.6)	0
Wound haemorrhage	1 (8.3)	1 (1.6)	2 (2.6)	0
Epistaxis	0	6 (9.4)	6 (7.9)	3 (8.8)
Influenza	0	4 (6.2)	4 (5.3)	2 (5.9)
Rash	2 (16.7)	4 (6.2)	6 (7.9)	2 (5.9)
Abdominal pain	0	2 (3.1)	2 (2.6)	1 (2.9)
Arthropod bite	1 (8.3)	2 (3.1)	3 (3.9)	1 (2.9)
Haematoma	2 (16.7)	2 (3.1)	4 (5.3)	1 (2.9)

Preferred Term	Rivaroxaban (Part A) N=12 n (%)	Rivaroxaban (Part B) N=64 n (%)	Total Rivaroxaban N=76 n (%)	Aspirin (Part B) N=34 n (%)
Lip injury	0	2 (3.1)	2 (2.6)	1 (2.9)
Viral infection	2 (16.7)	2 (3.1)	4 (5.3)	1 (2.9)
Dermatitis diaper	2 (16.7)	0	2 (2.6)	0
Upper respiratory tract infection	2 (16.7)	9 (14.1)	11 (14.5)	5 (14.7)
Diarrhoea	2 (16.7)	3 (4.7)	5 (6.6)	2 (5.9)
Ear infection	0	3 (4.7)	3 (3.9)	2 (5.9)
Rhinorrhoea	0	3 (4.7)	3 (3.9)	2 (5.9)
Respiratory tract infection	1 (8.3)	2 (3.1)	3 (3.9)	2 (5.9)
Otitis media	0	3 (4.7)	3 (3.9)	3 (8.8)
Pneumonia	1 (8.3)	3 (4.7)	4 (5.3)	3 (8.8)
Ecchymosis	0	6 (9.4)	6 (7.9)	5 (14.7)
Viral upper respiratory tract infection	3 (25.0)	0	3 (3.9)	2 (5.9)
Fall	0	2 (3.1)	2 (2.6)	5 (14.7)

Source: adae.xpt; Software: R
Duration is 12 months.
Treatment-emergent adverse events defined as those AEs that started on or after the first dose of study drug and up to 2 days after the last dose of study drug.
Coded as MedDRA preferred terms.
Abbreviations: CI, confidence interval; N, number of patients in treatment arm; n, number of patients with adverse event.

Reviewer's Comment: Pleural Effusion and Vomiting are reported with greater frequency by at least 5% in the rivaroxaban treatment group.

Table 48 Adverse Events by System Organ Class and FDA Medical Query (Narrow), Safety Population, Trial CHD3001

System Organ Class FMQ (Narrow)	Rivaroxaban (Part A) N=12 n (%)	Rivaroxaban (Part B) N=64 n (%)	Total Rivaroxaban N=76 n (%)	Aspirin (Part B) N=34 n (%)
Blood and lymphatic system disorders (SOC)				
Leukopenia	1 (8.3)	0	1 (1.3)	0
Cardiac disorders (SOC)				
Arrhythmia	0	3 (4.7)	3 (3.9)	0
Tachycardia	0	2 (3.1)	2 (2.6)	0
Palpitations	0	1 (1.6)	1 (1.3)	0

System Organ Class FMQ (Narrow)	Rivaroxaban (Part A) N=12 n (%)	Rivaroxaban (Part B) N=64 n (%)	Total Rivaroxaban N=76 n (%)	Aspirin (Part B) N=34 n (%)
Gastrointestinal disorders (SOC)				
Vomiting	3 (25.0)	10 (15.6)	13 (17.1)	3 (8.8)
Dyspepsia	0	2 (3.1)	2 (2.6)	0
Abdominal pain	0	3 (4.7)	3 (3.9)	1 (2.9)
Diarrhoea	2 (16.7)	3 (4.7)	5 (6.6)	2 (5.9)
Nausea	0	0	0	1 (2.9)
Constipation	0	0	0	2 (5.9)
General disorders and administration site conditions (SOC)				
Pyrexia	1 (8.3)	15 (23.4)	16 (21.1)	7 (20.6)
Decreased appetite	0	1 (1.6)	1 (1.3)	0
Local administration reactions	0	1 (1.6)	1 (1.3)	0
Hepatobiliary disorders (SOC)				
Hepatic injury	0	0	0	1 (2.9)
Infections and infestations (SOC)				
Nasopharyngitis	2 (16.7)	19 (29.7)	21 (27.6)	10 (29.4)
Pneumonia	1 (8.3)	3 (4.7)	4 (5.3)	3 (8.8)
Musculoskeletal and connective tissue disorders (SOC)				
Arthralgia	0	1 (1.6)	1 (1.3)	0
Nervous system disorders (SOC)				
Headache	0	1 (1.6)	1 (1.3)	0
Seizure	0	2 (3.1)	2 (2.6)	1 (2.9)
Syncope	0	0	0	1 (2.9)
Renal and urinary disorders (SOC)				
Acute kidney injury	1 (8.3)	0	1 (1.3)	0
Respiratory, thoracic and mediastinal disorders (SOC)				
Cough	0	10 (15.6)	10 (13.2)	3 (8.8)
Bronchospasm	0	1 (1.6)	1 (1.3)	1 (2.9)
Skin and subcutaneous tissue disorders (SOC)				
Pruritus	0	1 (1.6)	1 (1.3)	0
Rash	2 (16.7)	6 (9.4)	8 (10.5)	4 (11.8)
Urticaria	0	1 (1.6)	1 (1.3)	2 (5.9)

System Organ Class FMQ (Narrow)	Rivaroxaban (Part A) N=12 n (%)	Rivaroxaban (Part B) N=64 n (%)	Total Rivaroxaban N=76 n (%)	Aspirin (Part B) N=34 n (%)
Vascular disorders (SOC)				
Haemorrhage	3 (25.0)	21 (32.8)	24 (31.6)	11 (32.4)

Source: adae.xpt; Software: R
Treatment-emergent adverse events defined as those AEs that started on or after the first dose of study drug and up to 2 days after the last dose of study drug.
Duration is 12 months.
For specific preferred terms under each FMQ, see the table "Adverse Events by System Organ Class, FDA Medical Query (Narrow) and Preferred Term…"
Abbreviations: CI, confidence interval; FMQ, FDA medical query; N, number of patients in treatment arm; n, number of patients with adverse event; SOC, system organ class

Reviewer's Comment: The clinical review team carefully analyzed TEAEs. The Applicant proposed including ARs in the USPI which occurred in >5% of the Part B population and a relative risk of >1.5, the clinical review team agreed with this approach. ARs to be included in the USPI were vomiting, cough, rash, and gastroenteritis. Pleural effusions were not included as this was likely secondary to the procedure performed and unrelated to rivaroxaban, this is discussed further in section 8.5.3. Skin abrasions was also not included as this was not considered an AR as this is a common event in pediatric patients that is not related to rivaroxaban.

8.4.6. Laboratory Findings

EINSTEIN Jr
Hematology
Cytopenias occurred but were mostly attributed to receiving immunosuppressive therapies. Thrombocytopenia was further analyzed in section 8.5.4. PT and PTT – see Clinical Pharmacology review as this is PD marker.

Chemistry and lipids laboratory data were not collected in Trial 143472.

Patients on 143472 had serum creatinine laboratory data. Eleven patients who received rivaroxaban and five patients who received the comparator had creatinine elevations flagged as abnormal but less than 1.5 times upper limit of normal (ULN). Two patients who received rivaroxaban had creatinine elevations above 1.5 times ULN but less than 2 times ULN. One patient who received the comparator had creatinine elevation above 2 times ULN but less than 3 times ULN. Analyses of mean change from baseline for serum creatinine and glomerular filtration rate were performed and the changes were minimal. One patient in the rivaroxaban group had and a serious TEAE of acute kidney injury. The event acute kidney injury occurred 11 days after starting rivaroxaban (blood creatinine was 3.23mg/dL and 2.93 mg/dL, reference

range: 0.4-1.4). Blood creatinine improved (1.18mg/mL) with intravenous hydration and furosemide. The TEAE was likely related to dehydration, acute lymphoblastic leukemia, and chemotherapy.

Some liver laboratory were collected and no adverse events occurred resulting in study discontinuation, liver failure, or death. However, without complete testing including alkaline phosphatase no drug-induced liver injury screening, cholestatic injury or potential DILI screening could not be plotted.

The next tables show the distribution of liver biochemistry severity.

Table 49 Patients with One or More Liver Biochemistry Analyte Values Outside Specified Levels, Safety Population, Trial 14372

Laboratory Parameter	Rivaroxaban N=329	Comparator Group N=162
Alkaline phosphatase, high (U/L)		
Missing	NA	NA
Alanine aminotransferase, high (U/L)		
Level 1 (>3X ULN)	7/306 (2.3)	5/143 (3.5)
Level 2 (>5X ULN)	1/306 (0.3)	2/143 (1.4)
Level 3 (>10X ULN)	0/306 (0)	0/143 (0)
Aspartate aminotransferase, high (U/L)		
Level 1 (>3X ULN)	0/0 (NA)	0/0 (NA)
Level 2 (>5X ULN)	0/0 (NA)	0/0 (NA)
Level 3 (>10X ULN)	0/0 (NA)	0/0 (NA)
Bilirubin, total, high (mg/dL)		
Level 1 (>1.5X ULN)	4/304 (1.3)	7/142 (4.9)
Level 2 (>2X ULN)	2/304 (0.7)	4/142 (2.8)
Level 3 (>3X ULN)	2/304 (0.7)	3/142 (2.1)

Source: ad b.xpt; Software: R
Threshold levels 1, 2, and 3 as defined by the Standard Safety Tables & Figures Integrated Guide.
Duration is 90 days (main treatment period).
For specific evaluation of drug-induced liver injury (DILI), see the figures "DILI Case Screening Plot...," "Cholestatic Liver Injury Screening Plot...," and the table "Potential DILI..."
Abbreviations: DILI, drug-induced liver injury; ULN, upper limit of normal; N, number of patients in treatment arm; n, number of patients meeting criteria

UNIVERSE
Chemistry and lipids laboratory data were not collected in Trial 3001.

Hematology laboratory data were collected at specified times but occasionally checked in between protocol specified collection. Few patients experienced significant changes in their hematology labs. Analysis demonstrated no patients receiving rivaroxaban had neutrophil

decreases to less than 1000 cells/microliter and no patients receiving rivaroxaban had platelet counts decreased below 125K/microliter. Only one patient had a neutrophil increase to more than 15000/microliter. Only one patient receiving rivaroxaban reportedly had a hemoglobin value that was 2 gm/dl less than their baseline.

PT and PTT – see Clin Pharmacology review as this is PD marker.

In Trial 3001 patients had serum creatinine laboratory data. Eleven patients who received rivaroxaban and one patient who received ASA had creatinine elevations greater than 1.5 times baseline. Only one patient who received rivaroxaban had creatinine elevations greater than 2 times less than 3 times baseline. Analyses of mean change from baseline for serum creatinine and glomerular filtration rate were performed and the changes were minimal. No cases of acute kidney injury occurred during the trial.

Liver laboratory data were collected. No adverse events occurred resulting in study discontinuation, liver failure, or death.

The next tables show the distribution of liver biochemistry severity.

Table 50 Patients with One or More Liver Biochemistry Analyte Values Outside Specified Levels, Safety Population, Trial CHD3001

Laboratory Parameter	Rivaroxaban (Part A) N=12	Rivaroxaban (Part B) N=64	Total Rivaroxaban N=76	Aspirin (Part B) N=34
Alkaline phosphatase, high (U/L)				
Level 1 (>1.5X ULN)	0/12 (0)	2/60 (3.3)	2/72 (2.8)	0/32 (0)
Level 2 (>2X ULN)	0/12 (0)	1/60 (1.7)	1/72 (1.4)	0/32 (0)
Level 3 (>3X ULN)	0/12 (0)	0/60 (0)	0/72 (0)	0/32 (0)
Alanine aminotransferase, high (U/L)				
Level 1 (>3X ULN)	0/12 (0)	0/59 (0)	0/71 (0)	0/29 (0)
Level 2 (>5X ULN)	0/12 (0)	0/59 (0)	0/71 (0)	0/29 (0)
Level 3 (>10X ULN)	0/12 (0)	0/59 (0)	0/71 (0)	0/29 (0)
Aspartate aminotransferase, high (U/L)				
Level 1 (>3X ULN)	0/11 (0)	0/57 (0)	0/68 (0)	0/29 (0)
Level 2 (>5X ULN)	0/11 (0)	0/57 (0)	0/68 (0)	0/29 (0)
Level 3 (>10X ULN)	0/11 (0)	0/57 (0)	0/68 (0)	0/29 (0)

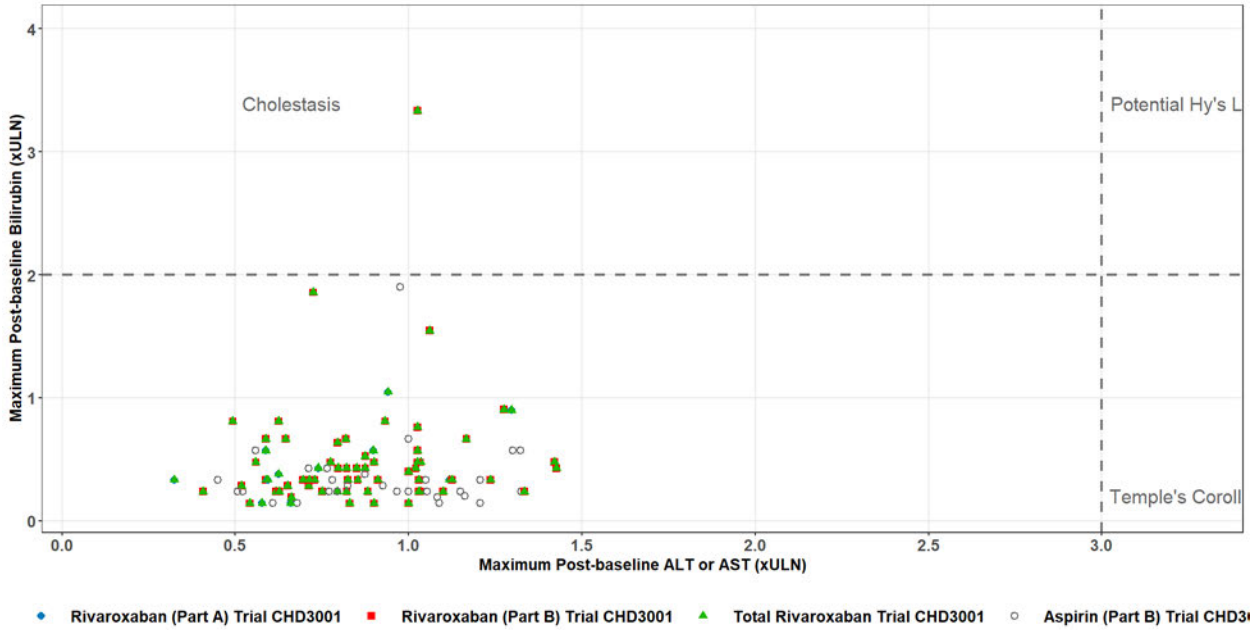
Laboratory Parameter	Rivaroxaban (Part A) N=12	Rivaroxaban (Part B) N=64	Total Rivaroxaban N=76	Aspirin (Part B) N=34
Bilirubin, total, high (mg/dL)				
Level 1 (>1.5X ULN)	0/12 (0)	3/59 (5.1)	3/71 (4.2)	1/30 (3.3)
Level 2 (>2X ULN)	0/12 (0)	1/59 (1.7)	1/71 (1.4)	0/30 (0)
Level 3 (>3X ULN)	0/12 (0)	1/59 (1.7)	1/71 (1.4)	0/30 (0)

Source: ad b.xpt; Software: R
Threshold levels 1, 2, and 3 as defined by the Standard Safety Tables & Figures Integrated Guide.
Duration is 12 months.
For specific evaluation of drug-induced liver injury (DILI), see the figures "DILI Case Screening Plot...," "Cholestatic Liver Injury Screening Plot...," and the table "Potential DILI..."
Abbreviations: DILI, drug-induced liver injury; ULN, upper limit of normal; N, number of patients in treatment arm; n, number of patients meeting criteria

Reviewer Comment: As shown in the table above very few patients developed significant elevations of liver function tests despite being on rivaroxaban for approximately a year.

This analysis concerns liver laboratory abnormalities occurring in Trial 3001.

Figure 1 Drug-Induced Liver Injury Case Screening Plot, Safety Population, Trial CHD3001



Source: adlb.xpt; Software: R
Each data point represents at least one visit (from a patient) with both ALT/AST and total bilirubin values in the postbaseline period. A potential Hy's Law case was defined as having a maximum postbaseline total bilirubin equal to or exceeding 2X ULN within 30 days after maximum postbaseline ALT or AST equal to or exceeding 3X ULN, without findings of cholestasis (defined as ALP <2X ULN).

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; TB, total bilirubin; DILI, drug-induced liver injury; ULN, upper limit of normal; ALP, alkaline phosphatase

Reviewer's Comment: Above is the DILI plot. There are no cases of Hy's Law.

Table 51 Potential DILI, Safety Population, Trial CHD3001

Quadrant	Rivaroxaban (Part A) N=12	Rivaroxaban (Part B) N=64	Total Rivaroxaban N=76	Aspirin (Part B) N=34
Potential Hy's Law (right upper)	0/12 (0)	0/57 (0)	0/69 (0)	0/29 (0)
Cholestasis (left upper)	0/12 (0)	1/57 (1.8)	1/69 (1.4)	0/29 (0)
Temple's corollary (right lower)	0/12 (0)	0/57 (0)	0/69 (0)	0/29 (0)
Total	0/12 (0)	1/57 (1.8)	1/69 (1.4)	0/29 (0)

Source: ad b.xpt; Software: R
Each data point represents at least one visit (from a patient) with both ALT/AST and total bilirubin values in the postbaseline period. A potential Hy's Law case was defined as having a maximum postbaseline total bilirubin equal to or exceeding 2X ULN within 30 days after maximum postbaseline ALT or AST equal to or exceeding 3X ULN, without findings of cholestasis (defined as ALP <2X ULN).
Abbreviations: DILI, drug-induced liver injury; N, number of subjects in treatment arm; n, number of subjects meeting criteria

Reviewer Comment: Only one patient had a potential DILI signal and the pattern suggested a cholestatic pattern and no Hy's Law cases were observed.

8.4.7. Vital Signs

EINSTEIN Jr
Baseline data were collected for blood pressure, pulse and respiratory rate and were similar between treatment groups. Post-baseline values were not routinely collected and reported.

UNIVERSE
For trial 3001, all patients had underlying cardiac issues and were post-operative from cardiac surgery and therefore this fact confounded an interpretation of blood pressure and heart rate. Only one patient receiving rivaroxaban reported supraventricular tachycardia and one patient reported bradycardia. One reported palpitations.

No respiratory and temperature data were collected and reported with this trial.

8.4.8. Electrocardiograms (ECGs)

ECGs were reviewed with the original NDA submission.

8.4.9. QT

QT analyses occurred during the original NDA review.

8.4.10. Immunogenicity

Not applicable as this product is a small molecule.

8.5. Analysis of Submission-Specific Safety Issues

8.5.1. Bleeding

EINSTEIN Jr
Bleeding events were adjudicated by the CIAC.

In total, 119 patients (36.2%) in the rivaroxaban group had a TEAE of bleeding, compared to 45 patients (27.8%) in the comparator group. No patient in the rivaroxaban group had a major bleeding event. In total, 2 patients (1.2%) in the comparator group had a major bleeding event. This included a 6-month-old with a severe subdural hemorrhage and a 16-year-old with a respiratory tract bleed following a right rib resection. Bleeding events that occurred during the main treatment period by severity and site are shown in Table 52 and Table 53Table 53. Bleeding TEAEs occurred across all age groups (Table 54Table 54).

Table 52. Trial 14372- Bleeding Events: Major, Clinically Relevant non-Major Bleeding and Trivial Bleeding in the Main Treatment Period

Bleeding Event Category	Rivaroxaban N=329 n (%)	Comparator Group N=162 n (%)
Any confirmed bleeding	119 (36.2)	45 (27.8)
Major bleeding	0	2 (1.2)
Clinically relevant non-major bleeding	10 (3)	1 (0.6)
Trivial bleeding	113 (34.3)	44 (27.2)

Source: adae.xpt, adfaae.xpt; Software: R
Treatment-emergent adverse events defined as AEs occurring between randomization and up to 2 days after the last dose.
Duration is 90 days (main treatment period).
Bleeding events with onset on the day of randomization are considered only if the investigator stated that the event was related to study medication.
Percentages calculated with number of subjects in each group as denominator.
Abbreviations: N, number of patients in treatment arm; n, number of patients who meet the specific criteria

Table 53. Trial 14372 - Severity of Bleeding by Site by Treatment

Bleed Site	Rivaroxaban (N=329)	Comparator (N= 162)
Gastrointestinal tract	4 (CRNMB), 13 (Trivial)	2 (Trivial)
Genital	1 (CRNMB), 24 (Trivial)	8 (Trivial)
Injection	1 (CRNMB), 3 (Trivial)	17 (Trivial)
Intracranial	0	1 (0.6%)
Nasal	2 (CRNMB), 37 (Trivial)	1 (CRNMB). 17 (Trivial)
Oral cavity	1 (CRNMB), 18 (Trivial)	1 (Trivial)
Respiratory tract	2 (Trivial)	1 (Major), 1(Trivial)
Skin	38 (Trivial)	14 (Trivial)
Urinary tract	1 (CRNMB), 7 Trivial	1 (Trivial)
Unknown	1 (Trivial)	0

Source: Clinical reviewer

Table 54. Trial 14372 Bleeding Events by Age Group

Age Bleeding Event	Rivaroxaban N=329 n (%)	Comparator Group N=162 n (%)
12 to < 18 years	N=180 (100)	N=89 (100)
Any confirmed	76 (42.2)	27 (30.3)
Major bleeding	0	1 (1.1)
CRNMB	3 (1.7)	1 (1.1
6 to < 12 years	N=67 (100)	N=34 (100)
Any confirmed	20 (29.9)	9 (26.5)
Major bleeding	0	0
CRNMB	2 (3)	0
2 to <6 years	N=46 (100)	N=22 (100)
Any confirmed	10 (21.7)	6 (27.3)
Major bleeding	0	0

CRNMB	3 (6.5)	0
Birth to <2 years	N=36 (100)	N=17 (100)
Any confirmed	13 (36.1)	3 (17.6)
Major bleeding	0	1 (5.9)
CRNMB	2 (5.6)	0
0.5 to < 2 years	N=21 (100)	N=9 (100)
Any confirmed	8 (38.1)	3 (33.3)
Major bleeding	0	1 (5.9)
CRNMB	1 (4.8)	0
Birth to <0.5 years	N=15 (100)	N=8 (100)
Any confirmed	5 (33.3)	0
Major bleeding	0	0
CRNMB	1 (6.7)	0

Source: CDS and clinically reviewer
Abbreviations: CRNMB= clinically relevant non major bleed

Below is a summary of bleeding events that occurred any time after randomization, including both the main treatment period and extended period. The most common CRNM bleeding event was hematemesis (2 occurrences).

Table 55. Trial 14372- Bleeding Events: Major, Clinically Relevant non-Major Bleeding and Trivial Bleeding Any Time After Randomization

Treatment/Type of Bleed	Rivaroxaban (N=329)	Comparator (N=162)
Major	0	2 (1.2%)
CRNMB	13 (4%)	2 (1.2%)
Trivial	123 (37.4%)	48 (29.6%)

Source: Applicant's CSR

Clinical reviewer comment: Bleeding was the most common TEAE to occur in EINSTEIN Jr. Bleeding TEAEs occurred more frequently in the rivaroxaban group compared to the comparator group (36.2% vs 28.7, respectively). Nasal, skin and genital were the most common sites of bleeding. While major bleeding was more common in the comparator group, CRNMB and trivial bleeding occurred more frequently in the rivaroxaban group across most age group (except 2 to <6 year old), in particular there were higher rates of bleeding events in the rivaroxaban group in the youngest age groups. Most bleeding events were trivial in the youngest age groups. Given the seriousness of VTE in the youngest age groups and need for oral anticoagulants, the benefit

continues to outweigh the risk as long as bleeding is included as a common AR in the USPI. Providers can weigh the risk of bleeding for their individual patients. Of note, in female patients who have experienced menarche, ages 12 to <18 years of age, menorrhagia occurred in 23 patients (27%)in the rivaroxaban group and 5 patients (10%) in the comparator group. This will be included in the USPI as it appears menorrhagia may occur more frequently in female patients receiving rivaroxaban, this will be an important consideration for providers.

UNIVERSE
Bleeding events were adjudicated by the CIAC.

One patient had a major bleed on Day 108 after the first rivaroxaban dose. The patient had epistaxis with a hemoglobin decrease of 2 g/dL and required a transfusion.

The next 2 tables below show the breakdown of bleeding events by category and site.

Table 56. Trial 3001 - Bleeding Events: Major, Clinically Relevant non-Major Bleeding and Trivial Bleeding

Bleeding Event Category Bleeding Site Groupings	Rivaroxaban (Part A) N=12 n (%)	Rivaroxaban (Part B) N=64 n (%)	Total Rivaroxaban N=76 n (%)	Aspirin (Part B) N=34 n (%)
Patients with 1 or more on-treatment bleeding events	4 (33.3)	23 (35.9)	27 (35.5)	14 (41.2)
Major bleed	0	1 (1.6)	1 (1.3)	0
Clinically relevant non-major bleeding	1 (8.3)	4 (6.2)	5 (6.6)	3 (8.8)
Major and clinically relevant non-major bleeding	1 (8.3)	5 (7.8)	6 (7.9)	3 (8.8)
Trivial bleeding	3 (25)	21 (32.8)	24 (31.6)	12 (35.3)

Source: adcebl.xpt; Software: R
Treatment-emergent adverse events defined as those AEs that started on or after the first dose of study drug and up to 2 days after the last dose of study drug.
Duration is on-treatment (The period starting from the first dose of study agent to 2 days after the last dose of the study agent administration inclusively).
Bleeding events: Adjudicated by CIAC.
Percentages calculated with number of subjects in each group as denominator.
Abbreviations: CIAC, Central and Independent Adjudication Committee; GI, gastrointestinal; N, number of patients in treatment arm; n, number of patients who meet the specific criteria.

Table 57 Trial 3001 - Severity of Bleeding by Site by Treatment

Bleed Site	Rivaroxaban (N=76)	ASA (N=34)
Epistaxis	8 (1 Major, 7 Trivial)	3 (Trivial)
Gastrointestinal – Total		
Gastrointestinal – Lower	2 (CRNMB)	1 (CRNMB), 1 (Trivial)
Gastrointestinal – Upper	1 (Trivial)	0
Gingival	1 (CRNMB), 4 (Trivial)	1 (Trivial)
Hematoma	9 (Trivial)	1 (CRNMB), 2 (Trivial)
Skin	2 (CRNMB), 14 (Trivial)	1 (CRNMB), 8 (Trivial)
Subconjunctival	0	1 (CRNMB)
Vascular Access Site	2 (Trivial)	0

Source: Clinical Reviewer

Clinical Comment: There was one major bleeding event in the UNIVERSE Study that occurred in the rivaroxaban group compared to none in the aspirin group. CRNMB occurred at lower rate in the rivaroxaban group compared to the aspirin group (6.6% vs 8.8%, respectively). Most bleeding events were trivial in both the rivaroxaban group and comparator group. Overall bleeding occurred at a lower rate in the rivaroxaban group. The most common bleeding sites in the rivaroxaban group was epistaxis, hematoma and skin.

8.5.2. Drug Induced Liver Injury

EINSTEIN Jr

There was one case of drug induced liver injury in the rivaroxaban group reported by the Applicant. Patient (b) (6) developed drug induced liver injury 43 days after starting rivaroxaban, although the investigator noted that the likely etiology was the concomitant medication levetiracetam. Rivaroxaban was interrupted during the event.

Patient narrative:
Approximately 43 days (b) (6) after starting rivaroxaban the patient was hospitalized due to pharmacological hepatotoxicity (MedDRA PT: drug-induced liver injury), which was of severe intensity. The event was considered serious as it required hospitalization. Prior to the start of rivaroxaban, the patient's ALT level was at 152 U/L (reference range: 10-40), AST 97 U/L (reference range: 10-50), bilirubin conjugated 3.5 mg/dL (reference range: 0-0.40), blood ALP 412 U/L (reference range: 42-98), blood bilirubin 5.00 mg/dL (reference range: 0.40-1.20), blood bilirubin unconjugated 1.5 mg/dL (reference range not provided), blood LDH 417 U/L (reference range: 91-190), GGT 220 IU/L (reference range: 0-50), and INR 1.10 (normal). On (b) (6) the subject's laboratory tests revealed: ALT at 861 U/L, AST 586 U/L, bilirubin conjugated 7.52 mg/dL, blood ALP 693 U/L, blood bilirubin 10.78 mg/dL, blood bilirubin unconjugated 3.26 mg/dL, blood LDH 763 U/L, GGT 241 IU/L, and INR 1.60 (abnormal). An ultrasound of the liver was normal and viral studies were negative. Rivaroxaban was interrupted due to the event. Liver enzymes improved. The investigator attributed the event to levetiracetam. Further follow up was not available as the patient withdrew consent.

Table 58. Adverse Events of Special Interest, Safety Population, Trial 14372

Drug-Induced Liver Injury Assessment	Rivaroxaban N=329 n (%)	Comparator Group N=162 n (%)
AE grouping related to AESI	9 (2.7)	7 (4.3)
Alanine aminotransferase increased	7 (2.1)	7 (4.3)
Aspartate aminotransferase increased	6 (1.8)	2 (1.2)
Bilirubin conjugated increased	3 (0.9)	0
Drug-induced liver injury	1 (0.3)	0
Maximum severity		
Death	0	0
Life-threatening	0	0
Severe	3 (0.9)	3 (1.9)
Moderate	2 (0.6)	1 (0.6)
Mild	4 (1.2)	3 (1.9)
Serious	2 (0.6)	0
Deaths	0	0
Resulting in discontinuation	0	0
Relatedness	2 (0.6)	0

Source: adae.xpt; Software: R
Treatment-emergent adverse events defined as AEs occurring between randomization and up to 2 days after the last dose. Duration is 90 days (main treatment period).
Relatedness is determined by investigator.
Abbreviations: AE, adverse event; AESI, adverse events of special interest; CI, confidence interval; N, number of patients in treatment arm; n, number of patients with adverse event

Clinical reviewer comment: There was one TEAE of drug induced livery injury. The patient had abnormal liver enzymes prior to initiating rivaroxaban and was receiving levetiracetam concurrently. In the levetiracetam USPI, hepatic failure, hepatitis, and abnormal liver function

test have been described in the postmarketing experience, therefore it is difficult to determine the cause of drug induced liver injury.

UNIVERSE
Only one case consistent with cholestatic pattern was observed. Discussed above under Laboratory in section 8.4.6.

8.5.3. Pleural Effusion

EINSTEIN Jr
In the EINSTEIN Study, pleural effusion was reported in 2 patients (0.6%) in the rivaroxaban group and 1 patient (0.6%) in the ASA group.

UNIVERSE
In the UNIVERSE Study, pleural effusion was the second most common TEAE reported in the rivaroxaban group. Pleural effusions were more frequently reported in the rivaroxaban group (Part A and B), occurring in 15 patients (19.7%) compared to 2 patients (5.9%) treated with ASA. Pleural effusions were the most common SAE and occurred more commonly in the rivaroxaban group (11 [14.5%]) compared to ASA group (2 [5.9%]). None of the pleural effusions were hemorrhagic. The Applicant conducted an analysis to further characterize pleural effusion events (Table 59).

Table 59. Subjects with Treatment-Emergent Pleural Effusion, CHD3001

Had Treatment Emergent Pleural Effusion?	Site ID	Subject ID	Treatment Group	Days between Fontan and First Dose	Fenestration?	Size of Baffle or Conduit Used	ACE inhibitor use after Fontan?	MH of pleural effusion?	Pleural Effusion Day	Days between Fontan and Pleural Effusion
Yes	BR10005	(b) (6)	Rivaroxaban (Part B)	103	Yes	18 mm	No	Yes	92	194
Yes	ES10001		Rivaroxaban (Part A)	2	No	18 mm	No	No	1	2
Yes	MX10001		Rivaroxaban (Part B)	37	Yes	16 mm	No	No	70	106
Yes	MY10001		Rivaroxaban (Part B)	19	Yes	18 mm	Yes	No	2	20
Yes	MY10001		Rivaroxaban (Part B)	18	Yes	19 mm	Yes	No	4	21
Yes	US10007		Rivaroxaban (Part B)	6	No	20 mm	Yes	No	9	14
Yes	US10009		Rivaroxaban (Part B)	2	Yes	14 mm	No	No	7	8
Yes	US10010		Rivaroxaban (Part B)	5	No	18 mm	No	Yes	4	8
Yes	US10013		Rivaroxaban (Part A)	4	No	18 mm	No	No	16	19
Yes	US10013		Rivaroxaban (Part A)	3	No	20 mm	No	No	13	15
Yes	US10013		Aspirin (Part B)	4	No	20 mm	No	No	8	11
Yes	US10013		Rivaroxaban (Part B)	5	No	20 mm	No	No	3	7
Yes	US10013		Rivaroxaban (Part B)	4	No	20 mm	No	No	14	17
Yes	US10013		Rivaroxaban (Part B)	4	No	20 mm	No	No	12	15
Yes	US10013		Rivaroxaban (Part B)	4	No	20 mm	No	No	12	15
Yes	US10013		Aspirin (Part B)	2	No	20 mm	No	No	10	11
Yes	US10013		Rivaroxaban	3	No	18 mm	No	No	12	14

Source: Applicant CSR of CHD3001
MH: medical history

Clinical Comment: The clinical team further reviewed pleural effusions given this was a common TEAE and SAE that occurred more frequently in the rivaroxaban group in the UNIVERSE Study. Of note, no patient discontinued therapy due to a pleural effusion in clinical trials.

Pleural effusions are common after Fontan surgery. Pleural effusions often occur due to an increase in hydrostatic capillary pressure, this in turn results in increased filtration in the interstitial space and excess drainage into the lymphatic system[28].

Fenestrations may be performed to help manage central pressures by allowing right to left shunting and has shown to decrease morbidity and mortality[29]. Patients with fenestration post-Fontan, may have a lower risk of developing pleural effusions[7, 30]. We agree with the Applicant that there was an imbalance of fenestrated-Fontan vs non-fenestration Fontan. In total, 45 patients (59%) treated with rivaroxaban had a non-fenestrated Fontan, compared to 13 patients (38%) treated with aspirin. Although, 5 patients who developed pleural effusions had fenestrations, all of which were in the rivaroxaban group.

Timing of the pleural effusions was also taken into consideration. All but two events occurred within 3 weeks of the Fontan procedure. The other two events occurred over 100 days after

starting rivaroxaban. This suggests the pleural effusion are more likely related to the procedure rather than rivaroxaban.

In addition, 9 out of 17 patients were reported from a single site (Site US10013), and none of those patients had a fenestration. This suggests that the pleural effusions were related to type of Fontan procedure performed and clinical practice at that institution.

Lastly, mechanistically there does not seem to be a clear rationale for increased rates of pleural effusions in the rivaroxaban group as none of them were reported to be hemorrhagic.

In conclusion, it appears unlikely that pleural effusions are related to rivaroxaban despite having a higher incidence of pleural effusion TEAEs. Rather, pleural effusions are most likely related to the Fontan procedure. Therefore, pleural effusions will not be listed as an AR in the USPI.

8.5.4. Thrombocytopenia

EINSTEIN Jr

The FDA medical query "thrombocytopenia" included the following preferred terms; thrombocytopenia, platelet count decreased and pancytopenia. In total, 17 (5.2%) patients in the rivaroxaban group had a TEAE of thrombocytopenia compared to 6 (3.7%) patients in the comparator group. In this study, 2 (0.6%) patients in the rivaroxaban group had a serious TEAE of thrombocytopenia compared to 1 (0.6%) patient in the comparator group. One patient in the rivaroxaban arm discontinued treatment due to thrombocytopenia.

There was one TEAE of thrombocytopenia that led to study discontinuation. Patient (b) (6) was 15 year old female with a medical history significant for Ewing sarcoma, recurrent thrombocytopenia and atypical pneumonia. She was diagnosed with a catheter related thrombosis in the atrium of the heart. The patient was randomized to rivaroxaban. Prior to starting rivaroxaban the patient had a platelet count of 42 GIGA/L (reference range: 140-400). Four days after starting rivaroxaban the patient was reported to have a serious event of thrombocytopenia, platelet count was 22 GIGA/L. The study drug was interrupted and only restarted for 3 days prior to stopping again. The patient was receiving chemotherapy at the time of the event.

Platelet count values were analyzed. Low platelet count of <125,000cell/uL occurred in 16/310 (5.2%) patients in the rivaroxaban group compared to 5/144 (3.5%) patients in the comparator group. Concomitant medications were reviewed, most patients were receiving chemotherapy in close proximity or during the treatment period (Table 60).

The Applicant reported a treatment emergent platelet count below 50x10^9 was reported for 12/329 (3.6%) patient in the rivaroxaban group and 3/162 (1.9%) patients in the comparator group.

Table 60**. List of Platelet Count Values ≥Level 2 Criteria (<125,000cells/uL), Safety Population, Trial 14372**

Patient ID	Treatment Arm	Parameter	Baseline Value	Laboratory Value	Study Day	Receiving Chemotherapy or immunosuppression
(b) (6)	Rivaroxaban (20 mg or equivalent)	Platelets (cells/uL)	351000	113000	90	Y
	Rivaroxaban (20 mg or equivalent)	Platelets (cells/uL)	129000	119000	91	N
	Rivaroxaban (20 mg or equivalent)	Platelets (cells/uL)	232000	108000	83	Y
	Rivaroxaban (20 mg or equivalent)	Platelets (cells/uL)	288000	69000	82	Y
	Rivaroxaban (20 mg or equivalent)	Platelets (cells/uL)	303000	13000	93	Y
	Rivaroxaban (20 mg or equivalent)	Platelets (cells/uL)	480000	37000	94	Y
	Rivaroxaban (20 mg or equivalent)	Platelets (cells/uL)	Missing	98000	90	Y
	Rivaroxaban (20 mg or equivalent)	Platelets (cells/uL)	173300	17010	77	N
	Rivaroxaban (20 mg or equivalent)	Platelets (cells/uL)	60000	30000	84	Y
	Rivaroxaban (20 mg or equivalent)	Platelets (cells/uL)	226000	61000	96	Y
	Rivaroxaban (20 mg or equivalent)	Platelets (cells/uL)	150000	114000	28	Y
	Rivaroxaban (20 mg or equivalent)	Platelets (cells/uL)	128500	32400	35	Y
	Rivaroxaban (20 mg or equivalent)	Platelets (cells/uL)	61900	67700	98	Y
	Rivaroxaban (20 mg or equivalent)	Platelets (cells/uL)	76000	61000	86	Y

Patient ID	Treatment Arm	Parameter	Baseline Value	Laboratory Value	Study Day	Receiving Chemotherapy or immunosuppression
(b) (6)	Rivaroxaban (20 mg or equivalent)	Platelets (cells/uL)	292000	94000	94	Y
	Rivaroxaban (20 mg or equivalent)	Platelets (cells/uL)	435000	48000	91	N
	Anticoagulants, comparator	Platelets (cells/uL)	263000	120000	88	Y
	Anticoagulants, comparator	Platelets (cells/uL)	178000	61000	87	Y
	Anticoagulants, comparator	Platelets (cells/uL)	74000	104000	94	N
	Anticoagulants, comparator	Platelets (cells/uL)	225000	82000	85	Y
	Anticoagulants, comparator	Platelets (cells/uL)	287000	114000	87	N

Source: Clinical reviewer and clinical data scientist, adlb.xpt and adcm.xpt; Software: R
Threshold level 2 as defined by the Standard Safety Tables & Figures Integrated Guide.
Duration is 90 days (main treatment period).
Study day is post-randomization
Abbreviations: ID, identification
*Receiving chemotherapy during main treatment period

Clinical reviewer comment: There were higher rates of thrombocytopenia in the rivaroxaban group than the comparator group. The significance of this is difficult to determine as this was a heterogenous patient population with multiple comorbidities, including some patients receiving chemotherapy. Platelet count of <125,000cell/uL occurred in 16/310 (5.2%) patients in the rivaroxaban group compared to 5/144 (3.5%). All but three events occurred in close proximity to chemotherapy. One event was likely due to bone marrow depression and liver toxicity secondary to levetiracetam. A second event a patient went from a baseline level of 129,000cell/uL to 119,000cell/uL, this significance of this small reduction in platelet count is not clear. No narrative was provided for the third event so causality could not be assessed.

Overall it appears that the majority of TEAEs were from concomitant medications, most notably chemotherapy agents. In EINSTEIN Jr, there were a higher proportion of patients with cancer in the rivaroxaban group compared to the comparator group (11.9% vs 9.7%, respectively). This could contribute to the higher rates of thrombocytopenia observed. Although, thrombocytopenia is listed as an adverse reaction identified post-marketing in the rivaroxaban USPI. At this time, in pediatric patients, it does not appear that rivaroxaban causes thrombocytopenia given that chemotherapy was likely the cause in most patients and therefore will not be listed as a common adverse reaction in section 6 of the USPI when describing pediatric studies.

UNIVERSE
There were no TEAEs of thrombocytopenia. One patient had a platelet count decrease greater than or equal to level 2 criteria (<125,000 cells/uL), the patient was on rivaroxaban.

8.5.5. Vomiting

EINSTEIN Jr
A list of gastrointestinal disorders are listed in Table 61. Overall, gastrointestinal TEAEs were more common in the rivaroxaban group compared to the comparator group (32.2% vs 26.5%, respectively. In total, 35 patients (10.6%) in the rivaroxaban group had a TEAE of vomiting compared to the comparator in which 13 patients (8%) had a TEAE of vomiting. Of these events, 6 (1.8%) were serious all occurred in the rivaroxaban group. In addition, 6 patients (1.8%) had rivaroxaban interrupted due to vomiting, compared to none in the comparator group.

Two (0.6%) vomiting events led to discontinuation of rivaroxaban, there were no events of vomiting that led to discontinuation in the comparator group.

1. One patient (ID: (b) (6) was a 7-month-old female with medical history of acute cardiac failure, ventricular septal defect (VSD), and pulmonary artery atresia who developed a catheter related thrombosis in the right internal jugular vein. She discontinued the study due to a moderate TEAE of vomiting 16 days after starting rivaroxaban. The patient was on multiple concomitant medications. Further information was not provided.
2. The second patient (ID: (b) (6)) was a 9-month-old female with history epilepsy. In (b) (6) the patient was diagnosed with a catheter-related thrombosis in the femoral vein. Six days after starting rivaroxaban the patient had an epileptic event of severe intensity and vomiting of mild intensity. The patient discontinued rivaroxaban due to these TEAEs. The investigator thought the vomiting was related to study drug, but the epileptic TEAE was related to underlying epilepsy. The patient was on multiple concomitant medications.

Table 61. Adverse Events by Gastrointestinal Disorders System Organ Class and FDA Medical Query (Narrow), Safety Population, Trial 14372

System Organ Class FMQ (Narrow)	Rivaroxaban N=329 n (%)	Comparator Group N=162 n (%)
Gastrointestinal disorders (SOC)	106 (32.2)	43 (26.5)
Vomiting	35 (10.6)	13 (8.0)
Nausea	21 (6.4)	7 (4.3)
Diarrhea	24 (7.3)	9 (5.6)
Dyspepsia	11 (3.3)	3 (1.9)
Dry mouth	1 (0.3)	0
Abdominal pain	26 (7.9)	13 (8.0)
Pancreatitis	0	1 (0.6)
Constipation	8 (2.4)	11 (6.8)

Source: Clinical data scientist, adae.xpt; Software: R
Treatment-emergent adverse events defined as AEs occurring between randomization and up to 2 days after the last dose. Duration is 90 days (main treatment period).
For specific preferred terms under each FMQ, see the table "Adverse Events by System Organ Class, FDA Medical Query (Narrow) and Preferred Term…"
Abbreviations: FMQ, FDA medical query; N, number of patients in treatment arm; n, number of patients with adverse event; SOC, system organ class

UNIVERSE

A list of gastrointestinal disorders are listed in Table 62. Adverse Events by System Organ Class and FDA Medical Query (Narrow), Safety Population, Trial CHD3001Table 62. In total, 13 out of 76 patients (17.1%) whom received rivaroxaban had a vomiting event (based on FMQ) compared to 3 out of 34 patients (8.8%) whom received aspirin. None of the events were serious or led to drug discontinuation.

Table 62. Adverse Events by System Organ Class and FDA Medical Query (Narrow), Safety Population, Trial CHD3001

System Organ Class FMQ (Narrow)	Rivaroxaban (Part A) N=12 n (%)	Rivaroxaban (Part B) N=64 n (%)	Total Rivaroxaban N=76 n (%)	Aspirin (Part B) N=34 n (%)
Gastrointestinal disorders (SOC)				
Vomiting	3 (25.0)	10 (15.6)	13 (17.1)	3 (8.8)
Dyspepsia	0	2 (3.1)	2 (2.6)	0
Abdominal pain	0	3 (4.7)	3 (3.9)	1 (2.9)
Diarrhoea	2 (16.7)	3 (4.7)	5 (6.6)	2 (5.9)
Nausea	0	0	0	1 (2.9)
Constipation	0	0	0	2 (5.9)

Source: adae.xpt; Software: R
Treatment-emergent adverse events defined as those AEs that started on or after the first dose of study drug and up to 2 days after the last dose of study drug.
Duration is 12 months.
For specific preferred terms under each FMQ, see the table "Adverse Events by System Organ Class, FDA Medical Query (Narrow) and Preferred Term…"
Abbreviations: FMQ, FDA medical query; N, number of patients in treatment arm; n, number of patients with adverse event; SOC, system organ class

Clinical Comment: Vomiting was common in both clinical trials (EINSTEIN Jr and UNIVERSE). It is difficult to determine causality given many of the pediatric patients had comorbidities and required concomitant medications. Although there was more drug interruptions and discontinuations due to vomiting in the rivaroxaban group. It is possible that rivaroxaban can cause vomiting in pediatric patients and therefore will be included in the USPI.

8.6. Safety Analyses by Demographic Subgroups

Age, gender and race subgroups were too small to make meaningful safety comparisons.

8.7. Specific Safety Studies/Clinical Trials

Study 17992
No cases of death, major bleeding, clinically relevant non-major bleeding events, or SAEs were reported. Treatment emergent trivial bleedings were reported for 2/47 (4.3%) - bruising with needlesticks and peri-PEG bleeding. Treatment emergent AEs were mild- prolonged APTT, viral infection, fatigue, epistaxis, and rash except for bronchiolitis which was moderate. TEAEs considered related to rivaroxaban were prolonged aPTT, vessel puncture site bruise, and rash.

Study 17618
No major and clinically relevant non-major bleeding occurred in this study.

One patient in the b.i.d. dose group and two in the t.i.d. dose group had at least one AE. One AE in the b.i.d. group and one AE in the t.i.d. group was reported as severe. One AE in the t.i.d. dose group was moderate. None of the AEs were considered related to rivaroxaban.

The AE in the b.i.d. dose group was reported as atrial thrombosis. Radiologic review of this atrial thrombosis case in a 30-day old with a history of transposition of the great arteries revealed the thrombosis had been present at study entry on imaging but somehow missed in the report.

Two TEAEs were identified: one in a pediatric patient in the bid group (vomiting) and the other was the case of the atrial thrombosis. A cardiac arrest occurred in a nine-week-old pediatric patient with a congenital hypoplastic left heart syndrome approximately 27 days after discontinuing rivaroxaban. The investigator determined the cardiac arrest to be unrelated to rivaroxaban. An elevated CRP was noted in one child approximately 15 days after discontinuing

rivaroxaban.

Study 12892

There were no cases of death, major bleeding or non-major clinically relevant bleeding observed in this study.

The only SAE observed in this study was a pelvic venous thrombosis that occurred 7 days after the single dose rivaroxaban administration. The SAE was considered by the investigator to be severe in intensity and not related to the study drug. The pediatric patient had a Factor V Leiden mutation and anti-thrombin III deficiency.

Sixteen patients reported TEAEs; however only four were reported to be related to rivaroxaban administration. TEAEs considered to be related to rivaroxaban by the investigator were reported in 4/59 children (6.8%): abdominal discomfort of mild intensity, allergic dermatitis of moderate intensity, dyspepsia of mild intensity, and urticaria of mild intensity.

Study 14373
There were no cases of death or major bleeding. Four treatment-emergent clinically relevant non-major bleeding events were reported in the rivaroxaban groups. Three of the four were menorrhagia and all classified as moderate. One bleed was classified as severe, lasted a day, and involved gingival bleeding. None of the patients changed their rivaroxaban dose and all resolved.

Treatment-emergent trivial bleedings were reported in 2 pediatric patients in the 12-18 years rivaroxaban tablet group, 2 pediatric patients in the 12-18 years comparator group, and 2 pediatric patients in the 6-12 years rivaroxaban tablet group. The bleeding events in the comparator group included bleeding after baby tooth fell out, epistaxis for a minute, and hematoma on arm after intravenous access. The bleeding events in the rivaroxaban groups included increased vaginal bleeding (2), increased bruising (2), epistaxis (2), and blood on toilet paper after wiping.

TEAEs were reported by 27/43 (62.8%) pediatric patients who received rivaroxaban and 10/20 (50%) pediatric patients who received the comparator. Drug related TEAEs were reported by 8/43 (18.6%) pediatric patients who received rivaroxaban and none for the comparator. Most TEAEs related to rivaroxaban were of mild (4/43; 9.3%) or moderate (3/43; 7%) intensity. The rivaroxaban related AEs were menorrhagia (3), dyspepsia, headache, vertigo, lower gastrointestinal bleed, epistaxis, increased bruising, rash, pruritus, and alopecia, and gingival bleeding. Rivaroxaban treatment continued despite AE development.

In 3/63 children (4.8%), treatment-emergent SAEs were reported: one patient on comparator

(VKA) and 2 patients on rivaroxaban suspension. In one patient a non-treatment emergent SAE was reported (low platelets – related to her underlying malignancy treatment) and a serious treatment emergent SAE of Influenza B infection was also reported. As assessed by the investigator, none of the SAEs were related to study drug or procedures required by the protocol.

Another patient aged 10 years with a central nervous system tumor (nongerminomatous germ cell tumor) and received a diagnosis of hypothalamic dysfunction while receiving rivaroxaban and had a second hospitalization for hypothalamic dysfunction. Both of these events were not deemed related to rivaroxaban treatment.

One child aged 14 years had a multiple sclerosis relapse while receiving VKA. Prior to study enrollment, the child received standard of care treatment with VKA for symptomatic venous thrombosis in her upper extremity deep vein. Anticoagulant treatment was not discontinued and was not deemed related to her relapse.

One child aged 17 had an SAE of post-thrombotic syndrome. She was originally diagnosed with a DVT and PE in (b) (6) and then later enrolled in this study in (b) (6) Prior to study enrollment, the child received standard of care treatment with both LMWH and VKA. A month after discontinuing rivaroxaban she was diagnosed with post-thrombotic syndrome. Her treating physician and the company do not think the post-thrombotic syndrome was related to her rivaroxaban treatment.

Review of laboratory abnormalities revealed that none could be attributed to rivaroxaban alone. The pediatric patients enrolled in these trials have significant comorbidities which could account for the laboratory abnormalities noted.

Study 14374

No deaths or major bleeding events occurred. No treatment-emergent clinically-relevant non-major bleeding was reported in children treated with rivaroxaban. However, two treatment-emergent clinically-relevant non-major bleeding events were reported in the comparator group – one treatment emergent and one non-treatment emergent. One patient had a treatment emergent rectal hemorrhage and the other had petechiae (patient had B-cell acute lymphoblastic leukemia, receiving chemotherapy and was pancytopenic). Both were classified as mild.

Treatment-emergent trivial bleedings were reported in 3 patients in rivaroxaban groups: 2 in the 2-6 years group and 1 in the 6 months-2 years group (lip injury and two subcutaneous hemorrhages. All were classified as mild. The patient with the lip injury had medicine held for one dose and then resumed at the same dose. No dosing changes as a result of these events. No treatment emergent trivial bleedings were reported for the comparator.

There were no discontinuations of study drug due to AEs or SAEs.

The most frequently reported AE was infection/infestations (35%) followed by gastrointestinal disorders (15%). Two TEAES were reported to be related to rivaroxaban – diarrhea in a pediatric patient aged 4 years and constipation in a pediatric patient aged 1 year. No TEAEs were reported to be related to the comparator.

There were 3 SAEs (2 for rivaroxaban and 1 for the comparator) which resulted in hospitalization: pyrexia (patient with B cell acute lymphoblastic leukemia/sickle cell disease), respiratory disorder (9 month old) in two pediatric patients aged 6 months to 2 years and a headache accompanied by optic atrophy in a pediatric patient (4 year old with a ventriculoperitoneal shunt) on the comparator. None of these were considered related to study drug.

None of the TEAEs led to a dose change or discontinuation of rivaroxaban.

No cases of post-thrombotic syndrome were reported.

Blood pressure elevations for either the diastolic or systolic measurement above the 95th percentile were noted for 14 at screening. Two children had known hypertension. For all the other cases the elevations were very mild (one or two points higher than the 95th percentile).

Most laboratory abnormalities that occurred during the study occurred in pediatric patients who had an underlying cancer diagnosis.

8.8. Additional Safety Explorations

8.8.1. Human Carcinogenicity or Tumor Development

Not applicable

8.8.2. Human Reproduction and Pregnancy

This trial specifically excluded pregnant pediatric patients. The approved label has information on nonclinical effects of rivaroxaban.

8.8.3. Pediatrics and Assessment of Effects on Growth

Rivaroxaban's effect on growth was not specifically evaluated in the submitted trials. However, all treatment groups demonstrated an increase in height and weight from study entry to Month 12 or end of study visit.

8.8.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Overdose management instructions are given in the rivaroxaban label. No drug abuse or withdrawal potential exists with this product. Patients on an anticoagulant for a hypercoagulable state will experience thrombosis if anticoagulation is stopped.

8.9. Safety in the Postmarket Setting

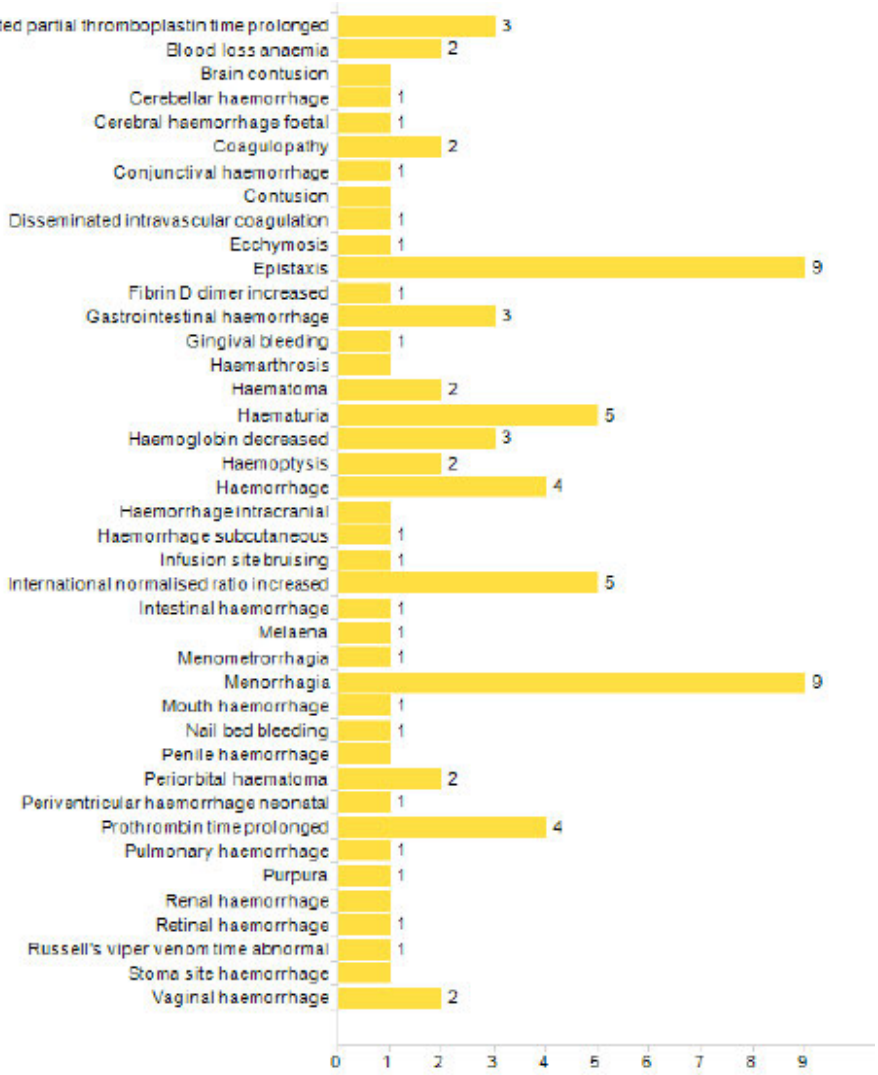
8.9.1. Safety Concerns Identified Through Postmarket Experience

Between the start of rivaroxaban marketing in 2008 and the data lock point in September 2020, the applicant's global safety database accumulated 355 postmarketing cases involving rivaroxaban use in pediatric patients.

There were two deaths. One death was due to a fatal intentional suicide in a 16-year-old female, in which the patient consumed multiple medications, including rivaroxaban. The second case was a pregnant mother who consumed rivaroxaban during pregnancy. The infant's death was attributed to lethal congenital anomaly with severe pulmonary hypoplasia.

Of these reports, 32 were retrieved form the literature, 28 were received from published reports by independent investigators and 295 cases were received spontaneously from across the globe. Of the 355 cases, 132 (37.2%) were considered serious including 43 (12.1%) with one bleeding event and 45 (12.7%) with at least one thromboembolic event, and 21 (5.9%) with bleeding and thromboembolic event. In total, there were 83 events of bleeding in 54 cases received. The most common bleeding events were menorrhagia, epistaxis, and gastrointestinal bleeding. All bleeding events are described in Figure 2. Also, there were 6 out of 355 cases (1.7%) in which there was an overdose, 42 (11.8%) cases with an accidental exposure.

Figure 2. Summary of Bleeding Events from Postmarketing Sources



Source: Applicant's Clinical Summary of Safety

Clinical reviewer comment: The safety profile of rivaroxaban in pediatric population does not change based on the postmarketing experience.

8.9.2. Expectations on Safety in the Postmarket Setting

Safety in the postmarket setting is expected to be similar to that observed in the clinical studies reviewed in this application and what is known from adult postmarketing safety data.

8.9.3. Additional Safety Issues From Other Disciplines

No additional safety issues were identified form other disciplines.

8.10. Integrated Assessment of Safety

Indication #1: Treatment of Venous Thromboembolism and Reduction in Risk of Recurrent Venous Thromboembolism in Pediatric Patients

Safety was primarily assessed from the EINSTEIN Jr study. The safety population consisted of 491 patients, 329 in the rivaroxaban group and 162 in the comparator group. Patients were randomized 2:1 to either weight-based dose of rivaroxaban (tablet or solution) or comparator group who received standard of care therapy for 3 months during the main treatment period with the option of extending treatment in 3-month blocks for up to 12 months, except for patients <2 years age and a CVC-VTE in which patients received 1 month of therapy with the option of extension for 1 month blocks up to 3 months. Overall, the median duration of therapy in the main treatment period was 13.4 weeks in the rivaroxaban group and 13.6 weeks in the comparator group.

There were two deaths that occurred in the rivaroxaban group. Both deaths were related to worsening progressive cancer and were not considered related to rivaroxaban. There were no major bleeding events in the rivaroxaban group and there were two (1.2%) major bleeding events in the comparator group. In the main treatment period, the incidence of SAEs in the rivaroxaban group was 71 out of 329 patients (21.6%) compared to the comparator group in which 32 out of 162 patients (19.8%). The most common SAEs in the rivaroxaban group compared to the comparator group was bleeding (3.3% vs 1.2%), pyrexia (3.3% vs 1.9%), leukopenia (2.1% vs 1.2%) and vomiting (1.8% vs 0%, respectively). Overall TEAEs leading to drug discontinuation and interruption were low but did occur at higher rates in the rivaroxaban group (3.3% vs 1.9%, respectively) and (14.9% vs 8.6%, respectively). The low rates of drug discontinuation support the tolerability of rivaroxaban.

Bleeding was an important adverse event. Bleeding TEAEs occurred more frequently in the rivaroxaban group compared to the comparator group (36.2% vs 28.7, respectively). Nasal, skin and genital were the most common sites of bleeding. Drug discontinuation due to bleeding occurred in 1.5% of patients in the rivaroxaban group and 1.9% in the comparator. Most bleeding events were trivial. CRNM bleeding occurred more in the rivaroxaban group compared to the comparator group (3% vs 0.6%, respectively). When examining the age groups, bleeding overall occurred in a higher proportion of patients in the rivaroxaban group in the youngest age group, birth to 2 years (36.1% in the rivaroxaban group vs 17.6% in the comparator). Although, small patient numbers much be taken into consideration. In female patients ages 12 to <18 years of age who experienced menarche, menorrhagia occurred at a higher rate in the rivaroxaban group compared to the comparator (27% vs 10%, respectively).

The most common TEAE (occurring in >10% of patients in the rivaroxaban group) were headache, nasopharyngitis, pyrexia and vomiting. Applicant proposed to include ARs in the USPI

that occurred in >5% of patients and had a relative risk of >1.5, this strategy had been used previously in the XARELTO USPI. The following ARs meet this threshold, pain in extremity and fatigue. This strategy is reasonable, although the clinical review team also recommends including vomiting as an AR. Vomiting was a common TEAE and drug interruption due to vomiting occurred in a higher proportion of patients in rivaroxaban compared to the comparator (1.8% vs 0%, respectively).

Thrombocytopenia and hepatotoxicity were important TEAEs identified by the clinical reviewer. Thrombocytopenia occurred in a higher proportion of patients in the rivaroxaban group, but most AEs were attributed to concomitant medications. In addition, one patient in the rivaroxaban group had DILI but, another medication (levetiracetam) was a plausible cause of the event.

There were no study deaths, major bleeding, or CRNMB in studies 17992, 17618, 12892, or 14374. In study 14373 there were no study deaths or major bleeding, but there were 4 TEAEs of CRNMB in the rivaroxaban group. Overall the safety profile of studies 17992, 17618, 12892, 14374 and 14373 was consistent with what was observed in EINSTEIN Jr.

Overall the safety profile is tolerable. Adverse reactions, including bleeding can be adequately managed with labeling.

Indication#2: Thromboprophylaxis in Pediatric Patients with Congenital Heart Disease after the Fontan Procedure

The safety analysis for indication #2 is based on the UNIVERSE study. This was a prospective, open-label, multicenter study in two parts enrolling pediatric patients between 2 to 8 years of age who have had the Fontan surgical procedure for single ventricle physiology within 4 months prior to enrollment. Part A was a single-arm part in which 12 patients continued rivaroxaban for 12 months. Part B was the randomized, active- controlled part in which 64 patients were randomized to receive rivaroxaban and 34 patients were randomized to receive ASA. Rivaroxaban in Part A and B was exposure matched to 10mg daily in adults. The median duration of therapy was 51.3 weeks in both treatment groups.

There were no deaths on study. SAEs were higher in the rivaroxaban group occurring in 24 patients (31.6%) (50% of patients in Part A and 28.1% of patients in Part B) compared to 8 (23.5%) patients in the aspirin group. The most common SAE was pleural effusion, occurring in 11 patients (14.5%) in the rivaroxaban group compared to 2 patients (5.9%) of patients in the aspirin group. The clinical reviewer did not consider pleural effusion as an AR as this was most likely related to the Fontan procedure itself given most events occurred within 3 weeks of the procedure and the majority were in non-fenestrated patients.

Bleeding was an important AE in the UNIVERSE study. There was one major bleeding event of epistaxis in the study, this occurred in one patient (1.3%) in the rivaroxaban group. Most bleeding events were trivial. The most common bleeding sites in the rivaroxaban group was epistaxis, hematoma and skin. Overall, bleeding occurred in a lower proportion of patients in the rivaroxaban group.

The most common TEAEs (occurring in >10% of patients in the rivaroxaban group) were nasopharyngitis, pyrexia, cough, upper respiratory tract infection, and vomiting. The Applicant proposed including ARs in the USPI which occurred in >5% of the population and a relative risk of >1.5, the clinical review team agreed with this approach. ARs to be included in the USPI were vomiting, cough, rash, and gastroenteritis.

Overall the safety profile is tolerable. Adverse reactions, including bleeding can be adequately managed.

9. Advisory Committee Meeting and Other External Consultations

This NDA was not taken to an Advisory Committee meeting because no substantial efficacy or safety issues arose during the review of this application which would merit a scientific discussion at an advisory committee meeting.

10. Labeling Recommendations

10.1. Prescription Drug Labeling

Summary of Significant Labeling Changes (High Level Changes)		
Section	Proposed Labeling	Approved Labeling
Highlights, Indications and Usage	No common pediatric adverse reaction data was proposed to be included by the Applicant	The Division requested inclusion of the most common pediatric adverse reactions.
Dosage and Administration (2.2)	Tables provided for recommended dosage in pediatric patients for both indications Added use in renal impairment in pediatric patients	The Division recommended revising tables to include units of measure (i.e., kg) after each numerical value in the "Body weight" column. In addition recommended revising tables to exact body weights to avoid the use of

		symbols. For example, “2.6 to <3 kg” to “2.6 kg to 2.9 kg”. The Division requested the Applicant to specify the renal function estimation equation that was used in clinical trials
Warnings and Precautions (5)	The Applicant proposed to include a statement regarding pediatric populations in which dosing cannot be reliably determined.	The Division recommended moving this information to Dosage and Administration (2.2)
Adverse Reactions (6.1)	The Applicant updated section 6.1 to include adverse reaction from EINSTEIN Jr and UNIVERSE studies.	For the treatment and reduction of risk of VTE the Division made the following recommendations: - Include a statement describing the incidence of menorrhagia - Describe bleeding events in the main treatment period only - Provide a table listing non-bleeding ARs - Include vomiting as a notable AR For thromboprophylaxis in pediatric patients with CHD after the Fontan procedure: - Include a table describing the most common non-bleeding ARs - Group related AR preferred terms
Clinical Studies (14.8)	The Applicant provided described the patient population included in EINSTEIN Jr. The Applicant included a table describing the efficacy results in EINSTIN Jr, this table did not include 95% CI or risk difference.	The Division recommended to state the following important exclusion criteria; Patients <6 months of age were excluded from enrolment if they were <37 weeks of gestation at birth, or had <10 days of oral feeding, or had a body weight of <2.6 kg. The division recommended to include 95% for all response rates and indicate the method in the footnote. In addition, the Division recommended to produce the risk difference and the corresponding 95% CI.

Clinical Studies (14.9)	The Applicant did not include a statement regarding time between Fontan procedure to the first dose of Xarelto. The Applicant included a table describing the efficacy results in EINSTIN Jr, this table did not include 95% CI or risk difference.	The Division recommended including the following; The median time between Fontan procedure and the first dose of XARELTO was 4 (range: 2-61) days in Part A and 34 (range: 2-124) days in part B. In comparison, the median time to initiating aspirin was 24 (range 2-117) days. The Division recommended to add the 95% CI for all the response rates, and also a column of the difference in response rate and the corresponding 95% CI.

10.2. Nonprescription Drug Labeling

Not applicable

11. Risk Evaluation and Mitigation Strategies (REMS)

None

12. Postmarketing Requirements and Commitments

None

13. Appendices

13.1. References

1. Monagle, P., et al., *American Society of Hematology 2018 Guidelines for management of venous thromboembolism: treatment of pediatric venous thromboembolism.* Blood Adv, 2018. 2(22): p. 3292-3316.
2. Witmer, C. and L. Raffini, *Treatment of venous thromboembolism in pediatric patients.* Blood, 2020. 135(5): p. 335-343.
3. Mahajerin, A. and S.E. Croteau, *Epidemiology and Risk Assessment of Pediatric Venous Thromboembolism.* Front Pediatr, 2017. 5: p. 68.
4. Marelli, A.J., et al., *Congenital heart disease in the general population: changing prevalence and age distribution.* Circulation, 2007. 115(2): p. 163-72.
5. Garcia, A.M., J.T. Beatty, and S.J. Nakano, *Heart failure in single right ventricle congenital heart disease: physiological and molecular considerations.* Am J Physiol Heart Circ Physiol, 2020. 318(4): p. H947-H965.
6. Monagle, P., et al., *A multicenter, randomized trial comparing heparin/warfarin and acetylsalicylic acid as primary thromboprophylaxis for 2 years after the Fontan procedure in children.* J Am Coll Cardiol, 2011. 58(6): p. 645-51.
7. Gersony, W.M., *Fontan operation after 3 decades: what we have learned.* Circulation, 2008. 117(1): p. 13-5.
8. Akintoye, E., et al., *National trends in Fontan operation and in-hospital outcomes in the USA.* Heart, 2019. 105(9): p. 708-714.
9. Ohye, R.G., D. Schranz, and Y. D'Udekem, *Current Therapy for Hypoplastic Left Heart Syndrome and Related Single Ventricle Lesions.* Circulation, 2016. 134(17): p. 1265-1279.
10. Akintoye, E., et al., *Optimum age for performing Fontan operation in patients with univentricular heart.* Congenit Heart Dis, 2019. 14(2): p. 138-139.
11. Wallace, M.C., et al., *Center variation in patient age and weight at Fontan operation and impact on postoperative outcomes.* Ann Thorac Surg, 2011. 91(5): p. 1445-52.
12. Viswanathan, S., *Thromboembolism and anticoagulation after Fontan surgery.* Ann Pediatr Cardiol, 2016. 9(3): p. 236-40.
13. Reddy, S., et al., *Proceedings From the 2019 Stanford Single Ventricle Scientific Summit: Advancing Science for Single Ventricle Patients: From Discovery to Clinical Applications.* J Am Heart Assoc, 2020. 9(7): p. e015871.
14. Firdouse, M., et al., *Thrombosis and thromboembolic complications in fontan patients: a literature review.* Clin Appl Thromb Hemost, 2014. 20(5): p. 484-92.
15. Coon, P.D., et al., *Thrombus formation after the Fontan operation.* Ann Thorac Surg, 2001. 71(6): p. 1990-4.
16. McCrindle, B.W., et al., *Challenges and priorities for research: a report from the National Heart, Lung, and Blood Institute (NHLBI)/National Institutes of Health (NIH) Working*

Group on thrombosis in pediatric cardiology and congenital heart disease. Circulation, 2014. 130(14): p. 1192-203.
17. Smith, R., S. Jones, and F. Newall, *Six Weeks Versus 3 Months of Anticoagulant Treatment for Pediatric Central Venous Catheter-related Venous Thromboembolism.* J Pediatr Hematol Oncol, 2017. 39(7): p. 518-523.
18. Alsaied, T., et al., *Strategies for thromboprophylaxis in Fontan circulation: a meta-analysis.* Heart, 2015. 101(21): p. 1731-7.
19. Monagle, P., et al., *Antithrombotic therapy in neonates and children: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines.* Chest, 2012. 141(2 Suppl): p. e737S-e801S.
20. McCrindle, B.W., et al., *Factors associated with thrombotic complications after the Fontan procedure: a secondary analysis of a multicenter, randomized trial of primary thromboprophylaxis for 2 years after the Fontan procedure.* J Am Coll Cardiol, 2013. 61(3): p. 346-53.
21. Giglia, T.M., et al., *Prevention and treatment of thrombosis in pediatric and congenital heart disease: a scientific statement from the American Heart Association.* Circulation, 2013. 128(24): p. 2622-703.
22. Attard, C., et al., *Long-term outcomes of warfarin versus aspirin after Fontan surgery.* J Thorac Cardiovasc Surg, 2021. 162(4): p. 1218-1228 e3.
23. Awtry, E.H. and J. Loscalzo, *Aspirin.* Circulation, 2000. 101(10): p. 1206-18.
24. Ikai, A., et al., *Feasibility of the extracardiac conduit Fontan procedure in patients weighing less than 10 kilograms.* J Thorac Cardiovasc Surg, 2008. 135(5): p. 1145-52.
25. Mosca, R.S., et al., *Early results of the fontan procedure in one hundred consecutive patients with hypoplastic left heart syndrome.* J Thorac Cardiovasc Surg, 2000. 119(6): p. 1110-8.
26. Parasuraman, S. and S.Z. Goldhaber, *Venous thromboembolism in children.* Circulation, 2006. 113(2): p. e12-6.
27. Ankola, A.A., et al., *Early Thromboprophylaxis Initiation is Associated With Reduced Fontan Thromboses in the Early Postoperative Period.* Semin Thorac Cardiovasc Surg, 2021. 33(3): p. 806-813.
28. Lo Rito, M., et al., *Chylothorax and pleural effusion in contemporary extracardiac fenestrated fontan completion.* J Thorac Cardiovasc Surg, 2018. 155(5): p. 2069-2077.
29. Fedderly, R.T., et al., *Factors related to pleural effusions after Fontan procedure in the era of fenestration.* Circulation, 2001. 104(12 Suppl 1): p. I148-51.
30. Lemler, M.S., et al., *Fenestration improves clinical outcome of the fontan procedure: a prospective, randomized study.* Circulation, 2002. 105(2): p. 207-12.

13.2. Financial Disclosure

Covered Clinical Study (Name and/or Number): UNIVERSE

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 36 Principal site investigators		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

Covered Clinical Study (Name and/or Number): EINSTEIN JR

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)

Total number of investigators identified: 796		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 796		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 6		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 6 Proprietary interest in the product tested held by investigator:0 Significant equity interest held by investigator in Sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 8 pages		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

CARRIE E DIAMOND
12/20/2021 10:54:51 AM

ANN T FARRELL
12/20/2021 10:59:04 AM