

## Supplementary Appendix

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

Supplement to: Lassen MR, Raskob GE, Gallus A, Pineo G, Chen D, Portman RJ. Apixaban or enoxaparin for thromboprophylaxis after knee replacement. *N Engl J Med* 2009;361:594-604.

## Appendix 1

- The members of the ADVANCE-1 committees were as follows:

Steering Committee – M. R. Lassen (Study Chair), Department of Orthopaedics, Spine Clinic and Clinical Trial Unit, Hørsholm Hospital, University of Copenhagen, Hørsholm, Denmark; A. Gallus, SA Pathology at Flinders Medical Centre, and Flinders University, Adelaide, Australia; G. Pineo, Department of Medicine and Oncology, University of Calgary, Calgary, Alberta, Canada; G. Raskob, College of Public Health, University of Oklahoma, Health Sciences Center, Oklahoma City, OK, USA

- Data and Safety Monitoring Board – J. Ansell (Chair), Department of Medicine, Lenox Hill Hospital, New York, NY, USA; J. R. Landis, University of Pennsylvania, Philadelphia, PA, USA; C.G. Elliott, University of Utah Medical School, Salt Lake City UT, USA; L. Borris, Department of Orthopedics, University of Aarhus, Aarhus, Denmark; M. Meyer Samama, Service d'hématologie, Hotel Dieu, Paris, France; L.K. Newby, Duke University Medical Center, Durham, NC, USA

- Independent Central Adjudication Committee – McMaster University, Hamilton, Canada; M. Levine (Chair), S. Bates, J.D. Douketis, J. Ginsberg, J. Hirsh, C. Kearon, A. Lee, S. Schulman, J.G. Thomson, A.G.G. Turpie, J. Weitz

**Investigators (in order of numbers of enrolled patients) -** G. Jasey (Dr. Gregory Jasey's Office, Windsor, ON, Canada) D. Stevens (Grand River Hospital, Waterloo, ON, Canada) D. Mackinlay (Dr Duncan Mackinlay's Office, Sarnia, ON, Canada) H. Williams (Capstone Clinical Trials, Inc, Birmingham, AL, USA) C. Lindsay (Dr. Christopher Lindsay, Private Office, Newmarket, ON, Canada) D. Fox (Unlimited Research, San Antonio, TX, USA) D. Armstrong (Dr. Donald Armstrong's Office, Guelph, ON, Canada) M. Jove (Atlanta Knee And Sports Medicine, Decatur, GA, USA) R.M. Murray (Capstone Clinical Trials, Inc, Birmingham, AL, USA) J. Leone (Dr. James Leone, Cambridge, ON, Canada) S.J. Waters (Americana Orthopedics, Boise, ID, USA) G. Jaroszynski (Dr. Grezegorz Jaroszynski, Private Office, Burlington, ON, Canada) F. Abuzgaya (Dr. Fathi Abuzgaya's Office, Ajax, ON, Canada) E. Berumen (Hospital Christus Muguerza Del Parque, Chihuahua, Chihuahua, Mexico) G. Gill (Gill Orthopedic Center, Lubbock, TX, USA) S.J. Siff (Bone & Joint Clinic Of Houston, Houston, TX, USA) E. Lenart (Bacs-Kiskun County Hospital, Kecskemet, , Hungary) D.G. Lorch, Jr. (Pab Clinical Research, Brandon, FL, USA) E. Gomez (Antiguo Hospital Civil De Guadalajara "Fray Antonio Alcalde", Guadalajara, Jalisco, Mexico) G. D'Angelo (Bluegrass Orthopaedics/Bmr, Lexington, KY, USA) M.R.Lassen (Hørsholm Hospital, Hørsholm, Denmark) H. Rosado (Centro Medico Pensiones, Merida, Yucatan, Mexico) J.R. Schwappach (Colorado Orthopedic Consultants, Pc, Aurora, CO, USA) A. Profitt (The Polyclinic Professional Centre, Charlottetown, PE, Canada) A.C. Woods (University Of Alberta Hospital, Edmonton, AB, Canada) A. Borgwardt (Frederiksberg University Hospital, Frederiksberg, , Denmark) P. Blomberg (Avenue Cv Ctr The Avenue Clinic, Windsor, Victoria, Australia) R.G. Josefchak (Dr. Robert Josefchak's Office, St. Catharines, ON, Canada) J.R. Turnbull (Dr. John Turnbull's Office, Chatham, ON, Canada) S. S. Mikkelsen (Regionshospitalet Silkeborg, Silkeborg, Denmark) G. Agar (Assaf Harofeh Medical Center, Zerifin, , Israel) H. Salem (Box Hill Hospital, Box Hill, Victoria, Australia) J.D. Papilion (Jdpmedical Research, Denver, CO, USA) A. Flores (Hospital Rafael Lucio -Centro De Especialidades Médicas, Jalapa, Veracruz, Mexico) C. Buettner (West Alabama Research, Inc., Tuscaloosa, AL, USA) D. Whitaker (Jacksonville Center For Clinical Research, Jacksonville, FL, USA) O. Mendoza (Hosp Universitario Dr Jose Eleuterio Gonzalez, Monterrey, Nuevo Leon, Mexico) A. Dietze (Sykehuset Vestfold Hf Tonsberg, Tonsberg, , Norway) J.A. Saa (Hospital Militar Central, Capital Federal, Buenos Aires, Argentina) B. Edshage (Kungälv Hospital, Kungälv, , Sweden) M. Hollmann (Mark W. Hollmann, MD, Orange City, FL, USA) P.G. Cimbalista De Alencar (Hospital De Clinicas Da Universidade Federal Do Parana, Curitiba, Parana, Brazil) J.B. De Miranda (Unicamp, Campinas, Sao Paulo, Brazil) J. Kassis (Hopital Maisonneuve-Rosemont, Montreal, QC, Canada) L. Bonilla (Hospital Pemex - Cd. Madero, Cd Madero, Tamaulipas, Mexico) C.E. Poole (Intermountain Orthopaedics, Boise, ID, USA) F.H Bello (Clinica Coronel Suarez, Buenos Aires, Buenos Aires, Argentina) R. Pototschnik (Dr. Ralph Pototschnik's Office, Stratford, ON, Canada) P. Holmich (Amager University Hospital, Kopenhagen S, Denmark) A. Hernandez (Hosp. Das Clínicas Da Faculdade De Medicina Da Univ De Sp, São Paulo, Sao Paulo, Brazil) G. De La Mora (Hospital Angeles Tijuana, Tijuana, Baja California, Mexico) J. Gomes (Hospital Das Clínicas De Porto Alegre - Ufrs, Porto Alegre, Rio Grande Do Sul, Brazil) S. Mejdahl (Herlev Hospital, Herlev, Denmark) B. Paulsson (Sjukhuset I Lidköping, Lidköping, Sweden) B.D. Haas (Colorado Joint Replacement, Denver, CO,

USA) N. Rozen (Haemek Medical Center, Afula, Israel) B. Eriksson (Sahlgrenska University Hospital/Ostra, Goteborg, Sweden) J. Sjogren (Sjukhuset Varberg, Varberg, Sweden) R.L. Kruse (Orthopaedic Physicians Of Colorado, P.C., Englewood, CO, USA) L. Flores (Greater Niagara General Hospital, Niagara Falls, ON, Canada) R. King (Robert R. King, MD, Lubbock, TX, USA) W. Bowen (Martin Bowen Hefley Orthopedics, Little Rock, AR, USA) A. Makino (Hospital Italiano De Buenos Aires, Buenos Aires, Buenos Aires, Argentina) G. Kuropatkin (Samara Regional Clinical Hospital M.I. Kalinin, Samara, Russian Federation) C. Andersson (Motala Lasarett, Motala, Sweden) S. Hakki (Bay Pines VA Medical Center, Bay Pines, FL, USA) K. Krumins (Jewett Orthopaedic Clinic, Winter Park, FL, USA) B.R. Duus (Bispebjerg Hospital, Copenhagen Nv, Denmark) B. Brenner (Rambam Medical Center, Haifa, Israel) K. Kwiatkowski (Wim Centralny Szpital Kliniczny Mon Klinika Ortopedii, Warszawa, Poland) P. Stalley (Royal Prince Alfred Inst. Of Rheumatology And Orthopaedics, Camperdown, New South Wales, Australia) W.A. Pisesky (Dr. Wayne Pisesky's Office, Kelowna, ON, Canada) A. Wykman (Lanssjukhuset Halmstad, Halmstad, Sweden) O. Skoldenberg (Danderyds Sjukhus, Danderyd, Sweden) P.S. Ali (Dr. Pervez Ali's Office, Scarborough, ON, Canada) E. Belzile (Hopital St-Francois D'Assise Du Chuq, Quebec, QC, Canada) J.F. Basulto (Hospital Star Medica Merida, Merida, Yucatan, Mexico) M. Synder (Wojewodzkie Centrum Ortopedii I Rehabilitacji Narzadu Ruchu, Lodz, Poland) J. Skowronski (Spsk Am W Bialymstoku Klinika Ortopedii I Traumatologii, Bialystok, , Poland) J.G. Guerra (Dr. Jose Guerra's Office, Scarborough, ON, Canada) J. Perez (Hospital De Traumatología Y Ortopedia M.De Las Salinas, Df, Distrito Federal, Mexico) T. Niedzwiedzki (Wojewodzki Szpital Specjalistyczny Oddz.Ortopedii I Traumat., Krakow, Poland) D.X. Cruz Sanchez (Hospital Regional "Adolfo López Mateos" Issste, Df, Distrito Federal, Mexico) A. Bohatyrewicz (Spsk Nr 1 Im.Sokolowskiego Klinika Ortopedii I Traumatologii, Szczecin, Poland) T. Mazurkiewicz (Spsk Nr 4 W Lublinie Klinika Ortopedii I Traumatologii, Lublin, Poland) B. Richards (Gold Coast Hospital, Gold Coast, Queensland, Australia) M.A. Teloken (Santa Casa De Misericordia De Porto Alegre, Porto Alegre, Rs, Rio Grande Do Sul, Brazil) O.F Bilgen (Uludag Universitesi Tip Fakultesi, Bursa, Turkey) C. Yilmaz (Mersin Universitesi Tip Fakultesi, Mersin, Turkey) R. Baker (Royal Perth Hospital, Perth, Western Australia, Australia) D. Jackson (Lismore Base Hospital, Lismore, New South Wales, Australia) M. Salai (Rabin Medical Center, Petach-Tikva, Israel) L. Garcia (Hospital Imss #21, Monterrey, Nuevo Leon, Mexico) H. Hendler (Instituto Dupuytren, Capital Federal, Buenos Aires, Argentina) J.M. Ceresetto (Hospital Britanico, Buenos Aires, Buenos Aires, Argentina) L. Samson (Mav Korhaz Es Rendelointezet Szolnok, Szolnok, Hungary) C. Lewis (Orthopedics Assocs Of Hartford, Hartford, CT, USA) U. Al Fahd (Ross Memorial Hospital, Lindsay, ON, Canada) V. Benkovich (Soroka University Medical Center, Beer-Sheva, Israel) A.E Graves (Pab Clinical Research, Brandon, FL, USA) C. Cameron (Dr. Christopher Cameron's Office, Nanaimo, ON, Canada) C. Tauber (Kaplan Medical Center, Rehovot, Israel) J.J Gomez (Centro Medico Abc, Df, Distrito Federal, Mexico) O. Talsnes (Sykehuset Innlandet Hf Elverum-Hamar, Elverum, Norway) R. Friedman (Charleston Orthopaedic Assocs., Charleston, SC, USA) H. A. Caviglia (Hospital Juan A. Fernandez, Buenos Aires, Buenos Aires, Argentina) J-P. Faucher (Hopital Charles Lemoyne (Cicm), Greenfield Park, QC, Canada) M. Malo (Hopital Du Sacre-Coeur De Montreal, Montreal, QC, Canada) C-G Forsberg (Sykehuset

*Innlandet Hf Tynset, Tynset, Norway) P. Skowronek (Katedra I Klinika Ortopedii I Traumatologii Narzadu Ruchu Am, Warszawa, Poland) A. Abolin (Hospital Of St. Elizabeth, St. Petersburg, Russian Federation) N. Goncharov (Central Clinical Hospital Russian Academy Of Science, Moscow Russian Federation) Y. Sarpel (Cukurova Universitesi Tip Fakultesi, Adana, Turkey) G.C. Landon (Kelsey Seybold Clinic, Houston, TX, USA) L. Bucsi (Szt.Gyorgy Hospital, Szekesfehervar, Hungary) K.E. Hansen (Sykehuset Buskerud, Drammen, Norway) L. Ahnfelt (Falkoping Hospital, Falkoping, Sweden) S. Minoldo (Sanatorio Allende, Cordoba, Cordoba, Argentina) B.H. Chong (Sutherland Hospital, Caringbah, New South Wales, Australia) I. Prosser (The Canberra Hospital, Garran, Act, Australia) H. Salem (Epworth Eastern Hospital, Box Hill, Victoria, Australia) D. Legay (Capital Health - Dartmouth General, Dartmouth, ON, Canada) A. Winder (Wolfson Medical Center, Holon, Israel) M. Nyska (Meir Medical Center, Kfar-Saba, , Israel) A.S. Unger (Anthony S. Unger, MD, Washington, DC, USA) C. Onder (Karadeniz Teknik Universitesi Tip Fakultesi Farabi Hastanesi, Trabzon, Turkey) W. Bowen (Martin Bowen Hefley Orthopedics, Little Rock, AR, USA) A. Gallus (Southpath Flinders Medical Centre, Bedford Park, South Australia, Australia) S. Mcrae (The Queen Elizabeth Hospital, Adelaide, South Australia, Australia)*

## **Appendix 2**

### **Inclusion Criteria**

#### **Signed written informed consent**

1) Subjects had to be willing and able to give written informed consent. Consent to participate in the study had to be obtained prior to any screening.

#### **Target population**

2) Subjects undergoing either elective unilateral or same-day bilateral total knee replacement or a revision of at least one component of a total knee replacement.

3) Subject had to be willing and able\* to undergo bilateral ascending contrast venography.

\* **Note:** Unless investigator/radiologist could assure that a bilateral venogram could be performed, subjects exceeding 300 lbs (136 kg) and/or body mass index  $\geq 35$  kg/m<sup>2</sup> were excluded because of technical limitations due to body habitus.

#### **Age and Sex**

4) Men and women, of any race, aged at least 18 (or legal age of consent if greater) years.

5) Women of childbearing potential (WOCBP) must have used an adequate method of contraception to avoid pregnancy throughout the treatment period of the study or for 2 weeks after the last dose of study drug, whichever was longer, in such a manner that the risk of pregnancy was minimized.

WOCBP included any female who had experienced menarche and who had not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation

or bilateral oophorectomy) or was not postmenopausal [defined as amenorrhea  $\geq 12$  consecutive months; or women on hormone replacement therapy (HRT) with documented serum follicle stimulating hormone level  $>35$  mIU/ml]. Even women who were using oral, implanted, or injectable contraceptive hormones or mechanical products such as an intrauterine device or barrier methods (diaphragm, condoms, spermicides) to prevent pregnancy or practicing abstinence or where partner was sterile (eg, vasectomy), were considered to be of childbearing potential. WOCBP must have had a negative serum or urine pregnancy test (minimum sensitivity 25 IU/l or equivalent units of HCG) within 48 hours prior to the start of study drug.

## **Exclusion Criteria**

### **Sex and Reproductive Status**

- 1) WOCBP who were **unwilling or unable** to use an acceptable method to avoid pregnancy for the entire treatment period of the study or for 2 weeks after the last dose of study drug, whichever was longer.
- 2) Women with a positive pregnancy test on enrollment or prior to study drug administration.
- 3) Women who were pregnant or breastfeeding.
- 4) WOCBP using a prohibited contraceptive method.

### **Medical History and Concurrent Diseases**

- 5) Hereditary (first degree) or acquired bleeding or coagulation disorder.
- 6) Known or suspected history of heparin-induced thrombocytopenia.

- 7) Need for ongoing treatment with a parenteral or oral anticoagulant (eg, subjects with mechanical valves, warfarin-eligible atrial fibrillation).
- 8) Known coagulopathy.
- 9) Active bleeding or at high risk for bleeding.
- 10) Brain, spinal, ophthalmologic, or major surgery or trauma within the past 90 days.
- 11) Two consecutive blood pressure readings within 15 to 30 minutes with supine systolic blood pressure >180 mm Hg or supine diastolic blood pressure >105 mm Hg (ie, initial reading above the limit is confirmed by a second reading).
- 12) Active hepatobiliary disease.
- 13) Alcohol and/or substance abuse within the past year.
- 14) Any condition, in the opinion of the investigator, for which surgery or administration of an anticoagulant was contraindicated.

### **Physical and Laboratory Test Findings**

- 15) Clinically significant laboratory abnormalities at enrollment visit.
  - Hemoglobin <10 g/dl.
  - Platelet count <100,000/mm<sup>3</sup>.
  - Creatinine clearance <30 mL/min as estimated by the method of Cockcroft and Gault.
  - ALT or AST >2 × upper limit of normal (ULN)
  - Total bilirubin ≥1.5 × ULN (unless an alternative causative factor such as Gilbert's syndrome was identified).

### **Allergies and Adverse Drug Reactions**

16) Hypersensitivity to unfractionated heparin, low molecular weight heparin, porcine products, or iodinated contrast medium.

### **Prohibited Therapies and/or Medications**

17) Current use of dextrans or fibrinolytics.

18) Treatment with medications affecting coagulation or platelet function unless they could be withdrawn as follows:

- Unfractionated heparin, low molecular weight heparin, warfarin (or any other vitamin K antagonists), glycoprotein IIb/IIIa inhibitors (eg, abciximab, eptifibatide, tirofiban) at least 4 days before surgery
- Clopidogrel, ticlopidine, dipyridamole, sulfipyrazone at least 7 days before surgery
- Nonselective nonsteroidal anti-inflammatory drugs with a half-life greater than 17 hours (eg, piroxicam and tinoxican) at least 7 days before surgery
- Fondaparinux at least 7 days before surgery
- Aspirin >165 mg/d at least 4 days before surgery.

### **Other Exclusion Criteria**

19) Prisoners or subjects who were compulsorily detained (involuntarily incarcerated) for treatment of either a psychiatric or physical (eg, infectious disease) illness.

20) Subjects who had been previously randomized into an apixaban clinical trial.

21) Administration of any investigational drug currently or within 30 days prior to enrollment into this study.

22) Subjects unwilling or unable to comply with study drug instructions or study procedures (eg, bilateral ascending contrast venography) specified in the protocol.

## **Bleeding Criteria**

### **Major Bleeding Criteria**

- Acute clinically overt bleeding was defined as new-onset, visible bleeding or signs or symptoms suggestive of bleeding with confirmatory imaging techniques which can detect the presence of blood
- Acute clinically overt bleeding accompanied by one or more of the following:
  - ◆ A decrease in hemoglobin of 2 g/dl or more over a 24-hour period
  - ◆ A transfusion of 2 or more units of packed red blood cells
  - ◆ Bleeding that occurred in at least one of the following critical sites:
    - Intracranial
    - Intraspinal
    - Intraocular (not conjunctival)
    - Pericardial
    - An operated joint and required reoperation or intervention
    - Intramuscular with compartment syndrome
    - Retroperitoneal

- ◆ Fatal bleeding

### **Clinically Relevant Nonmajor Bleeding:**

- Defined as acute clinically overt bleeding that did not satisfy any of the additional criteria to be defined as a major bleeding event and met at least one of the following criteria:
  - ◆ Epistaxis: requiring physician visit or intervention
  - ◆ Gastrointestinal bleed: endoscopically confirmed, hematemesis or melena
  - ◆ Hematuria: overt spontaneous bleeding persisting >24 after instrumentation
  - ◆ Bruising/ecchymosis: unusual
  - ◆ Hematoma: collection of blood associated with surgical wound
  - ◆ Hemoptysis.

### **Minor Bleeding**

- Clinically overt bleeding event that does not meet the criteria for either a major bleeding event or a clinically relevant nonmajor bleeding event.

## Supplemental Table 1

### Efficacy Outcomes During the Intended Treatment Period (per-protocol analysis)

Outcome	Apixaban	Enoxaparin	Relative Risk (RR) Apixaban/Enoxaparin	P Value	Absolute Risk Difference	P Value
All VTE and all-cause death <sup>a</sup> , n	99/1104 Rate: 8.97% Rate 95% CI: 7.42 to 10.81	95/1062 Rate: 8.95% Rate 95% CI: 7.37 to 10.83	1.01  RR 95% CI: 0.77 to 1.32	0.06 <sup>b</sup>	0.03  Risk Difference 95% CI: -2.38 to 2.43	<0.001 <sup>c</sup>
Major VTE <sup>d</sup> , or death from any cause, n	25/1099 Rate: 2.27% Rate 95% CI: 1.53 to 3.36	19/1047 Rate: 1.81% Rate 95% CI: 1.15 to 2.85	1.27  RR 95% CI: 0.7 to 2.29	0.79 <sup>e</sup>	0.47  Risk Difference 95% CI: -0.72 to 1.65	Not tested

<sup>a</sup> Data Set = evaluable subjects.

One-sided P value for noninferiority test on relative risk<sup>b</sup> or on absolute risk difference.<sup>c</sup>

<sup>d</sup> Major VTE defined as proximal DVT, nonfatal pulmonary embolism, and fatal pulmonary embolism.

<sup>e</sup> One-sided P value for superiority test on relative risk.

**Supplemental Table 2**

**Adverse events reported by investigators during the treatment period (not including study end points)**

	<b>Apixaban 2.5 mg twice daily</b>	<b>Enoxaparin 30 mg every 12 hours</b>
	<b>N=1596</b>	<b>N=1588</b>
<b>Adverse events (%)</b>	1149 (72.0%)	1172 (73.8%)
<b>AEs occurring in ≥5% of patients</b>		
Constipation	227 (14.2%)	234 (14.7%)
Nausea	208 (13.0%)	242 (15.2%)
Pyrexia	138 (8.6%)	152 (9.6%)
Edema (peripheral)	133 (8.3%)	154 (9.7%)
Dizziness	103 (6.5%)	88 (5.5%)
Vomiting	99 (6.2%)	102 (6.4%)
Pain in extremity	86 (5.4%)	79 (5.0%)
Insomnia	77 (4.8%)	86 (5.5%)
<b>Serious Adverse Events (%)*</b>	123 (7.7%)	123 (7.7%)
<b>Drug Related SAE (%)*</b>	15 (0.9%)	26 (1.6%)
<b>Drug Related AE (%)</b>	327 (20.5%)	344 (21.7%)
<b>Discontinuations due to AE (%)</b>	60 (3.8%)	58 (3.7%)
<b>Bleeding AE (%)</b>	110 (6.9%)	144 (9.1%)

\* No non-endpoint SAE occurred in ≥1% of patients

**Supplemental Table 3**

**Reasons for missing end-of-treatment venograms during intended treatment period – randomized subjects  
not included in primary efficacy analysis**

	<b>Apixaban 2.5 mg twice daily</b>	<b>Enoxaparin 30 mg every 12 hours</b>
	n=442	n=466
Subjects with missing venogram on both legs, n (%)	169 (38.2)	192 (41.2)
Left leg – reasons		
Attempted but failed to access vein, n (%)	53 (12.0)	49 (10.5)
Attempted but could not complete procedure, n (%)	9 ( 2.0)	8 (1.7)
Not attempted – investigator's decision, n (%)	14 (3.2)	16 (3.4)
Not attempted – subject refused/withdrew consent, n (%)	50 (11.3)	66 (14.2)
Not attempted – other reason, n (%)	21 (4.8)	34 (7.3)
Done after end of intended treatment period, n (%)	8 (1.8)	6 (1.3)
Not reported, n (%)	14 (3.2)	13 (2.8)
Right leg – reasons		

Attempted but failed to access vein, n (%)	54 (12.2)	59 (12.7)
Attempted but could not complete procedure, n (%)	10 (2.3)	8 (1.7)
Not attempted – investigator’s decision, n (%)	13 (2.9)	16 (3.4)
Not attempted – subject refused/withdrew consent, n (%)	50 (11.3)	63 (13.5)
Not attempted – other reason, n (%)	22 (5.0)	30 (6.4)
Done after end of intended treatment period, n (%)	7 (1.6)	5 (1.1)
Not reported, n (%)	13 (2.9)	11 (2.4)

**Supplemental Table 4**

**Assumed rate of primary efficacy endpoint in sensitivity analysis adjusted for missing values during intended treatment period – primary subjects and non-primary subjects.**

Apixaban	Enoxaparin	Measure	Non-inferiority Ratio	Non-inferiority Difference	Superiority
0%	0%	Point estimate	1.038	0.002	1.038
		Two-sided 95% CI	0.796 to 1.354	-0.015 to 0.019	0.796 to 1.354
		One-sided P value	0.0853	<0.0001	0.6097
	5%	Point estimate	0.844	-0.012	0.844
		Two-sided 95% CI	0.656 to 1.086	-0.030 to 0.0006	0.656 to 1.086
		One-sided P value	0.0010	<0.0001	0.0933

	10%	Point estimate	0.706	-0.027	0.706
		Two-sided 95% CI	0.555 to 0.899	-0.046 to -0.009	0.555 to 0.899
		One-sided P value	<0.0001	<0.0001	0.0023
5%	0%	Point estimate	1.258	0.016	1.258
		Two-sided 95% CI	0.977 to 1.620	-0.002 to 0.034	0.977 to 1.620
		One-sided P value	0.5204	<0.0001	0.9627
	5%	Point estimate	1.023	0.001	1.023
		Two-sided 95% CI	0.806 to 1.298	-0.017 to 0.020	0.806 to 1.298
		One-sided P value	0.0494	<0.0001	0.5735
	10%	Point estimate	0.856	-0.014	0.856

		estimate			
		Two-sided	0.682 to	-0.033 to 0.006	0.682 to
		95% CI	1.075		1.075
		One-sided	0.0005	<0.0001	0.0898
		P value			
	15%	Point estimate	0.740	-0.028	0.740
		Two-sided	0.594 to	-0.048 to -	0.594 to
		95% CI	0.922	0.008	0.922
		One-sided	<0.0001	<0.0001	0.0035
		P value			
10%	5%	Point estimate	1.201	0.015	1.201
		Two-sided	0.956 to	-0.004 to 0.035	0.956 to
		95% CI	1.510		1.510
		One-sided	0.3669	<0.0001	0.9422
		P value			
	10%	Point estimate	1.005	0.000	1.005

		Two-sided	0.809 to	-0.020 to 0.020	0.809 to
		95% CI	1.249		1.249
		One-sided	0.0245	<0.0001	0.5186
		P value			
	15%	Point estimate	0.869	-0.014	0.869
		Two-sided	0.705 to	-0.035 to 0.007	0.705 to
		95% CI	1.071		1.071
		One-sided	0.0003	<0.0001	0.0942
		P value			
	20%	Point estimate	0.762	-0.029	0.762
		Two-sided	0.622 to	-0.051 to -	0.622 to
		95% CI	0.932	0.0008	0.932
		One-sided	<0.0001	<0.0001	0.0041
		P value			
15%	15%	Point estimate	0.998	-0.000	0.998
		Two-sided	0.817 to	-0.022 to 0.021	0.817 to

		95% CI	1.221		1.221
		One-sided P value	0.0140	<0.0001	0.4937
	20%	Point estimate	0.875	-0.015	0.875
		Two-sided 95% CI	0.721 to 1.062	-0.037 to 0.007	0.721 to 1.062
		One-sided P value	0.0001	<0.0001	0.0881
	25%	Point estimate	0.782	-0.030	0.782
		Two-sided 95% CI	0.648 to 0.944	-0.053 to - 0.007	0.648 to 0.944
		One-sided P value	<0.0001	<0.0001	0.0052
20%	15%	Point estimate	1.133	0.014	1.133
		Two-sided 95% CI	0.933 to 1.376	-0.008 to 0.036	0.933 to 1.376

		One-sided P value	0.1617	0.0001	0.8972
	20%	Point estimate	0.933	-0.001	0.933
		Two-sided 95% CI	0.824 to 1.197	-0.024 to 0.021	0.824 to 1.197
		One-sided P value	0.0078	<0.0001	0.4718
	25%	Point estimate	0.888	-0.016	0.888
		Two-sided 95% CI	0.741 to 1.064	-0.039 to 0.008	0.741 to 1.064
		One-sided P value	<0.0001	<0.0001	0.0990
25%	20%	Point estimate	1.101	0.012	1.101
		Two-sided 95% CI	0.919 to 1.320	-0.011 to 0.035	0.919 to 1.320
		One-sided P value	0.0857	0.0001	0.8514

		P value			
	25%	Point estimate	0.985	-0.002	0.985
		Two-sided 95% CI	0.826 to 1.174	-0.026 to 0.021	0.826 to 1.174
		One-sided P value	0.0038	<0.0001	0.4309
	100%	Point estimate	0.377	-0.221	0.377
		Two-sided 95% CI	0.328 to 0.435	-0.250 to -0.192	0.328 to 0.435
		One-sided P value	<0.0001	<0.0001	<0.0001
100%	25%	Point estimate	2.512	0.205	2.512
		Two-sided 95% CI	2.181 to 2.893	0.177 to 0.234	2.181 to 2.893
		One-sided P value	1.0000	1.0000	1.0000

	100%	Point estimate	0.963	-0.013	0.963
		Two-sided 95% CI	0.876 to 1.059	-0.046 to 0.020	0.876 to 1.059
		One-sided P value	<0.0001	<0.0001	0.2180