Supplementary Appendix

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

Supplement to: Johnston SC, Amarenco P, Albers GW, et al. Ticagrelor versus aspirin in acute stroke or transient ischemic attack. N Engl J Med 2016;375:35-43. DOI: 10.1056/NEJMoa1603060

Contents

APPENDIX A – COMMITTEES, LEADERSHIP AND INVESTIGATORS

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Sponsor Leadership

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Steering Committee

J. Donald Easton, MD, (Chairman), Executive Committee Members, National Lead Investigators: Sebastiá F. Ameriso (Argentina), Geoffrey Donnan (Australia), Robin Lemmens (Belgium), Ayrton Massaro (Brazil), Ekaterina Titianova (Bulgaria), Michael D. Hill (Canada), Pablo Lavados (Chile), Yongjun Wang (China), David Skoloudik (Czech Republic), Pierre Amarenco (France), Joachim Röther (Germany) KS Lawrence Wong (Hong Kong), Szegedi Norbert (Hungary), Giancarlo Agnelli (Italy), Natan Bornstein (Israel), Norio Tanahashi (Japan), Angel Arauz Góngora (Mexico), Edwin Pretell (Peru), Maria Cristina Z. San Jose (Philippines), Anna Czlonkowska (Poland), Ovidiu Bajenaru (Romania), Ludmila Stakhovskaya (Russia), Miroslav Brozman (Slovakia), Jong-Sung Kim (South Korea), Carlos A. Molina (Spain), Nils Wahlgren (Sweden), Patrik Michel (Switzerland), Tsong Hai Lee (Taiwan), Nijasri Charnnarong Suwanwela (Thailand), Kursad Kutluk (Turkey), Sergii Moskovko (Ukraine), Scott Kasner (United States), Daniel Laskowitz (United States) Wayne Clark (United States), Huy Thang Nguyen (Vietnam).

Independent Data Monitoring Committee

Ralph L. Sacco, MD, FAHA (Chairman), Jonathan L. Halperin, MD, Bo Norrving, MD, PhD, Bruce Ovbiagele, MD, Stuart Pocock, MSc, PhD, David V. Glidden, PhD (non-voting, Statistical Data Analysis Centre Statistician)

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APPENDIX B

Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
• Men or women aged ≥40 years • Acute ischemic stroke or high-risk TIA • Able to be randomized within 24 hours after the onset of symptoms • Able to provide informed consent • Head CT or MRI ruling out hemorrhage or other pathology, such as vascular malformation, tumor, or abscess that could explain symptoms or contraindicate therapy	• Planned use of antithrombotic therapy in addition to study medication, including antiplatelets (e.g. open-label aspirin, GPIIb/IIIa inhibitors, clopidogrel, ticlopidine, prasugrel, dipyridamole, ozagrel, cilotazol) and anticoagulants (e.g. warfarin, oral thrombin and factor Xa inhibitors, bivalirudin, hirudin, argatroban, unfractionated and low molecular weight heparins) • Patients receiving or requiring dual antiplatelet therapy with aspirin and $P2Y_{12}$ inhibitors • Known hypersensitivity to ticagrelor or aspirin • Any history of AF, ventricular aneurysm, or suspicion of cardioembolic pathology for TIA or stroke • Planned carotid, cerebrovascular, or coronary revascularization that requires halting study medication within 7 days of randomization • Receipt of any IV or intra-arterial thrombolysis or mechanical thrombectomy within 24 hours prior to randomization • Anticipated concomitant oral or IV therapy with strong CYP3A inhibitors or substrates with narrow therapeutic indices that cannot be stopped for the course of the study

	• Anticipated requirement for long-term (>7 days) NSAIDs • Known bleeding diathesis or coagulation disorders (e.g. TTP) • History of previous symptomatic non-traumatic intracerebral bleeding at any time (asymptomatic microbleeds do not qualify), GI bleeding within past 6 months or major surgery within 30 days • Known severe liver disease (e.g. ascites or signs of coagulopathy) • Renal failure requiring dialysis • Pregnancy or lactation • Participation in another clinical trial with an investigational product during the last 30 days • Previous enrolment or randomization in SOCRATES • Inability to understand and/or comply with study procedures

Abbreviations: AF = atrial fibrillation; CT = computed tomography; CYP = cytochrome P450 enzymes; GI = gastrointestinal; GP = glycoprotein; IV = intravenous; MRI = magnetic resonance imaging; NSAID = non-steroidal anti-inflammatory drug; TIA = transient ischemic attack; TTP = thrombotic thrombocytopenic purpura

Definitions of acute ischemic stroke and high-risk TIA in the SOCRATES trial

Acute ischemic stroke	**High-risk TIA**
• Neurological deficit attributed to the focal brain ischemia AND either of the following: o Persistent signs or symptoms of the ischemic event at the time of randomization ***OR*** o Acute ischemic brain lesion documented by CT scan or MRI (diffusion-weighted imaging) within 24 hours of onset of symptoms • NIHSS score ≤5	• Neurological deficit of acute onset attributed to focal ischemia of the brain AND at least 1 of the following: o $ABCD^2$ score ≥4 and TIA symptoms not limited to isolated numbness, isolated visual changes, or isolated dizziness/vertigo o Symptomatic intracranial arterial occlusive disease documented by transcranial Doppler ultrasound or vascular imaging, defined as ≥50% narrowing in diameter of a vessel that could account for the clinical presentation o Documented internal carotid arterial occlusive disease, defined as ≥50% narrowing in diameter of a vessel that could account for the clinical presentation

Abbreviations: $ABCD^2$ = age, blood pressure, clinical features, duration of TIA, presence of diabetes; CT = computed tomography; MRI = magnetic resonance imaging; NIHSS = National Institute of Health Stroke Scale; TIA = transient ischemic attack

APPENDIX C
Endpoint definitions

DEATH

- Cardiovascular death includes sudden cardiac death, death due to acute MI, death due to heart failure, death due to stroke, death due to other cardiovascular causes (eg. dysarrhythmia unrelated to sudden cardiac death, pulmonary embolism, cardiovascular intervention [other than one related to an AMI - Acute myocardial infarction], aortic aneurysm rupture, or peripheral artery disease), and deaths for which there was no clearly documented non-cardiovascular cause (presumed CV death). Death due to intracranial haemorrhage (including fatal haemorrhagic stroke) will be considered CV death.
- Additionally, CV deaths will be sub-classified by coronary heart disease (CHD) death and non-CHD death. CHD death includes sudden cardiac death, death due to acute MI, and the subset of death due to other cardiovascular causes that are secondary to a coronary revascularization procedure.
- Non-cardiovascular death includes death due to haemorrhage (including gastrointestinal bleeding), pulmonary causes (respiratory failure, pneumonia) malignancy, trauma, suicide, infection/sepsis or any other clearly defined cause (eg. liver failure or renal failure).
- Deaths with unknown/uncertain cause will be categorised as cardiovascular death and included in the primary composite endpoint. Any death with unknown/uncertain cause within 30 days of a stroke, MI or procedure/surgery will be considered a death due to the stroke, MI or procedure/surgery, respectively.

MYOCARDIAL INFARCTION

Criteria for acute myocardial infarction: Third universal definition (Thygesen 2012)

The term acute MI should be used when there is evidence of myocardial necrosis in a clinical setting consistent with acute myocardial ischemia. Under these conditions any one of the following criteria meets the diagnosis for MI:

- Detection of a rise and/or fall of cardiac biomarker values (preferably cardiac troponin [cTn]) with at least one value above the 99th percentile upper reference limit (URL) and with at least one of the following:
    - Symptoms of ischaemia.
    - New or presumed new significant ST-segment–T wave (ST–T) changes or new left bundle branch block (LBBB)
    - Development of pathological Q waves in the ECG
    - Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality
    - Identification of an intracoronary thrombus by angiography or autopsy

- Cardiac death with symptoms suggestive of myocardial ischaemia and presumed new ischaemic ECG changes or new LBBB, but death occurred before cardiac biomarkers were obtained, or before cardiac biomarker values would be increased
- PCI-related MI is arbitrarily defined by elevation of cTn values (>5 x 99th percentile URL) in patients with normal baseline values (≤99th percentile URL) or a rise of cTn values >20% if the baseline values are elevated and are stable or falling. In addition, either (i) symptoms suggestive of myocardial ischaemia or (ii) new ischaemic ECG changes or (iii) angiographic findings consistent with a procedural complication, or (iv) imaging demonstration of new loss of viable myocardium or new regional wall motion abnormality are required
- Stent thrombosis associated with MI when detected by coronary angiography or autopsy in the setting of myocardial ischaemia and with a rise and/or fall of cardiac biomarker values with at least one value above the 99th percentile URL
- CABG- related MI is arbitrarily defined by elevation of cardiac biomarker values (>10 x 99th percentile URL) in patients with normal baseline cTn values (≤99th percentile URL). In addition, either (i) new pathological Q waves or new LBBB, or (ii) angiographic documented new graft or new native coronary artery occlusion, or (iii) imaging evidence of new loss of viable myocardium or new regional wall motion abnormality

Criteria for prior myocardial infarction

Any one of the following criteria meets the diagnosis for prior MI:

- Pathological Q waves with or without symptoms in the absence of non-ischaemic causes
- Imaging evidence of a region of loss of viable myocardium that is thinned and fails to contract, in the absence of a non-ischaemic cause
- Pathological findings of a prior MI

Type 1: Spontaneous MI

- Spontaneous myocardial infarction related to atherosclerotic plaque rupture, ulceration, fissuring, erosion, or dissection with resulting intraluminal thrombus in one or more of the coronary arteries leading to decreased myocardial blood flow or distal platelet emboli with ensuing myocyte necrosis. The patient may have underlying severe CAD but on occasion non-obstructive or no CAD

Type 2: Myocardial infarction secondary to an ischaemic imbalance

- In instances of myocardial injury with necrosis where a condition other than CAD contributes to an imbalance between myocardial oxygen supply and/or demand, eg. coronary endothelial dysfunction, coronary artery spasm, coronary embolism, tachy-/brady-arrhythmias, anaemia, respiratory failure, hypotension, and hypertension with or without left ventricular hypertrophy

Type 3: Myocardial infarction resulting in death when biomarker values are unavailable

- Cardiac death with symptoms suggestive of myocardial ischemia and presumed new ischaemic ECG changes or new LBBB, but death occurring before blood samples could be obtained, before cardiac biomarker could rise, or in rare cases cardiac biomarkers were not collected

Type 4a: Myocardial infarction related to percutaneous coronary intervention (PCI)

- Myocardial infarction associated with PCI is arbitrarily defined by elevation of cTn values >5 x 99th percentile URL in patients with normal baseline values (<99th percentile URL) or a rise of cTn values >20% if the baseline values are elevated and are stable or falling. In addition, either (i) symptoms suggestive of myocardial ischaemia, or (ii) new ischaemic ECG changes or new LBBB, or (iii) angiographic loss of patency of a major coronary artery or a side branch or persistent slow- or no-flow or embolization, or (iv) imaging demonstration of new loss of viable myocardium or new regional wall motion abnormality are required

Type 4b: Myocardial infarction related to stent thrombosis

- Myocardial infarction associated with stent thrombosis is detected by coronary angiography or autopsy in the setting of myocardial ischaemia and with a rise and/ or fall of cardiac biomarkers values with at least one value above the 99th percentile URL

Type 5: Myocardial infarction related to coronary artery bypass grafting (CABG)

- Myocardial infarction associated with CABG is arbitrarily defined by elevation of cardiac biomarker values >10 x 99th percentile URL in patients with normal baseline cTn values (<99th percentile URL). In addition, either (i) new pathological Q waves or new LBBB, or (ii) angiographic documented new graft or new native coronary artery occlusion, or (iii) imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.

STROKE

A stroke is defined as an acute episode of neurological dysfunction caused by focal or global brain, spinal cord, or retinal vascular injury.

Stroke will be further sub-classified as:

Ischaemic stroke: An acute focal infarction of the brain or retina (and does not include anterior ischaemic optic neuropathy [AION]).

Criteria:

1. Rapid onset of a new focal neurological deficit with clinical or imaging evidence of infarction and not attributable to a non-ischaemic etiology (not associated with brain infection, trauma, tumour, seizure, severe metabolic disease, or degenerative neurological disease); or,

2. Rapid worsening of an existing focal neurological deficit that is judged by the Investigator to be attributable to a new infarction. Criteria for symptoms attributable to new infarction *may*

include symptoms that persist and are judged by the investigator to be attributable to new infarction, imaging evidence of infarction, or no evidence of a non-ischaemic etiology.

TIA: A neurological deficit of sudden onset, resolving completely, attributed to focal brain or retinal ischaemia without evidence of associated acute focal infarction of the brain.

Criteria: Rapid onset of a focal neurological deficit that is without evidence of acute focal infarction of the brain, and is not attributable to a non-ischaemic etiology (brain infection, trauma, tumour, seizure, severe metabolic disease, or degenerative neurological disease)

Unknown/No imaging performed: If the type of stroke could not be determined by imaging or other means (from lumbar puncture, neurosurgery, or autopsy) but is judged to fulfil the stroke definition above, the stroke will be classified as ischaemic for purposes of the study.

Haemorrhagic stroke: Haemorrhagic stroke is defined as an acute episode of focal or global cerebral or spinal dysfunction caused by a nontraumatic intraparenchymal, intraventricular, or subarachnoid haemorrhage.

Cerebral microbleeds: SOCRATES defines a cerebral microbleed as <10 mm in greatest diameter on gradient recalled echo (GRE), or T2*, MRI sequences. Any blood visualized on a CT will be classified as a macrobleed. Microbleeds are incidental findings that are neither an exclusion criterion nor an outcome or adverse event. Rarely, a microbleed may occur in a strategic location and cause focal neurologic symptoms and/or signs in which case it will be reported as a stroke endpoint (haemorrhagic stroke) and bleeding event (intracerebral haemorrhage).

If an asymptomatic microbleed is inadvertently reported, it will be adjudicated in the same way but if the adjudicators judges it to be asymptomatic, and therefore an incidental finding, they will classify it as a “no event” and “no bleeding event”.

Ischaemic strokes with haemorrhagic transformation: Haemorrhagic transformation will be adjudicated to a new ischemic stroke endpoint with haemorrhagic transformation OR a haemorrhagic transformation of index stroke event.

In addition, a confirmed haemorrhagic transformation will be sub-classified by adjudicators to symptomatic OR asymptomatic. All haemorrhagic transformations must have an associated reported bleeding event (ICH, PLATO major bleed) submitted for adjudication. Adjudicated symptomatic haemorrhagic transformation will be adjudicated to PLATO major bleeding event, TIMI major bleeding and GUSTO severe bleeding (ICH). Adjudicated asymptomatic haemorrhagic transformations will not be considered PLATO, TIMI or GUSTO bleeding events, and will be adjudicated to “no bleeding event” (see Section 6.4.6.1).

Symptomatic haemorrhagic transformation of an ischaemic stroke: Any extravascular blood within an area of known acute/subacute infarction that is judged to be nontraumatic, and responsible for neurologic symptoms. To be considered symptomatic, the haemorrhagic transformation must be judged to be partially responsible for the patient’s clinical neurologic presentation (ie, the area of infarction is not

adequate to explain the neurologic deficit, or a secondary neurologic deterioration occurred corresponding to the timing of haemorrhagic transformation).

Criteria (must meet both of the following):

1. Imaging evidence (by CT scan or MRI) of extravascular blood within the area of infarction.

2. Symptoms judged to be related to the haemorrhagic transformation. Scenarios which may be judged as symptomatic:

(a) Symptoms are out of proportion to what would be expected for the size and location of the infarct at presentation;

(b) Clinical deterioration, defined by an increase of 4 points or more in the score on the NIHSS or leading to death, occurring after the initial ischaemic event, and identified as the result of the haemorrhagic transformation; or

(c) Mass effect secondary to the haemorrhagic transformation causing symptoms.

Asymptomatic haemorrhagic transformation of an ischaemic stroke: Any extravascular blood within an area of known acute/subacute infarct, judged to be nontraumatic, without any related neurologic symptoms.

Criteria (must meet both of the following)

1. Imaging evidence (by CT scan or MRI) of extravascular blood within the area of infarct.

No symptoms related to the haemorrhagic transformation, or clinical deterioration with less than a 4 point increase in score on the NIHSS judged to be related to the haemorrhagic transformation.

PLATO Bleeding classification

PLATO Major bleeding

Fatal/Life-threatening – includes bleeding events that meet any of the following criteria:

- Fatal bleeding

- Intracranial bleeding*

- Intrapericardial bleeding with cardiac tamponade

- Hypovolemic shock or severe hypotension due to bleeding and requiring pressors/inotropes or surgery

- Decline in haemoglobin of 5 g/dL or more (or, when Hgb is not available, a fall in haematocrit of ≥15%),

- Transfusion of 4 or more units (whole blood or PRBCs) for bleeding

Major bleed – other – includes bleeding events that meet any of the following criteria:

- Significantly disabling (eg, intraocular with permanent vision loss)

- Clinically overt or apparent bleeding associated with a decrease in Hgb of 3-5 g/dL (or, when Hgb is not available, a fall in haematocrit of 9 to <15%)

- Transfusion of 2-3 units (whole blood or PRBCs) for bleeding

PLATO Minor bleeding

Bleeding that does not meet criteria for PLATO Major bleeding, AND

Requires medical intervention to stop or treat bleeding (eg, epistaxis requiring visit to medical facility for packing)

PLATO Minimal bleeding

Bleeding that does not meet criteria for PLATO Major or Minor bleeding, AND

Includes all other bleeding events (e.g., bruising, bleeding gums, oozing from injection sites, etc) not requiring intervention or treatment

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*Stroke study adaptation of PLATO bleeding classifications:
Asymptomatic haemorrhagic transformations of ischemic brain infarctions and micro-haemorrhages <10mm evident only on gradient-echo MRI were excluded from PLATO Major Life threatening, intracranial bleeding

APPENDIX D – ADDITIONAL ANALYSES

Supplemental Table S1 – Patients follow up: contact information by visit

Table S1. Patient follow-up - contact information by visit after randomization visit (Visit 1) (full analysis set)

Visit	Type of contact	Ticagrelor (N=6589)	Aspirin (N=6610)
Visit 2 (Day 7 +-2d)	Overall	6367	6416
	Patient visit in person	5955 (93.5%)	5993 (93.4%)
	Telephone contact with patient	324 (5.1%)	338 (5.3%)
	Other*	88 (1.4%)	85 (1.3%)
Visit 3 (Day 30 +-7d)	Overall	6362	6406
	Patient visit in person	1322 (20.8%)	1342 (20.9%)
	Telephone contact with patient	4530 (71.2%)	4569 (71.3%)
	Other*	510 (8.0%)	495 (7.7%)
Visit 4 (Day 60 +-7d)	Overall	6368	6371
	Patient visit in person	820 (12.9%)	819 (12.9%)
	Telephone contact with patient	5025 (78.9%)	5002 (78.5%)
	Other*	523 (8.2%)	550 (8.6%)
Visit 5 (End of Treatment Visit Day 90 +-7d)	Overall	6324	6346
	Patient visit in person	5864 (92.7%)	5956 (93.9%)
	Telephone contact with patient	311 (4.9%)	266 (4.2%)
	Other*	149 (2.4%)	124 (2.0%)
Visit 6 (Study Closure Visit Day 120 +-7d)	Overall	6448	6468
	Patient visit in person	2247 (34.8%)	2290 (35.4%)
	Telephone contact with patient	3687 (57.2%)	3670 (56.7%)
	Other*	514 (8.0%)	508 (7.9%)
Premature Treatment Discontinuation Visit	Overall	966	789
	Patient visit in person	844 (87.4%)	685 (86.8%)
	Telephone contact with patient	66 (6.8%)	59 (7.5%)
	Other*	56 (5.8%)	45 (5.7%)

*Other includes collecting information from family member or caregiver, from primary/treating physician, or from medical records

Supplemental Table S2 - ASCOD Phenotypes

Table SX. ASCOD* phenotypes and grades of diseases in the patients in SOCRATES

Phenotype	Grades of diseases	Number (%) of patients	
		Ticagrelor N=6589	Aspirin N=6610
Atherosclerosis	1-3: disease is present	2471 (37.5%)	2506 (37.9%)
	0: absence of disease	2485 (37.7%)	2470 (37.4%)
	9: workup insufficient	1593 (24.2%)	1601 (24.2%)
Small vessel disease	1-3: disease is present	2768 (42.0%)	2771 (41.9%)
	0: absence of disease	2578 (39.1%)	2573 (38.9%)
	9: workup insufficient	1203 (18.3%)	1233 (18.7%)
Cardiac pathology	1-3: disease is present	309 (4.7%)	293 (4.4%)
	0: absence of disease	4003 (60.8%)	4021 (60.8%)
	9: workup insufficient	2236 (33.9%)	2263 (34.2%)
Other causes	1-3: disease is present	40 (0.6%)	47 (0.7%)
	0: absence of disease	4274 (64.9%)	4260 (64.4%)
	9: workup insufficient	2235 (33.9%)	2270 (34.3%)
Dissection	1-3: disease is present	30 (0.5%)	27 (0.4%)
	0: absence of disease	5203 (79.0%)	5233 (79.2%)
	9: workup insufficient	1316 (20.0%)	1317 (19.9%)

*In ASCOD, every patient should be graded into 5 predefined phenotypes: A (atheroclerosis); S (small-vessel disease); C (cardiac pathology); O (other cause), and D (dissection) and further classified by grades of diseases; 1: If the disease is present and can potentially be a cause; 2: If the disease is present, but the causal link is uncertain; 3: If the disease is present, but the causal link is unlikely; 0: If the disease is absent; 9: If the workup is insufficient to grade the disease. (Amarenco et al, 2013)

Supplemental Table S3 – Serious Adverse Events

Serious adverse events (SAEs), by system organ class - on treatment (safety analysis set)

	Number (%) of patients[a]	
System organ class	**Ticagrelor (N=6549)**	**Aspirin (N=6581)**
Patients with any SAE[b]	532 (8.1%)	533 (8.1%)
Nervous system disorders	161 (2.5%)	165 (2.5%)
Cardiac disorders	85 (1.3%)	68 (1.0%)
Infections and infestations	76 (1.2%)	57 (0.9%)
Gastrointestinal disorders	33 (0.5%)	42 (0.6%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	33 (0.5%)	36 (0.5%)
Vascular disorders	34 (0.5%)	34 (0.5%)
Respiratory, thoracic and mediastinal disorders	32 (0.5%)	29 (0.4%)
Injury, poisoning and procedural complications	25 (0.4%)	34 (0.5%)
Renal and urinary disorders	18 (0.3%)	20 (0.3%)
Metabolism and nutrition disorders	14 (0.2%)	23 (0.3%)
Musculoskeletal and connective tissue disorders	15 (0.2%)	15 (0.2%)
Psychiatric disorders	13 (0.2%)	15 (0.2%)
General disorders and administration site conditions	12 (0.2%)	14 (0.2%)
Hepatobiliary disorders	12 (0.2%)	12 (0.2%)

[a] Number (%) of patients with SAE, sorted by descending frequency for system organ class in all patients
[b] Efficacy endpoints are not reported as SAEs and are not included.
Includes adverse events with an onset date on or after the date of first dose and up to and including 7 days following the date of last dose of study medication.

Supplemental Table S4 – Adverse Events Leading to Study Drug Discontinuation

Adverse events leading to discontinuation of study drug, by system organ class - on treatment (safety analysis set)

	Number (%) of patients[a]	
System organ class	**Ticagrelor (N=6549)**	**Aspirin (N=6581)**
Patients with any AE leading to discontinuation[b]	634 (9.7%)	470 (7.1%)
Cardiac disorders	174 (2.7%)	156 (2.4%)
Nervous system disorders	98 (1.5%)	84 (1.3%)
Respiratory, thoracic and mediastinal disorders	118 (1.8%)	37 (0.6%)
Dyspnoea	91 (1.4%)	17 (0.3%)
Epistaxis	10 (0.2%)	4 (0.1%)
Gastrointestinal disorders	78 (1.2%)	58 (0.9%)
Diarrhoea	19 (0.3%)	8 (0.1%)
Nausea	12 (0.2%)	8 (0.1%)
Skin and subcutaneous tissue disorders	41 (0.6%)	18 (0.3%)
Rash	7 (0.1%)	5 (0.1%)
Pruritus	3 (0.0%)	3 (0.0%)
Urticaria	4 (0.1%)	2 (0.0%)
Blood and lymphatic system disorders	30 (0.5%)	10 (0.2%)
Increased tendency to bruise	13 (0.2%)	2 (0.0%)
Spontaneous haematoma	11 (0.2%)	2 (0.0%)
Vascular disorders	15 (0.2%)	21 (0.3%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	15 (0.2%)	20 (0.3%)
Infections and infestations	18 (0.3%)	13 (0.2%)
General disorders and administration site conditions	17 (0.3%)	12 (0.2%)
Injury, poisoning and procedural complications	13 (0.2%)	9 (0.1%)
Investigations	9 (0.1%)	11 (0.2%)
Renal and urinary disorders	14 (0.2%)	6 (0.1%)
Psychiatric disorders	10 (0.2%)	9 (0.1%)

[a] Number (%) of patients with an AE leading to discontinuation of study drug, sorted by descending frequency for system organ class. Patients with multiple AEs leading to discontinuation are counted once for each system organ class.

[b] Action taken, study drug permanently stopped.

Includes adverse events with an onset date on or after the date of first dose and up to and including 7 days following the date of last dose of study medication.

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