

Supplementary Appendix

Supplementary tables

Supplementary table 1. Cohort characteristics

	CANVAS	CANVAS-R	CRENCE	All
On-treatment population, N	4,327	5,807	4,397	14,531
Age, years	62 (8)	64 (8)	63 (9)	63 (9)
Female, n (%)	1,467 (34)	2,164 (37)	1,492 (34)	5,123 (35)
Race, n (%)				
White	3,177 (73)	4,761 (82)	2,928 (67)	10,866 (75)
Black or African American	105 (2)	230 (4)	233 (5)	588 (4)
Asian	795 (18)	489 (8)	877 (20)	2,161 (15)
Other	250 (6)	327 (6)	369 (8)	946 (7)
Region, n (%)				
North America	1,245 (29)	1,181 (20)	1,180 (27)	3,606 (25)
Central/ South America	167 (4)	854 (15)	941 (21)	1,962 (14)
Europe	1,335 (31)	2,271 (39)	862 (20)	4,468 (31)
Rest of the world	1,580 (37)	1,501 (26)	1,414 (32)	4,495 (31)
Body mass index, kg/m ²	32 (6)	32 (6)	31 (6)	32 (6)
Diabetes duration, years	13 (8)	14 (8)	16 (9)	14 (8)
Glycated haemoglobin, %	8 (1)	8 (1)	8 (1)	8 (1)
Estimated glomerular filtration rate, ml/min/1.73m ²	77 (19)	76 (22)	56 (18)	70 (22)
Heart failure, n (%)	515 (12)	944 (16)	652 (15)	2,111 (15)
Cardiovascular disease, n (%)	2,548 (59)	4,103 (71)	2,218 (50)	8,869 (61)
Peripheral vascular disease, n (%)	685 (16)	1,426 (25)	1,044 (24)	3,155 (22)
Neuropathy, n (%)	1,345 (31)	1,764 (30)	2,143 (49)	5,252 (36)
Medication at baseline				
Metformin	3,168 (73)	4,652 (80)	2,543 (58)	10,363 (71)
Insulin	2,172 (50)	2,921 (50)	2,882 (66)	7,975 (55)
GLP-1 agonist	96 (2)	311 (5)	183 (4)	590 (4)
Sulphonylurea	2,031 (47)	2,328 (40)	1,267 (29)	5,626 (39)
DPP-4 inhibitor	317 (7)	944 (16)	751 (17)	2012 (14)

Mean (SD) unless otherwise stated

Supplementary Table 2. MedDRA terms used to define SSTI and number of first events in primary analysis

<u>Non-genital Fungal SSTI</u>	<u>Number</u>	<u>Percent of Total</u>
Body tinea	12	1.3
Dermatophytosis	2	0.2
Dermatophytosis of nail	6	0.7
Fungal skin infection	72	8.0
Skin candida	9	1.0
Tinea capitis	0	0
Tinea cruris	15	1.7
Tinea infection	8	0.9
Tinea pedis	35	3.9
Tinea versicolour	2	0.2
<u>Non-genital Non-fungal SSTI</u>		
Acarodermatitis	6	0.7
Acne	6	0.7
Arteriovenous fistula site infection	1	0.1
Breast abscess	1	0.1
Burn infection	1	0.1
Carbuncle	6	0.7
Cellulitis	237	26.2
Cellulitis gangrenous	4	0.4
Cellulitis of male external genital organ	1	0.1
Cellulitis orbital	0	0
Cellulitis staphylococcal	4	0.4
Cutaneous larva migrans	1	0.1
Dermatitis infected	2	0.2
Diabetic foot infection	26	2.9
Diabetic gangrene	11	1.2
Erysipelas	45	5.0
Folliculitis	18	2.0
Furuncle	50	5.5
Gangrene	51	5.6
Gas gangrene	1	0.1
Graft infection	0	0
Groin abscess	7	0.8
Herpes dermatitis	1	0.1
Hordeolum	10	1.1
Impetigo	5	0.6
Incision site cellulitis	0	0
Infected dermal cyst	8	0.9
Infected skin ulcer	29	3.2
Injection site abscess	3	0.3
Injection site infection	1	0.1
Nail infection	8	0.9
Necrobiosis lipoidica diabetorum	3	0.3

Necrotising fasciitis	4	0.4
Otitis externa	36	4.0
Paronychia	38	4.2
Perineal abscess	2	0.2
Pilonidal cyst	4	0.4
Pyoderma	6	0.7
Scrotal abscess	7	0.8
Skin infection	21	2.3
Soft tissue infection	14	1.6
Staphylococcal skin infection	2	0.2
Stoma site infection	0	0
Subcutaneous abscess	20	2.2
Tropical ulcer	1	0.1
Wound infection	40	4.4
Wound infection staphylococcal	0	0
Total	903	100

Supplementary table 3. Excluded terms within “Infections and Infestations”, “Skin and subcutaneous tissue disorders” or “Musculoskeletal and connective tissue disorders”

Abdominal wall abscess
 Abscess limb
 Abscess oral
 Actinic keratosis
 Alopecia
 Alopecia universalis
 Angioedema
 Angular cheilitis
 Asteatosis
 Balanitis candida
 Blister
 Blister rupture
 Cholestatic pruritus
 Cutaneous sarcoidosis
 Decubitus ulcer
 Dermal cyst
 Dermatitis
 Dermatitis allergic
 Dermatitis atopic
 Dermatitis contact
 Dermatitis psoriasiform
 Dermatoses
 Diabetic bullosis
 Diabetic dermopathy
 Diabetic foot

Diabetic ulcer
Drug eruption
Drug reaction with eosinophilia and systemic symptoms
Dry skin
Dyshidrotic eczema
Ecchymosis
Eczema
Eczema asteatotic
Eczema nummular
Erythema
Gingival abscess
Gingivitis
Haemorrhage subcutaneous
Hand dermatitis
Hirsutism
Hyperhidrosis
Hyperkeratosis
Idiopathic angioedema
Ingrowing nail
Ingrown hair
Lipohypertrophy
Macule
Miliaria
Nail bed bleeding
Nail disorder
Nail dystrophy
Nail hypertrophy
Nail pigmentation
Neurodermatitis
Neuropathic ulcer
Onychalgia
Onychoclasia
Onychogryphosis
Pain of skin
Palmoplantar keratoderma
Peau d'orange
Pemphigoid
Penile infection
Petechiae
Photosensitivity reaction
Pityriasis rosea
Precancerous skin lesion
Prurigo
Pruritus
Pruritus generalised
Psoriasis

Rash
Rash erythematous
Rash generalised
Rash maculo-papular
Rash papular
Rash pruritic
Rash pustular
Scab
Skin discolouration
Skin disorder
Skin erosion
Skin exfoliation
Skin fissures
Skin hyperpigmentation
Skin hypopigmentation
Skin induration
Skin irritation
Skin lesion
Skin maceration
Skin mass
Skin plaque
Skin reaction
Skin ulcer
Solar lentigo
Stasis dermatitis
Swelling face
Telangiectasia
Toxic skin eruption
Urticaria
Xeroderma
Abdominal abscess
Abdominal hernia infection
Abdominal sepsis
Abscess
Acute hepatitis B
Acute sinusitis
Amoebiasis
Amoebic dysentery
Anal abscess
Ankylosing spondylitis
Appendicitis
Appendicitis perforated
Arthralgia
Arthritis
Arthritis bacterial
Arthritis infective

Arthropathy
Asymptomatic bacteriuria
Atypical pneumonia
Axillary mass
Back pain
Bacteraemia
Bacterial infection
Bacterial pyelonephritis
Bacterial sepsis
Bacterial vaginosis
Bacteriuria
Bladder candidiasis
Bone cyst
Bone lesion
Bone pain
Bronchiolitis
Bronchitis
Bronchitis bacterial
Bronchitis viral
Bursitis
Campylobacter colitis
Campylobacter infection
Candida infection
Cervical spinal stenosis
Chest wall haematoma
Chikungunya virus infection
Cholecystitis infective
Chondrocalcinosis
Chondrocalcinosis pyrophosphate
Chondromalacia
Chondropathy
Chronic hepatitis C
Chronic kidney disease-mineral and bone disorder
Chronic sinusitis
Clostridium colitis
Clostridium difficile colitis
Clostridium difficile infection
Coccydynia
Cold sweat
Conjunctivitis
Conjunctivitis bacterial
Conjunctivitis viral
Costochondritis
Cystitis
Cystitis klebsiella
Dengue fever

Device related infection
Device related sepsis
Diffuse idiopathic skeletal hyperostosis
Diverticulitis
Dupuytren's contracture
Dysentery
Ear infection
Emphysematous cystitis
Empyema
Endocarditis
Endocarditis bacterial
Endophthalmitis
Enteritis infectious
Enterobacter bacteraemia
Enterobacter infection
Enterocolitis bacterial
Enterovirus infection
Enthesopathy
Epididymitis
Epstein-Barr virus infection
Escherichia pyelonephritis
Escherichia sepsis
Escherichia urinary tract infection
Exostosis
Extremity contracture
Eye infection
Fasciitis
Femoroacetabular impingement
Fibromyalgia
Fistula
Flank pain
Flavivirus infection
Foot deformity
Fungal infection
Gastric ulcer helicobacter
Gastroenteritis
Gastroenteritis bacterial
Gastroenteritis enteroviral
Gastroenteritis norovirus
Gastroenteritis viral
Gastrointestinal bacterial infection
Gastrointestinal bacterial overgrowth
Gastrointestinal candidiasis
Gastrointestinal infection
Gastrointestinal viral infection
Genital candidiasis

Genital infection
Genital infection fungal
Giardiasis
Gouty arthritis
Groin pain
Haemarthrosis
Haematoma infection
Haemophilus infection
Hand-foot-and-mouth disease
Helicobacter gastritis
Helicobacter infection
Hepatic echinococcosis
Hepatitis A
Hepatitis B
Hepatitis C
Herpes pharyngitis
Herpes simplex
Herpes virus infection
Herpes zoster
Herpes zoster infection neurological
Hypercreatinemia
Infected cyst
Infection in an immunocompromised host
Infectious colitis
Infective exacerbation of chronic obstructive airways disease
Influenza
Intertrigo
Intervertebral disc degeneration
Intervertebral disc disorder
Intervertebral disc displacement
Intervertebral disc protrusion
Intervertebral disc space narrowing
Intervertebral discitis
Joint abscess
Joint effusion
Joint instability
Joint stiffness
Joint swelling
Keratitis fungal
Klebsiella infection
Labyrinthitis
Laryngitis
Latent tuberculosis
Limb discomfort
Limb mass
Liver abscess

Localised infection
Lower respiratory tract infection
Lower respiratory tract infection bacterial
Lower respiratory tract infection viral
Lumbar spinal stenosis
Lung infection
Lyme disease
Mediastinitis
Medical device site abscess
Meningitis
Meningitis bacterial
Meniscal degeneration
Metatarsalgia
Mobility decreased
Mucosal infection
Muscle atrophy
Muscle contracture
Muscle disorder
Muscle haemorrhage
Muscle spasms
Muscle twitching
Muscular weakness
Musculoskeletal chest pain
Musculoskeletal discomfort
Musculoskeletal pain
Musculoskeletal stiffness
Myalgia
Myiasis
Myofascial pain syndrome
Myopathy
Myosclerosis
Myositis
Nasopharyngitis
Neck mass
Neck pain
Neurocysticercosis
Neuropathic arthropathy
Night sweats
Oesophageal candidiasis
Onychomycosis
Opisthorchiasis
Oral candidiasis
Oral fungal infection
Oral herpes
Orchitis
Oropharyngeal candidiasis

Osteitis
Osteitis deformans
Osteoarthritis
Osteochondritis
Osteochondrosis
Osteomyelitis
Osteomyelitis acute
Osteomyelitis chronic
Osteonecrosis
Osteopenia
Osteoporosis
Osteoporosis postmenopausal
Osteosclerosis
Otitis media
Otitis media acute
Otosalpingitis
Pain in extremity
Pain in jaw
Papilloma viral infection
Parasitic gastroenteritis
Paraspinal abscess
Parotitis
Pathological fracture
Periarthritis
Perichondritis
Periodontitis
Periostitis
Peritonitis
Pharyngeal abscess
Pharyngitis
Pharyngitis streptococcal
Pharyngotonsillitis
Plantar fasciitis
Pneumococcal sepsis
Pneumonia
Pneumonia bacterial
Pneumonia influenzal
Pneumonia pneumococcal
Pneumonia pseudomonal
Pneumonia staphylococcal
Pneumonia streptococcal
Pneumonia viral
Polyarthritis
Polymyalgia rheumatica
Post procedural infection
Post procedural sepsis

Postoperative wound infection
Pseudomembranous colitis
Pseudomonas bronchitis
Psoas abscess
Psoriatic arthropathy
Pulmonary sepsis
Pulpitis dental
Pyelonephritis
Pyelonephritis acute
Pyelonephritis chronic
Pyuria
Rectal abscess
Respiratory syncytial virus bronchiolitis
Respiratory syncytial virus infection
Respiratory tract infection
Respiratory tract infection viral
Rhabdomyolysis
Rheumatic disorder
Rheumatoid arthritis
Rhinitis
Rotator cuff syndrome
Rotavirus infection
Sacroiliitis
Scoliosis
Scrub typhus
Seborrhoea
Seborrhoeic dermatitis
Senile pruritus
Sepsis
Septic shock
Shunt infection
Sialoadenitis
Sinobronchitis
Sinus tarsi syndrome
Sinusitis
Sinusitis bacterial
Sjogren's syndrome
Soft tissue necrosis
Soft tissue swelling
Spinal column stenosis
Spinal disorder
Spinal osteoarthritis
Spinal pain
Spondylolisthesis
Staphylococcal bacteraemia
Staphylococcal infection

Staphylococcal sepsis
Streptococcal bacteraemia
Streptococcal infection
Streptococcal sepsis
Symphysiolysis
Synovial cyst
Synovitis
Systemic lupus erythematosus
Systemic viral infection
Temporomandibular joint syndrome
Tendon discomfort
Tendon disorder
Tendonitis
Tenosynovitis
Tenosynovitis stenosans
Tonsillitis
Tooth abscess
Tooth infection
Torticollis
Tracheitis
Tracheobronchitis
Tracheostomy infection
Trigger finger
Tuberculosis
Typhoid fever
Upper respiratory tract infection
Upper respiratory tract infection bacterial
Urethritis
Urinary tract infection
Urinary tract infection bacterial
Urinary tract infection enterococcal
Urinary tract infection fungal
Urosepsis
Vaginal infection
Varicella
Varicella zoster virus infection
Vertebral foraminal stenosis
Vertebral osteophyte
Viral hepatitis carrier
Viral infection
Viral pharyngitis
Viral tonsillitis
Viral upper respiratory tract infection
Vulvitis
Vulvovaginal candidiasis
Vulvovaginal mycotic infection

Vulvovaginitis

Supplementary table 4. Infection type by treatment arms

	Canagliflozin N=7,990	Placebo N=6,541	All N=14,531
n (%)			
Location			
Skin	504 (6)	357 (5)	861 (6)
Soft tissue	29 (0.4)	13 (0.2)	42 (0.3)
Total	533 (7)	370 (6)	903 (6)

Number and % of total participants in group

Supplementary table 5. Risk of SSTI by analysis type

Analysis Method	Canagliflozin		Placebo		HR [95% CI]	P value
	n/N	Rate 1000 person-years	n/N	Rate 1000 person-years		
On treatment	533/ 7,990	24.0	370/ 6,541	23.9	0.97 [0.85-1.11]	0.70
Intention-to-treat	579/ 7,997	21.7	415/ 6,546	22.1	0.98 [0.87-1.12]	0.81