

Supplementary Online Content

Wysham C, Bhargava A, Chaykin L, et al. Effect of insulin degludec vs insulin glargine U100 on hypoglycemia in patients with type 2 diabetes: the SWITCH 2 randomized clinical trial. *JAMA*. doi:10.1001/jama.2017.7117

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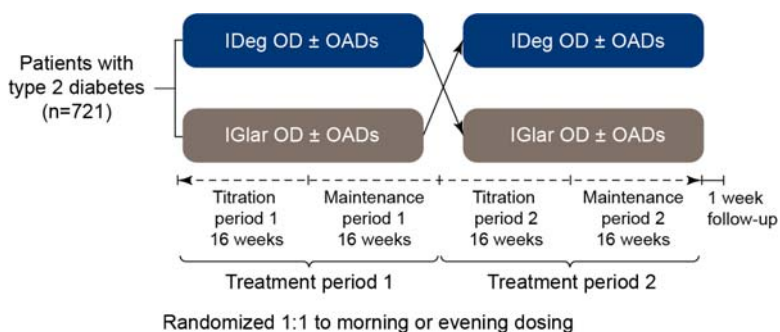
eTable 3. Multiple imputation tipping analysis for primary endpoint

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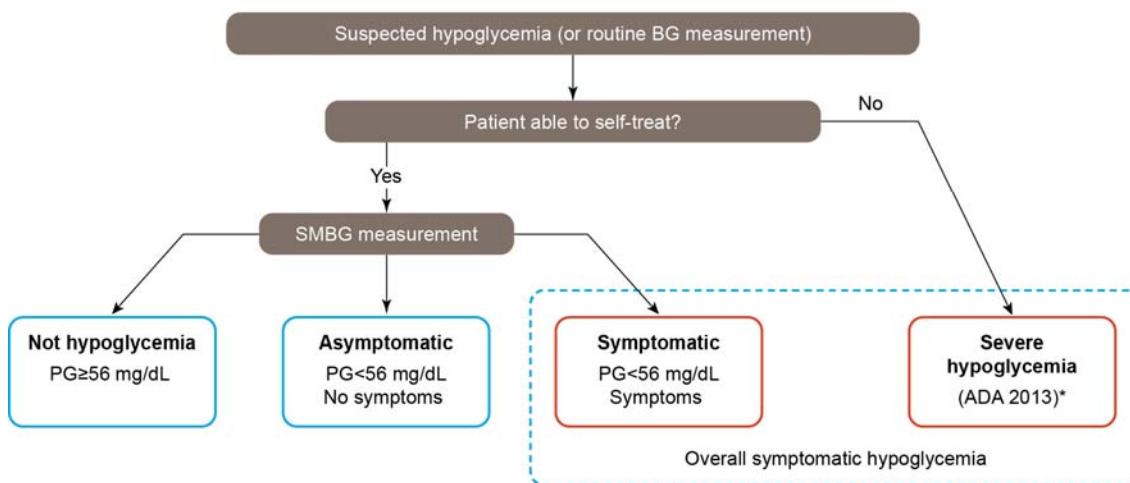
This supplementary material has been provided by the authors to give readers additional information about their work.

eFigure 1. Trial design



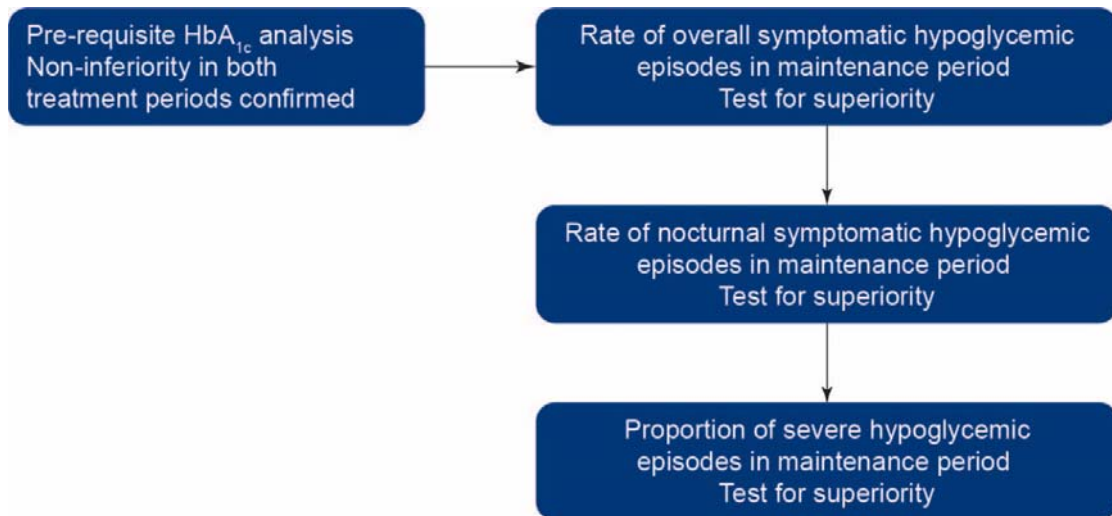
IDeg, insulin degludec; IGlar, insulin glargine U100; OAD, oral antidiabetic drug; OD, once daily.

eFigure 2. Hypoglycemia definition

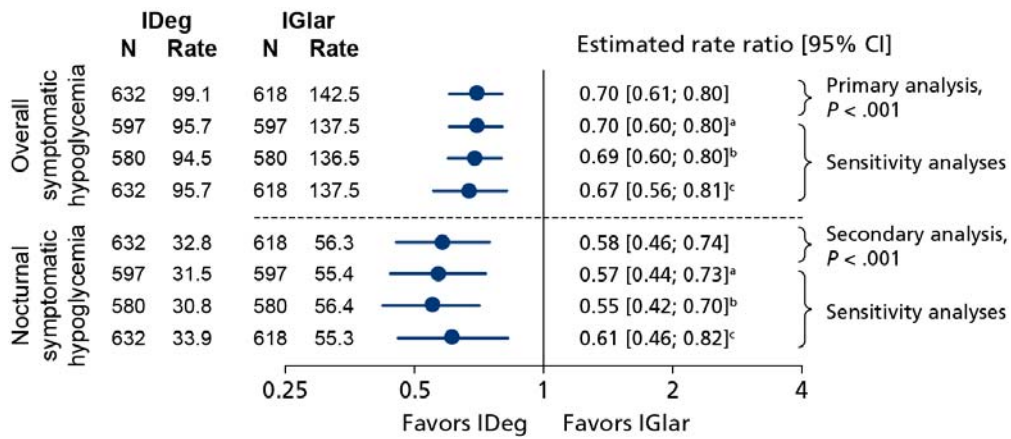


*An episode requiring assistance of another person to actively administer carbohydrate, glucagon, or take other corrective actions and/or neurological recovery following the return of plasma glucose to normal (ADA 2013; Seaquist et al. *Diabetes Care*. 2013;36(5):1384–95). Nocturnal episodes were defined as episodes occurring between 00:01 and 05:59 (both inclusive). Blue dashed box signifies endpoints included as confirmatory endpoints. To convert glucose to mmol/L, multiply by 0.0555. ADA, American Diabetes Association; BG, blood glucose; PG, plasma glucose; SMBG, self-measured blood glucose.

eFigure 3. Hierarchical testing procedure

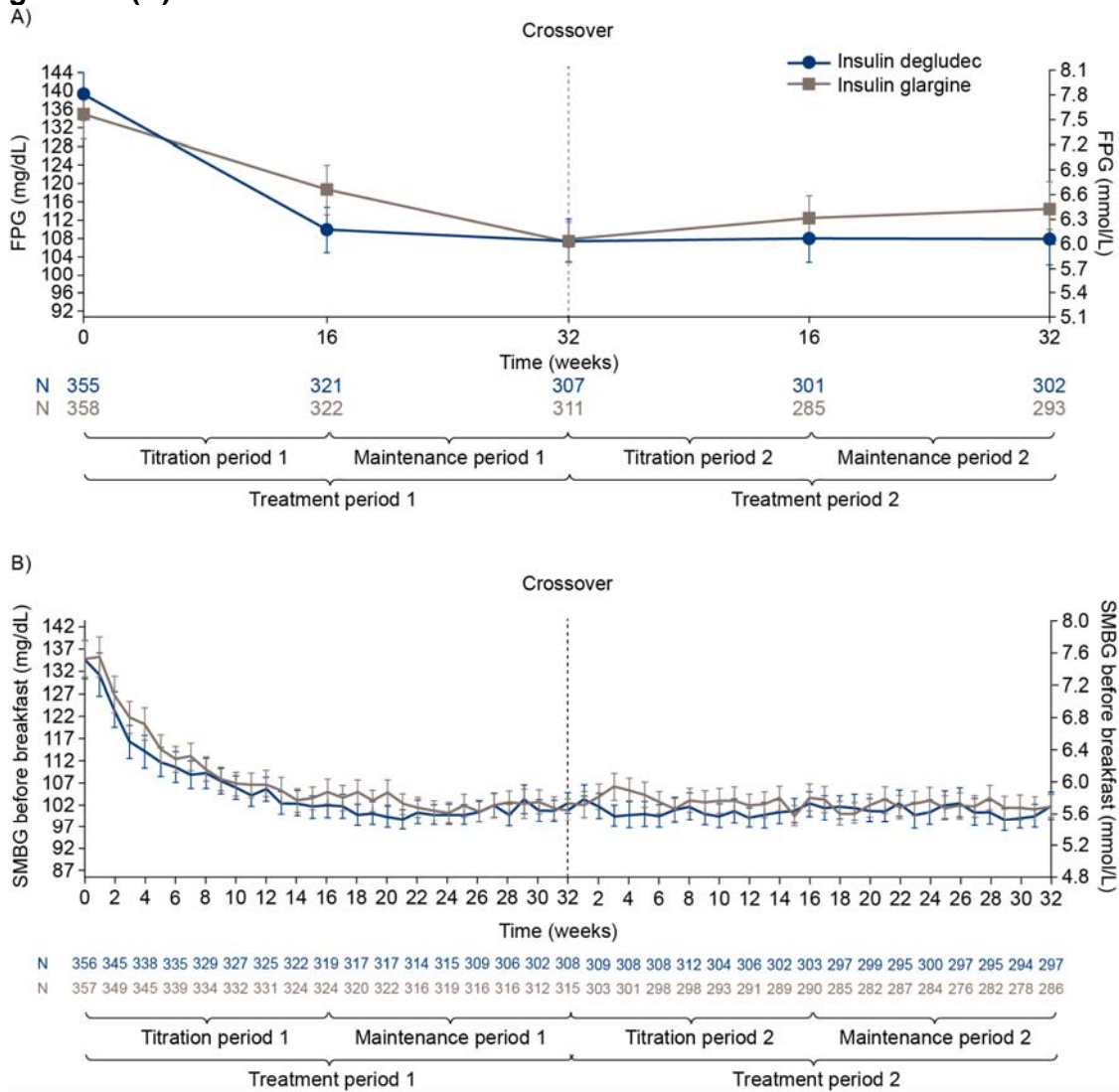


eFigure 4. Sensitivity analyses – maintenance period



All episodes of severe hypoglycemia were confirmed by external adjudication committee. Rates are least squares mean in events per 100 PYE; N, number of patients contributing to the analysis. ^aPoisson model on subset of patients with exposure in both maintenance periods; ^bPoisson model on the completer analysis set; ^cNegative binomial model. CI, confidence interval; IDeg, insulin degludec; IGlar, insulin glargine U100; PYE, patient-years of exposure.

eFigure 5. Fasting plasma glucose (A) and pre-breakfast self-measured blood glucose (B) over time



Data are observed mean \pm 95% CI for full analysis set. To convert glucose to mmol/L, multiply by 0.0555.
N, number of patients contributing to the data at that time point. CI, confidence intervals; FPG, fasting plasma glucose; SMBG, self-measured blood glucose.

eTable 1. Titration algorithm

Pre-breakfast blood glucose measurement ^a		Adjustment
mg/dL	mmol/L	Units
<56	<3.1	-4
56-70	3.1-3.9	-2
71-90	4.0-5.0	0
91-126	5.1-7.0	+2
127-144	7.1-8.0	+4
145-162	8.1-9.0	+6
>162	>9.0	+8

^aOnce-weekly titration based on the mean of 3 consecutive days' measurements.

eTable 2. Medical Dictionary for Regulatory Activities (MedDRA) predefined search of safety data

Standardized MedDRA queries (SMQ)	Preferred term	Term scope text
Accidents and injuries (SMQ)	Abdomen crushing	Narrow
Accidents and injuries (SMQ)	Abdominal injury	Narrow
Accidents and injuries (SMQ)	Accident	Narrow
Accidents and injuries (SMQ)	Accident at home	Narrow
Accidents and injuries (SMQ)	Accident at work	Narrow
Accidents and injuries (SMQ)	Accidental death	Narrow
Accidents and injuries (SMQ)	Acetabulum fracture	Narrow
Accidents and injuries (SMQ)	Acoustic shock	Narrow
Accidents and injuries (SMQ)	Acrotrophodynia	Broad
Accidents and injuries (SMQ)	Adrenal gland injury	Narrow
Accidents and injuries (SMQ)	Anal injury	Narrow
Accidents and injuries (SMQ)	Animal bite	Broad
Accidents and injuries (SMQ)	Ankle fracture	Narrow
Accidents and injuries (SMQ)	Aortic injury	Narrow
Accidents and injuries (SMQ)	Aortic rupture	Narrow
Accidents and injuries (SMQ)	Aponeurosis contusion	Narrow
Accidents and injuries (SMQ)	Arterial injury	Narrow
Accidents and injuries (SMQ)	Arterial rupture	Narrow
Accidents and injuries (SMQ)	Atrial rupture	Narrow
Accidents and injuries (SMQ)	Atypical femur fracture	Narrow
Accidents and injuries (SMQ)	Atypical fracture	Narrow
Accidents and injuries (SMQ)	Avulsion fracture	Narrow
Accidents and injuries (SMQ)	Axillary nerve injury	Narrow
Accidents and injuries (SMQ)	Back injury	Narrow
Accidents and injuries (SMQ)	Bile duct stenosis traumatic	Narrow
Accidents and injuries (SMQ)	Bladder injury	Narrow
Accidents and injuries (SMQ)	Bladder perforation	Narrow
Accidents and injuries (SMQ)	Blast injury	Narrow
Accidents and injuries (SMQ)	Blindness traumatic	Narrow
Accidents and injuries (SMQ)	Bone contusion	Narrow
Accidents and injuries (SMQ)	Bone fissure	Narrow
Accidents and injuries (SMQ)	Bone fragmentation	Narrow
Accidents and injuries (SMQ)	Bowman's membrane injury	Narrow
Accidents and injuries (SMQ)	Brachial plexus injury	Narrow
Accidents and injuries (SMQ)	Brain contusion	Narrow
Accidents and injuries (SMQ)	Breast injury	Narrow
Accidents and injuries (SMQ)	Burn oral cavity	Narrow
Accidents and injuries (SMQ)	Burns first degree	Narrow
Accidents and injuries (SMQ)	Burns fourth degree	Narrow
Accidents and injuries (SMQ)	Burns second degree	Narrow
Accidents and injuries (SMQ)	Burns third degree	Narrow
Accidents and injuries (SMQ)	Bursa injury	Narrow
Accidents and injuries (SMQ)	Buttock crushing	Narrow
Accidents and injuries (SMQ)	Cardiac contusion	Narrow
Accidents and injuries (SMQ)	Cartilage injury	Narrow
Accidents and injuries (SMQ)	Cataract traumatic	Narrow
Accidents and injuries (SMQ)	Cervical vertebral fracture	Narrow
Accidents and injuries (SMQ)	Chance fracture	Narrow
Accidents and injuries (SMQ)	Chemical burn of skin	Narrow
Accidents and injuries (SMQ)	Chemical burns of eye	Narrow

Standardized MedDRA queries (SMQ)	Preferred term	Term scope text
Accidents and injuries (SMQ)	Chemical eye injury	Narrow
Accidents and injuries (SMQ)	Chemical injury	Narrow
Accidents and injuries (SMQ)	Chemical iritis	Narrow
Accidents and injuries (SMQ)	Chest crushing	Narrow
Accidents and injuries (SMQ)	Chest injury	Narrow
Accidents and injuries (SMQ)	Chillblains	Broad
Accidents and injuries (SMQ)	Clavicle fracture	Narrow
Accidents and injuries (SMQ)	Closed globe injury	Narrow
Accidents and injuries (SMQ)	Cold exposure injury	Broad
Accidents and injuries (SMQ)	Colon injury	Narrow
Accidents and injuries (SMQ)	Comminuted fracture	Narrow
Accidents and injuries (SMQ)	Commotio retinae	Narrow
Accidents and injuries (SMQ)	Complicated fracture	Narrow
Accidents and injuries (SMQ)	Compression fracture	Narrow
Accidents and injuries (SMQ)	Concussion	Narrow
Accidents and injuries (SMQ)	Conjunctival abrasion	Narrow
Accidents and injuries (SMQ)	Conjunctival laceration	Narrow
Accidents and injuries (SMQ)	Contusion	Narrow
Accidents and injuries (SMQ)	Corneal abrasion	Narrow
Accidents and injuries (SMQ)	Corneal perforation	Broad
Accidents and injuries (SMQ)	Corrosive oropharyngeal injury	Narrow
Accidents and injuries (SMQ)	Cranial nerve injury	Narrow
Accidents and injuries (SMQ)	Craniocerebral injury	Narrow
Accidents and injuries (SMQ)	Crush injury	Narrow
Accidents and injuries (SMQ)	Crush syndrome	Narrow
Accidents and injuries (SMQ)	Crushing injury of trunk	Narrow
Accidents and injuries (SMQ)	Deafness traumatic	Narrow
Accidents and injuries (SMQ)	Decapitation	Narrow
Accidents and injuries (SMQ)	Deep dissecting hematoma	Broad
Accidents and injuries (SMQ)	Diaphragmatic injury	Narrow
Accidents and injuries (SMQ)	Diaphragmatic rupture	Narrow
Accidents and injuries (SMQ)	Diffuse axonal injury	Narrow
Accidents and injuries (SMQ)	Dislocation of sternum	Narrow
Accidents and injuries (SMQ)	Dislocation of vertebra	Narrow
Accidents and injuries (SMQ)	Drowning	Narrow
Accidents and injuries (SMQ)	Dural tear	Narrow
Accidents and injuries (SMQ)	Ear abrasion	Narrow
Accidents and injuries (SMQ)	Ear canal abrasion	Narrow
Accidents and injuries (SMQ)	Ear canal injury	Narrow
Accidents and injuries (SMQ)	Ear canal stenosis traumatic	Narrow
Accidents and injuries (SMQ)	Ear injury	Narrow
Accidents and injuries (SMQ)	Electric injury	Narrow
Accidents and injuries (SMQ)	Electric shock	Narrow
Accidents and injuries (SMQ)	Electrocution	Narrow
Accidents and injuries (SMQ)	Enophthalmos traumatic	Narrow
Accidents and injuries (SMQ)	Epidural hemorrhage	Broad
Accidents and injuries (SMQ)	Epiphyseal fracture	Narrow
Accidents and injuries (SMQ)	Epiphyseal injury	Narrow
Accidents and injuries (SMQ)	Epiphysiolysis	Broad
Accidents and injuries (SMQ)	Excoriation	Broad
Accidents and injuries (SMQ)	External genitalia crushing	Narrow
Accidents and injuries (SMQ)	Extradural hematoma	Broad
Accidents and injuries (SMQ)	Eye burns	Narrow

Standardized MedDRA queries (SMQ)	Preferred term	Term scope text
Accidents and injuries (SMQ)	Eye contusion	Narrow
Accidents and injuries (SMQ)	Eye injury	Narrow
Accidents and injuries (SMQ)	Eye luxation	Broad
Accidents and injuries (SMQ)	Eyeball avulsion	Narrow
Accidents and injuries (SMQ)	Eyelash injury	Narrow
Accidents and injuries (SMQ)	Eyelid contusion	Narrow
Accidents and injuries (SMQ)	Eyelid hematoma	Narrow
Accidents and injuries (SMQ)	Eyelid injury	Narrow
Accidents and injuries (SMQ)	Face crushing	Narrow
Accidents and injuries (SMQ)	Face injury	Narrow
Accidents and injuries (SMQ)	Facial bones fracture	Narrow
Accidents and injuries (SMQ)	Facial nerve injury due to birth trauma	Narrow
Accidents and injuries (SMQ)	Fall	Narrow
Accidents and injuries (SMQ)	Femoral neck fracture	Narrow
Accidents and injuries (SMQ)	Femoral nerve injury	Narrow
Accidents and injuries (SMQ)	Femur fracture	Narrow
Accidents and injuries (SMQ)	Fibula fracture	Narrow
Accidents and injuries (SMQ)	Flail chest	Narrow
Accidents and injuries (SMQ)	Foot fracture	Narrow
Accidents and injuries (SMQ)	Forearm fracture	Narrow
Accidents and injuries (SMQ)	Foreign body aspiration	Broad
Accidents and injuries (SMQ)	Foreign body in eye	Narrow
Accidents and injuries (SMQ)	Fracture	Narrow
Accidents and injuries (SMQ)	Fracture displacement	Narrow
Accidents and injuries (SMQ)	Fracture of clavicle due to birth trauma	Narrow
Accidents and injuries (SMQ)	Fracture of penis	Narrow
Accidents and injuries (SMQ)	Fracture pain	Broad
Accidents and injuries (SMQ)	Fractured coccyx	Narrow
Accidents and injuries (SMQ)	Fractured ischium	Narrow
Accidents and injuries (SMQ)	Fractured sacrum	Narrow
Accidents and injuries (SMQ)	Fractured skull depressed	Narrow
Accidents and injuries (SMQ)	Frostbite	Broad
Accidents and injuries (SMQ)	Gallbladder injury	Narrow
Accidents and injuries (SMQ)	Gallbladder perforation	Broad
Accidents and injuries (SMQ)	Gastrointestinal injury	Narrow
Accidents and injuries (SMQ)	Genital contusion	Narrow
Accidents and injuries (SMQ)	Genital injury	Narrow
Accidents and injuries (SMQ)	Gingival injury	Narrow
Accidents and injuries (SMQ)	Glaucoma traumatic	Narrow
Accidents and injuries (SMQ)	Greenstick fracture	Narrow
Accidents and injuries (SMQ)	Gun shot wound	Narrow
Accidents and injuries (SMQ)	Hematuria traumatic	Narrow
Accidents and injuries (SMQ)	Hemothorax	Broad
Accidents and injuries (SMQ)	Hand fracture	Narrow
Accidents and injuries (SMQ)	Head injury	Narrow
Accidents and injuries (SMQ)	Heart injury	Broad
Accidents and injuries (SMQ)	Heat cramps	Broad
Accidents and injuries (SMQ)	Heat exhaustion	Broad
Accidents and injuries (SMQ)	Heat stroke	Broad
Accidents and injuries (SMQ)	Hepatic rupture	Narrow
Accidents and injuries (SMQ)	Hernia perforation	Narrow
Accidents and injuries (SMQ)	Hip fracture	Narrow

Standardized MedDRA queries (SMQ)	Preferred term	Term scope text
Accidents and injuries (SMQ)	Human bite	Broad
Accidents and injuries (SMQ)	Humerus fracture	Narrow
Accidents and injuries (SMQ)	Hyperthermia	Broad
Accidents and injuries (SMQ)	Hyphemia	Narrow
Accidents and injuries (SMQ)	Hypothermia	Broad
Accidents and injuries (SMQ)	IIIrd nerve injury	Narrow
Accidents and injuries (SMQ)	IVth nerve injury	Narrow
Accidents and injuries (SMQ)	Ilium fracture	Narrow
Accidents and injuries (SMQ)	Impacted fracture	Narrow
Accidents and injuries (SMQ)	Inguinal hernia perforation	Narrow
Accidents and injuries (SMQ)	Injury	Narrow
Accidents and injuries (SMQ)	Injury corneal	Narrow
Accidents and injuries (SMQ)	Injury to brachial plexus due to birth trauma	Narrow
Accidents and injuries (SMQ)	Internal injury	Narrow
Accidents and injuries (SMQ)	Intervertebral disc injury	Narrow
Accidents and injuries (SMQ)	Iris injury	Narrow
Accidents and injuries (SMQ)	Jaw fracture	Narrow
Accidents and injuries (SMQ)	Joint dislocation	Narrow
Accidents and injuries (SMQ)	Joint hyperextension	Narrow
Accidents and injuries (SMQ)	Joint injury	Narrow
Accidents and injuries (SMQ)	Keratorhexis	Broad
Accidents and injuries (SMQ)	Kidney contusion	Narrow
Accidents and injuries (SMQ)	Kidney rupture	Narrow
Accidents and injuries (SMQ)	Laceration	Narrow
Accidents and injuries (SMQ)	Laryngeal injury	Narrow
Accidents and injuries (SMQ)	Lens dislocation	Broad
Accidents and injuries (SMQ)	Lenticular injury	Narrow
Accidents and injuries (SMQ)	Ligament injury	Narrow
Accidents and injuries (SMQ)	Ligament rupture	Narrow
Accidents and injuries (SMQ)	Ligament sprain	Narrow
Accidents and injuries (SMQ)	Limb crushing injury	Narrow
Accidents and injuries (SMQ)	Limb fracture	Narrow
Accidents and injuries (SMQ)	Limb injury	Narrow
Accidents and injuries (SMQ)	Limb reattachment surgery	Narrow
Accidents and injuries (SMQ)	Limb traumatic amputation	Narrow
Accidents and injuries (SMQ)	Lip injury	Narrow
Accidents and injuries (SMQ)	Liver contusion	Narrow
Accidents and injuries (SMQ)	Liver injury	Narrow
Accidents and injuries (SMQ)	Lower limb fracture	Narrow
Accidents and injuries (SMQ)	Lumbar vertebral fracture	Narrow
Accidents and injuries (SMQ)	Lumbosacral plexus injury	Narrow
Accidents and injuries (SMQ)	Lung perforation	Broad
Accidents and injuries (SMQ)	Lymphatic duct injury	Narrow
Accidents and injuries (SMQ)	Median nerve injury	Narrow
Accidents and injuries (SMQ)	Meniscus cyst	Narrow
Accidents and injuries (SMQ)	Meniscus injury	Narrow
Accidents and injuries (SMQ)	Metallosis of globe	Broad
Accidents and injuries (SMQ)	Mouth injury	Narrow
Accidents and injuries (SMQ)	Multiple fractures	Narrow
Accidents and injuries (SMQ)	Multiple injuries	Narrow
Accidents and injuries (SMQ)	Muscle contusion	Narrow
Accidents and injuries (SMQ)	Muscle injury	Narrow

Standardized MedDRA queries (SMQ)	Preferred term	Term scope text
Accidents and injuries (SMQ)	Muscle reattachment	Narrow
Accidents and injuries (SMQ)	Muscle rupture	Narrow
Accidents and injuries (SMQ)	Muscle strain	Narrow
Accidents and injuries (SMQ)	Musculocutaneous nerve injury	Narrow
Accidents and injuries (SMQ)	Musculoskeletal injury	Narrow
Accidents and injuries (SMQ)	Myocardial rupture	Narrow
Accidents and injuries (SMQ)	Nail avulsion	Narrow
Accidents and injuries (SMQ)	Nail injury	Narrow
Accidents and injuries (SMQ)	Near drowning	Narrow
Accidents and injuries (SMQ)	Neck crushing	Narrow
Accidents and injuries (SMQ)	Neck injury	Narrow
Accidents and injuries (SMQ)	Nerve compression	Broad
Accidents and injuries (SMQ)	Nerve injury	Narrow
Accidents and injuries (SMQ)	Nerve root injury	Narrow
Accidents and injuries (SMQ)	Nerve root injury cervical	Narrow
Accidents and injuries (SMQ)	Nerve root injury lumbar	Narrow
Accidents and injuries (SMQ)	Nerve root injury sacral	Narrow
Accidents and injuries (SMQ)	Nerve root injury thoracic	Narrow
Accidents and injuries (SMQ)	Esophageal injury	Narrow
Accidents and injuries (SMQ)	Esophageal rupture	Narrow
Accidents and injuries (SMQ)	Open fracture	Narrow
Accidents and injuries (SMQ)	Open globe injury	Narrow
Accidents and injuries (SMQ)	Optic nerve injury	Narrow
Accidents and injuries (SMQ)	Optic pathway injury	Narrow
Accidents and injuries (SMQ)	Osteochondral fracture	Narrow
Accidents and injuries (SMQ)	Pancreatic duct rupture	Narrow
Accidents and injuries (SMQ)	Pancreatic injury	Narrow
Accidents and injuries (SMQ)	Parasympathetic nerve injury	Narrow
Accidents and injuries (SMQ)	Patella fracture	Narrow
Accidents and injuries (SMQ)	Pellegrini Stieda disease	Narrow
Accidents and injuries (SMQ)	Pelvic fracture	Narrow
Accidents and injuries (SMQ)	Pelvic organ injury	Narrow
Accidents and injuries (SMQ)	Penetrating abdominal trauma	Narrow
Accidents and injuries (SMQ)	Penetrating eye injury repair	Narrow
Accidents and injuries (SMQ)	Penile contusion	Narrow
Accidents and injuries (SMQ)	Penis injury	Narrow
Accidents and injuries (SMQ)	Penis reattachment	Narrow
Accidents and injuries (SMQ)	Perforation bile duct	Broad
Accidents and injuries (SMQ)	Perineal injury	Narrow
Accidents and injuries (SMQ)	Peripheral nerve injury	Narrow
Accidents and injuries (SMQ)	Peritoneal perforation	Broad
Accidents and injuries (SMQ)	Peroneal nerve injury	Narrow
Accidents and injuries (SMQ)	Pharyngeal injury	Narrow
Accidents and injuries (SMQ)	Photoelectric conjunctivitis	Narrow
Accidents and injuries (SMQ)	Pneumothorax traumatic	Narrow
Accidents and injuries (SMQ)	Post-concussion syndrome	Broad
Accidents and injuries (SMQ)	Post-traumatic headache	Narrow
Accidents and injuries (SMQ)	Post-traumatic neck syndrome	Narrow
Accidents and injuries (SMQ)	Post-traumatic osteoporosis	Broad
Accidents and injuries (SMQ)	Post-traumatic pain	Broad
Accidents and injuries (SMQ)	Posterior capsule rupture	Narrow
Accidents and injuries (SMQ)	Posterior tibial nerve injury	Narrow
Accidents and injuries (SMQ)	Prevertebral soft tissue swelling of cervical space	Broad

Standardized MedDRA queries (SMQ)	Preferred term	Term scope text
Accidents and injuries (SMQ)	Product package associated injury	Narrow
Accidents and injuries (SMQ)	Pubis fracture	Narrow
Accidents and injuries (SMQ)	Pulmonary contusion	Narrow
Accidents and injuries (SMQ)	Radial head dislocation	Narrow
Accidents and injuries (SMQ)	Radial nerve injury	Narrow
Accidents and injuries (SMQ)	Radius fracture	Narrow
Accidents and injuries (SMQ)	Rectal injury	Narrow
Accidents and injuries (SMQ)	Renal injury	Broad
Accidents and injuries (SMQ)	Repair of diaphragm injury	Narrow
Accidents and injuries (SMQ)	Retinal detachment	Broad
Accidents and injuries (SMQ)	Retinal injury	Narrow
Accidents and injuries (SMQ)	Retinal tear	Broad
Accidents and injuries (SMQ)	Rib fracture	Narrow
Accidents and injuries (SMQ)	Road traffic accident	Narrow
Accidents and injuries (SMQ)	Sacroiliac fracture	Narrow
Accidents and injuries (SMQ)	Scapula fracture	Narrow
Accidents and injuries (SMQ)	Scapulothoracic dissociation	Narrow
Accidents and injuries (SMQ)	Sciatic nerve injury	Narrow
Accidents and injuries (SMQ)	Scratch	Narrow
Accidents and injuries (SMQ)	Sinus tarsi syndrome	Narrow
Accidents and injuries (SMQ)	Skeletal injury	Narrow
Accidents and injuries (SMQ)	Skin abrasion	Broad
Accidents and injuries (SMQ)	Skin injury	Narrow
Accidents and injuries (SMQ)	Skull fracture	Narrow
Accidents and injuries (SMQ)	Skull fractured base	Narrow
Accidents and injuries (SMQ)	Snake bite	Broad
Accidents and injuries (SMQ)	Soft tissue injury	Narrow
Accidents and injuries (SMQ)	Spinal column injury	Narrow
Accidents and injuries (SMQ)	Spinal compression fracture	Narrow
Accidents and injuries (SMQ)	Spinal cord injury	Narrow
Accidents and injuries (SMQ)	Spinal cord injury cauda equina	Narrow
Accidents and injuries (SMQ)	Spinal cord injury cervical	Narrow
Accidents and injuries (SMQ)	Spinal cord injury lumbar	Narrow
Accidents and injuries (SMQ)	Spinal cord injury sacral	Narrow
Accidents and injuries (SMQ)	Spinal cord injury thoracic	Narrow
Accidents and injuries (SMQ)	Spinal epidural hematoma	Broad
Accidents and injuries (SMQ)	Spinal epidural hemorrhage	Broad
Accidents and injuries (SMQ)	Spinal fracture	Narrow
Accidents and injuries (SMQ)	Spinal fusion fracture	Narrow
Accidents and injuries (SMQ)	Spinal shock	Narrow
Accidents and injuries (SMQ)	Spinal subarachnoid hemorrhage	Narrow
Accidents and injuries (SMQ)	Spinal subdural hematoma	Broad
Accidents and injuries (SMQ)	Spleen contusion	Narrow
Accidents and injuries (SMQ)	Splenic injury	Narrow
Accidents and injuries (SMQ)	Splenic rupture	Narrow
Accidents and injuries (SMQ)	Splenosis	Broad
Accidents and injuries (SMQ)	Splinter	Narrow
Accidents and injuries (SMQ)	Spondylopathy traumatic	Narrow
Accidents and injuries (SMQ)	Sports injury	Narrow
Accidents and injuries (SMQ)	Stab wound	Narrow
Accidents and injuries (SMQ)	Sternal fracture	Narrow
Accidents and injuries (SMQ)	Sternal injury	Narrow

Standardized MedDRA queries (SMQ)	Preferred term	Term scope text
Accidents and injuries (SMQ)	Stress fracture	Narrow
Accidents and injuries (SMQ)	Struck by lightning	Narrow
Accidents and injuries (SMQ)	Subdural hematoma	Broad
Accidents and injuries (SMQ)	Subdural hematoma evacuation	Broad
Accidents and injuries (SMQ)	Subdural hemorrhage	Broad
Accidents and injuries (SMQ)	Subretinal fluid	Broad
Accidents and injuries (SMQ)	Sunburn	Narrow
Accidents and injuries (SMQ)	Superficial injury of eye	Narrow
Accidents and injuries (SMQ)	Sympathetic nerve injury	Narrow
Accidents and injuries (SMQ)	Synovial rupture	Broad
Accidents and injuries (SMQ)	Tendon injury	Narrow
Accidents and injuries (SMQ)	Tendon rupture	Narrow
Accidents and injuries (SMQ)	Testicular injury	Narrow
Accidents and injuries (SMQ)	Thermal burn	Narrow
Accidents and injuries (SMQ)	Thermal burns of eye	Narrow
Accidents and injuries (SMQ)	Thoracic vertebral fracture	Narrow
Accidents and injuries (SMQ)	Tibia fracture	Narrow
Accidents and injuries (SMQ)	Tongue injury	Narrow
Accidents and injuries (SMQ)	Tooth avulsion	Narrow
Accidents and injuries (SMQ)	Tooth fracture	Narrow
Accidents and injuries (SMQ)	Tooth injury	Narrow
Accidents and injuries (SMQ)	Torus fracture	Narrow
Accidents and injuries (SMQ)	Tracheal injury	Narrow
Accidents and injuries (SMQ)	Traumatic amputation	Narrow
Accidents and injuries (SMQ)	Traumatic anuria	Narrow
Accidents and injuries (SMQ)	Traumatic arthritis	Narrow
Accidents and injuries (SMQ)	Traumatic arthropathy	Narrow
Accidents and injuries (SMQ)	Traumatic arthrosis	Narrow
Accidents and injuries (SMQ)	Traumatic coma	Narrow
Accidents and injuries (SMQ)	Traumatic ear amputation	Narrow
Accidents and injuries (SMQ)	Traumatic fracture	Narrow
Accidents and injuries (SMQ)	Traumatic hematoma	Narrow
Accidents and injuries (SMQ)	Traumatic hemorrhage	Narrow
Accidents and injuries (SMQ)	Traumatic hemothorax	Narrow
Accidents and injuries (SMQ)	Traumatic intracranial hemorrhage	Narrow
Accidents and injuries (SMQ)	Traumatic iritis	Narrow
Accidents and injuries (SMQ)	Traumatic liver injury	Narrow
Accidents and injuries (SMQ)	Traumatic lung injury	Narrow
Accidents and injuries (SMQ)	Traumatic pancreatitis	Narrow
Accidents and injuries (SMQ)	Traumatic renal injury	Narrow
Accidents and injuries (SMQ)	Traumatic shock	Narrow
Accidents and injuries (SMQ)	Traumatic spinal cord compression	Narrow
Accidents and injuries (SMQ)	Traumatic torticollis	Narrow
Accidents and injuries (SMQ)	Traumatic ulcer	Narrow
Accidents and injuries (SMQ)	Traumatic ulcerative granuloma with stromal eosinophilia	Broad
Accidents and injuries (SMQ)	Trench foot	Broad
Accidents and injuries (SMQ)	Tympanic membrane perforation	Broad
Accidents and injuries (SMQ)	Ulna fracture	Narrow
Accidents and injuries (SMQ)	Ulnar nerve injury	Narrow
Accidents and injuries (SMQ)	Upper limb fracture	Narrow

Standardized MedDRA queries (SMQ)	Preferred term	Term scope text
Accidents and injuries (SMQ)	Ureteric injury	Narrow
Accidents and injuries (SMQ)	Ureteric perforation	Broad
Accidents and injuries (SMQ)	Ureteric rupture	Narrow
Accidents and injuries (SMQ)	Urethral injury	Narrow
Accidents and injuries (SMQ)	Urethral perforation	Broad
Accidents and injuries (SMQ)	Urethral stricture traumatic	Narrow
Accidents and injuries (SMQ)	Urinary bladder rupture	Narrow
Accidents and injuries (SMQ)	Urinary tract injury	Narrow
Accidents and injuries (SMQ)	Uterine perforation	Broad
Accidents and injuries (SMQ)	Uveal prolapse	Broad
Accidents and injuries (SMQ)	VIIIth nerve injury	Narrow
Accidents and injuries (SMQ)	VIIth nerve injury	Narrow
Accidents and injuries (SMQ)	VIth nerve injury	Narrow
Accidents and injuries (SMQ)	Vaginal laceration	Narrow
Accidents and injuries (SMQ)	Vaginal perforation	Broad
Accidents and injuries (SMQ)	Vascular injury	Narrow
Accidents and injuries (SMQ)	Vascular rupture	Narrow
Accidents and injuries (SMQ)	Vena cava injury	Narrow
Accidents and injuries (SMQ)	Venous injury	Narrow
Accidents and injuries (SMQ)	Ventricle rupture	Narrow
Accidents and injuries (SMQ)	Vitreous detachment	Broad
Accidents and injuries (SMQ)	Vitreous injury	Narrow
Accidents and injuries (SMQ)	Vitreous loss	Broad
Accidents and injuries (SMQ)	Vitreous prolapse	Broad
Accidents and injuries (SMQ)	Vth nerve injury	Narrow
Accidents and injuries (SMQ)	Vulval laceration	Narrow
Accidents and injuries (SMQ)	Vulvovaginal injury	Narrow
Accidents and injuries (SMQ)	Wound	Broad
Accidents and injuries (SMQ)	Wrist fracture	Narrow
Accidents and injuries (SMQ)	XIIth nerve injury	Narrow
Accidents and injuries (SMQ)	XIth nerve injury	Narrow
Convulsions (SMQ)	Acquired epileptic aphasia	Narrow
	Acute encephalitis with refractory, repetitive partial seizures	Narrow
Convulsions (SMQ)	Alcoholic seizure	Narrow
Convulsions (SMQ)	Amygdalohippocampectomy	Broad
Convulsions (SMQ)	Atonic seizures	Narrow
Convulsions (SMQ)	Atypical benign partial epilepsy	Narrow
Convulsions (SMQ)	Aura	Broad
Convulsions (SMQ)	Automatism epileptic	Narrow
Convulsions (SMQ)	Autonomic seizure	Narrow
Convulsions (SMQ)	Baltic myoclonic epilepsy	Narrow
	Benign familial neonatal convulsions	Narrow
Convulsions (SMQ)	Benign rolandic epilepsy	Narrow
Convulsions (SMQ)	Biotinidase deficiency	Narrow
Convulsions (SMQ)	Change in seizure presentation	Narrow
Convulsions (SMQ)	Clonic convulsion	Narrow
Convulsions (SMQ)	Complex partial seizures	Narrow
Convulsions (SMQ)	Convulsion in childhood	Narrow
Convulsions (SMQ)	Convulsion neonatal	Narrow
Convulsions (SMQ)	Convulsion prophylaxis	Broad
Convulsions (SMQ)	Convulsions local	Narrow

Standardized MedDRA queries (SMQ)	Preferred term	Term scope text
Convulsions (SMQ)	Convulsive threshold lowered	Narrow
Convulsions (SMQ)	Corpus callosotomy	Broad
Convulsions (SMQ)	Deja vu	Narrow
Convulsions (SMQ)	Double cortex syndrome	Narrow
Convulsions (SMQ)	Dreamy state	Narrow
Convulsions (SMQ)	Drop attacks	Broad
Convulsions (SMQ)	Drug withdrawal convulsions	Narrow
	Early infantile epileptic encephalopathy with burst-suppression	Narrow
Convulsions (SMQ)	Eclampsia	Narrow
Convulsions (SMQ)	Epilepsy	Narrow
Convulsions (SMQ)	Epileptic aura	Narrow
Convulsions (SMQ)	Epileptic psychosis	Narrow
Convulsions (SMQ)	Febrile convulsion	Narrow
Convulsions (SMQ)	Foaming at mouth	Broad
Convulsions (SMQ)	Frontal lobe epilepsy	Narrow
	Generalized non-convulsive epilepsy	Narrow
Convulsions (SMQ)	Generalized tonic-clonic seizure	Narrow
Convulsions (SMQ)	Hyperglycemic seizure	Narrow
Convulsions (SMQ)	Hypocalcemic seizure	Narrow
Convulsions (SMQ)	Hypoglycemic seizure	Narrow
Convulsions (SMQ)	Hyponatremic seizure	Narrow
Convulsions (SMQ)	Idiopathic generalized epilepsy	Narrow
Convulsions (SMQ)	Infantile spasms	Narrow
Convulsions (SMQ)	Juvenile myoclonic epilepsy	Narrow
Convulsions (SMQ)	Lafora's myoclonic epilepsy	Narrow
Convulsions (SMQ)	Lennox-Gastaut syndrome	Narrow
Convulsions (SMQ)	Migraine-triggered seizure	Narrow
	Molybdenum cofactor deficiency	Narrow
Convulsions (SMQ)	Myoclonic epilepsy	Narrow
	Myoclonic epilepsy and ragged-red fibers	Narrow
Convulsions (SMQ)	Narcolepsy	Broad
Convulsions (SMQ)	Partial seizures	Narrow
	Partial seizures with secondary generalization	Narrow
Convulsions (SMQ)	Petit mal epilepsy	Narrow
Convulsions (SMQ)	Polymicrogyria	Narrow
Convulsions (SMQ)	Post stroke epilepsy	Narrow
Convulsions (SMQ)	Post stroke seizure	Narrow
Convulsions (SMQ)	Post-traumatic epilepsy	Narrow
Convulsions (SMQ)	Postictal headache	Narrow
Convulsions (SMQ)	Postictal paralysis	Narrow
Convulsions (SMQ)	Postictal psychosis	Narrow
Convulsions (SMQ)	Postictal state	Narrow
Convulsions (SMQ)	Preictal state	Broad
Convulsions (SMQ)	Psychomotor seizures	Narrow
Convulsions (SMQ)	Schizencephaly	Narrow
Convulsions (SMQ)	Seizure	Narrow
Convulsions (SMQ)	Seizure anoxic	Narrow

Standardized MedDRA queries (SMQ)	Preferred term	Term scope text
Convulsions (SMQ)	Seizure cluster	Narrow
Convulsions (SMQ)	Seizure like phenomena	Narrow
Convulsions (SMQ)	Severe myoclonic epilepsy of infancy	Narrow
Convulsions (SMQ)	Simple partial seizures	Narrow
Convulsions (SMQ)	Status epilepticus	Narrow
Convulsions (SMQ)	Sudden unexplained death in epilepsy	Narrow
Convulsions (SMQ)	Temporal lobe epilepsy	Narrow
Convulsions (SMQ)	Tongue biting	Broad
Convulsions (SMQ)	Tonic clonic movements	Narrow
Convulsions (SMQ)	Tonic convulsion	Narrow
Convulsions (SMQ)	Tonic posturing	Narrow
Convulsions (SMQ)	Topectomy	Narrow
Convulsions (SMQ)	Uncinate fits	Narrow
nmq_hypo	Blood glucose decreased	Narrow
nmq_hypo	Hyperinsulinaemic hypoglycemia	Narrow
nmq_hypo	Hypoglycemia	Narrow
nmq_hypo	Hypoglycemia neonatal	Narrow
nmq_hypo	Hypoglycemia unawareness	Narrow
nmq_hypo	Hypoglycemic coma	Narrow
nmq_hypo	Hypoglycemic encephalopathy	Narrow
nmq_hypo	Hypoglycemic seizure	Narrow
nmq_hypo	Hypoglycemic unconsciousness	Narrow
nmq_hypo	Neuroglycopenia	Narrow
nmq_hypo	Shock hypoglycemic	Narrow

eTable 3. Multiple imputation tipping analysis for primary endpoint

	Insulin degludec	Insulin glargine U100	ERR [95%CI]
Rate per 100 PYE – MI analysis	99.1	142.1	0.70 [0.61; 0.80]
Rate per 100 PYE – MI tipping point analysis	4 episode penalty		0.92 [0.81; 1.04]
Completers			
N	607	599	
PYE	186.6	184.3	
Total no. of episodes	344	492	
Mean no. of episodes	0.6	0.8	
Rate per 100 PYE	184.4	267.0	
Non-completers multiple imputation			
N	64	66	
PYE	19.7	20.3	
Total no. of episodes	67	70	
Mean no. of episodes	1	1.1	
Rate per 100 PYE	340.0	343.5	
Non-completers tipping point			
N	64	66	
PYE	19.7	20.3	
Total no. of episodes	323.0	70	
Mean no. of episodes	5	1.1	
Rate per 100 PYE	1640.0	343.5	

CI, confidence interval; ERR, estimated rate ratio; MI, multiple imputation; N, number of patients; PYE, patient-years of exposure

For the tipping-point analysis, 4 episodes are added to the values obtained from multiple imputation for all patients on insulin degludec.

eTable 4. Insulin dose

Insulin dose (Units)			
Treatment arm	Baseline	End of treatment period 1	End of treatment period 2
IDeg/IGlar	40 (22)	70 (41)	83 (50)
IGlar/IDeg	43 (26)	74 (41)	83 (54)

Data are arithmetic mean (standard deviation) for the safety analysis set. IDeg, insulin degludec; IGlar, insulin glargine U100. Only patients with exposure time in both maintenance periods contribute to the analysis.

eTable 5. Adverse events

	IDeg (n = 671) PYE = 388.8				IGlar (n = 665) PYE = 383.5			
	n	%	E	Rate/ 100 PYE [95% CI]	n	%	E	Rate/ 100 PYE [95% CI]
AEs	384	57.2	1293	332.6 [314.5; 350.7]	406	61.1	1381	360.1 [341.1; 379.1]
Serious AEs	64	9.5	80	20.6 [16.1; 25.1]	65	9.8	96	25.0 [20.0; 30.0]
Severe AEs	58	8.6	89	22.9 [18.1; 27.7]	52	7.8	90	23.5 [18.6; 28.3]
AEs probably related to trial product	9	1.3	14	3.6 [1.7; 5.5]	18	2.7	20	5.2 [2.9; 7.5]
Serious AEs probably related to trial product	2	0.3	2	0.5 [-0.2; 1.2]	7	1.1	7	1.8 [0.5; 3.2]

Data are for safety analysis set. AE, adverse event; CI, confidence interval; E, number of events; IDeg, insulin degludec; IGlar, insulin glargine U100; n, number of patients with events; PYE, patient-years of exposure; Rate, unadjusted event rate (events/100 patient-years of exposure); %, proportion of patients with events.