SUPPLEMENTAL MATERIAL

Data S1. Supplemental Methods

Inclusion Criteria

Subjects must meet all of the following criteria:

1 In Part A, subjects aged 18 through 65 inclusive at screening. In Part B, male subjects aged 18 through 65 inclusive, and female subjects aged 40 to 65 inclusive, at screening.

2 For the Japanese cohort A6, subjects must be Japanese (eg, natives of Japan or Japanese Americans), defined as having both parents and four grandparents who are Japanese. This includes second and third generation subjects of Japanese descent whose parents or grandparents are living in a country other than Japan.

3 Body mass index of 18 to 45kg/m^2.

4 Subjects with type 2 diabetes mellitus (T2DM) on stable medical therapy for at least 6 weeks prior to screening, and no clinically significant dose change and/or new medications added during the 6 weeks prior to screening.

5 Capable of giving written informed consent.

6 Able and willing to meet all eligibility requirements for randomization within 28 days after signing the informed consent form, to adhere to visit/protocol schedule, and to complete the follow-up period.

7 Female subjects must be of nonchildbearing potential, confirmed at screening by one of the below.

   (a) Postmenopausal, defined as amenorrhea for ≥12 months following cessation of all exogenous hormonal treatments, and luteinizing hormone and follicle stimulating hormone levels in the postmenopausal range.

(b) Documentation of irreversible surgical sterilization by hysterectomy, bilateral oophorectomy, or bilateral salpingectomy. Tubal ligation is not considered to be irreversible surgical sterilization.

8 Nonsterilized male subjects who are sexually active with a female partner of childbearing potential must use a male condom plus spermicide, and in addition the female partner must use one highly effective method of contraception (Appendix **Error! Reference source not found.**), from day 1 through 190 days post final dose.

9 In Part B, subjects must meet computed tomography angiography (CTA) criteria as follows:

(a) estimated glomerular filtration rate (eGFR) ≥60mL/min/1.73m^2

(b) no allergy to iodinated contrast

(c) no history of contrast induced nephropathy

(d) no contraindication to beta blockers or nitroglycerin

(e) no pulmonary embolism in the past 2 years

(f) able to hold breath for at least 6 seconds

(g) no history of coronary bypass surgery

(h) no active arrhythmia on day of CTA scan (atrial fibrillation, atrial flutter, frequent premature atrial, or ventricular contractions).

Exclusion Criteria

Any of the below would exclude the subject from participation in the study.

1 History of any clinically important disease or disorder (not including T2DM) which, in the opinion of the investigator, may either put the subject at risk because of participation in the study, or influence the results or the subject's ability to participate in the study.

2 History or presence of hepatic or renal disease, or any other condition known to interfere with absorption, distribution, metabolism, or excretion of drugs.

3 Any clinically important illness, medical/surgical procedure, or trauma within 4 weeks of the first administration of investigational product, or planned surgical procedure before study completion.

4 Female subjects who are pregnant and/or currently lactating.

5 Any clinically important abnormalities in clinical chemistry, hematology, coagulation parameters, or urinalysis results as judged by the investigator, including but not limited to:

(a) aspartate transaminase >2.0×upper limit of normal (ULN)

(b) alanine transaminase >2.0×ULN

(c) total bilirubin >ULN (unless due to Gilbert's syndrome)

(d) hemoglobin <lower limit of normal

(e) platelet count <100 000/μL

(f) impaired renal function, defined as eGFR <60mL/min/1.73m^2 assessed by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.

6 History of blood dyscrasia, hemostatic disorder, systemic bleeding, or prior trauma that places the subject at a higher risk of bleeding.

7 History of hemophilia, von Willebrand disease, lupus anticoagulant, or other diseases/syndromes that can either alter or increase the propensity of bleeding.

8 History of vascular abnormalities including aneurysms or prior dissections; history of severe hemorrhage, hematemesis, melena, hemoptysis, severe epistaxis, severe thrombocytopenia, intracranial hemorrhage, rectal bleeding, or major surgery/procedure within 3 months prior to visit 1; or a history suggestive of active peptic ulcer disease or prior intracranial hemorrhage as judged by the investigator.

9 History of a clinically significant nontraumatic bleed or clinically significant enhanced bleeding risk as judged by the investigator.

10 Dual-antiplatelet therapy, anticoagulation therapy (ie, warfarin, factor Xa inhibitors, direct thrombin inhibitors, or heparin), or thrombolytic use, in the past month or planned use during the duration of the study.

11 Chronic aspirin therapy (aspirin therapy is acceptable at doses ≤150mg daily), or chronic anti-inflammatory therapy including nonsteroidal anti-inflammatory drugs.

12 Any clinically important abnormalities in rhythm, conduction, or morphology of the resting electrocardiography (ECG) that in the opinion of the investigator may interfere with the interpretation of corrected QT interval (QTc) changes. Clinically important abnormalities include, but not limited to (based on the mean values of triplicate ECGs):

(a) prolonged QT interval corrected by Fredericia's formula (QTcF) >450ms, shortened QTcF <340ms, or family history of long QT syndrome

(b) PR (PQ) interval shortening <120ms (PR >110ms; <120ms is acceptable if there is no evidence of ventricular preexcitation)

(c) PR (PQ) interval prolongation (>240ms) intermittent second (Wenckebach block while asleep is not exclusive), third degree atrial ventricular (AV) block, or AV dissociation.

13 Persistent or intermittent complete bundle branch block, incomplete bundle branch block, or intraventricular conduction delay with QRS >110ms (based on the mean values of triplicate ECGs). Subjects with QRS >110ms but <115ms are acceptable if there is no evidence of ventricular hypertrophy or preexcitation.

14 Abnormal vital signs after 10 minutes of supine rest, defined as any of the following identified at screening or on day –1:

(a) systolic blood pressure (BP) <90mmHg or >150mmHg

(b) diastolic BP <50mmHg or >90mmHg

(c) heart rate <45 or >85 beats per minute.

15 Subjects using insulin.

16 Hemoglobin A1c >9.0% measured at screening. HbA1c can be retested once after approximately 4 weeks.

17 Active/ongoing diabetic foot ulceration and/or clinical evidence of critical limb ischemia.

18 Clinically significant late diabetic complications including symptoms consistent with angina, congestive heart failure, and peripheral arterial disease (claudication), or other complications such as proliferative retinopathy, maculopathy, or gastroparesis.

19 Any positive result at screening for serum hepatitis B surface antigen, hepatitis C antibody, or HIV.

20 History of cancer in the last 5 years, with the exception of nonmelanoma skin cancer.

21 History of alcohol or substance abuse within the past 6 months. A positive drug screen will be exclusionary, including recreational marijuana. However, subjects with a documented medical need or prescription may be included at the discretion of the principal investigator.

22 History of hypersensitivity or ongoing severe allergy as judged by the investigator, or history of hypersensitivity to drugs with a similar chemical structure or class to MEDI6570.

23 History of ongoing infection or febrile illness within 30 days prior to day 1.

24 Current or previous use of systemic corticosteroids within 28 days prior to screening. Topical, intra-articular, nasal, inhaled, and ophthalmic corticosteroids are permitted.

25 Receipt of any investigational product or use of any biologics within 6 months or five half-lives prior to screening (whichever is longer), or planned participation in an additional study of an investigational product therapy or biologic prior to end of follow-up period.

26 Donation of blood, or clinically significant blood loss >500mL within 3 months prior to day 1.

27 Subjects who are legally institutionalized.

28 An employee, or close relative of an employee, of AstraZeneca, MedImmune, the contract research organization, or the study center, regardless of the employee's role.

Table S1. Treatment-Emergent Adverse Events by System Organ Class in Part A

System organ class* Preferred term (MedDRA version 23.0)	Part A, single ascending dose								
	Placebo (n=12)	10mg (n=6)	30mg (n=6)	90mg (n=6)	250mg (n=6)	500mg (n=6)	500mg Japanese (n=6)	MEDI6570 total (n=36)	Total (N=48)
Participants with at least one event	6 (50.0%)	2 (33.3%)	5 (83.3%)	3 (50.0%)	3 (50.0%)	4 (66.7%)	5 (83.3%)	22 (61.1%)	28 (58.3%)
General disorders and administration site conditions	1 (8.3%)	0	1 (16.7%)	0	2 (33.3%)	0	1 (16.7%)	4 (11.1%)	5 (10.4%)
Injection site erosion	1 (8.3%)	0	0	0	0	0	0	0	1 (2.1%)
Injection site reaction	0	0	0	0	1 (16.7%)	0	0	1 (2.8%)	1 (2.1%)
Medical device site reaction	0	0	1 (16.7%)	0	0	0	0	1 (2.8%)	1 (2.1%)
Pyrexia	0	0	0	0	1 (16.7%)	0	1 (16.7%)	2 (5.6%)	2 (4.2%)
Immune system disorders	0	0	0	0	1 (16.7%)	0	0	1 (2.8%)	1 (2.1%)

Drug hypersensitivity	0	0	0	0	1 (16.7%)	0	0	1 (2.8%)	1 (2.1%)
Infections	1 (8.3%)	0	2 (33.3%)	3 (50.0%)	1 (16.7%)	2 (33.3%)	3 (50.0%)	11 (30.6%)	12 (25.0%)
Arthritis infective	0	0	0	0	0	1 (16.7%)	0	1 (2.8%)	1 (2.1%)
Influenza	0	0	0	0	0	0	1 (16.7%)	1 (2.8%)	1 (2.1%)
Nasopharyngitis	0	0	0	1 (16.7%)	0	0	0	1 (2.8%)	1 (2.1%)
Osteomyelitis	0	0	0	0	0	1 (16.7%)	0	1 (2.8%)	1 (2.1%)
Pyelonephritis	0	0	0	0	1 (16.7%)	0	0	1 (2.8%)	1 (2.1%)
Sinusitis	0	0	0	1 (16.7%)	0	0	0	1 (2.8%)	1 (2.1%)
Streptococcal infection	0	0	0	0	0	0	1 (16.7%)	1 (2.8%)	1 (2.1%)
Upper respiratory tract infection	1 (8.3%)	0	2 (33.3%)	0	0	1 (16.7%)	1 (16.7%)	4 (11.1%)	5 (10.4%)
Urinary tract infection	0	0	0	1 (16.7%)	0	0	0	1 (2.8%)	1 (2.1%)
Injury, poisoning, and procedural complications	3 (25.0%)	0	1 (16.7%)	0	2 (33.3%)	1 (16.7%)	1 (16.7%)	5 (13.9%)	8 (16.7%)
Ankle fracture	1 (8.3%)	0	0	0	0	0	0	0	1 (2.1%)
Arthropod bite	0	0	0	0	0	1 (16.7%)	0	1 (2.8%)	1 (2.1%)
Contusion	1 (8.3%)	0	0	0	1 (16.7%)	0	0	1 (2.8%)	2 (4.2%)

Ligament sprain	1 (8.3%)	0	0	0	0	0	0	0	1 (2.1%)
Limb injury	0	0	1 (16.7%)	0	0	0	0	1 (2.8%)	1 (2.1%)
Muscle strain	1 (8.3%)	0	0	0	1 (16.7%)	0	0	1 (2.8%)	2 (4.2%)
Skin abrasion	0	0	0	0	0	0	1 (16.7%)	1 (2.8%)	1 (2.1%)
Musculoskeletal and connective tissue disorders	3 (25.0%)	0	1 (16.7%)	1 (16.7%)	1 (16.7%)	3 (50.0%)	2 (33.3%)	8 (22.2%)	11 (22.9%)
Arthralgia	1 (8.3%)	0	0	0	0	0	0	0	1 (2.1%)
Arthritis	0	0	0	0	0	1 (16.7%)	0	1 (2.8%)	1 (2.1%)
Back pain	1 (8.3%)	0	1 (16.7%)	0	0	1 (16.7%)	0	2 (5.6%)	3 (6.3%)
Neck pain	0	0	0	0	0	0	1 (16.7%)	1 (2.8%)	1 (2.1%)
Osteoarthritis	0	0	0	1 (16.7%)	0	0	1 (16.7%)	2 (5.6%)	2 (4.2%)
Osteopenia	1 (8.3%)	0	0	0	0	0	0	0	1 (2.1%)
Synovitis	0	0	0	0	0	1 (16.7%)	0	1 (2.8%)	1 (2.1%)
Systemic lupus erythematosus	0	0	0	0	1 (16.7%)	0	0	1 (2.8%)	1 (2.1%)

*Patients are counted once per category regardless of the number of events.

Table S2. Treatment-Emergent Adverse Events by System Organ Class in Part B

System organ class* Preferred term (MedDRA version 23.0)	Part B, multiple ascending dose					
	Placebo (n=10)	90mg (n=10)	150mg (n=10)	250mg (n=10)	MEDI6570 total (n=30)	Total (N=40)
Participants with at least one event	7 (70.0%)	7 (70.0%)	6 (60.0%)	9 (90.0%)	22 (73.3%)	29 (72.5%)
Gastrointestinal disorders	2 (20.0%)	2 (20.0%)	1 (10.0%)	2 (20.0%)	5 (16.7%)	7 (17.5%)
Abdominal pain upper	0	1 (10.0%)	0	0	1 (3.3%)	1 (2.5%)
Colitis ischemic	0	0	0	1 (10.0%)	1 (3.3%)	1 (2.5%)
Constipation	0	1 (10.0%)	1 (10.0%)	0	2 (6.7%)	2 (5.0%)
Dental caries	0	0	0	1 (10.0%)	1 (3.3%)	1 (2.5%)
Diarrhea	2 (20.0%)	0	0	0	0	2 (5.0%)
Dyspepsia	0	0	1 (10.0%)	0	1 (3.3%)	1 (2.5%)
Feces discolored	0	1 (10.0%)	0	0	1 (3.3%)	1 (2.5%)
Vomiting	0	0	0	1 (10.0%)	1 (3.3%)	1 (2.5%)
General disorders and administration site conditions	1 (10.0%)	2 (20.0%)	1 (10.0%)	3 (30.0%)	6 (20.0%)	7 (17.5%)
Injection site erythema	0	1 (10.0%)	0	1 (10.0%)	2 (6.7%)	2 (5.0%)

Injection site reaction	1 (10.0%)	1 (10.0%)	0	0	1 (3.3%)	2 (5.0%)
Nodule	0	0	0	1 (10.0%)	1 (3.3%)	1 (2.5%)
Edema	0	0	0	1 (10.0%)	1 (3.3%)	1 (2.5%)
Peripheral swelling	0	0	1 (10.0%)	0	1 (3.3%)	1 (2.5%)
Infections	2 (20.0%)	2 (20.0%)	2 (20.0%)	4 (40.0%)	8 (26.7%)	10 (25.0%)
Bronchitis	1 (10.0%)	0	0	1 (10.0%)	1 (3.3%)	2 (5.0%)
Cellulitis	0	0	0	1 (10.0%)	1 (3.3%)	1 (2.5%)
Ear infection	0	0	1 (10.0%)	0	1 (3.3%)	1 (2.5%)
Influenza	0	0	0	1 (10.0%)	1 (3.3%)	1 (2.5%)
Nasopharyngitis	0	1 (10.0%)	0	0	1 (3.3%)	1 (2.5%)
Postoperative wound infection	1 (10.0%)	0	0	0	0	1 (2.5%)
Sepsis	1 (10.0%)	0	0	0	0	1 (2.5%)
Sinobronchitis	0	1 (10.0%)	0	0	1 (3.3%)	1 (2.5%)
Upper respiratory tract infection	1 (10.0%)	1 (10.0%)	1 (10.0%)	1 (10.0%)	3 (10.0%)	4 (10.0%)
Viral upper respiratory tract infection	1 (10.0%)	0	0	0	0	1 (2.5%)
Injury, poisoning, and procedural complications	3 (30.0%)	2 (20.0%)	2 (20.0%)	2 (20.0%)	6 (20.0%)	9 (22.5%)
Animal bite	1 (10.0%)	0	0	0	0	1 (2.5%)

Arthropod bite	0	0	0	1 (10.0%)	1 (3.3%)	1 (2.5%)
Burns first degree	1 (10.0%)	0	0	0	0	1 (2.5%)
Joint dislocation	0	0	0	1 (10.0%)	1 (3.3%)	1 (2.5%)
Ligament sprain	0	0	0	1 (10.0%)	1 (3.3%)	1 (2.5%)
Limb injury	1 (10.0%)	0	0	0	0	1 (2.5%)
Muscle strain	0	1 (10.0%)	0	0	1 (3.3%)	1 (2.5%)
Skin abrasion	0	0	1 (10.0%)	0	1 (3.3%)	1 (2.5%)
Skin laceration	0	0	1 (10.0%)	0	1 (3.3%)	1 (2.5%)
Sunburn	0	1 (10.0%)	0	0	1 (3.3%)	1 (2.5%)
Musculoskeletal and connective tissue disorders	3 (30.0%)	0	1 (10.0%)	2 (20.0%)	3 (10.0%)	6 (15.0%)
Arthralgia	1 (10.0%)	0	0	0	0	1 (2.5%)
Back pain	0	0	0	1 (10.0%)	1 (3.3%)	1 (2.5%)
Intervertebral disc protrusion	1 (10.0%)	0	0	0	0	1 (2.5%)
Myalgia	1 (10.0%)	0	0	0	0	1 (2.5%)
Pain in extremity	0	0	1 (10.0%)	1 (10.0%)	2 (6.7%)	2 (5.0%)

*Patients are counted once per category regardless of the number of events.