SUPPLEMENTARY MATERIALS

Inclusion and exclusion criteria for eligibility to participate in CHIPS study

Inclusion criteria
1. Males or females, aged 18 - 40 years (inclusive).
2. Body mass index of 18.0 - 32.0 kg/m^2, inclusive, and body weight ≥ 50.0kg
3. Medically healthy, determined by medical history, physical examination, transthoracic echocardiogram, laboratory profiles without any clinically significant abnormalities, vital signs, and 12-lead ECG at screening.
4. Systolic blood pressure (SBP) of 90 mmHg – 140 mmHg and diastolic blood pressure (DBP) of 40 mmHg - 90 mmHg.
5. Resting heart rate (HR) of 40-100 bpm
6. Females must be non-pregnant, non-lactating or postmenopausal.
7. Females of childbearing potential must agree to use a barrier method for the duration of study
8. Must be willing and able to read, understand, and sign the participant information and consent form. Willing to comply with all study requirements.
9. Willing to abstain from the use of mouthwash from the day of screening until the first outpatient visit.
10. Must be willing for insertion and have adequate sites for placement of indwelling intravenous cannulae and midline intravenous catheter.
Exclusion criteria

1. Evidence of pre-existing immunity to the challenge strain, defined for this study as a high serum IgG to a peptide comprising the first fifty amino acids of the M75 protein (N-terminal hypervariable region) measured by ELISA.
2. Currently taking penicillins or use of any penicillin-based antibiotics from screening through to the final study visit. The use of probenecid, NSAIDs, or other medications which may significantly alter penicillin PK will also not be permitted within 14 days prior to study drug administration until completion of the final follow-up visit.
3. Any corticosteroid, immunomodulator or anticoagulant use in the previous 3 months, antiplatelet use in the previous 2 weeks, or anticipated use of such drugs during the study period. Any participant currently receiving or having previously received immunosuppressive therapy, including systemic steroids including adrenocorticotrophic hormone (ACTH) or inhaled steroids in dosages which are associated with hypothalamic-pituitary-adrenal axis suppression such as 1 mg/kg/day of prednisone (or its equivalent) or chronic use of inhaled high potency corticosteroids (budesonide 800 µg or fluticasone 750 µg per day). Intranasal corticosteroid use is not allowed from 14 days prior to admission, during the confinement period, and is discouraged prior to the first outpatient visit. Topical corticosteroid use is allowed.
4. Use of prescription or non-prescription drugs (except for oral contraceptive pill in healthy adult females) and herbal supplements (such as St John´s Wort) within 14 days or 5 half-lives (whichever is the longer) prior to the inoculation administration.
5. History of any clinically important cardiac, endocrine, haematological, hepatic, immunologic, metabolic, urologic, pulmonary, neurologic, dermatologic, psychiatric, and renal, or other major disease.
6. History of hospitalisation for illness within the six months prior to enrolment into study, or major surgery within the 12 months prior to enrolment into study.

7. History of tonsillectomy, adenoidectomy or splenectomy.
8. Known or suspected autoimmune disease or impairment/alteration of immune function resulting from:
    a. Congenital or acquired immunodeficiency (including IgA deficiency)
    b. Receipt of immunosuppressive therapy such as anti-cancer chemotherapy or radiation therapy within the preceding 6 months.
9. History of a severe drug reaction or severe allergic reaction (eg. anaphylaxis, convulsions) or clinically significant allergic disease diagnosed by a Physician.
10. Personal or family history of severe *S. pyogenes* infection or sequelae (such as acute rheumatic fever, rheumatic heart disease, post-streptococcal glomerulonephritis) or invasive *S. pyogenes* disease (toxic shock syndrome, necrotizing fasciitis, bloodstream infection, pleural empyema, meningitis, puerperal sepsis).
11. Clinically significant disease or any condition or disease that might affect drug absorption, distribution, or excretion, e.g. gastrectomy, diarrhoea.
12. Any vaccination within the last 28 days (except for COVID-19 or seasonal influenza) or use of any antibiotic therapy during the 14 days before challenge.
13. Presence of an acute infectious disease or febrile illness (e.g., sub-lingual temperature ≥ 37.5°C) within the five days prior to challenge with *S. pyogenes* M75.
14. Significant acute or chronic infection within 14 days prior to inoculation that the Investigator deems may compromise participant safety.
15. Any clinically significant abnormal finding on biochemistry or haematology blood tests, urine analysis, ECG or transthoracic echocardiogram at screening.
16. Laboratory tests that fail to meet the following thresholds:

a. Haematology: Haemoglobin, haematocrit, red cell count, white cell count with differentials, platelet count, MCH, MCV, MCHC– parameters within gender-specific reference intervals from the local laboratory unless deemed not clinically significant by the investigator.
b. Clinical chemistry within gender-specific reference intervals from the local laboratory unless deemed not clinically significant by the investigator: urea, glucose, creatinine, sodium, potassium, chloride and bicarbonate, lactate dehydrogenase, calcium, total protein, magnesium, phosphate, albumin, cholesterol, and uric acid. For renal function, an eGFR >90ml/min/m^2 will be considered normal using the CKD-EPI without albuminuria on dipstick.
c. Liver function tests: aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, total bilirubin, conjugated bilirubin, gamma-glutamyl transferase [<1.5 x ULN (ALT, GGT, Total Bilirubin; local laboratory gender-specific reference ranges) will be considered not clinically significant].
d. Negative HIV serology, Hepatitis B Surface Ag testing and hepatitis C serology.
e. Females with a negative serum pregnancy test at screening and negative urine pregnancy test at Baseline and admission

17. Ex-smoker with a >10 pack year smoking history or a current smoker who is unable to stop smoking for the duration of the study.
18. History or presence of alcohol abuse (defined as regular alcohol consumption of more than 40g or 4 standard drinks per day) or drug habituation, or any prior intravenous usage of an illicit substance.
19. A positive urine drug test at screening or admission for confinement (e.g., amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, and opiates) unless there is an explanation acceptable to the Investigator (e.g. the participant has stated in advance that they consumed a

prescription or OTC product which contained the detected drug) and the participant has a negative urine drug screen on retest.

20. A positive alcohol breath test at screening or admission for confinement.
21. Known hypersensitivity or other contraindication to use of penicillin, azithromycin or any other beta-lactam or macrolide antibiotic(s).
22. Known hypersensitivity to soya protein.
23. Intolerance of throat swab procedure (exaggerated gag reflex).
24. Participation in a research study that involved blood sampling of more than 450 mL of blood, received or donated blood, blood products and/or plasma derivatives or any parenteral immunoglobulin preparation within 3 months of screening.
25. History of severe infections requiring hospitalisation for intravenous antibiotics (within the last 10 years). Exceptions to this would include a short course of intravenous antibiotics for appendicitis, biliary sepsis, diverticulitis and cellulitis.
26. History of cancer (except adequately treated squamous cell or basal cell carcinoma of the skin and cervical intraepithelial neoplasia).
27. Presence of implants (except for contraceptive implants) or prosthesis (e.g. artificial joints, pacemakers).
28. Receipt of another investigational product within the 30 days prior to screening involving an investigational product or other intervention that might affect risk of invasive *S. pyogenes* infection or compromise the integrity of the study (e.g. significant volumes of blood already taken in previous study).

29. Any significant disease or disorder which, in the opinion of the Investigator, may either put the participants at risk because of participation in the study, or may influence the results of the study, or the participant's ability to participate in the study.
30. Any employee of the sponsor or research site personnel directly affiliated with this study or their immediate family members defined as a spouse, parent, sibling, or child whether biological or legally adopted.