Trial Review

Trial registered on ANZCTR

Trial ID	ACTRN12616000846426
Ethics application status	Approved
Date submitted	20/06/2016
Date registered	29/06/2016
Date last updated	17/07/2017
Type of registration	Prospectively registered

Titles & IDs

Public title	Dose escalation, placebo-controlled phase 1 study to assess the safety and tolerability of CSL324 in healthy adults
Scientific title	A single dose ascending and repeated dose, randomised, double-blind, placebo-controlled study to assess the safety, pharmacokinetics and pharmacodynamics of CSL324 in healthy, adult male and female subjects.
Secondary ID [1]	CSL324_1001
Universal Trial Number (UTN)	
Trial acronym	
Linked study record	

Health condition

Health condition(s) or problem(s) studied:	
Inflammatory and immune system disorders	
Condition category	**Condition code**
Inflammatory and Immune System	Other inflammatory or immune system disorders

Intervention/exposure

Study type	Interventional
Description of intervention(s) / exposure	The study will consist of 3 parts (Parts A, B and C). Subjects can participate in only 1 part and in only 1 dose group; in each part, subjects will be randomly assigned to either CSL324 or placebo. In Parts A and B a single infusion of either CSL324 or placebo will be administered; dose escalation may occur in these parts. There may be up to 6 subjects per dose in Parts A and B. In Part C, 10 subjects will receive 3 infusions at 21 day intervals of either CSL324 or placebo (according to their randomisation and at the same dose per infusion). Intervention 1: Single (Parts A and B) or repeat (Part C) dose(s) of anti-human granulocyte-colony stimulating factor (G-CSF) receptor monoclonal antibody (CSL324) will be administered intravenously (0.1, 0.3, 1, 3, 10 mg/kg or another intermediate dose decided by the SRC, but the highest single dose will not exceed 15 mg/kg). The dose and infusion volume will be based upon the subject's body weight and the allowable drug concentration. Dose escalation requires Safety Review Committee review (of available blinded safety, tolerability, PK and selected PD data) and approval. In addition to CSL324 or placebo, subjects may also receive other interventions (G-CSF and/or Cantharidin) as described below. Intervention 2: Filgrastim (Registered Trademark: Neupogen), a recombinant form of human G-CSF, will be administered subcutaneously once a day, at approximately the same time each day on up to 6 consecutive days (from 3 days before and/or up to 3 days after CSL324 or placebo infusion depending upon the CSL324 or placebo dose amount) at a dose based upon the subject's body weight (5 microgram/kg; all Part B subjects only) Intervention 3: Cantharidin (Registered Trademark: Cantharone), will be applied topically to the skin (on the arm), to induce a blister (all Parts A and B subjects only). Cantharidin (25 microlitres at 0.1 % weight/volume) will be administered once a day, on 2 separate days, 2 or 3 days apart (from 1 day before and up to 2 days after CSL324 or placebo infusion depending upon the CSL324 or placebo dose amount).
Intervention code [1]	Treatment: Drugs
Comparator / control treatment	Placebo (saline) will be administered as an IV infusion at the same frequency, volume and duration as the CSL324 infusion(s) in Parts A, B and C.
Control group	Placebo

Outcomes

Primary outcome [1]	Percentage of subjects with adverse events (AEs) overall and by relatedness and severity. AEs will be assessed through evaluation of physical and neurological examinations, vital signs, electrocardiograms, clinical laboratory parameters, and monitoring of AEs. AEs will be recorded during the study and summarised by relatedness and severity using descriptive statistics.
Timepoint [1]	For the duration of the subject's participation in the study, up to 5 months per subject
Secondary outcome [1]	Area under the plasma concentration versus time curve (AUC) of CSL324 from the time of dosing extrapolated to time infinity (AUC0-inf) (Parts A and B)
Timepoint [1]	Before study drug infusion, at the end of infusion, and at approximately 6, 12, 24, 36, 48, 72 and 96 hours after the end of infusion, and at approximately 8, 11, 15, 23, 29, 41, 51 and 85 days after infusion
Secondary outcome [2]	Area under the plasma concentration versus time curve of CSL324 from the time of dosing up to collection time t (AUC0-t)
Timepoint [2]	Parts A and B: Before study drug infusion, at the end of infusion, and at approximately 6, 12, 24, 36, 48, 72 and 96 hours after the end of infusion, and at approximately 8, 11, 15, 23, 29, 41, 51 and 85 days after infusion Part C: Before each study drug infusion, at the end of infusion for the 1st and 3rd infusions, at 1, 2, 4 and approximately 7 days after the 1st infusion, at 1 and approximately 7 days after the 2nd infusion, and at approximately 6 hours and at approximately 1, 2, 6, 13, 20, 27 and 83 days after the 3rd infusion.
Secondary outcome [3]	Area under the plasma concentration versus time curve of CSL324 during dosing interval at steady state (AUC0-tau; Part C). AUC0-tau will be derived from serum CSL324 concentration-time profiles.
Timepoint [3]	Part C: Before each study drug infusion, at the end of infusion for the 1st and 3rd infusions, at 1, 2, 4 and approximately 7 days after the 1st infusion, at 1 and approximately 7 days after the 2nd infusion, and at approximately 6 hours and at approximately 1, 2, 6, 13, 20, 27 and 83 days after the 3rd infusion.
Secondary outcome [4]	Maximum serum CSL324 concentration (Cmax; Parts A and B), and Cmax at steady state (Cmax,ss; Part C)
Timepoint [4]	Parts A and B: Before study drug infusion, at the end of infusion, and at approximately 6, 12, 24, 36, 48, 72 and 96 hours after the end of infusion, and at approximately 8, 11, 15, 23, 29, 41, 51 and 85 days after infusion. Part C: Before each study drug infusion, at the end of infusion for the 1st and 3rd infusions, at 1, 2, 4 and approximately 7 days after the 1st infusion, at 1 and approximately 7 days after the 2nd infusion, and at approximately 6 hours and at approximately 1, 2, 6, 13, 20, 27 and 83 days after the 3rd infusion.
Secondary outcome [5]	Clearance of CSL324 (CLtot; Parts A and B), and Clearance at steady state (Cltot,ss; Part C). Clearance will be derived from the serum CSL324 concentration-time profiles.
Timepoint [5]	Parts A and B: Before study drug infusion, at the end of infusion, and at approximately 6, 12, 24, 36, 48, 72 and 96 hours after the end of infusion, and at approximately 8, 11, 15, 23, 29, 41, 51 and 85 days after infusion. Part C: Before each study drug infusion, at the end of infusion for the 1st and 3rd infusions, at 1, 2, 4 and approximately 7 days after the 1st infusion, at 1 and approximately 7 days after the 2nd infusion, and at approximately 6 hours and at approximately 1, 2, 6, 13, 20, 27 and 83 days after the 3rd infusion.
Secondary outcome [6]	Time to maximum serum CSL324 concentration (Tmax; Parts A and B), and Tmax at steady state (Tmax,ss; Part C)
Timepoint [6]	Parts A and B: Before study drug infusion, at the end of infusion, and at approximately 6, 12, 24, 36, 48, 72 and 96 hours after the end of infusion, and at approximately 8, 11, 15, 23, 29, 41, 51 and 85 days after infusion. Part C: Before each study drug infusion, at the end of infusion for the 1st and 3rd infusions, at 1, 2, 4 and approximately 7 days after the 1st infusion, at 1 and approximately 7 days after the 2nd infusion, and at approximately 6 hours and at approximately 1, 2, 6, 13, 20, 27 and 83 days after the 3rd infusion.
Secondary outcome [7]	Terminal elimination half-life of CSL324 (t1/2; Parts A and B), and t1/2 at steady state (T1/2,ss; Part C). t1/2 will be derived from serum CSL324 concentration-time profiles.
Timepoint [7]	Parts A and B: Before study drug infusion, at the end of infusion, and at approximately 6, 12, 24, 36, 48, 72 and 96 hours after the end of infusion, and at approximately 8, 11, 15, 23, 29, 41, 51 and 85 days after infusion. Part C: Before each study drug infusion, at the end of infusion for the 1st and 3rd infusions, at 1, 2, 4 and approximately 7 days after the 1st infusion, at 1 and approximately 7 days after the 2nd infusion, and at approximately 6 hours and at approximately 1, 2, 6, 13, 20, 27 and 83 days after the 3rd infusion.
Secondary outcome [8]	Volume of distribution (Vz; Parts A and B), and Vz at steady state during the terminal phase (Vz,ss; Part C). Vz will be derived from serum CSL324 concentration-time profiles.
Timepoint [8]	Parts A and B: Before study drug infusion, at the end of infusion, and at approximately 6, 12, 24, 36, 48, 72 and 96 hours after the end of infusion, and at approximately 8, 11, 15, 23, 29, 41, 51 and 85 days after infusion. Part C: Before each study drug infusion, at the end of infusion for the 1st and 3rd infusions, at 1, 2, 4 and approximately 7 days after the 1st infusion, at 1 and approximately 7 days after the 2nd infusion, and at approximately 6 hours and at approximately 1, 2, 6, 13, 20, 27 and 83 days after the 3rd infusion.
Secondary outcome [9]	Concentrations of CSL324 and G-CSF in cerebrospinal fluid (Part A only)
Timepoint [9]	At approximately 3 days after the end of infusion of the last dose of study drug
Secondary outcome [10]	Number of subjects with anti-CSL324 antibodies in serum

Timepoint [10]	Parts A and B: Before study drug infusion and at approximately 29, 51 and 85 days after infusion. Part C: Before each study drug infusion and at approximately 20, 27 and 83 days after the last infusion.
Secondary outcome [11]	Maximum neutrophil concentration after filgrastim dosing (Emax,ANC; Part B). Maximum effect of blood absolute neutrophil count after filgrastim dosing will be assessed using non-compartmental method
Timepoint [11]	Before each filgrastim infusion, and at approximately 8 hours after filgrastim infusions 1 to 5, and at approximately 8, 12 and 24 hours after the last filgrastim infusion.
Secondary outcome [12]	Area under the effect curve for absolute neutrophil count after filgrastim dosing (AUEC0-24,ANC; Part B). AUEC0-24, ANC for blood absolute neutrophil count after filgrastim dosing will be assessed using non-compartmental method.
Timepoint [12]	Before each filgrastim infusion, and at approximately 8 hours after filgrastim infusions 1 to 5, and at approximately 8, 12 and 24 hours after the last filgrastim infusion.
Secondary outcome [13]	Minimum (trough) serum CSL324 concentration at steady state (Cmin,ss; Part C)
Timepoint [13]	Part C: Before each study drug infusion, at the end of infusion for the 1st and 3rd infusions, at 1, 2, 4 and approximately 7 days after the 1st infusion, at 1 and approximately 7 days after the 2nd infusion, and at approximately 6 hours and at approximately 1, 2, 6, 13, 20, 27 and 83 days after the 3rd infusion.

Eligibility

Key inclusion criteria	- Healthy, male or female, 18 to 55 years of age - Body mass index range of 18.5 to 32.0 kg/m^2, inclusive, and weight at least 50 kg and less than 100 kg - Females must be of non-childbearing potential - Male subject and their female spouse/partners who are of childbearing potential must be using 2 forms of highly effective birth control
Minimum age	18 Years
Maximum age	55 Years
Gender	Both males and females
Can healthy volunteers participate?	Yes
Key exclusion criteria	- History or evidence of any clinically significant cardiovascular, gastrointestinal, endocrine, hematologic, hepatic, immunologic, metabolic, urologic, pulmonary, neurologic, dermatologic, psychiatric, renal and/or other major disease or malignancy - History of venous thrombosis, polycythaemia or thrombophilia - History of autoimmune disease with the exception of seasonal allergic rhinitis managed without systemic glucocorticoid treatment - Any history of cyclic neutropenia or a Screening absolute neutrophil count < 2.0 × 10^9/L

Study design

Purpose of the study	Treatment
Allocation to intervention	Randomised controlled trial
Procedure for enrolling a subject and allocating the treatment (allocation concealment procedures)	
Methods used to generate the sequence in which subjects will be randomised (sequence generation)	
Masking / blinding	Blinded (masking used)
Who is / are masked / blinded?	The people receiving the treatment/s The people assessing the outcomes
Intervention assignment	Other
Other design features	Sequential single ascending dose groups (Parts A and B); repeat dose group (Part C).
Phase	Phase 1
Type of endpoint(s)	Safety
Statistical methods / analysis	

Recruitment

Recruitment status	Recruiting

Date of first participant enrolment			
Anticipated	30/06/2016	**Actual**	30/06/2016

Date of last participant enrolment			

Anticipated		**Actual**	

Date of last data collection			
Anticipated		**Actual**	

Sample size					
Target	58	**Current**		**Final**	

Recruitment in Australia	
Recruitment state(s)	VIC

Funding & Sponsors

Funding source category [1]	Commercial sector/Industry
Name [1]	CSL Limited
Address [1]	45 Poplar Rd, Parkville, VIC 3052
Country [1]	Australia
Primary sponsor type	Commercial sector/Industry
Name	CSL Limited
Address	45 Poplar Rd, Parkville, VIC 3052
Country	Australia
Secondary sponsor category [1]	None
Name [1]	
Address [1]	
Country [1]	

Ethics approval

Ethics application status	Approved
Ethics committee name [1]	Alfred Hospital Ethics Committee
Ethics committee address [1]	Office of Ethics & Research Governance 55 Commercial Road Melbourne, VIC, 3004
Ethics committee country [1]	Australia
Date submitted for ethics approval [1]	
Approval date [1]	12/05/2016
Ethics approval number [1]	

Summary

Brief summary	This is a first-in-human, randomised, double-blind, placebo-controlled study. The study is designed to assess the safety, tolerability and pharmacokinetics of single ascending dose (Parts A and B) and repeated (Part C) intravenous infusions of CSL324 or placebo (saline) in healthy subjects. Subjects will have blood collected at various time points for safety laboratory evaluations, absolute neutrophil count (ANC) and pharmacokinetic (PK) and pharmacodynamic (PD) sampling, and will be assessed for 3 months after infusion to assess immunogenicity and longer term safety. Skin test(s) will be used to assess the anti-inflammatory effect of CSL324 in response to an inflammatory stimulus (Parts A and B). Cerebrospinal fluid will be collected by lumbar puncture from subjects in the highest dose group in Part A after the last infusion of CSL324 or placebo, to determine whether CSL324 distributes into the cerebrospinal fluid. Subjects in Part B will also receive multiple subcutaneous doses of filgrastim to stimulate an increase in circulating neutrophils and provide additional PD data.
Trial website	
Trial related presentations / publications	
Public notes	

Contacts

Principal investigator	
Name	Dr Jason Lickliter
Address	Nucleus Network 89 Commercial Road

	Melbourne, VIC 3004
Country	Australia
Phone	+61 3 9076 8960
Fax	
Email	j.lickliter@nucleusnetwork.com.au

Contact person for public queries	
Name	Ms Biljana Georgievska
Address	Nucleus Network 89 Commercial Road, Melbourne VIC 3004
Country	Australia
Phone	1800 243 733
Fax	
Email	b.georgievska@nucleusnetwork.com.au

Contact person for scientific queries	
Name	Ms Biljana Georgievska
Address	Nucleus Network 89 Commercial Road, Melbourne VIC 3004
Country	Australia
Phone	1800 243 733
Fax	
Email	b.georgievska@nucleusnetwork.com.au