GSK MAG: Proof of Concept Study for GSK249320 versus placebo in Stroke Patients

Objective: The primary objective is to demonstrate a clinically meaningful improvement in lower limb motor recovery, specifically by evaluating changes in gait velocity from baseline to Day 90/Month 3 in subjects who have a measurable leg deficit and an impaired ability to walk at 24-72 hours post stroke.

Key secondary efficacy objectives are to characterize the extent and duration of motor recovery after treatment with GSK249320, and to characterize the level of disability and neurological impairment after treatment with GSK249320 and explore how these relate to motor recovery. This PoC study will also further characterize the safety, PK, and immunogenicity of GSK249320, will explore pharmacodynamic (PD) markers, and will explore use of actigraphy to measure motor recovery.

Study Design: This is a Phase II, placebo-controlled, double-blind, multicenter, randomized, repeat dose study. The study consists of a 6 month Core Study Period to measure efficacy, safety, PK, PD and immunogenicity, and a flexible Extended Follow up Period to allow for complete monitoring of the immunogenicity profile if required.

Subjects will be centrally randomised to GSK249320 15mg/kg or placebo in a 1:1 allocation ratio, and treatment will be stratified according to baseline gait velocity (0m/s, > 0m/s - < 0.4m/s, ³ 0.4m/s – 0.8m/s). Each subject will receive two intravenous infusions of Investigational Product; the first on Study Day 1 and the second on Study Day 6±2 days.

Number of Subjects: Total sample size for the study is 162 subjects.

Inclusion Criteria

1. Have a confirmed diagnosis of stroke according to the World Health Organization definition which is, 'a rapid onset event of vascular origin reflecting a focal disturbance of cerebral function, excluding isolated impairments of higher function, and persisting longer than 24 hours [World Health Organization, 1989].
2. Stroke onset must be within the last 24-72 hours of the first infusion of Investigational Product. Time of stroke onset is defined as the time at which the patient/relative is first aware of the stroke deficit. For patients who awake with deficits, or who are found unconscious, the time of onset is defined as the time at which they were last known to be symptom free.
3. Have a stroke that is radiologically confirmed to be ischemic and supratentorial. The diameter of the ischemic lesion is >15mm in any single direction or the volume is >4cc.
4. Have a total NIHSS score of 3-21.

5. Have a lower limb deficit from the incident stroke which is defined as a score of 1-4 on the NIHSS Motor Leg question (question #6).
6. Aged 18-90, inclusive.
7. Expectation the subject will receive standard physical, occupational and speech rehabilitation therapy as indicated for the post stroke deficits.
8. Male subjects and female subjects of non-child-bearing and child-bearing potential are allowed to participate in this study. Females of child-bearing potential must have a negative pregnancy test prior to enrollment and must agree to use one of the contraceptive methods specified in the Protocol.

Exclusion Criteria

1. Ability to walk >0.8m/s as measured by the Gait Velocity assessment.
2. History of a previous symptomatic stroke within 3 months prior to study entry.
3. Presence of significant disability prior to the current stroke. Significant disability is defined as having a pre-stroke Rankin score of >2.
4. Subjects who are not alert or are unresponsive as defined by a score of 2 or 3 on the NIHSS Level of Consciousness question (Question 1a).
5. Presence of significant aphasia likely to confound or interfere with completion of the study assessments.
6. Presence of a significant pre-existing gait deficit prior to study entry that is likely to confound clinical evaluations
7. Presence of pre-existing neurologic or psychiatric disease which is active and not adequately controlled such that it interfered with major activities of daily living immediately prior to the current stroke and is likely to interfere with study participation/visits or confound clinical evaluations.
8. The subject poses a significant suicide risk, in the opinion of the investigator.
9. Current or chronic history of liver disease, known hepatic or biliary abnormalities (except Gilbert's syndrome or asymptomatic gallstones), or known history of hepatitis B or hepatitis C infection.
   A positive hepatitis B or hepatitis C result on the GSK labs drawn at baseline/Study Day 1 do not exclude a subject from continuing in the study unless there are associated clinical signs/symptoms of liver disease; however, the subject should be treated as clinically indicated and the GSK Medical Monitor should be contacted for further discussion.
10. Presence of either a central or peripheral demyelinating disease, such as multiple sclerosis or IgM monoclonal gammopathy of unknown significance (MGUS).
11. Expected death due to the incident stroke, or evidence of a chronic co-morbid condition or unstable acute systemic illness which, in the opinion of the investigator, could shorten the subject's survival such that it would limit his/her ability to complete the study.
12. Presence of the following ECG values on baseline ECG: QTc > 500 msec (using either Bazett's formula (QTcB) or Fridericia's formula (QTcF)); or uncorrected QT >600msec (machine or manual over-read).

If the ECG indicates a prolonged QTc interval value outside these limits, two further ECGs should be performed during the same sitting and the average QTc value of these triplicate ECGs calculated. If the average value exceeds the stated limits, the subject is not eligible.

13. Participation in any investigational rehabilitation paradigm targeting stroke recovery during the duration of this study.
14. Have a contraindication to MRI as per local hospital practice/guidelines.
15. The subject has participated in a clinical trial and has received an investigational product within the following time period prior to the first dosing day in the current study: 30 days, 5 half-lives or twice the duration of the biological effect of the investigational product (whichever is longer).
16. Prior treatment with GSK249320.
17. History of sensitivity to Investigational Product excipients (acetate buffer, polysorbate 80 and sodium chloride) that, in the opinion of the investigator or GSK Medical Monitor, contraindicates the subject's participation.
18. Pregnant females as determined by positive urine hCG test prior to enrollment.
19. Lactating females.
20. Subjects considered unwilling or unable to comply with the procedures and study visit schedule outlined in the protocol.