Repurposing the PDE5 inhibitor tadalafil for vascular cognitive impairment. A test of concept in older people

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Country

United Kingdom

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Repurposing the PDE5 inhibitor tadalafil for vascular cognitive impairment. A test of concept in older people

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Alzheimer's Society

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€ 199,920

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03/02/2015

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2

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Research Abstract

The study will determine whether oral tadalafil augments deep cerebral blood flow in the brain areas relevant
to small vessel disease, the commonest cause of vascular cognitive impairment (VCI) and vascular dementia.
Tadalafil (Cialis®) is widely used as an oral agent for sexual dysfunction and is also licensed for

treatment of
pulmonary hypertension and benign prostatic hyperplasia. As an inhibitor of phosphodiesterase 5 (PDE5)
tadalafil has a well-established pharmacological profile as a small vessel vasodilator. Side-effect profile and
pharmacokinetics of tadalafil are well known and the drug is well-tolerated in the target population, over a
range of oral doses and regimens. The choice of tadalafil over other PDE5 inhibitors (e.g. sildenafil, Viagra®)
is based on potency, selectivity for PDE5, plasma half-life and brain penetration. PDE5 is expressed in the cerebral white matter microvasculature (our unpublished data). This project matches the terms of this Drug Discovery call, viz. it is: i) a hypothesis-test within human subjects, and ii) further human clinical testing on a re-purposed drug for dementia. This will be a clinical study based at St Georges Hospital, London. We
will examine older subjects (age > 65 years) relevant to the population of interest. Inclusion will be based on a recognised clinical phenotype for cerebral small vessel disease. Subjects will be recruited through stroke, TIA and cognitive clinics (n = approx. 50 over the two year study). Subjects will be randomised to tadalafil or placebo formulation, administered in a blinded fashion. Cerebral blood flow (CBF) will be mapped up to 3 hours before and 2-5 h after dosing. Deep brain CBF will be quantified using MRI-arterial spin labelling (ASL) which is currently in use at St George's, as part of other studies. VCI and vascular dementia urgently require novel pharmacological therapy. The brain penetrant PDE5
inhibitor tadalafil has potential to be such a novel therapy. This study will test the concept that tadalafil
augments deep brain blood flow, in a dementia-vulnerable population with symptomatic small vessel disease.
If positive the data will inform a test of efficacy (Phase III trial) in collaboration with an industrial partner.

Further information available at:

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United Kingdom

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