Trial Summary Report (as described in Annex 1 of ICH Topic E3)

<table>
<tr><td>Name of Sponsor/Company:
London School of Hygiene & Tropical Medicine</td><td rowspan="3">Individual Study Table Referring to Part of the Dossier
Volume: N/A – academic investigator-led clinical trial.
Page:</td><td rowspan="3">(For National Authority Use only)</td></tr>
<tr><td>Name of Finished Product:
Asvagandha 250mg tablets</td></tr>
<tr><td>Name of Active Ingredient:
Withania somnifera aqueous root extract</td></tr>
<tr><td colspan="3">Title of Study: Clinical trial of Ashwagandha for promoting recovery from COVID-19 in the UK</td></tr>
<tr><td colspan="3">Investigators: Chief Investigator: Sanjay Kinra.
Academic Co-Investigator: Poppy Mallinson, Tim Clayton, Alexander Perkins, Anoop Shah, Mahesh Mathpati, Rohini Mathur, Prof Tanuja Nesari, Dr S Rajagopala, Dr Galib, Dr G Geetha Krishnan.
Clinical PIs (trial sites): Professor Kamlesh Khunti, Dr Jonathan Wimborne / Paula Melrose, Dr Zelda Cheng, Dr Anthony Renton, Dr Andrew Potter, Dr Jesse Jaremek, Dr Andrew Collins, Dr Rohit Kotnis, Dr MaryKate Kirkaldy, Dr. Nadeem Ahmed, Dr Michael Wong, Dr Drummond Beg.</td></tr>
<tr><td colspan="3">Study centre(s): Coordinating centre: London School of Hygiene & Tropical Medicine.
Trial sites: Hockley Farm Medical Centre, Bay Medical Centre, Highcliffe Medical Centre, Oaks Healthcare, Whaddon Healthcare, Finchampstead Surgery, Hedena Health, St Clements Surgery, KES@Northgate, Melrose surgery, Lancaster Medical Practice, Penicuik Medical Practice.</td></tr>
<tr><td colspan="3">Publication (reference): TBD (under review).</td></tr>
<tr><td colspan="2">Studied period (years):
01/02/2023 (first randomisation) – 18/06/2025 (official trial end date)</td><td>Phase of development:
Phase 2/3</td></tr>
<tr><td colspan="3">Objectives: To determine whether taking 1000mg Ashwagandha root extract tablets daily for 3 months is safe and effective for improving functional status (primary outcome), quality of life and symptoms in adults with Long COVID.</td></tr>
<tr><td colspan="3">Methodology: We conducted an investigator-initiated 1:1 randomised parallel group superiority trial to evaluate the safety and effectiveness of a three-month course of Ashwagandha for improving functional status in adults with Long COVID (The APRIL Trial). The primary outcome was self-reported functioning on the Post COVID-19 Functional Status Scale at 3 months. The trial was conducted at 12 primary care centres or Long COVID clinical in the UK. The trial protocol has been peer-reviewed and published: https://doi.org/10.1136/bmjopen-2024-094526</td></tr>
<tr><td colspan="3">Number of patients (planned and analysed): The trial had planned originally to recruit 2500 patients, but with an understanding that after initial safety data were available on 100-200 participants, the trial team would apply to the regulator to reduce the patient monitoring procedures to facilitate more streamlined trial procedures. The trial recruitment was terminated early after 105 participants were randomised due to slow recruitment rate and decision by the TSC to analyse the safety data from the initial 105 participants, so that a new trial with more streamlined recruitment and patient monitoring procedures could be planned.</td></tr>
<tr><td colspan="3">Diagnosis and main criteria for inclusion: Adults who have a diagnosis of Long COVID as per the NICE Guidelines (NG188), and who report that their Long COVID has reduced their ability to carry out day-to-day activities compared with the time before they had COVID-19.</td></tr>
<tr><td colspan="3">Test product, dose and mode of administration, batch number: Asvagandha (Withania somnifera aqueous root extract) 250mg tablets. Daily dose of 1000mg (2 tablets in the morning, 2 tablets in the evening), taken orally. Single batch manufactured for this study by Archimedis Healthcare Private Limited (batch number: 2122400).</td></tr>
</table>

Duration of treatment: 90 days.

Reference therapy, dose and mode of administration, batch number: Placebo tablet based on microcrystalline cellulose (no active ingredient). Daily dose of 4 tablets (2 tablets in the morning, 2 tablets in the evening), taken orally. Single batch manufactured for this study by Archimedis Healthcare Private Limited (batch number: 21225001).

Criteria for evaluation:
Efficacy: The primary outcome was self-reported functional status at 3 months, measured using the Post-COVID-19 Functional Status Scale (PCFSS). The key secondary outcomes were quality of life at 3 months assessed by the PROMIS 29+2 (v2.1) summary score and the EuroQol Visual Analogue Scale, both widely used and validated global quality of life scales. Other secondary outcomes were individual Long COVID symptoms at 3 months (self-reported fatigue, pain, sleep, anxiety, depression and social, physical and cognitive function by PROMIS 29+2 individual dimensions, self-reported breathlessness by an adapted version of the Modified Medical Research Council Dyspnoea Scale, total count of self-reported symptoms and prevalence of other self-reported symptoms); health utility by the EuroQoL 5-Dimension 5-Level utility score; and work status and productivity.

Safety: The main safety outcomes were the number of: serious adverse events, adverse reactions involving liver function test abnormality, adverse events involving liver function test abnormality, total adverse reactions, total adverse events, pregnancies while on trial medication, and withdrawals due to perceived symptoms. Differences in mean liver function test results between trial arms were examined to check for subclinical liver abnormality on treatment.

Statistical methods: Pre-specified statistical analysis plan has been uploaded to the trial registry (https://www.isrctn.com/ISRCTN12368131). The primary analysis for all outcomes was on an intention-to-treat basis, including complete cases only, and adjusted for baseline levels of the same outcome. For the primary outcome of Post-Covid Functional Status Scale we used ordinal logistic regression. For secondary outcomes we used linear regression, ordinal logistic or binary logistic regression for continuous, ordinal and binary outcomes respectively.

Summary – Conclusions:

This trial evaluated the safety and effectiveness of a 3-month course of daily Ashwagandha for promoting recovery in adults with Long COVID.

Efficacy Results: We did not find strong evidence that Ashwagandha impacted self-reported functional status, quality of life or symptoms, although these analyses were underpowered due to early termination of trial recruitment. Therefore, we are unable to draw a conclusion about the effectiveness of the product.

Safety Results: Ashwagandha appeared to be safe, with no adverse events occurring on Ashwagandha that study physicians deemed related to the trial medication. The same number of patients experienced mild liver function abnormalities in both arms (none of which were deemed related to the trial medication), while liver function test results did not differ substantially on average between the arms. There were fewer adverse events overall in the Ashwagandha arm than the placebo arm.

Conclusion: This was the first MHRA-regulated trial of Ashwagandha, a product widely sold as an over-the-counter supplement in the UK. We conducted rigorous monthly safety monitoring of N=105 participants diagnosed with Long COVID, finding Ashwagandha to be safe and well-tolerated in this patient population. As the trial did not reach sufficient sample size for the primary outcome, we are unable to draw conclusions about its effectiveness for improving functional status in people with Long COVID.

Date of the report: 18/06/2026