Supplementary Appendix for

Mendelian randomization and tocilizumab phase 2 trials do not to support IL-6 as a drug target in group 1 pulmonary arterial hypertension

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UK Phase 2 clinical trial participating centres
Freeman Hospital, Newcastle
Golden Jubilee Hospital, Glasgow
Hammersmith Hospital, London
Royal Brompton Hospital, London
Royal Free Hospital, London
Royal Hallamshire, Sheffield
Royal Papworth Hospital, Cambridge
Royal United Hospital, Bath

Supplementary methods
Inclusion/Exclusion criteria

Inclusion
- Subject must be between 18 and 70 years of age, inclusive, at the Screening visit
- Subject must weigh >40 kg at the Screening Visit.

PAH Diagnosis and Classification
- Subjects must have a diagnosis of group 1 PAH due to the following:
  - Idiopathic or Heritable PAH
  - PAH associated with connective tissue disease excluding SLE, RA, mixed CTD (e.g. limited scleroderma, diffuse scleroderma, or overlap syndrome)
  - Drug or toxins
- Subject must have a current diagnosis of being in WHO Functional Class II-IV.
- Subject must meet all of the following haemodynamic criteria by means of a RHC prior to screening:
  - mPAP of ≥25 mmHg
  - PVR ≥ 300 dynes/sec/cm5
  - PCWP or LVEDP of ≤12 mmHg if PVR ≥300 to <500 dyne/sec/cm5, or
  - PCWP/LVEDP <15 mmHg if PVR ≥500 dynes/sec/cm5
- Subject must meet all of the following pulmonary function tests completed no more than 24 weeks before the Screening visit: Total lung capacity (TLC) ≥60% of predicted normal and Forced expiratory volume in one second (FEV1) ≥60% of predicted normal
- Subjects are required to have a documented negative V/Q scan or pulmonary arteriogram confirming the absence of CTEPH prior to screening.
- Subject must walk a distance of ≥100m and ≤500m at the screening visit.
- Subject, with or without supplemental oxygen, must have a resting arterial oxygen saturation (SaO2) >85% as measured by pulse oximetry at the Screening Visit.
- Female subject of childbearing potential, if sexually active, must agree to use 2 reliable methods of contraception from the Screening Visit until study completion and for at least 30 days following the last dose of Investigational Product. Subjects who have had a Copper T 380A IUD or LNG 20 IUD inserted are not required to use additional methods of contraception.
- Subject must agree not to participate in a clinical study involving another investigational drug or device throughout this study.
- Subject must be competent to understand the information given in the Institutional Review Board (IRB) or Independent Ethics Committee (IEC) approved Informed Consent Form and must sign the form prior to the initiation of any study procedures.
• Subject must be stable on an unchanged PAH therapeutic regime for at least 1 month prior to screening.

Exclusion Criteria
Subjects meeting any of the following criteria must not be enrolled in the study

PAH Treatments
• Subjects on continuous infusions either intravenously or subcutaneously.
• Subject has a known hypersensitivity to the Investigational Products, the metabolites, or formulation excipients.
• Subject has severe renal impairment (creatinine clearance <30 mL/min) at the Screening Visit

Medical History/Current Medical Conditions
Liver
• Subject has severe hepatic impairment (Child-Pugh class C with or without cirrhosis) at the Screening Visit.
**Haematology and bleeding disorders**
- Subject has clinically significant anaemia in the opinion of the investigator, in particular from pyruvate kinase and G6PD deficiencies.
- Subjects with bleeding disorders or significant active peptic ulceration in the opinion of the investigator.
- Subject has peripheral blood platelets <100x10^9/L.
- Subject has a neutrophil count <2x10^9/L.

**Cardiovascular**
- Subject has had an acute myocardial infarction within the last 90 days prior to screening.

Subjects must **not** have 3 or more of the following left ventricular disease/dysfunction risk factors:
- Body Mass Index (BMI) ≥ 35
- Historical evidence of significant coronary disease established by any one of:
  - history of myocardial infarction
  - history of percutaneous intervention
  - angiographic evidence of CAD (>50% stenosis in at least one vessel), either by invasive angiography or by CT Angiography
  - positive stress test with imaging (either pharmacologic or with exercise)
  - previous coronary artery surgery
  - chronic stable angina

**Ophthalmic**
- Subject has a past medical history of macular degeneration or visual field defect of any cause.
- Subject has a hereditary degenerative retinal disorder (e.g. retinitis pigmentosa).

**General Medical Conditions**
- Subject with cardiovascular, liver, renal, haematologic, gastrointestinal, immunologic, endocrine, metabolic, or central nervous system disease that, in the opinion of the Investigator, may adversely affect the safety of the subject and/or efficacy of the investigational product or severely limit the lifespan of the subject other than the condition being studied.
- Subject has a history of malignancies within the past 5 years, except for a subject with localized, non-metastatic basal cell carcinoma of the skin, in situ carcinoma of the cervix, or prostate cancer who is not currently or expected, during the study, to undergo radiation therapy, chemotherapy, and/or surgical intervention, or to initiate hormonal treatment.

**General Criteria**
- Female subject who is pregnant or breastfeeding.
- Subject has demonstrated noncompliance with previous medical regimens.
- Subject has a recent (within 1 year) history of abusing alcohol or illicit drugs.
- Subject has participated in a clinical study involving another investigational drug or device within 4 weeks before the Screening Visit.
## Appendix Table S1 RNAseq pathway and enrichment analyses

<table>
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<th>complex name</th>
<th>set size</th>
<th>candidates contained</th>
<th>p-value</th>
<th>q-value</th>
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<tr>
<td>mIg</td>
<td>47</td>
<td>6 (12.8%)</td>
<td>7.84e-06</td>
<td>4.52e-05</td>
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<tr>
<td>BCR complex</td>
<td>49</td>
<td>6 (12.2%)</td>
<td>1e-05</td>
<td>4.52e-05</td>
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<tr>
<td>S1P/S1P3/G12/G13</td>
<td>3</td>
<td>2 (66.7%)</td>
<td>0.000313</td>
<td>0.000705</td>
</tr>
<tr>
<td>TGAV-P2RY2-GNA12 complex</td>
<td>3</td>
<td>2 (66.7%)</td>
<td>0.000313</td>
<td>0.000705</td>
</tr>
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</table>

Enriched protein complex-based sets.

## Appendix Table S2 Enriched gene ontology-based sets

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<thead>
<tr>
<th>Gene ontology terms</th>
<th>Set size</th>
<th>Candidate(s) contained</th>
<th>P value</th>
<th>Q value</th>
</tr>
</thead>
<tbody>
<tr>
<td>GO:0002443 leukocyte mediated immunity</td>
<td>867</td>
<td>22 (2.5%)</td>
<td>0.000103</td>
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<tr>
<td>GO:0006887 exocytosis</td>
<td>880</td>
<td>22 (2.5%)</td>
<td>0.000126</td>
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<tr>
<td>GO:0001882 nucleoside binding</td>
<td>391</td>
<td>13 (3.3%)</td>
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<td>0.0142</td>
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<tr>
<td>GO:0045321 leukocyte activation</td>
<td>1258</td>
<td>27 (2.2%)</td>
<td>0.000266</td>
<td>0.0166</td>
</tr>
<tr>
<td>GO:0001775 cell activation</td>
<td>1408</td>
<td>29 (2.1%)</td>
<td>0.00031</td>
<td>0.0166</td>
</tr>
<tr>
<td>GO:0002252 immune effector process</td>
<td>1237</td>
<td>26 (2.1%)</td>
<td>0.000478</td>
<td>0.017</td>
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<tr>
<td>GO:0043299 leukocyte degranulation</td>
<td>538</td>
<td>15 (2.8%)</td>
<td>0.000512</td>
<td>0.0357</td>
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<tr>
<td>GO:0002433 immune response-regulating</td>
<td>138</td>
<td>7 (5.1%)</td>
<td>0.000612</td>
<td>0.0357</td>
</tr>
<tr>
<td>cell surface receptor signaling pathway</td>
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<td></td>
<td></td>
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<tr>
<td>involved in phagocytosis</td>
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</tr>
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</table>
Appendix Figure S1 Serum change in inflammatory mediators

Changes in serum cytokines A) Interleukin-1β B) Interleukin-6 C) Interleukin-8 D) Tumour necrosis factor-α E) C reactive protein.
EOS- end of study

Appendix Figure S2 Immunophenotyping of B and T cell subsets by flow cytometry

Flow cytometric evaluation of change in lymphocyte subsets from baseline to end of study in A) B cell and subsets and B) T cells and subsets
Appendix Figure S3 Principal Component Analyses of RNAseq data from peripheral blood

Principal component scores for samples by timepoint. The two measurements for a given individual are reflections in the x-y line. Lines are drawn from each point to the mean of points of that colour. Base (baseline); EOS (end of study)
Appendix Figure S4 Penalised regression model (LASSO)

Cross-validated error in lasso model by Lambda value. Higher lambda corresponds to fewer variables included. The error was lowest at maximal lambda, with no variables included at all.
## Table S3. Study assessments and procedures

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<tr>
<th>PERIODS</th>
<th>Name</th>
<th>SCREENING</th>
<th>TREATMENT*</th>
<th>PREMATURE STUDY TERMINATION</th>
<th>SAFETY FOLLOW UP</th>
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<td>Duration</td>
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<tr>
<td>VISITS</td>
<td>Name</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Up to 4 weeks</td>
<td>24 Weeks</td>
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<td></td>
<td>Name</td>
<td>Screening</td>
<td>Baseline</td>
<td>Week, 4, 8, 12, 16 + 20</td>
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<td></td>
<td></td>
<td>Unscheduled</td>
<td>Week24 EOS</td>
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<td>Time</td>
<td>Day-30 to Day 1</td>
<td>Day 1</td>
<td>Visits + 3 days</td>
<td>Day +3 days</td>
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<td></td>
<td></td>
<td>Inclusion/exclusion</td>
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<td>Visit within 7 days of premature termination</td>
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<td>Medical History</td>
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<td>Demographics</td>
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<td>Urine Pregnancy Test</td>
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<td>Physical Exam</td>
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<td>Who Class</td>
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</table>
Study Cohorts used for Mendelian Randomisation

As described in reference 23 (Rhodes et al) the meta-analyses data were taken from the following cohorts. UK National Institute of Health Research BioResource (NIHRBR) for Rare Diseases study – PAH was defined by right heart catheterization measurements including mean pulmonary artery pressure (mPAP) > 25 mmHg, pulmonary capillary wedge pressure (PCWP) < 15 mmHg, and pulmonary vascular resistance (PVR) > 3 Woods Units. Eligible cases were recruited from the UK National Pulmonary Hypertension Centres, as well as Université Sud Paris (France), the VU University Medical Center Amsterdam (The Netherlands), the Universities of Gießen and Marburg (Germany), and San Matteo Hospital, Pavia (Italy). Study recruitment was undertaken between 29 Jan 2003 and 4 Jan 2017, and patients were followed up to 24 Mar 2017. Cases were excluded if they were not able to provide written informed consent or were diagnosed with other forms of PAH. One patient withdrew from the study. Controls consisted of patients with other rare diseases from the NIHRBR rare disease study.

US National Biological Sample and Data Repository for Pulmonary Arterial Hypertension/PAH Biobank (PAHB) study - PAH was defined by right heart catheterization measurements including mPAP > 25 mmHg, PCWP < 18 mmHg, and PVR > 2.5 Woods Units. Eligible cases were recruited from 29 pulmonary hypertension centers across the United States and enrolled as part of the National Biological Sample and Data Repository for Pulmonary Arterial Hypertension (PAH Biobank, www.pahbiobank.org) funded by the National Institutes of Health/National Heart Lung and Blood Institute (R24HL105333). PAH cases were recruited between October 3, 2012 to March 14, 2016. Controls were selected from the Vanderbilt Electronic Systems for Pharmacogenomic Assessment (VESPA) cohort2-4 ascertained at Vanderbilt University (VU). The VESPA project used BioVU, VU’s large DNA repository coupled to de-identified data from electronic health records (EHRs), to investigate the genetic component of individual response to medications for 28 pharmacogenomic phenotypes unrelated to PAH, including angiotensin-converting enzyme (ACE) inhibitor-induced cough, vancomycin-induced kidney dysfunction, heparin-induced thrombocytopenia, and others2. BioVU was approved by the Institutional Review Board at Vanderbilt University as described previously5. BioVU recruited using an opt-out model until January 2015, at which time an opt-in model was adopted. The complete VESPA project population includes 11,639 genotyped individuals from BioVU (84% Caucasian and 12% African American) with a median age of 61.6 years. Only samples of European descent that were genotyped on the Illumina® Omni5-Quad BeadChip array were included in the control population for this study (n=2,144). The controls include individuals with type 1 diabetes (n=251) and connective tissue diseases (n=56). 31 controls with a diagnosis of pulmonary hypertension were excluded. Combining cases with controls data (n=2,144), a total of 4,245 subjects were available for analysis.

Paris Pulmonary Hypertension Allele-Associated Risk cohort (PHAAR) study - Diagnosis with PAH was defined by hemodynamic measurement during right-heart catheterization for all cases identified by the French PAH Network between 1 January, 2003, and 1 April, 2010. For all cases, PAH was defined as a mPAP >= 25 mmHg associated with normal PCWP. Cases with known pathogenic mutations in BMPR2 or ACVRL1 were excluded. Further details have been published7. The control group was composed of a random sample of 1,140 subjects who were free of any chronic disease from the 3C Study8. The 3C Study is a population-based prospective cohort with a 4-year follow-up carried out in three French cities: Bordeaux (southwest France), Montpellier (southeast France) and Dijon (central eastern France).

British Heart Foundation Pulmonary Arterial Hypertension GWAS (BHFPAH) study - The BHFPAH cohort comprised IPAH patients recruited from the Pulmonary Hypertension Division at University Hospital Giessen or from specialist PAH centres in the UK, namely Royal Hallamshire Hospital Pulmonary Vascular Unit, Northern Pulmonary Vascular Unit – Freeman Hospital, Papworth Hospital NHS Foundation Trust, National Pulmonary Hypertension Service – Hammersmith Hospital, Royal Brompton and Harefield NHS Foundation Trust, and the Scottish Pulmonary Vascular Unit. Patients were recruited between 3 Dec 1998 and 1 Dec 2011 and all provided written informed consent to participate in the study. The BHFPAH control cohort was population based, comprising of individuals ascertained through the Wellcome Trust Case Control Consortium, UK or recruited as part of the Food Chain Plus (FoCus) cohort, Germany. Individuals in
the Focus cohort with BMI>30 were excluded. All IPAH cases and UK controls were genotyped at King's College London on an Illumina HiScan system, whilst genotype data for the German controls were generated by Popgen

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