A randomised placebo-controlled Phase III multicentre trial: low-dose intravenous immunoglobulin treatment for long-standing complex regional pain syndrome (LIPS trial)

Andreas Goebel,1* Jatinder Bisla,2 Roy Carganillo,3 Claire Cole,1 Bernhard Frank,4 Rima Gupta,5 Mairi James,6 Joanna Kelly,2 Candy McCabe,7,8 Holly Milligan,1 Caroline Murphy,2 Nick Padfield,3 Ceri Phillips,9 Helen Poole,10 Mark Saunders,11 Mick Serpell,6 Nick Shenker,12 Karim Shoukrey,13 Lynne Wyatt4 and Gareth Ambler14

1Pain Research Institute, Clinical Sciences Centre, Liverpool, UK
2King’s Clinical Trials Unit, Institute of Psychiatry, Psychology and Neuroscience, London, UK
3Pain Management and Neuromodulation Centre, Guy’s and St Thomas’ Hospital, London, UK
4The Walton Centre NHS Foundation Trust, Liverpool, UK
5Modepharma Ltd, Beckenham, UK
6University Department of Anaesthesia, Queen Elizabeth University Hospital, Glasgow Clinical Research Facility, Glasgow, UK,
7Royal National Hospital for Rheumatic Diseases, Bath, UK
8University of the West of England, Bristol, UK
9College of Human and Health Sciences, Swansea University, Swansea, UK
10Faculty of Science, Liverpool John Moores University, Liverpool, UK
11Norfolk and Norwich University NHS Trust, Norwich, UK
12Department of Rheumatology, Cambridge University Hospitals, Cambridge, UK,
13University Hospital of Leicester NHS Trust, Leicester General Hospital, Leicester, UK
14Statistical Science, University College London, London, UK

*Corresponding author andreasgoebel@rocketmail.com/andreas.goebel@liv.ac.uk
Declared competing interests of authors: Andreas Goebel reports grants from the National Institute for Health Research (NIHR) Medical Research Council (MRC) Efficacy and Mechanism Evaluation (EME) programme, other funds from Biotest AG, Germany, and grants from Biotest AG during the conduct of the study. Furthermore, he received personal fees from Biotest AG and Axsome Therapeutics outside the submitted work. Mick Serpell reports grants from NIHR EME programme (a MRC and NIHR partnership), grants for additional funding obtained by the Pain Relief Foundation Liverpool, and non-financial support was received from Biotest UK Ltd, which provided the active study medication at no cost during the study. He has also received research support, consulting fees or honoraria in the past 3 years from Astellas Pharma, Grünenthal Ltd, NAPP and Pfizer. Nick Shenker reports NIHR funding for researchers’ time during the conduct of the study.

Published November 2017
DOI: 10.3310/eme04050

Plain English summary

The LIPS trial
Efficacy and Mechanism Evaluation 2017; Vol. 4: No. 5
DOI: 10.3310/eme04050

NIHR Journals Library www.journalslibrary.nihr.ac.uk
Complex regional pain syndrome (CRPS) is a condition that causes persistent severe pain, usually at the site of a previous injury, although pain can affect other parts of the body. CRPS can cause skin around the affected area to become oversensitive to touch.

Although CRPS symptoms can improve or completely resolve, for some people CRPS causes long-term pain. For many of those with moderate to severe CRPS, current pain treatments do not adequately reduce pain.

Exploratory research on a small number of people with moderate to severe CRPS showed that being given intravenous immunoglobulin (IVIg) can reduce pain. IVIg is from blood plasma and contains antibodies that protect against diseases. When people donate blood, the plasma can be separated out. IVIg is given to patients through a vein in their arm.

We conducted a second, much larger, study to see whether or not giving IVIg reduced the pain from CRPS. Participants were randomly assigned to two groups and received two infusions of either IVIg or of placebo (saline solution) 3 weeks apart. Following this, all participants also had the chance to receive two further infusions, at which time they definitely received IVIg. During both parts of the study, participants completed diaries that recorded how much pain they were in on a scale of 1–10.

For the 103 participants in the study, there was no significant difference found in pain reduction between the IVIg and placebo groups. Low-dose IVIg is not an effective treatment for moderate to severe CRPS.
Criteria for inclusion in the Efficacy and Mechanism Evaluation journal
Reports are published in Efficacy and Mechanism Evaluation (EME) if (1) they have resulted from work for the EME programme, and (2) they are of a sufficiently high scientific quality as assessed by the reviewers and editors.

EME programme
The Efficacy and Mechanism Evaluation (EME) programme was set up in 2008 as part of the National Institute for Health Research (NIHR) and the Medical Research Council (MRC) coordinated strategy for clinical trials. The EME programme is broadly aimed at supporting ‘science driven’ studies with an expectation of substantial health gain and aims to support excellent clinical science with an ultimate view to improving health or patient care.

Its remit includes evaluations of new treatments, including therapeutics (small molecule and biologic), psychological interventions, public health, diagnostics and medical devices. Treatments or interventions intended to prevent disease are also included.

The EME programme supports laboratory based or similar studies that are embedded within the main study if relevant to the remit of the EME programme. Studies that use validated surrogate markers as indicators of health outcome are also considered.

For more information about the EME programme please visit the website: http://www.nets.nihr.ac.uk/programmes/eme

This report
The research reported in this issue of the journal was funded by the EME programme as project number 11/14/33. The contractual start date was in December 2012. The final report began editorial review in August 2016 and was accepted for publication in April 2017. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The EME editors and production house have tried to ensure the accuracy of the authors’ report and would like to thank the reviewers for their constructive comments on the final report document. However, they do not accept liability for damages or losses arising from material published in this report.

This report presents independent research. The views and opinions expressed by authors in this publication are those of the authors and do not necessarily reflect those of the NHS, the NIHR, the MRC, NETSCC, the EME programme or the Department of Health. If there are verbatim quotations included in this publication the views and opinions expressed by the interviewees are those of the interviewees and do not necessarily reflect those of the authors, those of the NHS, the NIHR, NETSCC, the EME programme or the Department of Health.

© Queen’s Printer and Controller of HMSO 2017. This work was produced by Goebel et al. under the terms of a commissioning contract issued by the Secretary of State for Health. This issue may be freely reproduced for the purposes of private research and study and extracts (or indeed, the full report) may be included in professional journals provided that suitable acknowledgement is made and the reproduction is not associated with any form of advertising. Applications for commercial reproduction should be addressed to: NIHR Journals Library, National Institute for Health Research, Evaluation, Trials and Studies Coordinating Centre, Alpha House, University of Southampton Science Park, Southampton SO16 7NS, UK.

Published by the NIHR Journals Library (www.journalslibrary.nihr.ac.uk), produced by Prepress Projects Ltd, Perth, Scotland (www.prepress-projects.co.uk).
Efficacy and Mechanism Evaluation Editor-in-Chief

Professor David Crossman  Bute Professor of Medicine and Dean and Head of Faculty of Medicine, University of St Andrews, and Honorary Consultant Cardiologist, NHS Fife Health Board, UK

NIHR Journals Library Editor-in-Chief

Professor Tom Walley  Director, NIHR Evaluation, Trials and Studies and Director of the EME Programme, UK

NIHR Journals Library Editors

Professor Ken Stein  Chair of HTA and EME Editorial Board and Professor of Public Health, University of Exeter Medical School, UK

Professor Andrée Le May  Chair of NIHR Journals Library Editorial Group (HS&DR, PGfAR, PHR journals)

Dr Martin Ashton-Key  Consultant in Public Health Medicine/Consultant Advisor, NETSCC, UK

Professor Matthias Beck  Chair in Public Sector Management and Subject Leader (Management Group), Queen's University Management School, Queen's University Belfast, UK

Dr Tessa Crilly  Director, Crystal Blue Consulting Ltd, UK

Dr Eugenia Cronin  Senior Scientific Advisor, Wessex Institute, UK

Dr Peter Davidson  Director of the NIHR Dissemination Centre, University of Southampton, UK

Ms Tara Lamont  Scientific Advisor, NETSCC, UK

Dr Catriona McDaid  Senior Research Fellow, York Trials Unit, Department of Health Sciences, University of York, UK

Professor William McGuire  Professor of Child Health, Hull York Medical School, University of York, UK

Professor Geoffrey Meads  Professor of Wellbeing Research, University of Winchester, UK

Professor John Norrie  Chair in Medical Statistics, University of Edinburgh, UK

Professor John Powell  Consultant Clinical Adviser, National Institute for Health and Care Excellence (NICE), UK

Professor James Raftery  Professor of Health Technology Assessment, Wessex Institute, Faculty of Medicine, University of Southampton, UK

Dr Rob Riemsma  Reviews Manager, Kleijnen Systematic Reviews Ltd, UK

Professor Helen Roberts  Professor of Child Health Research, UCL Institute of Child Health, UK

Professor Jonathan Ross  Professor of Sexual Health and HIV, University Hospital Birmingham, UK

Professor Helen Snooks  Professor of Health Services Research, Institute of Life Science, College of Medicine, Swansea University, UK

Professor Jim Thornton  Professor of Obstetrics and Gynaecology, Faculty of Medicine and Health Sciences, University of Nottingham, UK

Professor Martin Underwood  Director, Warwick Clinical Trials Unit, Warwick Medical School, University of Warwick, UK

Please visit the website for a list of members of the NIHR Journals Library Board:
www.journalslibrary.nihr.ac.uk/about/editors

Editorial contact: journals.library@nihr.ac.uk