



# Effect of topical imiquimod on lentigo maligna.

## Protocol

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## 2. STUDY PERSONNEL AND CONTACT DETAILS

	<b>Name and Address</b>	<b>Telephone</b>	<b>Email</b>
Sponsor	University Hospitals Birmingham NHS Foundation Trust Research and Development HSRC Building, College of Medical and Dental Sciences, West Campus, University of Birmingham, Edgbaston, Birmingham, B15 2TT		
Chief Investigator and Medical Expert	Dr Jerry Marsden Consultant Dermatologist University Hospital Birmingham NHS Foundation Trust Selly Oak Hospital 1 <sup>st</sup> Floor, Old Matron's House Raddlebarn Road, Selly Oak Birmingham, B29 6JD	0121 6278442	jerry.marsden@uhb.nhs.uk
Trial Coordinating Centre	Clinical Trials Unit University of Nottingham Room B39, Medical School Queen's Medical Centre Nottingham, NG7 2UH		
Trial Manager	Ms Nazia Boota Clinical Trials Unit B39, Medical School Queens Medical Centre Nottingham, NG7 2UH	0115 8230579	nazia.boota@nottingham.ac.uk
Trial Statistician	Prof Keith Wheatley Professor of Medical Statistics Cancer Research UK Clinical Trials Unit School of Cancer Sciences Vincent Drive, University of Birmingham Edgbaston Birmingham, B15 2TT	0121 4159119	k.wheatley@bham.ac.uk
Trial Methodology Advisor	Professor Lucinda Billingham Professor of Biostatistics Director, MRC Midland Hub for Trials Methodology Research University of Birmingham Edgbaston, Birmingham, B15 2TT	0121 414 9078	l.j.billingham@bham.ac.uk
Data Management	Mr Daniel Simpkins Clinical Trials Unit Office B39, Medical School Queens Medical Centre Nottingham, NG7 2UH	0115 8230508	daniel.simpkins@nottingham.ac.uk
Trial Pharmacist	Ms Sheila Hodgson Clinical Trials Pharmacist Nottingham University Hospitals NHS Trust QMC Campus Derby Road Nottingham, NG7 2UH	0115 9194450	Sheila.Hodgson@nuh.nhs.uk
Histopathology	Professor Martin Cook Histopathology Department The Royal Surrey County Hospital NHS Trust Egerton Road Guildford, GU2 7XX	01483 571122	m.cook@nhs.net
Translational studies	Dr Neil Steven Clinical Senior Lecturer and Honorary Consultant in Medical Oncology Wellcome Trust Clinical Research Facility University Hospital Birmingham NHS Foundation Trust The University of Birmingham Edgbaston Birmingham, B15 2TT	0121 472 1311	n.m.steven@bham.ac.uk

### 3. ABBREVIATIONS

AR	Adverse Reaction
AE	Adverse Event
CCR	Clinical Complete Regression
CI	Chief Investigator
CNC	Clinical No Change
CPD	Clinical Progressive Disease
CPR	Clinical Partial Regression
CR	Complete regression
eCRF	Electronic Case Report Form
DMC	Data Monitoring Committee
GCP	Good Clinical Practice
IMP	Investigational Medicinal Product
LM	Lentigo maligna
LMM	Lentigo maligna melanoma
MHRA	Medicines and Healthcare products Regulatory Agency
NHS	National Health Service
PCR	Pathological Complete Regression
PNC	Pathological No Change
PPD	Pathological Progressive Disease
PPD	Pathological Partial Disease
PI	Principal Investigator at a local centre
REC	Research Ethics Committee
R&D	Research and Development department
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SmPC	Summary of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMG	Trial Management Group
TSC	Trial Steering Committee
WTCRF	Wellcome Trust Clinical Research Facility

## 4. STUDY DESIGN

### 4.1. Overview

This is a multicentre, open label, non-randomised, single-stage trial to discriminate between a pathological CR rate of <60% and >85%. It is anticipated that approximately fourteen recruiting centres will take part.

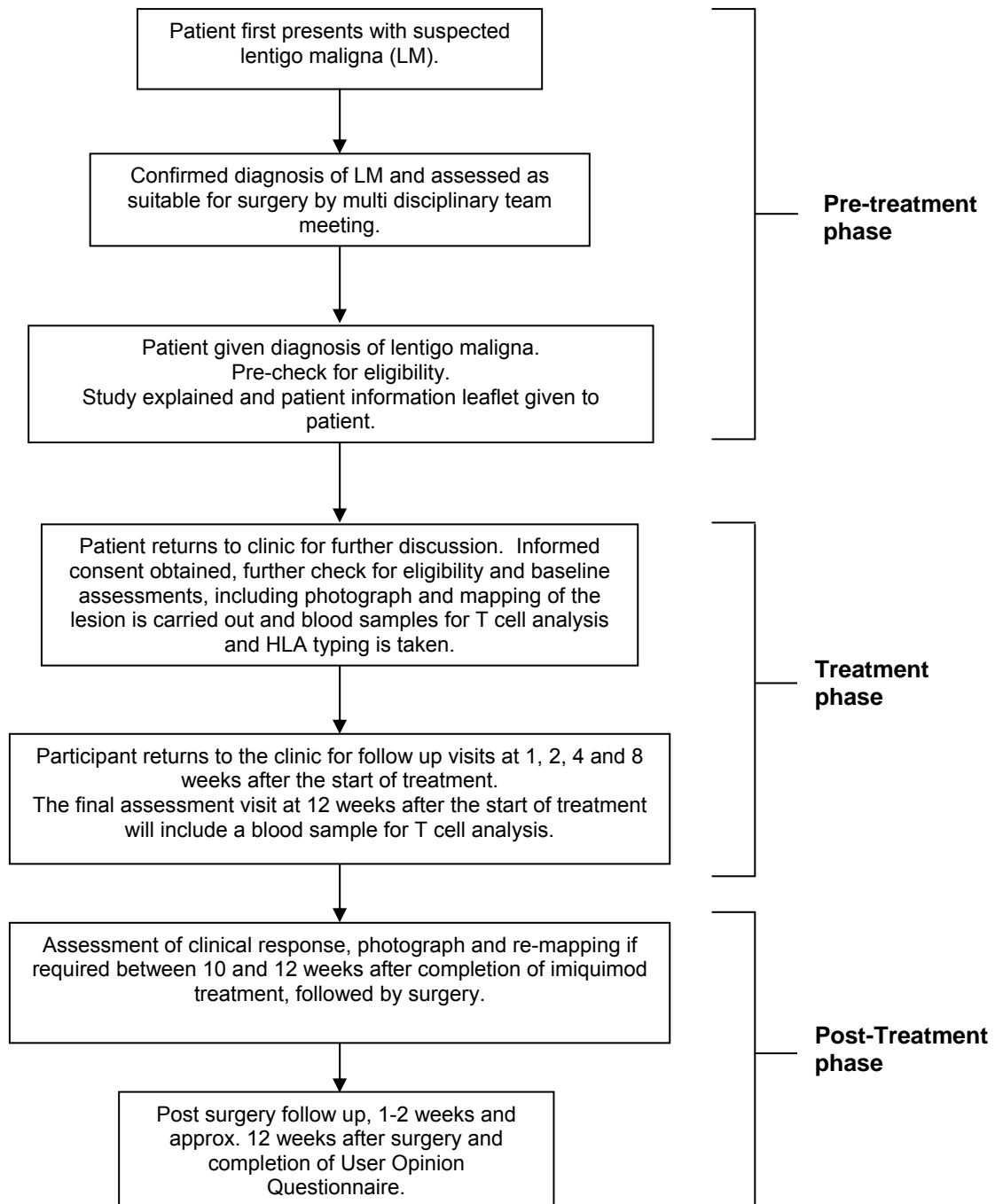
A maximum of forty patients with lentigo maligna (LM) will undergo clinical lesion mapping (map 1) followed by 12 weeks topical imiquimod treatment. The dose of imiquimod will be adjusted according to local toxicity. Scheduled study visits during treatment will be at 1, 2, 4, 8 and 12 weeks. At these visits, tolerability and adverse reactions will be recorded with the aid of patient diaries. Any unscheduled consultations for dose adjustments will be recorded. After treatment, clinical response will be determined and the LM will be re-mapped if there is contiguous pigmentation outside the previously mapped area (map 2). This visit will be at 10 to 12 weeks after the last application of imiquimod. All patients will progress to biopsy, then surgical excision. This will include map 1 in all patients, and map 1 plus map 2 in those with pigmentation outside map 1, plus a margin of apparently healthy tissue. The entire specimen will be sectioned and examined histologically to determine pathological clearance and the presence of LM outside the mapped area. Patients who withdraw from imiquimod treatment prior to 12 weeks will still require surgical excision. This will be done at least 12 weeks after the first application of imiquimod and 10 to 12 weeks after the last application of imiquimod.

The immune response against melanocyte differentiation antigens will be measured by ELISpot assays using blood samples drawn at baseline and the week 12 visit.

An overview of the study design is shown in figure 1.

**Figure 1**

Flow diagram showing progression of participants through the study.



**Schedule of Assessments Table**

Week	Pre-study	Baseline -1	0	1	2	4	8	12	22-24 (Post TX)	S U R G E R Y	1-2 wks post SX	12 wks post SX
Biopsy	X								X			
Informed consent		X										
Pregnancy test		X										
Medical history		X										
Demographic data		X										
Mapping of lesion		X							X			
Photograph lesion		X							X			
Blood samples for immune assay		X						X				
Blood Sample for HLA typing		X										
User Opinion Questionnaire												X
Study drug administered			X	X	X	X	X	X				
Study diary			X	X	X	X	X	X				
Adverse event recording			X	X	X	X	X	X				
Concomitant medications recording			X	X	X	X	X	X				
Collect unused drug/ drug accountability								X				
Histological report											X	
Definition of pathological response										X		

**Please refer to section 9.0 for full requirements of study visit schedule and procedures.**



## 5. SYNOPSIS

Title	Effect of topical imiquimod on lentigo maligna.
Acronym	LIMIT-1
Short title	Lentigo maligna imiquimod trial
Chief Investigator	Dr J R Marsden
Objectives	<p>Primary objective:</p> <ul style="list-style-type: none"> <li>To establish the pathological complete regression (CR) rate for lentigo maligna following topical treatment with imiquimod</li> </ul> <p>Secondary objectives:</p> <ul style="list-style-type: none"> <li>To define the accuracy of the clinical assessment of response after imiquimod treatment using visual assessment and biopsy</li> <li>To investigate the tolerability of imiquimod treatment</li> <li>To investigate the NHS resource associated with imiquimod treatment</li> <li>To determine whether imiquimod therapy might vaccinate against melanoma</li> <li>To establish patient treatment preferences for future trial design</li> </ul>
Trial Design	A multicentre, open label, non-randomised, single-stage trial
Setting	Secondary care – local and specialist skin cancer multidisciplinary teams
Number of participants	40
Main eligibility criteria	<ul style="list-style-type: none"> <li>Clinical diagnosis of lentigo maligna (LM)</li> <li>Histological findings consistent with LM</li> <li>The upper limit of the lesion is not defined by size, but must be suitable for complete surgical excision using a 5 mm lateral margin.</li> <li>The outline of the lesion must be easily defined visually in daylight around its entire circumference.</li> <li>Patient fit enough and willing to undergo surgery as required by the protocol.</li> </ul>
Study interventions	Topical imiquimod to lesional skin plus 2 cm for 12 weeks, then surgical excision

Duration of study	<p>The patient will be in the study for a maximum of 36 weeks.</p> <p>This trial is estimated to last a total of 68 weeks, from initiation of the (first) study site to completion of the last patient.</p>
Randomisation and blinding	None
Outcome measures	<p>Primary outcome measure:</p> <ul style="list-style-type: none"> <li>• Pathological complete regression (PCR) in the mapped biopsied and resected LM using 2 mm slices.</li> </ul> <p>Secondary outcome measures:</p> <ul style="list-style-type: none"> <li>• Clinical assessment of response after imiquimod treatment</li> <li>• Clinical feasibility of imiquimod treatment</li> <li>• Number of consultations with NHS staff during imiquimod treatment.</li> <li>• Frequency of functional T cell responses recognising peptide epitopes in melanocyte differentiation and cancer-testis antigens.</li> <li>• Measurement of hypothetical treatment preferences for surgery or imiquimod for LM using standard gamble technique.</li> </ul>

## 6. STUDY BACKGROUND AND RATIONALE

Lentigo maligna (LM) is an early form of melanoma usually located on chronically sun-exposed skin in the over 50's. Characteristically, it presents as a slowly developing flat pigmented patch with gradual enlargement on the skin surface over several years. At this stage it is harmless because the cancer is confined to the outer layer of the skin. However, there is a significant, but poorly quantified risk of progression to invasive lentigo maligna melanoma (LMM) (1) which is accompanied by risk of the cancer spreading. Like other types of melanoma, the incidence of LM is increasing; in the South West of the UK incidence is estimated at 3.3 per 100,000 population per year (source: South West Public Health Observatory Cancer Intelligence Service, 2007); in the West Midlands at 3.0 per 100,000 per year (source: West Midlands Cancer Intelligence Unit, 2007). In both areas this has increased by more than 50% between 1993 and 2003. LM is no longer considered a disease of the elderly as the age of onset is decreasing.

Due to the nature of LM, effective early treatment is important. The current standard treatment for LM in the UK is surgery to completely remove the lesion with a safety margin of normal appearing skin. Surgery has a cure rate at 5 years of over 90% in unselected patients (2). Although effective, this invasive procedure is stressful and unpleasant to undergo. The head and neck is the most common site for LM and so surgery can produce significant functional and cosmetic disability. The surgical margin required for 95% cure rates is unclear, though is unlikely to be over 10 mm and may be as little as 2 mm (2,3). Although treatment failures are uncommon with surgery, when they do occur, multiple further operations are frequently required, and many treatment failures are never cured. Therefore an alternative, non-surgical treatment for LM is sought.

Other currently used treatments include radiotherapy, laser ablation, cryotherapy and more recently imiquimod (4-10). There is some evidence for efficacy of radiotherapy, but all reported studies are retrospective, numbers are small and it has not yet been compared with surgery. Cure rates vary from 86% to 100%, and treatment seems well tolerated. Cryotherapy is generally felt to be much less effective because LM frequently involves skin appendages, requiring treatment to be effective to a depth of several mm: there are reports of invasive melanoma following apparently effective cryotherapy. Similar reservations apply to laser treatment.

Imiquimod is an immune response modifier and binds to Toll-like receptor-7 (TLR-7). It is manufactured as a 5% cream (Aldara™) and is currently licensed for the treatment of actinic keratosis, superficial basal cell carcinoma and genital warts. Whilst the exact mechanism of action is not known, when used to treat pre-cancerous lesions and skin cancers, imiquimod results in inflammation, which destroys the lesion and can result in complete regression (CR).

Imiquimod is a topical treatment that has significant potential as a first line treatment for LM for several reasons:

- it may avoid the cosmetic and functional disabilities resulting from surgery or radiotherapy
- it may have potential significant cost saving for the NHS as surgery and radiotherapy are resource-intensive treatments

- it can be applied by the patient at home and so may reduce the inconvenience of accessing surgery and radiotherapy

In addition, if effective, imiquimod would be a very attractive treatment option if it were shown to result in an immune response that might protect against invasive melanoma in the future.

Given these potential advantages, imiquimod is increasingly being used off label by dermatologists in the UK. There have been several recent reports of topical treatment with imiquimod (8-14). Whilst the evidence for efficacy is striking with response rates of 77-90% being reported, our own unreported observations suggest that significant numbers may not respond to treatment, and published response rates may reflect reporting bias (15). There is no systematic evidence-base from clinical trials to support this use and so the place of this new treatment requires definition before it becomes firmly embedded in clinical practice (16-19). If it is shown to be safe and effective, understanding the mechanism of action could have major significance for the future management of other types of melanoma.

The results of this study will allow recommendations to be made regarding the use of imiquimod for LM and inform the need for a further definitive randomised trial. A low cure rate or residual sub-clinical disease which could allow LMM to develop undetected would mean a recommendation that imiquimod should not be used as a primary treatment for LM. However, if imiquimod is effective and safe, it is likely to have a role in the management of LM and further research would be warranted. A definitive randomised controlled trial would compare imiquimod with surgery to define CR duration. This approach depends critically on this method of assessment of CR being accurate; this is assessed in this trial. Furthermore, a positive outcome from this study may lead to evaluation of imiquimod as a treatment for other types of melanoma. If the two approaches were equivalent for long term cure of LM, use of imiquimod for LM might spare the majority of patients from surgery and reduce NHS resource use.

## **7. STUDY PURPOSE AND OBJECTIVES**

### **7.1. Purpose**

The purpose of this study is to determine whether imiquimod is a sufficiently effective treatment for lentigo maligna to progress to a randomised controlled trial (RCT) which would compare imiquimod with the current standard treatment (surgery).

This study will not determine treatment strategy; instead it is a tool to help make a decision about whether to proceed to a RCT. The subsequent RCT would then fully define the role of imiquimod in treating lentigo maligna. The use of imiquimod as a primary treatment could spare patients from undergoing potentially disfiguring surgery.

### **7.2. Primary Objective**

To establish the pathological complete regression (CR) rate for lentigo maligna following topical treatment with imiquimod.

### **7.3. Secondary Objectives**

- To define the accuracy of the clinical assessment of response after imiquimod treatment using visual assessment and biopsy
- To investigate the tolerability of imiquimod treatment
- To investigate the NHS resource associated with imiquimod treatment
- To determine whether imiquimod therapy might vaccinate against melanoma
- To establish patient treatment preferences for future trial design

## **8. Selection and Recruitment of Participants**

### **8.1. Participants**

Adults aged at least 45 years with lentigo maligna presenting to secondary care will be considered for this study.

### **8.2. Setting**

40 participants will be recruited from approximately fourteen hospitals in the UK over an 8 month recruitment period.

### **8.3. Recruitment**

Patients will initially be approached by a member of their treating team, which may include the investigator. If the patient is interested in finding out more about the study, they will agree to their details being passed to a member of the study team and be referred for further discussion.

If needed, the usual hospital interpreter and translator services will be available to assist with discussion of the trial, the participant information sheets, and consent forms, but the consent forms and information sheets will not be available printed in other languages. It will be explained to the potential participant that entry into the trial is entirely voluntary and that their treatment and care will not be affected by their decision. It will also be explained that they can withdraw at any time but attempts will be made to avoid this occurrence. In the event of their withdrawal it will be explained that their data collected so far will be retained and used as part of the study analysis.

### **8.4. Inclusion criteria**

- Clinical diagnosis of lentigo maligna (LM) (acquired pigmented macule present for more than 12 months with no change in skin surface texture or contour, no palpability, diameter >10 mm, sited on the head or neck). The lower anatomical limit is the root of the neck – a line joining the medial end of the clavicles with the medial insertion of trapezius.
- Histological findings consistent with LM (increased numbers of atypical melanocytes confined to the epidermis, sun damaged skin) in one or more 4mm punch biopsies(s) from the darkest area, reported by a pathologist with expertise in

the diagnosis of melanocytic lesions, and part of a recognised NHS skin cancer Multi-Disciplinary Team.

- The upper limit of the lesion is not defined by size, but it must be suitable for complete surgical excision using a 5 mm lateral margin.
- The outline of the lesion must be easily defined visually in daylight around its entire circumference.
- Patient fit enough and willing to undergo surgery as required by the protocol.

## **8.5. Exclusion criteria**

The following criteria will exclude the patient from the study:

- Clinical or histological evidence of invasive melanoma including any palpability of the lesion, or clinical and/or histological evidence of regression or dermal invasion
- Aged less than 45 years
- Recurrent LM – the index lesion must not have been previously treated
- Life expectancy of less than 12 months
- Other skin lesions which may compromise the ability to complete this study, such as co-existing or adjacent melanoma or non-melanoma skin cancer. Co-existing adjacent actinic keratoses would not exclude the patient from the study
- Women of childbearing potential, who are pregnant, plan to become pregnant during their study participation or breastfeeding.
- Hypersensitivity to imiquimod or to any of the excipients (methylhydroxybenzoate (E218), propylhydroxybenzoate (E216), cetyl alcohol and stearyl alcohol).
- Taking immunosuppressive medication.
- Taking part in any other intervention study.
- Unable to give informed consent.

## **8.6. Informed consent**

All participants will provide written informed consent before taking part in the study. When the patient is given the diagnosis of LM, and if the patient is potentially eligible, the study will be explained by their treating team (which may include the investigator). Patients will be given the study patient information leaflet to take home and read. If they are willing to participate, they will be asked to return to discuss the study further and in detail with the Investigator or co-investigator. They will answer any questions that the participant has concerning study participation.

The informed consent form will be signed and dated by the participant before they enter the trial and countersigned by the person explaining the study to the patient and taking the consent. One copy of the consent form will be kept by the participant, one will be kept by the Investigator and one copy will be retained in the patient's hospital records.

Should there be any subsequent amendment to the final protocol, which might affect a participant's participation in the trial, continuing consent will be obtained using an amended consent form which will be signed by the participant.

## 9. Details of Study Visit Schedule and Procedures

### 9.1. Pre-study phase

#### ***Diagnosis***

Diagnosis of LM will be confirmed following biopsy by a specialist skin histopathologist and by clinico-pathological correlation. The biopsy will be one or more 4mm punch biopsies(s) from the darkest area. Surplus diagnostic material (1 H&E stained slide with three levels) will be required by the study histopathologist. This diagnostic slide will be sent by same day courier to the study histopathologist along with the post treatment specimens. The appropriateness of surgery will be confirmed by case review by a skin cancer multi-disciplinary team meeting. The patient will then be given the diagnosis of LM, a pre-check for eligibility will be made and, if appropriate, the study will be explained and the patient offered the chance to participate. Patients will then be given the study patient information leaflet to take home and read.

#### ***Baseline visit (week -1)***

The patient will be given the opportunity to have a further discussion about the study and receive answers to any questions they may have. The patient will give their written informed consent to take part in the study. The investigator will confirm that the patient is eligible to enter the study, a medical history will be taken and demographic data collected. Before treatment is started, the patient's General Practitioner will be contacted to inform them about their patient's involvement with study, details of the study and the potential local toxicity of imiquimod.

The area of skin involved in the LM will be defined by using temporary surgical skin marking ink, and small point tattoos on the outline of the lesion at 4 sites on its periphery at 12, 3, 6 and 9 o'clock, using established methods for defining radiotherapy treatment sites. The size of the LM will be measured in mm using the largest diameter and its perpendicular. The map will be made under adequate artificial lighting and standardised magnification. The outline of the lesion will be traced onto a transparent sheet, known as 'map 1'. Therefore, map 1 defines the pre-treatment lesion.

A standardised (i.e. same camera, setting and distance) digital clinical photograph of the outlined lesion will be taken as a baseline, pre-treatment reference.

Blood samples will be taken before treatment starts and after the treatment finishes to find out if the imiquimod treatment has resulted in an immune response. Some of the blood taken at this visit is also used for HLA typing.

At this visit two blood samples are taken, 10ml in EDTA tubes and 50ml sodium heparin tubes, and are sent by same day courier to the scientific study centre in Birmingham at the address below (refer to section 13 for further details).

Dr Julie Williams  
Wellcome Trust Clinical Research Facility (WTCRF)  
University Hospitals Birmingham NHS Foundation Trust  
Queen Elizabeth Hospital, Edgbaston  
Birmingham, B15 2TH  
Tel: 0121 627 2034

The investigator site should inform the WTCRF that a sample is to be taken, giving 48 hours notice preferably. Samples should not be sent on a Friday if possible.

Female participants of childbearing potential will be required to have a negative pregnancy test.

Approved site personnel will enrol the patient into the study using the online eCRF. A trial number will be allocated for the participant. The local investigator will then complete a study specific prescription including the patient trial number. The local pharmacy will dispense sufficient imiquimod as required by each participant, taking into account any dose adjustments made during treatment visits.

## **9.2. Treatment phase**

### ***Week 0***

The date of the first application of imiquimod will be day 1, week 0. Day 1 will be a Monday to facilitate adherence; imiquimod will be applied Monday to Friday with no treatment on Saturday and Sunday. The co-ordinating centre will ensure the investigator is aware of this date as this becomes the reference point for scheduling subsequent treatment phase visits.

Participants will be instructed to apply imiquimod for 12 weeks to the lesion plus a 20 mm margin of surrounding normal skin.

Participants will be asked to keep a study diary during the treatment phase (starting from day 1, week 0) and to bring to each clinic visit to be used as an aide memoir during the consultation. The following information will be recorded in the diary:

- Whether participants have applied imiquimod
- If not whether this was a scheduled day off, or missed due to toxicity .
- The response to “How acceptable have you found the imiquimod treatment over the past week?” answered on a 10cm visual analogue scale ranging from totally acceptable to totally unacceptable
- The name of any topical treatment used on the LM other than imiquimod
- If any of the following adverse reactions have occurred:
  - Local reactions - redness, swelling, discomfort or pain at the site of application
- There will be space for participants to record anything else they feel is important or that they would like to discuss with the investigator.

### ***Weeks 1, 2, 4 and 8***

Scheduled clinic visits will be at 1, 2, 4, 8 weeks after the start of treatment. At these visits, the following will be recorded:

- The contents of the patient daily diary will be reviewed and checked for completeness, and a new diary issued
- The investigator will rate the local site reaction on the following scale:
  - none



- mild reaction (slight redness, discomfort, no swelling, no ulceration)
  - moderate reaction (redness, pain and swelling, no ulceration)
  - severe reaction (redness, pain, swelling and ulceration)
- The participant will be specifically asked about any flu like symptoms they have experienced since the last visit. If present, these will be documented on the AE eCRF.
  - The dose of imiquimod will be adjusted according to the following algorithm:  
 If intolerable at 5 days per week; stop completely for 1 week then restart but at a reduced dose of 3 days per week. Increase to 5 days per week as soon as tolerable.  
 If intolerable at 3 days per week, a further week off, start again at 3 days per week. Stop if intolerable.  
 If 5 days per week is tolerated increase to 7 days per week. If intolerable repeat algorithm as before.
  - Any other new medication usage and health service usage data will be recorded using the diary as an aide memoir.

If treatment of the LM with imiquimod is stopped because of local toxicity, this will prompt an unscheduled clinic visit so that the dose adjustment algorithm can be implemented.

If at any point during the treatment phase, the lentigo maligna is judged to have progressed to invasive melanoma then the patient will progress immediately to surgery. Simple enlargement of the LM macular area does not count as progression to invasive melanoma.

## **Week 12**

At this final scheduled treatment phase visit, the following will be recorded:

- Adverse reaction data at the application site will be recorded from the participant diary and discussion with the participant. The investigator will rate the local site reaction on the following scale:
  - none
  - mild reaction (slight redness, discomfort, no swelling, no ulceration)
  - moderate reaction (redness, pain and swelling, no ulceration)
  - severe reaction (redness, pain, swelling and ulceration)
- Imiquimod treatment will stop at this point.
- The participant will be specifically asked about any flu like symptoms they have experienced since the last visit. If present, these will be documented on the AE eCRF.
- Any new medication usage and health service usage data will be recorded using the diary as an aide memoir.
- All unused medication will be returned and quantified.
- The final diary will be collected.

At this visit the post-treatment blood sample for the immune response is taken, 50ml sodium heparin tube, and is sent by same day courier to the scientific study centre in Birmingham at the address below (refer to section 13 for further details).

Dr Julie Williams  
Wellcome Trust Clinical Research Facility (WTCRF)  
University Hospitals Birmingham NHS Foundation Trust  
Queen Elizabeth Hospital, Edgbaston  
Birmingham, B15 2TH  
Tel: 0121 627 2034

The investigator site should inform the WTCRF that a sample is to be taken, giving 48 hours notice preferably. Samples should not be sent on a Friday if possible.

### **9.3. Post treatment phase**

#### ***Clinical assessment and surgery (week 22 to week 24)***

This visit will occur once inflammation has subsided at 10-12 weeks after completing treatment (i.e week 22-24). All patients will proceed to surgery irrespective of the amount and frequency of imiquimod used.

Clinical response will be quantified by reference to the pre-treatment clinical photographs and to map 1 by the same observer, and recorded.

Clinical response is categorised as follows:

- Clinical complete regression (CCR) - complete disappearance of abnormal pigmentation.
- Clinical partial regression (CPR) - reduction in the size of the pigmented area or an obvious reduction in its intensity.
- Clinical No change (CNC) - appearance identical to that pre-treatment.
- Clinical progressive disease (CPD) - Increased size or increased intensity of pigmentation, or development of a nodule within the LM indicating invasive melanoma.

Before surgery, map 1 will be superimposed on the skin, and the outline positioned over the 4 point tattoos. Map 1 will be drawn on the skin with ink using a 0.5 mm nib surgical marker pen. If there is new pigmentation contiguous with map 1 but outside it, this too will be outlined and recorded (map 2).

A standardised (i.e. same camera, setting and distance) digital clinical photograph will be taken of map 1, and map 1 plus map 2 where appropriate.

One 4 mm punch biopsy will be taken from normal looking skin within map 1. One 4mm punch biopsy will also be taken from any areas of residual pigmentation. In addition, one 4 mm punch biopsy will be taken from pigmentation apparent in map 2.

The area excised will include; the tattoos; the area defined by map 1; the area if any defined by map 2; plus a 5 mm surgical margin of clinically normal skin, and all underlying subcutaneous fat until a deep anatomic margin – either muscle, muscle fascia, periosteum, or perichondrium is reached, or at least 5mm of fat if there is no definable anatomic deep margin. The surgical margin will be marked with normal surgical marking

ink. Excision of both map 1 and 2 is necessary to minimise risk of false positive CR, as it is possible that sub-clinical pre-treatment disease apparent as post-treatment pigmentation may extend beyond the boundaries of map 1. It should be noted that surgery will remove all biopsy and tattoo sites.

The surgical specimen will be orientated, marked at each quadrant, a ligature put at 12 o'clock and placed in formalin. The specimen must sit flat in the formalin filled container, and a screw top or specialised leak proof container must be used. Along with the biopsies and the surgical specimen, 1 H&E (with three levels) stained slide from the initial diagnostic biopsy along with the corresponding histopathology report will be sent to the study histopathologist. The specimens will be transported by same-day courier to the address below.

FAO: Lisa Baker  
LIMIT-1 Study  
Histopathology Department  
The Royal Surrey County Hospital NHS Trust  
Egerton Road  
Guildford, GU2 7XX

Telephone: 01483 464065

Fax: 01483 452718

Please contact the Histopathology Department at The Royal Surrey County Hospital to let them know when to expect arrival of specimens.

The gross appearance of the specimen will be recorded with a digital photograph so that the orientation of the specimen, biopsies, and subsequent pathological sections can be related. Sections will be cut at 2 mm intervals throughout the whole specimen and examined by the study histopathologist and characterised as either:

- Pathological complete regression (PCR) – absence of LM in all biopsies and excision specimen
- Pathological partial regression (PPR) - atypical melanocytes are present in the epidermis, and are of abnormal distribution and number, but without sufficient features to define LM in either biopsies, or excision specimens or both
- Pathological no change (PNC) – presence of LM in either biopsies or excision specimens, or both
- Pathological progressive disease (PPD) – presence of invasive melanoma in biopsies, excision specimens, or both

This will determine the predictive value of the clinical appearance and the biopsy pathology compared with the excision pathology. If the clinical or biopsy results give significant numbers of false negatives, imiquimod is unlikely to have a future in the management of LM. The histopathologist will complete a histopathology report for the participant and send to sites within 2 weeks of surgery.

### ***Post-surgery follow up***

There will be two post surgery follow up visits at 1-2 weeks and at 12 weeks after surgery. The patient will be asked to complete the User Opinion Questionnaire at the 12 week post surgery visit.

The histopathology report will be available to the local investigator by two weeks following surgery. If histopathology shows residual LM at a surgical margin, or if invasive melanoma has been found in the biopsies or excision specimen, further treatment will be at the discretion of the patient and treating team.

#### **9.4. Extra visits**

Participants will be encouraged to call the investigator if they are experiencing problems and an unscheduled visit will be arranged if required. Toxicity requiring discontinuing imiquimod treatment will mandate an unscheduled visit so that the dose reduction algorithm can be implemented

The same procedures as for weeks 1-8 will be carried out. However, if the participant wishes to stop imiquimod treatment and so the unscheduled visit becomes the final treatment phase visit, a standardised (i.e. same camera, setting and distance) digital clinical photograph of the lesion will be taken. Imiquimod treatment will be stopped at this point.

### **10. Study Treatment**

#### **10.1. Dose escalation and de-escalation**

The start dose will be to apply imiquimod cream 5 days per week. The aim is to apply imiquimod cream daily if tolerable.

The following dosing algorithm will be used at the 1, 2, 4 and 8 week visits and unscheduled visits due to local toxicity to adjust the frequency of application accordingly.

- If intolerable at 5 days per week; stop completely for 1 week then restart but at a reduced dose of 3 days per week. Increase to 5 days per week as soon as tolerable.
- If intolerable at 3 days per week, a further week off, start again at 3 days per week. Stop if intolerable.
- If 5 days per week is tolerated increase to 7 days per week. If intolerable repeat algorithm as before.

Participants and their General Practitioners will be requested to contact the local investigator for advice before stopping or changing treatment.

#### **10.2. Rescue Medication**

Topical antiseptics, topical and oral antibiotics and emollients may be used as required and their use will be recorded. The use of topical corticosteroids (e.g. hydrocortisone cream) to treat acute pain and swelling during the treatment phase will be discouraged but any usage will be recorded.

#### **10.3. Concomitant Medications**

Concomitant medications/treatment should be kept to a minimum during the study. However, if considered necessary for the participant's welfare they may be given at the discretion of the investigator according to the local standard of care. The drug, dose and duration should be recorded

Immunosuppressive medications including oral corticosteroids are specifically excluded for the duration of this study.

#### **10.4. Adherence**

The participant will be asked to record in their study diary each day to indicate whether or not they have applied imiquimod. In addition, the number of unused sachets will be recorded by the local investigator or delegated person.

#### **10.5. Accountability**

Detailed dispensing records will be kept by the dispensing pharmacy including participant study number and name, treatment given, batch number, expiry date, dose and date of dispensing.

Unused supplies will be returned to pharmacy for destruction.

#### **10.6. Management of study drug overdose**

When applied topically, systemic overdosage with imiquimod cream is unlikely due to minimal percutaneous absorption. Studies in rabbits reveal a dermal lethal dose of greater than 5g/kg. Persistent dermal overdosing of imiquimod cream could result in severe local skin reactions. This should be self-limiting if the treatment dosing algorithm is followed.

#### **10.7. Withdrawing from the study / stopping medication early**

The participant will stop imiquimod treatment early for the following reasons:

- Intolerable local or systemic toxicity from imiquimod
- Progression of lentigo maligna suggesting the development of invasive disease. These participants will progress immediately to surgery.
- Any participant who becomes pregnant during the study.
- Withdrawal of consent.

Patients who withdraw from imiquimod treatment will still require surgical treatment. If the patient agrees, they will be treated by mapping and surgical excision at least **12 weeks** after the **first** application of imiquimod and a minimum of **10 weeks** after the **last** application of imiquimod (once the inflammation has subsided). These data will be included in the outcome analysis and these patients will not be replaced. By continuing to surgery, at least the primary outcome data will be collected.

Patients who refuse surgery will be included in the total dataset but will be replaced as it will not be possible to obtain primary outcome data for these patients. All attempts will be made to encourage participants to remain in the study.

Participants who withdraw consent will be withdrawn from the trial. The participants will be made aware that this will not affect their standard of care. Participants will be made aware (via the information sheet and consent form) that should they withdraw the data collected will be retained and used as part of the study analysis.

Participants will not be accepted as lost to follow-up unless phone calls, letters or visits to the participant or GP have been fruitless.

## 11. Adverse Events

### 11.1. Collection of Adverse Event Data

This study is using a licensed drug, imiquimod, for which the side-effect profile is well established. Only adverse events that are likely to be related to the imiquimod use will be collected. These are:

- Redness
- Discomfort / pain
- Swelling
- Inflammation
- Ulceration
- Influenza like symptoms
  - Aching
  - Fatigue
  - Malaise
  - Rigors

At each study visit, the investigator will record whether the participant had experienced any of the above adverse events and their severity. The investigator will also be given the opportunity to record any other significant adverse reactions that are not listed if they feel it is necessary. If the event constitutes a serious adverse event or a suspected unexpected serious adverse reaction (SUSAR) it will be reported according to the current regulations.

All available sources of information will be used to collect information on adverse reactions including hospital notes, the participant diary and discussion with the participant.

### 11.2. Definitions

All AEs, as defined by the protocol, occurring during the trial will be reported and documented as described below in terms of seriousness, severity and causality.

For the purposes of this study an AE only includes:

1. any study drug related event as listed above in section 11.1
2. any condition detected or diagnosed after medical product has been administered and has a possible, probable or definite causal relationship with the study drug.

An AE does not include a / an:

1. medical or surgical procedure (e.g., surgery, endoscopy, tooth extraction, transfusion); but the condition that leads to the procedure is an AE.

2. pre-existing disease or conditions present or detected at the start of the study that did not worsen.
3. situations where an untoward medical occurrence has not occurred (e.g., hospitalisations for cosmetic elective surgery, social and / or convenience admissions).
4. disease or disorder being studied or sign or symptom associated with the disease or disorder unless more severe than expected for the participant's condition.
5. overdose of concurrent medication without any signs or symptoms.

A **Serious Adverse Event (SAE)** is any adverse event as defined by the protocol that results in any of the following outcomes:

- Death
- Life-threatening
- Inpatient hospitalisation or prolongation of existing hospitalisation
- Persistent or significant disability / incapacity
- A congenital anomaly or birth defect in the offspring of a participant
- Other medical events may be considered to be a SAE if they require medical or surgical intervention to prevent one of the outcomes listed in this definition.

An adverse event whose causal relationship to the study drug is assessed by the Chief Investigator as “possible”, “probable”, or “definite” is an Adverse Reaction (AR). If the AR is classed as serious then it is a Serious Adverse Reaction (SAR). A distinction is drawn between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined using the criteria above. Hence, a severe AE need not necessarily be serious.

A serious adverse event that is either sudden in its onset, unexpected in its severity and seriousness or not a known side effect of the Investigational Medicinal Product (IMP) *and* related or suspected to be related to the IMP is classed as **Suspected Unexpected Serious Adverse Reaction (SUSAR)** and requires expedited reporting as per the clinical trials regulations.

All serious adverse events that fall or are suspected to fall within these criteria shall be treated as a SUSAR until deemed otherwise.

The event shall be reported immediately of knowledge of its occurrence to the Chief Investigator. The Chief Investigator will:

- Assess the event for seriousness, expectedness and relatedness to the study IMP
- Take appropriate medical action, which may include halting the trial and inform the Sponsor of such action
- If the event is deemed a SUSAR, shall, within seven days, complete the CIOMS form and send to the Medicines and Healthcare products Regulatory Agency (MHRA).
- Shall inform the REC using the reporting form found on the NRES web page within 7 days of knowledge of the event

- Shall, within a further eight days send any follow-up information and reports to the MHRA and REC.
- Make any amendments as required to the study protocol and inform the ethics and regulatory authorities as required

All adverse events will be recorded and closely monitored until resolution, stabilisation, or until it has been shown that the study medication or treatment is not the cause.

### 11.3. Causality

**Not related or improbable:** a clinical event including laboratory test abnormality with temporal relationship to trial treatment administration which makes a causal relationship incompatible or for which other drugs, chemicals or disease provide a plausible explanation. This will be counted as “unrelated” for notification purposes.

**Possible:** a clinical event, including laboratory test abnormality, with temporal relationship to trial treatment administration which makes a causal relationship a reasonable possibility, but which could also be explained by other drugs, chemicals or concurrent disease. This will be counted as “related” for notification purposes.

**Probable:** a clinical event, including laboratory test abnormality, with temporal relationship to trial treatment administration which makes a causal relationship a reasonable possibility, and is unlikely to be due to other drugs, chemicals or concurrent disease. This will be counted as “related” for notification purposes.

**Definite:** a clinical event, including laboratory test abnormality, with temporal relationship to trial treatment administration which makes a causal relationship a reasonable possibility, and which can definitely not be attributed to other causes. This will be counted as “related” for notification purposes.

An AE whose causal relationship to the study IMP is assessed by the Chief Investigator as “possible”, “probable”, or “definite” is an Adverse Drug Reaction.

With regard to the criteria above, medical and scientific judgment shall be used in deciding whether prompt reporting is appropriate in that situation.

### 11.4. Reporting of Adverse Events

Participants will be asked to contact the study site immediately in the event of any significant adverse event. The Chief Investigator shall be informed immediately of any reportable serious adverse events and shall determine seriousness and causality in conjunction with any treating medical practitioners.

In the event of a pregnancy occurring in a trial participant or the partner of a trial participant monitoring shall occur during the pregnancy and after delivery to ascertain any trial related adverse events in the mother or the offspring. Where it is the partner of a trial participant consent will be obtained for this observation from both the partner and her medical practitioner.

All reported serious adverse events will be recorded and reported to the MHRA and REC as part of the regular mandatory reports. SUSARs will be reported within the statutory



timeframes to the MHRA and REC as stated below. The Chief Investigator shall be responsible for all adverse event reporting.

### **11.5. Participant Removal from the Study due to Adverse Events**

Any participant who experiences an adverse event may be withdrawn from treatment at the discretion of the Investigator.

## **12. Duration of Study and Participant Involvement**

### **12.1. Duration of Participant Involvement in the Study**

Treatment (including surgery) will last for a minimum of 22 and a maximum of 24 weeks. The patient will then have a final post surgery follow-up at 12 weeks, making the total maximum duration 36 weeks.

### **12.2. Duration of the Study**

This trial is estimated to last a total of 68 weeks, from initiation of the (first) study site to completion of the last patient.

### **12.3. End of Study**

The end of the trial will be defined as the last patient last visit.

## **13. Laboratory sub-study: Autologous self-vaccination against melanoma antigens**

Peripheral blood lymphocytes will be isolated and cryopreserved. HLA typing will be done. Both pre and post treatment samples from each patient will be analysed in the same ELIspot assay. The frequency of lymphocytes releasing interferon  $\gamma$  in response to stimulation with peptide epitopes derived from melanocyte differentiation and cancer-testis antigens will be measured using a validated assay.

### **13.1. Blood sample processing at the investigator site**

The investigator site should inform the WTCRF that a sample is to be taken, giving 48 hours notice preferably. Samples should not be sent on a Friday if possible.

Pre-addressed secure packaging and sodium heparin vacutainer bottles will be provided by the study centre.

Samples will be labeled with the date and patient study number and placed within the secure packaging. A trial specific form recording the study participant number, date, evidence of patient consent, time and date the samples were taken, and any untoward events in sample handling will be completed and sent.

Extremes of temperature should be avoided. Blood samples should be maintained between 10-20°C.

Samples will be dispatched by same day courier to:

Dr Julie Williams  
Wellcome Trust Clinical Research Facility  
University Hospitals Birmingham NHS Foundation Trust  
Queen Elizabeth Hospital  
Edgbaston  
Birmingham, B15 2TH  
Tel: 0121 627 2034

### **13.2. Sample storage and custodian**

At the Wellcome Trust Clinical Research Facility in Birmingham the samples will be stored at -150°C in liquid nitrogen in swipe access controlled area and therefore only authorised personnel have access. The samples will be kept in a dedicated tank.

Dr Julie Williams is the custodian of the samples. Analysis will be conducted by a research assistant, overseen by Dr Julie Williams and Dr Jane Steele (Director of the Human Biomaterials Resource Unit).

If any samples remain at the end of this study they will either (i) be stored by the research group pending further ethical approval, or (ii) be transferred to the University of Birmingham HTA-licensed tissue bank. It will be made clear in the information sheet and the consent form that samples may be stored for use in future ethically approved research.

## **14. Details of Investigational Medicinal Products**

### **14.1. Description**

This study will investigate the effectiveness of imiquimod as a treatment for lentigo maligna. Participants will apply imiquimod 5% cream (Aldara<sup>®</sup>) supplied by MEDA Pharmaceuticals Ltd. (UK). Each sachet contains 12.5 mg of imiquimod in 250 mg cream (5 %). The appearance is white to slightly yellow cream. The CAS number for imiquimod is 99011-02-6.

The excipients are:

- isostearic acid
- benzyl alcohol
- cetyl alcohol
- stearyl alcohol
- white soft paraffin
- polysorbate 60
- sorbitan stearate
- glycerol
- methyl hydroxybenzoate (E218)
- propyl hydroxybenzoate (E216)

- xanthan gum
- purified water

Details of the chemical and pharmacological properties of imiquimod can be found in the current Summary of Product Characteristics document (SmPC).

## **14.2. Packaging and Labelling**

As there is no blinding in this study, the imiquimod will be prescribed in its standard packaging, with additional labelling to comply with regulatory requirements. MEDA will ship the imiquimod to a central pharmacy at the Clinical Trial Pharmacy Department, University Hospitals Nottingham, Queens Medical Centre Campus, Nottingham. The central pharmacy will then dispatch study drug to the local site pharmacies where the final labelling will be put on prior to dispensing.

Imiquimod is prescribed in sachets. Participants will be advised that sachets should not be re-used once opened.

## **14.3. Storage, dispensing and Return**

The study supplies will be kept separately to other pharmacy supplies and labelled accordingly. Storage will be at not more than 25°C. After dispensing, participants will be instructed to store the sachets at not more than 25°C. Unused supplies will be returned to local pharmacy for destruction.

The clinical trials pharmacist or designee at the hospital will dispense the medication and keep detailed dispensing records.

## **14.4. Known Side Effects of imiquimod**

These are detailed in the Summary of Product Characteristics (SmPC).

# **15. Outcome Measures**

## **15.1. Primary Outcome Measure**

- Pathological complete regression (PCR) in the mapped biopsied and resected LM using 2 mm slices.

## **15.2. Secondary Outcome Measures**

- Clinical assessment of response after imiquimod treatment:
  - Assessment of clinical response based on examination and presurgical biopsies
  - Pathological assessment of residual LM outside the clinically mapped margins of disease
  - Accuracy of map 1 and map 2 and 5mm surgical margin in predicting complete excision of lentigo maligna

*The pathological response in the entire resected lesion will be compared with that predicted from clinical examination and biopsies taken before surgery, post imiquimod treatment. We will assess whether adequate surgical margins can be determined using clinical maps. It is essential to know the accuracy of the method of clinical assessment of response.*

- Clinical feasibility of imiquimod treatment:
  - Number of reported local adverse reactions and systemic adverse reactions. These will be collected from the patient held diary and assessment by the investigator
  - Adherence to treatment schedule
  - Acceptability of imiquimod treatment. This will be collected by a visual analogue scale completed weekly by the participant.
  - Number and reasons for withdrawal from imiquimod treatment
- Number of consultations with NHS staff during imiquimod treatment
- Frequency of functional T cell responses recognising peptide epitopes in melanocyte differentiation and cancer-testis antigens.

*Circulating immune responses to proteins expressed within melanoma will be measured using blood draws taken before imiquimod treatment and after completion of imiquimod therapy but before surgery. The demonstration of a circulating immune response would be an important finding that would strongly support the investigation of imiquimod as primary therapy for melanoma, even if coupled with subsequent surgery because of the potential for such an immune response to be preventative against recurrence or invasive disease.*

- Measurement of hypothetical treatment preferences for surgery or imiquimod for LM using standard gamble technique.

*The clinical significance of the findings of this trial were pre-determined by consultation with UK dermatologists. This small scale trial will be used to enable patients to actively contribute to the interpretation of results and design of clinical guidelines or a randomised controlled trial.*

### **15.3. Stopping Guideline and Discontinuation**

The following will result in the trial being terminated:

- Unexpected toxicity or other major safety concerns. The DMC will be pivotal in making recommendations around safety.
- Insurmountable issues with trial conduct (e.g. poor recruitment, loss of resources).
- A regulatory decision, a change in opinion of the Research Ethics Committee (REC) or sponsor withdrawal.

Recruitment at a particular study site may be stopped for reasons of low recruitment or compliance issues.

The Sponsor reserves the right to discontinue this trial at any time for failure to meet expected enrolment goals, for safety or any other administrative reasons. The Sponsor shall take advice from the Trial Steering Committee and Data Monitoring Committee as appropriate in making this decision.

## **16. STATISTICS**

### **16.1. Sample size**

This trial enables the discrimination of a pathological CR rate of 60% from 85%. These limits were established using the responses of 174 UK dermatologists to a questionnaire about how the results of treating LM would impact on their practice. A CR rate >85% would be persuasive evidence for imiquimod as primary treatment for LM for 75% dermatologists; a CR rate <60% would be persuasive against the use of imiquimod.

Using A'hern's method (20) and with 95% power, the probability of a false positive is 5%. The probability of a false negative is also 5%. The study requires 33 patients and an observed CR rate of 25/33 (76%) or above would be sufficient to support proceeding to a RCT. To account for attrition, the target will be 40 patients.

There is a decision rule regarding whether to proceed to a randomised controlled trial or not based on the primary outcome measure (observed pathological complete regression (CR) rate), exceeding 25/33 evaluable patients (20). The secondary outcome measurements are very important and might contribute to decision making, particularly if the primary outcome falls in between the 60% and 85% limits. Highly positive secondary outcomes might support some kind of further research despite failing to meet the primary objective. Alternatively, highly adverse secondary outcomes might dissuade from a RCT despite achieving the primary objective. However, overall their role will remain secondary. The secondary objectives will also guide the design of a subsequent RCT.

### **16.2. Analysis**

The primary analysis will be conducted on an intent-to-treat basis. This will include those who discontinue treatment early and proceed to surgery as soon as the local inflammation has resolved to allow a clinical assessment to be made. Secondary analysis will be per protocol – i.e those who have completed the 12 weeks of imiquimod treatment.

Response rate will be presented as a percentage, with 95% confidence intervals. Other endpoints will be presented descriptively, with an appropriate measure of variation (e.g. standard deviation) if necessary. Patient demographics will be summarised. As this is a Phase II study, there will be no formal statistical testing.

## **17. Trial Management**

### **17.1. Trial Co-ordination**

The role of the Trial Management Group (TMG) is to monitor all aspects of the conduct and progress of the trial, ensure that the protocol is adhered to and take appropriate action to

safeguard participants and the quality of the trial. The Trial Management Group will include the Chief Investigator, the statistician, trial manager and data manager. They will meet regularly (face-to-face or by conference call) to facilitate the smooth running of the study. Other members of the study team will be invited to the TMG meetings as appropriate. The day-to-day co-ordination of the trial will be the responsibility of the Trial Manager who will be situated at the Nottingham Clinical Trials Unit.

## **17.2. Trial Oversight Committees**

The trial will be overseen by a Trial Steering Committee (TSC). The role of the Trial Steering Committee is to provide overall supervision of the trial and ensure that it is being conducted in accordance with the principles of GCP and the relevant regulations. The Trial Steering Committee will agree the trial protocol and any protocol amendments and provide advice to the investigators on all aspects of the trial. Decisions about continuation or termination of the trial or substantial amendments to the protocol will be the responsibility of the Trial Steering Committee. The Trial Steering Committee will comprise an independent chair and at least one other independent member, along with the Chief Investigator (CI), statistician, patient representation and other members of the study team as appropriate.

An independent Data Monitoring Committee (DMC) will also be convened for this study. The purpose of the DMC is to review the accruing trial data and to assess whether there are any safety issues that should be brought to participants' attention or any reasons for the trial not to continue. The DMC will make recommendations to the Trial Steering Committee. All members will be independent of the applicants and study team and will meet at least once a year, more frequently if required

## **18. Ethics Committee and Regulatory Aspects**

### **18.1. Ethical and Regulatory Approval**

The trial will not be initiated before the protocol, informed consent forms and participant and GP information sheets have received approval / favourable opinion from the Medicines and Healthcare products Regulatory Agency (MHRA), Research Ethics Committee (REC), and the respective National Health Service (NHS) Research & Development (R&D) departments. Should a protocol amendment be made that requires MHRA and REC approval, the changes in the protocol will not be instituted until the amendment and revised informed consent forms and participant and GP information sheets (if appropriate) have been reviewed and received approval / favourable opinion from the MHRA and REC. A protocol amendment intended to eliminate an apparent immediate hazard to participants may be implemented immediately providing that the MHRA, R&D and REC are notified as soon as possible and an approval is requested. Minor protocol amendments only for logistical or administrative changes may be implemented immediately; and the REC will be informed.

The trial will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, 1996; the principles of Good Clinical Practice, in accordance with the Medicines for Human Use Regulations, Statutory Instrument 2004, 1031 and its subsequent amendments and the Department of Health Research Governance Framework for Health and Social care, 2005.

## **18.2. Informed Consent and Participant Information**

The process for obtaining participant informed consent will be in accordance with the REC guidance, and Good Clinical Practice (GCP) and any other regulatory requirements that might be introduced.

The investigator or nominee will discuss the study with the patient and also give them a copy of the Participant Information Leaflet which will contain all the details of the study. There will be opportunity for the patient to ask questions about the study and the investigator or nominee will ensure the questions are fully answered.

The investigator or their nominee and the participant shall both sign and date the Informed Consent Form before the person can participate in the study. The original will be kept in the Investigator Site File, one copy given to the participant and a copy will be retained in the participant's hospital records.

The decision regarding participation in the study is entirely voluntary. The investigator or their nominee shall emphasize to them that consent regarding study participation may be withdrawn at any time without penalty or affecting the quality or quantity of their future medical care, or loss of benefits to which the participant is otherwise entitled. No trial-specific interventions will be done before informed consent has been obtained.

The investigator will inform the participant of any relevant information that becomes available during the course of the study, and will discuss with them, whether they wish to continue with the study. If applicable they will be asked to sign revised consent forms.

If the Informed Consent Form is amended during the study, the investigator shall follow all applicable regulatory requirements pertaining to approval of the amended Informed Consent Form by the REC and use of the amended form (including for ongoing participants).

## **18.3. Electronic Case Report Forms**

Access to the online eCRF will be provided by the Nottingham Clinical Trials Unit and paper worksheets will be provided to sites where online access is not available. All paper worksheet pages which have entries will be transcribed to the online eCRF, and any changes on the paper worksheets must also be made online, where all data will be stored in a secure dedicated server with access restricted by use to appropriate identified password holders. Original paper worksheets where utilised, will remain with the investigator as a permanent record. The Principal Investigator at each centre must ensure that their worksheets are kept in a secure location (i.e. in a locked cabinet or cupboard, or a locked room). Completion and access to the worksheets and eCRFs must be restricted to those personnel approved by the Principal Investigator and recorded on the trial's 'Site Responsibility Delegation Log'. The investigator will make a separate confidential record of the participant's name, date of birth, local hospital number or NHS number, and Patient Trial Number, to permit identification of all participants enrolled in the trial, in case additional follow-up is required.

The investigator must sign a declaration ensuring accuracy of data recorded in the eCRF.

Each participant will be assigned a patient trial number, allocated at enrolment, for use on trial documentation. The documents and database will use a sequential site number (starting from 1), sequential patient trial number (starting from 1) at each site giving a concatenated patient trial number with 2 digits for site and 2 digits for the participant and

also use their initials (of first and last names separated by a hyphen or a middle name initial when available) and date of birth (dd/mmm/yy).

#### **18.4. Source documents**

Source documents provide evidence for the existence of the participant and permit verification of the data collected. Source documents shall be filed at the investigator's site and may include (but are not limited to), consent forms, current medical records, laboratory results and pharmacy records. Data reported on the eCRFs that are derived from source documents must be consistent with the source documents or the discrepancies must be explained. The questionnaires will serve as their own source data.

Source documents must therefore be available. The following data to be reported on the eCRF should be included and derived from the source documents:

1. Subject identification (name, initials, gender, date of birth).
2. Participation in the trial identified by Patient Trial Number and date the informed consent was obtained.
3. Date of each clinic visit for the study, who performed the visit, and date of end of trial visit/participation.
4. Inclusion and exclusion criteria
5. Serious Adverse Events (SAEs)
6. Physical Exam

#### **18.5. Direct access to source data / documents**

The principal investigators and their institutions will provide direct access when required to the paper worksheets and all source documents, and other trial documentation e.g. signed consent forms, for the purpose of trial monitoring and audit and other lawful regulatory inspection.

The eCRF and all source documents, including progress notes and copies of laboratory medical test results must be made available at all times for review by the trial coordinator, sponsor's designee and inspection by relevant health authorities and Regulatory Authorities. The accuracy of the data will be verified by reviewing the documents described in the source data section above.

#### **18.6. Data Protection**

Due respect for data protection and confidentiality will be maintained.

All trial staff and investigators will endeavour to protect the rights of the trial's participants to privacy and informed consent, and will adhere to the Data Protection Act, 1998. The eCRF will only collect the minimum required information for the purposes of the trial. Worksheets will be held securely, in a locked room, or locked cupboard or cabinet. Access to the information will be limited to the trial staff and investigators and relevant regulatory authorities. Computer held data including the trial database will be held securely and password protected. All data will be stored on a secure dedicated web server. Access will be restricted by user identifiers and passwords (encrypted using a one way encryption method).



Information about the trial in the participant's medical records / hospital notes will be treated confidentially in the same way as all other confidential medical information.

Electronic data will be backed up every 24 hours to both local and remote media in encrypted format.

## **19. Quality Assurance and Audit**

### **19.1. Insurance and Indemnity**

Insurance and indemnity for trial participants and trial staff is covered within the NHS Indemnity Arrangements for clinical negligence claims in the NHS, issued under cover of HSG (96)48. There are no special compensation arrangements, but trial participants may have recourse through the NHS complaints procedures.

### **19.2. Trial Conduct**

This trial will be conducted in adherence with the protocol, International Conference on Harmonisation Good Clinical Practice E6 (ICH-GCP) and the applicable regulatory requirements. The protocol will undergo peer review by the Nottingham Clinical Trial Unit to ensure compliance with GCP. All study documents and SOPs will be prepared to ensure compliance with GCP.

The Trial Manager will ensure that all study procedures are followed and any deviations documented and investigated and will put in place measures to avoid a repeat.

One or more study training days will be arranged for training recruiting centres. This training day will cover all relevant aspects of GCP and all study procedures and SOPs. In addition, the trial manager will visit sites where necessary to conduct further training and provide assistance.

### **19.3. Trial Monitoring and Audit**

The trial oversight committees will oversee the progress of the trial and its conduct, as well as the safety of the participants. The Data Monitoring Committee will be completely independent of the Study team. The Trial Steering Committee will have an independent chair as well as two independent experts.

On-site monitoring and in-house data checking will be carried out by the Trial Manager as per monitoring plan and Trust Monitoring will be performed under existing governance arrangements. In-house data checking will be carried out by the Trial Manager and the Data Manager as the data are received at the co-ordinating centre.

Monitoring visits will cover as a minimum:

- Primary outcome variable and major secondary outcome variables
- Adverse events
- Informed consent
- Completion/withdrawal

Monitoring visits will be followed by a monitoring report, summarising the findings during the visit and recommending remedial actions as necessary.

An internal audit of the Central Trial Master File for inclusion of essential documents as defined by Good Clinical Practice will be conducted at least yearly and an audit report shall be generated.

#### **19.4. Record Retention and Archiving**

In compliance with the ICH/GCP guidelines, regulations and in accordance with University Hospitals Birmingham NHS Foundation Trust policy, the Chief or local Principal Investigator will maintain all records and documents regarding the conduct of the study. These will be retained for at least 5 years or for longer if required. If the responsible investigator is no longer able to maintain the study records, a second person will be nominated to take over this responsibility.

The Trial Master File, trial documents and database will be held by the Trial Manager at the Nottingham Clinical Trial Unit, University of Nottingham on behalf of the Sponsor. They shall be finally archived at secure archive facilities at the University of Nottingham.

#### **19.5. Risk Assessment**

There is some additional risk to the individual participant by entering this study:

- The effectiveness of imiquimod in treating lentigo maligna has not yet been proven so it is possible that at the end of the imiquimod treatment there is still residual lentigo maligna present.
- The imiquimod treatment is in addition to normal treatment (surgery). Therefore any side effects of the treatment are an additional. However, all participants will have surgery to remove the entire area of the lesion.

Imiquimod is a licensed drug and as such the side effects are well documented. All participants in the study will receive the active drug (imiquimod) as there is no placebo arm.

The results of this study will help inform clinical treatment decisions that will benefit society as a whole.

#### **19.6. Confidentiality**

Individual participant medical information obtained as a result of this study is considered confidential and disclosure to third parties is prohibited with the exceptions noted above. Participant confidentiality will be further ensured by utilising identification code numbers to correspond to treatment data in the computer files.

Such medical information may be given to the participant's medical team and all appropriate medical personnel responsible for the participant's welfare.

Data generated as a result of this trial will be available for inspection on request by the participating physicians, representatives of the Sponsor, the ethics committees, host institutions and the regulatory authorities.

## **20. PUBLICATION AND DISSEMINATION POLICY**

The results of the study will be submitted for publication in a peer review journal as soon as possible after analysis, in which the role of all principle investigators will be acknowledged. Participants will not be identified in any publications.

## **21. USER AND PUBLIC INVOLVEMENT**

The consumer representative of the NCRN Melanoma Clinical Studies Group contributed to the development of this protocol. However, the main user involvement is built in to this study. All patients who have been approached to enter this trial will be invited to contribute to a process that will guide the translation of results to a RCT clinical trial or to drawing up clinical guidance regarding imiquimod use.

## **22. STUDY FINANCES**

### **22.1. Funding source**


This study is funded by the National Institute for Health Research (NIHR) Research for Patient Benefit programme (Department of Health, UK).

### **22.2. Participant stipends and payments**

Participants will not be paid to participate in the trial. Travel expenses will be offered for any costs incurred for hospital visits in excess of usual care, and will be in the form of vouchers wherever possible.

## 23. Signature Page

Chief Investigator: JERRY MARSDEN

Signature: 

Date: 8-6-10

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I confirm I have read and understood this protocol and I agree to conduct the study in accordance with the protocol.

Principal Investigator: \_\_\_\_\_

Centre name: \_\_\_\_\_

Signature: \_\_\_\_\_

Date: \_\_\_\_\_

## 24. References

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