	CLINICAL RESEARCH PROTOCOL	

PHASE I/IIA INVESTIGATIONAL STUDY

A Phase I/IIa Safety and Acceptability Investigation of an Imiquimod (IMQ) Oromucosal film [0.1575 mg/cm²] in Patients with Oral Leukoplakia (OL)

(Short title: IMQ Oromucosal film for Oral Leukoplakia Phase I/IIa)

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Sponsor:	Mucora Therapeutics Ltd Laburnum House, East Grimstead Salisbury, SP5 3RT, UK
Protocol Number:	MUC01
IRAS Number:	1014103
Version Number:	Final 1.2
Date:	22nd October 2026

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The information should not be disclosed to any third party without written authorisation from Mucora Therapeutics Ltd, except to the extent necessary to obtain informed consent from those persons to whom the IMP may be administered.

Overview

Protocol code	MUC01
Study phase	Phase I/IIa: Safety and Acceptability Investigation
Indication	Oral Leukoplakia (OL)
Study period	Q1 2027 – Q3 2027
Individual treatment period	A 3-week Treatment period with Clinical assessment and subsequent 1 month Follow up
Investigational product	Imiquimod (IMQ) Oromucosal Film 0.1575mg/cm^2 (SAY_V2)
Active ingredient	Imiquimod
Dosage	One 'active' oromucosal film (Each 1x2cm^2 film contains 1.05% IMQ=0.315mg (0.1575 mg/cm^2)) and One 'control' matching placebo film Each film applied daily to the selected lesion for 1h every day for 3 weeks (1-week placebo, 2-week IMQ oromucosal film). With removal and mouth rinsing after each application
Responsibilities:	Manentia Ltd (appointed CRO). David Fleet - protocol content David Fleet - statistical content

This clinical study will be conducted in compliance with the protocol, ICH GCP (E6R3) Guidelines, The Declaration of Helsinki and any applicable local regulatory requirements.

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Document History

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Signature Page(s)

Authorisation* **Name And Qualifications**		
David Fleet, M.Sc., C. Stat. **CEO** Mucora Therapeutics Ltd Laburnum House East Grimstead, Salisbury SP5 3RT UK	Date (ddmmyyyy)	Signature
Dr. Caroline McCarthy, **BDS (Hons) PhD FDS(OM)** **RCS(Eng) FHEA** **Chief Investigator** Clinical Senior Lecturer Honorary Consultant in Oral Medicine School of Dentistry University of Liverpool Liverpool, UK	Date (ddmmyyyy)	Signature
David Fleet, M.Sc., C. Stat. **Statistician** Manentia Ltd Laburnum House East Grimstead, Salisbury SP5 3RT UK	Date (ddmmyyyy)	Signature

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* Authorisation – protocol can be amended by the named individuals

Declaration of the Investigator

All documentation for this study that is supplied to me, and that has not been previously published will be kept in the strictest confidence. This documentation includes this study protocol, Investigator's Brochure, electronic Case Report Form, and other scientific data.
The study will not commence without the prior written approval of a properly constituted Independent Ethics Committee (IEC). No changes will be made to the study protocol without the prior written approval of the Sponsor and the IEC, except where necessary to eliminate an immediate hazard to the participants.
I have read and understood and agree to abide by all the conditions and instructions contained in this protocol.

Responsible Investigator of the local study centre

Signature Date (ddmmyyyy)

Name (block letters)

Title (block letters)

Institution (block letters)

Phone Number

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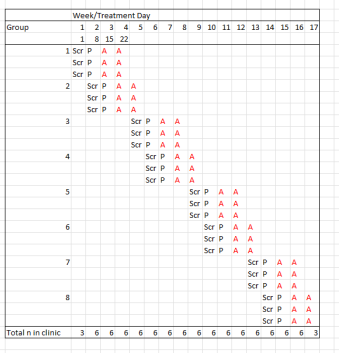
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Synopsis

Short title	IMQ Oromucosal film for Oral Leukoplakia Phase I/IIa
Sponsor	**Mucora Therapeutics Ltd**
Protocol Number	**MUC01**
Protocol Date	22nd October 2026
Development Phase	Phase I/IIa: Safety And Acceptability Investigation
Indication	Oral Leukoplakia (OL)
Investigational drug	Imiquimod (IMQ) Oromucosal film (SAY_V2)
Objectives	• To investigate the safety profile of the IMQ film • To investigate acceptability of the IMQ film following daily use by participants Secondary interests are: • To investigate local tissue and systemic absorption kinetics with IMQ (PK) • To investigate the pharmacodynamic response to IMQ (PD) Efficacy and impact on Quality of Life (QoL) will also be assessed but is for information only
Design	An open label investigation of both IMQ Oromucosal film and a matching placebo (2 treatments) in a single group of participants.
Number of Subjects	A single group total of 25 participants in required. This allows for 20 participants to complete with <20% dropout.
Anticipated Sites	One Specialist oral cancer clinic (Liverpool School of Dentistry UK.) with management at the Clinical Research Facility
Anticipated Duration and Preliminary Schedule	Clinical completion: 7 months This is based theoretically on selecting 3 suitable participants from each weekly clinic (~30 participants) and allows for only 6 attending at any one week (Therefore total required in ~21 weeks/ ~6m). With participants followed up for 1 month the clinical investigation may be completed in 7 months.

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	 NB: The actual practice of recruitment may be different depending on site requirements and participant availability Analysis and Reporting will take a further 2 months. The End of Study is defined as the point of final data capture, Last Patient, Last Visit (LPLV). This will be when the 25th participant completes the one month follow up visit (Visit 6). Subsequent to this, and resolution of any outstanding data queries, the database will be locked and released for statistical analysis and reporting.
Subject diagnosis	Eligible participants will be male or female aged 18 years or older with Oral Leukoplakia (OL) classified with mild, moderate or severe dysplasia which has been present and not treated for at least one month (but less than 6 months) and who have supporting biopsy assessment and photographs on record. Eligibility at Screening is assessed with selection of a suitable lesion (>100mm^2). The OL diagnosis and grading is confirmed based on histology findings from biopsy results on record. Lesion size and type will also be assessed at the clinic visit. The OL diagnosis will be based on defined best practices (van der Waal 2019, Maloney 'OL update for dental practitioners' 2024. Single or multiple oral lesions may be present but for the purposes of this investigation a single lesion will be chosen for treatment with a single film applied daily. Eligible participants selected should be unlikely to progress to malignant transformation or to need other therapeutic procedures during the investigational period. However, participants at potentially 'higher risk' may be included if elective surgery can be accommodated into the treatment schedule

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Criteria for Subject Selection	**Inclusion Criteria** To be eligible, the following conditions must be met: 1. Men or women with a diagnosis of mild, moderate or severe oral epithelial dysplasia. 2. Eighteen (18) years of age or more. 3. Active oral lesion present and not treated for at least one month (but less than 6 months). 4. Clinical evidence of one or more OL lesions affecting the oral at least 100mm^2. 5. Involvement in study fits with planned clinical management strategy (Low/Medium risk: 'Watch and Wait only'-no action planned, High risk: 'Elective surgery' date schedule fits with trial requirements) 6. General health status acceptable for participation up to 2-month (3-week treatment plus 1-month follow up) in clinical trial. 7. Able to easily apply films themselves after instruction 8. Signed informed consent prior to the initiation of any study specific procedure. 9. Good level of understanding of spoken and written English language. 10. Women of childbearing potential must have a negative serum pregnancy test at screening and must be practicing adequate, medically acceptable method of birth control which is approved by the Investigator. 11. Women not of childbearing potential must be in a menopausal state for at least a year or had a hysterectomy, a bilateral oophorectomy or be clinically diagnosed infertile (*Full details as specified by the Clinical Trial Facilitation Group (CTFG) are given in the protocol*). **Exclusion Criteria** Prohibited Associated Conditions: 1. Any previous diagnosis of synchronous or metachronous OSCC 2. Any hypersensitivity (allergies) to either IMQ or excipients in film 3. Any pre-existing cardiovascular issues, reduced haematologic reserve, compromised immunity, inflammatory conditions, autoimmune or organ transplant situations which may impact IMQ use. 4. Any other chronic co-morbidity which is not controlled by appropriate medication. Prohibited Medications: 5. Any OL treatment in the last one month. 6. Any systemic immunosuppressive agent in the last

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	one month, including Prednisolone >10mg daily 7. Any treatments for the relief of oral irritation or pain in the last one month (eg: Anbesol (2% lidocaine)) 8. Any investigational drug treatment (i.e.: clinical trial involvement) in the last one month General Exclusions: 9. Any history of cutaneous or systemic medical illness or psychiatric disease which will put pat at risk or interfere with assessments. 10. Any known HIV or hepatitis B or C positive conditions. 11. Any vaccination with herpes zoster or any live virus in the last one month 12. Hospitalisation or change of chronic concomitant medication in the last one month. Or any planned hospitalisation during the treatment period. 13. Symptoms of severe cardiovascular disease or heart related problems. 14. Drug or alcohol abuse. 15. Women who are pregnant or nursing. 16. Any condition which in the opinion of the Investigator makes the participant unsuitable for inclusion.
Duration of treatment	Treatment and clinical assessment for a period of 3 weeks. Follow up for assessment of safety then for a further 1-month period.
Assessment Timing	A total of 6 clinic visits are scheduled (including Screening Visit 1). Screening is performed at least 7 days prior to enrolment (Day -14 to -7) to enable diagnosis, suitability assessment and participant assessment of involvement. At Enrolment, treatment dispensing and baseline assessments are performed (Visit 2 Day 1) and this is followed by three treatment visits, 1-week with the placebo biofilm and a further 2-weeks with the IMQ film treatment (Visits 3-5 on Days 8, 15, 22). A further visit one month following completion of treatment is performed (Follow-Up Visit 6). With the follow-up, patient involvement in the study lasts for a total of no more than 2 months. Participants who prematurely discontinue before the end of the treatment return for an Early Termination visit and complete all the assessments as planned at 3-

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	weeks Visit 5, Day 22. **See Investigation Schedule of Events (attached)**
Outcome Measures	Safety, Acceptability, PK, PD, Efficacy and QoL are endpoints of interest A pre-treatment tissue biopsy is not performed and participants are identified from hospital database records (with biopsy performed within the last 6 months of the scheduled investigation). A biopsy will be performed after completion of the biofilm treatment period (3-week (Day 22, Visit 5) or earlier in the event of withdrawal)). However, the biopsy may be delayed until the 1m follow up visit if the clinician considers there is significant irritation which may subject the participant to considerable pain and invalidate diagnostic testing **Photography:** At each visit (Visit 1-6, Day -14 to 1, Day 8, 15, 22 and 1 month follow up) two sets of photography will be performed, one of the mouth, and one the treated lesion. A strict protocol and standardised equipment will be used to allow storage of a complete record of the participant condition. **Safety**: Safety will be assessed on a continuous ongoing basis at each visit and will include monitoring: Adverse events and Physical examination and Vital signs. Laboratory tests will be performed for safety purposes at Screening (Visit 1), after completion of the IMQ biofilm treatment (3-week (Visit 5) or earlier in the event of withdrawal) and at Follow up **Acceptability**: Following daily use of the film participant undergo a questionnaire at Day 8 (Visit 3) following placebo and 22 (Visit 5) following IMQ film treatment to assess their experiences. The questions cover: • Compliance with requirements and ease of use • Film characteristics • Effects of the film • Effect on daily activities **PK:** Plasma samples are obtained at Pre-dose 0h and 1-4h (end of clinic) on Days 1, 8, 15, 22 (Visits 2, 3, 4, 5). Individual drug concentrations pre and post dose at each visit and separately by drug trough levels (Pre-dose 0h each day) will be presented.

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	Saliva samples are obtained at Pre-dose 0h and 1h (immediately prior to removal of oromucosal film) on Days 1, 8, 15, 22 (Visits 2, 3, 4, 5). Individual drug concentrations pre and post dose will be presented **PD:** Biopsy tissue samples obtained post treatment completion (Visit 5) (or at Follow up (Visit 6) in the event of severe irritation) to grade dysplasia will also be used to measure potential useful immunohistopathology protein markers: CD3, CD4, CD8, CD68, Cd1a, CD66b, CD56, Ki67 Where possible the results will be compared with previous biospy records. **Efficacy measures of interest include**: • Lesion size • Histology Response • Complete Resolution (100% reduction in size) • Partial Resolution (>=50% reduction in size) • Change in Dysplasia severity (Mild, Moderate, Severe) • Incidence of oral cancer development • Clinical Global Impression–Improvement (CGI-I) **QoL measures include:** • Oral Health Impact Profile scale (OHIP-14) All efficacy/QoL measures will be recorded at Screening (Visit 1) and after completion of the IMQ biofilm treatment (3-week (Visit 5) or earlier in the event of withdrawal)
Safety	Safety will be monitored throughout the investigation in line with standard clinical practice and subject care. This includes AEs (spontaneously reported), clinically relevant changes of laboratory values and any abnormalities following physical examination. With participants taking medication at home there will be daily phone call contact, a study diary card for adverse events, concomitant medication reporting, treatment film application and recue medication reporting. An emergency card is also provided. An overall review will be performed according to treatment as data accrue and after 10 participants have been enrolled and completed treatment
Sample size justification	Sample size and power estimations, although not critical for this initial Phase I/IIa investigation, are useful

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	for future planning and to indicate the likely precision (95% confidence intervals) for actual proportions (Active, Control) and for differences in proportions of responses between the two treatment groups (Active – Control). With the chosen sample size of 20 participants for each group the two-sided 95% confidence interval for the difference between a Group 1 proportion, π_1, of 0.5 and a Group 2 proportion, π_2, of 0.2 will extend 0.281 from the observed difference in proportions. Therefore a difference estimate of 30% will extend from 2% to 58%. On application of a maximum dropout rate of 20% then the total required sample size is 25 participants.
Analysis sets	Three analysis sets (Safety, Full analysis set, Per protocol) will be defined for investigation. Given the stage of development, the Per protocol set will be considered primary. A last observation carried forward (LOCF) approach will be applied in the event of withdrawal or early termination.
Statistical methods	The null hypothesis assumed throughout, is that there is no difference between the 'active' treatment and 'control' placebo. As only within participant treatment and ordered comparisons are possible, although statistical significance (p values) will be reported these will not be emphasized. Statistical models and tests performed are only to aid assessment of variability of estimates. **Efficacy/QoL/PK/PD:** Complete resolution or Partial resolution or Incidence of oral cancer after 2-weeks treatment will be derived (responder rate %). This binary outcome measure will be analysed using Fisher's exact test and treatment differences quantified in terms of odds ratios and 95% confidence intervals using a binary logistic regression. Other efficacy endpoints including: Lesion grade, Histology response, Dysplasia score, Dysplasia severity and CGI-I are considered ordered categorical data and will be analysed using Cochran-Mantel-Haenzsel (CMH) tests and quantified with ordered logistic regression.

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	Interval data (eg: Lesion size, PK, PD parameters, QoL scores) will be analysed using analysis of covariance (ANCOVA) models using change from baseline at endpoint (3-weeks or earlier in the event of withdrawal) as response variable, Treatment group as fixed effect and baseline as covariate. An ANOVA will be used if no baseline available. Estimates of treatment group estimates and effect sizes will be presented as odds ratios or adjusted means (as appropriate) each with 95% confidence intervals with minimal emphasis on associated p-values **Acceptability**: The participant questionnaire includes four main categories: Compliance with treatment requirements and ease of use, film characteristics, Effects of the film and the Effect on daily activities and individual items will be presented as overall summaries (n/% responses) but total ranked scores for each category may be of interest. **Safety**: Evaluations performed at all post randomisation visits will be described as interval or categorical summaries. These include: reported adverse events, physical examination (plus weight), vital signs and prior and concomitant medications. Laboratory safety will be summarised as actual values, changes from Screening (Visit 1) and also after classification as low, normal, high in relation to the laboratory normal range. No formal analyses of differences between the Active or Control group phases will be performed. All Physical examinations, Medications, Adverse events and Laboratory tests will be summarised as descriptive statistics (frequency and percentages for categorical variables and mean, median, range, standard deviation, and 25th/75th quartiles for the continuous variables.
Miscellaneous Details	
Product details, Manufacturer	The IMQ oromucosal film (SAY_V2) and matching placebo film are manufactured, packaged and distributed by **Labtec Labtec R&D GmbH** Raiffeisenstraße 4, 40764 Langenfeld, Germany

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Safety Committees	Safety will be reviewed on an ongoing basis by the Medical Safety Officer using subject listing and overall summaries produced on a monthly basis and after 10 participants have been recruited and completed treatment. These will form part of the overall continual data evaluation process. As no blinding is involved a separate Data Safety Monitoring Committee (DSMC) will not be required.
Interim Analysis	A single analysis is planned at the conclusion of the clinical phase. No Interim analyses are planned or will be undertaken. No formal statistical analyses or claims associated with presentation of significance levels planned. Therefore preservation of the overall Type 1 error rate (<0.05) is maintained and no adjustment for the multiplicity of testing is required given the stage of development

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Administrative Responsibilities

Name	Title	Address
David Fleet	Sponsor	Mucora Therapeutics Ltd Laburnum House East Grimstead Salisbury SP5 3RT United Kingdom Tel: +44(0) 1722 712980 e-mail: davidfleet@manentia.co.uk
Professor Richard Shaw	Medical Monitor	Professor of Head and Neck Surgery Aintree University Hospitals University of Liverpool Group Lower Lane Fazakerly Liverpool L9 7AL Tel; +44(0) 7769 711038 e-mail: rjshaw@liverpool.ac.uk
Ruth Joslyn	Clinical Monitoring Project Manager	Manentia Ltd Laburnum House East Grimstead Salisbury SP5 3RT United Kingdom Tel: +44(0) 7777 686595 e-mail: ruthjoslyndugdale@manentia.co.uk
Yvette Ayliffe	Clinical Management Project Manager	Manentia Ltd Laburnum House East Grimstead Salisbury SP5 3RT United Kingdom Tel: +44(0) 1722 712980 e-mail: yvetteayliffe@manentia.co.uk
Matthew Curtis	Quality Assurance	Copperhead QARA/RP Services Ltd 7 The Broadway Broadstairs Kent CT10 2AD Tel: +44(0) 7841 762426 e-mail: matt@copperqarp.co.uk
David Fairlamb	Regulatory-Pharmacovigilance Reporting	ProTherax Ltd 3 Stepping Stones East Morton Keighley West Yorkshire BD20 5UG UK

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Name	Title	Address
		Tel: +44(0) 7880 795256 e-mail: davidfairlamb@protherax.com
Kevin Jacobs & Sarah Devaney	Photography	ClinPhoto Ltd 5A Ack Lane East Bramhall Stockport SK7 2BE Tel: +44(0) 7792 226863 Kevin Tel: +44(0) 7843 559761 Sarah e-mail: kjclinphoto@outlook.com & sdclinphoto@outlook.com
David Fleet	Statistician	Data Magik Ltd Laburnum House East Grimstead Salisbury SP5 3RT United Kingdom Tel: +44(0) 1722 712980 e-mail: davidfleet@datamagik.co.uk
Amanda Prowse	Medical Report Writer	Lochside Medical Communications 1 Drumbeg Terrace Milngavie Glasgow G62 7RH Tel: +44(0) 7879 632648 e-mail: aprowsemilling@gmail.com

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List of Abbreviations

AE	Adverse Event
AK	Actinic Keratosis
BP	Blood Pressure
BCC	Basal Cell Carcinoma
CDMS	Clinical Data Management System
CGI-I/S	Clinical Global Impression Scale- Improvement/Severity
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EGW	External Genital Warts
FAS	Full Analysis Set
FDA	Food and Drug Administration [US Regulator]
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
GRAS	Generally Regarded as Safe
ICH	International Council for Harmonisation
ICF	Informed Consent Form
IEC	Independant Ethic Committee
IFN-α	Interferon-Alpha
IFNγ	Interferon Gamma
IL	Interleukin
IMP	Investigational Medicinal Product
IMQ	Imiquimod
IMV	Interim Monitoring Visit
ISF	Investigator Site File
IRS	Interactive Response System
LOCF	Last Observation Carried Forward
LOH	Loss Of Heterozygosity
MedDRA	Medical Dictionary for Regulatory Activities
MM	Medical Monitor
MTR	Malignant Transformation Rates
NF-kB	Nuclear Kappa B
OHIP-14	Oral Health Impact Profile scale
OL	Oral Leukoplakia
OSCC	Oral Small Cell Carcinoma
PD	Pharmacodynamics
PI	Principal Investigator
PK	Pharmacokinetics
PPI	Patient and Public Involvement
PPS	Per Protocol Set
QbD	Quality By Design
QMS	Quality Management System
QoL	Quality of Life
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAR	Serious Adverse Reaction
sBCC	Superficial Basal Cell Carcinoma
SCC	Small Cell Carcinoma
SD	Standard Deviation
SIV	Site Investigation Site
SOP	Standard Operating Procedures
SS	Safey Set
SUSARs	Suspected Unexpected Serious Adverse Reactions
TEAE	Treatment-Emergent Adverse Event
TMT	Mean Transformation Time
TNF-α	Tumour necrosis Factor-Alpha

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WHO World Health Organisation

1. Introduction

This is a Phase I/IIa investigation to assess the safety and acceptability of Imiquimod (IMQ) when applied directly to affected oral mucosa using a novel oromucosal film (SAY_V2) for the treatment of Oral Leukoplakia (OL). Participants of the study will involve patients rather than volunteers, to give more representative information on safety and usage particularly regarding experience and perspective of the quality, relevance and impact of the treatment. It will also provide information on drug permeation in oral dysplastic lesions

IMQ is licensed and widely used for the treatment of skin lesions such as: Actinic Keratosis (AK), superficial Basal Cell Carcinoma (sBCC) and External Genital Warts (EGW) (Aldara [PLGB 46302/0206], Zyclara [PLGB 46302/0209]). It has a well-known safety profile with no history of serious adverse events and has been suggested as a possible treatment option in OL as well as other mucosal indications (Palma 2024, Gkoulioni 2010).

Although the topical cream formulation (Aldara 5%) has already been used 'off label' in pilot clinical trials to assess its potential efficacy (with 3 trials and 64 patients in total (see Investigator Brochure), this is not a viable licensing option given the inclusion of emollients and preservatives specifically intended for topical [dermal] application. As a cream it is also limited by the likelihood of swallowing or cream foaming with saliva which therefore also presents associated difficulties with retention time, taste, texture and compliance.

Mucoadhesive buccal films have been developed as promising drug delivery systems with an extensive range of polymer forms investigated (Abdalmalk 2024, Shipp 2022). Promising initial findings specifically with IMQ have shown prolonged drug retention at the buccal site, sustained immune activation and minimal systemic absorption (Ramineni 2013).

Mucora Therapeutics Ltd have therefore specifically formulated an IMQ loaded oromucosal film (SAY_V2) enabling direct targeting of the drug substance to the affected area of the mucosa. It includes excipients that solubilise and stabilise the active product ingredient (API) together with polymers that ensure the film adheres to the area applied. The film is a two layered structure which includes a mucosal facing 'active' layer containing the drug substance and a protective inert backing layer that prevents backwards permeation into the mouth and swallowing. Although the IMQ loading of the SAY_2 film is always less than the Aldara 5%/Zyclara 3.75% creams depending on various recommended dose regimens, the maximum daily exposure possible without crystalisation (each 2cm^2 film loaded with 1.05% IMQ=0.315mg). *Ex vivo* tissue permeation experiments resulted in wet tissue concentrations after 1 hour of, 0.001ug/mg with the film and 0.004ug/mg Aldara 5% cream, representing around x4 times less exposure (see Section 1.4) when ~0.13ug and ~0.30ug IMQ was applied with the oromucosal film and Aldara 5% cream IMQ respectively. These data are therefore indicative of a safety margin of around 50%.

The oromucosal film structure will allow direct targeting and permeation of IMQ into the affected area, reduce the required applied dose and also any local or systemic adverse reactions. The SAY_V2 film is intended to be applied to the affected area, on a once daily basis for up to 1 hour before removal, 7 days a week for a total of 2 weeks. Total exposure expected therefore is 4.41mg over 2 weeks. The use of the active IMQ oromucosal film will be preceded by a similar 7-day treatment period with a matched placebo film, allowing for a determination of any local reactions, such as irritation (mucositis) that could be attributed to the film. This additionally allows, treatment to be temporarily halted for a few days or the application time may be reduced to allow the event to settle. Any modifications in clinical use will be recorded.

Previous trials with IMQ typically expect treatment benefit within 6 weeks. As this is not specifically an investigation of efficacy, 2 weeks of clinical use is sufficient for evaluation of safety, acceptability and kinetics given an IMQ half-life of 29h and reported steady state by day 7 with topical application (Wu 2013, Kulp 2010) and given permeability similarities between skin and buccal mucosa (Galey 1976).

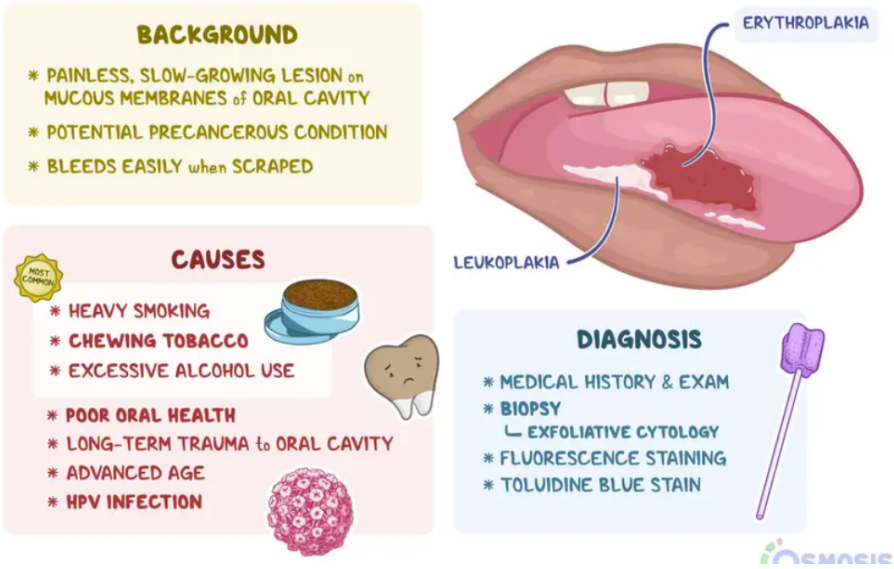
1.1.1 Background

Oral Leukoplakia (OL) is a potentially malignant disorder affecting the mucosa on the inside of the mouth. It is defined as “essentially an oral mucosal white lesion that cannot be considered as any other definable lesion.” The white patch or plaque develops in the oral cavity and is strongly associated with smoking. Risk factors include: age, male sex, all forms of tobacco use, alcohol consumption, and fungal infections (Figure 1).

There are two main clinical sub-types, homogenous and non-homogenous. Homogenous OL comprises uniformly white plaques that are usually asymptomatic in nature with lower likelihood of malignancy. Non-homogenous OL is irregular, flat, nodular, or exophytic in nature and resembles mixed red and white non-uniform patches, and has a greater probability of malignant transformation. Typical oral sites include: gingiva, tongue, buccal mucosa and hard palatel mucosa.

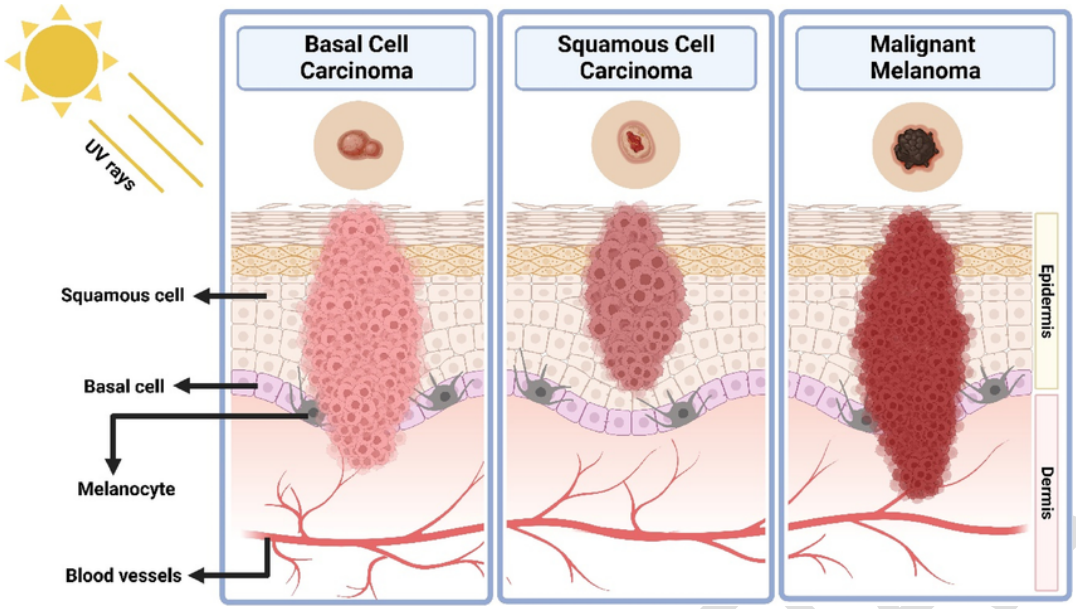
Typically factors such as: sex (females), duration (longer), non-smokers (idiopathic OL), site (tongue/floor of the mouth), size (>200 mm), type (non-homogeneous), presence of Candida albicans and presence of epithelial dysplasia are indicators of concern for future malignancy. (Mohammed 2023)

Figure 1: Aetiology



Pathophysiology suggests that tissue cells exposed to irritant carcinogens in the epidermis (excluding basal layer) typically adapt by increasing cell proliferation, shrinking the cytosolic capacity and the allied organelle load. In the oral epithelium, hyperplasia is then the initial sequelae. Then with further irritation, the epithelium shows features of cellular degeneration (atrophy). However, at some point irrevocable cell damage occurs and this manifests as either apoptosis or malignant transformation to oral squamous cell carcinoma (OSCC) (Figure 2).

Figure 2: Pathophysiology (From OL to OSCC)



The gold standard for diagnosis is biopsy from the site of the lesion with the demonstration of major histopathological changes (Epithelial keratinisation, Epithelial increased thickness, Acanthosis, Thin basement membrane, Inflammation of connective tissue, Change in the cellular layer, Increased nuclear-cytoplasmic ratio, Hyperchromatic nuclei, Nuclear hyperplasia, Abnormal mitotic figures, Increased mitosis, Pleomorphic nuclei, Basilar hyperplasia, Drop-shaped rete pegs and Loss of polarity). An original definition was given by van der Waal and subsequently updated **(**Van der Waal 2015, Van der Waal 2019)

Oral leukoplakias are histologically graded as either hyperkeratosis (thickening outer layer of mucosa), mild dysplasia, moderate dysplasia or severe dysplasia. The WHO defines the grades the dysplasia as:

Mild Dysplasia: Characterized by slight cellular changes, often considered a lower-risk category.
Moderate Dysplasia: Represents more significant cellular changes and a moderate risk of malignant transformation.
Severe Dysplasia: Indicates substantial cellular changes and a higher risk of progression to cancer.
(Warnakulasuriya 2020)

Currently the WWOM IX Leukoplakia group (world workshop for oral is aiming to propose standardisation of outcomes measured in clinical trials recruiting patients with OL. Verbal recommendations are included and future guidelines will be adopted in the Phase II programme.

1.1.2 Unmet Need

A recent systematic review and meta-analysis estimated a global prevalence of OL of 1.39% based on 69 studies (Zhang 2023).

Further review suggests oral cancer malignant transformation rates (MTR) of 12.1% with a mean transformation time (TMT) of 4.3 years with severe dysplasia cases showing higher progression rates compared to mild/moderate (24.1% vs 10.3%) (Mehanna 2009). Typically, oral cancers such as oral squamous cell carcinoma (OSCC) then have notably high rates of mortality and morbidity, with only 50–60% achieving 5-year survival (Muller 2016). However, there is a treatment window as most cases are preceded by long-standing pre-malignant clinical

phase with the mucosa progressing sequentially through stages of mild, moderate and severe dysplasia.

Currently there are no approved treatments although various treatment strategies including chemoprevention options have been considered. The standard practice is to focus on providing advice and recommending lifestyle changes aimed at reducing or eliminating the causative factor. Then a process of 'watch and wait' is adopted before ultimately deciding, based on severity, when to progress to invasive therapeutic procedures such as surgical excision, cryosurgery or CO2-laser ablation. Unfortunately, this approach has notable limitations, particularly in preventing recurrence and progression to oral cancer. At this time, no chemo-preventive agent is in routine clinical use, representing an unmet need in this patient population.

Consequently, treatment modalities are considered limited or insufficient and new improved methods are required to address patient needs (Palma 2023).

At this stage of development (Phase I/IIa), our aim is to demonstrate the safety and utility of the IMQ oromucosal film as an oral treatment (prolonging drug contact time with the mucosa and preventing drug removal by salivary flow). Phase II will then aim to investigate efficacy at the various stages of OL with remission of dysplasia symptoms and likely side effects.

The ultimate goal (Phase III) will then be treatment confirmation with chemoprevention of malignant transformation and cancer-free survival. This will involve large sample size and long-term follow-up of treated patients.

1.2 Investigational Drug and Formulation

1.2.1 Imiquimod (IMQ)

Imiquimod (IMQ) is a chemotherapeutic and immunostimulant drug, with antitumor and antiviral effects, currently licensed for use in dermatological conditions as a topical cream (Aldara, Zyclara).

IMQ was first approved by the US FDA in 1997 for the treatment of external genital warts (EGW) and later approved for actinic keratosis (AK) and superficial basal cell carcinoma (sBCC) (Sauder & Mofid 2004). It is commercially available in 5% and 3.75% cream formulations.

Under the Aldara brand, the 5% formulation is approved in the EU, UK [PLGB 46302/0206], US, and other countries for the treatment of sBCC in adults and nonhyperkeratotic, non-hypertrophic AK on the face or scalp. It is also indicated for external genital and perianal warts in adults within the UK and EU, and for individuals aged 12 years and older in the US (FDA, 2010b). The 3.75% formulation (Zyclara) [PLGB 46302/0209] is indicated specifically for AK in immunocompetent adults. Additional brand names include Bascellex (UK) and Vyloma (Canada, US), while generic forms of IMQ are widely available (DrugBank, 2024; EMC, 2024).

IMQ [1-(2-methylpropyl)-1H-imidazo(4,5-c)quinoline-4-amine] functions as a 'toll-like' receptor 7 (TLR7) agonist, triggering both innate and adaptive immune responses. It is a tricyclic heterocyclic amine with a molecular formula of $C_{14}H_{16}N_4$ and a molecular weight of 240.30 g/mol. Its moderate lipophilicity (logP ~2.2–3.2) supports membrane permeability while limiting systemic absorption when applied topically (Baumann 2013).

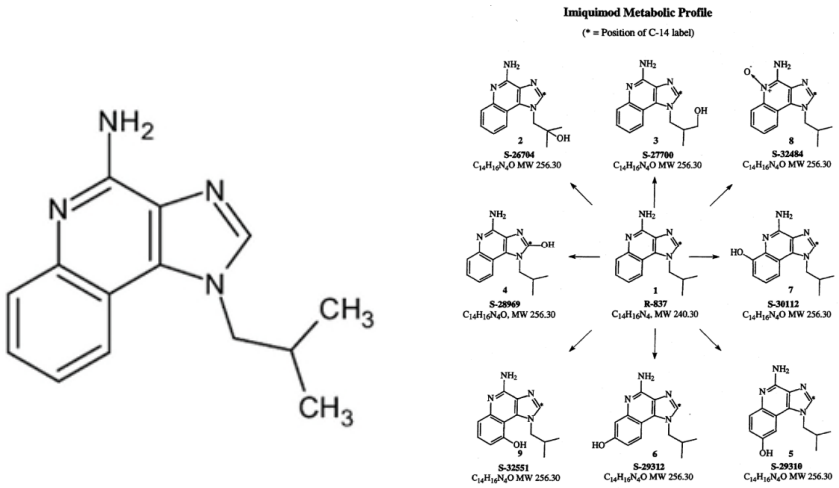
The action of binding to TLR7 receptors on dendritic cells (plasmacytoid DCs), monocytes, macrophages, and B cells leads to stimulation of nuclear factor kappa B (NF-κB) and the release of pro-inflammatory cytokines, including interferon-alpha (IFN-α), tumour necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and interleukin-12 (IL-12) (Hemmi et al., 2002).

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IMQ itself is metabolised in the liver and skin by cytochrome P450 enzymes, particularly the CYP1A isoforms (Mescher 2019). Pharmacokinetic studies indicate that IMQ exhibits minimal systemic absorption following topical application, with less than 1% of the applied dose entering systemic circulation (Harrison 2004).

Mucoadhesive drug delivery was found to enhance localised immune responses, improve therapeutic efficacy whilst at the same time prolonging mucosal contact time and ensuring IMQ effectively bound to TLR7 receptors to stimulate strong immune responses (Ramineni 2013).

Schematic: Imiquimod IMQ and its Metabolites



Zyclara: 3.75% (250mg (1/2 FTU) = 9.4mg IMQ). Aldara: 5% (250mg (1/2 FTU) = 12.5mg IMQ). NB: % is g/100ml
Figure from 201153 Imiquimod Clinpharm PREA FDA docs

1.2.2 Pharmacological effect and mode of action

Imiquimod's (IMQ) mechanism of action is via stimulation of innate and acquired immune responses, which ultimately leads to inflammatory cell infiltration of the diseased tissue which is followed by apoptosis. IMQ does not have direct antiviral activity. Studies of mice show that imiquimod may induce cytokines, including interferon-alpha (IFNA) as well as several IFNA genes (IFNA1, IFNA2, IFNA5, IFNA6, and IFNA8) as well as the IFNB gene. IMQ also induced the expression of interleukin (IL)-6, IL-8, and tumour necrosis factor alpha genes. In the treatment of basal cell carcinoma, Imiquimod appears to act as a toll-like receptor-7 agonist, and is thought to exert its anti-tumour effect via modification of the immune response and stimulation of apoptosis in BCC cells. In treating basal cell carcinoma, it may also increase the infiltration of lymphocytes, dendritic cells, and macrophages into the tumour lesion (Wagner 1997, Drugbank 2024).

The planned examination of immunohistopathological protein markers, such as CD3, CD4, CD8 staining, may indicate infiltration of T-lymphocyte in the treated area and infer the cytokine-producing profile.

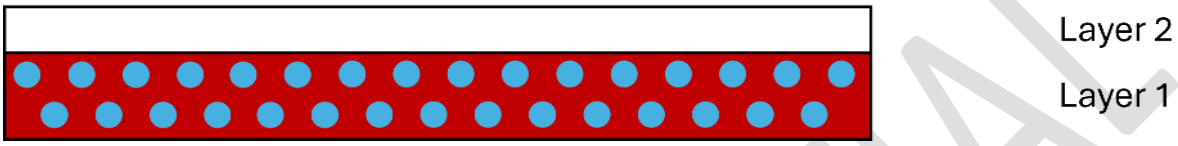
1.3 Oromucosal Film Formulation

The most challenging aspect to treating OL and oral mucosal conditions in general is ensuring drug is delivered to the affected area and remains in situ for a practical and sufficient period to stimulate effect. A polymer film format was chosen primarily as it could be specifically constructed to ensure adhesion to wet mucosal tissue and target the delivery of drug without swallowing.

The SAY_V2 oromucosal film drug delivery mechanism (active layer with drug concentration gradient and protective backing layer) has the potential therefore to offer optimal targeting and release characteristics.

The oromucosal film has been constructed using a 'quality by design' (QbD) strategic approach employed to ensure the highest-quality product. With each of the excipients (polymers, solvents, stabilisers, antioxidants and plasticisers) included to perform a specific and optimised task. Each of the excipients are approved by the FDA and within the safety margins specified for 'generally regarded as safe' (GRAS) products (see Table 1)

Table 1: Film Formulation (SAY_2)



Ingredients	Quantity (mg)	Ratio (%)	Function
Active Layer 1			
Imiquimod	0.3150	0.90	Active drug
Oleic acid	7.5000	21.43	Solvent
Carbomer homopolymer Type A	0.7200	2.06	Bioadhesive
Povidone K-90	16.2150	46.33	Dissolution
Silica, colloidal hydrated	0.6000	1.71	Emulsion stabiliser
Ferric oxide red	0.1500	0.43	Active layer colourant
Polysorbate 80	3.0000	8.57	Emulsifier
Glycerol	1.5000	4.29	Plasticizer
Potassium hydroxide	q.s	q.s	pH adjuster
Water, purified*	-	-	
Backing Layer 2			
Ethylcellulose N10	2.3750	6.79	insoluble backing
Ethylcellulose N22	1.1875	3.39	insoluble backing
Titanium dioxide	0.2500	0.71	Backing layer pigment
Triethyl citrate	1.1875	3.39	Plasticizer
Ethyl acetate*	-	-	Backing layer solvent
PET film 100 µm*	-	-	Processing liner
Total weight	35.0000	100.00	

* Not present in the final IMP, evaporated during production process.

The oromucosal film constructed provides a convenient and easy to use application with targeted short term drug delivery and local mucosal kinetics to enable significant treatment effect with minimal safety issues.

1.4 Nonclinical Investigations with Clinical Safety Background

The nonclinical work undertaken was used to identify a suitable film formulation of the drug product to take forward to clinical trials. Approximately 10-15 prototypes of the formulation were developed and optimised for content, solvent, stability, and informally adhesion (with different drug loadings) and also for assessment of permeation characteristics in *ex-vivo* models with excised oesophageal and subsequently buccal mucosal tissue. SAY_V2 was selected to

progress into clinical trials and permeation characteristics of this film are summarised here (see Investigator Brochure for full details).

The *ex-vivo* experiment involved porcine mucosal tissue to assess likely permeation of IMQ from the SAY_V2 prototype film (batch SAY235) with reference to the standard Aldara 5% cream product. Four application times (8 replicates) were selected to represent clinical situations (1h, 2h, 4h, 8h) with 1h representing the reasonable treatment period for participants.

For all cells with the SAY_V2 film (0.82cm^2) 0.129mg of IMQ was applied whilst with the Aldara 5% cream (~5mg) approximately 0.250mg IMQ was applied (1h=0.305mg, 2h=0.324mg, 4h=0.254mg, 8h=0.259mg). Therefore, approximately twice the amount of IMQ was applied via the cream versus the film at the outset. Full mass balance determination was used to ensure accountability of all drug applied. Total recoveries were very good, particularly with respect to the film (90-93%).

Tissue Recovery

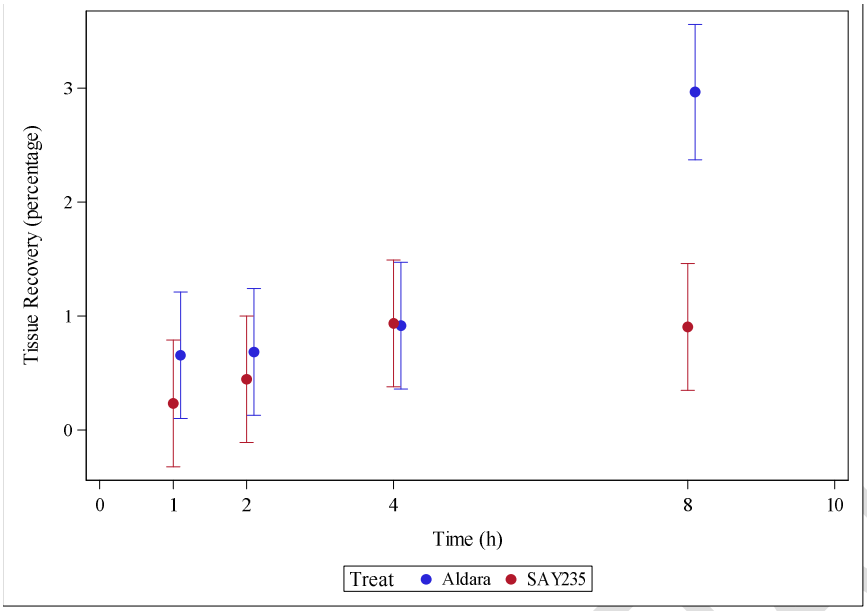
IMQ recoveries from tissue demonstrate a consistent permeation pattern with a maximum of <1.5% IMQ with the film and <6.0% IMQ with Aldara recovered in the mucosal tissue even after the 8h application (Table 2, Figure 3). It is worth noting lower IMQ tissue concentrations are likely with Aldara *in-vivo* situations where patients are more likely to swallow most of the cream applied.

Table 2: IMQ Tissue Recovery (%): Descriptive Summary (Actual Means)

		Tissue Recovery (percentage)						
		Mean	Median	Min	Max	StdDev	StdErr	N
Treat	Time (h)							
Aldara	1	0.66	0.54	0.17	1.24	0.38	0.13	8
	2	0.69	0.51	0.37	1.28	0.38	0.13	8
	4	0.92	0.72	0.24	2.36	0.72	0.25	8
	8	2.97	3.10	0.51	5.86	2.02	0.76	7
SAY235	1	0.23	0.24	0.10	0.35	0.08	0.03	8
	2	0.45	0.45	0.11	0.95	0.25	0.09	8
	4	0.94	0.98	0.31	1.44	0.43	0.15	8
	8	0.91	0.83	0.18	1.52	0.53	0.19	8

Figure 3: IMQ Tissue Recovery (%): LSMeans +/-95% CI At Each Time

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It is worth noting that after 1h and 2h application with the film specifically <0.02% IMQ (and only 0.17% after 8h) was recovered in the receptor fluid suggesting excellent tissue targeting and minimal systemic absorption.

Drug Permeation

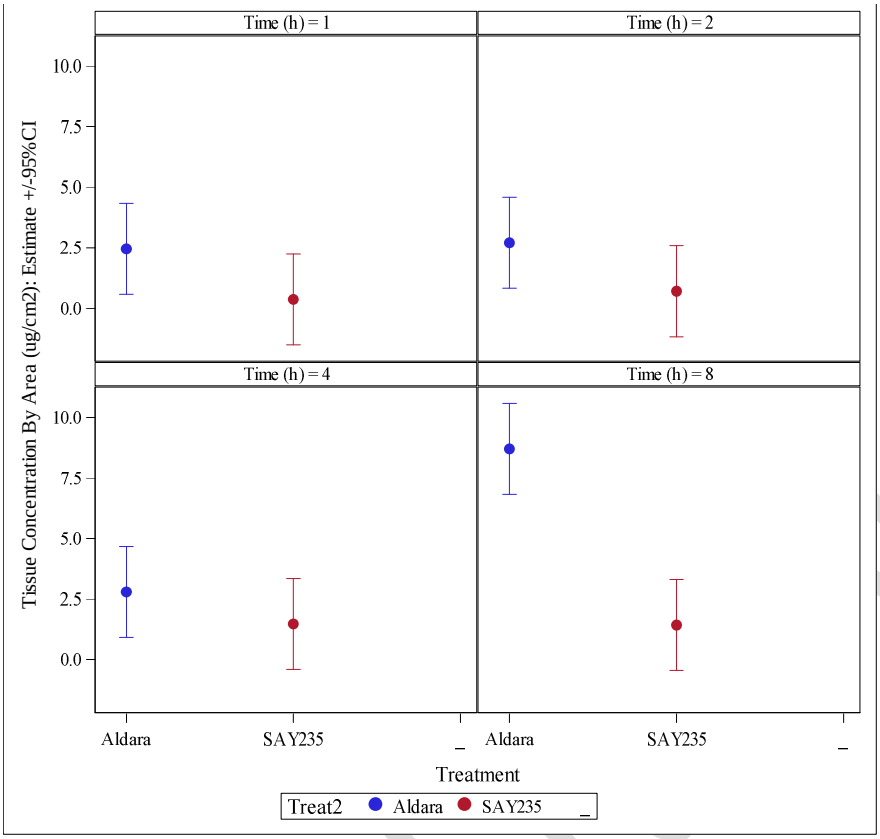
IMQ concentrations were measure as: Tissue concentration by area, Wet and Dry concentration by tissue weight. All showed similar and consistent findings.

Tissue concentration by area measured as ug/cm^2 (Table 3, Figure 4) show that although film IMQ concentrations are always less than Aldara cream by 8h there is little difference between the products after 1h an 2h as implied by the overlapping confidence intervals for the least square means (SAY_V2 film (LSmean+/-95% CI: 1h: 0.368 (0-2.244), 2h: 0.704 (0-2.580))

Table 3: IMQ Tissue Concentration By Area (ug/cm^2): Descriptive Summary (Actual Means)

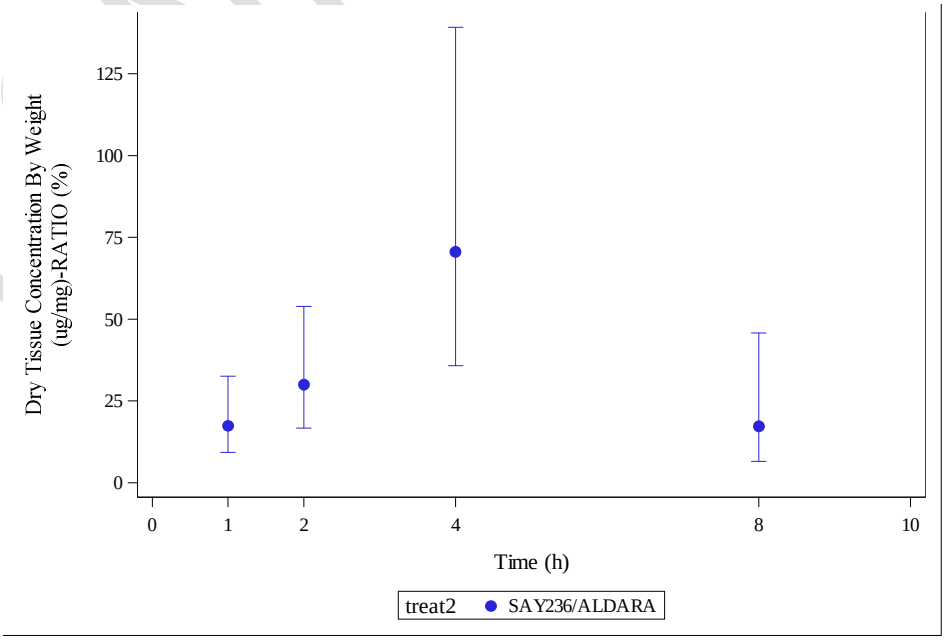
		Tissue Concentration By Area (ug/cm2)						
		Mean	Median	Min	Max	StdDev	StdErr	N
Treat	**Time (h)**							
Aldara	**1**	2.451	2.154	0.579	4.732	1.429	0.505	8
	2	2.704	1.904	1.438	5.539	1.562	0.552	8
	4	2.796	2.423	0.663	7.300	2.133	0.754	8
	8	8.696	8.257	1.634	19.811	6.769	2.393	8
SAY235	**1**	0.368	0.374	0.159	0.552	0.129	0.046	8
	2	0.704	0.712	0.179	1.490	0.388	0.137	8
	4	1.476	1.539	0.494	2.261	0.669	0.236	8
	8	1.427	1.302	0.277	2.398	0.828	0.293	8

Figure 4: IMQ Tissue Concentration By Area (ug/cm^2) : LSMeans +/-95% CI At Each Time



A subsequent analysis of the ratio of means for the Dry tissue weights (SAY_V2 film / Aldara 5% cream product) (Figure 5) demonstrates that the film IMQ tissue concentrations achieved are always 20-25% those of the Aldara 5% cream at 1h 2h and 8h. However, this does not allow for the fact that ~50% less IMQ was applied at outset with the film which would then suggest a ratio of around ~50% IMQ to be more reasonable

Figure 5: IMQ Dry Tissue Concentration Weight As Ratio SAY235/Aldara (%): LS Means +/-95% Confidence Intervals



NB: 4h includes 2 Aldara cells with low concentrations which explain extent of upper confidence interval (Cells 43, 44 <0.01ug/mg)

Conclusion

Actual IMQ recoveries from mucosal tissue are, as expected, low (<1.5%) when compared to the total amount applied with the SAY_V2 film. This is often seen with topical products, particularly hydrophobic ones, and certainly these are not dissimilar from the results with the standard Aldara 5% cream, except for the 8h application time. Negligible amounts were recovered from receptor fluid.

Tissue concentrations of IMQ both by tissue area and weight for both the SAY_V2 film and Aldara 5% cream at the relevant 1h and 2h application times appear reasonably comparable. This is confirmed when comparing ratios of the two products and accounting for the fact that approximately twice the amount was applied with the Aldara 5% cream than the film.

Overall, the results suggest accurate tissue targeting and very little going through the tissue with the 1.05% IMQ loaded SAY_V2 film (IMQ=0.1557mg/cm^2, total=0.31mg) thus supporting minimal systematic safety concerns. Particularly noticeable is that 5% Aldara has already been used in clinical trials with no significant reports (Investigator Brochure (Section 5.2)).

In addition, although the film intended dose is 60 times less in absolute terms, approximately the same concentration per unit area (~0.1mg/cm^2) is noted as the approved dose of Zyclara in AK, where two sachets of 3.75% (total 2*9.375mg=18.75mg IMQ) are applied to an area 200cm^2 on a daily basis.

1.5 Clinical Trial Experience

There is a wealth of clinical information available for IMQ relating to topical treatment of Actinic Keratosis (AK), superficial Basal Cell Carcinoma (sBCC) and external genital warts (EGW), the primary licensed indications. There are three trials specifically related to the oral mucosa and OL, including a total of 64 patients treated with the Aldara 5% topical cream. A summary of previous clinical trials conducted is compiled in the Investigator Brochure (Section 5.2). Overall, there was considerable efficacy (Improvement in >60% subjects) and minimal safety concerns (local mucosal irritation and minor systemic events as fever, chills and fatigue).

These findings were confirmed in a complete review (including pilot trials and individual cases) of the disease area where reduction or elimination of lesions with products such as: Vitamin A, Lycopene, Celecoxib, ZengShengPing (ZSP) and Bleomycin typically showed complete resolution in >50% subjects and <20% in controls (Palma 2023).

This previous clinical investigative work with IMQ (see Investigator Brochure) generally involved small, uncontrolled, or retrospectively designed investigations with subject group sizes typically less than 30 with limited power and the potential for observer bias. However, combining these clinical data gives a general clinical impression supporting the potential for both good efficacy and safety even when the topical cream is administered. The clinical endpoints of primary interest reported involved: Lesion size (complete/partial resolution), Histological grading and Molecular markers (Loss of heterozygosity LOH, DNA aneuploidy (abnormal number of chromosomes)). All are generally relevant to assessing the risk of malignant transformation although the utility of some molecular markers may be debated.

Follow up on oral cancer development and progression with long term safety will be of particular interest in later phase II and III trials.

1.6 Risk/Benefit Assessment

General
In general, the risks involved to participants taking part in this study are considered minimal.

They specifically relate to the active drug itself, the form of the product, the indication for use, the exposure of the participant and the type of participant recruited.

Firstly, IMQ itself has been used for many years with no evidence of any long-term toxicity. This is specifically supported by three clinical studies orally treating patients with OL with a cream form of IMQ (Aldara 5%) which was also well-tolerated. Minor risks arise with local events of non-severe irritation (mucositis) and systemically from fever and chills. All of which were generally reversible upon stopping treatment for short periods.

Risks of adverse events occurring with the IMQ film product (SAY_V2) are further reduced as the film used is loaded with 50% less drug compared to the cream and our nonclinical experimental evidence with porcine buccal mucosa suggests there will be no drug permeation through tissue into systemic circulation (Section 1.4).

Risks to the participants of the study are also minimised with specific training and monitoring of subjects to ensure proper use of the product associated rigorous daily monitoring for issues with safety during the initial stages of treatment.

At this stage participants are carefully selected for inclusion and a minimally short treatment period of 2-weeks is also selected to confidently and carefully assess safety given steady state kinetic of the drug.

Not only are all participants closely monitored individually for safety issues but all the safety data will be reviewed on a monthly basis as these data accrue and also when 10 participants have completed the three-week investigation. Full details of the safety profile are given in the Investigator Brochure.

Individual Participants
From a participant perspective every care is taken to ensure safety of the individual in the study when exposed to IMQ and they are encouraged to stop at any time, if they so wish, without prejudice or change in their routine standard of medical care.

Participants with OL will be carefully selected (see inclusion/exclusion) to ensure they are not exposed to any other safety issues, through other illnesses or prescribed medications, which may put the individual at any risk. Those recruited will otherwise be in good health and able to perform the tasks involved without any doubt or concern for their health.

Advice on applying the oromucosal film is given with demonstration at the outset, to ensure the utmost care. Instructions include: using the tip of the finger to apply the film, thoroughly washing hands after handling and avoiding swallowing or repositioning the film when in the mouth. Avoiding contact with the eyes, gingiva, and non-target mucosa is also carefully instructed.

Daily contact is mandated during the home treatment period and if any individuals report any untoward event (such as irritation) to the Investigator/nurse staff they may stop treatment for a period of time to allow the event to settle. They may also, if instructed, apply the rescue lidocaine gel medication provided at the outset. They may alternatively return to the clinic for assessment or to immediately withdraw from the study if preferred.

Benefit
Although the participants are unlikely to benefit from improvement in their condition during this investigation their involvement will help with the decision to progress development of the product into an area where currently there are no treatment alternatives. Currently the only strategy involves a very stressful ‘watch and wait’ period prior to the need for surgical removal should lesion severity worsen and malignancy develop. Certainly, contributing participants may be eligible for inclusion in future efficacy driven clinical trials which could be of direct benefit.

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2. Study Objectives

Primary Objectives

In order to assess the initial potential for an IMQ oromucosal film (SAY_V2) the primary objectives are:

- To investigate the safety profile of the IMQ oromucosal film
- To investigate acceptability of the IMQ oromucosal film following daily use by participants.

Secondary interests will investigate the extent of local tissue and systemic absorption with IMQ pharmacokinetics (PK)

Additionally, with pharmacodynamic (PD) evaluation of biopsy tissue will be also be performed using potential immunohistopathology markers to investigate IMQ activity.

Efficacy and Quality of Life will also be assessed but these measures are only to aid with future trial development

Ultimately the aim is to collect sufficient information and confidence in the drug product to be able to progress to a Phase II clinical evaluation of efficacy in OL.

3. Clinical Trial Design

3.1 Overall study design

This is intended as an open label investigation of both IMQ loaded oromucosal film and vehicle (placebo) in a within-participant design utilising a single group of participants recruited from a single-site. The clinical trial will be conducted in compliance with the Medicines for Human Use (Clinical Trials) (Amendment) Regulations 2025, the Declaration of Helsinki (Revised version of 2013), ICH-Good Clinical Practice Guidelines (ICH E6R3), and has been designed in accordance with ICH E8 (R1): General Considerations for Clinical Trials in participants diagnosed and classified with oral leukoplakia (OL) according to defined best practices (van der Waal 2019, Maloney 'OL update for dental practitioners' 2024,).

This study will contribute to a Participation and Public Involvement (PPI) assessment of acceptability in accordance with ICH E8 (R1) and will be reported separately.

Participation and Public Involvement (PPI) in Trial Design

Relevant health experts, service providers and potential participants attending the oral medicine clinic and a dental practice will be questioned in advance of the start of the trial to provide feedback on the requirements of the study described in the Participant Information Sheet and the Informed Consent Form. Following its completion, the recruited participants will be questioned regarding the conduct of the study and contribute to improvements in the clinical development programme and future trial designs with the oromucosal film. Separate PPI reports will be generated summarising findings for hospital trial management group and this will involve a participant as representative of the trial.

Study Visits

Participants will be enrolled from a specialist clinic in Oral Medicine at the School of Dentistry, Liverpool and then managed in the study at the nearby Clinical Research Facility. Enrolment will continue until the required number of participants is achieved. It is anticipated the screening period will commence in Q1 2027 and the study completed (last participant followed up) by Q3

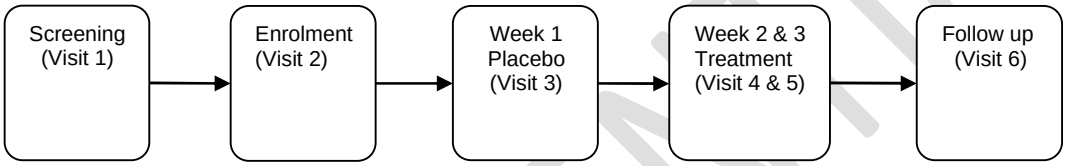
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2027. Participants will be reimbursed for reasonable 'out of pocket costs' (food and travel). Participants will be provided with a Participation Information Sheet in relation to the study, and allowed at least one week to assess the information before consenting to enrolment and any study related procedures.

The study will evaluate the safety and acceptability of an IMQ oromucosal film (SAY_V2) administered once daily for 14 days, preceded by 7-days with comparable daily administration of a matched vehicle (placebo) film. Each film will be applied to the selected lesion for 1h, thereafter removed and the mouth rinsed

There will be 6 scheduled visits in total, involving Screening and Enrolment followed by 3 'weekly' in Clinic assessments, one to assess the Placebo treatment week (Visit 3) and two to assess Active treatment weeks (Visit 4 and Visit 5) with a final Follow up visit one month after completion (Figure 6).

Figure 6: Study Assessment Visits



NB: Details of all assessments performed at each visit are given in Table 4.

A total of 25 participants will be enrolled (allowing for <20% dropout)) at a baseline visit on successful completion of screening.

Potential participants will be sourced from the clinic's data base of patients with a confirmed diagnosis of OL, who are considered clinically suitable for treatment with the IMQ oromucosal film and satisfy defined inclusion/exclusion criteria. Eligibility will be confirmed at the formal screening visit. Where further medical intervention (e.g. surgical resection) is planned or likely during the period of treatment and follow up (total 2 months in total) then this should be taken into account to be in keeping with the scheduled events of the protocol to allow collection of mucosal tissue at the end of treatment.

During the Screening (Visit 1) eligible patients will be provided with a patient information leaflet and the consent form to review. One week following this the Enrolment/Baseline (Visit 2) will involve confirmation of suitability, baseline assessment and treatment dispensing. Here the attending Investigator/nurse will also provide instructions and demonstrate how to apply the oromucosal film. These two visits will be at least 7 days apart. This clinic is then followed by three treatment visits: during the 7-day placebo oromucosal film week and 14-day IMQ oromucosal film treatment weeks (Visits 3-5 on Days 8, 15, 22). Finally, a further month after completion of treatment a follow up assessment is performed (Follow-Up Visit 6).

Eligible participant will have a lesion that is accessible, measurable (at least 100 mm^2), amenable to clinical photography and located in the oral cavity. Tissue biopsy records (obtained within last 6 months) will confirm a histological diagnosis of at least mild dysplasia. Histology samples will be assessed by microscopic evaluation of haematoxylin and eosin (H&E) stained tissue sections to identify architectural and cytological abnormalities, by a consultant oral pathologist as per standard NHS care.

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Blood sampling for pharmacokinetic purposes will be performed at the clinical visits on Day 1, 8, 15 and 22 by trained investigators and nursing staff. On all other treatment days (non-blood sampling times) participants will apply the oromucosal film themselves at home. Dosing compliance on these days will be recorded via a provided study diary.

Participant Eligibility:

Participants with OL that show mild, moderate or severe dysplasia (according to the WHO definition Section 1.1.1) and that are considered medically suitable for treatment by the Investigator, may be enrolled into the clinical trial.

Single or multiple oral lesions may be present but for the purposes of this investigation the most appropriate lesion will be chosen by the investigator.

The inclusion/exclusion criteria have been designed such that eligible participants are very unlikely to develop oral cancer during the treatment window; the mean time to transformation to cancer following a diagnosis of OED is over 4 years. The need for other therapeutic procedures in particular surgical excision, cryosurgery or CO2-laser ablation during the 7-week investigational period are exclusion criteria unless these can be accommodated at the end of treatment.

Participants with other comorbid conditions or major illness (as per exclusion criteria), pregnant and lactating females will be excluded.

Before enrolment all participants will receive counselling regarding future health (including advice on tobacco and alcohol consumption cessation)

Screening/Enrolment/Baseline Assessment:

At the screening visit, inclusion and exclusion criteria will be checked (including a serum pregnancy test (hCG)), and documented biopsy results will be reviewed and must be dated within the previous 6 months. Eligible participants will provide written informed consent at Visit 2 (Enrolment/Baseline), demographic/medical history and basic clinical data will be recorded

Lesion biopsy details recorded within the prior 6 months are used to confirm an OL diagnosis and additional ‘in clinic’ assessment of lesion at Visit 1 can be used to identify any apparent clinical changes in severity and/or grade of dysplasia. If the lesion appears to have changed clinically since the biopsy was taken, standard clinical care will dictate onward management, with further biopsy arranged as determined by the clinical team.

Photographic images of the mouth and intended lesion for treatment will also be taken prior to treatment.

Histopathological examination of the biopsy on record will be used to confirm presence of dysplasia and classify noteworthy changes (Epithelial keratinisation, Epithelial increased thickness, Acanthosis, Thin basement membrane, Inflammation connective tissue, Change in the cellular layer, Increased nuclear-cytoplasmic ratio, Hyperchromatic nuclei, Nuclear hyperplasia, Abnormal mitotic figures, Increased mitosis, Pleomorphic nuclei, Basilar hyperplasia, Drop-shaped rete pegs, Loss of polarity)

A blood sample will be obtained for Safety laboratory tests (Haematology (RBC FBC LFT Clotting), Clinical chemistry and Urinalysis see Section 8.3.3).

Key participant demographic and clinical characteristics include: Age, Sex, Number of lesions (n), Lesion type (local or multi-focal/proliferative), Lesion site (gingiva, tongue, vestibular mucosa, hard & soft palatal mucosa), Severity of dysplasia (Mild, Moderate, Severe), Smoking (current/former, mean pack-year history), Personal history of cancer/oral cancer, Family history,

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and other related OL treatments and surgical details (previous excision) will be recorded into the eCDF.

The Risk of malignant transformation will be classified as Low (with observation only required) or High (with surgery/predicted future date anticipated). High risk is defined as Severe dysplasia OR Mild/moderate dysplasia with additional characteristics (ie: Non-smoker/Lesion >200mm^2/Situated on lateral tongue/Mucosal speckling or heterogenous appearance/Previous excised OSCC lesion in last 5 years).

Physical examination will be performed in accordance with the Principal Investigator's normal clinical practice to assess: ear, nose, throat, eyes, respiratory system, abdomen, musculoskeletal system, lymph nodes, skin, cardiovascular system on an individual basis, for baseline assessment. Any abnormalities identified during physical examination will be recorded in the eCRF.

Prior and concomitant medication will also be recorded at Screening.

A baseline CGI rating will be performed by the Investigator for comparison following completion of treatment (Clinical Global Impression – Severity scale (CGI-S)). Similarly, a baseline OHIP-14 (Oral Health Impact Profile scale) will be performed by the participant.

Enrolment takes place at Visit 2 (see Section 3.2.1 for details).

Three Weekly Clinic Visits (Visit 3, 4, 5 – (Day 8, 15, 22))
Participants who satisfied the eligibility criteria at Screening (Visit 1) and Enrolment (Visit 2 – Baseline (Day 1)) will be instructed to apply the placebo oromucosal film daily for 7 days and then from Day 8 to apply the active IMQ oromucosal film (SAY_V2) daily for 14-days. Both treatments will be applied daily for an hour, followed by rinsing the mouth twice with water

On Day 1, 8, 15 and 22 the participant will attend the clinic for assessment. During these visits, blood samples (5mL) will be collected for pharmacokinetic evaluation. Plasma and saliva samples will be collected pre and post dose:

Plasma

- Pre-dose (0h)
- Post dose (1-4h) after clinical assessments

Saliva

- Pre-dose (0h)
- Immediately prior to oromucosal film removal and rinsing (1h) – Post dose

In between the visits to the clinic, application of the treatment will be performed at home by the participant. It is only on Day 8, 15 and 22 when participants will be asked to return to the clinic for assessment and blood sampling that they will be instructed not to apply the oromucosal film before attending.

At each visit adverse events and concomitant medications will be monitored. Participants will also be asked to record any adverse events and concomitant medications within a participant study diary at any time between visits.

During the first week of each treatment, participants will receive a daily phone call from the site to assess participant conduct and progress. They will also receive reminder texts, emails or

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phone calls (as appropriate and agreed with the participant) shortly before scheduled visits. A safety card is provided to all participants in case of emergency.

Final Clinic Visit (Completion of Treatment (Visit 5 - Day 22):

At the last treatment visit final details of treatment compliance, safety, acceptability and efficacy will be assessed. Although clinical efficacy is not a primary endpoint, assessments performed will enable future trial planning and provide valuable placebo control data.

As well as overall treatment outcomes (including efficacy and safety measures below) a 6mm punch biopsy from the most appropriate area of the lesion (determined by the Investigator) will be taken for analysis together with a repeat set of photographic images of the mouth and treated lesion. The biopsy can be delayed up to 4 weeks post-treatment to allow mucosa healing, if required.

The biopsy sample will be divided into 2x3mm sections for: diagnostic histopathology and bioanalytical analysis (drug content). Part of the histopathology fixed sample will be used for pharmacodynamic (PD) evaluation of useful stains of immunohistopathology protein markers: CD3, CD4, CD8, CD68, Cd1a, CD66b, CD56, Ki67.

Safety Measures

Safety assessments performed at all visits will include adverse events and assessment of vital signs (systolic, diastolic and heart rate). In addition, any concomitant medications used prescribed during treatment will also be recorded.

Other safety assessments at treatment completion include routine: safety laboratory blood tests (Haematology (RBC FBC LFT Clotting), Clinical chemistry and Urinalysis see Section 8.3.3) and a suitable physical examination, as performed at Screening. Further safety details are given in Section 8.5. Results will be reviewed once available, within 24 hours and actioned according to clinical need.

Efficacy Measures

Pre and Post treatment clinical/laboratory assessments will be compared and changes from baseline calculated to assess the potential for IMQ efficacy Although in no particular order these include:

Change in Lesion size, calculated based on an estimated elliptical area given by the longest length of the lesion (diameter/2=a) and the associated perpendicular width (diameter/2=b). The area of the ellipse is then A = πab. *For correlation, images of lesions may subsequently be used to determine lesion size using Image-J software*.

Change in Histology response following sample review and dysplasia grading

Other endpoints investigated include: Complete Resolution (100% reduction in size of the treated lesion), Partial Resolution (>=50% reduction in size of treated lesion), Change in Dysplasia grade (classified at each assessment as Mild, Moderate or Severe) and any Incidence of Oral cancer development following treatment

A final subjective assessment of the treatment benefit will be performed by the Investigator and this compared to the baseline score (Clinical Global Impression – Improvement scale (CGI-I)) and this will be supported with a repeat of the OHIP-14 (Oral Health Impact Profile scale) performed by the participant.

Full details of all efficacy and QoL measures are given in Section 8.1.1

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Acceptability Measures
Participants acceptability of the IMQ oromucosal film will be assessed using a structured questionnaire at Visit 5 - Day 22 or earlier in the event of withdrawal (See Section 8.2). This will provide relevant PPI information

Withdrawal/Clinical Progression
In the event of the need for early termination of treatment, a complete set of efficacy, safety and acceptability assessments will be performed at a Withdrawal visit.

This includes: any major safety issues, clear lack of efficacy (although less relevant in this investigation) and administrative issues such as non-compliance, loss to follow up and/or withdrawal of consent.

On withdrawal the participant will revert to the investigator's routine standard of care.

Follow Up Period
Participants who complete the 3-week treatment period will then be asked to return to the clinic one month after stopping treatment for an observational assessment.

A tissue sample may be obtained at this visit but only if the biopsy was not performed at Visit 5 Day 22 due to severe irritation making biopsy too inconvenient and limited diagnostic value. This delayed tissue sampling will be used to replace diagnostic and pharmacodynamic assessment at Day 22. No bioanalytical analysis of the sample for drug content is required.

End Of Study
The End of Study is defined as the point of final data capture, Last Patient, Last Visit (LPLV). This will be when the 25th participant completes the one month follow up visit (Visit 6). Subsequent to this, and resolution of any outstanding data queries, the database will be locked and released for statistical analysis and reporting.

3.2 Study Design

3.2.1 Randomisation and Drug Management

As an open label study, in which all participants are treated initially with placebo control for 7 days and then with active treatment for 14 days, randomisation is not applicable. However, an interactive randomisation system (IRS) will be used for drug dispensing and management.

Once eligibility is confirmed at Visit 2 (Baseline), all drug dispensing details will be logged, using the Kapture IRS system, by reference to participant 'allocation' number (in alphanumeric sequence) and assigned study medication pack numbers.

Participant allocation numbering is described in section 5.1. No link between identifiable participant information and the participant number will available outside of the clinical site.

The study site will receive a specific number of study medication packs (1 pack per participant). Each pack contains the allocated study medication identified by pack number. Each pack will contain two wallets: one with 10 sachets of the placebo oromucosal film (sufficient for 7 days treatment with 3 extras) and one with 20 sachets of the IMQ oromucosal film (sufficient for 14 days treatment with 6 extras)

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3.2.2 Treatment Groups and Treatment Regimen

The investigation involves two treatment groups (1 Active treatment, 1 Placebo control) using 'within-subject' control. Both treatments are identical 1x2cm^2 oromucosal films. The active treatment group film (SAY_V2) contains 1.05% IMQ, 0.315mg. Each film is to be applied to the affected oral area (as directed), on a once daily basis for up to 1 hour before removal. A new film is applied each day for 7 days a week and for a total of 3 weeks.

At Enrolment (Visit 2 – Day 1) the participant will be provided with a sufficient number of placebo sachets from the medication pack for the first week of treatment, along with instructions for use. Further sachets will then be prescribed at Day 8 and Day 15 for continued treatment this time with active therapy.

At Enrolment a tube of lidocaine gel/cream (Anbesol) is also provided in case of irritation and if analgesic/anti-inflammatory relief is needed (see section 6.3 for instructions on use)

Instructions and help with application of the first oromucosal film will be provided on Day 1 (Visit 2-Enrolment) and on this day, participants will provide: a Pre-dose (0h) blood and saliva sample together with a saliva sample at 1h Prior to removal of the oromucosal film and Post dose (1-4h) blood sample after completion of clinical assessments for baseline pharmacokinetics.

Subsequent application of the treatment will be performed at home although on Day 8, 15 and 22, participants will be asked to return to the clinic for assessment and blood sampling (They will be instructed not to apply the oromucosal film before attending clinic on these days).

In the event of any intolerant local reactions, such as irritation (mucositis), and following consultation with the Investigator, then treatment can be temporarily halted for up to 3 days to allow the event to settle. Requirement for cessation beyond three days would necessitate participant withdrawal from the trial.

Overdose:
Accidental overdosage is extremely unlikely with the oromucosal film. However, purposeful repeated mucosal application or chewing and swallowing of the IMQ oromucosal film could result in an increased incidence of severe local mucositis and may increase the risk for systemic reactions. Topical application of the Aldara 5% cream (multiple oral IMQ doses of >200 mg (>16 packets)) resulted in hypotension, which resolved following oral or intravenous fluid administration.

In the event of serious untoward event (eg: overdose, serious adverse event, or suspected disease progression) then treatment will be terminated and the participant withdrawn.

3.2.3 Duration of Treatment

Treatment Phase:
In total a 3-week treatment period (1-week placebo oromucosal film followed by 2-week IMQ oromucosal film) has been chosen, to allow sufficient time to assess safety and acceptability of the oromucosal film (SAY_V2) together with the likelihood of observing any changes in systemic pharmacokinetics of IMQ and/or pharmacodynamics (e.g. upregulation of immunological markers).

The treatment period will also help to assess potential efficacy outcomes and particularly placebo control effects to support future Phase II trial investigations.

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Follow-up phase:
A post treatment follow-up phase of one month is considered sufficient to investigate potential safety issues following the termination of treatment.

4. Population

The study population will consist of participants with diagnosed OL (within the last 6 months) who satisfy the minimum requirements of the inclusion/exclusion criteria. Up to 25 participants will be enrolled.

The Informed consent must be signed by the participant prior to the initiation of any study specific procedure. All participants must have a good level of understanding of spoken and written English language.

All inclusion criteria and none of the exclusions (specific conditions, medications or general criteria) listed below will be satisfied before subject enrolment.

4.1 Inclusion Criteria

To be eligible, the following conditions must be met:

1. Men or women with a diagnosis of mild, moderate or severe oral epithelial dysplasia.
2. Eighteen (18) years of age or more.
3. Active oral lesion present and not treated for at least one month (but less than 6 months).
4. Clinical evidence of one or more OL lesions affecting the oral at least 100mm^2.
5. Involvement in study fits with planned clinical management strategy (Low/Medium risk: 'Watch and Wait only'-no action planned, High risk: 'Elective surgery' date schedule fits with trial requirements)
6. General health status acceptable for participation up to 2-month (3-week treatment plus 1-month follow up) in clinical trial.
7. Able to easily apply oromucosal films themselves
8. Signed informed consent by subject prior to the initiation of any study specific procedure.
9. Good level of understanding of spoken and written English language.
10. Women of childbearing potential must have a negative serum (blood) pregnancy test (minimum sensitivity 25 IU/L or equivalent units of human chorionic gonadotropin [hCG]) at screening and must be practicing adequate, medically acceptable method of birth control**.
11. Women of nonchildbearing potential must be in a menopausal state for at least a year or had a hysterectomy, a bilateral oophorectomy or be clinically diagnosed infertile. The following age-specific requirements apply:

Women <50 years of age would be considered post-menopausal if they have been amenorrhoeic for 12 months or more following cessation of exogenous hormonal treatments and if they have luteinizing hormone and follicle-stimulating hormone levels in the post-menopausal range for the institution or underwent surgical sterilization (bilateral oophorectomy, bilateral salpingectomy, or hysterectomy).

Women ≥50 years of age would be considered post-menopausal if they have been amenorrhoeic for 12 months or more following cessation of all exogenous hormonal treatments, had radiation-induced menopause with last menses >1 year ago, had chemotherapy-induced menopause with last menses >1 year ago, or underwent surgical sterilization (bilateral oophorectomy, bilateral salpingectomy, or hysterectomy).

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**Women of childbearing potential who are sexually active with a non-sterilized male partner must be willing to use a method of contraception which is acceptable to the Investigator for the period from consent through 30 days following the last administration of the study drug (NB: A vasectomized partner is acceptable).

Further information on methods of birth control are provided in Appendix 1. The use of abstinence is considered an acceptable form of contraception if this is the usual lifestyle and preferred by the subject however periodic abstinence, the rhythm method, and the withdrawal method are not recommended.
The investigator will evaluate the effectiveness of the contraceptive method in relationship to the first dose of the study drug.

4.2 Exclusion Criteria

Specific exclusion criteria are classified as:

Prohibited Associated Conditions:

1. Any participants with previous diagnosis of synchronous or metachronous OSCC
2. Any participants with hypersensitivity (allergies) to either IMQ or excipients of the oromucosal film
3. Any participants with pre-existing cardiovascular issues, reduced haematologic reserve, compromised immunity, inflammatory conditions, autoimmune or organ transplant situations which may impact IMQ use.
4. Any other chronic co-morbidity which is not controlled by appropriate medication.

Prohibited Medications:

5. Any OL treatment in the last one month.
6. Any systemic immunosuppressive agent in the last one month, including Prednisolone >10mg daily
7. Any treatments for the relief of oral irritation or pain in the last one month (eg: Anbesol (2% lidocaine))
8. Any investigational drug treatment (i.e.: clinical trial involvement) in the last one month

General Exclusions:

9. Any history of cutaneous or systemic medical illness or psychiatric disease which will put participant at risk or interfere with assessments.
10. Any known HIV or hepatitis B or C positive conditions.
11. Any vaccination with herpes zoster or any live virus in the last one month
12. Hospitalisation or change of chronic concomitant medication in the last one month. Or any planned hospitalisation during trial involvement.
13. Symptoms of severe cardiovascular disease or heart related problems.
14. Drug or alcohol abuse.
15. Women who are pregnant or nursing.
16. Any condition which in the opinion of the Investigator makes the subject unsuitable for inclusion.

4.3 Removal of Subjects from Treatment

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In accordance with the informed consent and the Declaration of Helsinki, all participants have the right to discontinue the study at any time for any reason without any penalty or loss of benefits to which the participant is otherwise entitled. If volunteered, reason(s) for a premature termination should be documented in the eCRF and a final examination performed in such cases for safety reasons.

Participants may be withdrawn from the study by the Investigator at any time if the investigator believes it is in the best interests of the subject (e.g. pregnancy). Participants will also be withdrawn if consent is revoked.

Once enrolled, every possible effort will be made to ensure that all participants remain in the study for the total 2 months duration. This will ensure that investigator bias does not influence the treatment outcome and that an Intention to treat analysis policy can be fairly applied.

Participants discontinuing the study will be fully documented. Those who prematurely discontinue before the end of the treatment will be asked to return for an Early Termination visit and complete all the assessments planned at 3-weeks (Visit 5-Day 22) together with a study completion form. Provided consent is not withdrawn, participants should also, if possible, return for reassessment at Follow Up: at week 7. If any participants prematurely discontinue during follow-up, they should, if possible, also complete the required Visit 6 assessment at week 7.

For participants who are lost to follow-up (i.e. those subjects whose status is unclear because they fail to appear for study visits without stating an intention to withdraw), the Investigator should show "due diligence" by documenting in the source documents steps taken to contact the subject, e.g. dates of telephone calls, follow-up letters, etc.

Participants who drop-out or withdraw will not be replaced.

Participants who are withdrawn due to serious adverse events will be treated according to standard clinical practice and will be followed up until the events are resolved or stabilised or until a plausible explanation for the cause of the event has been found. Further details are given in Section 8.3.4.2. All pertinent information concerning the outcome of the adverse event will be documented in the eCRF.

In emergency situations, when confirmation of the study drug is required to enable appropriate treatment, even in this open label study the Investigator can access the logged treatment allocated to individual subjects through the interactive randomisation system (Kapture-IRS).

Conditions developing during the course of the study which are listed in the exclusion criteria as well as other protocol deviations that do not necessarily lead to participant withdrawal will be appropriately logged in the eCRF as protocol deviations and these will be categorised and classified as major and minor deviations/violations prior to database lock, unblinding and analysis.

The Investigator or Sponsor may terminate the study (see Section 4.4), which may cause premature discontinuation of the study for enrolled participants. Any early termination and/or suspension of the clinical study will be immediately reported to MHRA and REC, and specific authority will be required from MHRA before the study can recommence.

4.4 Premature Termination or Suspension of the Investigation

The clinical investigation may be prematurely terminated or suspended by the Sponsor after assessing any risks arising during the course of the study.

Premature termination may be necessary for any of the following reasons:

- The incidence of adverse events which constitutes a potential health hazard.
- New scientific data on the investigational product that do not justify a continuation of the investigation.
- Serious and/or persistent non-adherence to the protocol, ICH GCP and/or applicable regulatory requirements by an Investigator/institution.

If the study is prematurely terminated or suspended for any reason, the Investigator must inform the subjects and assure appropriate follow-up for the subjects. The Sponsor should promptly inform the Investigators/institutions, and the regulatory authorities of the termination or suspension and the reason(s) for them, as specified by the applicable regulatory requirement(s). The ethics committee should also be informed promptly and provided the reason(s) for the termination or suspension by the Sponsor or by the Investigator/institution, as specified by the applicable regulatory requirement(s).

Stopping Rules

If a participant experiences any Serious Adverse Reaction (SAR) then the treatment will be stopped. If more than 3 participants (12%) experience SARs then the study will be suspended.

Rescue Treatment

If in the opinion of the investigator there is serious deterioration in the participant's condition then treatment will be immediately discontinued and the participant withdrawn from study. The investigator will then decide on the appropriate course of action whether surgical or medication based.

If the event of minor irritation events, then analgesic/anti-inflammatory relief may be provided with the lidocaine gel provided on the instruction of the investigator/nurse during telephone contact as needed.

5 Participant Identification and Randomisation

5.1 Participant Identification

Participants will be allocated a unique 6-digit subject number (subject identification number), which will include the site number (3 digits), as well as a consecutive individual number (3 digits) (e.g. 001-001, 001-002,001-003 etc). The participant number will be assigned at the study site on confirmation of eligibility at enrolment Visit 2 (i.e., after provision of written informed consent) in chronological order of enrolment and will be used throughout the study. If a subject is screened but not enrolled, then the screening number will not be reallocated. Each screened participant will therefore have a unique identifier.

5.2 Randomisation Scheme

Participant randomisation does not apply as each participant will receive active IMQ film and matching placebo control. No specific unblinding rules apply although a log of assigned mediation is maintained in the IRS.

5.3 Randomisation of Participant to Treatment

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Although randomisation does not apply in this investigation participants will be allocated a unique pack number at Enrolment (Visit 2 - Baseline).

Each pack will have a unique pouch identifying number (Pouch 1-30)

The interactive randomisation system (Kapture-IRS) will be used to assign treatment pack and to manage and control allocation details. Full details on how to use the IRS are given in Kapture-IRS manual and online in the Kapture system.

The Investigator will be provided with access to the interactive randomisation system (Kapture-IRS) for allocation of participants.

6 Study Drug

6.1 Identity

The IMQ oromucosal film (SAY_V2) and the identically matched placebo will be produced (formulated, packed and distributed) according to good manufacturing practice (GMP) by the licensed manufacturer (Labtec GmbH, Germany). A medication pack for each participant will be provided containing 30 oromucosal films (10 placebo control and 20 active IMQ oromucosal films). Individual oromucosal films will be supplied in sealed envelope packaging and appropriately labelled with instructions for use and participant identifier.

The documentation supplied with the study medication will ensure it is possible to retrace the composition and pharmaceutical quality of the product.

6.2 Packaging, Transportation, Storage, Dispensing and Labelling

Each medication pack will contain sufficient medication for the 1- week (7 days) and 2-weeks (14 days) of treatment with placebo and active IMQ oromucosal films. At each clinical visit on Day 1, 8 and 15, participants will be provided with sufficient oromucosal films for a single week of treatment.

The medication packs will be transported at below 25°C from the manufacturer/packer to the investigational site by courier. Each parcel will be temperature controlled and contain a temperature monitor which will identify any temperature excursions during transit. Details will be recorded at the site pharmacy and any problems will be reported in the interactive response system (Kapture-IRS). Where necessary packs may be rejected and replacement packs subsequently provided. Prior to dispensing, the packs will be stored in a secure area, only accessible to authorised personnel.

All drug supplies will be stored in a pharmacy at a temperature of consistent with labelled recommendations “Store below 25°C.” (but not refrigerated) in accordance with the manufacturer instructions. Participants will be instructed to also store the medication at room temperature, but away from external sources of heat, prior to use.

At each visit and especially the last treatment visit (Visit 5) participants will be asked to return the medication either used or unused in the Ziplock bag provided. All returns will be logged and unused oromucosal films stored at the pharmacy prior to return to Sponsor. Used oromucosal films will be destroyed. Drug accountability and reconciliation will be fully monitored by the Study Monitor prior to unused oromucosal films being authorised for destruction. In the event of loss, participants will contact the same dispensing staff for replacement.

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On each day of treatment (Days 1-22) a new oromucosal film will be taken from a sachet and applied to the selected lesion for treatment (as directed by the attending investigator). A fixed time of day is recommended to aid compliance. The oromucosal film is a two layered structure with an active 'sticky' side coloured red and a protective white backing. The colour coding indicates the red side should be applied to the inside of the mouth. Participants will receive training on application at visit 2, before allowing the participant to perform "at-home" dosing.

The oromucosal film should remain in place for one hour. After one hour, the participant should remove the used film and replace it in the opened envelope. The participant will then rinse the mouth with water to remove any residue. This process will be repeated each day and over the three-week study duration. In the event that the oromucosal film comes loose in the oral cavity and will not re-cover the lesion, then the participant will be instructed to remove the film, replace it into the open sachet and record the time period applied for in the participant study diary.

In the event of intolerant local reactions, such as irritation (mucositis), which are reported between visits during telephone contact with participants then an appropriate course of action will be decided by the Investigator. This may involve a temporarily halt of treatment for a few days to allow the event to settle. Alternatively, the lidocaine gel/cream (eg: Anbesol), provided at the outset to the participant, may be prescribed by the Investigator. If necessary, the Investigator may request early return of the participant to the clinic for investigation.

Prior to clinic visits on Days 8, 15, 22 (Visits 3, 4, 5) participants will be asked not to apply the oromucosal film until attendance at the clinic. *If participants do apply medication beforehand then the investigator/nurse will repeat the instructions for use to prevent further reoccurrence but the clinical assessments will be performed without blood sampling*.

Participants will return all medication at each visit to the clinic. Returned oromucosal films will be recorded in the pharmacy and IRS log plus the eCRF at each visit.

6.4 Breaking the Blind

The study will be performed in an open label manner with ordered treatment allocation therefore no unblinding mechanism is required.

6.5 Drug Accountability

A drug supply inspection for inventory assessment and to ensure proper storage, dispensing and return will be conducted as part of the monitoring visits at each site.

6.6 Prior and Concomitant Medication

Prior medication is defined as any treatment associated with the participant history over the three months prior to enrolment, obtained from medical records and questioning the participant. These are recorded on the prior medication form in the eCRF at the Screening visit. Any prior medication that is intended to be continued during the 2-month investigational period should also be recorded as a concomitant medication.

Concomitant medications are defined as any treatment, other than the investigational drug, which is taken during the 7 weeks treatment/follow up, including all prescription and over the counter medications. These are recorded in the participant studv diary and updated on the

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concomitant medication form in the eCRF at each visit assessment. Wherever possible these concomitant medication should be maintained throughout the investigational period.

Any new medication and any subsequent changes (dose or frequency) in the medications should be recorded. Where concomitant medication amendments relate to a new or worsened condition then the associated event should be also be recorded as an adverse event.

A list of the prohibited medications at screening is given in the exclusion criteria (Section 4.2). These medications particularly should also be avoided for the duration of the investigation. *However, if other medications are necessary for any arising illness, then the potential impact on OL treatment outcome will be considered at the conclusion of the study.* As already described, lidocaine gel will be allowed as a rescue medication during the trial treatment period.

When recording medications site staff should wherever possible use the generic name. However, trade names are acceptable for combinations of active ingredients.

7 Study Procedures

7.1 Study Procedures and Schedule of Events

Including the pre-study qualification visit (Screening Visit 1) a of total 6 visits are scheduled over 7 weeks. After an Enrolment visit for treatment dispensing and baseline assessments (Visit 2) there are then three 'On' treatment visits during the 1-week placebo oromucosal films stage and subsequent 2-week IMQ oromucosal film treatment stage (Visits 3-5 on Days 8, 15, 22). This is followed by a further visit at week 7, scheduled one month after discontinuation of treatment (Follow-Up Visit 6). With the follow-up visit, participant involvement in the study lasts for a total of 7 weeks. Table 4 shows the schedule of events including all the assessments which are to be performed at each visit.

Participants who prematurely discontinue before the end of the treatments will be asked to return for an Early Termination visit and complete all the assessments planned at 3-weeks Visit 5 together with a study completion form. Participants who prematurely discontinue during follow-up will complete the required Follow-Up assessments after one month (Visit 6) and the early date specified. If consent is withdrawn, participants have the right to refuse use of any future data.

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Table 4: Investigation Schedule of Events

Schedule	Screening	Enrolment / Start Placebo Phase	IMQ Oromucosal -Treatment Phase			Follow Up
	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5 Completion	Visit 6
Activities	**-2 Weeks**	**Day 1**	**Day 8**	**Day 15**	**Day 22**	**Week 7**
Visit Windows (days)	-14 to -7 days	Baseline	+/- 1 day	+/- 1 day	+/- 1 day	+/- 7 days
Screening						
Informed Consent[1]	X	X (confirmation)				
Diagnosis**	X					
Serum Pregnancy Test	X				X	X
Urine Pregnancy Test		X	X	X		
Inclusion-Exclusion criteria	X	X (confirmation)				
Demography and Medical history	X	X (confirmation)				
Lifestyle Management (Smoking/Drinking habits and changes)	X				X	
ECG	X	X (confirmation)				
Prior/Concomitant medication	X	X (confirmation)				
Efficacy/QoL						
Lesion Biopsy (Diagnosis/Efficacy)	X** (database record)				X*** (irritation dependent)	X*** (if not V5)
Photography	X	X	X	X	X	X
Lesion Size (Elliptical area)	X	X	X	X	X	X
Histological Analysis	X** (database record)				X	
Overall Outcome (CGI)		X			X	
OHIP-14		X			X	
Pharmacodynamics						
Tissue for immunohistopathology protein markers					X(End h)***	X*** (if not V5)
Pharmacokinetics						
Plasma/Saliva sample for drug assay (trough)		X (0h)	X (0h)	X (0h)	X (0h)	
Saliva sample for drug assay		X (1h)	X (1h)	X (1h)	X (1h)	
Plasma sample for drug assay		X(End h)	X(End h)	X(End h)	X(End h)	
Tissue for drug assay					X(End h)***	
Safety						
Adverse events	X	X	X	X	X	X
Physical examination[2]	X				X	X
Vital signs (systolic, diastolic, heart rate)	X	X	X	X	X	X

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Concomitant medication		X	X	X	X	X
Safety laboratory tests[3] (blood sample)	X				X	X
Acceptability						
Participant questionnaire					X	
Administration						
Randomisation (Medication allocation)		X				
Oromucosal film administration		X**** (Placebo)	X**** (SAY_V2)	X**** (SAY_V2)	X**** (SAY_V2)	
Film compliance (Daily application)			X	X	X	
Completion/Termination record					X	X

NOTES:

On Day 1 participants will start to apply the placebo film each day for a 7-day period

** Confirmed from biopsy results on record

*** Biopsy performed at Visit 5 (Day 22) or Visit 6(1m Follow up) dependent on lesion irritation**. NB: No PK/PD samples from tissue biopsy required at Visit 6.**

**** Oromucosal film administered in clinic

(0h) prior to administration of Oromucosal film

(1h) Immediately before removal of Oromucosal film.

(End h) After completion of clinical assessments and prior to the end of the visit (1-4h).

1….Informed consent will be obtained before any study examination is performed

2….Physical examination will include height and body weight at Screening

3….Laboratory tests including Haematology (RBC FBC LFT Clotting), Clinical chemistry and urinalysis

NB: In the event of withdrawal, assessments scheduled for the end of the treatment period (Visit 5) will be performed.

NB One month is considered 4 weeks

Screening Procedures (Visit 1)

Screening will be performed up to 2 weeks prior to Enrolment (and at least 7 days beforehand).

The following assessments will be performed at Screening for each participant:

- Informed consent
- OL diagnosis and baseline assessment (Lesion biopsy on record for Histology, and possibly Immunohistopathogy biomarkers)
- OL clinic assessment (Lesion size, type, severity)
- Clinical photography of index lesion
- Serum pregnancy test
- Compliance with inclusion/exclusion criteria
- Demographics
- Medical history
- Prior medications record (any prescribed in last 3 months prior to Screening)
- Adverse event record (defined pre-treatment signs and symptoms)
- Physical examination including height and weight to calculate BMI
- Vital signs, systolic/diastolic blood pressure and heart rate (taken sitting)
- 12-lead ECG (for exclusion of pre-existing conditions only)
- Safety laboratory blood sample (Haematology (RBC FBC LFT Clotting), Clinical chemistry)

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(*2.7ml EDTA vacutainers for haematology, 9ml plain vacutainers for clinical chemistry).* Participants will not be enrolled if safety laboratory results are abnormal at Screening.
- Urinalysis (dipstick)). If urinalysis is abnormal, appropriate additional tests will be performed and reported.
- Screening status record (specification of pass/failure of the screening process)

Enrolment Procedures (Visit 2, Baseline, Day 1)

The following assessments will be performed at Enrolment for each participant:

- Participant confirmation of consent, inclusion/exclusion demography, medical history, prior medication and ECG result.
- Participant allocation unique identification number
- Clinical photography of index lesion

- Treatment dispensing and instruction on use
- First oromucosal film application with assistance at this visit specific to day 1

- Clinical Global Impression – Severity scale (CGI-S) for staging assessment
- Oral Health Impact Profile (OHIP-14) – Quality of life scale for participant rating
- Adverse events (defined pre-treatment events)
- Vital signs including systolic/diastolic blood pressure and heart rate (taken sitting)
- Concomitant medication recording
- Urine pregnancy test

When satisfactorily completed these are then followed by:
- 0h Pre-dose blood sample for pharmacokinetics (in *9ml EDTA vacutainer*).
- 0h Pre-dose saliva sample for pharmacokinetics *(in Salivette chewable swab)*
- 1h Post dose (before film removal) saliva sample for pharmacokinetics *(in Salivette chewable swab)*
- End of clinic (1-4h) Post dose blood sample for pharmacokinetics (in 4*ml EDTA vacutainer*).

Clinical Assessments at Day 8, 15, 22 (Visit 3, 4, 5)

This assessment visit may be performed within one day of the schedule (+/- 1 day window) and will include:

* 0h Pre-dose blood sample for pharmacokinetics (in 4ml EDTA vacutainer)
* 0h pre-dose saliva sample for pharmacokinetics *(in Salivette chewable swab)*
* Treatment administration (return, dispensing)
* Oromucosal film application
* 1h Post dose (before oromucosal film removal) saliva sample for pharmacokinetics *(in Salivette chewable swab)*
* End of clinic (1-4h) Post treatment blood sample for pharmacokinetics (in 4*ml EDTA vacutainer*)
* Adverse events record (defined on-treatment events)
* Vital signs, systolic/diastolic blood pressure and heart rate (taken sitting)
* Concomitant medication recording
* Urine pregnancy test at Visit 3 and Visit 4 and a Serum pregnancy test at Visit 5

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Additional Clinical Assessments At Treatment Completion At Day 22 (Visit 5)

* 6mm punch biopsy of index lesion
* Biopsy sample bisected in the laboratory: 3mm for exploratory immunohistochemistry and 3mm for standard histopathological assessment (dysplasia grading)
* Efficacy measures (Lesion size recorded as mm^2)
* Clinical photography of index lesion
* Participant treatment acceptability assessment (Questionnaire)
* Clinical Global Impression – Improvement scale (CGI-I) for overall assessment
* Oral Health Impact Profile (OHIP-14) – Quality of life scale for participant rating
* Physical examination with weight to calculate BMI change
* Safety laboratory blood sample (Haematology (RBC FBC LFT Clotting), Clinical chemistry) (*2.7ml EDTA vacutainers for haematology, 9ml plain vacutainers for clinical chemistry).*
* *NB: Stored as part of blood sample for plasma (End of clinic (<4h) post dose). (4ml EDTA vacutainer)*
* Urinalysis (dipstick)). If urinalysis is abnormal, appropriate additional tests will be performed and reported.
* Treatment administration (return)
* Termination record
* Serum pregnancy test

Early Termination Visit (When required)

If subjects discontinue the study prior to completion of 22 days of treatment then participants will be invited to return for safety monitoring, at which time all the assessments scheduled at the Treatment completion visit (Visit 5) will be performed and wherever possible, the reason for discontinuation recorded.

Follow Up After Treatment Completion At +1 Month (Visit 6 Off Treatment)

This assessment visit may be performed up to one week early or one week later than scheduled (+/- 7-day window) 4 weeks after completing treatment. Assessments include:

* Adverse events record for any off-treatment events
* Physical examination with weight to calculate BMI change
* Vital signs, systolic/diastolic blood pressure and heart rate (taken sitting)
* Concomitant medication recording
* Safety laboratory blood sample (Haematology (RBC FBC LFT Clotting), Clinical chemistry) (*2.7ml EDTA vacutainers for haematology, 9ml plain vacutainers for clinical chemistry).*
* Serum pregnancy test
* Termination record

In addition, a tissue sample for diagnostic and immunohistopathology may need to be obtained at this visit in the event of the occurrence of severe irritation at the scheduled Day 22 (Visit 5) assessment which prevented biopsy. Due to the timing of this tissue sample bioanalytical assessment for drug content will not be required.

8 Safety, Acceptability and Efficacy

8.1 Appropriate Measures

Safety and Acceptability are of primary interest but efficacy measures are also assessed to provide valuable information for future planning and investigations.

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Safety of IMQ in the oromucosal film will be assessed by monitoring the frequency and/or severity of local and systemic adverse events.

Any issues arising with use of the medication will be assessed through a detailed participant questionnaire of Acceptability.

8.1.1 Safety Variables

Adverse events are assessed at all clinic visits each with reference to the period from the previous visit. Physical examination and laboratory evaluations will be assessed at Screening, at the end of the treatment period and at Follow up (Visits 1, 5, 6). Vital signs taken sitting will be recorded at all clinic visits. Clinically significant changes in any of these evaluations will be assessed and recorded by the site as an AE if appropriate. Laboratory variables will be imported from the hospital laboratory after which Investigators at site will assess the results for significant changes.

8.1.2 Physical Examination

Physical examination will be performed according to the investigator's normal clinical practice and include measurement of weight (kg), height (cm) and an automatic calculation of BMI at baseline. The physical examination will cover assessment of the ear, nose, throat, eyes, respiratory system, abdomen, musculoskeletal system, lymph nodes, skin, cardiovascular system and any other physical conditions of note. These evaluations will be carried out at Visits 1, 5 (or Early termination if appropriate) and Visit 6.

The investigator will decide on the extent of the Physical examination required (which body systems to include) and will also decide if any abnormal value or change constitute adverse events.

8.1.3 Vital Signs

Vital signs will be performed at each visit. Vital signs will consist of systolic blood pressure, diastolic blood pressure and heart rate. Vital signs should be measured before blood is drawn for laboratory tests. Measurements of systolic and diastolic blood pressure and heart rate should be made with the subject resting for at least 5 minutes in a sitting position.

Blood pressure (BP - systolic and diastolic) will be measured using a standard manual or an automatic blood pressure measuring device. However, the same method should be used in individual subjects during the entire investigation. The same arm should be used for each measurement of blood pressure. These evaluations will be carried out at all visits and results actioned according to clinical need.

Any clinically significant value or change should be considered as an adverse event.

8.1.4 Laboratory Safety Tests

All laboratory safety tests will be assayed at the hospital laboratory. The laboratory will provide instructions on blood sampling, storage and collection in the laboratory manual. Supplies of collection tubes will be provided by the laboratory prior to initiation of the study. The complete battery of safety laboratory tests will be performed Visits 1, 5, 6 or Early termination (if appropriate).
Urine samples taken will be evaluated locally using dipstick tests.

Standard 2.7ml EDTA vacutainers will be used for haematology screens and 9ml PLAIN vacutainers used for clinical chemistry screens at each of the 3 visits.

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Additional 4ml EDTA vacutainer (3ml collected) will be required for the plasma sample used for pharmacokinetic analysis at each of Day 1 (0h-Visit1/2) and Day 8, 15, 22 (0h and End of clinic (<4h)-Visit 3, 4, 5).

Blood samples will be assayed for:
Haematology: Haematocrit, Haemoglobin, Erythrocytes, MCV, MCH, Total Leucocyte Count, Neutrophils, Lymphocytes, Monocytes, Eosinophils, Basophils and Thrombocytes.

Clinical chemistry: AST, ALT, Alkaline Phosphatase, Gamma-GT, LDH, Creatine Kinase, Sodium, Potassium, Calcium, Chloride, Inorganic Phosphorous, Magnesium, Glucose, Total Cholesterol, Triglycerides, Creatinine, Total Bilirubin, Total Protein, Albumin, Uric Acid, Blood Urea Nitrogen, Serum – β hCG (pregnancy test) and Creatinine Clearance.

Dipstick urinalysis will be assessed for: pH, Leukocytes, Protein, Glucose, Ketones and Blood. (These results will be manually entered within the eCRF).

The hospital laboratory will assay the samples and send the results back to the site. The data will then be integrated into the eCRF and made available to the site for review and interpretation. If any sample profile is missing (sample not taken or not evaluable) or incomplete (specific assays not possible (e.g. Haematology)) then this is appropriately recorded in the eCRF.

Results will be reviewed within 24 hours and actioned according to clinical need. The laboratory automatically inform the requesting physician of any grossly abnormal results as soon as they are reported to allow swift action. Any notable safety laboratory values outside the reference range will be classified as either clinically significant or not by the Investigator.

Repeat samples may be requested by the Investigator and identified by date for subsequent assignment to appropriate visit. Clinically significant abnormalities will be recorded in the eCRF as adverse events and followed-up by the Investigator.

The total blood volume collected from each individual during the whole study will be: <60ml (Lab safety: (2.7+9ml)*3 + Pharmacokinetics: (3ml*8)).

8.1.5 Adverse Events

Adverse events are any untoward medical occurrence in a subject or clinical investigation subject administered with a pharmaceutical product which does not necessarily have a causal relationship with the treatment. An adverse event (AE) can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of a medicinal product, whether or not related to the medicinal product.

All adverse events should be recorded, whether considered minor or serious, treatment-related or not. Adverse events will be recorded from after confirmation of informed consent until the end of the study, either visit 6 or the early termination visit depending on whether the subject discontinues. Adverse events will be ascertained on the basis of volunteered symptoms, responses to non-leading non-specific questions and clinical observation and assessment.

All notable abnormal laboratory findings considered to be clinically significant are to be recorded as adverse events.

An adverse event can therefore be any unfavourable and unintended sign, symptom or disease including inter-current illness, deterioration of a pre-existing illness, accident, any suspected

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drug reaction or a clinically relevant change of laboratory values, etc., whether or not considered related to the study treatment.

8.1.5.1 Event Definitions and Documentation

Data relating to adverse events will be collected during each visit based on subject spontaneous description, by Investigator inquiry or discovered in the course of examinations performed. The Investigator should first ask a general question, e.g., "Have you experienced any other/new health problems since your last visit?" rather than searching for specific symptoms. If the answer is "no", no further questions are asked. If the answer is "yes", the Investigator will assess and record any event in detail on the 'adverse event' section of the eCRF. After all visit investigations (e.g. physical examination, vital signs, safety laboratory evaluation) are performed, the Investigator will document any events arising from these visits.

All of the following details should be recorded in the subject eCRF for each event:

- Description of adverse event.
- Date (and time, if available) of onset.
- Date (and time, if available) of resolution, if appropriate.
- Severity of event, to be assessed by the Investigator in accordance with definitions given.
- Seriousness
- Relationship to study treatment received to be assessed by the Investigator in accordance with definitions given. Action taken with study medication (if any).
- Other action taken
- Outcome and details of any further follow-up.

Definitions regarding severity and relationship to the study treatment received are given in Tables 5 and 6 respectively and these should be used by the Investigator to appropriately describe the event. One definition should be used for each event.

Table 5: Adverse Event Severity*

Severity	Definition
Mild	The adverse event does not interfere with the daily routines. It causes slight discomfort.
Moderate	The adverse event interferes with some aspects of the daily routines.
Severe/Medically significant	The adverse event causes inability to carry out the daily routine.
Life threatening	Consequence with urgent intervention indicated
Death	Death related to AE.

*According to CTCAE v5.0 classification

Table 6: Adverse Event Relationship

Relationship to Study Treatment	Definition

Almost Definite	• Distinct temporal relationship with drug treatment. • Known reaction to agent or chemical group, or predicted by known pharmacology. • Event cannot be explained by clinical state or other factors.
Probable	• Reasonable temporal relationship with drug treatment. • Likely to be known reaction to agent or chemical group, or predicted by known pharmacology. • Event cannot easily be explained by clinical state or other factors.
Possible	• Reasonable temporal relationship with drug treatment. • Event could be explained by clinical state or other factors.
Unlikely	• Poor temporal relationship with drug treatment and/or • Event easily explained by clinical state or other factors.
Unrelated	• Event occurred before dosing • Event or inter-current illness due wholly to factors other than drug treatment.
Not assessable	• Relationship to treatment cannot be assessed in this instance

In addition, specific classifications are also provided for: *Action taken* (IMP withdrawn, Dose reduced, Dose unchanged or Not applicable) and *Outcome of event* (Completely recovered/resolved, Recovering/resolving, Not recovered/not resolved, Recovered/resolved with sequelae or Fatal or Unknown)

8.1.5.2 Serious Adverse Events Reporting

An adverse event is classified as 'Serious' if it can be classified as: resulting in death, is life-threatening, requiring hospitalisation or prolongation of existing hospitalisation, resulting in persistent or significant disability or incapacity, a congenital anomaly or birth defect, is considered a medically significant event.

All serious events which occur during the 3-week of treatment and to 1 month follow up, whether or not related to the treatment will be entered into the eCRF and study documentation no later than 24 hours after the knowledge of the occurrence of the serious adverse event. This will trigger automatic email notifications to the appropriate persons (i.e. Medical Monitor, Project Manager, Pharmacovigilance).

The Investigator will, as soon as is possible (but every effort should be made to ensure this is within 24 hours of becoming aware of the event), complete a serious adverse event report form and send it to Pharmacovigilance following instructions in the safety management plan.
Part of the information to enter for adverse events requires some decisions on how to classify severity, causality and expectedness of the adverse event. Principal Investigators (or Investigators on the delegation log with permission to assess adverse events) must decide the most appropriate description for each adverse event and seek advice if necessary (i.e. contact the Medical Monitor).

This initial pharmacovigilance report and any subsequent follow-up reports should identify the subject by a unique code number assigned by the Pharmacovigilance team to create an SAE tracker, and not by the actual subject name, personal identification number, and/or any personal information such as home address.

8.1.5.3 Monitoring All Adverse Events

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Any adverse event which occurs in the course of the study should be monitored and followed up until:

- It has resolved.
- There is a return to normal or baseline values or reaches clinical stability.
- A plausible explanation for the cause of the event has been found
- All requested follow up items have been received or confirmed as not available.

8.1.5.4 Definition of Severe and Serious Terms

To ensure no confusion or misunderstanding of the difference between the terms “serious” and “severe,” which are not synonymous, the following note of clarification is provided:

The term “severe” is used to describe the severity of a specific event (as in mild, moderate, or severe); the event itself, however, may be of relatively minor medical significance. This is not the same as “serious,” which is based on subject/event outcome or action criteria usually associated with events that pose a threat to a subject’s life or functioning. Thus, a headache due to migraine could be severe but would not generally be considered serious, whilst a headache due to subarachnoid haemorrhage would normally meet the serious criteria. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

8.1.5.5 Definition of Expected and Unexpected Adverse Events

As for any medicinal product it is possible that the application of study treatment may lead to side effects. The sites should refer to the reference safety information in the Investigator brochure for known events reported from other AA clinical trials with IMQ.

Expected events are known side effects that have been previously reported with standard IMQ preparations when used in other topical indications. Commonly reported with IMQ in topical preparations include irritation at the application site plus minor systemic issues including fever and chills.

An unexpected adverse event is an experience not previously reported in nature, severity or incidence in the current investigator brochure.

8.1.5.6 Expedited Event Reporting to Competent Authorities

It is the responsibility of the Sponsor to report unexpected events to the relevant authorities providing approval for the study at the outset.
Adverse events which are considered Serious, Unexpected (i.e. not consistent with the applicable product information) and which have a reasonable possibility that there is a causal relationship between the event and the drug, will be classified as Suspected Unexpected Serious Adverse Reactions (SUSARs). As such these will be reported to the research ethics committee, PIs and to the regulatory authorities in accordance with applicable regulatory requirements for expedited reporting.

Pharmacovigilance will report SUSARs to these bodies on behalf of the Sponsor in a timely manner. Complete details of the SAE handling and SUSAR reporting will be documented in a specific safety management plan.

8.2 Participant Acceptability of Treatment with Oromucosal Film

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A series of 'survey like' questions regarding Acceptability of the film will be asked of each participant following up to 3-weeks of use with the oromucosal film (Visit 5 End of treatment or Early termination). Four main categories will be covered by the Investigator: Compliance with treatment requirements and ease of use, oromucosal film characteristics, Effects of the oromucosal film and the Effect on daily activities (Table 6).

Each response will be assigned a score and across each of the categories a higher score is better (except for daily activities where a low score is best). Although overall summaries (n/% responses) of each question and category are of primary interest, total ranked scores for each category may be of interest. Results will be pooled by treatment group and overall. No formal statistical will be applied.

Table 7: Participant Acceptability Questionnaire

Category	Question	Response	Score Range
Compliance with treatment requirements and ease of use (High score good)			
Compliance	How easy was it to follow the treatment instructions and use the film?	Poor-Fair-Good	-1, 0, 1
Residence time	How easy was it to keep the film in place for the required time?	Poor-Fair-Good	-1, 0, 1
In Situ 1	What did the film feel like when in place?	Poor-Fair-Good	-1, 0, 1
In Situ 2	Did you swallow or chew the film?	Yes-No	-1, 1
Removal	Was it easy to remove the film?	Yes-No	1, -1
Taste	Was there a residue 'taste' after removing the film?	Yes-No	-1, 1
Film characteristics (High score good)			
Size	Rate the size of the films	Too small-Appropriate-Too large	-1, 2, -1
Appearance	Rate the appearance of the films (in the mouth)	Poor-Fair-Good	-1, 0, 1
Adhesion	How good was the adhesion to the lining of the mouth?	Poor-Fair-Good	-1, 0, 1
Effects of the film (High score good)			
Lesion	What was the effect of the film on the lesion?	Poor-Fair-Good	-1, 0, 1
Irritation 1	Did the film cause any irritation?	Yes-No	-1, 1
Irritation 2	Rate any irritation to the lining of the mouth	None-Mild-Moderate-Severe	0, -1, -2,-3
Taste 1	Did the film have a taste?	None-Weak-Moderate-Strong	0, -1, -2,-3
Taste 2	What was the taste like?	Unpleasant-Neutral-Pleasant	-1, 0, 1
Daily Activities (Low score good)			
Speech	Did the film interfere with speech?	None, A little, A lot	0, -1, -2
Swallowing	Did the film interfere with swallowing?	None, A little, A lot	0, -1, -2
Saliva	Did wearing the film alter saliva production?	None, A little, A lot	0, -1, -2
Soreness	Did the film cause soreness when you brushed teeth, ate food, drank liquids, smiled, breathed through mouth, talked or touched the area?	None, A little, A lot	0, -1, -2
Bother	How bothersome were the films?	None, A little, A lot	0, -1, -2

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8.3. Efficacy

Given the stage of development all the responses to treatment measured can be considered surrogate endpoints. At this stage no particular order of importance is assigned to the efficacy measures used.

For all clinical/laboratory assessments, Pre and Post treatment will be compared and changes from baseline calculated where possible. The higher the score with each scale used, the worse the condition. If the change in the score increases over time, then the condition is worsening and malignant transformation is more likely to occur. Therefore, if the change in the score decreases over time this then indicates improvement or stabilising of the condition possibly related to medical treatment or lifestyle changes made during the intervening period.

Lesion Size

Lesion size will be measured at the time of assessment and calculated based on an estimated elliptical area given by the longest length of the lesion (diameter/2=a) and the associated perpendicular width (diameter/2=b). The area of the ellipse is then $A = \pi ab$.

Supporting photographs of the mouth and a close-up lesion selected for treatment will be taken at each visit (Visit 1, 2, 3, 4, 5, 6 (Visit 2 suitable for baseline)) in order to build a complete record of any changes in the oral cavity over the treatment period (see Section 8.2).

The Change in lesion size from baseline following treatment is calculated as a percentage (((Post treatment - Pretreatment)/Pretreatment)*100) is calculated and then graded using 7-point scale as: -3: ≥ 75% decrease -2: 50–74 % decrease -1: 25–49% decrease 0: 0–24% decrease or increase 1: 25–49% increase 2: 50–74% increase 3: ≥ 75% increase. Higher score indicates worsening/deterioration over time. Lower scores indicate improvement

Histology Response

Pre and Post treatment histology samples are reviewed and the dysplasia observed graded using 9-point scale as: 0: Normal with or without hyperkeratosis 1: Atypia with crisply defined clinical margins 2: Mild dysplasia 3: Mild-moderate dysplasia 4: Moderate dysplasia 5: Moderate-severe dysplasia 6: Severe dysplasia 7: Carcinoma in situ 8: Invasive squamous cell carcinoma

The Change in histology score from baseline following treatment (Post treatment – Pre-treatment) is calculated by subtraction. Higher scores are worse and Higher score over time indicate worsening/deterioration. Lower scores are better and decrease in changes indicate improvement

Analysis involves microscopic evaluation of hematoxylin and eosin (H&E) stained tissue sections to identify architectural and cytological abnormalities of histology, performed by a qualified histologist.

Clinical Changes of Interest

include:

- Complete Resolution (100% reduction in size of the treated lesion)
- Partial Resolution (>=50% reduction in size of treated lesion)

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- Change in Dysplasia severity (classified at each assessment as Mild, Moderate or Severe)
- Incidence of oral cancer development following treatment

Clinical Global Impression (CGI):

In addition to the objective efficacy measures a subjective assessment of overall treatment effect will be provided by the Site Investigator using the Clinical Global Impression. This is recorded as severity at baseline and then improvement on treatment completion.

* Clinical Global Impression – Severity scale (CGI-S)
  Investigator rates each participant relative to their past experience with other participants with the same diagnosis (Visit 2 Enrolment (Baselne)) with severity of illness ranging from 1 (normal) to 7 (most severely ill participants).

* Clinical Global Impression – Improvement scale (CGI-I)
  Investigator rates improvement using a 7-point scale with CGI-I ranges from 1 (very much improved) to 7 (very much worse) at completion (Visit 5 Day 21).

The CGI-S and CGI-I questionnaires along with specific training and standard guidelines will be included in the eCRF.

Oral Health Impact Profile Scale (OHIP-14):

An exploratory assessment of the 'day to day' impact of the condition on the participant will be performed using the OHIP-14 (Husein 2017) at baseline and completion of treatment Day 22 (Visit 5). The OHIP-14 consists of 14 items that describe health aspects related to quality of life in a context of oral health each question response is a 5 point categorised classification (0=Never, 1=Seldom, 2=Sometimes, 3=Often, 4=Always). The participant rates each question in turn. Higher scores are worse and the total score is calculated with the change from baseline. Reduction in scores from baseline indicate improvement. Specific training and standard guidelines will be included in the eCRF.

Table 8: Oral Health Impact Profile Scale (OHIP-14)

Item	Question	Responses	Score Range (Low score good)
1	Have you had trouble pronouncing any words because of problems with your teeth, mouth or dentures?	Never-Seldom-Sometimes-Often-Always	0-4
2	Have you felt that your sense of taste has worsened because of problems with your teeth, mouth or dentures?	Never-Seldom-Sometimes-Often-Always	0-4
3	Have you had painful aching in your mouth?	Never-Seldom-Sometimes-Often-Always	0-4
4	Have you found it uncomfortable to eat any foods because of problems with your teeth, mouth or dentures?	Never-Seldom-Sometimes-Often-Always	0-4
5	Have you been self-conscious because of problems with your teeth, mouth or dentures?	Never-Seldom-Sometimes-Often-Always	0-4
6	Have you felt tense because of problems with your teeth, mouth or dentures?	Never-Seldom-Sometimes-Often-Always	0-4

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Item	Question	Responses	Score Range (Low score good)
7	Have your diet been unsatisfactory because of problems with your teeth, mouth or dentures?	Never-Seldom-Sometimes-Often-Always	0-4
8	Have you had to interrupt meals because of problems with your teeth, mouth or dentures?	Never-Seldom-Sometimes-Often-Always	0-4
9	Have you found it difficult to relax because of problems with your teeth, mouth or dentures?	Never-Seldom-Sometimes-Often-Always	0-4
10	Have you found it difficult to relax because of problems with your teeth, mouth or dentures?	Never-Seldom-Sometimes-Often-Always	0-4
11	Have you been a bit irritable with other people because of problems with your teeth, mouth or dentures?	Never-Seldom-Sometimes-Often-Always	0-4
12	Have you had difficulties doing your usual jobs because of problems with your teeth, mouth or dentures?	Never-Seldom-Sometimes-Often-Always	0-4
13	Have you felt that life in general was less satisfying because of problems with your teeth, mouth or dentures?	Never-Seldom-Sometimes-Often-Always	0-4
14	Have you been totally unable to function because of problems with your teeth, mouth or dentures?	Never-Seldom-Sometimes-Often-Always	0-4

8.4 Photographic Images

A set of photographs of the mouth together with a close-up image of the selected lesion for treatment will be undertaken at Visits 1, 2, 3, 4, 5 and 6. A specific imaging protocol will detail the photographic process and detail how images are stored and accessed. Clinical staff will ensure no recognisable features are identified when taking photographs and ensure anonymity when transferring images to the imaging specialist service provider.

To ensure consistent imaging, multiple photographs will be taken (in line with standard practice) by the Investigator or nominated site staff using provided standardised camera equipment. Prior to site initiation comprehensive training and assessment of individuals will be completed. The oral cavity images will be uploaded to the central image management service alongside close-up lesion images also taken. The imaging specialist service provider will ensure the clarity. These will then be uploaded to the data management EDC system (Kapture)

Once uploaded the close-up lesion images will be presented for evaluation and software analysis (ImageJ). Baseline assessment images provided will be characterised as 'Reference' images to ensure that the same lesion is identified and aligned at all future visits and to ensure that the same analysis criteria are applied. All lesion measurements will be performed according to the ImageJ software protocol for setup and evaluation. The calculated lesion area (mm2), together with the relevant images will be stored in the eCRF for each appropriate visit. The change from baseline in the affected lesion area at each assessment visit will be derived and statistically analysed to support the clinical record

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8.5 Pharmacokinetic Variables

Plasma and saliva samples provided will be assayed using a fully validated and documented method incorporating storage conditions, stability times and assay conditions. Results will be reported by the analysing laboratory and included with the clinical study report (CSR).

Plasma samples for kinetic analysis are obtained at Pre-dose 0h and End of clinic (1-4h) on Days 1, 8, 15, 22 (Visits 2, 3, 4, 5). Individual drug concentration on the two occasions will be summarised to demonstrate the extent of systemic absorption. Drug concentration over time profile parameters such as C_{max}, T_{max} and AUC will not be possible with only two samples and a restricted collection time of around 4 hours. Drug trough levels (Pre-dose 0h each day) will enable identification of steady state which is expected after 5 days of treatment.

Saliva samples for kinetic analysis are obtained at Pre-dose (0h) and just before Post dose (1h), prior to oromucosal film removal and rinsing. This will enable the maximum IMQ concentration in the mouth to be determined on Days 1, 8, 15, 22 (Visits 2, 3, 4, 5) to determine suitability of the film backing layer. Individual drug concentration at pre and post dose times will be constructed.

A tissue sample for kinetic analysis is obtained at the End of clinic (1-4h) on Day 22 (Visit 5) from the biopsy sample (3mm tissue provided for analytics). *NB: If tissue sampling is delayed until follow up one month later then no kinetic analysis will be required*.

Methodology for assays for parent drug IMQ with sample handling will be described in an assay specific manual. Other PK studies indicate the 2 main metabolites are predominantly LLOQ and will only be measured if parent drug is demonstrated in the systemic circulation.

8.6 Pharmacodynamic Variables

Biopsy tissue samples obtained at treatment completion (Visit 5) (or at Follow up (Visit 6) in the event of severe irritation) for diagnostic histopathology will also be used to measure potential useful immunohistopathology protein markers: CD3, CD4, CD8, CD68, Cd1a, CD66b, CD56, Ki67 and where possible these results will be compared with the previous biopsy records database.

Assay methodology used for biomarkers will be according to standard hospital practices.

9 Data Management

The data management and statistical analysis will be performed by a dedicated service provider on behalf of the Sponsor. Prior to the study commencing, a data management plan detailing the procedures and processes required for the collection, recording, management and quality control of the data will be produced and issued. Specifically, this plan will include details concerning:

- Roles and responsibilities
- Introduction of methods applied
- Database system and design
- Data processing
- Database closure

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- Medical monitoring reviews
- Database export and transfer
- Archiving

9.1 Data Collection

Data required will be recorded by a bespoke integrated electronic data capture/clinical data management and interactive response system (Kapture EDC/CDMS/IRS). This complies with 21 CFR Part 11 and is fully validated for use in clinical trials. It will first be recorded on source documents then transcribed into Kapture v7 by authorised and trained site staff accurately and in a timely manner using eCRFs as part of the EDC system. The Study Monitor will review all source data (via access to medical records, laboratory data and other source documents) to allow the required eCRF entries to be verified as accurate (Section 9.3 Clinical Monitoring).

Only the Investigator and authorised support staff are entitled to make entries on the eCRF in the EDC system and all entries will be made in English. Instructions and site training for using the EDC system will be provided within the system and supplemented with direct training by Data Management trainer staff.

The cleaned and locked data will be approved and electronically signed by the Investigator. Each will subsequently be provided with a copy of the site anonymised eCRF subject data for archiving with the site file at study close-out. The Sponsor only has access to anonymised data and no personal identifiable data will be shared.

9.2 Database Management and Control

All data will be recorded, handled and stored in a way that allows accurate reporting, interpretation and verification. Data management will review the data received for accuracy, completeness and sensibility, working according to the data management plan. Queries will be raised as appropriate. Thorough quality control procedures will be performed before database lock.

Current medications entered into the database will be coded by data management using the latest available WHO Drug dictionary at the start of the study. Similarly, relevant medical history and adverse events will be coded using the latest available medical dictionary for regulatory activities (MedDRA). Versions of dictionaries used for the duration of the study will be described in the data management plan. All coding will be subsequently reviewed by the Medical Monitor before final database lock and subsequent analysis.

Laboratory blood samples will be processed by the hospital laboratory. Blood samples for pharmacokinetic and pharmacodynamic biomarker analysis will be processed separately. Results from both laboratories will be provided to data management in a pre-specified and agreed electronic format. Consideration will be given to the timing of these transfers to prevent any potential for bias during the analysis.

Protocol deviations will be recorded by Investigator, site staff or Monitor staff as appropriate on the deviations page of the eCRF. Prior to database lock and analysis, these will be reviewed by clinical and data management teams. These deviations together with any other information specified in the statistical analysis plan will be used to assign subjects to the appropriate statistical analysis populations.

9.3 Clinical Monitoring

The clinical site will be monitored regularly by assigned Site Monitors according to ICH GCP Guidelines and the respective standard operating procedures (SOPs). Selected sites will be

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visited, assessed and selected as suitable to participate in the study by the Sponsor. A site initiation visit (SIV) will be held at each before study start to ensure the site staff are fully trained. Interim monitoring visits (IMVs) will take place on a regular basis according to a schedule fixed by mutual agreement with the site, Sponsor and Monitoring Manager. During these visits, the Site Monitor will conduct source data review, source data verification and will check for completion and accuracy of the entries in the eCRFs, their compliance with the study protocol and with Good Clinical Practice, and will compare the eCRF entries with the source data and IMP accountability record.

In the unlikely event of any untoward actions and activities (such as misconduct or fraud) then these will be notified to the Sponsor by the Monitor Manager and full investigations will be performed by the Sponsor.

A monitoring plan will include extensive details regarding responsibilities of the Site Monitors, Investigator responsibilities in providing access to records and addressing issues identified, frequency and structure of monitoring visits and adherence to subject confidentiality as outlined in the informed consent form (ICF). This will include details concerning the individual subject medical records and verification procedures for those data sources.

For source data verification, at least the following information must be included in the participant records held on site:

- date and copy of written informed consent (original in investigator site file (ISF))
- notification of participation in a clinical study (study number, participant number)
- visit dates and clinical progress
- all adverse events including serious AEs
- confirmation of the diagnosis of the indication being treated
- investigational product administration (e.g. start of treatment, medication pack number)
- concomitant medication
- primary efficacy variables
- secondary efficacy variables

Source data is the original record of study data and could be in medical records (paper or electronic), clinic diaries, lab reports or other diagnostic reports; study-specific questionnaires and photographic imaging. Prior to study start a detailed source data agreement will be completed at each site and signed by the Investigator. This agreement details the exact location of each piece of source data on site and confirms the generation and retention of source data for all eCRF entries. The source data agreement may be used by site auditors or inspectors to identify source data for their review.

Laboratory print-outs are considered as copies of source data and should be printed, signed and dated by the Investigator (or delegate) and filed in the subject records at each occurrence.

At monitoring visits (IMVs) the Site Monitor will regularly review the pharmacy drug accounting and reconciliation records during the study conduct, and will verify the correct use of the study treatment. At a final visit, the Site Monitor will check all remaining material including the remaining quantities of the study treatment and will organise return to Sponsor. At the end of the study copies of these pharmacy records will be collected as part of the study records.

Treatment is only supplied to the site following satisfactory ethics committee, regulatory authority and Sponsor approval is obtained.

In addition, the Site Monitor will determine whether all serious adverse events have been appropriately reported within the time periods required.

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All essential documents will be safely retained by the Sponsor and the Investigator according to regulatory guidelines (ICH Topic E6 (R3) Guideline for GCP and EudraLex Vol 10).

Essential documents at the investigational site include:

- Subject list
- Signed copy of the final study protocol and any amendment(s)
- Investigator copies of the eCRFs and any associated subject-related source data or, where applicable, authorised copies of source data
- Signed participant informed consent forms
- Signed Research staff *curricula vitae*
- Copies of correspondence with the ethics committee and any with the regulatory authority (if applicable)
- Relevant laboratory reference ranges and methods
- Copies of study supplies receipt
- Copies of all study correspondence
- Delegation log

In addition, all site files will be stored and subsequently archived according to local legislation. Management of site files is the responsibility of the site team, with support from the monitoring staff. The site files must be kept up to date and complete. In the unlikely event of intended destruction post study, prior permission in writing from the Sponsor is required.

The Investigator and their staff will be expected to co-operate with the Site Monitor throughout. The Investigator must be available to answer questions arising during regular monitoring.

In addition, the Investigator guarantees:

- Prior to each monitoring visit, all data will be properly recorded in the eCRF and subject files.
- At the monitoring visits, source documentation will be available.
- All medication dispensed must be recorded in the eCRF and drug inventory form.
- All subjects who are screened but not entered into the study will be listed on the form provided and recorded in the eCRF for Sponsor review.

The clinical site will permit trial-related monitoring, audits, ethics committee review, and regulatory inspection(s).

The quality assurance team (nominated by the Sponsor) may, where indicated, arrange to visit the site in order to audit performance and assess documentation. The Site Monitor and/or Project Manager will usually accompany the auditor(s). The Investigator will be informed about the outcome of the audit.

In addition, site inspections by regulatory authority representatives and ethics committees are possible. The Investigator should notify the Sponsor of any such impending inspection.

10 Statistical Methods

The outline for all analyses is described. However, a separate detailed statistical analysis plan (SAP) document to expand and justify on all methods used will be prepared.

10.1 General Considerations

All data derivations, manipulations and reporting procedures will use a fully validated analysis environment (SAS v9.4 with Windows 11 operating system).

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For all evaluations, data will be described and analysed according to Treatment group (SAY_V2 IMQ oromucosal film (Active) and placebo (Control)), and assessment (Screening, Baseline (Day 1), Day 8, 15, 22, Withdrawal and At Endpoint (Day 8 and 22 accounting for Early termination) and Follow Up (Month +1) will be included. Consideration for severity of dysplasia and site number will be given (depending on group sizes) where appropriate.

All the data collected and derived will be described appropriately accounting for the nature and distribution. For continuous variables, data will be presented as number (n), mean, median (Q1-Q3), standard deviation, and range (min-max). For discrete variables data will be presented as frequencies and proportions (as appropriate) and the denominator will be the number of subjects available in the relevant population.

As only within patient treatment and ordered comparisons are possible no statistical significance (p values) will be emphasised or reported. Statistical models and tests performed are only to aid assessment of variability of estimates.

10.1.1 Objectives

In order to assess the initial potential for an IMQ oromucosal film (SAY_V2) the objectives are primarily defined:

- To investigate the safety profile of the IMQ oromucosal film
- To investigate acceptability of the oromucosal film following daily use by participants.

Secondary interests will investigate the extent of systemic absorption of IMQ pharmacokinetics (PK) in plasma samples.

Additionally, with pharmacodynamic (PD) evaluation of biopsy tissue will be performed to investigate potential immunohistopathology markers of IMQ activity

10.1.2 Null Hypothesis

The Null Hypothesis throughout the investigations is that there is no difference between active treatment (SAY_V2) oromucosal film and Control (matching placebo).

That is: H_0: $\mu1 = \mu2$, where H_0 = the null hypothesis, $\mu1$ = the mean/proportion of active group, and $\mu2$ = the mean/proportion of control group.

10.1.3 Sample Size/Power

Sample size and power estimations, although not critical for this initial Phase I investigation, are useful for future planning and to indicate the likely precision (95% confidence intervals) for actual proportions (Active, Control) and for differences in proportions of responses between the two treatment groups (Active – Control).

With the chosen sample size of 20 participants for each group the two-sided 95% confidence interval for the difference between a Group 1 proportion, π_1, of 0.5 and a Group 2 proportion, π_2, of 0.2 will extend 0.281 from the observed difference in proportions. Therefore, a difference estimate of 30% will extend from 2% to 58%.

On application of an overall <20% dropout rate then the total required sample size is 25 participants.

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The confidence interval for differences between two proportions test (nQuery 9 Power and sample size for group sequential trials v9.4.1 Statistical Solutions Ltd) was used for all calculations.

10.1.4 Statistical Analysis Plan (SAP)

The detailed statistical analysis plan (SAP) will be prepared in advance of database 'lock' and unblinding. The SAP will include all analysis methods (hypothesis tests, statistical modelling), definitions of analysis sets, assumptions made (and tested) and strategies applied in the event of missing data. The output format for all analyses and results will be prepared as template shells for all tables, figures and listings (TFLs). The SAP may also document any updates or subsequent changes to the analyses described here.

10.1.5 Analysis Sets

Three subject populations will provide the basis for all statistical analyses, data evaluations and summaries included in the investigation. These will be the full analysis set, per protocol set and safety set. Given the stage of development, the per protocol set will be considered primary.

The 'Full analysis set' (FAS) will include all subjects who apply at least one dose of medication and who subsequently provide any post baseline information. All subjects in this group will be analysed according to the treatment allocation scheduled.

However, the primary analysis ‘Per-protocol’ (PP) set will be a subset of the FAS set and include only subjects who satisfactorily complete the 3-weeks treatment and fully comply with requirements of the protocol and any per protocol criterion specified in the SAP. By definition, all subjects in this group will be analysed according to the treatment they actually received.

For all safety evaluations an overall ‘Safety’ set (SS) is also be described. This will include all subjects who apply at least one dose of medication and consider all subjects according to the treatment they actually received.

10.1.6 Missing Data

All possible efforts will be made to ensure that subjects complete all the required assessments at each clinic visit and in general there will be no imputation of any missing data for any of the assessments performed.

However, in the event of early termination and subject withdrawal where incomplete data are collected the application of a ‘last observation carried forward’ (LOCF) strategy will be used to evaluate the effect of completely missing assessment visit data.

This will be applied to the FAS analysis set and will involve substitution of the final visit information with the last immediately preceding non-missing evaluation. The overall ‘drop-out’ rates in each of the active treatment dose groups and placebo control group will also be considered to determine the proportion of data substitution.

10.1.7 Data Analysis

In general, all data will be summarised according to endpoint or visit, treatment group and overall for each analysis set. In addition, the actual visit windows specified will be considered (Day 8, 15, 22 all +/- 1 day).

10.1.8 Efficacy Analysis

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All efficacy analyses will be used for information purposes only. These will include:

- Change from baseline in lesion area size (Area = πab)
- Change from baseline in lesion graded response (7-point scale)
- Change from baseline in histology response (9-point scale)
- Complete Resolution (100% reduction in size of the treated lesion)
- Partial Resolution (>=50% reduction in size of treated lesion)
- Change in Dysplasia severity (Mild, Moderate or Severe)
- Incidence of oral cancer development following treatment
- CGI – Improvement scale (7-point scale)
- OHIP-14 – Quality of Life scale (14 items each scored on a 0-4 scale)

With all clinical/laboratory efficacy assessments performed, Pre and Post treatment will be compared and changes from baseline calculated. The higher the score with each scale used, the worse the condition (except CGI). If the change in the score increases over time, then the condition is worsening and malignant transformation is more likely to occur. Therefore, if the change in the score decreases over time this then indicates improvement or stabilising of the condition possibly related to medical treatment or lifestyle changes made during the intervening period.

The proportion of subjects who are classified with Complete resolution or Partial resolution or Incidence of oral cancer after 3-weeks treatment will be derived and analysed for both the PP and FAS analysis sets (responder rate %). This binary outcome measure will be analysed using Fisher's exact test and treatment differences quantified in terms of odds ratios and 95% confidence intervals using a binary logistic regression.

Efficacy endpoints including: Lesion grade, Histology response, Dysplasia score, Dysplasia severity and CGI-Iwhich are considered ordered categorical data will be analysed using Cochran-Mantel-Haenzsel (CMH) tests and quantified with ordered logistic regression.

Interval data (eg: Lesion size and OHIP-14 total score) will be analysed using analysis of covariance (ANCOVA) models using change from baseline at endpoint (3-weeks or earlier in the event of withdrawal) as response variable, Treatment dose as fixed effect and baseline as covariate.

Stratification variables dysplasia severity and site will also be incorporated in line with the randomisation process and to assess the homogeneity of the treatment effect across participant severity and across the participating sites.

Following all analyses estimates of treatment effect sizes and the magnitude of treatment group differences compared to placebo will be presented as odds ratios or adjusted means (as appropriate) each with 95% confidence intervals and associated p-values

Further exploratory investigation of the extent of observed treatment effects will then be explored across a range of potentially influencing cofactors: Age, Sex, Tobacco (Use/Duration), Type (Homogenous/Non homogenous), Oral site of lesion.

10.1.9 Demographic and Baseline Characteristics

Assessments performed prior to randomisation, at Screening and Baseline will be displayed using summary statistics. These include: demographics, medical history and physical

examination (height and weight at screening) and ECG. Treatment groups and analysis sets will be identified. All data will be described appropriately as interval or categorical summaries.

No formal statistical analyses are planned.

10.1.10 Diagnostic Characteristics

All diagnostic assessments performed at Screening will be summarised. All data will be described as interval or categorical summaries according to Treatment groups and the analysis sets as appropriate.

No formal statistical analyses will be performed.

10.1.11 Participant Acceptability

Four main categories will be covered by the Investigator: Compliance with treatment requirements and ease of use, oromucosal film characteristics, Effects of the oromucosal film and the Effect on daily activities (Table 6).

In order to the overall participant rating of the use of the oromucosal film the response to each question is assigned a score and across each of the categories a higher score is better (except for daily activities where a low score is best). Overall summaries (n/% responses) of each question and category are of primary interest but total ranked scores for each category may be of interest. Results will be present by Treatment group and overall. No formal statistical will be applied.

10.1.12 Safety

Clinical safety evaluations performed at all post randomisation visits during the 3-week ‘On’ treatment period will be described as interval or categorical summaries as appropriate. These include: reported adverse events, physical examination (plus weight), vital signs and prior and concomitant medications. Laboratory safety will be summarised as actual values, changes from screening/baseline (Visit1/2) and also after classification as low, normal, high in relation to the laboratory normal range. These categorical summarised will be presented over the time course of the study as ‘Shift’ tables in relation to baseline values.

No formal analyses of differences between the active treatment group and placebo control will be performed.

10.1.13 Follow up Assessments

All data collected after 1 month Follow up (Visit 6) will be summarised and analysed in the same manner as all efficacy and safety data collected during the initial 3-week ‘On’ treatment period. Change in efficacy endpoints may help to assess maintenance of treatment effect following completion of treatment

10.2 Interim Analysis

10.2.1 Interim Statistical Analysis

Not applicable

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10.2.2 Data Safety Review

Participant safety is of upmost importance and will be reviewed on an individual basis throughout the conduct of this clinical investigation and on a monthly basis as data accrue. Both the Investigator and supporting clinical and data management staff will be involved.

However, in line with good clinical management practice frequent reviews of the accumulating safety data according to treatment (adverse events, physical examination, vital signs and laboratory safety blood samples) for all available subjects will be performed. These will be in the form of compiled data listings and will be produced after 10 participants have completed treatment. The listings will be reviewed in conjunction with the principal investigator. In the unlikely event of any concerns these may be escalated to pharmacovigilance for consideration of changes to the reference safety information

11 Ethics

11.1 Independent Ethics Committee (IEC)

The study protocol (and any subsequent amendment to the protocol that is not solely of an administrative nature), the investigator brochure, the subject information sheet, the informed consent form as well as consent form updates (if applicable), subject recruitment procedures (if applicable) and evidence of insurance and indemnity will be submitted to the responsible ethics committee for approval.

11.2 Ethical Conduct of the Study

The study will be conducted in accordance with the ethical principles that have their origins in the Declaration of Helsinki, and that are consistent with ICH GCP (ICH E6 RE3) Guidelines and the applicable regulatory requirements.

11.3 Permissible Recruitment Methods

The clinical site will individually identify participants for recruitment to the study. This will predominantly be by evaluation of departmental database records but other methods may be introduced if appropriate.

A range of methods may be employed but permissible methods of recruitment will include:

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- Participants who are already attendees at the site clinic.
- Participants who were formerly, but not currently, attendees at the site clinic. Sites may initiate contact with suitable subjects by email, phone call or letter of invitation, as appropriate.
- Participants who are referred to the trial by their Dentist/GP or other regional clinics managing patients with oral leukoplakia

11.4 Participant Information and Consent

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In compliance with the Declaration of Helsinki, prior to inclusion of the subject into the study, the subject (or legally acceptable representative) will be given full verbal and written information on the nature, objective, significance, expected benefits, potential risks and consequences of the study by the Investigator or authorised designee. The obligations of the Investigator as set forth in the Declaration of Helsinki, the ICH Guideline for Good Clinical Practice (ICH GCP (R3) 2025), and the respective national legislation are to be respected.

During the course of the study, the subject (or legally acceptable representative) will be informed in a timely manner if information becomes available that may be relevant to the subject's willingness to continue participation in the study.

The subject (or legally acceptable representative) will be informed that the recorded data will be passed on to authorised persons in an anonymous form. Only for the purpose of checking the validity of the data, authorised persons (e.g. Sponsor, person authorised by the Sponsor, auditors, regulatory authorities, members of independent ethics committees), being bound to confidentiality, will have access to non-anonymous data. If the results of the study are published, the subject's identity will remain confidential. Furthermore, the obligations of the subject (or legally acceptable representative) and the fact that he/she is free to withdraw the consent at any time without stating the reason are described. However, in case of adverse events or poor tolerability the subject (or legally acceptable representative) should inform the Investigator. Each subject (or legally acceptable representative) will have the opportunity to discuss the informed consent form with the Investigator or authorised designee prior to giving his/her written consent. The subject (or legally acceptable representative) will be given a copy of the signed and dated written informed consent form and consent form updates (if applicable).

Details of the informed consent procedure will be recorded in the subject's notes and transcribed onto the eCRF.

11.5 Insurance

From the outset of the study until its termination each subject is insured against any health impairment occurring as a result of participation in the study in accordance with the laws and regulations of the country in which the study is performed.

Each subject will be informed by the Investigator of the insurance and resulting obligations. A copy of the insurance certificate and conditions will be provided, if requested. Any medical deviation from this study protocol undertaken by the subject or the investigator is not covered by this insurance.

11.6 Data Handling and Record Keeping

11.6.1 Data Handling and Quality Assurance

The Sponsor and/or Clinical Monitoring team (as designated) will conduct a visit to each study site to verify the qualifications of each Investigator, inspect the site facilities and inform the Investigator of their responsibilities and the procedures for ensuring adequate and correct documentation. A site qualification form and site selection log will be maintained during the site selection process.

The Investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the study for each participant. All information recorded in the eCRF for this study must be consistent with each subject's source documentation (i.e. medical records).

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11.6.2 Database Management and Quality Control

All study-related data generated by site personnel will be captured electronically at each study site using the eCRF. Laboratory assays (safety, pharmacodynamics, pharmacokinetics) will be managed by the hospital and results will be transferred for inclusion in the study analysis database.

Once the eCRF clinical data have been submitted, corrections to the data fields will be captured in an audit trail. The reason for change, the name of the person who performed the change, and the time and date will be logged to provide an audit trail.

The specific procedures to be used for data entry and query resolution using the eCRF will be provided to study sites in CRF completion instructions. In addition, site personnel will receive training on the eCRF. Once the source data verification is complete and all queries are closed, data management will freeze the eCRF page.

11.6.3 Case Report Forms and Source Documentation

All data obtained during this study must be promptly entered in the eCRF. All source documents from which eCRF entries are derived should be placed in the subject medical records. Measurements for which source documents are usually available include laboratory assessments.

Data that will be entered directly into the eCRF (i.e., for which there is no prior written or electronic record) are considered to be source data. The eCRF entries for each subject will be checked against source documents at the study site by the Monitoring staff.

11.6.4 Data Collection

The Investigators (and appropriately authorised site staff) will be given access to the EDC/CDMS/IRS system Kapture an online web-based electronic data-capture and processing system that is compliant with US Food and Drug Administration Title 21 Code of Federal Regulations Part 11.

This system is specifically designed for the collection of clinical data in electronic format. Access rights to the electronic data-capture system will be carefully controlled and configured according to each individual's role throughout the study. Only the Investigator and authorised staff will be able to enter and correct data in the eCRF.

The eCRF should be completed for each subject included in the study and should reflect the latest observations on the subjects participating in the study. Therefore, the eCRF is to be completed as soon as possible during or immediately after each subject visit or assessment.

The Investigator must verify that all data entries in the eCRF are accurate and correct. If some assessments cannot be done, or if certain information is unavailable, not applicable or unknown, the Investigator should indicate this in the eCRF.

Computerised data-check programs and manual checks will identify any data discrepancies for resolution. Corresponding queries will be generated in the system and the site will be informed online about new issues to be resolved. All discrepancies must be resolved online directly by the Investigator or by staff authorised to do this by formal listing of delegation of authority stored in the site study file.

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After completion, the Investigator will be required to electronically 'sign off' and approve validity of the clinical data for each subject as an accurate representation of that subject's conduct in the study.

11.6.5 Access to Source Data

During the study, the Monitoring team will make regular site visits to review protocol compliance, conduct source data verification by comparing eCRF entries and individual subject medical records, assess drug accountability and management, assess laboratory procedures and ensure that the study is being conducted according to regulatory and protocol requirements. The review of medical records will be performed in a manner that ensures subject confidentiality is maintained.

Source data verification will be required to monitor the progress of the study. Moreover, the Sponsor Quality Assurance team may, if necessary, carry out such source data checks and/or on-site audit inspections. Direct access to source data will be required for these inspections and audits; they will be carried out giving due consideration to data protection and medical confidentiality. The Investigator must assure the Monitor staff and the Sponsor that they will provide the necessary support at all times.

11.6.6 Archiving Study Records

According to ICH guidelines, essential documents should be retained for a minimum of 25 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 25 years have elapsed since the formal discontinuation of clinical development of the investigational product. However, these documents should be retained for a longer period if required by the applicable legal requirements.

The site should provide the Sponsor through the Monitoring team details of an adequate archive facility. If this is not available and indicated the Sponsor may arrange alternative storage facilities.

11.6.7 Good Clinical Practice

The procedures set out in this study protocol are designed to ensure that the Sponsor and Investigator abide by the principles of the Good Clinical Practice guidelines of the ICH (ICH E6 R3) and the Declaration of Helsinki. The study will also be carried out in keeping with local legal requirements.

11.7 Quality Assurance and Audit Procedures

The Sponsor maintains a robust quality management system (QMS) that includes all activities involved in quality assurance and quality control to ensure compliance with written standard operating procedures (SOPs) as well as applicable GCP regulations and ICH guidelines.

Audits of investigator sites, vendors and Sponsor systems are performed regularly by auditors that are independent from those involved in conducting, monitoring or performing quality control of the clinical study. The clinical audit process uses a risk-based approach.

Audits are conducted to assess GCP compliance with applicable regulatory requirements, protocols and internal SOPs and are performed according to written Sponsor processes.

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11.8 Financing

The financial aspects of the study will be documented in an agreement between the Sponsor/Clinical Management team and each Investigator or any other involved party and must be confirmed in writing before the study commences.

11.9 Publication policy

The results of this study and any discoveries related, regardless if they have technical or medical merit, remain the exclusive properties of the Sponsor.

However, publication of the results of this study is certainly a priority for the Sponsor as this will provide valuable insight into the treatment of the condition under investigation. To this end a collaborative approach with the Investigators and the Sponsor is encouraged. However, if Investigators wish to publish separately then the Sponsor asks for prior opportunity to review and approve drafted text. Approval will not be unreasonably withheld.

11.10 Roles and Responsibilities

Sponsor, sub-contractor and supplier functions are specified in Table 9.

Table 9: Functions and Responsibilities

Function	Responsible Person/Organisation
IMP Supplier	Labtec GmbH (part of AdhexPharma)
IMP Packaging	Labtec GmbH
IMP Distribution	Labtec GmbH.
Clinical Management	Manentia Ltd
Clinical Monitoring	Manentia Ltd
Data Management/Statistical Analysis	Data Magik Ltd.
Pharmacovigilance	ProTherax Ltd
Imaging Service Provider	ClinPhoto Ltd
Medical Monitoring	Professor Shaw with responsible for overseeing the regular safety reviews
Pharmacy	Participating hospital
Medical Writing	Lochside Medical Communications
Quality Assurance (Sites and Subcontractors as necessary)	Manentia Ltd

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APPENDICES

APPENDIX 1

BIRTH CONTROL METHODS	
Highly effective birth control methods	
Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation	
• Oral	
• Intravaginal	
• Transdermal	
Progestogen-only hormonal contraception associated with inhibition of ovulation	
• Oral	
• Injectable	
• Implantable	
	Intrauterine device (IUD)
	Intrauterine hormone-releasing system (IUS)
	Bilateral tubal occlusion
	Vasectomised partner
	Sexual abstinence*
Less effective birth control methods	
Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action	
Male or female condom with or without spermicide	
Cap, diaphragm or sponge with spermicide	
***Sexual abstinence method**	
The practice of refraining from all types of sexual intercourse and genital contact thereby ensuring that sperm never enters the vagina or reaches an egg This requires no medical devices, and is the only form of birth control that is 100% effective at preventing pregnancy However periodic abstinence, the rhythm method, and the withdrawal method are not 100% effective and are not recommended.	

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