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Protocol Title:

Protocol for the Novoglan-01 clinical trial to confirm the safety, efficacy and tolerability of the Novoglan product in treating adult phimosis

Principal Investigator:	Professor David Gillatt
Contact Details:	Phone: (02) 9812 3617
Protocol Number:	2.1
Protocol Authors:	Prof D. Gillatt, Mr A. James and Dr H. Mazure
Protocol Version #:	2.1
Protocol Date:	29 September 2020
Supersedes previous Version / Date	Version V2.0 dated 15 March 2019

Signature: _____

Date: _____

Ethics Statement:

The study will be conducted in accordance with the National Statement on Ethical Conduct in Human Research (2007), the CPMP/ICH Note for Guidance on Good Clinical Practice and consistent with the principles that have their origin in the Declaration of Helsinki. Compliance with these standards provides assurance that the rights, safety and well-being of trial participants are respected.

Contents

Summary

Study title:

Novoglan-01 clinical trial to confirm the safety, efficacy and tolerability of the Novoglan product in treating adult phimosis

Protocol version: 2.1

Objectives

Primary objective: Confirm the efficacy of the Novoglan product as measured by the improvement in foreskin retraction against a standardised scale.

Secondary objectives: Confirm the safety and satisfaction with treatment as assessed by quality of life improvement and treatment tolerability.

Study design

Single arm, observational prospective trial

Planned sample size

Single cohort of 24 participants

Selection criteria

Participants 18 years or older consulting the Macquarie University Hospital and Princess Alexandra Hospital Urology Clinics with symptoms of adult phimosis, inability to fully retract the foreskin accompanied with pain or discomfort and including participants with prior frenuloplasty or Balanitis Xerotica Obliterans.

Study procedure

Enrolment Visit – Participant meets with physician who confirms eligibility criteria, measures the degree of phimosis and enrols the participant into the study.

Study Visit 1 – Participant meets with clinical trial nurse for phimosis measurement, to complete the Quality of Life questionnaire and receive training and Novoglan materials and documentation.

Study Visit 2 and 3 – By phone between the clinical trial nurse and the participant at Week 1 and Week 4 post Study Visit 1 to review treatment progress.

Final Study Visit – At 6 to 8 weeks following Study Visit 2, participant meets with clinical trial nurse to measure foreskin retraction, complete the treatment tolerability questionnaire and the quality of life questionnaire – End of participant study

Statistical considerations Sample size calculation - As described in Section 8.

Analysis plan – As described in Section 8.

Duration of the Study

Completion by February 2022 from study start in September 2019

PREAMBLE – Clinical trial contributors and contact details

Responsibility	Person(s) and credentials	Contact details
Principal Investigator (MUH)	Prof. David Gillatt, M.D.	(02) 9812 3617
Clinical research nurse (MUH)	Mr Bernard Riley, RN	(02) 9812 3617
Administrative assistant to Prof Gillatt (MUH)	Mrs Maizie Barakat	(02) 9812 3031
Second Site Investigator (PAH)	A/Prof. Eric Chung, M.D.	(07) 3832 1168
Clinical research nurse (PAH)	Mr Bill Bailey, R.N.	(07) 3832 1168
Administrative assistant to Prof Chung (PAH)	Ms Lynette Li	(07) 3832 1168
Trial sponsor	Macquarie University	(02) 9850 7111
Investigative product supply	Mr Andrew James, CEO, Platigo Solutions Pty Ltd, manufacturer of the Novoglan product.	0411 808 020
Study coordinator	Dr Hubert Mazure, PhD, Scientific and Clinical Trials consultant to Platigo Solutions Pty Ltd	0404 199 146
Biostatistical analysis	Dr Hassan Doosti, Lecturer, Department of Mathematics and Statistics, Macquarie University	0415 609 544

1. BACKGROUND AND INTRODUCTION

1.1. Disease/Proposed Intervention Background

Male phimosis is characterised by a stenosis of the foreskin resulting in the inability of the prepuce to retract over the glans. Physiological phimosis is a normal condition in infants and boys under the age of 10 which usually disappears after 3-4 years of age. [Cord CJ, 1999; Hayashi, 2011] Pathologic phimosis can occur at any age among uncircumcised adult men and is frequently associated with infections such as balanitis. Phimosis can be graded according to a scale originally developed by Kikiros, Beasley and Woodward [Kikiros, 1993].

The incidence of adult phimosis is poorly documented. Most authors report an incidence of around 1% [EAU Guidelines, 2016] but the incidence of adult circumcision typically linked to phimosis has been reported as high as 15.8% in the UK [Raj, 2013]. Schoberlein [Schoberlein, 1967] found phimosis in 8.5% of 3,000 men mostly aged 18 to 22 and representing 10.4% of the uncircumcised men.

Adult phimosis can cause significant and often painful symptoms such as urinary difficulties, frequent infections or ballooning of the foreskin during urination. Such conditions can require treatment. The most common treatment for adult phimosis is circumcision. Circumcision is a radical treatment but there are alternative conservative treatment options such as the application of steroid creams to relieve the symptoms of tight foreskins.

Phimosis treatment guidelines published by the British Association of Urological Surgeons (BAUS) destined to participants discourage the manual stretching of the foreskin and

recommend the use of steroid creams or circumcision. The professional guidelines from the BAUS refer physicians to the guidelines published by the European Association of Urology (EAU) [EAU Guidelines, 2016] which address phimosis in the section dedicated to paediatric urology. The treatment recommendations include the use of steroid creams and if unsuccessful, the circumcision of the penis.

The main problem with using steroid creams to treat phimosis is the narrow range of stretching motion that will provide suitable stimulation for the foreskin to grow without exacerbating the inflammation or tearing of the foreskin. Recently, a new conservative treatment option, the Novoglan product, has shown promising results, with a very high success rate and satisfaction reported by users. The Novoglan product is designed to be used by participants 18 years and over. Its main component is a small balloon that can be inserted underneath the opening of the foreskin and progressively inflated while avoiding the complications frequently observed with the use of steroid creams. The Novoglan balloon is guided under the foreskin between the glans and the inner side of the foreskin (prepuce) using a purpose moulded rod. Once the balloon is in place the rod is removed and the stop cock and plunger is attached to the Novoglan device. The balloon is inflated by pressing the plunger. The procedure is painless and pressure is under the control of the user to ensure no discomfort. Foreskin cells are placed under tension and tight junctions are loosen under stretching leading to tissue adaptation and cell mitosis. This process increases the column of foreskin cells and increases the foreskin circumference. Treatment is continued for a period of 4 to 8 weeks until full normal retraction is achieved.

The Novoglan product is a medical device commercialised in Australia since 2006 and listed with the Australian Therapeutics Goods Administration (ARTG 168962). The Novoglan product has been used successfully in the Urology Clinic in the past year at Macquarie University Hospital but only with a few adult male participants. The observation of these few adult participant treatments indicated that the Novoglan product is simple and safe to use, effective at treating adult phimosis and comparatively inexpensive. It appears that the Novoglan product produces relief from the symptoms of phimosis in 3 to 4 weeks.

References, in order of citation, are as follows.

The prepuce.

Cold CJ, Taylor JR.

BJU Int. 1999 Jan;83 Suppl 1:34-44.

Prepuce: phimosis, paraphimosis, and circumcision.

Hayashi Y, Kojima Y, Mizuno K, Kohri K.

ScientificWorldJournal. 2011 Feb 3;11:289-301. doi: 10.1100/tsw.2011.31.

The response of phimosis to local steroid application

CS Kikiros, SW Beasley, AA Woodward

Pediatric surgery international, 1993 8: 329-332

European Association of Urology - Guidelines

2016 Edition – Update March 2016

How painful is adult circumcision? A prospective, observational cohort study.

Rai BP, Qureshi A, Kadi N, Donat R.

J Urol. 2013 Jun;189(6):2237-42. doi: 10.1016/j.juro.2012.12.062.

Significance and incidence of phimosis and smegma

Schöberlein W.

Munch Med Wochenschr. 1967 Feb 18;108(7):373-7.

1.2. Rationale for Performing the Study

The aim of the Novoglan-01 clinical trial is to conduct a scientific study in compliance with good clinical practice in order to confirm the safety, efficacy and tolerability of the Novoglan product as a conservative treatment for adult phimosis. This study is expected to provide evidence for the use of the Novoglan product as an alternative to steroid creams in the conservative treatment of adult phimosis and have the urological treatment guidelines for adult phimosis updated accordingly.

2. HYPOTHESIS

The hypothesis for the Novoglan-01 study is that the Novoglan product is an alternative conservative treatment for adult phimosis that is safe, efficacious and well tolerated by participants.

3. STUDY OBJECTIVES

3.1. Primary Objectives

The primary study objective is to measure the efficacy of the Novoglan treatment by measuring the degree of phimosis at the time of enrolment into the study and at the end of the participant study.

3.2. Secondary Objectives

The first of secondary objectives is to assess the safety of the Novoglan treatment by observing and reporting any treatment discomfort or adverse event mentioned by the participants during the treatment.

The second of secondary objectives is to confirm the participant satisfaction with the Novoglan treatment by assessing the improvement of quality of life reported by the participant and the treatment tolerability as reported by the participant at the end of the trial.

4. STUDY DESIGN

4.1. Design

The Novoglan-01 clinical trial is an investigator-initiated, single arm, non-randomised, observational, prospective study.

4.2. Expected Participant Numbers

The Novoglan-01 study is expected to enroll 24 participants.

4.3. Duration Of The Study

The Novoglan-01 study is expected to complete by February 2022 from a start in September 2019. The expected participant recruitment period would span the duration of the trial, starting with the trial start date and finishing 1 or 2 months before the expected end date.

4.4. Endpoints

Primary Endpoints

Primary endpoint – Efficacy of the device demonstrated by the improvement in foreskin retraction as measured using the Kikiros-inspired phimosis assessment scale.

Secondary Endpoints

First secondary endpoint – Safety of the device as evidenced by the reporting of any adverse effect or complication as observed and noted by the clinical trial team during the participant's treatment.

Second secondary endpoint – Participant satisfaction with the treatment as confirmed by treatment tolerability reported by the participant with a standardised treatment tolerability questionnaire and improvement in quality of life post-treatment as assessed by a standardised quality of life questionnaire before and after treatment.

4.5. Centres

The Novoglan-01 study will be running at two sites of the Macquarie University Hospital Urology clinic, New South Wales and at the Urology clinic of Princess Alexandra Hospital, Queensland, and a total of 24 participants are expected to be enrolled into the study.

5. STUDY PARTICIPANTS

5.1. Inclusion Criteria

The Novoglan-01 study inclusion criteria are as follows.

1. Male 18 or older referred to the urology clinic
2. Symptoms of adult phimosis with inability to fully retract the foreskin
3. Reporting of pain or discomfort

4. Potential participant may have Balanitis Xerotica Obliterans or undergone prior frenuloplasty
5. Willingness to provide informed consent and willingness to participate and comply with the study requirements.

5.2. Exclusion Criteria

The Novoglan-01 study exclusion criteria are as follows.

1. Any known allergy to latex or silicones
2. Any bleeding, ulcer or active infection of the penis
3. Any prior prepuce surgery, except for frenuloplasty
4. Any hypospadia
5. Any severe scaring of the glans or foreskin
6. Any history of penile cancer
7. Participants with a history of a psychological illness or other conditions which may interfere with their ability to understand the study requirements

6. STUDY PROCEDURES

6.1. Study Flow Chart

Pre-study enrolment visit – Eligibility and enrollment

Study visit 1 – Minimum 7 days post enrolment visit - Quality of life questionnaire, phimosis measurement, Novoglan product supply and training

Study visits 2 and 3 by phone - Follow-up phone call to review treatment progress and any adverse event or complication at Week 1 and Week 4 post Study visit 2

Final study visit – Quality of life questionnaire, phimosis measurement, any report of complication or adverse event and treatment tolerability questionnaire – End of participant study

6.2. Investigation Plan

Methodology

This section clearly describes how the study procedures/interventions will be conducted in order to ensure the results are reproducible. It includes a table listing all the potential study visits and the procedures that will be conducted at each visit.

Interventions	**Enrolment Visit**	**Visit 1**	**Visit 2 (phone)**	**Visit 3 (phone)**	**Final Study Visit**
Timing	**Week 0**	**Week 1**	**Week 2**	**Week 5**	**Week 7 to 9**
Baseline demographics	✓				
Medical history	✓				
Concomitant medications	✓		✓	✓	✓
Inclusion / Exclusion criteria	✓				
Participant Consent	✓				
Phimosis measurement		✓			✓
Quality of life questionnaire		✓			✓
Novoglan supply and training		✓			
Treatment progress, adverse event or complication			✓	✓	✓
Treatment tolerability questionnaire					✓

The participant journey during the Novoglan-01 study can be described as follows.

Enrolment visit

Potential participants identified during the Novoglan-01 recruitment process will be seen by the Principal Investigator, Prof. David Gillatt, during the Enrolment Visit. At that time, the following information will be collected from the participant:

- Demographics including date of birth, race and ethnicity
- Medical and medication history, with particularly focus on phimosis
- Penile examination to confirm phimosis and medical examination including height and weight measurements
- Review of eligibility for the Novoglan-01 study against inclusion and exclusion criteria

If the participant meets the eligibility criteria, Prof Gillatt will propose participation into the Novoglan-01 study, explain the study, explain the informed consent and review with the participant the informed consent form, pointing out the option of withdrawal at any time and the minimum delay of 1 week between Enrolment Visit and Study Visit 1 to provide sufficient time for careful consent consideration.

At that time, participants wanting to participate in the Novoglan-01 study will:

- Sign the Novoglan-01 Informed Consent Form (see details in Section 9)
- Be asked to make an appointment for Study Visit 1 with the Clinical Trial Nurse
- Be assigned a Novoglan-01 Study unique participant identifier

If the participant agrees to participate to the Novoglan-01 Study, all the above information will be recorded by Prof Gillatt in the Participant Case Report Form (see details further in Section 9).

Study Visit 1

At Study Visit 1 the participant will meet with the Clinical Trial Nurse who will:

- Carry out a measurement of the participant phimosis using the standard measurement scale based on Kikiros *et al.,* 1993 and using the Novoglan-01 Study Phimosis Measurement Form (see details further in Section 9)
- Carry out an evaluation of the participant quality of life prior to treatment and using the Novoglan-01 Quality of Life Questionnaire (see details further in Section 9)
- Supply the participant with Novoglan investigative product in sufficient quantity for the duration of the study, explain the various components of the Novoglan product and train the participant in its appropriate and safe use (see details further in Section 9)
- Hand out to the participant a printed "how to use" guide for the Novoglan product (see details further in Section 9)
- Schedule a date and time for the Study Visit 2 by telephone

Study Visit 2 – By phone

At Study Visit 2, the Clinical Trial Nurse will phone the participant to inquire and record in the participant Case Report Form about the following points:

- Overall progress with treatment by the participant and any problem in using the Novoglan product requiring further clarifications or training
- Any report by the participant of any adverse effect
- Any change to the concomitant medication list provided at the Enrolment Visit

The Clinical Trial Nurse will conclude the Study Visit 2 phone call by confirming a date and time for the Study Visit 3 phone call.

NOTE: During the phoned Study Visit 2 the participant will be offered the option to schedule a face-to-face follow-up training with the Clinical Trial Nurse at Macquarie University Hospital. If carried out, the outcome of such a follow-up training will be recorded in the Study Visit 2 Case Report Form.

Study Visit 3 – By phone

At Study Visit 3, the Clinical Trial Nurse will phone the participant to inquire and record in the participant Case Report Form about the following points:

- Overall progress with treatment by the participant and any problem in using the Novoglan product requiring further clarifications or training
- Any report by the participant of any adverse effect
- Any change to the concomitant medication list provided at the Enrolment Visit

The Clinical Trial Nurse will conclude the Study Visit 3 phone call by confirming a date and time for the Final Study Visit.

NOTE: During the phoned Study Visit 3 the participant will be offered the option to schedule a face-to-face follow-up training with the Clinical Trial Nurse at Macquarie University Hospital. If carried out, the outcome of such a follow-up training will be recorded in the Study Visit 3 Case Report Form.

Final Study Visit

At the Final Study Visit, the participant will initially meet with the Clinical Trial Nurse and subsequently with the Principal Investigator, Prof David Gillatt.

The Clinical Trial Nurse will investigate and record in the participant Case Report Form the following information:

- Measurement of the participant phimosis at study end using the Novoglan-01 Study Phimosis Measurement Form (see details further in Section 9)
- Evaluation of the participant quality of life at the end of treatment and using the Novoglan-01 Quality of Life Questionnaire (see details further in Section 9)
- Evaluation of the participant perceived tolerability of the Novoglan product during the treatment and using the Novoglan-01 Novoglan Treatment Tolerability Questionnaire (see details further in Section 9)

After meeting with the Clinical Trial Nurse, the participant will meet with the Principal Investigator, Prof Gillatt, to review the outcomes of his Novoglan treatment and sign the Novoglan-01 Participant Completion section on the Final Study Visit case report form (see details in Section 9).

6.3. Study Procedure Risks

The following risk assessment for the Novoglan-01 study was prepared using Trial Risk Assessment for the NSLHD Investigator-led/Collaborative Group Clinical Trials published by the NSW Department of Health, Version 2.0 dated April 2016 (on file at Platigo Solutions).

Additionally, all measures designed to reduce risks are presented in the ***Novoglan-01 clinical trial Safety Plan*** submitted for review together with the Study Protocol.

- Participant Journey

The participant journey is described above in section 6.2.

- Additional risks with participants' physical integrity and safety

The Novoglan-01 study involves a medical device that is currently listed on the Australian Therapeutics Goods registry under the reference #168962 as a Class 1 (non-sterile) device indicated for the treatment of phimosis in adults. Furthermore, the Novoglan product will be used as per indications in the device TGA listing during the Novoglan-01 clinical trial.

Despite the Novoglan product having been commercialised without any reported adverse event, the Novoglan product safety has never been scientifically analysed and it is therefore reasonable to consider the study risk as Type B or somewhat higher than that of standard of medical care for adult phimosis, the standard of care being either the use of steroid creams or circumcision.

- Safety monitoring of the trial and DSMC

The establishment of a Data Safety and Monitoring Committee (DSMC) is not considered being necessary in view of the Type B risk category of the Novoglan-01 clinical trial and the fact that the Novoglan product will be used as on male adults as per usage instructions described in the listing of the device with the TGA.

- Risks to participants' rights

Risks to participants rights in taking part to the Novoglan-01 study have been assessed and mitigation strategies developed to minimise these risks. The risks evaluated fall into 2 categories and are presented in the following table.

Risks to participants' rights – The consent process		
Risk	**Concerns**	**Risk minimisation strategy**
Consent procedure	Does the consent process allow sufficient time for participants to consider their decision and discuss it with third parties	• Specific training on the consent/assent process will be provided to the clinical team. • First study visit following participant enrolment will be scheduled at least 1 week following the enrollment visit.

Risks to participants' rights – Protection of personal data		
Risk	**Concerns**	**Risk minimisation strategy**
Breach of confidentiality	Identifiable data disclosed inappropriately	• Trial conducted by health professionals experienced in clinical trials and their confidentiality requirements • The safety of the confidentiality of participant data including forms used on paper or electronic will be assessed in the Safety and Confidentiality audit conducted

		prior to trial commencement and described in Section 10.2.

- Risks to data integrity

Risks to participants' rights – Risk to data integrity		
Risk	**Concerns**	**Risk minimisation strategy**
Data integrity	Protocol violations	• Protocol specific training provided at trial start-up meeting • Periodic monitoring visit to include checks of clinical records of eligibility and endpoint data
	Lack of reliability of results and data quality	• Measurements of phimosis, quality of life and treatment tolerability using robust methods and designs • Well-designed and unambiguous case report forms • Data management and transfer methods that ensure an audit trail is maintained from the primary data to the database, and from the database to the analysis files (with changes that are controlled, attributable, and properly authorised

6.4. Participant Recruitment and Screening

The Novoglan-01 Recruitment Plan is attached to this study Protocol and can be summarised as follows.

Target participants for the Novoiglan-01 study are males 18 years and over suffering from phimosis or tight foreskins. The accrual rate aims at 2 to 3 participants per months over the 12 to 18 months course of the study. The participant recruitment for the Novoglan-01 study will rely on the following means of advertising:

- Information Letter to general practitioners in Prof Gillatt's contact database located in greater Sydney. The draft wording of this document is presented in the Novoglan-01 Recruitment Plan.
- Information Letter to urologists in Prof Gillatt's contact database located in greater Sydney. The draft wording of this document is presented in the Novoglan-01 Recruitment Plan.
- Information Notice to the Sydney branch of the Royal Australian College of General Practitioners for advertisement on their website or newsletter. The draft wording of this document is presented in the Novoglan-01 Recruitment Plan.
- Poster advertisement to be placed in specific locations at Macquarie University. The proposed locations and the draft wording of this document is presented in the Novoglan-01 Recruitment Plan.
- Online advertising on the Novoglan website and dedicated Novoglan-01 web page. Details of this advertisement and draft wording of these documents is presented in the Novoglan-01 Recruitment Plan.

The Novoglan-01 Recruitment Plan also describes the logistics of referral processing to Prof Gillatt's secretariat and the participant compensation scheme to cover transport or parking costs.

6.5. Participant Enrolment

Potential participants will be enrolled into the study after the informed consent process has been completed and the participant has been assessed to meet all the inclusion criteria and none of the exclusion criteria and provided full demographics, relevant medical history of phimosis and concomitant medication information. Study participants will receive a study enrolment number and this will be documented in the participant's medical (or personal) record and on all study documents.

Study participants will also be offered to have clinical trial cost travel or parking expenses reimbursed in line with guidelines stated in the ***ICH Harmonised Guidelines for Good Clinical Practice E6(R2)*** dated November 2016.

Once formally enrolled in the Novoglan-01 study and following signature of the ***Participants Information Consent Form*** (attached to this study protocol), a date for the first Novoglan-01 Visit 1 or arrangements on how to schedule Visit 1 will be provided to the enrolled participants.

The scheduling of Study Visit 1 will ensure that this date is at least 1 week after the Enrollment Visit, thus providing sufficient time for participants to consider their informed consent and if need be to withdraw from the study prior to receiving any treatment intervention.

6.6. Information and Consent

Novoglasn-01 study investigators must ensure that participants are clearly and fully informed about the purpose, potential risks, and other critical issues regarding clinical studies in which they volunteer to participate. In situations where consent cannot be given to participants, their legally acceptable representatives are clearly and fully informed about the purpose, potential risks, and other critical issues regarding clinical studies in which the participant volunteers to participate. Participants will be provided with an appropriate sample informed consent form, which will include all elements required by ICH GCP and applicable regulatory requirements. The sample informed consent form adheres to the ethical principles that have their origin in the Declaration of Helsinki. Investigators must:

1) Provide a ***copy of the consent form and written information about the study*** in the language in which the participant is most proficient prior to clinical study participation. The language must be non-technical and easily understood. ***A copy of the Novoglan-01 study Participant Information and Consent Form is attached to this Protocol.***

2) Allow ***time necessary for participant or participant's legally acceptable representative to inquire about the details*** of the study. During the Enrollment Visit and if the participant meets the eligibility criteria, Prof Gillatt will propose participation into the Novoglan-01 study, explain the study, explain the informed consent and review with the participant the informed consent form, pointing out the option of withdrawal at any time and the minimum delay of 1 week between Enrolment Visit and Study Visit 1 to provide sufficient time for careful consent consideration.

3) Obtain an ***informed consent signed and personally dated by the participant***. This will be completed as mentioned above.

4) Obtain ***the IRB/IEC's written approval/favourable opinion*** of the written informed consent form and any other information to be provided to the participants, prior to the beginning of the study, and after any revisions are completed for new information. A copy of the Novoglan-01 study Participant Information and Consent Form will be submitted for review to the Macquarie University Health Research Ethics Committee review.

5) ***Revise the informed consent whenever important new information becomes available*** that is relevant to the participant's consent. The investigator, or a person designated by the investigator, should fully inform the participant, of all pertinent aspects of the study and of any new information relevant to the participant's willingness to continue participation. Any revision to the Novoglan-01 study Participant Information and Consent Form will be carried out if important new information becomes available that is relevant to the participant's consent.

6.7. Randomisation Procedure

The Novoglan-01 study does not require randomisation. It is a single arm, observational, open label, prospective clinical trial on a cohort of 24 participants all undergoing the same treatment with a product listed as a Class 1 device by the Australian Therapeutics Goods Administration for the treatment of adult phimosis.

6.8. End of Study Treatment

At the end of a Novoglan-01 study and during the Final Study Visit, each participant will be:

- Measured for phimosis using the same measuring scale as used during Visit 1
- Surveyed for any adverse effect experienced during the study and not as yet reported
- Surveyed for quality of life using the same questionnaire as used during Visit 1
- Surveyed for tolerability of treatment using a purpose-designed questionnaire

Finally, at the end of each participant Final Study visit, all clinical trial documents related to the participant will be collected and stored in the ***Clinical Trial Master File*** for subsequent analysis and storage as per guidelines from the Australian Clinical Trial Handbook Version 2.0 dated March 2018.

6.9. Participant Withdrawal

The voluntary participant withdrawal during the Novoglan-01 Study Protocol follows the guidelines from the ***National Statement on Ethical Conduct in Human Research*** (2007, updated 2018).

Voluntary withdrawal

Participants enrolled in the Novoglan-01 clinical trial are entitled to withdraw at any stage. Before consenting to be involved in the Novoglan-01 study, participants will be informed about any consequence of such withdrawal. The withdrawal of any participant will be registered by the signature by both the Principal Investigator and the withdrawing Participant of the ***Novoglan-01 – Form for Withdrawal of Participation*** attached to this study protocol. Participants withdrawing prior to visit 1 where investigative product and training is provided will be replaced.

7. OUTCOMES

7.1. Definition of Outcomes

The expected outcomes from the Novoglan-01 study are as follows.

- Confirmation of the ability of the Novoglan product to effectively relieve phimosis as measured by foreskin retraction before and after treatment against the Phimosis Measurement Scale used at Study Visit 1 and Final Study Visit.
- Confirmation of the safety of the Novoglan treatment as evidenced by the lack of any severe adverse effect or any complication during treatment.
- Confirmation of the satisfaction of participants with the Novoglan treatment as measured by improved quality of life measured by questionnaire filled in by the participants before and after treatment.
- Confirmation of the tolerability of the Novoglan treatment as measured by the treatment tolerability questionnaire filled in by the participants during the Final Study Visit.
- Confirmation of the Novoglan treatment as a valid conservative first line treatment alternative to steroid creams in adult males presenting with phimosis.

Additionally, the publication of the Novoglan-01 study results at urology conferences and in a peer review journal is likely to encourage a review of clinical recommendations in the treatment of adult phimosis. Phimosis treatment guidelines published by the British Association of Urological Surgeons (BAUS) discourage the manual stretching of the foreskin and recommend the use of steroid creams or circumcision. The professional guidelines from the BAUS also refer physicians to the guidelines published by the European Association of Urology (EAU) which address phimosis in the section dedicated to paediatric urology.

Assuming a positive outcome from the Novoglan-01 study that demonstrates the safety, efficacy and tolerability of the Novoglan product in adult phimosis, the aim would be to:

- Convince the phimosis treatment guidelines published by the Urology Society of Australian and New Zealand (USANZ), EAU or BAUS to include a section dedicated to the treatment of adult phimosis.
- Convince the phimosis treatment guidelines published by the USANZ, EAU or BAUS to list the Novoglan product as a recommended conservative treatment for adult phimosis

Finally, the publication of the Novoglan-01 study results is likely to position MQ Health as the centre of reference for adult phimosis treatment in Australia. It is also likely to stimulate similar studies in Australia and overseas.

8. STATISTICAL CONSIDERATIONS

Professor David Gillatt in a Note-To-File dated 15 September 2020 has decided to appoint Dr Hassan Doosti as biostatistician to the Novoglan-01 study. The credentials of Dr Doosti as a staff member of Macquarie University will better address the requirement for a highly professional and experienced biostatistical analysis of the Novoglan-01 study results than what Mrs Russell Sia could provide.

In view of the cohort size of 24 participants and in view of the single arm, observational nature of the Novoglan-01 study, it is reasonable to consider the statistical analysis of the Novoglan-01 study as relatively simple. It has been documented by the study biostatistician in a controlled document stored in the Trial Master File and entitled "***Novoglan-01 clinical study – Statistical Plan***". This document is attached to the Novoglan-01 Protocol. The main points of this document are summarised as follows.

8.1. Sample Size or Power Calculation

A power calculation was performed to assess which sample size (N) was appropriate for the Novoglan-01 clinical trial. Calculations show that 29 participants must be recruited to reach N = 24, considering a potential drop-out rate of 20%.

8.2. Detailed Analysis Plan

The Novoglan-01 clinical trial involves the following measurement variables, which will be measured pre- and post-treatment:

Primary outcome variable (ordinal, scalar): Kikiros-inspired phimosis assessment scale (Kikiros, Beasley & Woodward 1993)

Secondary outcome variable (ordinal, scalar): A standardized treatment tolerability questionnaire

Secondary outcome variable (ordinal, scalar): A QoL scale questionnaire

The trial will also involve descriptive variables collected for each patient:

Physical parameters (e.g. age, weight, height – numerical variables)

Medical history (categorical, binary)

Record of Adverse Events (categorical, binary)

Evaluating Patient Descriptive Variables

The recommended analysis plan for the descriptive variables is to use a univariate analysis to contribute to the descriptive statistics of N. From there, tables showing frequency with medians, range, and standard deviations can be generated to describe the population.

Evaluating the Primary and Secondary Outcome Variables

An initial validation of each primary and secondary outcome variable will be applied using the Principal Component Analysis. If this analysis is successful, then each variable will be evaluated in an ordinal regression model (De Leeuw, Mair & Groenen 2017). If the outcome variables are to be evaluated at the same time, then a Multivariate Multinomial Logit Model will be applied (Bel & Paap 2014).

Further tests may be applied to evaluate any distributions and homogeneity within and between descriptive and outcome variables such as a Chi-Squared Test, Linear-by-linear Association Test, or Mann-Whitney U Test.

REFERENCES

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9. DATA COLLECTION

9.1. Participant Registration

Participant registration in the Novoglan-01 study will be documented using the ***Case Report Form*** completed during the Enrolment Visit. Following execution of the Participant Information and Consent Form at the Enrolment Visit, the participant will be allocated a unique participant identifier that will figure in all documents relating to that particular participant and the enrolment will be logged in the Novoglan-01 Participant Enrolment Registry.

9.2. Forms and Procedure for Collecting Data

During the study, all information collected about the Participant will be compiled in an individual Participant Case Report Form Folder (ring binder) containing the Case Report Forms and related documents.

Novoglan-01 Case Report Form Folders will be kept in a dedicated lockable filing cabinet at the study site as part of the Trial Master File.

The Novoglan-01 study data collection forms and documents are listed as follows.

- Novoglan-01 **Clinical Data Management Plan**
- Novoglan-01 **Participant Information and Consent Form** (PICF)
- Novoglan-01 Trial Participant Enrolment Registry included in the Recruitment Plan
- Participant Unique Identifier – Included in Participant Enrolment Registry
- Participant Compensation Log included in the Recruitment Plan
- Potential Participant Contact Registry included in the Recruitment Plan
- Novoglan-01 **Participant Case Report Forms Folder** for all study visits and including the Participant Withdrawal Form
- Novoglan-01 **Clinical Trial Research Agreement** (CTRA)
- Novoglan-01 – **Product Liability Insurance** certificate / cover letter
- Novoglan-01 clinical trial – MQ **Clinical Research Governance** approval
- Novoglan-01 **– HREA form**
- Novoglan-01 MQ Final HREC approval
- Novoglan-01 **Investigator Brochure** (IB)
- Novoglan-01 Investigator Site File (ISF)
- Novoglan-01 **Clinical Trial Protocol**
- Novoglan-01 **IP Manual** with Novoglan User Instructions and Illustrated User Guide
- Novoglan-01 **Recruitment Plan**
- Novoglan-01 **Safety Plan**
- Novoglan-01 **Statistical Plan**
- Novoglan-01 **Clinical Team CV's**
- Novoglan-01 Study Phimosis Measurement Form included in Participant CRF Folder
- Novoglan-01 Study Health-Related Quality of Life Questionnaire included in Participant CRF Folder
- Novoglan-01 Treatment Tolerability Questionnaire included in Participant CRF Folder
- Novoglan-01 **Participant Withdrawal Form** included in Participant CRF Folder

9.3. Case Report Forms and Schedule for Completion

The Case Report Forms to be used during the Novoglan-01 study are contained in the ***Novoglan-01 Participant Case Report Form Folder***. They are listed in Section 9.2 and attached to this protocol. The paper format of all the Case Report Forms and their layout have been designed to facilitate completion of the CRF during each Study Visit by the Principal Investigator and the Clinical Trial Nurse or at most within 2 working days following the Study Visit. All Case Report Forms are to be compiled in the individual Participant Case Report Forms Folder, set up at enrolment for each study participant and based on a blank folder kept in a ring binder in the lockable filing cabinet at the trial site containing the Clinical Trial Master File.

9.4. Data Flow

The Case Report Forms, questionnaires and all other study documents relating to a particular participant will be provided blank and collected once completed in 12 ring binders, each corresponding to a particular participant. Additional ring-binders will be used should

the study cohort exceed 12 participants. These ring binders will be kept in a lockable cabinet at the trial site and constitute part of the Novoglan-01 Trial Master File.

The access to the Study Data is strictly limited to the research team which includes Prof Gillatt and Prof Chung as study investigators, Mr Riley and Mr Bailey as study research nurses, Mrs Barakat and Ms Li as study investigator assistants and Dr Doosti as study biostatistician. On conclusion of the study when 24 participants have been accrued and on advice from Dr Doosti, Mrs Barakat will collate all Participants Folders and transfer the required information from the Case Report Forms into an Excel Novoglan-01 study spreadsheet prepared and communicated to Mrs Barakat by Dr Doosti. To ensure correct transfer of data, Mr Bailey will review the correctness of the data transfer information from the Participant Folders into the Excel Novoglan-01 study spreadsheet. On receipt of the Excel Novoglan-01 study spreadsheet, Dr Doosti will carry out the statistical analysis that concludes the Novoglan-01 study.

10. QUALITY CONTROL AND ASSURANCE

10.1. Control of Data Consistency

The control of data consistency for the Novoglan-01 clinical trial is detailed in the Novoglan-01 **Clinical Data Management Plan**, attached to this Study Protocol, the main sections of which are as follows.

- Investigator Site File (ISF)
- Participant Case Report Form Folders
- Protocol Amendments
- Site Initiation Visit (SIV)
- SIV Training and Training Certificates
- Trial Activation Audit and Monitoring Report
- Trial Master File – Confidentiality, storage and archiving of study data
- Trial Master File – Set-up audit report and trial completion audit report

10.2. Audits

As ***detailed in the Novoglan-01 Clinical Data Management Plan***, the audit schedule for the Novoglan-01 trial is as follows.

- Trial Activation – Audit and Monitoring Report
- Trial Master File Set Up – Audit and Monitoring Report
- Trial Master File at study completion - Audit and Monitoring Report

10.3. Protocol Amendments

As detailed in the Novoglan-01 Clinical Data Management Plan, Protocol Amendments will be recorded, processed and compiled in the Investigator Site File.

11. ETHICS

11.1. Investigator Authorisation Procedure

As an Investigator Initiated Study, a CTN notification will not be required for the Novoglan-01 study. However, a Clinical Trial Research Agreement will be prepared by the parties to this Novoglan-01 Investigator Initiated Study: Macquarie University as the Institution and Platigo Solutions, the supplier of the Novoglan investigational product, as the Organisation. ***An executed copy of the Novoglan-01 CTRA is attached to this Study Protocol.***

In order to comply with the ethical rules applicable in Good Clinical Practice and Macquarie University policies in that matter, the Novoglan-01 study core documentation (Protocol, Investigator Brochure, Participant Information and Consent Form, Clinical Trial Research Agreement, Statistical Plan, Recruitment Plan, Safety Plan, Clinical Trial insurance cover letter and all Case Report Forms with related appendices such as questionnaires) will be submitted successively for review to:

- The Macquarie University Clinical Research Governance for initial review.
- The Macquarie University Clinical Research Governance for final governance authorisation review
- The Macquarie University Human Research Ethics Committee (HREC) for review.

Upon satisfactory completion of these reviews and authorisations to proceed with the Novoglan-01 study by the Macquarie University Human Research Ethics Committee, the Novoglan-01 study will be registered in the Australian government Clinical Trials database and the study will commence its implementation phase.

Additionally, and on the direction of Principal Investigator Professor Gillatt in a Note-To-File dated 15 September 2020, it has been decided that all research team staff at Macquarie University (Professor David Gillatt, Mr Bernard Riley, Mrs Maizie Barakat, Dr Hassan Doosti) and at Princess Alexandra Hospital (Associate Professor Eric Chung, Mr Bill Bailey, Ms Lynette Li) will sign a declaration committing to the unbiased analysis of the study results and the publication of the study results.

11.2. Participant Protection

As Principal Investigator, Professor David Gillatt will ensure that the study is completed in accordance with the guidelines set out in the National Statement on Ethical Conduct in Human Research (2007) (the National Statement) and the CPMP/ICH Note for Guidance on Good Clinical Practice and any other relevant legislation/guidelines.

12. SAFETY

12.1. Adverse Event Reporting

The Novoglan product is a medical device, not a therapeutic product. As such, any adverse event encountered during the Novoglan-01 clinical trial should be recorded and processed as per the ***Therapeutics Goods Administration IRIS Reporting Scheme*** applicable to medical devices and which is detailed in the ***Novoglan-01 Safety Plan*** attached to this Study Protocol.

Devices Adverse Events - Definition

Any undesirable clinical occurrence in a participant whether it is considered to be device related or not, that includes a clinical sign, symptom or condition and/or an observation of an unintended technical performance or performance outcome of the device.[1]

For devices is any adverse medical occurrence that:

- led to a death;
- led to a serious deterioration in health of a participant, including:
  - a life-threatening illness or injury;
  - a permanent impairment of body function or permanent damage to a body
  - structure;
  - a condition requiring hospitalisation or increased length of existing
  - hospitalisation;
  - a condition requiring unnecessary medical or surgical intervention; or
  - foetal distress, foetal death or a congenital abnormality/birth defect;
- might have led to death or a serious deterioration in health had suitable action or intervention not taken place. This includes:

- a malfunction of a device such that it has to be modified or temporarily/permanently taken out of service; or
- a factor deterioration in characteristics or performance) found on examination of the device.

An adverse event or serious adverse reaction can also be any event or experience which compromises the ethical acceptability of the protocol. This can be a non-medical event for clinical trials that are not medical or testing drugs or devices, such as those clinical trials conducted in different fields such as psychology.

12.2. Serious Adverse Event Reporting

Any serious adverse events occurring during the Novoglan-01 study will be recorded and reported as per the ***Therapeutics Goods Administration IRIS Reporting Scheme*** applicable to medical devices and which is detailed in the **Novoglan-01 Safety Plan** attached to this Study Protocol. Any serious adverse event will be immediately reported by the Principal Investigator, Prof Gillatt, to the Macquarie University HREC. The reports should be followed by a detailed written report. Follow-up reports should identify the participant/s by unique code assigned to participants (rather than by name).

[1] Ibid.

12.3. Data Safety and Monitoring Committee (DSMC)

Following advice from the Macquarie University Clinical Research Manager, the Novoglan-01 study will not require the appointment of a DSMC.

12.4. Early Termination

Aside from an injunction from Macquarie University HREC, there are several possible cases where the Novoglan-01 clinical trial could be prematurely terminated, such as:

- Administrative reasons – An organisation with administrative control over the study decided to terminate it.
- Change in practice – Methods or practices have changed in a way that alters the necessity or practicality of the study - Example: Manufacturing change in one of the two types of balloons used in the Novoglan device pack
- Change in study design – The study protocol needs to be altered – Example: Trial suspended pending approval of an amended protocol.
- Enrolment completed – The goal for 12 participants to be recruited has been achieved.
- Resources – Materials or personnel required for the study could not be obtained. – Example: Temporary suspension until resources supply resumes.
- Insufficient enrolment – Not enough participants enrolled in the study – Example: termination due to lack of participant recruitment.
- Key staff departure – A critical member of the clinical team has left the study.
- Non-compliance – Either the participants or the investigators failed to follow the study protocol – Example: Inability to keep participants following the treatment protocol.

In fairness and in view of the commercialisation track record of the Novoglan product, any of these possibilities can be seen as very unlikely. However, if the Novoglan-01 clinical trial needs to be terminated early, then:

- The Sponsor (Macquarie University) and the Macquarie University HREC will be immediately informed of the situation and any planned remediation.
- The participants in the study will be informed of the situation and of any planned remediation.
- If the study cannot resume, the final study report will be compiled.

13. BLINDING AND UNBLINDING

The Novoglan-01 clinical trial is an open label study that does not require blinding.

14. CONFIDENTIALITY AND STORAGE AND ARCHIVING OF STUDY

The confidentiality, storage and ***archiving for a minimum of 15 years*** of the Novoglan-01 study data is detailed in the Novoglan-01 **Clinical Data Management Plan**.

15. TRIAL SPONSORSHIP AND FINANCING

Being an Investigator Initiated study, the Novoglan-01 study is governed by a Clinical Trial Research Agreement (CTRA). An executed copy of the CTRA is attached to the Study Protocol and clearly states the roles and responsibilities of Macquarie University as the Institution and study Sponsor and of Platigo Solutions Pty Ltd as the Organisation supporting financially and in-kind the Novoglan-01 study initiated by Professor David Gillatt.

16. INDEMNITY

As confirmed by Macquarie University Clinical Research Manager, the Novoglan-01 study being an Investigator Initiated Study the sponsor of which being Macquarie University will not require a separate indemnity and will be covered by the general provisions applicable to Investigator Initiated Studies sponsored by Macquarie University.

17. KEY REFERENCES

Kikiros. C.S., Beasley, S.W. & Woodward, A.A. 1993. The response of phimosis to local steroid application. Pediatric Surgery International, Vol. 8, no. 4, pp.329-32

Raj, B.P., Qureshi, A., Kadi, N., & Donat, R. 2013. How painful is adult circumcision? A prospective, observational cohort study. Journal of Urology, vol. 189, no. 6, pp. 2237-42.

18. APPENDICES

The list of all appendices is as follows:

1. Clinical Data Management Plan
2. Clinical Trial Research Agreement executed by Sponsor and Organisation (CTRA)
3. Participant Information and Consent Form (PICF)
4. Investigator Brochure (IB)
5. IP Manual including Novoglan User Instructions and Illustrated User Guide
6. Recruitment plan, including advertisements, participant compensation scheme, participant enrolment registry, potential participant contacts registry and participant compensation log.
7. Statistical plan
8. Safety Plan
9. Clinical team CV's and Disclosure of Financial Interests
10. Participant Case Report Forms Folder including all visit Case Report Forms, as well as phimosis measurement form, health-related quality of life questionnaire, treatment tolerability questionnaire and participant withdrawal form
11. Letter of cover for Novoglan product liability insurance including coverage during the Novoglan-01 clinical study
12. HREA submission form for Novoglan-01 study