

# CLINICAL TRIAL PROTOCOL

## (Phase IV Trial)

### 1. General Information

#### 1.1. Protocol

##### 1.1.1. Title

An Open Label, Single Dose, Bioavailability Study of Topical Transdermal Glucosamine Cream on the Synovial Fluid Tapped from Osteoarthritic Adult, Male and Female Human Subjects already undergoing Arthrocentesis

##### 1.1.2. Protocol Identifying Number: ASC/CPROJ/14/15/16 (as approved by the IRB)

##### 1.1.3. Protocol date: 21 AUG 2015

#### 1.2. Sponsor

##### 1.2.1. Name: Lynk Biotechnologies Pte Ltd

##### 1.2.2. Address

48 Lorong 21 Geylang, Greatland Building #03-01 Singapore 388464

##### 1.2.3. Authorized person to sign the protocol

Dr Tan Boon Tiong, Executive Director.

#### 1.3. Principal Investigator / Qualified physician / Sponsor's medical expert

##### 1.3.1. Name: Dr Ting Choon Meng

##### 1.3.2. Title: Medical Doctor

##### 1.3.3. Address of the trial site

T&T Family Health Clinic and Surgery. 181 Kitchener Road, #01-32 to 39 New Park Shopping Arcade, Singapore 208533.

##### 1.3.4. Telephone number of the trial site: 6293-4071

#### 1.4. Other institutions involved

##### 1.4.1. Name: Temasek Analytical Services Facility

##### 1.4.2. Address

Temasek Polytechnic, School of Applied Sciences. 21 Tampines Avenue 1, Singapore 529757.

##### 1.4.3. Role

Independent lab accredited by SAC-Singlas. They will carry out the analysis of glucosamine in the synovial fluid.

## 2. **Background Information**

### 2.1. Investigational product / Test product

#### 2.1.1. Name and description

Topical Glucosamine cream, Lynk Biotechnologies Pte Ltd, TGC® Transdermal Glucosamine Cream Plus Capsaicin containing 10% w/w Glucosamine Sulphate.2 KCl, presented as a finished product.

#### 2.1.2. Manufactured by DynaLynk Pharma Pte Ltd (GMP certified).

### 2.2. Findings from non-clinical studies and clinical trials that are relevant to the trial.

Osteoarthritis (OA) is the most common form of arthritis which affects 9.6% of men and 18% of women over 60 years old worldwide <sup>[1,2]</sup>. OA is a degenerative disease which causes inflammation of the joints with thinning of the articular cartilage. The cartilage in our joints allows for the smooth movement of joints. When it becomes damaged due to injury, infection or gradual effects of ageing, joints movement is hindered. As a result, the tissues within the joint become irritated causing pain and swelling within the joint <sup>[1]</sup>.

Glucosamine is commonly used as a treatment for OA and is commonly available over the counter in local pharmacies without a doctor's prescription <sup>[1]</sup>. OA patients who have failed to respond to analgesics and non-pharmacologic measures and want to try glucosamine may be given glucosamine sulphate 1500 mg once daily as pharmacologic studies suggest that maximal benefit is better achieved at this dose <sup>[3]</sup>.

The use of glucosamine for the treatment of Osteoarthritis (OA) has been extensively studied and numerous reports and notable reviews were published in recent years <sup>[4-6]</sup>. Glucosamine is known to have beneficial effects on joint functions by acting as a precursor in the production of glycosaminoglycans, a major component in the cartilage <sup>[7]</sup>. A 3 year randomized placebo controlled double blind study on 202 patients reported a retardation of knee OA <sup>[8]</sup>. A more recent study by Selvan et al. comparing the efficacy of glucosamine with a combination of glucosamine and nonsteroidal anti-inflammatory drugs revealed that both groups have significant improvement in pain, stiffness and physical function <sup>[9]</sup>.

While oral dosage of glucosamine has been well established, drug developers are turning to transdermal drug delivery technology, as a way to overcome the negative effects of the passage of the drug through the digestive system <sup>[7,10]</sup>. Transdermal delivery can combine the advantages of IV infusion with the convenience of oral administration.

Traditional studies measured the glucosamine level in blood plasma to predict the efficacy of glucosamine for the treatment of OA. The major shortcoming of this approach is that we have no certainty that the glucosamine is actually delivered to the affected areas that need it. Glucosamine is one of the important basic natural components of cartilage and synovial fluid <sup>[11]</sup>. It is believed that glucosamine may help to stop cartilage breakdown, build cartilage and decrease swelling of the OA joints <sup>[9]</sup>.

Unpublished clinical data from Lynk Biotechnologies Pte Ltd studies show that:

- Transdermal Glucosamine Cream (TGC) can deliver glucosamine transdermally in mice. The study demonstrated that the plasma concentration of glucosamine is dose dependent <sup>[12]</sup>.
- TGC has shown superiority over the placebo cream, for the treatment of knee osteoarthritis. Significant reduction in pain and increase in mobility was observed after 3 weeks of drug application <sup>[13]</sup>.

- TGC can deliver glucosamine transdermally into horses' blood and synovial fluid<sup>[14]</sup>.

The present study is conducted to assess the bioavailability of glucosamine in the synovial fluid of OA joints, following topical application of a transdermal glucosamine cream.

To our knowledge this is the first study describing the bioavailability of glucosamine in human synovial fluid following the application of a topical cream.

### 2.3. Summary of the known and potential risks and benefits, if any, to human subjects.

OA patients with swollen knees will normally seek treatment for pain relief by having the synovial fluid extracted (tapped) from the diseased knee by the Clinician. This procedure is independent from the clinical trial. The Clinician will collect as much as synovial fluid as he would have done in a non-clinical trial situation, in order to reduce swelling and relieve the patient from pain. Volume collected will vary depending on the patient's medical condition (typically 5 to 50ml of synovial fluid will be collected).

This trial synchronizes the application of the Test product with the above procedure so that no additional invasive clinical intervention is needed to determine the bioavailability of glucosamine in the synovial fluid.

Therefore the only additional risk brought about by this trial is the risk associated with topical application of the Test product. Based on the history of usage of the Test product over the last 10 years with over 250,000 tubes sold OTC, the only adverse effect reported by the consumers relates to minor rashes over prolonged usage. Less than 10 complaints of this nature have been received over this period.

No health related benefits is being promoted for a single application of the Test product.

### 2.4. Description of and justification for the route of administration, dosage, dosage regimen, and treatment period(s)

#### 2.4.1. Dosage form: topical cream

#### 2.4.2. Dose

Single dose of 2g of the Test Product containing 200mg of Glucosamine Sulphate. 2KCl

#### 2.4.3. Rationale of Dose

2g of Test product contains 200mg of Glucosamine Sulphate.2 KCl which is in the order of magnitude of the usual dosage for oral glucosamine (500mg or 1g). As the knee surface area is limited any dosage of Test product above 2g is not practical for topical application.

#### 2.4.4. Justification for the route of administration

While oral dosage of glucosamine has been well established, drug developers are turning to transdermal drug delivery technology, as a way to overcome the negative effects of the passage of the drug through the digestive system<sup>[7,10]</sup>. Transdermal delivery can combine the advantages of IV infusion with the convenience of oral administration.

### 2.5. A statement that the trial will be conducted in compliance with the protocol, GCP and the applicable regulatory requirement(s).

This Clinical Trial will be conducted in compliance with Singapore guidelines for Good Clinical Practice (GCP) and in compliance with this protocol. The protocol has been reviewed and approved by Temasek Polytechnic Institutional Review Board (IRB).

## 2.6. Description of the population to be studied.

Osteoarthritic adult male and female patients (21 to 80 years old) fulfilling the inclusion and none of the exclusion criteria (refer to section 5) will be enrolled for this study. **Subjects are recruited from patients who are already seeking arthrocentesis treatment (synovial fluid aspiration) for Osteoarthritis (OA) at the clinic on their own accord.**

Patients diagnosis of Osteoarthritis is based on standard protocol which includes detailed medical history, blood test if necessary, to exclude other causes like RA, gout etc. and confirmed on standing view X Ray findings. Patients will also be graded (stages of OA) based on that X Rays as well. Only those with primary OA will be included. **Diagnosis would be determined during prior appointment(s) with the clinician.**

Evidence of effusion is determined by manual palpation of the knees directly. There is no need to use ultrasound scan to determine the presence of effusion. Basically, if it can be “felt”, it can be tapped.

- Test Group: 120 subjects regardless of gender (Test product topically applied prior to arthrocentesis)
- Control group: 120 subjects regardless of gender (no Test product applied)

## 2.7. References

- [1] Singhealth. Conditions and Treatments of Osteoarthritis. Retrieved March 24, 2015, from: <http://www.singhealth.com.sg/PatientCare/ConditionsAndTreatments/Pages/Osteoarthritis-knee-pain.aspx>
- [2] World Health Organisation (WHO). Chronic rheumatic conditions. Retrieved March 24, 2015, from <http://www.who.int/chp/topics/rheumatic/en>
- [3] Ministry Of Health (MOH), Singapore (May 2007) Osteoarthritis of the knees. Clinical Practice Guidelines 4/2007.
- [4] Reginster JY, Neuprez A, Lecart MP, Sarlet N, Bruyere O (2012) Role of glucosamine in the treatment for osteoarthritis. *Rheumatol Int* 32:2959-2967.
- [5] Towheed TE, Anastassiades T (2007) Glucosamine therapy for osteoarthritis: An update. *J Rheumatol* 34: 1787-1790
- [6] Towheed TE, Maxwell L, Anastassiades TP, Shea B, Houpt JB, Welch V, Hochberg MC, Wells GA (2005) Glucosamine therapy for treating osteoarthritis. *Cochrane Database Syst Rev* 2: CD002946
- [7] Lavery S, Sandy JD, Celeste C, Vachon P, Marier JF, Plaas AHK (2005) Synovial Fluid Levels and Serum Pharmacokinetics in a Large Animal Model Following Treatment With Oral Glucosamine at Clinically Relevant Doses. *Arthritis Rheum* 52:181-191
- [8] Pavelka, K., Gatterova, J., Olejarova, M., Machacek, S., Giacobelli, G., and Rovati, L. C. (2002). Glucosamine Sulfate Use and Delay of Progression of Knee Osteoarthritis.

- [9] Selvan, T., Rajiah, K., Nainar, S., Mathew, E. M. (2012). A Clinical Study on Glucosamine Sulfate versus Combination of Glucosamine Sulfate and NSAIDs in Mild to Moderate Knee Osteoarthritis. *The Scientific World Journal vol 2012*.
- [10] Anderson JW, Nicolosi RJ, Borzelleca JF (2005) Glucosamine effects in humans: a review of effects on glucose metabolism, side effects, safety considerations and efficacy. *Food and Chemical Toxicology* 43: 187-201
- [11] Jorg Jerosch (2011) Effects of Glucosamine and Chondroitin Sulfate on Cartilage Metabolism in OA: Outlook on Other Nutrient Partners Especially Omega-3 Fatty Acids. *International Journal of Rheumatology Volume 2011, Article ID 969012, 17 pages*
- [12] Evaluation of the dose dependency and stability of the Transdermal Property of Lynk Biotechnologies TGC® (Transdermal Glucosamine Cream) – Lynk Biotechnologies Pte Ltd internal document. Effective date: 30 July 2014
- [13] Bambang Setyohadi (2008) Efficacy and Safety Study of Medilynk TGC® Transdermal Glucosamine Cream in Management of Osteoarthritis of knee in Man. Hospital, Jakarta, Indonesia.
- [14] Summary on TGC Animal Studies Using Horses (2007) – Lynk Biotechnologies Pte Ltd internal document.

### 3. **Trial Objectives and Purpose**

#### 3.1. Hypothesis

The Test product, a topical transdermal glucosamine cream (TGC® Transdermal Glucosamine Cream Plus Capsaicin, Lynk Biotechnologies Pte Ltd) is able to deliver glucosamine, through the skin, to the synovial fluid of osteoarthritic (OA) joints.

#### 3.2. Objective

To assess the bioavailability of the Test product: a topical transdermal glucosamine cream (TGC® Transdermal Glucosamine Cream Plus Capsaicin, Lynk Biotechnologies Pte Ltd containing 10% w/w Glucosamine Sulphate.2KCl presented as a finished product) in the synovial fluid of OA joints.

#### 3.3. Purpose / Importance of the research

Glucosamine is commonly administered orally to human patients in the form of tablets or capsules with a recommended dosage of 20mg/kg/day <sup>[7]</sup>. As some patients are not able to swallow these solid dosages, and due to the potential issues in drug absorption in the gastro-intestinal tract and in the first-pass effect of the liver <sup>[7, 10]</sup>, this transdermal drug delivery technology can offer an alternative route to deliver glucosamine.

Another advantage of this technology is that it offers a targeted approach; glucosamine can be delivered to the area where it is the most needed for the patient. Lastly the study will allow us to establish a baseline for the endogenous glucosamine concentration in the synovial fluid of diseased knee in OA joints.

### 4. **Trial design**

- 4.1. A specific statement of the primary endpoints and the secondary endpoints, if any, to be measured during the trial.

4.1.1. Primary endpoints

To show that the level of glucosamine in synovial fluid has statistically increased after the Test product topical application.

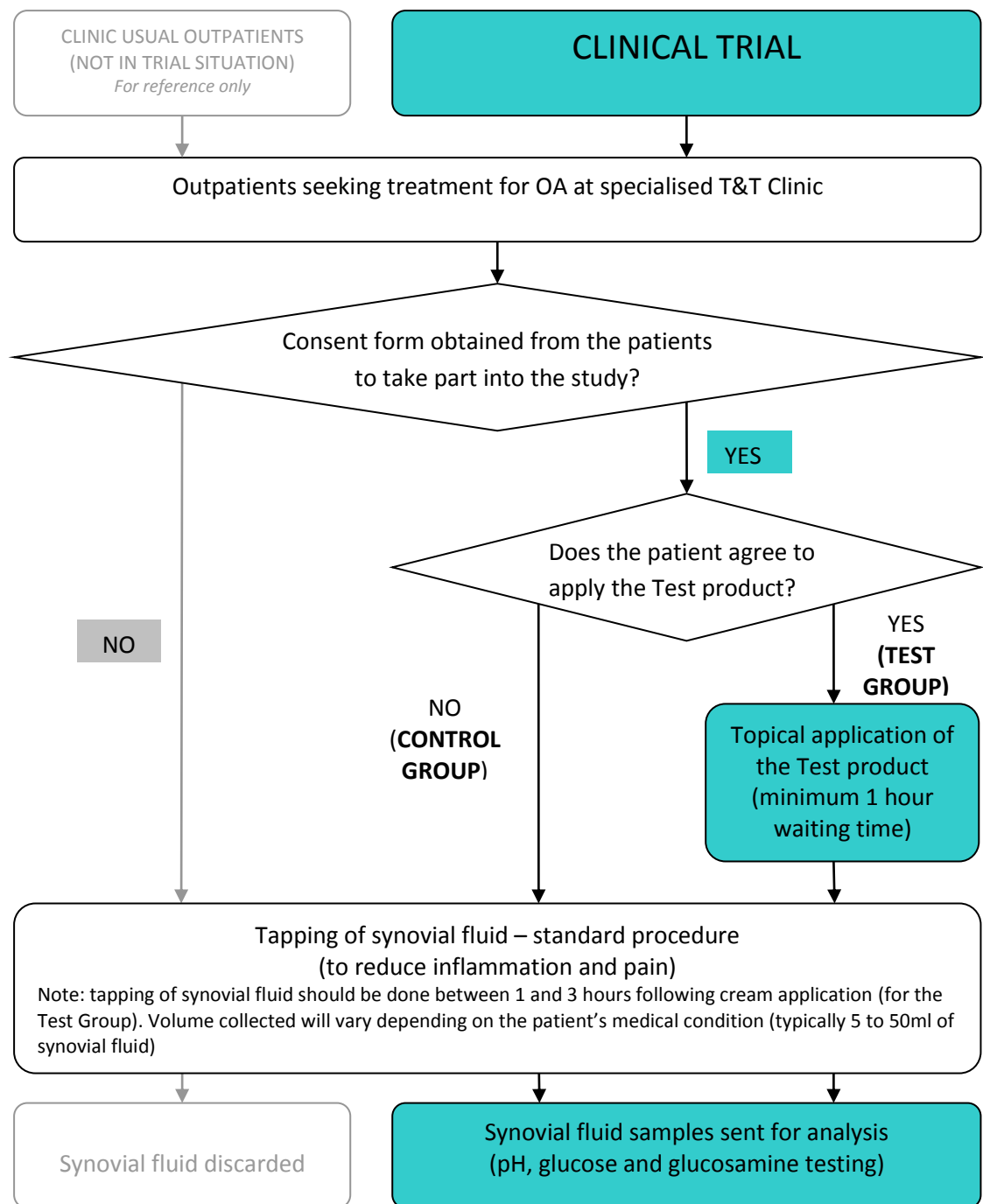
4.1.2. Secondary endpoints

To determine the endogeneous level of glucosamine in synovial fluid and establish a baseline for OA joints.

4.2. Trial design

This is an open label, single dose design to examine the glucosamine content in the synovial fluid after applying the Test product on OA patient's knee.

4.3. Procedure flowchart:



#### 4.4. A description of the measures taken to minimise / avoid bias, including randomisation / blinding:

The analytical results are objective. There is no possibility of subjective bias or placebo effect. Therefore there is no measure necessary and hence no randomization needed.

As for the selection of subjects, there is no need to have measures to minimise bias. There is no bias since we take all patients that come in to the clinic for treatment. Patients are not selected for control or test group, they select themselves by choosing (yes or no) to apply the Test product.

- 4.5. A description of the trial treatment(s) and the dosage and dosage regimen of the investigational product(s). This also includes description of the dosage form, packaging, and labelling of the investigational product(s).

A single dose of 2g of the Test product will be applied topically on the affected knee of the Test Group subjects. The Test product is presented in a white tub, labelled with the product name, Batch Number and Expiry date.

- 4.6. The expected duration of subject participation, and a description of the sequence and duration of all trial periods, including follow-up, if any.

Single session, up to 4 hours, for the cream application and joint's fluid aspiration. The tapping of synovial fluid should be done between 1 and 3 hours following cream application (for the Test group). No follow-up needed.

- 4.7. A description of the "stopping rules" or "discontinuation criteria" for individual subjects, parts of trial and entire trial.

Subjects participation may be terminated if:

- Allergy occurs after cream application and before tapping of synovial fluid
- Non-compliance to any of the exclusion/inclusion criteria

Subjects are free to withdraw at any time, without giving a reason. This will not affect the standard of care they receive.

- 4.8. Accountability procedures for the investigational product(s), including the placebo(s) and comparator(s), if any.

There is no risk of any mix up since there is no comparator or placebo arm in this study.

- 4.9. Maintenance of trial treatment randomisation codes and procedures for breaking codes.

The subjects will be identified via subject ID, a 3 digits number (e.g: 123). Samples will be labelled with the subject ID.

Personal information will be treated as confidential and accessible only to the investigators of this study.

Scientific analysis and testing will be carried out first before revelation of codes.

- 4.10. The identification of any data to be recorded directly on the CRFs (i.e. no prior written or electronic record of data), and to be considered to be source data.

To refer to the Data Record Form attached. Gender and age may be used for sub-group analysis.

## **5. Selection and Withdrawal of Subjects**

### **5.1. Subject inclusion criteria**

- 5.1.1. Male and non pregnant female human subjects
- 5.1.2. 21 to 80 years old
- 5.1.3. Subjects who need to undergo arthrocentesis following medical assessment by the Clinician:  
Patients diagnosis of Osteoarthritis is based on standard protocol which includes detailed medical history, blood test if necessary, to exclude other causes like RA, gout etc. and confirmed on standing view X Ray findings.

Patients will also be graded (stages of OA) based on that X Rays as well. Only those with primary OA will be included. Diagnosis would be determined during prior appointment(s) with the clinician.

Evidence of effusion is determined by manual palpation of the knees directly. There is no need to use ultrasound scan to determine the presence of effusion. Basically, if it can be “felt”, it can be tapped.

- 5.1.4. Willingness to follow the protocol requirements

## 5.2. Subject exclusion criteria

- 5.2.1. Known allergy to shellfish
- 5.2.2. Known history of hypersensitivity to Glucosamine or related drugs.
- 5.2.3. Known history of hypersensitivity to Capsaicin (Capsicum extract)
- 5.2.4. Known history of skin sensitivity
- 5.2.5. Subjects who have taken any kind of glucosamine during the last 24 hours
- 5.2.6. Subjects who have taken any kind of treatment for joint pain during the last 24 hours
- 5.2.7. Subjects having scars/cut/dermatological abnormality at application site
- 5.2.8. Pregnant or nursing women

## 5.3. Subject withdrawal criteria

Subjects are free to withdraw at any time, without giving a reason. This will not affect the standard of care they receive.

## 6. Treatment of Subjects

### 6.1. The treatment to be administered

- 6.1.1. Name: Topical Glucosamine cream, Lynk Biotechnologies Pte Ltd, TGC® Transdermal Glucosamine Cream Plus Capsaicin containing 10% w/w Glucosamine Sulphate.2 KCl, presented as a finished product.
- 6.1.2. Manufactured by DynaLynk Pharma Pte Ltd. GMP certified.
- 6.1.3. Dose: A single dose of 2g (containing 200mg of Glucosamine Sulphate. 2KCl) of the Test product will be applied topically on the knee of the subjects (for Test Group only).
- 6.1.4. Dosing schedule: single dose for subjects of the Test group only. Subjects from the Control Group will not receive any treatment.
- 6.1.5. Route / mode(s) of administration: topical application on the affected knee
- 6.1.6. Follow-up – Not applicable

### 6.2. Medication(s) / treatment(s) permitted (including rescue medication) and not permitted before and/or during the trial.

Please refer to the exclusion criteria in section 5.2. There is no rescue medication needed.

### 6.3. Procedures for monitoring subject compliance.

There is no need to monitor the patient's compliance since the Test product (single dose) will be applied by the nurse on the trial site and the extraction of the synovial fluid will be done by the PI.

## 7. **Assessment of Efficacy**

There is no efficacy being promoted with a single dose application of the Test product. The objective of the study is to assess the bioavailability of the Test product: in the synovial fluid of OA joints.

## 8. **Assessment of Safety**

Based on the history of usage of the Test product over the last 10 years with over 250,000 tubes sold, the only adverse effect reported by the consumers relates to minor rashes. Less than 10 complaints of this nature have been received over this period. Adverse side effects related to the Test product topical application are extremely rare.

The emergency number to call when required is 62934071 (T&T FAMILY HEALTH CLINIC & SURGERY) or 67451550 (Lynk Biotechnologies' main line). Subjects may also contact Temasek Polytechnic IRB for any questions. IRB contact number is: 67804002. These contact numbers are given to each subject in the Informed Consent Form.

Adverse events will be recorded in adverse event form or appropriate documents. We will report to Temasek Polytechnic IRB, within 7 calendar days, the occurrence of any serious adverse events, adverse drug reactions and unanticipated episodes that may occur in the course of this research.

All serious adverse events (SAEs) that are unexpected and related to the Test product will be reported to HSA. The investigator is responsible for informing HSA no later than 15 calendar days after first knowledge that the case qualifies for expedited reporting. For fatal or life-threatening cases, HSA will be notified as soon as possible but no later than 7 calendar days after first knowledge that a case qualifies, followed by a complete report within 8 additional calendar days.

All reports will be sent to the Clinical Trial Branches (HSA), and other official parties requiring them (e.g: IRB).

The PI will take all appropriate measures to ensure the safety of the patients, including referral to a specialist if indicated.

## 9. **Statistics**

9.1. A description of the statistical methods to be employed, including timing of any planned interim analysis(es), and the level of significance to be used.

Statistical analysis will be performed using a one-sided Z-test, which will be used to determine if the glucosamine content in synovial fluid obtained from the Test group is significantly higher than the glucosamine content in synovial fluid obtained from the Control group. The statistical evaluation will be determined at  $P < 0.01$ .

9.2. The number of subjects planned to be enrolled. In multicentre trials, the numbers of enrolled subjects projected for each trial site should be specified. Reason for choice of sample size, including reflections on (or calculations of) the power of the trial and clinical justification.

A total of 240 osteoarthritic adult male and female patients (120 for the Test group, and 120 for the Control group) will be enrolled in this study. It is assumed that under single dose and with this study design the planned number of subjects is sufficient to achieve the objective of the study.

The sample sizes are sufficient to assume normality while generating a meaningful statistical comparison using the Z-test.

This trial relies on the scientific analysis of the synovial fluid collected, from patients. Therefore it eliminates patient's subjectivity and bias. Hence the trial sample size could be correspondingly reduced.

All eligible subjects will be included in the analyses.

#### 9.3. Criteria for the termination of the trial.

Subjects participation may be terminated if:

- Allergy occurs after cream application and before tapping of synovial fluid
- Non-compliance to any of the exclusion/inclusion criteria

Subjects are free to withdraw at any time, without giving a reason. This will not affect the standard of care they receive.

#### 9.4. Procedure for accounting for missing, unused, and spurious data.

Using glucosamine concentrations ascertained from the standard addition method, the mean absolute deviation method will be used to eliminate outliers. In addition, non-linear results, with  $r^2 < 0.95$ , will also be discarded. Data from outliers will be excluded from main analysis.

Missing, unused or spurious data: not applicable in this protocol.

#### 9.5. Procedures for reporting any deviation(s) from the original statistical plan (any deviation(s) from the original statistical plan should be described and justified in protocol and/or in the final report, as appropriate).

Any deviation, if any, will be described in the final report.

#### 9.6. The selection of subjects to be included in the analyses (e.g. all randomised subjects, all dosed subjects, all eligible subjects, evaluable subjects).

All subjects that go for treatment and sign consent form will be part of the study. All samples collected will be analysed.

### **10. Direct Access to Source Data / Documents**

For the purpose of ensuring compliance with the Clinical Trial Protocol, Good Clinical Practice and applicable regulatory requirements, the Investigator should permit auditing by or on the behalf of the Sponsor and inspection by applicable regulatory authorities.

The Investigator agrees to allow the auditors/inspectors to have direct access to his/her study records for review, being understood that these personnel are bound by professional secrecy, and as such will not disclose any personal identity or personal medical information.

The Investigator will make every effort to help with the performance of the audits and inspections, giving access to all necessary facilities, data, and documents.

As soon as the Investigator is notified of a future inspection by the authorities, he will inform the Sponsor and authorize the Sponsor to participate in this inspection.

The confidentiality of the data verified and the protection of the patients should be respected during these inspections.

Any result and information arising from the inspections by the regulatory authorities will be immediately communicated by the Investigator to the Sponsor.

The Investigator shall take appropriate measures required by the Sponsor to take corrective actions for all problems found during the audit or inspections.

#### **11. Quality Control and Quality Assurance**

The Quality Assurance department will confirm that the study is conducted in adherence to the protocol for each activity.

In process quality checks and review procedures carried out by the quality assurance department will ensure that the activities and the documentation of the data are done as per the protocol. Deviation from the protocol observed during the quality checks/review will be verified.

#### **12. Ethics**

The protocol was reviewed and approved by Temasek Polytechnic IRB. The approval letter is attached in Annex 9.

All the subjects participating in this study will receive full details about the study, the procedures, the risks and the treatment involved by verbal and written form in the Informed Consent Form (Annex 3). Subjects need to sign the Informed Consent Form to confirm their informed agreement to undergo the study.

Remuneration of subjects:

The subjects are already presenting themselves at T&T Family Health Clinic & Surgery for OA treatment.

The subjects who completed the study and agreed to apply the Test product will be adequately compensated. Arthrocentesis cost will be offered free (value \$100 per patient – not per sample).

Patients who do not wish to apply the Test product, but who signed the consent form (i.e Control group) so that their samples can be used for scientific research will be offered a free 45g tube of the Test product.

There is no added inconvenience or impost on them besides the application of a cream on the affected knee. Therefore, the reimbursement is fair and reasonable.

#### **13. Data Handling and Record Keeping**

13.1. The holder of the certificate will keep adequate clinical records of each subject for the duration of the clinical trial.

13.2. The holder of the certificate will ensure that such records are:

13.2.1. Kept up to date at all times;

13.2.2. Available at all times for inspection by the licensing authority or any person authorised by him in that behalf; and

13.2.3. Kept at least for whichever of the following periods expires later:

- until there are no pending or contemplated marketing applications of the Test product in Singapore;
- 2 years after the last approval of a marketing application for the test material in Singapore;
- where the clinical trial is discontinued, 2 years after the licensing authority has been informed of the discontinuation of the clinical trial under regulation 9;
- 6 years after the completion of the clinical trial; or
- such other period as the licensing authority may direct.

13.3. The holder of the certificate will maintain a record containing the names and such other particulars of every person assisting or participating in a clinical trial.

#### **14. Financing and Insurance**

14.1. Source of funding for the study: the Sponsor.

14.2. Insurance

Based on the history of usage of the Test product over the last 10 years with over 250,000 tubes sold, the only adverse effect reported by the consumers relates to minor rashes. Less than 10 complaints of this nature have been received over this period. Adverse side effects related to the Test product topical application are extremely rare.

The emergency number to call when required is 62934071 (T&T FAMILY HEALTH CLINIC & SURGERY) or 67451550 (Lynk Biotechnologies' main line).

The risk related to the joint's fluid aspiration procedure is covered by T&T FAMILY HEALTH CLINIC & SURGERY.

The Sponsor has a Product Liability Insurance (\$ 1.5 million) for the TGC product used for the trial. This insurance would cover the users for this trial and the trial users would be compensated in the very unlikely event of injury or loss.

#### **15. Publication Policy**

Publication of the results is at the sole discretion of the study Sponsor.