PROPOSAL FOR

CLINICAL EVALUATION OF AN INVESTIGATIONAL DRUG IN THE MANAGEMENT OF KALAANJAKAPADAI

CLINICAL PROTOCOL: SUMMARY INFORMATION

Title:

Clinical Evaluation of an investigational drug in the Management of Kalaanjakapadai.

Phase of clinical investigation **:**Phase- 3

Investigational drug(s) **:**xxx

Sponsor **:**Central Council for Research in Siddha

Authorized Signatories **:**

Trial centres **: CCRS, Peripheral Institutes**

Investigators:

Clinical Laboratory(ies), Technical Department(s) and Institution(s) providing Clinical Study Service:

Pathology – Head of the Department.

Bio- chemistry- Head of the Department.

Phamacognosy- Head of the Department.

Pharmacology- Head of the Department.

Chemistry- Head of the Department.

1. INTRODUCTION

1.1 Background

Psoriasis is one of the most prevalent auto-immune diseases. It is a common chronic non-infectious skin disease said to be idiopathic, according to modern medicine. According to current studies as many as 7.5 million Americans have psoriasis. 125 million people worldwide – 2-3% of total population[1]have psoriasis, according to World Psoriasis Day Consortium. Psoriasis is not a cosmetic problem. Nearly 60% of people with psoriasis reported the disease to be a large problem in their everyday life[2]. Patients with moderate to severe psoriasis have experienced a greater negative impact on their quality of life[3].

Psoriasis often appears between the ages of 15 and 25, but can develop at any age. About 1 out of 3 people with psoriasis report having a relative with psoriasis. If a patient has psoriasis his / her child has about 10% chance of getting psoriasis. If both parents have psoriasis, a child has approximately 50% chance of developing the disease.

In Psoriasis, the main abnormality is increased epidermal proliferation due to excessive multiplication of cells in the basal layers. The transit time of keratinosite is shortened and epidermal turnover is reduced from 28 to 34 days. Even though the etiology is unknown, the factors involved are genetic, biochemical, immunopathological and dermal. These factors may not be fully sufficient to develop psoriasis. Precipitating factors like trauma, infections, sunlight, some drugs and emotions may cause flare - up of the disease. There are different types of psoriasis like stable plaque psoriasis, guttate psoriasis, erythrodermic psoriasis, pustular psoriasis. Of these, stable plaque psoriasis will produce dry silvery white scales. The elbow, knee, lower back are commonly involved areas and other sites include scalp, nails, flexures, palms and napkin areas. Psoriasis is a chronic inflammatory disease of the skin with red raised lesions characterized by severe itching, dryness of the skin and white silvery scales. It is a non infectious disease which may go into remission for years. In Siddha System of Medicine, the symptoms of psoriasis may be correlated to *Kalaanjaga vatham*[4]and *Eka sarma kuttam (Gaja kuttam)* [4]. It is a form of vitiated Vatham and Kapham. In practice, psoriasis is termed as *Kalaanjagapadai* among the Siddha community.

காளாஞ்சகம்

மாதமாங் கால்கையில் குரங்கு ரண்டும்
வகுத்துசந்து முறுக்கியே குடைந்து நொந்து
நாதமா நடைதானுந் தான்கொ டாம
நலிந்துமே முடமாகிக் கரடு கட்டிச்
சேதமாஞ் சடந்தானு மிகவெளுத்துத்
தினவோடு சிரங்குமாய்ச் சேட்ப மாகிக்
காதமா யருசியொடு மயக்க மாகும்
கருதிய காளாஞ்சகமாம் வாத மாமே.

- Verse 259, Yugi Vaithiya Chintamani

The above verse explains about the clinical manifestations in Kalaanjaga Vatham, one of the 80 Vatha diseases mentioned in the ancient Siddha text, Yugi Vaithiya Chintamani. The main features include pain in the limbs, pallor of skin, severe itching with rashes and anorexia.

கஜ குட்டம் (அ) ஏகசர்ம குட்டம்

தானாகச் சடந்தானு மிகக்கறுப்பாம்
சடமெங்குந் தோலுரியுஞ் சிவப்பு மாகும்
வேனான வெறவெறனத் தானிழுக்கும்
வெடிக்குமே சொரிச்சலாய் தினவுண்டாகும்
கானாகச் சர்மகுட்ட மிதிலுண்டாகும்
கடினமாய்க் கால்விரல்கள் கனப்புண்டாகும்
கூனாகத் தேகமெங்கும் வலியெடுக்கும்
குறியான ஏகசர்ம குட்டந்தானே.

- Verse 500, Yugi Vaithiya Chintamani

The above verse describes the clinical features of Kaja Kuttam (Ekasarma Kuttam), one of the 18 types of Kuttam. Blackening of the skin, shedding of layers of skin, reddishness, itching, pain in joints and all over the body are the main features of this skin disorder.

The symptoms of the above discussed disease conditions simulate those of Psoriasis.

Rationale:

Earlier study [5]on 777oil has shown that it helps in postponing the subsequent attacks. Even when there is recurrence the severity and extent of the lesion is very much minimised. The aim of the study is to evaluate the efficacy of the selected investigational drug and compare its action with 777 Oil as control.

2. Clinical Study Objectives:

2.1 Primary objective:

To evaluate the efficacy of an investigational drug (External application) in Kalaanjakapadai.

2.2 Secondary objective:

To evaluate the effect of the drug in reducing the recurrence of psoriasis in comparison with 777 Oil as Control.

3. Study Design:

Multi Centric Open Randomized Control Trial.

Duration of study: 60 days.

3.1 Allocation to treatment:

Proposed study involves 2 arms i.e. Test group and Control group. 20 patients will be recruited in each group in simple randomization method.

4. Subject Selection:

The trial subjects will be recruited from the patients visiting the peripheral Institutes of CCRS as per the inclusion and exclusion criteria.

4.1 Subject inclusion criteria

- Age between 15-60 years of either sex
- Duration of the disease below 10 years
- Well defined non-indurated dry erythematus with silvery scales
- Auspitz sign
- Koebner's phenomenon

4.2 Subject exclusion criteria

- Pustular psoriasis
- Infection – parasitic / bacterial / fungal
- Eczema
- Metabolic disorders
- Associated renal / CVS/RS involvement
- Malignancy
- Skin manifestation of syphilis
- Pregnant and lactating mothers

1. Study Drug(s):

Investigational drug (External application) – Trial group
777 – Oil (External application) – Control group

5.1 Study drug compliance/adherence

- The investigational drug should be given in the form of oil in plastic containers.
- The outpatients are advised to come back for review with the drug compliance form and bring the empty oil containers. For in-patients record will be maintained by the Institute.

5.1.1 Withdrawal of subjects due to non-compliance/ adherence

During the course of treatment, if any serious condition or any serious adverse reactions occur or if the subject volunteers to withdraw from the study, he/she will be withdrawn from the study.

5.2 Study drug supplies

Drugs may be supplied by the Pharmacy of SCRI, Chennai, CCRS

5.2.1 Formulation and packaging

The oil will be packed in plastic containers.

5.2.2 Preparing and dispensing

The investigational drug will be prepared in the SCRI pharmacy and dispensed by investigators.

1.2.3 Drug administration: External application.

2. Research Study Procedures:

- Selecting the Research subjects as per inclusion and exclusion criteria.
- Obtaining patient informed consent form.
- Recruiting the subjects.

6.1 Screening procedures:

As mentioned in the Proforma -CRF- Screening

6.2 Study drug procedures:

The investigational drug will be prepared in the SCRI pharmacy and dispensed through OPD/IPD for fifteen days. The recruited subject will be reviewed once in every 15 days during the study period of sixty days. Follow-up will be done in the 1st and 2nd month after stopping the medicine.

6.3 Schedule of activities (Study Table):

1	**Screening**	0th day
2	**Recruitment date**	1st day
3	**Treatment period**	60 days
3	**Follow up**	1st and 2nd month after stopping the medicine

7. Assessment of Safety and Effectiveness:

7.1 Effectiveness assessments

Using PASI (Psoriasis Area Severity Index)score.

8. Adverse Event Reporting:

In case of any Adverse Event / Adverse Drug Reaction, it will be reported immediately to the Pharmacovigilance members of the respective institutes.

9. Statistical Methods/Data Analysis:

Data on clinical symptoms and objective tests before and after the treatment will be tabulated and analyzed using appropriate statistical tools.

9.1 Study endpoints

9.1.1. Primary endpoint(s)

At least 50% of reduction in PASI Score will be treated as significant.

9.1.2. Secondary endpoints

Time taken for remission of psoriasis.

9.2 Sample size determination

Two groups with 20 subjects in each.

9.3 Trial Monitoring and Data Analysis

The progress of the trial will be monitored by CCRS Headquarters. Data analysis will be undertaken by the monitoring units of respective institutes.

10.Ethics:

10.1. Ethical and scientific conduct of the clinical research study

The clinical research study will be conducted in accordance with the current IEC-approved clinical protocol and ICH GCP Guidelines.

10.2. Subject informed consent

The Sponsor-investigator will make certain that an appropriate informed consent process is in place to ensure that potential research subjects or their authorized representatives are fully informed about the nature and objectives of the clinical study, the potential risks and benefits of study participation and their rights as research subjects. The Sponsor-investigator, or a sub-investigator(s) designated by the Sponsor-investigator, will obtain the written, signed, informed consent of each subject, or the subject's authorized representative, prior to performing any study-specific procedures on the subject. The date and time that the subject, or the subject's authorized representative, signs the informed consent form and a narrative of the issues discussed during the informed consent process will be documented in the subject's case history. The Sponsor-investigator will retain the original copy of the signed informed consent form and a copy will be provided to the subject or to the subject's authorized representative.

11. Study Discontinuation Criteria:

During the course of treatment if, any serious condition or serious adverse reactions occurs or if the subject volunteers to withdraw from the study, he/she will be withdrawn from the study. Also if the subject misses the drug regimen, will be withdrawn from the study.

12. References:

1. Gelfand JM, Stern RS, Nijsten T, Feldman SR, Thomas J, Kist J, Rolstad T, Margolis DJ. The prevalence of psoriasis in African Americans: results from a population-based study. J Am Acad Dermatol. 2005 Jan;52(1):23-6.
2. Stern RS, Nijsten T, Feldman SR, Margolis DJ, Rolstad T. Psoriasis is common, carries a substantial burden even when not extensive, and is associated with widespread treatment dissatisfaction. J Investig Dermatol Symp Proc. 2004 Mar;9(2):136-9.
3. Gelfand JM, Feldman SR, Stern RS, Thomas J, Rolstad T, Margolis DJ. Determinants of quality of life in patients with psoriasis: a study from the U.S. population. J Am Acad Dermatol. 2004 Nov;51(5):704-8.

4. Yugimunivar, Yugimuni Vaithiya Chinthamani, Compiled by Thamarai Publications, Chennai, 1st Edition, 1998.
5. Rao K.K, Krishnamurthi J.R, Shetty B.M.V, Pandiyarajan and Veluchamy G, Herbal Treatment (Siddha) for Psoriasis(A report on clinical research with special focus on Histopathological aspect), *J R.A.S. Vol. IX, No. 3-4,* 1986, *pp. 124-134*

CENTRAL COUNCIL FOR RESEARCH IN SIDDHA

INFORMED CONSENT FORM

Certificate by Investigator

I certify that I have disclosed all details about the study entitled "Clinical Evaluation of investigational drug in the Management of Kalaanjakapadai." in the terms easily understood by the patient.

Date: _____ Signature _____

Name of the Investigator_____

Consent by Subject

I have been informed to my satisfaction, by the attending physician, the purpose of the clinical trial and the nature of drug treatment and follow-up, including the laboratory investigations to be performed to monitor and safeguard my body functions.

I am also aware of my right to opt out of the trial at any time during the course of the trial without having to give the reasons for doing so. I am willing to undergo any risk for inclusion inthis study.

I, exercising my free power of choice, hereby give my consent to be included as a subject in the study entitled "Clinical Evaluation of investigational drug in the Management of Kaalanjakapadai."

Date: _____ Name of the subject _____

Signature or Thumb impression_____

Date: _____Name of the witness: _____

Signature or Thumb impression: _____

(To be translated into regional language)

மத்திய சித்த மருத்துவ ஆராய்ச்சி கழகம்

சென ்னை .

ஒப்புதல் சான்று

"காளாஞ்சகப்படைக்கு ஒஓஒ தைலம்" என்ற இந்த ஆய்வு பற்றிய விவரங்களை நோயாளா்க்குப் புரியும் வகையில் விளக்கமாக கூறியுள்ளேன் என்று சான்று அளிக்கிறேன்

தேதி: **மருத்துவா் கையொப்பம்:**

மருத்துவா் பெயா்:

நோயாளரின் ஒப்புதல் படிவம்

நான்,""

(பெயா் மற்றும் முகவரி)

"காளாஞ்சகப்படைக்கு ஒஓஒ தைலம்" என்ற இந்த ஆய்வின் விவரங்களையும், இந்த சித்த மருந்தின் நன்மை மற்றும் பக்கவிளைவுகள் பற்றியும் தெளிவாகப் புரிந்து கொண்டேன். இந்த ஆய்வின் போது எனக்குத் தேவையான உடல் மற்றும் இரத்த பரிசோதனைகள் செய்யப்படும் என அறிந்து கொண்டேன். இந்த ஆய்வினால் ஏதேனும் பக்கவிளைவுகள் ஏற்பட்டால் தகுந்த மருத்துவம் இலவசமாக வழங்கப்படும் என்றும் அதற்கு ஈட்டுத்தொகையாக எதுவும் வழங்கப்படமாட்டாது எனவும் அறிந்து கொண்டேன். இந்த ஆய்வில் என்னைச் சேர்த்துக் கொள்ள மனப்பூர்வமாக ஒப்புதல் அளிக்கிறேன்.

நான் இந்த ஆய்வு மருந்தினால் ஏற்படும் நன்மைகள் மற்றும் பக்கவிளைவுகள் பற்றி ஆய்வாளரிடம் உடனடியாக தெரிவிக்க ஒப்புதல் அளிக்கிறேன்.

மேலும் என் விருப்பத்தின ்பேரில், தகுந்த காரணங்களோடு எந்த நேரமும் இந்த ஆய்விலிருந்து விலகிக்கொள்ள முடியும் என அறிந்து கொண்டேன்.

இந்த ஆய்வு சம்பந்தமான என்னுடைய மருத்துவ ஆவணங்களை ஆய்வு அறிக்கை, மற்றும் ஆய்வு இதழ்களில் வெளியிடுவதற்கும், தேவைப்படும் பொழுது தகுந்த நெறிமுறை ஆணையத்திடமோ வெளியிட சம்மதிக்கிறேன்.

பங்கு கொள்பவரின் கையொப்பம் **சாட்சியாளரின் கையொப்பம்**

பெயா்: **பெயா்:**

முகவரி: **முகவரி:**

தேதி: **தேதி:**

CENTRAL COUNCIL FOR RESEARCH IN SIDDHA

MULTICENTRIC CLINICAL TRIAL ON KALAANJAGAPADAI

FORM 1 - SCREENING PROFORMA

NAME OF TRIAL CENTRE:

OPD No: IPD No:

DATE OF ADMISSION:

DATE OF DISCHARGE:

1. Name of the patient: _____

2. Gender: Male: ☐ Female: ☐

3. Date of Birth ☐☐ ☐☐ ☐☐ Age in Years ☐☐

D D M M Y Y

4.Address:

CRITERIA FOR INCLUSION	**Yes**	**No**
1. Age between 16 & 60 years of either sex	☐	☐
2. Duration of the disease < 10 years	☐	☐
3. Well defined, non - indurated, dry erythemtous area with silvery scales	☐	☐
4. Auspitz sign	☐	☐
5. Koebner's phenomenon	☐	☐

CRITERIA FOR EXCLUSION	**Yes**	**No**
1. Pustular Psoriasis		
2. Duration of the illness more than 10 years		
3. Infection-Parasitic/Bacterial/Fungal		
4. Eczema		
5. Matabolic disorders		
6. Associated Renal/CVS/RS involvement		
7. Malignancy		
8. Skin manifestation of syphilis		
9. Pregnancy		

Whether the patient is suitable for enrollment **Yes** **No**

If enrolled, Patient's S.No:

Date: Signature of the Research Official

CENTRAL COUNCIL FOR RESEARCH IN SIDDHA
MULTICENTRIC CLINICAL TRIAL ON KALANJAGAPADAI

FORM 1 A - HISTORY PROFORMA

NAME OF THE INSTITUTION:

1. S,No of the subject:_____

2. Name of the subject: _____

3. Gender Male ☐ (1) Female ☐ (2)

4. Date of Birth ☐☐ ☐☐ ☐☐ Age in years ☐☐

5. Educational Status:
Illiterate (1) ☐ Read&Write (2) ☐

Educational Qualifications _____

6. Past occupation

Desk work: (1) ☐

Fieldwork with physical labour (2) ☐

Fieldwork - Intellectual (3) ☐

Indicate the nature of work (4) _____

7. Occupation:-

Deskwork (1) ☐

Fieldwork with physical labour (2) ☐

Fieldwork- intellectual (3) ☐

Indicate the nature of work (4) ☐

Addiction

8. Smoking: No ☐ (0) Yes ☐ (1)

9. If yes, specify:
[a] Quantity[packs] _____
[b] Total duration in years: _____

☐ ☐

10. Tobacco: No (0) Yes (1)

11. If yes specify:
[a] Quantity _____
[b] Total duration in years: _____

12. Alcohol No ☐ (0) Yes ☐ (1)

13. If, yes specify:
[a] Quantity[ml] _____

[b] Total duration in years: _____

14. Prakriti

Vatham	☐ (1)	Pitham	☐ (2)
Kabam	☐ (3)	Vatha-kabam	☐ (4)
Vatha-Pitham	☐ (5)	Pitha-Kabam	☐ (6)
Mukkutram	☐ (7)		

Physical Examination:

15. Height (cm) _____

16. Weight (kg): _____

MEDICAL HISTORY:

17. Exacerbation with

Cold climate	☐	Sunlight	☐	Dialysis	☐
Infection	☐	Trauma	☐	Emotional factor	☐
Puberty	☐	Pregnancy	☐	Menopause	☐

18. Drug intake

Lithium	☐	Beta blockers	☐	Antimalarials	☐
Steroid withdrawal	☐	Clonidine	☐	Potassium Iodide	☐
Amiodarone	☐	Digoxin	☐	Trazadone	☐
Gemfibrozil	☐	Penicillin	☐	Terfenadine	☐
NSAIDS	☐	Natural remedies	☐		

19. EXAMINATION

General:

Systemic: CVS ☐ RS ☐ ABDOMEN ☐ CNS ☐

Dermatological:

Auspitz sign: No ☐ Yes ☐

Clinical type: Chronic stable plaque ☐

Scalp ☐

Palmoplantar ☐

Others-Guttate/Erythrodermic/Unstable/Flexural/Sebo/Rupioid ☐

Nail changes: None ☐ Pitting ☐ Onycolysis ☐

Sub ungual hyperkeratosis ☐ Oil drop sign ☐

Splinter hemorrhages ☐ Ridges ☐

Joint involvement:

None ☐
Asymmetrical oligoarthritis ☐
Classical DIP joints arthritis ☐
Symmetrical polyarthritis ☐
Axial arthritis ☐
Arthritis mutilans ☐

Focal sepsis ENT ☐ Dental ☐ Others ☐

Surface area involved ☐

ENVAGAI THERVUGAL:

NAADI:

SPARISM:

NAA:

NIRAM:

MOZHI:

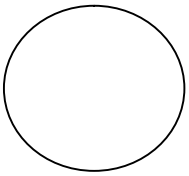
VIZHI:

MALAM:

MOOTHIRAM:

Neerkkuri:

Neikkuri:



Date: Signature of the Research Official

CENTRAL COUNCIL FOR RESEARCH IN SIDDHA

MULTICENTRIC CLINICAL TRIAL ON KALANJAGAPADAI

FORM II – CLINICAL ASSESSMENT

NAME OF THE INSTITUTION:

1.S.No. of the Subject: _____

2.Name: _____

3. Gender Male ☐ (1) Female ☐ (2)

4.Date of Birth ☐☐ ☐☐ ☐☐ Age: ☐☐ Years

5.Date of assessment: _____Before / After treatment

6.Clinical Photos

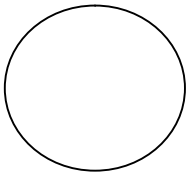
Dates:

1.

2.

3.

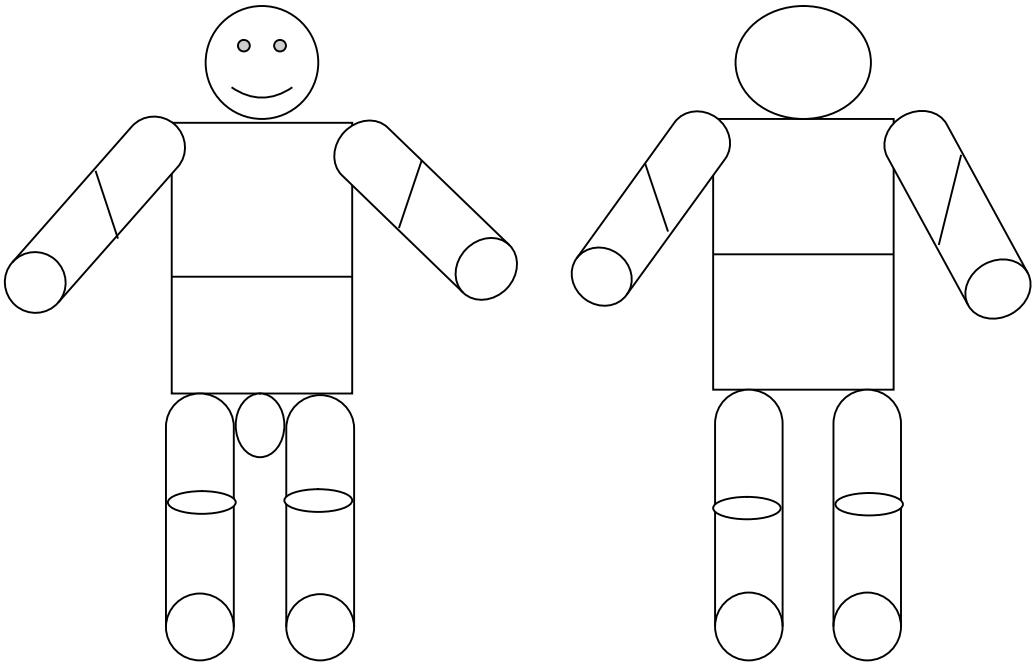
Neikkuri:



Date: Signature of the Research Official

Review:																		
Date	No.of Weeks	Face				Trunk				Upper Limb				Lower Limb				PASI Score
		E	I	D	A	E	I	D	A	E	I	D	A	E	I	D	A	

E – Erythema; I – Infiltration; D – Desquamation; A - Area



ANTERIOR POSTERIOR

Sites of involvement

Erythema/Infiltration/Desquamation Scoring:

0 – Nil
1 – Mild
2 – Moderate
3 – Severe
4 – Very high

Area of Scoring

0 – Nil
1 – Less than 10%
2 – 10% - 30%
3 – 31% - 50%
4 – 51% - 70%
5 – 71% - 90%
6 – 91% - 100%

PASI = $0.1(E_H + I_H + D_H)\ A_H + 0.2\ (E_U + I_U + D_U)A_U + 0.3\ (E_T + I_T + D_T)\ A_T + 0.4\ (E_L + I_L + D_L)\ A_T$

Date: Signature of the Research Official

CENTRAL COUNCIL FOR RESEARCH IN SIDDHA

MULTICENTRIC CLINICAL TRIAL ON KALANJAGAPADAI
FORM III – LABORATORY INVESTIGATIONS

NAME OF THE INSTITUTION:

1. S.No. of the subject: _____

2. Name_____

3. Gender Male Female

4. Age ____ yrs.

5. Date of Assessment _____ Before / After treatment

URINE

i. Colour
ii. pH
iii. Sugar
iv. Albumin
v. Pus cells
vi. R.B.Cs
vii. Casts / Deposit
viii. Bile pigments / Bile salts

HAEMATOLOGY

i. T.C
ii. D.C
iii. Hb%
iv. E.S.R

BIOCHEMISTRY

i. Blood Urea
ii. Serum Creatinine
iii. VDRL

Confirmatory test

Histo-pathological study

Date: Signature of Research Official