COMMERCIAL PRODUCTION AND CLINICAL TRIAL OF NIPRIMUNE®

Executive Summary

Introduction:

This project proposes upgrading the NIPRD-Drug Manufacturing Facility to a cGMP-compliant finished herbal medicine manufacturing facility, enabling industrial-scale production of NIPRIMUNE with potential to produce other solid dosage herbal products. NIPRIMUNE is a trademarked phytomedicine derived from *Andrographis paniculata*, with demonstrated immunomodulatory, antiviral, and anti-inflammatory benefits developed by National Institute of Pharmaceutical Research and Development (NIPRD).

The project aims are to:

a. Upgrade the NIPRD-Drug Manufacturing Facility to cGMP standards for industrial-scale production of NIPRIMUNE®.
b. Optimize the extraction of NIPRIMUNE® the active ingredient and formulation processes for large scale industrial manufacture.
c. Conduct Phase 1 clinical trials to evaluate the safety of NIPRIMUNE® as an immune booster.

Expected Outcomes:

a. A cGMP-compliant facility for manufacturing NIPRIMUNE® solid dosage form finished herbal medicines.
b. Optimized large scale industrial extraction and formulation protocols for NIPRIMUNE® production that meet international quality standards using optimized cGMP compliant processes.
c. Clinical safety data for NIPRIMUNE® as an immune-modulatory phytomedicine.

Project Impact:

This project aligns with the growing demand for standardized herbal products and innovative solutions in the pharmaceutical industry. It promises to:

a. Sustainable availability of high-quality, potent immunomodulatory phytomedicines that are safe and efficacious that will be beneficial in many emerging diseases.
b. Contribute to the promotion of phyto-industrial development and phyto- research and development.
c. Increased productivity and stimulation of phyto- economic investment.
d. Align with Mr. President's Renewed Hope Agenda and NASENI's objectives of driving economic impact and societal well-being.

The major activities will include developing and validating a standardized process for NIPRIMUNE® production, conducting pilot commercial production and distribution with stringent quality control, as well as undertake Phase 1 clinical trial to evaluate the safety and efficacy of the product. The project is estimated to cost one hundred and ninety three million eight hundred and eighty thousand naira only (₦193,880,000) and will be completed within 12 months.

Conclusion:

Ultimately, this project will position Nigeria as a hub for herbal medicine research and development, and production, which is sure to drive economic growth and improving healthcare outcomes. By

achieving these objectives, the project will make a lasting impact on the nation's pharmaceutical industry and contribute to the well-being of Nigerians.

Label on NIPRIMUNE® Secondary package

Background

Medicinal plants have been used for centuries in Nigeria and globally to prevent and treat various diseases. Nigeria's rich biodiversity, with over 7,895 plant species, offers a vast array of natural remedies that have been harnessed by traditional healers and modern practitioners. The use of herbal medicines is gaining popularity worldwide, driven by growing recognition of their efficacy, safety, and cultural relevance.

The benefits of herbal medicines are multifaceted. They provide a natural and sustainable healthcare option, leveraging traditional knowledge and the country's rich biodiversity. This approach can lead to relief from chronic diseases, improved overall well-being, and promotion of holistic health. Additionally, herbal medicines have the potential to contribute to wealth creation and poverty reduction, making them an attractive option for many individuals and communities.

Globally, many people are turning to traditional medicine as a complementary or alternative approach to conventional healthcare. This shift is motivated by factors such as better tolerance and relief from chronic diseases, emerging new diseases due to climate change, and the desire to improve overall well-being and promote holistic health. As the world grapples with the challenges of emerging diseases, and chronic health conditions due climate change. The potential benefits of herbal medicines are becoming increasingly apparent.

The growing interest in herbal medicines reflects a broader recognition of the importance of traditional knowledge and natural remedies in modern healthcare. Similar to practices in India and China, Nigeria's rich cultural heritage and biodiversity offer a unique opportunity to harness the potential of herbal medicines. By exploring and developing these natural remedies, Nigeria can improve healthcare outcomes, promote economic growth, and preserve its cultural heritage.

One of the significant challenges in the production of herbal medicines is standardization, particularly in relation to extraction, formulation, and quality control protocols, as well as corroborating folk safety and efficacy claims. To address this challenge, our proposed research and development project aims to strengthen the NIPRD's facility for producing granules of water extracts from various medicinal plants, with NIPRIMUNE® serving as a prototype. We will utilize innovative optimized procedures and technology to ensure the production of high-quality herbal products.

NIPRIMUNE® is a phytomedicine developed by NIPRD through meticulous research and development efforts. It is derived from *Andrographis paniculata* and has been standardized and formulated using innovative techniques. NIPRIMUNE® is registered under the trademark and listed with NAFDAC, ensuring its authenticity and quality. This herbal medicine is designed as an immune booster that alleviates several health conditions, including antiviral, antibacterial, flu-like symptoms, diarrhea, fevers, inflammation, and high blood pressure, thereby promoting general well-being.

The goal of this project is to effect commercial production of NIPRIMUNE by upgrading NIPRD's drug manufacturing facility to a cGMP-compliant phyto-medicine factory and conduct Phase 1clinical trial to establish the clinical safety of the product.

The commercial development of NIPRIMUNE aligns ultimately with the Renewed Hope Agenda of Mr. President as well as the working objective NASENI as far as innovative research and development, entrepreneurship, sustainable healthcare options and wealth creation.

Funding this project will unlock the full potential of Nigeria's biodiversity and break the ice for sustainable healthcare and economic growth. We believe that this project will make a significant contribution to the development of the herbal medicine industry in Nigeria and improve the health and well-being of Nigerians. It is sure to offer a bright future and opportunity for innovation, entrepreneurship, and collaboration in Nigeria.

Objectives of project:

a. To establish a cGMP-compliant facility for the production and quality control of NIPRIMUNE®.
b. To develop and validate a standardized cGMP-compliant process for industrial-scale NIPRIMUNE® production.
c. To conduct pilot commercial production and quality control of NIPRIMUNE®.
d. Carry out phase 1 clinical trials to assure clinical safety.
e. To facilitate commercial distribution of NIPRIMUNE® to pharmacies.

Significance

The successful completion of this project will:

a. Sustainable availability of a safe and effective immune booster in the face of new emerging diseases.
b. Contribute to the growth of the herbal pharmaceutical industry in Nigeria and beyond.
c. Provide a platform for the development of standardized herbal products with proven efficacy and safety.
d. Enhance the utilization of medicinal plants and promote their potential therapeutic benefits.

Conceptual Framework

The conceptual framework of this project is directed towards upgrading the NIPRD-Drug Manufacturing Facility also known as NIPRD –Pharmaceutical Company Limited (NIPCO-Ltd)]to a cGMP-compliant facility for industrial-scale production of NIPRIMUNE, as well as the proof of safety by carrying out phase 1 clinical study. These goals are set to be achieved by:

a. Upgrading the facility to meet cGMP standards for industrial-scale production of NIPRIMUNE.
b. Optimizing the extraction and formulation processes for large-scale production of NIPRIMUNE.
c. Implementing validated quality assurance protocols to ensure the product meets international standards.
d. Conducting Phase 1 clinical trials to evaluate the safety and efficacy of NIPRIMUNE.
e. Facilitating commercial distribution of NIPRIMUNE to pharmacies.

Hypothesis:

Null Hypothesis:

Industrial-scale production of NIPRIMUNE granules using a cGMP-compliant facility and phase 1 clinical trial will not significantly improve the quality, safety, and effectiveness of NIPRIMUNE, nor its market acceptability and penetration.

Alternative Hypothesis:

Industrial-scale production of NIPRIMUNE granules using a cGMP-compliant facility and phase 1 clinical trial will significantly improve the quality, safety, and effectiveness of NIPRIMUNE, thereby enhancing its market acceptability and increasing its market penetration.

Expected Outcomes:

a. A cGMP-compliant herbal active ingredient extraction facility for industrial-scale production of NIPRIMUNE and other herbal granules
b. Standardized NIPRIMUNE granules and other herbal products that meet international quality standards
c. By conducting Phase 1 clinical trials of NIPRIMUNE will ensure:
    a. Regulatory Approval by generating data to support regulatory approval and listing with NAFDAC.
    b. Evidence-Based Medicine by providing scientific evidence for the safety and efficacy of NIPRIMUNE.
    c. Increased Confidence by enhancing confidence in the use of NIPRIMUNE among healthcare professionals and patients.
    d. Market Potential by increasing the potential for NIPRIMUNE to be marketed and sold globally.
d. Increased capacity for research and development of herbal medicines
e. Job creation and economic growth through the commercialization of herbal products

By establishing a facility for producing herbal granules, this project will contribute to the development of innovative and effective herbal products, promoting public health and well-being.

The successful completion of this research projected: Production and Clinical Trial of NIPRIMUNE achieve several far reaching benefits that will make a significant contribution to Nigeria's economic growth, healthcare outcomes, and cultural preservation.

Some benefits of the NIPRIMUNE project:

1. Improved healthcare outcomes and overall well-being for Nigerians by preventing and treating diseases through enhanced immune systems.

2. Easy access to NIPRIMUNE as a standardized herbal product with proven efficacy and safety.

3. Creation of employment opportunities, thus boosting Nigeria's economic growth.

5. Advancement of research and development in the herbal pharmaceutical industry.

6. Development of standardized production and quality control processes and protocols.

7. Generation of valuable safety and efficacy data through Phase 1 clinical trials that will confer confidence in its integration into mainstream healthcare system.

8. Boosting the phyto-pharmaceutical industry's growth.

9. Increase in the acceptability and competitiveness of Nigerian herbal products globally.

Investigators and Environment

The National Institute for Pharmaceutical Research and Development (NIPRD) is a Federal Government parastatal under the Federal Ministry of Health. NIPRD plays a pivotal role in advancing pharmaceutical research and development in Nigeria through its multifaceted activities.

NIPRD Pharmaceutical Company Limited (NIPCO): NIPRD operates a functional Drug Manufacturing Unit registered under the Corporate Affairs Commission (CAC) as NIPRD Pharmaceutical Company Limited (NIPCO). This unit collaborates closely with various technical departments within NIPRD through a Memorandum of Understanding (MOU) to carry out its businesses and research. The 5 technical departments in NIPRD are:

i. Medicinal Plant and Traditional Medicine
ii. Microbiology and Biotechnology
iii. Pharmacology and Toxicology
iv. Pharmaceutical Technology and Raw Materials Development
v. Chemistry and Quality Control

NIPRD also have a state of the act herbarium and, botanical farms and gardens for nursing and planting medicinal plants under the department of Medicinal Plant and Traditional Medicine. It also has an animal house facility and a central laboratory facility.

Accreditation and Certification of Laboratories: The laboratories within the technical departments are ISO 9001:2015 certified, demonstrating their commitment to quality management systems. Additionally, they are accredited by the ANSI-ASQ National Accreditation Board (ANAB) for ISO 17025:2017, which attests to their technical competence in testing.

NIPRD Research Clinic: NIPRD also has an accredited Research Clinic, further enhancing its capacity for rigorous research and development in the pharmaceutical sector. This clinic serves as a healthcare center for the communities around NIPRD namely Karmo, Idu, Gwagwa and Deidei and plays a crucial role in conducting clinical trials and studies that contribute to the advancement of healthcare solutions.

cGMP protocols practiced in the NIPCO

NIPCO production facility is arranged in such a manner that will ensure the production of quality products by preventing mix-ups, and contamination in the processing, encapsulation, packaging, and quality control areas through measures such as:

1. Organized arrangement of the work area such that a seamless flow of activities in a progressive coordination of activities: Separate areas for different stages of production, such as raw material storage, processing, encapsulation, and packaging, to prevent cross-contamination.
2. A one-way flow of materials and personnel to prevent mix-ups and contamination.
3. Designated points for every operation to maintain a controlled environment: such as weighing, encapsulation and packaging.
4. All containers and equipment in contact with raw materials, intermediates and finished materials are of stainless steel surfaces to prevent corrosion and facilitate cleaning.
5. Continuous regular in-process checks during every batch production to ensure product quality and detect any deviations.
6. A quality control section independent of manufacturing staff interferences for testing and analysis of raw materials, intermediates, and finished products.
7. Qualified and trained personnel to carry out the various activities such as production, quality control tests and other sundry activities that related to quality assurance.
8. Regular cleaning and sanitization of equipment, machinery, and facilities to prevent contamination.
9. Standard operating procedures (SOPs) for cleaning and sanitization to ensure consistency.
10. A controlled area for packaging to prevent mix-ups and contamination.
11. Strict controls on labeling to ensure accurate product identification and information.
12. Slated regular training programs for personnel on GMP, quality control, and production procedures.
13. Strict gowning procedures to prevent contamination from personnel.
14. Availability of detailed batch records to track production, quality control, and packaging.
15. Availability of documents such as Drug master File (NIPRIMUNE DMF), Standard operating procedures (SOPs) for production and quality control activities.
16. Strict control over documentation to prevent errors and ensure traceability.

METHODOLOGY FOR NIPRIMUNE PRODUCTION

Extraction Method (Maceration): *A. parnicula* extraction process involves the authentication of the herb followed by transfer to the grinder to reduce the article size before transfer to maceration tank which is equipped with a stirrer. A predetermine quantity of water is introduced to the tank and maceration tank and temperature set to 60 ^{o}C. Maceration is carried out with continues stirring for 12 h.

The macerated mass is transfared to a sieving tank. The marc is collected and the residual solid waste is then transferred for waste disposal deposit.

The maceration tank decoction methods. Their products are refined through extraction, concentration, and granulation.

Spray Drying Process:

Spray drying is a method used to convert liquid extracts into powders by rapidly drying the liquid droplets in a hot gas stream.

The inlet and outlet temperatures are set to produce optimal drying and yield of extract.

The dry extract are harvested from the spray dryer tank and collected into suitable waterproof bags weighed, labelled and placed API store.

Quality Control on Herbal Extract:

The under listed tests are carried out on any batch extracted herbal active ingredient:

i. Finger print
ii. Heavy metal content
iii. Moisture content
iv. Pesticide content
v. Aflatoxin
vi. Shelf life determination

Production of NIPRIMUNE Capsules

Using predetermined quantities of the herbal extract and excipients (starch and microcrystalline cellulose) following an predetermined formula.

The powders are appropriately mixed and encapsulated using an automatic capsulating machine. Gelatin capsule shell size 0; black and green shell.

Quality Control on NPRIMUNE Capsules

The under listed tests are carried out on every finished batch of NIPRIMUNE:

i. Organoleptic evaluation
ii. Weight uniformity
iii. Disintegration time
iv. Dissolution
v. Shelf life determination

Primary packaging

NIPRIMUN is packed:

i. Blister pack x10 capsules, size zero.
ii. Bulk plastic container with label x 60.

Secondary package

Simple glossy paper box packaging labelled appropriately.

CLINICAL TRIAL PHASE 1

Title: A Phase I, Randomized, Double-blind, Placebo-controlled, Single Ascending Dose and Multiple Ascending Dose Clinical Study to Assess the Safety, Tolerability and Pharmacokinetics of NIPRIMUNE in Healthy Adult Volunteers.

Introduction

This is a Phase I clinical study of NIPRIMUNE, the Investigational Medicinal Product (IMP). The current study is designed to evaluate the safety and tolerability and pharmacokinetics of single and multiple oral doses of the IMP NIPRIMUNE, in healthy volunteers.

This phase 1 clinical trial is being undertaken to determine the safety of NIPRIMUNE in healthy human participants. Physical well-being, including laboratory investigations, will be closely monitored and evaluated. The clinical trial will be carried out in NIPRD Research Clinic and other accredited laboratory. The use of appropriate health diary by the patients will be introduced in the study.

NIPRIMUNE is a phyto-medicine that has demonstrated positive outcomes during in vitro and in vivo studies with anti-inflammatory ,antiviral and strong immunomodulatory characteristics.

This clinical study is planned as a double blind, randomised, placebo-controlled, combined clinical study of two parts: Single Ascending Dose (SAD) and Multiple Ascending Dose (MAD) studies, respectively. Pharmacokinetic (PK) profile of the NIPRIMUNE, will also be assessed in both parts of the study. The safety, tolerability and pharmacokinetic data and results obtained from this study will determine the potentially efficacious doses of the IMP NIPRIMUNE in the subsequent efficacy studies.

Between each cohort, an interim analysis of PK, safety and tolerability will be performed. The available data will be evaluated by an independent Drug Safety Monitoring Board (DSMB). Once a dose level is judged to be safe, the DSMB will allow the escalation to the next cohort.

Both the Investigator and study participants will remain blinded to the treatment administered (drug or placebo) till the final results of the study are obtained.

DSMB will provide recommendations about stopping, modifying or continuing the study. Decision to escalate to next dose level/ Cohort, will be based on interim analysis of pharmacokinetic data, 36-hr post-dose, and 30-days post dose safety follow-up.

Patient Selection

Healthy adult volunteers eligible for participations in the study will be enrolled as study participants. They will be randomly assigned to the IMP NIPRIMUNE and placebo arm of the SAD/MAD part.

Inclusion/Exclusion Criteria

Inclusion Criteria:

i. Age: Healthy adult volunteers between 18 and 55 years old.

ii. Health Status: Normal vital signs and laboratory parameters, with no significant medical history.
iii. Informed Consent: Ability to understand and sign the informed consent form.
iv. Reproductive Status: Women of childbearing potential must have a negative pregnancy test and agree to use effective contraception.

Exclusion Criteria:

i. Medical Conditions: Presence of significant medical conditions, such as liver or kidney disease, heart conditions, or neurological disorders.
    a. AST and/or ALT >3x upper limit of normal or any sign of hepatic impairment limit of normal or any other significant renal or hepatic impairment.
    b. QTc interval of >470 msec at screening and patients with congenital long QT syndrome/or creatinine >2x renal dysfunction.
ii. Medications: Use of medications that may interact with NIPRIMUNE or affect the study outcomes.
iii. Lifestyle Habits: Smoking, alcohol or drug abuse, or extreme diets and exercise routines.
iv. Pregnancy or Lactation: Pregnant or breastfeeding women.
v. Allergies: Known hypersensitivity to *Andrographis paniculata* or similar herbal products

Study Site: NIPRD Research Clinic IDU

Study Population: *Fifty six healthy participants will recruited from our pool of clients and from the eleven communities located around the institute.*

Study Design

Interventional Model Description: Phase I, Randomized, Double-blind, Placebo-controlled, Single Ascending Dose and Multiple Ascending Dose Clinical Study to Assess the Safety, Tolerability and Pharmacokinetics of the Investigational Product in Healthy Adult Volunteers

Both the Investigator and study participants will remain blinded to the treatment administered (drug or placebo) till the final results of the study are obtained.

The placebo will identical to the investigational medicinal product in smell, taste, and appearance.

Arms and Interventions

Participant Group/Arm	Intervention/Treatment
Experimental: NIPRIMUNE is a phytomedicine that has demonstrated positive outcomes during in vitro and in vivo studies for immune	Drug: NIPRIMUNE • NIPRIMUNE is a small molecule with demonstrated antiviral and immunomodulatory activity in-vitro & in

Participant Group/Arm	Intervention/Treatment
booster with antiviral charactreristics Formulated as Capsules intended for oral dosing to trial participants.	vivo studies. , it was anticipated that NIPRIMUNE can also be a promising immune booster
Placebo Comparator: Placebo placebo will be identical in smell, taste, and appearance to the Capsule of NIPRIMUNE	Other: Placebo • Placebo capsules identical in appearance, taste and smell to the capsules of NIPRIMUNE

This clinical study is planned as a double blind, randomised, placebo-controlled, combined clinical study of two parts: Single Ascending Dose (SAD) and Multiple Ascending Dose (MAD) studies, respectively. Pharmacokinetic (PK) profile of the NIPRIMUNE, will also be assessed in both parts of the study. The safety, tolerability and pharmacokinetic data and results obtained from this study will determine the potentially efficacious doses of the IMP NIPRIMUNE, in the subsequent efficacy studies .

Fifty six (56) healthy volunteers will be recruited age for sex. Randomised, The SAD Part will consist of 5 cohorts of 8 healthy adult volunteers, each volunteer will be randomly (blinded) allocated to NIPRIMUNE or placebo (each cohort will consist of 6 volunteers receiving NIPRIMUNE and 2 volunteers receiving placebo). Five (5) dose level of the investigational medicinal product are selected for oral administration. The MAD Part will consist of 2 cohorts of 8 healthy adult volunteers, each volunteer will be randomly (blinded) allocated to NIPRIMUNE or placebo (each cohort will consist of 6 volunteers receiving NIPRIMUNE and 2 volunteers receiving placebo). Two (2) dose levels of the investigational medicinal product are selected for oral administration. Additional Volunteers will be enrolled to replace(volunteers withdrawing consent from the study for reasons other than safety). Additional volunteers will also be enrolled if a Cohort needs to be repeated.

Safety evaluation during both the SAD & MAD pars of the clinical study will include adverse events, clinical laboratory/ pathological test results, electrocardiogram (ECG), and measurement of vital signs.

Pharmacokinetics will be determined at pre-dose, and 30 min, 1h, 2h, 4h, 8h, 12h, and 24, post-dose, and 36 hrs post-dose on Day 2, for the SAD Part of the Study.

Pharmacokinetics will be determined at pre-dose, and 30 min, 1h, 2h, 4h, 8h, 12h, and 24h, of Day 1 and Day 7, at pre-dose on Days 2-6 and 36 hrs post final dose of Day 7 for the MAD Part

Safety analysis: frequency and severity of adverse events. The sample size is estimated to produce a good clinical effect at a 95% confidence and a power of 90. The participants will be randomized into two groups labeled A and B.

Study Procedure

***Study Procedures*:** An appropriate health diary has been designed which will be completed daily by each participant for one month prior to the administration of the NIPRIMUNE. The participants are also expected to continue to complete the health diary for the duration of the clinical evaluation, which will last for 12 weeks

The purpose of this study is to determine the dose tolerability and safety of NIPRIMUNE when given to normal healthy participants. Pre-dose blood sampling will be done at zero (0) minute, and post-administration of NIPRIMUNE or Placebo at pre-dose, and 30 min, 1h, 2h, 4h, 8h, 12h, and 24, post-dose, and 36 h. post-dose on Day 2, for the SAD Part of the Study.

Pharmacokinetics will be determined at pre-dose, and 30 min, 1h, 2h, 4h, 8h, 12h, and 24h, of Day 1 and Day 7, at pre-dose on Days 2-6 and 36 h post final dose of Day 7 for the MAD Part

The participants will be followed up 24 h, 72 h, one week, and then weekly during the first 4 weeks and subsequently at the end of every 4 weeks for 8 weeks.

During each visit, they will be physically examined, and any side effects and adverse events will be recorded. At the end of 12 weeks, the following investigations taken at baseline will be repeated: urinalysis, urea and creatinine, random blood sugar, full blood count and differentials, serum electrolytes, liver function tests, immunomodulator and anti inflammatory markers, ECG, and chest X-ray.

Pre – Entry Tests: Within seven days prior to dosing and as close to the first day of dosing as possible, the following tests must be performed to determine patient eligibility and baseline values:

*Medical history, Complete physical examination,*Weight, height

*Vitals signs*ECG; Chest X-ray

*Complete haematology WBC, differential, HCT, Hgb, platelets, I

*Blood chemistry (Na, K, Cl, CO_2, BUN, Creatinine, albumin, alkaline phosphatese,LDH, ALT,AST, bilirubin total and direct, hepatitis panel, glucose, cholesterol, serum iron). C – reactive protein ,ESR

Immune modulator markers CD4+, T cells ,CD8 + T cells IL-2, IL-6, IL-10, TNF-α, IFN-γ, IL-17, CXCL9, CXCL10

*Urinalysis (pH, gram strain, colour, glucose, cells, protein, specific gravity).

*Ova and parasites

*TB test (if the patient did not receive BCG)

*On day 1, immediately prior to beginning dosing, repeat measurement of vital signs.

*At any reasonable time before entry (i.e more than 7 days if necessary) determine HIV positivity.

*If the patient is female, confirm that she is not pregnant and is practicing appropriate contraception.

Test During Study, Recording

DAY 1, until the end of treatment course (see schedule of visits)

*Vital signs: Immediately pre-treatment and after the dose at 2 and 4 hours.

*Weight, Height and Vital Signs are to be taken at each visit.

*Stool Microscopy is to be done pre-trial and after the clinical evaluation.

* A repeat ECG is to be taken within the first 4 weeks.

*Haematology: Complete haematology including reticulocytes; pretreatment and at each visit.

*Blood chemistry: Na, Ca, K, Cl, CO_2, BUN, Creatinine, albumin, total protein, alkaline phosphatese, LDH, ALT,AST, bilirubin total and direct, , glucose, cholesterol, pretreatment and at each visit

Parameters to be Evaluated in the NIPRIMUNE Phase 1 Clinical Trial

1. Demographic and Baseline Characteristics: Collecting data on participants' age, sex, weight, and medical history.
2. Vital Signs: Vital signs, such as blood pressure, heart rate, and temperature.
3. Laboratory Parameters: Laboratory tests, such as blood chemistry, hematology, and urinalysis will be carried out on volunteers.
4. Electrocardiogram (ECG): Cardiac function and rhythm.
5. Safety and Tolerability: Critical observation of adverse events (AEs) and serious adverse events (SAEs).
6. Pharmacokinetics (PK): Absorption, distribution, metabolism, and excretion (ADME) of NIPRIMUNE will determined using developed markers.
7. Maximum Tolerated Dose (MTD):The highest dose that can be safely administered will be determined.
8. Pharmacodynamics (PD): The general effect of NIPRIMUNE on the body.
9. Immunogenicity: Evaluating the immune response to NIPRIMUNE.

Ethical Approval, Consent, Confidentiality, and Withdrawal

Ethical approval will be obtained from the National Health Research Ethics Committee of Nigeria, Federal Ministry of Health (NHREC). Informed written consent and assent will be obtained from participants.

Consent: The evaluation procedure will be explained to each subject and a written consent will be signed or thumb-printed before enrollment for the evaluation. Subjects may withdraw voluntarily at any point of evaluation.

Adverse Events: Adverse events are any undesirable experiences or events, which occur during the study or during a reasonable time thereafter, whether or not considered related to administration of the drug. ***Serious Adverse Events***

Serious adverse events should be reported within 24 to 48 hours.This will ensure that other investigators are promptly cautioned

Response Outcome Measures

Current Primary Outcome Measures:

Determine the safety, tolerability, and dose-limiting toxicities of medication. Determine the safety, tolerability, and dose limiting toxicities of NIPRIMUNE Assessed by frequency and severity of adverse events(AEs), and changes in vital signs, 12-lead ECGs and laboratory assessments as compared to baseline [Time Frame: From the time the participant is administered the first dose through the final follow up clinic visit, for a total of 12weeks

Primary outcome measures

Outcome Measure	**Measure Description**	**Time Frame**
Number of participants with adverse events [Time Frame-]	To assess safety & tolerability of NIPRIMUNE in Human	30 days post last dose for each cohort
Incidence of serious adverse events (SAEs) by relation to the IMP (related/not related)	To assess safety & tolerability of NIPRIMUNE in Human	30 days post last dose for each cohort
Percentage of volunteers who experience at least 1 Treatment Emergent Adverse Event (TEAE)	To assess safety & tolerability of NIPRIMUNE in Human	30 days post last dose for each cohort
Percentage of volunteers who discontinue due to an Adverse Event (AE).	To assess safety & tolerability of NIPRIMUNE n Human	30 days post last dose for each cohort
Percentage of volunteers who meet the markedly abnormal criteria for safety laboratory tests at least once post dose.	To assess safety NIPRIMUNE in Human	7 days post last dose for each cohort

Outcome Measure	Measure Description	Time Frame
Percentage of volunteers who meet the markedly abnormal criteria for vital sign measurements at least once post dose	To assess safety NIPRIMUNE in Human	7 days post last dose for each cohort
Percentage of volunteers who meet the markedly abnormal criteria for safety electrocardiogram (ECG) parameters at least once post dose.	To assess safety NIPRIMUNE in Human	7 days post last dose for each cohort

Secondary Outcome Measures

Outcome Measure	Measure Description	Time Frame
Plasma Cmax	Maximum plasma concentrations	post-dose in Single ascending Dose trial & post dose on days 1 & 7 in Multiple ascending dose part of the trial
Plasma Tmax	Time to Maximum plasma concentrations (tmax)	post-dose in Single ascending Dose trial & post dose on days 1 & 7 in Multiple ascending dose part of the trial
Plasma AUC0-t	Area under the concentration-time curve	Single ascending Dose

Outcome Measure	Measure Description	Time Frame
	from dosing (time 0) to time t [AUC0-t]	
Plasma AUC0-inf	Area under the concentration-time curve from dosing (time 0) extrapolated to infinite time [AUC 0-inf]	Single ascending Dose
Plasma AUC0-tau	Area under the concentration-time curve to the end of the dosing period [AUC 0-tau]	post dose on days 1 & 7 in Multiple ascending dose part of the trial
Plasma AUC0-t	Area under the concentration-time curve from dosing (time 0) to time t [AUC0-t]	post dose on day 7 in Multiple ascending dose part of the trial
Plasma Kel	Elimination constant [Kel]	in Single ascending Dose trial & post-dose on day 7 in Multiple ascending dose part of the trial
Plasma t1/2	Elimination half life [t1/2]	in Single ascending Dose trial & post dose on day 7 in Multiple ascending dose part of the trial
Plasma Ctrough	Pre-dose plasma trough concentration (Ctrough)	on days 2 & 6 in Multiple ascending dose part of the trial

Outcome Measure	Measure Description	Time Frame
Plasma Racc	Accumulation ratio Racc (Cmax on Day 7/Cmax on Day 1), (AUC0-τ on Day 7/AUC0-τ on Day 1) and (Ctrough on Day 7/Ctrough on Day 1)	post dose on days 1 & 7 in Multiple ascending dose part of the trial

DATA ANALYSIS

Statistical Analysis: All data will be collected and analysed using the REDCap (Research Electronic Data capture) Descriptive statistics to summarize demographic and baseline characteristics. The analysis will include a description of the study population. Safety analysis: frequency and severity of adverse events. The sample size is estimated to produce a good clinical effect at a 95% confidence and a power of 90 The participants will be randomized into two groups labeled A and B Inferential statistics (e.g., ANOVA, regression analysis) to evaluate dose-proportionality and pharmacokinetic parameters.

Data Collection Forms

1. Consent form
2. Schedule of Visits
3. Personal Data
4. Prior History
5. Physical Examination/Vital Signs and Symptoms Monitoring
6. Cardiac Study (ECG, Chest X-Ray)
7. Haematological Monitoring
8. Chemistry Monitoring
9. Microbiology Monitoring
10. Adverse Experiences/ Concomitant Treatment
11. Discontinuation/Termination

Anticipated Problems in NIPRIMUNE's Phase 1 clinical trial:

a. Patient Recruitment Challenges: Difficulty enrolling participants due to lack of awareness, skepticism about the treatment's efficacy, or concerns about potential risks.
    i. This problem will be solved by using digital technologies and decentralized trials (other centers to reach a wider audience.
b. Funding and Resource Constraints due release of funding and resources to conduct the trial effectively.
    i. Timely release of fund and strict adherence to budget.
c. Data Quality and Accuracy: Ensuring accurate and reliable data collection and analysis.
    i. Advanced analytics and real-time data monitoring will be employed to detect any errors to ensure data quality.

RESEARCH TEAM

Name	Institution	Expertise Coordination	Qualification/Position	Contribution to Project
Prof. Philip Builders	NIPCO LTD Coordinator-NIPRD-DMU/NIPCO	Production and Quality Control	Ph.D	Principal Investigator
Dr. Bola Mustapha	Department of Chemistry and Quality Control (HOD)	Chemical Analytical processes and Quality Control	Ph.D	Investigator
Dr. Peter Oladosu	Department of Microbiology and Human Virology	Microbial instability and Quality Control	Ph. D	Investigator
Dr. Bulus Adzu	Department of Pharmacology and Toxicology (HOD)	Pharmacokinetic Evaluation	Ph.D	Investigator
Dr. Margaret Ekpenyong	NIPRD Clinic	Clinical Trial	MBBS	Investigator
Dr. Olubunmi Olayemi	Pharm. Tech & RMD (HOD)	Formulation and Packaging	Ph.D	Investigator
Dr. Jemilat Ibrahim	Medicinal Plant And Traditional Medicine (HOD)	Plant Collection, Identification and Extraction processes	Ph.D	Investigator

Budget of Expenditure

Presented is a detailed budget in relation to the activities and cost.

Activity	**Items Required**	**Cost (₦aira)**
Documentation (Secretariat)		
	Laptop (1) and Printer Storage devices, Internet connectivity	N2.500, 000.00
	Stationaries	N500, 000.00
	Statistical package (SPPS)	N300, 000.00
Packing of bulk raw materials, intermediates and processed materials	Storage containers for storage of raw materials and processed materials	N3,500,000.00
	Packaging and labelling materials	N 1, 800,000.00
Extraction of Tank. (Stainless steel, Stirrer, heater and filters)	Fabrication: 2 Stainless Steel tanks with heating and string facility.	12,000, 000.00
Quality Control evaluation of starting materials, NIPRIMUNE	Analytical balances, Glass wares, gloves, phase masks.	4, 850 000.00
	Chemicals and reagents for QC analytical procedures (HPLC grade reagents)	4,100 000.00
	HPLC + extra Column	24,500,000.00
Capsule filling Machine accessories	Size 1 Size 2	1, 500 000. 00 1, 500 000. 00

Spray dryer	Extract concentration	21, 500, 000. 00
Alternative power supply for 24h/7days power supply.	Diesel purchase, Generator servicing	7,000,000.00
	Sub-total	**N85,550,000.00**

Budget for Clinical Trial

Activity Category	Subheads	Amount (N)
Pre-study Activities	Protocol development/ Review	1,800,000
	Stakeholders Meetings	1,860,000
	Ethical Approvals	2,250,000
	Protocol Training / Facilitators Meeting	2,250,000
Trial Study	Participants Screening and Enrolment (sample collection, lab tests and examination)	9,000,000
	Follow-up (sample collection, lab tests and examination)	4.5,000,000
	Participant logistic cost (refund of transport and lost man-hour)	2,250,000
Data Management	Digital entry devices	3,000,000
	Software and storage	3,000,000
Study Personnel Cost	Principal Investigators, Co-Investigators, Site-PIs, Lab scientists, Nurses, Pharmacists, Social workers,and consultant, Administrative Assistants, Clinical Research Assistant, Data Entry personnel	30,000,000
Monitors/ Regulatory compliance	NAFDAC and DSMB	1,720,000
Logistics: Samples and personnel movement, and communication.		3,000,000
Clinical Record Materials and Stationeries	CRF, Folders, Lab test request forms, hand cards, etc	4.5,000,000
Report Writing	Report writing, review meetings	4.5,000,000
	Dissemination	2.500,000
Contingencies	10%	9,210,000
Administrative cost	25% of total cost	23,025,000
	Sub-total Cost	**108,330,000**
Grand Total		**196,880,000.00**

Activities

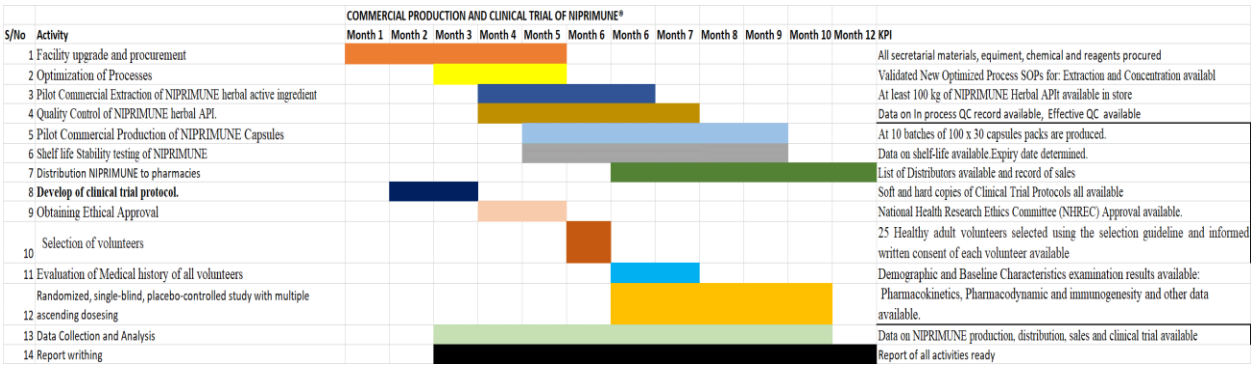
2.3 Project Activities and Output

S/No	ACTIVITIES	KPI	DURATION (Months)
1.	Facility upgrade • Procurements	1. All Secretarial Materials: • Stationaries • Analytical soft ware • Laptop 2. Chemicals and Reagents 3. Equipment (Spray dryer, HPLC,) are available and in store 4. Collection of Plant Biomass, Excipients.	5
2.	Optimization of Processes	Validated New Optimized Processes for: Extraction and Concentration available: SOPs and Protocols available. Prepared according to ISO 17025 and cGMP Standard.	3
3.	Pilot Commercial Extraction of NIPRIMUNE herbal active ingredient.	At least 100 kg of NIPRIMUNE Herbal extract available in store.	4
4.	Quality Control of NIPRIMUNE herbal active ingredient.	Data on the QC of the different batches of NIPRIMUNE herbal active ingredient available.	5
7.	Pilot Commercial Production of NIPRIMUNE Capsules	At least 10 batches of NIPRIMUNE capsules (Each batch 100 x 30 capsules Batches for Clinical Trial produced NIPRIMUNE Batches for commercial distribution available. In process QC record available Effective QC data available.	6
8.	Shelf life Stability testing of NIPRIMUNE	Data on shelf life available. Expiry date of batches available.	6
9	Distribution to pharmacies	• List of Distributors available • Record of sales	6
10	Develop of clinical trial protocol.	Soft and hard copies of Clinical Trial Protocols all available	2

	Obtain Ethical Approval	Approval from: • National Health Research Ethics Committee (NHREC).	2
	Selection of volunteers	• 25 Healthy adult volunteers selected using the selection guideline. • Informed written consent of each volunteer available.	1
	Evaluation of Medical history of all volunteers	Demographic and Baseline Characteristics examination result available: i. Sex ii. Weight, height iii. Vital signs: Blood pressure, pulse, and temperature iv. Complete hematology: WBC, differential, HCT, Hgb, platelets v. Body Mass Index (BMI) vi. Blood chemistry (Na, K, Cl, CO2, BUN, Creatinine, albumin, alkaline phosphatase, LDH, ALT, AST, bilirubin total and direct, glucose, cholesterol, triglycerides, Serum pregnancy Test vii. Urinalysis (pH, gram stain, color, glucose, cells, protein, specific gravity).	2
	Randomized, single-blind, placebo-controlled study with multiple ascending dosing of volunteers.	**Data available on each volunteer:** Data available: • Pharmacokinetics (PK) (Absorption, distribution, metabolism, and excretion (ADME) of NIPRIMUNE.	5

		• Data on Maximum Tolerated Dose (MTD) • Pharmacodynamics (PD): The general effect of NIPRIMUNE on the body. • Immunogenicity: Evaluating the immune response to NIPRIMUNE.	
	Data Collection and analysis	Processed data available and are adequately stored.	10
	Report writhing	**Report for all activities compiled**	11

Gant chart of activities and key performance indicators



Milestones and Deliverables

- cGMP-Compliant Facility: A facility that meets international quality standards for industrial-scale production of NIPRIMUNE.
- Standardized NIPRIMUNE Granules: NIPRIMUNE granules that meet international quality standards.
- Phase 1 Clinical Trial Report: A report on the safety, tolerability and immunomodulatory activity of NIPRIMUNE in healthy volunteers.
- Commercialization Plan: Commercial distribution of NIPRIMUNE.

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