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# Clinical Study Report

## Protocol No: BNL-005

# An Interventional / Prospective Phase III Accelerated Study To Determine The Efficacy and safety Of RECEPTOL® Liquid Spray Used As A Stand-Alone Mono Therapy in HIV / AIDS Patients With Multiple Symptoms

## 1. TITLE PAGE

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| **STUDY TITLE** | An Interventional / Prospective Phase III accelerated Study To Determine The Efficacy and safety Of RECEPTOL® Oral SprayUsed As A Stand-Alone Mono Therapy In HIV / AIDS Patients With Multiple Symptoms |
| **PROTOCOL CODE** | BNL-005 |
| **NAME OF INVESTIGATIONAL PRODUCT TESTED** | RECEPTOL® Oral Spray |
| **DEVELOPMENT PHASE OF STUDY** | Phase III |
| **INDICATION STUDIED** | HIV/AIDS and related communicable diseases |
| **TRIAL DESIGN** | A stand-alone, Interventional / Prospective, 12-week study in 51 subjectsto determine effect of treatment with RECEPTOL® on HIV Viral Load, Clinical & Physical Symptoms and Absolute CD4/CD8 counts in subjects with HIV / AIDS. |
| **STUDY INITIATION DATE** | October, 2006 |
| **STUDY COMPLETION DATE** | April, 2007 |
| **SPONSOR** | A2101 -04, Mansarovar, Neelkanth heights ,<br>Pokhran Rd 1, Thane West 400606, India<br><br>What's all contact : +91 82910 84108 |

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| **PARTICIPATING INSTITUTES** | **PRINCIPAL INVESTIGATOR:**<br><br>Dr. G.C. Rajadhyaksha, MD Medicine, Associate Professor: Dept. of Medicine, LTM Medical College and LTMG Hospital, Sion Mumbai – 400 022, INDIA<br><br>**STUDY CENTER:**<br><br>Lokmanya Tilak Municipal Medical College & General Hospital Sion, Mumbai – 400 022, INDIA. Phone No: 2407 6381, Fax No: 2407 6100<br><br>**CENTRAL LABORATORY:**<br><br>**National Institute of Immuno-Hematology (IIH)**, ICMR Institute, 13th Floor, New Multistoried Building, KEM Hospital Campus, Parel, Mumbai – 400 012, INDIA |

## 2. SYNOPSIS

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| **NAME OF THE PRODUCT**<br>• RECEPTOL® Oral Spray |
| **ACTIVE INGREDIENTS**<br>• RADHA 108 Series and Proline Rich Peptides (PRP) |
| **TITLE OF THE STUDY**<br>• An Interventional / Prospective Phase III Accelerated Study To Determine The Effect Of RECEPTOL® Oral Spray Used As A Stand-Alone Mono Therapy In HIV / AIDS Patients With Multiple Symptoms. |
| **STUDY SITE**<br>• Lokmanya Tilak Municipal Medical College and General Hospital, Sion, Mumbai, INDIA |

**PUBLICATION(S)**

None

**TREATMENT PERIOD**

3 Months (12 Weeks)

**OBJECTIVES**

**Primary Objective**

**To evaluate the efficacy of RECEPTOL® liquid in HIV/AIDS patients in terms of reduction in HIV viral load and HIV/AIDS related clinical symptoms.**

**Secondary Objectives**

To determine the effect of oral spray administration of RECEPTOL® liquid on:

- Change in Body Weight of patients
- Absolute CD4 and CD8 cell counts
- Overall Assessment of Efficacy and Safety/Tolerability of RECEPTOL®

**METHODOLOGY**

- This trial was a 12-week, stand-alone, study to evaluate the Efficacy and Safety/Tolerability of RECEPTOL® liquid in HIV/ AIDS patients.
- The potential subjects were screened after obtaining a written informed consent (As per Schedule Y) from the subject or LAR (Legally Acceptable Representative)/impartial witness.
- The study was designed to investigate efficacy of RECEPTOL® therapy in reducing Viral Load, clinical symptoms, & increase in Absolute CD4/CD8 cell count & change in body weight.
- The study subjects received RECEPTOL® liquid as a spray self-administered by patients on either side of the oral buccal surface 6 times daily at every 4 hour's interval. Each administration consist a metered dose of 0.75 ml spray directly on the buccal mucosa.
- Subjects' body weight was monitored at every visit to determine the effect of RECEPTOL® therapy on change in the weight.
- The subjects were also assessed for clinical symptoms and physical findings which included HIV related Fatigue/Malaise, Diarrhoea, Nausea, Vomiting, Fever, Cough, Sleep Disturbance, Skin Rash, Herpes Zoster, Lymphadenopathy, Hair Changes, Oral Thrush and Leukoplakia.
- Physician and Patient Overall Assessment were used to evaluate the efficacy and safety/tolerability of RECEPTOL® liquid at the end of the treatment.

**NUMBER OF PATIENTS**

A total of 51 patients completed the study.

**INCLUSION CRITERIA**

**For recruitment in the study, the subjects were required to be :-**

• Male and Female subjects between 18 and 60 years of age.

• Documentation of HIV infection by any approved ELISA test, and the disease contracted heterosexually (no drug abuse) preferably within six months of participation in this trial.

• **With CD4 count greater than 100 cells/cmm**

• With a measurable HIV viral load

• Subjects willing to give informed consent for their stay in the hospital and / or follow up visits.

**EXCLUSION CRITERIA**

**Patients were not included in the study if they were :-**

• Pregnant or nursing women, women of childbearing potential not using an adequate method of birth control.

• Subjects with kidney failure with Serum Creatinine greater than 1.5 mg/dL.

• With a history of Hepatic Cirrhosis.

• Suffering from Congestive Heart Failure (CHF).

• With current alcohol or substance abuse that could interfere with patient compliance.

• Organ transplant recipient.

• With Preexisting Uncontrolled Seizure Disorder.

• **Using long term systemic corticosteroids, Immuno-suppressive and ART.**

**CRITERIA FOR EVALUATION**

**Safety**

• Safety assessments consisting of monitoring and recording all Adverse Events including Serious Adverse Events.

**Efficacy**

• **The primary efficacy variables were statistically significant reduction in HIV viral load and HIV related clinical/physical symptoms based on weekly symptom assessment as per Case Report Forms (CRFs).**

• The secondary efficacy variables were change in body weight and increase in Absolute CD4 and CD8 counts based on Flow Cytometry Analysis of blood.

• An Overall Assessment of Efficacy and Safety/Tolerability were made by both, the Principal investigator (treating physician) and the subjects (participating patients)

**STATISTICAL METHODS**

• Case Report Forms completed in all respects and reports from the Principal Investigator were evaluated at the **Department of Biostatistics, All India Institute of Medical Sciences, New Delhi**

• The primary efficacy end points were the effect of therapy on the markers of HIV disease including reduction in HIV viral load and HIV related clinical symptoms while the secondary efficacy end points included body weight gain and increase in absolute CD4/CD8 cell count along with the general well being of the patients. The data on absolute CD4/CD8 counts and HIV viral load was taken from the CRFs provided at baseline and at Week 12 (End of Treatment) while body weight of the subjects was monitored every week. Clinical symptoms and physical findings were analyzed by using Frequency and percentage of responders, at every week. Whereas the body weight gain was calculated using paired sample t-test at 5% level of significance.

• The mean change in HIV viral load and Absolute CD4 and CD8 count were statistically calculated from Baseline to Week-12 using paired sample t-test at 5% level of significance.

• Other Laboratory Assessments included in the Study (Hb, WBC, SGOT and SGPT, Albumin, Serum Creatinine and Bilirubin) were also calculated using paired sample t-test at 5% level of significance.

• Overall Assessment of Efficacy and Safety/Tolerability recorded at the end of treatment by Physicians and Patients was calculated by using frequency distribution and percentage.

**STUDY RESULTS**

**Efficacy Results**

• **HIV Viral Load based on PCR Diagnosis**: At the end of 12-Weeks Treatment (end of the study) with RECEPTOL®, **mean Viral Load showed a significant reduction ($p<0.001$) from baseline** as evident in the statistical analysis. These measurements were made at the Institute of Immuno- Hematology (IIH), ICMR centre, KEM Hospital, Mumbai at the beginning (baseline) and at the end of the 12 weeks trial treatment.

• **Improvement In Clinical Symptoms**: There was a marked improvement in HIV related clinical symptoms and many patients became asymptomatic at the end of 3 weeks therapy ($p <$

0.001) At baseline, all the patients exhibited symptoms of fatigue malaise however, all were asymptomatic at the end of 4 weeks treatment with RECEPTOL®. HIV related Diarrhoea and Nausea was cured in all patients from 3rd week onwards with significant fall from 2nd week while a significant fall in HIV related Vomiting was seen in patients within 1st week of treatment with RECEPTOL®. All patients became asymptomatic form 3rd week onwards. There was a significant fall in the incidence of Fever, Cough and related symptoms in all patients at the end of 1st week of treatment and all became asymptomatic after 3rd week onwards with the therapy. While HIV related symptoms of Disturbed Sleep and Skin Rash had a significant fall after 2nd week of treatment and patients showed no signs of these symptoms after 3rd week of the therapy. Lastly, number of subjects with HIV related Herpes Zoster showed a significant reduction at the end of 1st week and became asymptomatic after 3$^{rd}$ week with the treatment of RECEPTOL®.

• **Absolute CD4 and CD8 counts**: At the end of 12-Weeks Treatment (end of the study) with RECEPTOL®, **67% of patients (34 out of 51) showed an absolute increase in CD4 counts**, **75% of patients (38 out of 51) showed an absolute increase in CD8 counts** and mean CD4 and CD8 counts showed significant increase ($p=0.042$ & $p=0.0080$ respectively), based on Flow Cytometry Analysis conducted at the Institute of Immuno-Heamatology (IIH), ICMR centre, KEM Hospital, Mumbai

• **Body Weight Gain (Monitored Weekly)**: A significant increase was evident in bodyweight of all the 51 HIV positive patients who completed the trial treatment. A mean gain of 4.68 ± 1.9 kg in body weight ($p<0.001$) was seen at the end of 12 weeks trial treatment with RECEPTOL®.The gain in body weight ranged between 2 to 9 kgs.

**Safety & Tolerability Results**

• All patients tolerated RECEPTOL® well with No Adverse or Serious Adverse Events reported.

**Overall Efficacy & Safety/Tolerability Assessment by Principal Investigator & Patient**

• **According to Principal Investigators Assessment:**

- 52% of patients showed an absolute increase in CD4 Cell Counts
- 62% of patients showed an absolute decrease in viral load
- 32% of the patients showed increase in CD4 Cell Counts and decrease in HIV Viral load for efficacy of the trial drug treatment.

- 98% of the patients showed Good and Satisfactory results in terms of the safety/tolerability of the trial drug treatment.

• **According to Patients Assessment:**

- 94% of the patients showed Good and Satisfactory results for efficacy of the trial drug treatment.
- All patients showed Good and Satisfactory results for the safety/ tolerability of the trial drug treatment.

**CONCLUSION**

Treatment with RECEPTOL® had a clinically relevant and consistent effect in patients with HIV/AIDS disease. The HIV viral load assessed by PCR method showed a significant reduction from the baseline values. The Absolute CD4 and CD8 counts showed a significant increase from baseline, at the end of 12 weeks therapy with RECEPTOL® as analyzed by Flow Cytometry method. The Clinical and Physical HIV related symptoms also improved with the therapy and the patients became asymptomatic within 3 weeks after the start of RECEPTOL®. The 12 weeks trial treatment with RECEPTOL® was well tolerated with no incidence of any side effects/contraindications reported in any of the patients studied. The results showed that RECEPTOL® is an effective and safe drug in increasing weight and general well being of patients, decrease in HIV viral load and increase in absolute CD4 & CD8 cell counts. Thus RECEPTOL® is a new, safe and natural therapeutic option for HIV / AIDS and other immuno-compromised patients. It can also work as an immunomodulator and can boost the immunity as an adjunct therapy for life-threatening critical ailments and recurrent infections from communicable diseases.

## 3. STATEMENT OF COMPLIANCE

This study was conducted in compliance with the Protocol as well as the Sponsor's and CRC's (CRO) **Standard Operating Procedures**. These were designed to ensure adherence with the ethical principles that have their origin in the **Declaration of Helsinki, Good Clinical Practice (GCP)** and applicable regulatory requirements. Also in accordance with **'Guidelines for Clinical Trials on Pharmaceutical Products in India-GCP Guidelines'** issued by the Central Drugs Standard Control Organization (CDSCO), Ministry of Health, Government of India.

## 4. LIST OF ABBREVIATIONS AND DEFINITIONS

***List of Abbreviations***

- **AIDS** Acquired Immunodeficiency Syndrome
- **ART** Anti-Retroviral Therapy
- **ARS** AIDS Related Complex
- **CD4** Cluster Of Differentiation 4
- **CD8** Cluster Of Differentiation 8
- **CHF** Congestive Heart Failure
- **CRF** Case Report Form
- **CRC** Clinical Research Coordinator
- **CRO** Contract Research Organization
- **CDSCO** Central Drugs Standard Control Organization
- **cmm** Cubic Millimeter
- **DCGI** Drug Controller General of India
- **DGHS** Director General Health Services
- **dL** Deciliter

- **ELISA** Enzyme Linked Immuno Sorbent Assay
- **GCP** Good Clinical Practice
- **Hb** Haemoglobin
- **HIV** Human Immunodeficiency Virus
- **ICMR** Indian Council Of Medical Research
- **IIH** Institute of Immuno-Heamatology
- **INF** Interferon
- **LFT** Liver Function Test
- **$mm^3$** Per cubic millimetre
- **ml** Millilitre
- **mg** Milligram
- **NABL** National Accreditation Board for Testing and Calibration Laboratories
- **NACO** National AIDS Control Organization
- **NKC** Natural Killer Cell
- **NNRTI** Non-Nucleoside Reverse Transcriptase Inhibitor
- **NRTI** Nucleoside Reverse Transcriptase Inhibitor
- **PCR** Polymerase Chain Reaction
- **PRP** Proline-Rich Polypeptide
- **RFT** Renal Function Test
- **SGOT** Serum Glutamic Pyruvic Transaminase
- **SGPT** Serum Glutamic Oxaloacetic Transaminase
- **TNF** Tumor Necrosis Factor

• **WBC** White Blood Corpuscle

• **WHO** World Health Organization

***Definitions of Terms***

• **Eligible:** Qualified for enrolment into the study based on strict adherence to inclusion and exclusion criteria.

• **Evaluable:** Meeting all eligibility criteria, complying with the procedures defined in the Protocol and therefore included in analysis.

• **Investigator:** Treating physician

• **Subject(s):** Term used throughout this report to denote the enrolled individual(s)

**5. TABLE OF CONTENTS**

## 6. ETHICS COMMITTEE

This study was conducted in accordance with the ethical principles of Declaration of Helsinki. Ethical approval of the Study Protocol was obtained from the Ethics Committee at Institution (Lokmanya Tilak Municipal Medical College and General Hospital, Sion, Mumbai) where the study was conducted before the study was undertaken. The approval of the Ethics Committee was given in writing on **February 24, 2005.** The original documents were sent to Sponsor and the Investigator filed a copy. In addition, all local regulatory requirements were adhered to. All attempts will be made to protect the interest of the study patients. The Institution review broad consisting of scientific and ethics committee's under the research society of LTMMC and LTMG Sion hospital, Mumbai has approved the following: Study Protocol/Amendment(s), written

Informed Consent Form including patient information sheet, consent form updates and patient recruitment procedures.

The EC notifications were followed as per Good Clinical Practice Guidelines issued by Central Drugs Standard Control Organization (CDSCO) and Ethical Guidelines for Biomedical Research on Human Subjects issued by Indian Council of Medical Research (ICMR).

## 7. INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

***Investigators:***

**PRINCIPAL INVESTIGATOR**

Dr. G.C. Rajadhyaksha, MD Associate Professor: Dept. of Medicine, LLT Medical College and Sion Hospital, Mumbai – 400 022, INDIA

***Project Coordinator:***

Dr. Pawan Saharan *, Chairman and CEO Biomix Network Ltd. Millennium Business Park, Unit No.303, Building 6, Sector-3, M. I. D. C., Mahape, Navi Mumbai, Maharashtra – 400 709, INDIA

*Based on January 12, 2005 notification of Ministry of Health, Government of India.

***Study Centre:*** Lokmanya Tilak Municipal Medical College and General Hospital Sion, Mumbai – 400 022, INDIA

***Sponsor:***

Ministry of Health; National AIDS control Organisation (NACO), Government of India and Biomix Network Limited Millennium Business Park, Unit No.303, Building 6, Sector-3, M. I. D. C., Mahape, Navi Mumbai, Maharashtra – 400 709, INDIA

***Central Laboratory:***

National Institute of Immuno-Hematology (IIH), ICMR Center, 13th Floor, New Multistoried Building, KEM Hospital Campus, Parel, Mumbai – 400 012, INDIA

***Trial Statistician:***

Dr. Guresh Kumar (Scientist), M.Sc., M.Phil., PhD (Statistics): Dept of Biostatistics, All India Institute of Medical Sciences, Ansari Nagar, New Delhi – 110 029, INDIA

## 8 INTRODUCTION

***Introduction: HIV/AIDS and Types of Treatment:***

The advent of HIV/ AIDS has graphically demonstrated that our knowledge of viruses and how to treat viral infections was not adequate. According to the joint United Nations program on HIV/AIDS and World Health Organization (WHO), some 25 million people have died of HIV / AIDS in the past 25 years and an estimated 38.6 million are infected with the virus, making it

one of the most lethal epidemic in the history of mankind. Currently five classes of drugs are approved by US FDA for treatment of HIV infected patients. These five classes are Nucleoside Reverse Transcriptase Inhibitor (NRTI/NtRTI), Non-Nucleoside Reverse Transcriptase Inhibitor (NNRTI), Protease Inhibitor (PI), entry inhibitors and Integrase Inhibitor. Anti Retroviral Therapy (ART) regimen is complicated due to the high cost of treatment, poor compliance, pill burden, peculiar storage requirements, drug-drug interactions, comorbidities like tuberculosis, liver disease, cardiovascular complications and importantly treatment failure due to resistance to drugs acquired by the virus through mutation. All the antiviral drugs developed so far to fight HIV infection, exhibit serious side effects like Nausea, Diarrhoea, Vomiting, Pancreatitis, Anaemia, Peripheral Neuropathy, Lactic Acidosis, Dyslipidemia and others. Currently, the US FDA has approved 29 drugs for use in the treatment of HIV Infection5. The presently available ART is very expensive. The future outlook for HIV / AIDS treatment from a pharmaceutical perspective remains bleak despite significant gains in understanding of the virus. This situation has forced scientists to look for alternative effective solutions.

A promising alternative which may prove more effective can be to stimulate the body's own defenses against the virus as well as the infected cells. Dietary supplementations of many naturally occurring substances have been claiming to boost human immunity by activating human Natural Killer (NK) cell activity. One such area of investigation is based on an age-old remedy, the Colostrum, the first milk produced by a mammal following the birth of a newborn, which was widely used as an immunity booster and natural antibiotic before modern antibiotics were developed. Colostrum and various components of it have already been demonstrated to be useful in treating opportunistic infections related with HIV/ AIDS such as Diarrhoea caused by Clostridium, Campylobacter and Amoeba spp.13. Specifically one of the components of Colostrums, the nano-peptides classified under Radha 108 series (Patent pending by Biomix Network Ltd.) and Proline Rich Polypeptide (PRP) – Infopeptide has shown great promise. This unique polypeptide (a peptide fraction of whole Colostrum) has been shown to exhibit Immunomodulatory activity as well as antiviral activity14. The advantage of these compounds over conventional antiretroviral drugs is that these display a much shorter response time for alleviation of physical and clinical symptoms of the disease and a relatively quick normalization of NK activity. It is the only Immunomodulator produced by mammals themselves for their progeny. The key factor is however, the protein fractionation and ultra filtration technology needed to extract Radha 108 and Proline-Rich Polypeptide (PRP) extraction which is developed now by Biomix Network Ltd using patented technology and molecular weight exclusion columns to ensure consistency of product batch after batch in every bottle of RECEPTOL®.

***RECEPTOL®: Product Development Rationale***

The application of RECEPTOL® is, in the medical field of Immuno-therapy which is a quiet revolution taking place in medicine. It is a form of treatment that uses the different aspects of your immune system, its cells and molecules and its various stratagems to tip the balance in your favor as your body battles to maintain health.

RECEPTOL® comes to us after nearly fifty years of research and over 3,500 scientific medical papers, which prove its effectiveness. It is found in colostrum and is a natural way of strengthening our immune systems against disease.

RECEPTOL® contains the Nano-Informational Peptides (RADHA108) and Proline-Rich Polypeptides (PRPs), derived from bovine Colostrum, which helps in strengthening the body's own immune system against diseases in a natural way. The Nano-polypeptides have been known for long for their antiviral, anti-inflammatory and immune enhancing properties. However, the molecular mechanism of their action in conjunction with low molecular weight Nano-peptides was not known until *Dr. Theodore Damodar Singh*, an Applied Biochemist from University of California Irvine and Founder Director, Chaitanya Healthcare, India and Dr. Pawan Saharan, Chief Scientific Officer and Founder Director, Chaitanya Healthcare and Biomix Network Ltd., India identified and studied a series of *Nano- Informational Peptides (RADHA1081-100)* from Bovine Colostrum.

The fusion of viral particles with human white blood cells occurs with the aid of glycoprotein epitopes on the viral wall. The informational proteins (RADHA1081-100) in RECEPTOL® have been shown to mitigate cell fusion. The RADHA1081-100 series of molecules may dock on the glycoprotein receptors of the viral surface mimicking their receptors on the cell surfaces and thus block the virus entry into the immune cells. One of the Immunomodulatory action of RECEPTOL® is to stimulate the maturation of immature thymocytes into either helper or suppressor T cells4,5, depending on the need of the body at a given time. Helper T cells present antigens (such as viral protein) to B lymphocytes, which in turn produce antibodies to that antigen6. Helper T cells also help produce memory T cells which retain the memory of an antigen in order to expedite the production of antibodies in the event the antigen is reencountered in the future7. Suppressor T cells, on the other hand, have been shown to deactivate other lymphocytes after an infection has been cleared to avoid damage to healthy tissues8. RECEPTOL® may also promote growth and differentiation of B-cells in response to an infection9 and the differentiation and maturation of macrophages and monocytes10. The activity of Natural Killer (NK) cells, cytotoxic cells of the innate immune system, is increased by up to 5-fold by RECEPTOL®11, 12. RECEPTOL® may modulate the cytokine system as well. Its constituents have been shown to stimulates the production of a wide range of cytokines, including the pro-inflammatory cytokines Tumor Necrosis Factor – Alpha (TNF-_) and Interferon Gamma (INF–_) and anti-inflammatory cytokines Interleukin – 6 and – 1013.

The constituents of RECEPTOL® may function as a molecular signaling device which works through receptors on target cell surfaces14 to initiate or suppress the production of specific proteins. This property is not species specific2; and hence the constituents of RECEPTOL® derived from bovine Colostrum may work as effectively in humans too like the PRP of human Colostrum. There are no known side effects or drug interactions with the constituents of Colostrum, and it may be taken safely by patients of all ages. In an experimental in vitro system, the constituents of RECEPTOL® have been shown to effectively block HIV infection of cells15.

RECEPTOL® in combination with Zidovudine®, a known anti-retroviral drug, has been shown to be effective in patients suffering from HIV/AIDS Related Complex (ARC), effecting an increase in White Blood Cells, CD8 lymphocytes and IL-216.

RECEPTOL® has shown to be effective in treating many different diseases and conditions including Allergies, Thrush, Diabetes (type II), Rheumatoid Arthritis, Corneal Regeneration, Diarrhoea, Hemolytic Anemia, Tuberculosis, HIV, Hepatitis A & C, Acute Viral Infections, Pharangitis (Viral), Viral Respiratory Infection, Plantar Warts, Colds and Flues, Herpes Simplex I& II etc.

***Results of Previous Phase I, II & III International Studies***

RECEPTOL® demonstrated in-field and clinical use with more than 10,000 HIV infants, children and adults in many countries. There have been no known exceptions to the ability to affect theprogression of many chronic degenerative diseases for which it has been used. In many cases, the formula has induced what appears to be complete and lasting cellular recovery.

RECEPTOL® has shown to be effective in treating many different diseases and condition. However, it is prudent to focus attention on a few well-known diseases. Initially, Rheumatoid Arthritis was the selected disease to put under the microscope. The success of treating this autoimmune condition led to the selection of a high profile disease – HIV. RECEPTOL® has beenused with positive results in more than 10,000 patients globally for HIV & other Viral infections, Tuberculosis, immunological diseases.

*RECEPTOL® Phase I trial in Ohio, USA::* This trial was conducted on 12 HIV patients with 30 days treatment of moderate control of product use. Results obtained from this trial were 10 out of 12 patients gained weight during the thirty-day trial period, of the 10 that gained weight, 7 (70%) gained an average of 6 lbs, 5 patients gained 6 lbs in one month, while 2 others 5.5 and 6.6 lbs respectively, the highest weight gain of 12 lbs was recorded for a patient who had been HIV positive since 1986 (10 years). 8 out of 10 patients had various levels of diarrhoea (mild, moderate or severe) at the beginning of the trial period. Out of the 8, 5 patients (62%) went from varying levels of diarrhoea severity to No diarrhoea symptoms. The 1 patient without weight

gain experienced total elimination of severe chronic diarrhoea and a return to solid stool formation. 8out of 12 patients had various levels of nausea at the beginning of the trial period. Of the 8, 5patients (62%) went from varying levels of severity of nausea symptoms to No nausea. Of theremaining 3 patients, with some degree of nausea, 2 experienced a reduction in the severity oftheir symptoms. 9 out of 10 patients, who reported fatigue symptoms at the beginning of the trial,experienced an increase in their level of energy. 3 out of 10 experienced a significant increase inenergy, from initial varying levels of fatigue to No fatigue. 4 out of 12 had either a mild tomoderate cough at the beginning of the trial. 2 of the 4 reported No cough at the end of the trailperiod. Of the remaining 2 individuals, 1 reported a reduction in the severity of his cough. All 12patients experienced an improvement in their overall symptoms assessment score. The averagereduction approached 2/3 (63%) – Dr Brandt. Since 1996, several improvements in the process engineering were made to increase the efficacy of RECEPTOL®.

*RECEPTOL® Phase II trial in Nairobi, Kenya (August 2000):* This trial was conducted in 30 HIV patients with 90 days treatment of moderate control of product use. The objectives of this study were to demonstrate, under clinical conditions, the Efficacy and Safety of Infoprotein supplementation in patients known to have advanced disease (HIV/AIDS), compromised immune resources and limited access to conventional treatment. Positive clinical results were observed in the Nairobi patients. The results demonstrated that the product appeared to be free of side effects and generally well tolerated by the participants. Some signs, consistent with detoxification, were noted but resolved when the patients increased their water consumption. The product demonstrated significant value by reducing or resolving the symptoms of opportunistic infections most commonly related with the dynamic of HIV/AIDS. Patients often experienced weight gains as part of an overall pattern of positive response.

Conclusion: Because of differences in size, cohort profile and length of evaluation period, the Nairobi study yielded a greater quantity of information that included positive clinical responses in three additional areas: hypertension, systemic lupus and tuberculosis. Several patients that had been bedridden for some time became ambulatory and were able to come to the clinic for continued participation in the study.

*RECEPTOL® Phase III trial Rwanda, Africa (November 2002):* This trial was conducted in 60 HIV patients with 365 days treatment of moderate control of product use. The objectives of this study were to demonstrate, under clinical conditions, the Efficacy and Safety of Infoprotein supplementation in patients known to have advanced disease (HIV/AIDS). Cohorts were all symptomatic, ambulatory, compliant and native to Anti-Retroviral Therapy. All patients received RECEPTOL® every 6 hours for a period of 365 days. Positive clinical results were continually observed in the Rwanda patients. The results demonstrated that the product appeared to be free of side effects and generally well tolerated by the participants. Some signs, consistent with

detoxification, were noted but resolved when the patients increased their water consumption. The product demonstrated significant value by reducing or resolving the symptoms of opportunistic infections most commonly related with the dynamic of HIV/AIDS. Patients often experienced weight gains as part of an overall pattern of positive response. After 1 day of use there was a moderate level of relief of fever and diarrhoea. After 14 days of use all patients experienced relief of skin lesions, mouth thrush, fever, diarrhoea and tuberculosis. After 90 days of use all patients experienced relief of all symptoms. After 330 days all patients did not experience any negative symptoms.

*Subsequent to finding positive results of Efficacy and Safety/Tolerability in phase I, II & III trials with RECEPTOL® in the US and Africa, the Ministry of Health and Family Welfare, Government of India, under the Pharmaceuticals Research and Development Support Fund, had funded a phase III trial of its efficacy in HIV / AIDS patients coordinated by National AIDS Control Organization (NACO) / Indian Council of Medical Research (ICMR) / Director General Health Services (DGHS) / Drug Controller General of India (DCGI) in consultations with Dr. Pawan Saharan, Chairman, Biomix Network Limited, India at Lokmanya Tilak Municipal Medical College, Sion, Mumbai during October 2005 & October 2006. Study I included 50 patients with HIV/AIDS in which RECEPTOL® showed positive results in terms of its Efficacy and Safety/Tolerability. On recommendation of ICMR and NACO Study was extended and Study II including 51 patients with HIV / AIDS was planned with Clinical Diagnostic Testing at Indian Institute of Heamatology (ICMR Institute), KEM Hospital, Mumbai. The objective of this study was to determine the efficacy of a novel dosage form of an oral spray of RECEPTOL® liquid in the HIV infected patients with respect to effect on the HIV viral load, AIDS related clinical symptoms/physical findings, absolute CD4 & CD8 cell counts and effect on body weight.*

***Background of RECEPTOL® Trials in HIV Patients***

- Phase I: HIV trial, USA
- Phase II : HIV trial, Nairobi – Kenya
- Phase III: HIV trial, Rwanda for 365 days.

**Phase III: Revalidation trial by Government of India on HIV patients**

- Jan 12, 2005: Ministry of Health & Family Welfare, approval for the Phase III Receptol
- March 03, 2005: Scientific and Ethics Committee of L. T. M. M. college, Sion approval for clinical trial
- May 11, 2005: ICMR –Toxicology Review Panel Approval
- June 27, 2005: ICMR appointed Dr. Khedkar (NARI, Pune) & Dr. Thatte (Clinical Pharmacologist, BYL Nair Hospital) as observer for the trial with ICMR recommended protocol.

• Dec 19, 2005: NACO Apex Research Committee approval and funding for Phase III Receptol Trial
• March 30, 2006: Department of Science and Technology funding for the project under PRDSF with recommendation of the President of India
• Study I (2006-07): Accelerated, prospective Phase III efficacy study for RECEPTOL® was conducted for 50 HIV seropositive patients at Lokmanya Tilak Municipal Medical College, Mumbai - Clinical Trial Registry No: 2009 000181

Study II (2007-08): Accelerated, prospective Phase III efficacy study for RECEPTOL® was conducted for 51 HIV seropositive patients at Lokmanya Tilak Municipal Medical College, Mumbai - Clinical Trial Registry No: 2009 000182

## 9 STUDY OBJECTIVES

***Primary Objective***

**To evaluate the efficacy of RECEPTOL® liquid in HIV/AIDS patients in terms of reduction in HIV viral load and HIV/AIDS related clinical symptoms.**

***Secondary Objectives***

To determine the effect of oral administration of RECEPTOL® liquid spray on:
• Change in Body Weight of patients
• Absolute CD4 and CD8 cell count
• Overall Assessment of Efficacy and Safety/Tolerability of RECEPTOL®

## 10 INVESTIGATIONAL PLAN

***Overall Study Design and Plan: Description***

• This was a stand-alone, 12-week study undertaken to determine the effect of treatment with RECEPTOL® on HIV viral load and clinical symptoms in 51 subjects with HIV / AIDS. Both Male and Female HIV/AIDS subjects between 18 and 60 years of age who fulfilled the Inclusion and Exclusion Criteria were enrolled for this study. Written Informed Consent from these subjects was obtained prior to their enrollment.

• Stand alone trials were conducted because drugs of Anti Retroviral therapy are so strong that they mask the effect of any other drug given along with it. Also placebo controlled trials were not conducted as they were not approved by Ethics Committee.

• This study was conducted to determine the efficacy of RECEPTOL® liquid spray administered daily for 12 weeks. The study was designed to investigate for the effect of RECEPTOL® therapy on viral load and clinical symptoms and physical findings. Also, to monitor the effect on Absolute CD4 and CD8 cell counts. The primary endpoints of the study included effect of this therapy on markers of HIV disease including the reduction in HIV viral load and improvement in clinical symptoms. The secondary endpoints included increase in Absolute CD4 and CD8 cell counts, body weight gain, along with the general well being of the patients.

• Participants were evaluated in the clinic once every week through the first 4 weeks of therapy, and then onwards at every 2 weeks interval for the remaining 8 weeks of the study. Patients were evaluated for clinical and physical symptoms through symptom assessment forms, physical examination, incidence of side effect of treatment and compliance to trial treatment on follow up visits. Blood tests to measure CD4/CD8 cell counts, HIV viral load, Haemoglobin, White Blood Corpuscles (WBC) Count, Liver Function Tests (LFT) and Renal Function Tests (RFT) were done at baseline and at end of study treatment.

• Absolute CD4 and CD8 cell counts were analyzed by Flow Cytometry and HIV viral load using Polymerase Chain Reaction at the Institute of Immuno Hematology (IIH), an ICMR Institute, KEM Hospital, Mumbai.

***Subject Selection Criteria***

• The selection of subjects for this trial was based on the following Inclusion and Exclusion criteria.

**INCLUSION CRITERIA**

• Male and Female Subjects between 18 and 60 years of age.
• Documentation of HIV infection by any licensed ELISA test, disease contracted heterosexually (no drug abuse) preferably within six months.
• **Subjects having CD4 count greater than 100 cells/cmm**.
• Subjects will have measurable HIV viral load.
• Willingness to give informed consent for the stay in the hospital and or follow up visits.

**EXCLUSION CRITERIA**

• Pregnant or nursing women, women of childbearing potential not using an adequate method of birth control.
• Subjects with kidney failure with serum creatinine greater than 1.5 mg/dL.
• A history of Hepatic Cirrhosis.
• Congestive Heart Failure (CHF).
• Current alcohol or substance abuse that could interfere with patient compliance.

• Organ transplant recipient.
• Pre-existing Uncontrolled Seizure Disorder.
• **Subjects using long term systemic corticosteroids, Immuno-Suppressive and ART**.

***Treatment Procedures***

• RECEPTOL® liquid spray used in the study was a Colostrum product, containing natural microscopic molecules of Radha108 of 800 – 1200 Dal molecular weight (below 2000 DaL that enable to cross bbb- Blood brain barrier) and PRPs consisting of oligoribonucleotides attached to a peptide molecule. RECEPTOL® was manufactured by Biomix Network Ltd., Mumbai by protein fractionation and ultra nano filtration technology the only nanotechnology based plant in India. Eligible patients were evaluated for medical history, physical examination, blood and urine tests, and other tests as determined by the Principal Investigator. Patients had received RECEPTOL® liquid in pump spray form and were taught to self-administer the medication. The Frequency of dose administration was 6 times per day at every 4 hour intervals. Each single administration consisted of 5 sprays directly on the buccal mucosa (inner cheek). The patients were advised to gargle the medication in the mouth for 1 minute before swallowing it. Each pump of the spray device delivered 0.75 ml of RECEPTOL® liquid. The trial treatment as described above was continued for a period of 12 weeks.

**Assesment schedule**

| Study Activities | Screening (Week 0) | Visit 1 (Week 1) | Visit 2 (Week 2) | Visit 3 (Week 3) | Visit 4 (Week 4) | Visit 5 (Week 6) | Visit 6 (Week 8) | Visit 7 (Week 10) | Visit 8 (Week 12) |
|---|---|---|---|---|---|---|---|---|---|
| Inclusion/Exclusion Criteria | X | | | | | | | | |
| Patient Informed Consent | X | | | | | | | | |
| Relevant Medical History | X | | | | | | | | |
| Physical And Systemic Examination | X | | | | | | | | X |
| Demography | X | | | | | | | | |
| Chest X-ray And ECG | X | | | | | | | | |
| CD4/CD8 Cell Count And HIV Viral Load Examination | X | | | | | | | | X |
| Hb, WBC And Differential Count | X | | | | | | | | X |
| Clinical and Physical Symptoms | | X | X | X | X | X | X | X | X |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Body Weight | X | X | X | X | X | X | X | X | X |
| Overall Assessment Of Efficacy And Tolerability | | | | | | | | | X |
| Liver Function Test | X | | | | | | | | X |
| Renal Function Test | X | | | | | | | | X |
| Study Medication Dispensed | | X | X | X | X | X | X | X | |
| Adverse Events | | | X | X | X | X | X | X | X |

***Compliance***

• Each patient self administered 4 sprays (each measuring 0.75 ml of the liquid) of RECEPTOL®liquid, daily, at every 4 hour intervals. They were advised to have a 6 hrs sleep, at a time, to facilitate 6 hourly medication and were also advised to follow a regular daily exercise.

• Patients were instructed to spray the study drug in mouth and allow it to circulate in mouth for 1 minute and then swallow it.

• Patients were asked to follow a well balanced diet of 40% Carbohydrates, 30% Protein, 30% Fats and Oils, to drink plenty of clean fresh water and avoid any such food that may cause increased gastric acidity.

***Blinding/Randomization Technique***

• Not Applicable

***Assessment of Efficacy and Safety/Tolerability Criteria***

• Blood Samples to assess the HIV viral load, Absolute CD4 and CD8 cell counts and other laboratory parameters including Haemoglobin (Hb), White Blood Corpuscles Count (WBC), Liver Function Tests (LFT) and Renal Function Tests (RFT) were collected at baseline (Week 0) and end of treatment (Week 12).

• HIV viral load was assessed on basis of PCR Diagnosis while Absolute CD4 and CD8 cell counts were based on Flow Cytometry System Analysis.
• Clinical symptoms and Physical Findings which included HIV related Fatigue Malaise, Diarrhoea, Nausea, Vomiting, Fever, Cough, Sleep Disturbance, Skin Rash, Herpes Zoster, Lymphadenopathy, Hair Changes, Oral Thrush and Leukoplakia were assessed using Symptom Assessment Form which was recorded in patients every visit.
• Safety parameters were assessed by measuring the number of Adverse and Serious Adverse Events
• An Overall Assessment of Efficacy and Safety/Tolerability was made by both, the treating Physician and the participating patients.

***Statistical Methods Used***

• The primary efficacy parameter i.e. HIV viral load was analyzed statistically by using paired sample t-test at 5% level of significance. A mean change in this parameter was observed from Baseline to Week-12 (End of Treatment).
• While HIV related clinical symptoms and physical findings were calculated using frequency and percentage of patients showing / reporting these symptoms.
• Secondary efficacy parameters including body weight gain and absolute CD4/CD8 cell counts was analyzed using paired sample t-test at 5% level of significance.
• Overall Assessment of Efficacy & Safety/Tolerability by Physicians & Patients was calculated by using frequency distribution and percentage.

## 11 TRIAL SUBJECTS

A total of 51 patients were enrolled and all completed study without any drop-out. Thus, at the end of study, pre and post treatment data of 51 patients mentioning clinical symptoms and biochemical profile including CD4/CD8 cell count and HIV viral load were available for analysis. *Based on the experience gained in study 1 the drop out for study 2 was NIL.*

***(Total no. of Patients Enrolled = 51 and Analyzed = 51)***

## 12 STUDY RESULTS

***Demography Details***

***Table Showing Demography Of Subjects Enrolled:***

| Demography | | Statistics | Result |
|---|---|---|---|
| Age (years) | | Mean | 43.35 |
| | | SD | 9.14 |
| | | Range | (21-60) |
| Sex | Male | N% | 21(41.18) |
| | Female | N% | 30(58.82) |
| Body Weight (kg) | | Mean | 49.21 |
| | | SD | 12.33 |
| | | Range | (29.00-73.80) |

In this study group the age of patients ranged from 21 to 60 years with the mean age of 33.5. Mean body weight of the patients was 49.21 Kg. Out of the total 51 cases, 41.18% were male and 58.82% were female.

***Efficacy Evaluation***

**Primary Efficacy Results:**

***Table Showing HIV Viral Load Measured at Baseline and at the End of 12 Weeks Treatment with* RECEPTOL®**

| ***Parameter*** | ***Baseline Mean ± SD*** | ***Week 12 Mean ± SD*** | ***Difference (Week 12-Baseline Mean ±*** | ***P-Value*** |
|---|---|---|---|---|

| | | | ***SD)*** | |
|---|---|---|---|---|
| ***Viral load (Cop/ml)*** | 119243.49 ± 215799.83 | 38814.33 ± 53077.97 | - 80429.16 ± 199920.54 | 0.006* |

**HIV Viral Load: At the end of 12 weeks treatment with RECEPTOL® the mean Viral Load showed a significant fall ($p < 0.01$) from that determined at the baseline. There was a fall in mean Viral Load from baseline value of 119243.49 to 38814.33 at the end of 12 weeks treatment.**

**Table Showing Number of Patients Showing Various Clinical and PhysicalSymptoms (Incidence) and Its % Frequency at Baseline and Week 2 Visits.**

| Clinical Symptoms | N | At Baseline | Responders At Week-2 |
|---|---|---|---|
| Diarrhoea | 51 | 51(100%) | 12(23.53%) |
| Nausea | 51 | 51(100%) | 3(5.9% |
| Vomiting | 51 | 51(100%) | 17(33.3%) |
| Fever | 51 | 51(100%) | 13(25.5%) |
| Cough | 51 | 51(100%) | 13(25.5%) |
| Fatigue | 51 | 51(100%) | 51(100%) |
| Paraesthesia | 51 | 51(100%) | 16(31.4%) |
| Disturbed Sleep | 51 | 51(100%) | 0(0%) |
| Skin Rash | 51 | 51(100%) | 7(13.7%) |
| Herpes Zoster | 51 | 51(100%) | 18(35.3%) |
| Lymphadenopathy | 51 | 51(100%) | 37(72.5%) |
| Hair Changes | 51 | 51(100%) | 16(31.4%) |
| Oral Thrush | 51 | 51(100%) | 0(%) |
| Leukoplakia | 51 | 51(100%) | 5(9.8%) |

51 (100%) patients showed all Clinical and Physical Symptoms at baseline and it reduced significantly from week 2 onwards and most symptoms disappeared during and at the end of 12 weeks of treatment with RECEPTOL® ($p < 0.05$). *Refer Table 12.2.2* All Clinical and Physical Symptoms reduced in 50% of the patients at week 2. Patients with HIV/AIDS related clinical symptoms of disturbed sleep and oral thrush became asymptomatic at week 2.

***Figure 1: Reduction in Number of Patients with Diarrhoea During the 12 Weeks Trial Treatment with RECEPTOL®***

**51 patients (100%) had Diarrhoea at baseline and all patients had relief from Diarrhoea from 3rd week onwards with the treatment of RECEPTOL®. (Figure 1)**

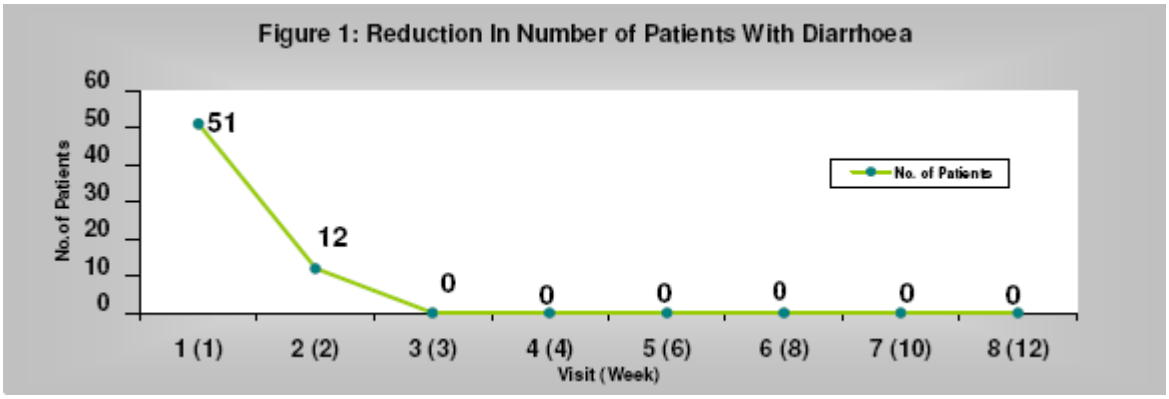



***Figure 2: Reduction in Number of Patients with Nausea During the 12 Weeks Trial Treatment with RECEPTOL®***

**100 % of the total study cases had Nausea at baseline and all patients had relief from Nausea from 3rd Week onwards. (Figure 2)**

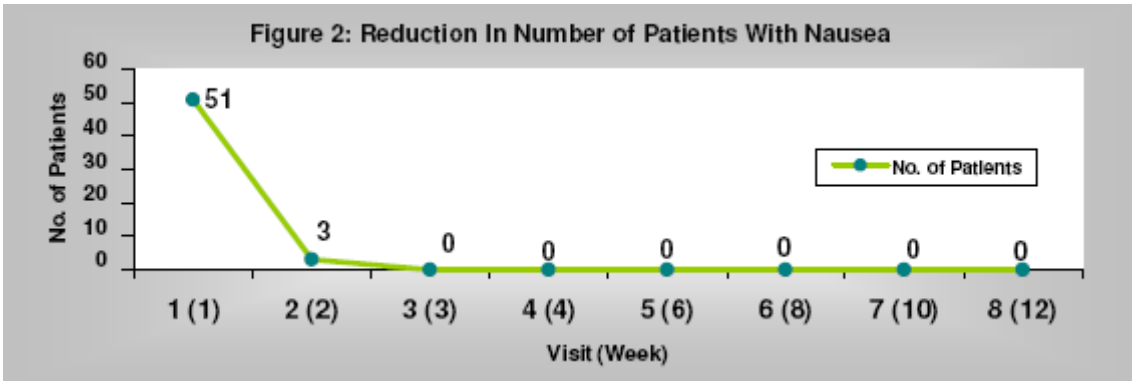



***Figure 3: Reduction in Number of Patients with Vomiting During the 12 Weeks Trial Treatment with RECEPTOL®***

**100 % of the total study cases had Vomiting at baseline and all the patients had relief from Vomiting after treatment from 3rd Week onwards. (Figure 3)**

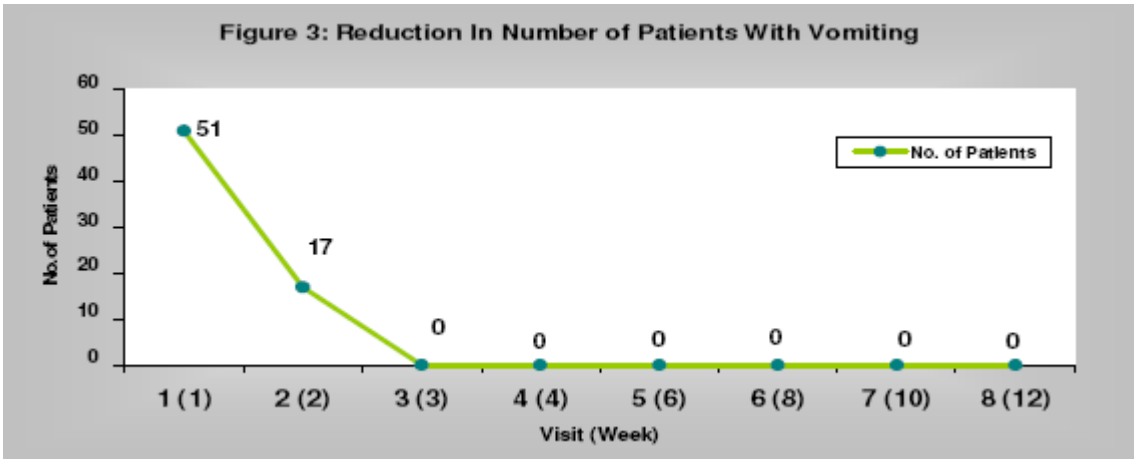



***Figure 4: Reduction in Number of Patients with Fever During the 12 Weeks Trial Treatment with RECEPTOL®***

**100 % of the total study cases had Fever at baseline and all the patients had relief from Fever from 3rd Week onwards. (Figure 4)**

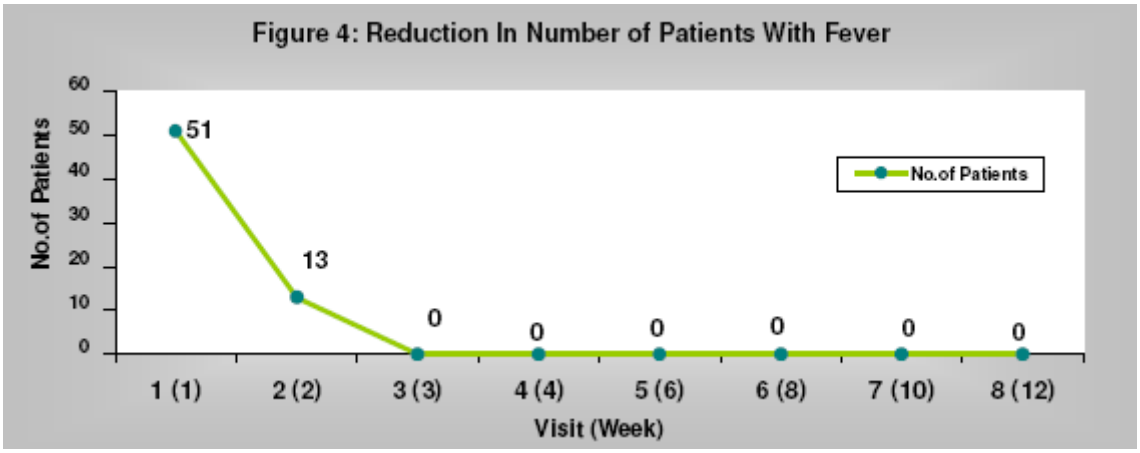



***Figure 5: Reduction in Number of Patients with Cough During the 12 Weeks Trial Treatment with* RECEPTOL®**

**100 % of the total study cases had Cough at baseline and all the patients had relief from Cough from 3rd Week onwards. (Figure 5)**

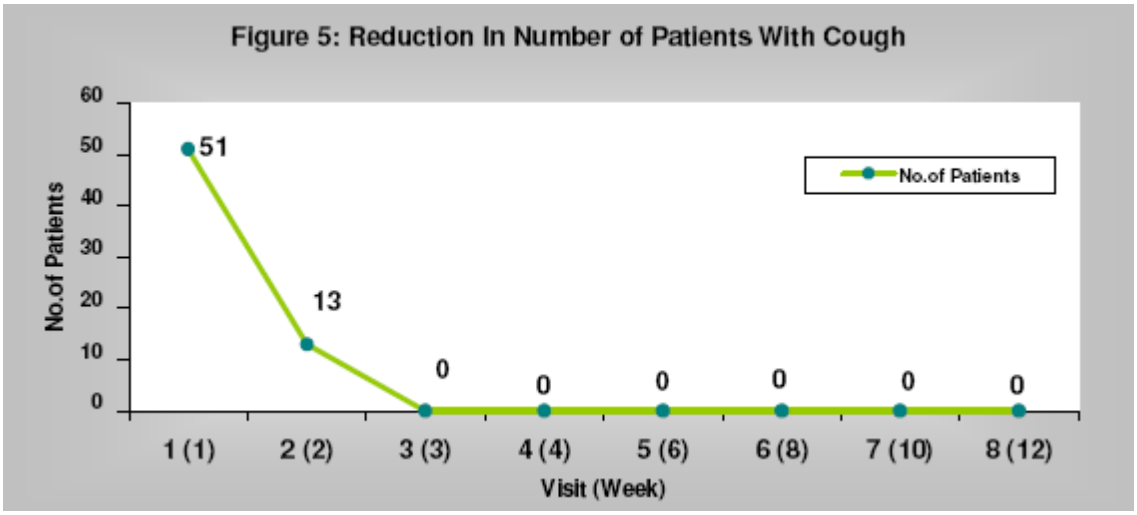



***Figure 6: Reduction in Number of Patients with Fatigue/Malaise During the 12 Weeks Trial Treatment with RECEPTOL®***

**100 % of the total study cases had Fatigue/Malaise at baseline which reduced from 3rd week onwards and all the patients had relief from Fatigue/Malaise from week 5 of the treatment with RECEPTOL® (Figure 6)**

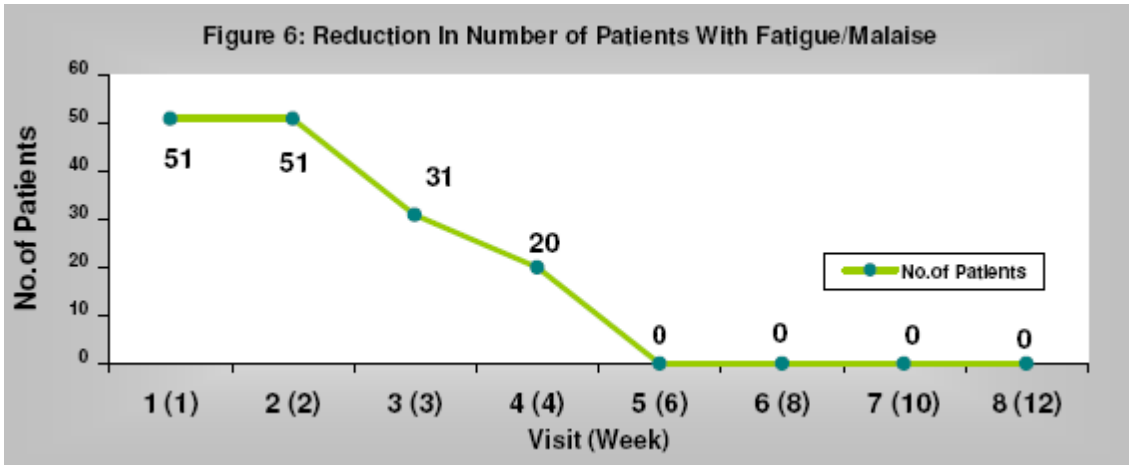



*Figure 7: Reduction in Number of Patients with Paraesthesia During the 12 Weeks Trial Treatment with RECEPTOL®*

**51 patients (100%) had HIV/AIDS related Paraesthesia at baseline and all patients became asymptomatic after 3rd Week onwards with treatment of RECEPTOL®. (Figure 7)**

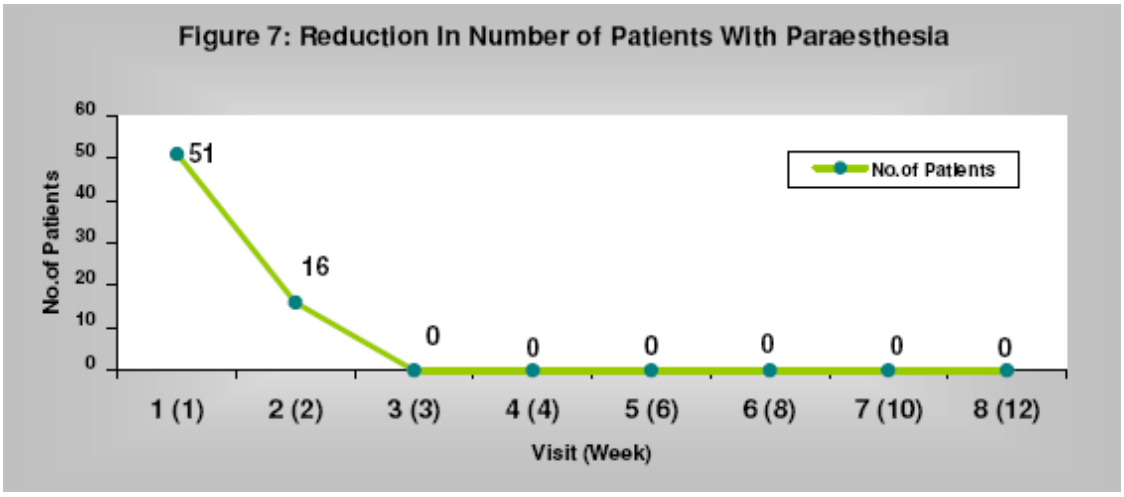


***Figure 8: Reduction in Number of Patients with Disturbed Sleep During the 12 Weeks Trial Treatment with RECEPTOL®***

**All the patients had HIV/AIDS related Disturbed Sleep at baseline and all patients became asymptomatic after 3rd Week onwards with treatment of RECEPTOL®. (Figure 8)**

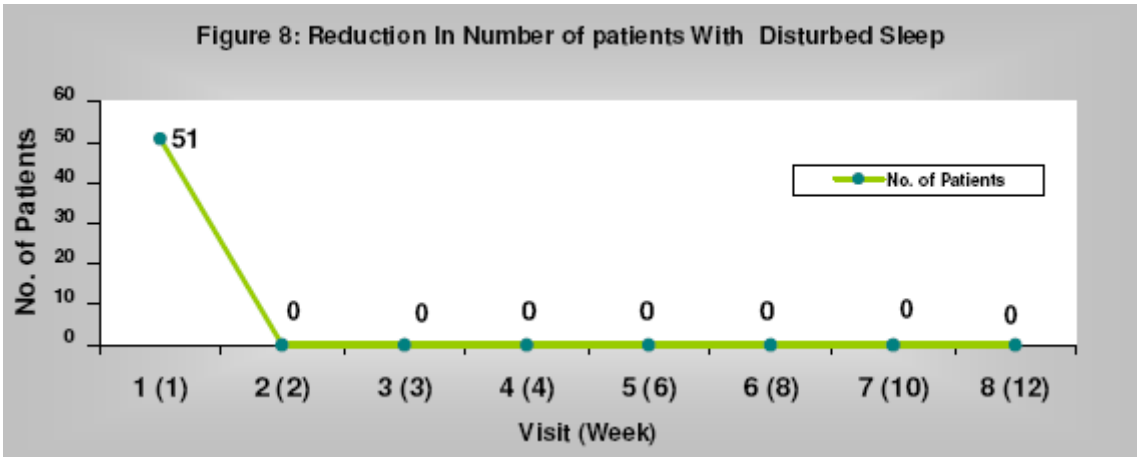



***Figure 9: Reduction in Number of Patients with Skin Rash during the 12 Weeks Trial Treatment with RECEPTOL®***

**All the patients had HIV/AIDS related Skin Rash at baseline which became asymptomatic after 3rd Week onwards with treatment of RECEPTOL®. (Figure 9)**

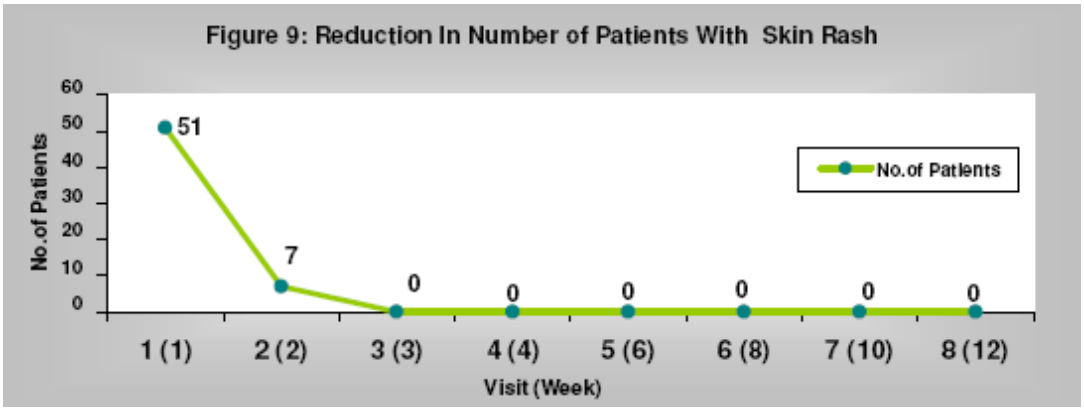


***Figure 10: Reduction in Number of Patients with Herpes Zoster after During the 12 Weeks Trial Treatment with RECEPTOL®***

**All the patients had HIV/AIDS related Herpes Zoster at baseline which became asymptomatic after 3rd Week onwards with treatment of RECEPTOL®. (Figure 10)**

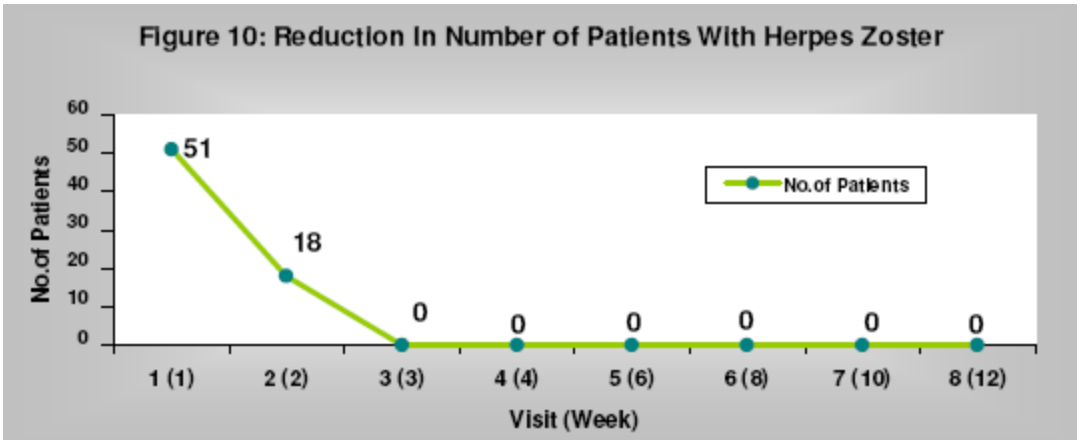



***Figure 11: Reduction in Number of Patients with Lymphadenopathy During the 12 Weeks Trial Treatment with RECEPTOL®***

**All the patients had HIV/AIDS related Lymphadenopathy at baseline which became asymptomatic after 3rd Week onwards with treatment of RECEPTOL®. (Figure 11)**

***Figure 12: Reduction in Number of Patients with Hair Changes During the 12 Weeks Trial Treatment with RECEPTOL®***

**All the patients had HIV/AIDS related Hair Changes at baseline which became asymptomatic after 3rd Week onwards with treatment of RECEPTOL®. (Figure 12)**

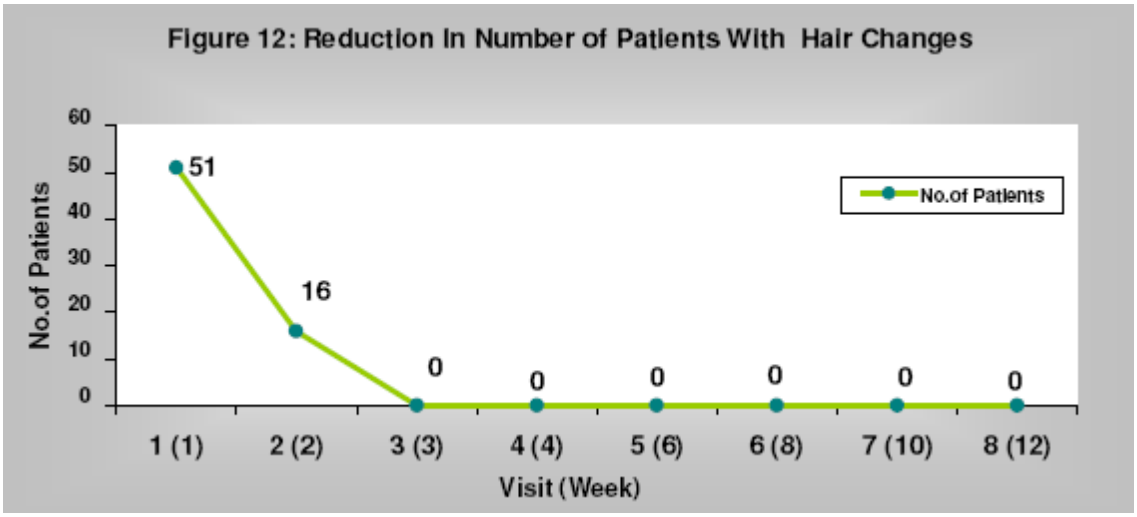



***Figure 13: Reduction in Number of Patients with Leukoplakia During the 12 Weeks Trial Treatment with RECEPTOL®***

**All the patients had HIV/AIDS related Leukoplakia at baseline which became asymptomatic after 3rd Week onwards with treatment of RECEPTOL®. (Figure 13)**

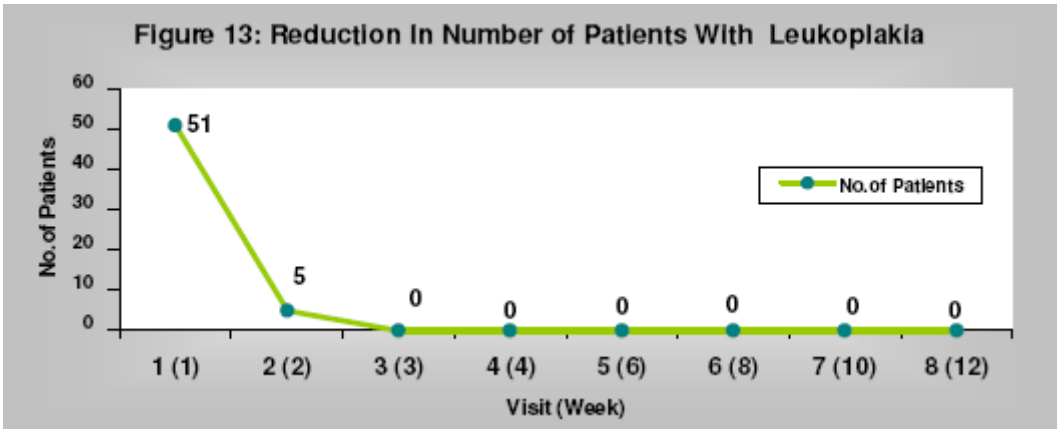
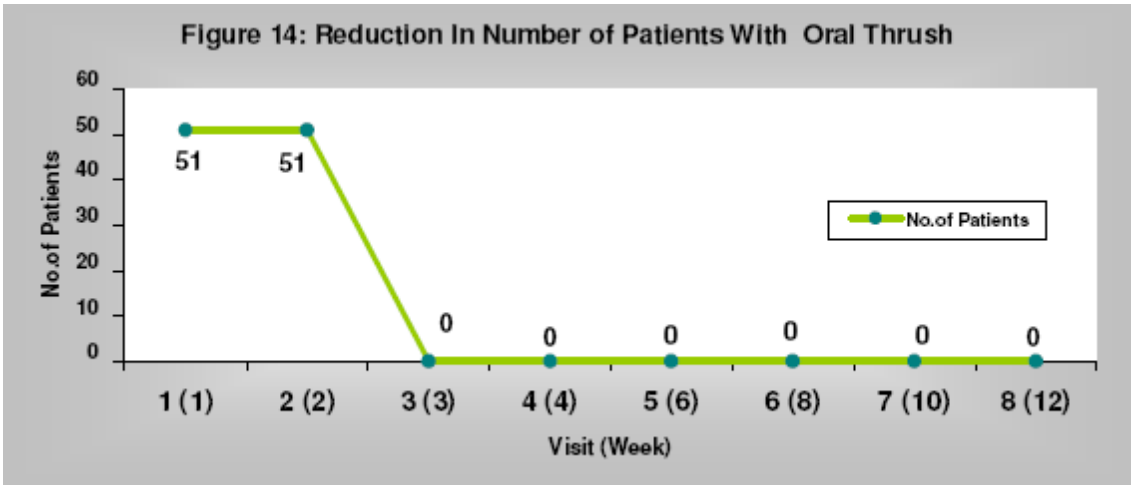



***Figure 14: Reduction in Number of Patients with Oral Thrush During The 12 Weeks Trial Treatment with RECEPTOL®***

**All the patients had HIV/AIDS related Oral Thrush at baseline which became asymptomatic after 3rd Week onwards with treatment of RECEPTOL®. (Figure 14)**



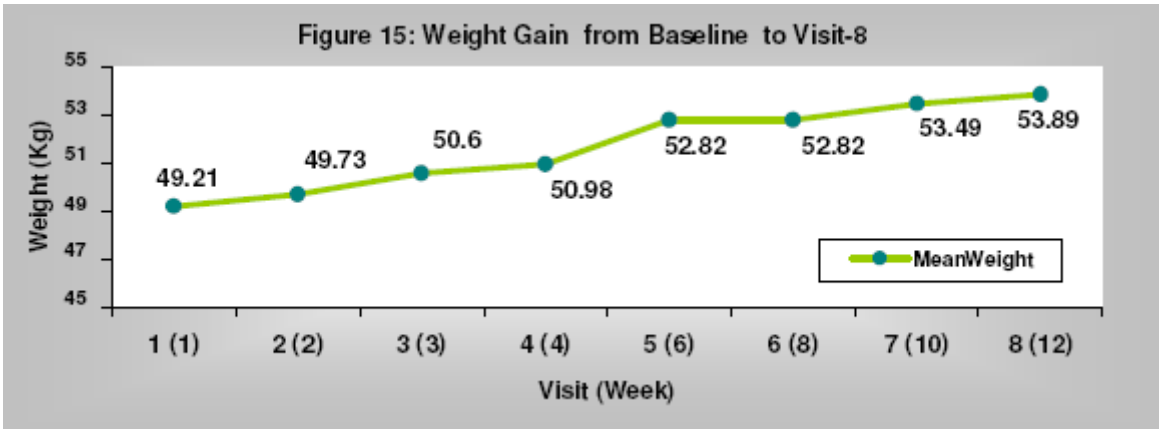

**Secondary Efficacy Results:**

***Table Showing Comparison of Mean Body Weight of Subjects at Baseline (Week 0)with End of Treatment Measurements.***

| Body weight | Mean ± SD | Median | Range | P-value |
|---|---|---|---|---|
| Visit 1 | 49.21±12.33 | 48.00 | 29.00-73.80 | - |
| Visit 2 | 49.73±12.23 | 49.00 | 30.00-74.00 | 0.0001* |
| Visit 3 | 50.60±12.18 | 50.00 | 32.00-75.00 | 0.0001* |
| Visit 4 | 50.98±12.41 | 51.00 | 32.00-76.00 | 0.0001* |
| Visit 5 | 52.82±12.29 | 52.00 | 34.00-77.00 | 0.0001* |
| Visit 6 | 52.82±12.56 | 53.00 | 34.00-78.00 | 0.0001* |
| Visit 7 | 53.49±12.38 | 54.00 | 34.00-79.00 | 0.0001* |
| Visit 8 | 53.89±12.35 | 54.00 | 34.50-80.00 | 0.0001* |

**Mean body weight of patients measured at end of 12 weeks treatment showed a significant increase when compared with those measured at baseline. ($p < 0.05$)**

***Figure 15: Effect of 12 Weeks Treatment with RECEPTOL® on Mean Body Weight of Patients.***




**Weight monitored on every visit showed significant gain in all 51 HIV patients with mean weight gain of 4.68 ± 1.9 kg after 12 weeks of RECEPTOL® therapy (p< 0.001).(Figure 15)**

***Table Showing Absolute CD4 & CD8 Counts Measured at Baseline and at the End of 12 Weeks Treatment with RECEPTOL®***

| Parameter | Baseline Mean ± SD | Week 12 Mean ± SD | Difference (Week 12-Baseline) Mean ± SD | P-value |
|---|---|---|---|---|
| CD4 Counts (cells / cmm) | 317.16±128.67 | 344.24±165.79 | +27.08±92.47 | 0.042* |
| CD8 Counts (cells / cmm) | 1037.06±285.02 | 1139.75±386.76 | +102.69±267.44 | 0.008* |

**Absolute CD4 and CD8 cell count:**

**• CD4 cell counts were available for all 51 patients with pre and post treatment values. There was an absolute increase in CD4 counts for 67% patients and an average increase in CD4 count by 27 (The median CD4 cell counts increased from 276 to 305). This effect was found statistically significant (p < 0.05). CD4 cell counts range with number of patients at baseline and at the end of study is shown in figure 16a.**

**• While there was a significant improvement in CD8 count with 75% of patients showing an increase in CD8 counts and the average difference in CD8 count from baseline to the week-**

**12 was found to be 102.69 ± 267.44. This effect was statistically significant ($p < 0.05$). (Figure 16b)**

***Figure 16a: Comparison of the Number of Patients in CD4 Cell Count Ranges at Baseline and End of Treatment Measurements.***

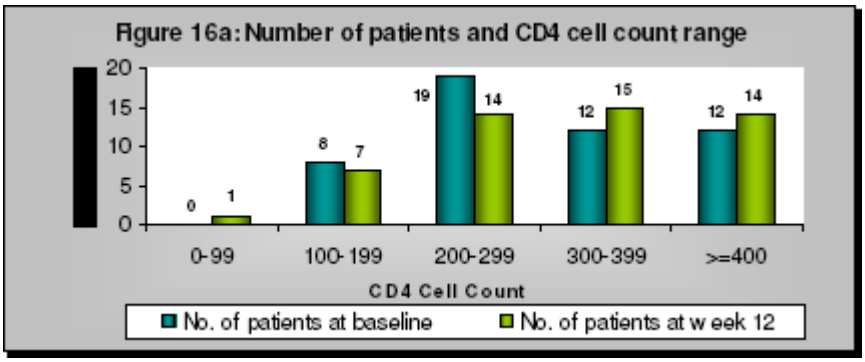
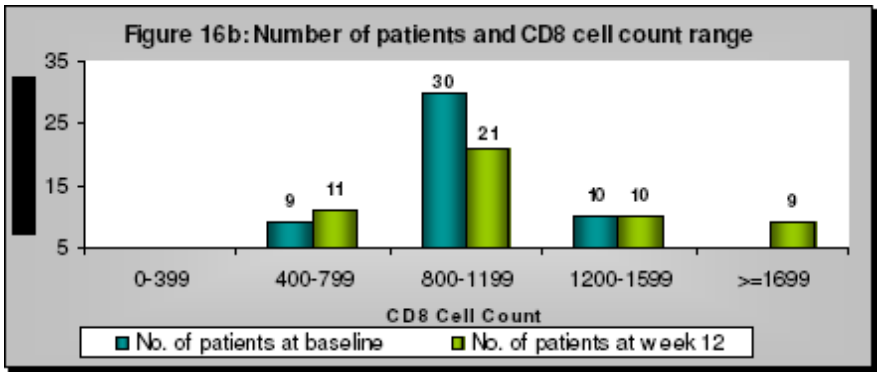



***Figure 16b: Comparison of the Number of Patients in CD8 Cell Count Ranges at Baseline and End of Treatment Measurements.***



***Results of Laboratory Parameters***

***Table of Changes in Laboratory Parameters from Baseline to Week 12***

| **Laboratory Test** | **Baseline**<br>**Mean ± SD** | **Week-12**<br>**Mean ± SD** | **Gain**<br>**(Week12-Baseline)**<br>**Mean ± SD** | **P-value** |
|---|---|---|---|---|
| HB (g/dl) | 11.48±1.77 | 11.64±2.19 | 0.16±2.02 | 0.567 |
| WBC | 7301.96±2738.87 | 7966.67±2000.67 | 664.71±2653.21 | 0.080 |
| SGPT (IU/L) | 32.10±7.88 | 26.76±10.84 | -5.33±11.28 | 0.001* |
| SGOT (IU/L) | 26.80±6.58 | 21.81±7.58 | -4.99±6.28 | <0.001* |
| Bilirubin (mg/dl) | 0.71±0.21 | 0.67±0.15 | -0.04±0.20 | 0.213 |
| Albumin (g/dl) | 3.95±0.37 | 3.83±0.46 | -0.13±0.43 | 0.042* |
| S. Creatinine (mg/dl) | 0.94±0.15 | 0.95±0.13 | 0.01±0.13 | 0.610 |

• There was no significant change observed in Hemoglobin Level as well as in WBC count at Week 12, as compared to baseline, ($p < 0.05$).

• The Mean SGPT at Baseline was found to be 32.10 ± 7.88 IU/L which reduced to 26.76 ± 10.84 at Week 12. While the Mean SGOT was 26.80 ± 6.58 IU/L at Baseline and decreased to 21.81 ± 7.58 at Week 12 (End of Treatment).

• There was no significant change observed in mean Bilirubin and mean Serum Creatinine form baseline to week-12 ($p < 0.05$).

• While, a significant change was observed in mean Albumin from Baseline to Week-12 (End of Treatment).

***Safety Evaluation***

• Safety/Tolerability assessments consisted of monitoring and recording all Adverse Events and Serious Adverse Events. All patients tolerated RECEPTOL® well with no side effects. Milk allergies are caused by the large milk proteins, primarily casein, and to a lesser extent the Immunoglobulins. These proteins are completely removed from the RECEPTOL®. As RECEPTOL® is a food substance derived from Colostrum, it was found to be safe for human consumption.

***Overall Assessment by Principal Investigator & Patient***

***Table of Principal Investigators Assessment for Efficacy of Trial Drug Treatment***

| Principal Investigator's comment for Efficacy | N | Percentage | Cumulative Frequency | Cumulative Percentage |
|---|---|---|---|---|
| CD4 Increase, Viral Load Decrease | 16 | 32 | 16 | 32 |
| CD4 Decrease, Viral Load Decrease | 16 | 32 | 32 | 64 |
| CD4 Decrease, Viral Load Increase | 8 | 16 | 40 | 80 |
| CD4 Increase, Viral load Increase | 10 | 20 | 50 | 100 |

***Table of Principal Investigators Assessment for Safety/Tolerability of Trial Drug Treatment***

| Patient's feedback for Safety/Tolerability | N | Percentage | Cumulative Frequency | Cumulative Percentage |
|---|---|---|---|---|
| **Good** | 21 | 42 | 21 | 42 |
| **Satisfactory** | 28 | 56 | 49 | 98 |
| **Others** | 01 | 02 | 50 | 100 |

***Table of Patients Assessment for Efficacy of Trial Drug Treatment***

| **Patient's feedback for Efficacy** | N | Percentage | Cumulative Frequency | Cumulative Percentage |
|---|---|---|---|---|
| Good | 16 | 32 | 16 | 32 |
| Satisfactory | 31 | 62 | 47 | 94 |
| Others | 06 | 06 | 50 | 100 |

***Table Of Patients Assessment For Safety/Tolerability Of Trial Drug Treatment***

| **Patient's feedback for Safety/Tolerability** | ***N*** | ***Percentage*** | ***Cumulative Frequency*** | ***Cumulative Percentage*** |
|---|---|---|---|---|
| **Good** | ***28*** | ***56*** | ***28*** | ***56*** |
| **Satisfactory** | ***22*** | ***44*** | ***50*** | ***100*** |

**• According to Principal Investigators Assessment:**

1. 52% of patients showed an absolute increase in CD4 Cell Counts

2. 62% of patients showed an absolute decrease in viral load

3. 32% of the patients showed increase in CD4 Cell Counts and decrease in HIV Viral load for efficacy of the trial drug treatment.

4. 98% of the patients showed Good and Satisfactory results in terms of the safety/tolerability of the trial drug treatment.

**• According to Patients Assessment:**

94% of the patients showed Good and Satisfactory results for efficacy of the trial drug treatment. All patients showed Good and Satisfactory results for the safety/ tolerability of the trial drug treatment.

## 13 DISCUSSION AND OVERALL CONCLUSIONS

• A total of 51 patients diagnosed with HIV/AIDS were followed up during a 12 weeks continuous treatment period with RECEPTOL® liquid spray as a mono-therapy. All 51 patients completed the 12 week treatment without a single drop-out. Thus, at the end of the study, pre and post treatment data from all 51 patients on their clinical symptoms and biochemical profile including Absolute CD4 and CD8 cell counts and HIV viral load were available for analysis.

• **Sample size for this stand alone monotherapy with RECEPTOL® only was calculated by following recommendations as per the End-Points used in any WHO study:**

**1) Institutional Review Board of LTMMC & LTMG Sion Hospital consisting of Scientific Committee, Ethics Committee & Biostatistics Department of LTMMC & LTMG Sion Hospital**

**2) ICMR (Indian Council of Medical Research, National Institute of Medical Statistics)**

**3) All India Institute of Medical Sciences (AIIMS) – Biostatistics Department**

**4) Ministry of Health & Family Welfare notification no. F-207 dated 12/01/05**

• Of the 51 subjects studied, 21 (41.18%) were males and 30 (58.82%) females, with a mean body weight of 49.21 + 12.33 kg , and mean age of 33.35 + 9.14 years (range: 21-60 years).

• 12 weeks continued treatment with RECEPTOL® resulted in with a **significant reduction in HIV viral load.**

• The results also showed a **marked improvement in HIV Related Clinical Symptoms and Physical Findings** and all patients were relieved of their symptoms by the treatment with RECEPTOL®.

• At the end of the 12-Week Treatment Period (end of the study), majority of the patients showed reduced HIV viral load based on PCR Diagnostic Test. At the end of 12-Weeks Treatment (end of the study) with RECEPTOL®, **mean Viral Load showed a significant reduction ($p<0.001$)**

**from baseline as evident in the statistical analysis**. These measurements were made at the Institute of Immuno-Hematology (IIH), ICMR centre, KEM Hospital, Mumbai at the beginning (baseline) and at the end of the 12 weeks trial treatment.

• Patients treated with RECEPTOL® therapy were relieved of their HIV related symptoms of Diarrhoea, Nausea and Vomiting, Fatigue/Malaise, Fever and Cough, Disturbed Sleep, Skin Rashes, Herpes Zoster, Paraesthesia, Hair Changes, Oral Thrush, Lymphadenopathy and Leukoplakia. There was a marked improvement in HIV related clinical symptoms and many patients became **asymptomatic at the end of 3 weeks therapy ($p < 0.001$)**. At baseline, all the patients exhibited symptoms of fatigue malaise. However, all were asymptomatic at the end of 4 weeks treatment with RECEPTOL®.

• HIV related **Diarrhoea and Nausea** was cured in all patients from 3rd week onwards with significant fall from 2nd week while a significant fall in HIV related Vomiting was seen in patients within 1st week of treatment with RECEPTOL®. All patients became asymptomatic form 3rd week onwards.

• There was a **significant fall in the incidence of Fever, Cough** and related symptoms in all patients at the end of 1st week of treatment and all became asymptomatic after 3$^{rd}$ week onwards with the therapy.

• While HIV related symptoms of **Disturbed Sleep and Skin Rash** had a significant fall after 2nd week of treatment and patients showed no signs of these symptoms after 3$^{rd}$ week of the therapy.

• Lastly, number of subjects with HIV related **Herpes Zoster** showed a significant reduction at the end of 1st week and became asymptomatic after 3rd week with the treatment RECEPTOL®.

• At the end of the 12-Week Treatment Period (end of the study), **mean CD4 and CD8 counts showed significant increase ($p=0.042$ & $p=0.0080$ respectively based on Flow Cytometry Analysis).**

• All patients showed a significant gain in Body Weight during the 12 Week trial therapy with RECEPTOL® with an **average gain of 4.68 ± 1.9 Kg** and range of variation from 2 to 9 kgs.

• The 12 weeks trial treatment with **RECEPTOL® was well tolerated by all 51 patients and no patient experienced any Adverse or Serious Adverse Events**.

• The overall results obtained from this trial prove that continued treatment with RECEPTOL® Oral Spray for 12 consecutive weeks resulted in a **significant decrease in HIV viral load & a**

**significant increase in the Absolute CD4 and CD8 cell counts** along with a significant gain in body weight and to relief of symptoms in all the 51 HIV/AIDS patients studied.

• **As per the previous international studies of Phase I, II & III trials conducted in USA & Africa, RECEPTOL® showed good clinical results**. Also, this Phase III trial conducted in India at Sion Hospital, Mumbai showed positive efficacy and safety results.

• Thus, RECEPTOL®, a natural Nano-Informational Peptides (RADHA1081-100) and Proline Rich Polypeptides (PRPs) derived from the Bovine Colostrum holds good promise for a safe and effective alternative treatment for HIV Patients across all age group.

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