

# **Executive summary: Innovation at Biomix Providing Health for all via Receptol® - Creating a Paradigm shift**

## **1. Introduction**

Our health is directly influenced by our immune system. A balanced and healthy immune system is of utmost importance for our body's ability to defend against infections. "It is our ability to create a healthy immune system that represents the greatest potential for gains in human health. Therefore, creating a healthy immune system harnesses maximum benefit towards human health".

Today, however, many factors contribute to the general weakening of the body's defences. Antibiotics have begun to fail as resistance towards multiple infectious strains develops over time. Due to the failure of government control of health codes, deterioration of water quality, and lack of adequate quarantine measures following frequent international travel, diseases now spread more easily than ever before. Fortunately, recent research has uncovered a natural agent, which can increase our ability to fight disease and improve the quality of life for many people.

The Receptol® oral spray, consisting of Radha 108 Nanopeptides from mammalian colostrum (1<sup>st</sup> milk), stimulates our body's own immune system as a broad-spectrum anti-viral and a new generation immunomodulator to fight against several diseases & prevents all communicable infections. It is a natural product manufactured by Nano-biotechnology patented proprietary ultra-nano filtration processes from bovine colostrum.

Receptol® oral spray consists of low molecular weight active pharmaceutical ingredients (API) - Proline Rich Polypeptides (PRPs) & Radha-108 peptide. Receptol® is registered under Ayush License # GA/1647 (Validity 2018). PRPs & Radha-108 are a class of nano informational peptide, consisting of an oligo-ribonucleotide attached to a peptide molecule. It acts as a broad spectrum immuno-modulator & antiviral via increasing body's own immune system naturally.

The innovation of Receptol® in the field of immunotherapy is a quiet revolution in therapeutic and preventive medicine. It is a form of treatment that uses different aspects of your immune system, its cells and molecules, and its various stratagems to tip the balance in your favour as your body battles to maintain a healthy state.

The uniqueness of Receptol is in Radha 108 8 sequences of amino acid monomers responsible for providing mode of action in a vaccine like manner with active immunity that led to US and European Patent and license authorities to grant exclusivity for 58 indications including Cancer, Auto immune disease like RA etc., Allergy & Asthma, infectious disease like AIDS and hepatitis etc. for 21 years. Such attributes are missing in all other colostrum forms available world over.

Almost all individuals, healthy or diseased, with a few exceptions have benefited from regular Receptol<sup>®</sup> supplementation. The use of Receptol<sup>®</sup> did not cause any side effects even when given in high doses, exceeding the normal doses for prolonged periods. It has shown benefit in people with specific ailments as well.

Numerous studies have shown the effectiveness of Receptol<sup>®</sup> in eliminating or alleviating symptoms of herpes, chronic fatigue syndrome, viral infections including Epstein Barr, hepatitis, secondary infection due to AIDS, *Candida*, cancer and many other diseases and infections. Studies have also shown that continued use provides the greatest benefit, with maximum immune activity occurring 24 to 48 hours after taking the first dose.

The need for Receptol<sup>®</sup> for better health stems from the growing awareness that prevention is the best cure. With the increasing risks of antibiotic resistance and significant health threats, such as Severe Acute Respiratory Syndrome (SARS), the medical community increasingly turns to the inherent concept of immunization using vaccinations.

Receptol<sup>®</sup> is akin to a vaccine. But, rather than exposing the patient's immune system to the actual disease or a deactivated version of the same, Receptol<sup>®</sup> exposes the patient's immune system to the memory of a health threat, whether foreign or native, and the knowledge of how to best respond to protect itself. In view of proven global safety & efficacy, the product is now ready for a global launch with the product having been patented in several countries like the United States, Africa, Canada and Asia (Singapore & India).

### **The background of the invention**

Colostrum is the pre-milk substance produced from the mother's breast of all mammals during the first 24 hours of lactation, typically the first 3 milks. Colostrum has been known as an immune booster since time immemorial. Colostrum triggers at least 50 processes in the newborn, including transferring all immune factors and the entire immune defense memory from the mother's own immune system.

Bovine colostrum is up to 40 times richer than human colostrum in immune factors including nano information peptides, PRPs, immunoglobulins, cytokines, interferon, lactoferrin, and transfer factor. They are produced by T-lymphocytes and can transfer the ability to recognize a pathogen to native cells. However, no one till date has been able to isolate active ingredients especially nano information low molecular weight nano peptides and formulate a product that has the same effect as that of the mother's first three milks, after the birth of the child.

It has been indicated that "Colostrum stimulates the lymphoid tissue providing benefits in aged or immuno- deficient people" (Drs. Bocci, Bremen, Corradeschi, Luzzi and Paulesu in Journal Biology). In addition, Dr. M. Julius, McGill University, Montreal observed in Science News that "Researchers reported that colostrum stimulates maturation of B Lymphocytes (type of white blood cell) and primes them for the production of antibodies, enhances growth and the differentiation of white blood cells. Similar activity in cow human colostrum can also activate Macrophages".

Furthermore, as indicated by Drs. Oda, Shinnichi et. al. “Bovine colostrum contains high levels of growth factors that promote normal cell growth and DNA synthesis”. Besides, it has been suggested that an important role for growth factors is in promoting wound healing. Accelerated healing is possible for treatment with trauma and surgical wounds (Drs. Bhora et. al. in Journal of Surgical Research).

As such, colostrum contains hundreds of small peptides which serve numerous purposes. Studies have documented the presence of a number of bioactive peptides but no mention has been made of the use of these peptides fragments, their specific sequence or information regarding their isolation. Therefore, their segregation and isolation will facilitate gathering of further information with regard to their individual function and help formulate specific and targeted therapies for numerous diseases that are cured by colostrum. The challenge with this task is that the peptides are extremely sensitive to temperature, pH, stress, and shear factors. This poses several difficulties in their isolation and in preserving their biological activity and in the method of collection of colostrum so as to be able to deliver it to the patient while retaining its full biological activity.

The present invention addresses these shortcomings by providing isolated nanopeptides from colostrum, their method of isolation and the therapeutic uses of the isolated nanopeptide fragments. With reference to this innovation, the US patent for this product, US 20070212367 is notable:

US 20070212367- This patent application discloses an immunologically active PRP isolated from mammalian colostrum fluids for treatment of viral and non- viral diseases, a method and a system for processing mammalian colostrum fluids and a pharmaceutical formulation.

### **Summary of the invention as per granted US patent (patent no.: us 8,518,454 b2)**

As per US patent No.: US 8, 518,454 B2 issued on date Aug. 2013. An introduction of the same is presented below:

**Title:** Mammalian colostrum derived nanopeptides for broad spectrum viral and recurrent infections with a method of isolation thereof.

**Abstract:** The present invention relates to Nano peptides isolated from mammalian colostrum with vaccine like antiviral and immunodulator activity via building body’s own immune system and attachment inhibition on the cell surface receptors.

One embodiment of the present invention provides for a formulation comprising peptides isolated from mammalian colostrum having sequences as recited in SEQ ID 1-8 here in after referred to as peptides of Radha 108 series, wherein the peptides function to modulate cell immunity and provide attachment inhibition for foreign antigen/ virus on cell surface receptors along with crossing the blood brain barrier (BBB) and treating a host of diseases in the brain.

Colostrum is the pre-milk substance produced from the mother’s breasts of all mammals during the first 24 hours of lactation, typically the first 3 milks. In one embodiment, colostrum used in the present invention is of bovine origin. Bovine colostrum has 40 times higher immune factors than human colostrum and has the ability to cure a number of viral, immune and auto- immune disorders.

In another embodiment, there is provided a method of treatment of immune related disorders including auto immune disorders the method comprising of administering a patient suffering from such disorders a therapeutically effective amount of formulation comprising the peptides of SEQ ID 108.

In yet another embodiment, embodiment there is provided a method of treatment of Acquired Immune Deficiency Syndrome (AIDS) 1, the method comprising administering a patient suffering from AIDS, a therapeutically effective amount of formulation comprising the peptides of SEQ ID 1-8.

The formulation can be provided in a liquid, powder gel and any other pharmaceutical delivery forms. It can be administered orally, intravenously or by means of dermal patch for adsorption through skin.

The present invention is illustrated with the help of accompanying drawings and detailed descriptions and examples given below. The drawings and example are for explanation and clarity purpose and do not in any way limit the scope of the invention being defined by the appended claims and equivalents thereof. The foregoing aspects and advantages of the present invention will become clearer and appreciated by the detailed description and examples.

#### **Mode of action:**

- The informational proteins (RADHA108) in Receptol<sup>®</sup> are active in mitigating cell fusion
- RADHA108 series docks on glycoprotein receptor on the cell surface and thus closing doors and windows for viral entry into the immune cells.
- RADHA108 series get absorbed in the blood stream through buccal mucosa and crosses the BBB.
- The levels of Interleukins & Cytokines are increased substantially.
- It supports the regulation of the thymus by producing functionally active natural killer (NK) cells
- RADHA108 augments cell-mediated immunity & activates T-cell precursors to produce helper & suppresser T-cells increasing CD4/8 counts.
- RADHA108 promotes growth & differentiation of stem cells in response to any disease

Fusion of human immunodeficiency virus (HIV) particles with human white blood cells, particularly CD4 cells occurs with the aid of glycoprotein epitopes on the viral wall. The informational proteins in Radha108 are active in mitigating cell fusion. Radha108 docks on HIV glycoprotein gp120 mimicking receptor on the cell surface and thus closing doors and windows for virus/antigen entry into the immune cells.

Receptol<sup>®</sup> proteins directly support the NK cells of the immune system. NK cells provide the front line of defense specially equipped to locate and kill disease cells. NK cells attach to the surfaces of foreign substances or their outer cell wall, and inject a chemical “grenade” (granule) into the interior. Once inside, the granules explode and destroy the foreign invader within five minutes.

The NK cell itself remains intact and moves on to destroy the next immune attacker. Many doctors and clinicians are finding Receptol<sup>®</sup> helpful in promoting NK function and activity as well as supporting a

healthy immune system for all patients. The immune system plays a great role in the quality of our health. Strong, active and optimally functioning NK cells promote optimal health and deter foreign substances from affecting immune function.

- Radha108 (PRP) promotes differentiation of B cells, differentiation and maturation of macrophages and monocytes.
- Activates NK cells, cytotoxic cells of the innate immune system.
- Mitigates cell fusion and docks on HIV glycoprotein like Gp120, 180, 160 and 41 mimicking receptor on the cell surface closing entry of viruses.
- Stimulates production of cytokines interleukin (IL)-1 to IL-11, tumor necrosis factor (TNF)- $\alpha$ , Interferon (INF)- $\gamma$ .
- Stimulates the maturation of immature thymocytes into either helper or suppressor T cells.
- Mitigates cell fusion and docks on HIV glycoprotein like Gp120, 180, 160 and 41 mimicking receptor on the cell surface closing spectrum entry of viruses.
- Radha108 also functions as a molecular signaling device which works through receptors on target cell surfaces.

## 2. Summary of pre- clinical & clinical trials

1. **Pre-clinical study (for acute and sub-chronic toxicity):** Carried out as per the International Conference on Harmonization (ICH) guideline at Nation Institute of Nutrition, Hyderabad.

2. **Phase I clinical trial:** Ohio, USA.

The trial was conducted to evaluate the safety of Receptol<sup>®</sup> Oral Spray on 12 HIV patients for a period of 30 days.

- No adverse effects were reported during the study.
- Improvement was observed in HIV associated clinical symptoms.
- Week after week weight gain showed a positive response.

**Table 1: Clinical improvement during Phase I - USA**

Symptom	Number of patients with symptom N=12	Number of patients with elimination of symptoms N=12
<b>Diarrhea</b>	8	5
<b>Fatigue</b>	9	9
<b>Nausea</b>	8	5
<b>Cough</b>	4	2

3. **Phase II study:** Nairobi, Kenya.

A t-Trial was conducted on 30 patients with HIV/AIDS, who received a 90 day treatment with Receptol<sup>®</sup> Oral Spray with an objective to demonstrate efficacy and safety under clinical conditions.

- Receptol<sup>®</sup> Oral Spray appeared to be safe and well tolerated.
- Significant viral load reduction in minimizing the infection associated with HIV/AIDS.
- Week after week weight gain showed a positive response.
- Marked reduction in symptoms
- Significant increase in CD4 count.

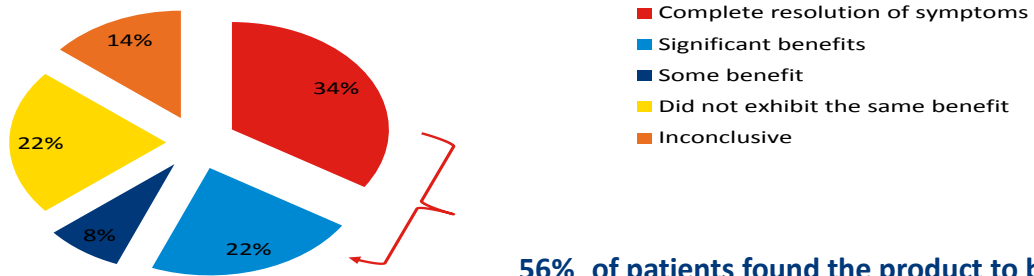
**4. Phase III study: Rwanda, Africa**

A t-Trial was conducted in 60 patients with HIV/AIDS, where patients received a 12 month treatment with Receptol® Oral Spray with an objective to study the efficacy and safety under clinical conditions.

- Patients were unaware of positive potential of drug so as to avoid any bias
- After day 1 moderate level of relief of diarrhea and fever
- Week after week weight gain showed a positive response.
- After 14 days, relief from skin lesion, mouth thrush, fever, diarrhea, tuberculosis symptoms.
- After 90 days relief of all symptoms with increase in absolute CD4 Counts and reduction in viral load
- No adverse effects observed over 12 months follow up even after 5 years of therapy, and an improvement in Quality of Life was noted.

**Receptol® in Non-communicable Diseases (NCDs): Rheumatoid Arthritis Study**

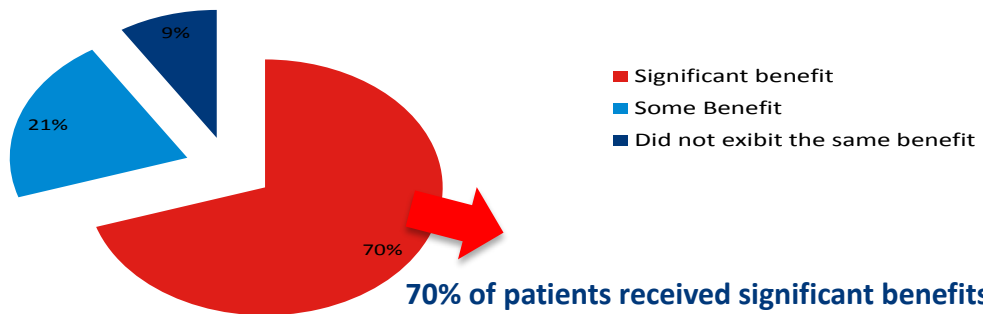
Reporting Patients\*: 63  
Duration of Treatment: 6 months



**56% of patients found the product to be highly effective!**

**Receptol® in NCDs: Fatigue Syndrome Study**

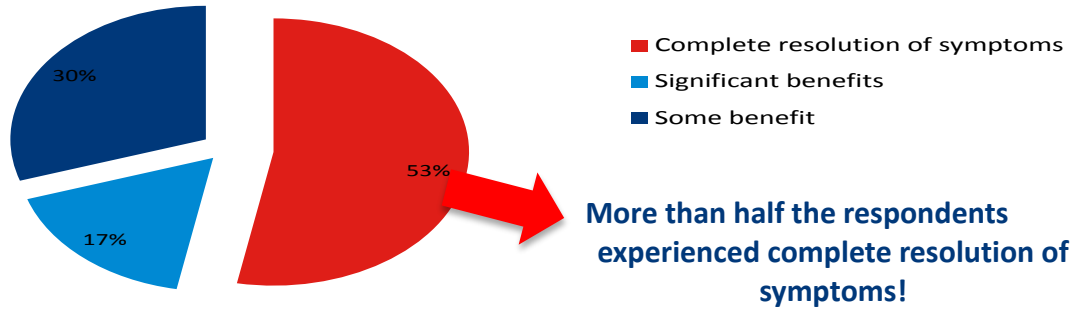
Reporting Patients\*: 108  
Duration of Treatment: 6 months



**70% of patients received significant benefits!**

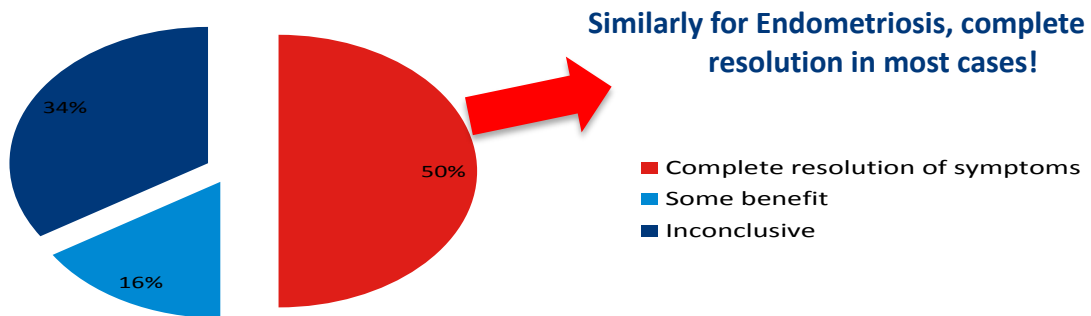
### Receptol® in NCDs: Allergies Study

Reporting Patients\*: 24  
Duration of Treatment: 6 months



### Receptol® in NCDs: Endometriosis Study

Reporting Patients\*: 106  
Duration of Treatment: 6 months





**Summary: Safety & Efficacy data as per global study on Receptol®**

KEY DIMENSIONS	PHASE I, II & III INTERNATIONAL TRIALS	STUDY I	STUDY II
Phase	Phase I – HIV trial, US Phase II – HIV trial, Nairobi, Kenya Phase III – HIV trial, Rwanda	Phase III validation trial by GOI on HIV patients, Standalone monotherapy	Phase III validation trial by GOI on HIV patients, Standalone monotherapy
No. of patients	Phase I – 12 cohorts Phase II – 30 cohorts Phase III – 60 cohorts	50 HIV seropositive patients	51 HIV seropositive patients
Duration	365/ 30 days	3 months	3 months
Compliance	Very good	Very good	Very good
Side effect	None	None	None
Weight gain	6 lbs average gain	4.73 kg per patient, p<0.05	4.68 ± 1,9 kg per patient, p<0.001
Clinical symptoms	90 days relief from symptoms	Improved within 3 weeks from starting of therapy	Improved within 3 weeks from starting of therapy
CD4 cell count	Phase II: Average by 31	Average by 51, median CD4 cell count from 312 to 363 (p = 0.06)	On an average by 27 (p = 0.042)
HIV Viral load	Phase II: Mean HIV log viral load from 4.6 to 2.5	Mean HIV log viral load from 4.63 to 4.18 (p = 0.001)	Mean HIV log viral load from 4.41 to 4.02 (p = 0.009)

**5. Phase III revalidation trial in Indian ethnic population: At Mumbai**

**Study I – LTMMS Tertiary Care Sion Hospital, Mumbai on 50 patients who were HIV+ Absolute CD4 cell count & HIV Viral Load – tested at CAP, USA accredited Metropolis lab, Mumbai. Clinical & Physical symptoms study - at ART Center, Sion Hospital, Mumbai.**

**Objective:** To evaluate safety & efficacy of Receptol®

**Symptoms:** HIV, Diarrhea, Fatigue/Malaise, Nausea, Cough.

**Inclusion criteria** – Absolute CD4 cell count greater than 100 cells/mm<sup>3</sup>

**Exclusion criteria** – no pre- exposure to ART

Statistically significantly reduction in mean HIV log viral load (p<0.001)

- Marginal statistically significant increase in CD4 cell count (p=0.06)
- Clinical symptoms disappeared in 3 weeks of treatment in all patients (p<0.05)

- Statistically significant weekly weight gain in all patients ( $p < 0.001$ )

**Table 2: Summary of Study 1 data**

Visit (Weeks)	No. of Subjects with Nausea	No. of Subjects with Vomiting	No. of Subjects with Fatigue/ Malaise	No. of Subjects with Diarrhea	No. of Subjects with Fever	No. of Subjects with Cough
1	8	7	44	9	12	14
2	3	2	32	5	3	10
3	2	2	26	1	6	6
4	1	1	17	1	1	3
6	0	1	1	0	0	1
8	0	0	1	0	0	2
10	0	0	1	0	0	0
12	0	0	0	0	0	0

**Table 3: Summary CD4 count, baseline vs week 12**

Sr. No.	CD4 count N=48	Baseline	After 12 Weeks	p-value
1.	Median	312.5	363.5	0.06
2.	25 <sup>th</sup> Percentile	275.5	294.2	
3.	75 <sup>th</sup> Percentile	430	435	

**Table 4: Summary CD4 count, baseline vs week 12**

Sr. No.	Parameter	Baseline	After 12 Weeks	p-value
1.	Log of HIV-1, RNA (N=34)	5.11(0.090)	4.103(1.32)	< 0.001
2.	Median	206057	25280	< 0.001
3.	25 <sup>th</sup> Percentile	62884	1665	
4.	75 <sup>th</sup> Percentile	508038	87511	

### Study II – Sion Hospital, Mumbai on 51 AIDS Patients

Absolute CD4 cell count & HIV viral load – tested at Institute of Immuno Hematology (IIH), Indian Council of Medical Research (ICMR), King Edward Memorial (KEM) Hospital, Mumbai.

**Inclusion criteria** – Absolute CD4 cell count greater than 100 cells/mm<sup>3</sup> and 100% symptomatic patients at baseline.

**Exclusion criteria** – No pre-exposure to ART

- The drop in the mean HIV log viral load was statistically significantly ( $p < 0.009$ )
- Statistically significant increase in the CD4 cell count ( $p < 0.042$ )

- Clinical symptoms disappeared in 3 weeks of treatment in all patients (p<0.001)
- Statistically significant weekly weight gain in all patients (p<0.001)

**Table 5: Indian re-validation phase III trials, Mumbai - Study II**

Clinical Symptoms	N	At Baseline	Responders At Week-2
Diarrhea	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%)
Paraesthesia	51	51(100%)	16 (31.4%)
Disturbed Sleep	51	51(100%)	0 (0%)
Skin Rash	51	51(100%)	7 (13.7%)
Fatigue/Malaise	51	51 (100%)	51 (100%)
Herpes Zoster	51	51 (100%)	18 (35.3%)
Hair Changes	51	51 (100%)	16 (31.4%)
Leukoplakia	51	51 (100%)	5 (9.8%)
Oral Thrush	51	51 (100%)	51 (100%)

**Table 6: CD4 Count, Baseline vs Week 12**

Parameter	Baseline Mean ± SD	Week 12 Mean ± SD	Difference (Week 12-Baseline) Mean ± SD	P-value
CD4 Counts (cells/mm)	317.16 ± 128.67	344.24 ± 165.79	+ 27.08 ± 92.47	0.042
CD8 Counts (cells / mm <sup>3</sup> )	1037.06 ± 285.02	1139.75 ± 386.76	+102.69 ± 267.44	0.008

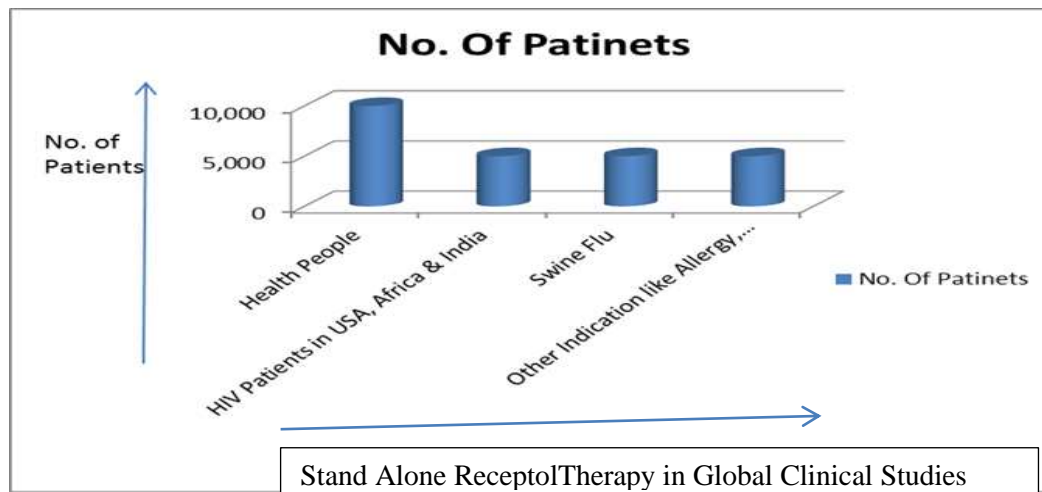
## Meta-Analysis Data:

- Meta-Analysis is a combined Statistical analysis of 25,000 subjects across HIV, Swine Flu, Allergy/Asthma, Rheumatoid Arthritis , Endometriosis & NCD: Chronic Fatigue Syndrome showing increase in weight gain as an Indication of overall wellness showing Safety & Efficacy of RADHA 108 Nano Peptide.

**Table 7: Stand Alone Receptol® Therapy in Global clinical studies**

Sr.No.	Stand Alone Receptol® Therapy in Global clinical studies	No. of Patients
1	Healthy People	10,000
2	HIV Patients in USA, Africa and India	5000
3	Swine Flue	5000
4	Other Indication like Allergy, Asthma Rheumatoid Arthritis,Chronic Fatigue Syndrome, Endometriosis study	5000
	<b>Total</b>	<b>25,000</b>

Figure 1: Chart for Meta-Analysis data for 25,000 Patients



### **3. Patents**

#### **1. US Product Patent brief**

**Title:**

Mammalian colostrum derived nano-peptides for broad-spectrum viral and recurrent infections for the treatment of AIDS.

**Patent No. US,8,518,454 B2**

As per the granted US Product Patent claim, “A method for the treatment of Acquired Immune Deficiency Syndrome (AIDS) the method comprising administering to a patient suffering from such disorder a therapeutically effective amount of the formulation comprising peptides of SEQ ID 1-8 in Receptol<sup>®</sup>”

#### **2. Singapore patent**

**Title:**

Mammalian colostrum derived nano-peptide for broad spectrum viral 7 recurrent infections with method of isolation thereof

**Patent No. 172793**

#### **3. South Africa Patent**

**Title:**

Mammalian Colostrum Derived Nano-peptides For Broad-spectrum Viral and Recurrent Infections with a Method of Isolation Thereof

**Patent No. # 2011/04687**

#### **4. Europe**

**Title:**

Mammalian Colostrum Derived Nano-peptides for Broad-spectrum Viral and Recurrent Infections with a Method of Isolation Thereof

**Application no. EP 09827010.1**

**Patent Status: Entered in National phase**

#### **5. India**

**Title:**

Novel Immunologically Active Peptide Fragments of Proline-Rich Polypeptide Isolated From Mammalian Colostrum For Treatment Of Viral And Non-Viral Diseases or Diseased Conditions.

**Application no. 1874/MUM/08**

**Patent Status: Approved but not issued**

#### **4. Manufacturing process**

Receptol® Oral Spray is manufactured at a Nano biotechnology FDA approved facility managed by highly trained and skilled personnel in class 1,00,000 areas. The brief manufacturing process is outlined in below Process steps.

- 1) Collection of raw colostrum:** Collection of raw colostrum containing high concentration of API is done under aseptic condition by highly skilled veterinarians and is stored at -20°C.
- 2) Colostrum whey processing:** Raw colostrum stored at -20°C is processed under control propriety conditions to generate colostrum whey.
- 3) Pre-filtration of colostrum whey:** The colostrum whey is subjected to pre-filtration through a series of micron filters at low pressure. The obtained permeate is checked for critical parameters and analyzed.
- 4) Ultra Filtration (UF) I:** The permeate obtained after pre-filtration is subjected to UF I through series of ultra-filters at low pressure. The obtained permeate is checked for critical parameters and analyzed.
- 5) Ultra filtration (UF) II:** The permeate obtained after UF I is subjected to UF II through series of ultra-filters at low pressure. The obtained permeate is checked for critical parameters and analyzed.
- 6) Bulk manufacturing:** The permeate obtained from UF II is added with preservatives. The pH of the bulk is adjusted and flavor is added under continuous stirring. The final bulk is mixed for specified time prior to final filtration.
- 7) Final filtration:** The manufactured bulk is subjected to absolute biological filters to ensure total removal of microorganisms and provides safe liquid containing Proline rich polypeptides containing Radha108 sequences. The obtained permeate is checked for critical parameters and analyzed.
- 8) Filling, Sealing and storage:** The filtered bulk product filled, sealed and stored at room temperature.

#### **Manufacturing facility:**

Receptol® is manufactured in a plant, approved for Current Good Manufacturing Practices (cGMP) & ISO 22000 by TUV Nord Germany (cGMP # 02 00003 & ISO 22000 # 44281090870), via patented Nano-biotechnology process to isolate Nano informational peptides using proprietary molecular weight exclusion ultra-filters of Nano Technology from Millipore, US & France.

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