Stempeutics Research Pvt Ltd
Bangalore, India

Corporate Presentation, 2022

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Company Overview

Leading regenerative medicine company in India with a stem-cell platform technology for the development of treatment of immune-mediated and inflammatory diseases

Company

- Founded in 2006 by Manipal Group (>$1B revenue) headquartered in Bangalore, India
- Lead product Stempeucel® has received market authorization in India for the treatment of Critical Limb Ischemia
- Co-development agreements with major pharma companies Cipla (CIPLA.BO , Market Cap US$ 10.25B) and Alkem Laboratories (ALKEM.BO, Market Cap US$ 5.41B)
- Alliance/Partnership with leading CDMO Kemwell Biopharma for manufacturing

Products

- **Stempeucel®** is an off the shelf, allogeneic Mesenchymal Stromal Cell (MSC) product with broad therapeutic applications including Critical Limb Ischemia, Osteoarthritis & Diabetic Foot Ulcer, Perianal Fistula and Covid-19 ARDS
  - Patented Pooling Technology makes it Best-in-Class MSC product
- **Stempeucare™**: Cosmetic products based on bioactive factors secreted by Mesenchymal Stromal Cells
  - Marketing approval granted for three products i.e. Cutisera (Skin Care), Trichosera (Hair Care) and Peri-Optisera (Under Eye application). Few more products are in the pipeline

Share Holders: Manipal Education & Medical Group, Cipla & Kemwell Biopharma

Strong Global Opportunities

Large target markets with significant unmet needs and limitations of existing treatment options provides significant opportunities for Stempeucel®

	Buerger's Disease (BD)	CLI (PAD)	DFU	OA
Eligible population	**1m**	**5m**	**6m**	**190m**
Estimated market size	**US$ 1.5bn**	**US$ 4bn**	**US$ 6bn**	**US$ 15bn**
Limitation of existing treatment options	■ Lack of approved drugs for BD. Current standard of care focuses only on pain alleviation ■ Natural disease progression leads to amputation	■ Only 50% estimated to be managed with existing vascular techniques ■ Only 25% estimated to witness satisfactory clinical outcomes	■ Limitations on efficacy, ease of use and cost challenges with existing treatments ■ High instance of wound re-opening	■ Apart from surgery, treatment options largely symptomatic in nature ■ Physicians' focus restricted to controlling pain and reducing disability
Stempeucel® status / advantages	■ **Marketing approval granted in India based on Phase I /Phase II/ Phase IV data** ■ EMA awarded Stempeucel® ATMP classification and ODD status ■ PreIND meeting with US FDA/ Pre-consultation meeting with PMDA	■ **Marketing approval granted in India based on Phase I and Phase III data**	■ **Strong preclinical data on ulcer healing** ■ Currently double blind, placebo controlled, Phase III clinical trial is in progress in India	■ **Attractive Phase II safety and efficacy results** ■ Completed double blind, placebo-controlled Phase III clinical trial in India

Global CLI + DFU + OA Target Market: US$ 25B

Stempeucel® Product Development in India

Critical Limb Ischemia
Marketing Authorization Granted
"Regenacip" Product Launched

Product Licensed to Cipla for India Territory

Osteoarthritis
Phase 3 Trial in progress
Expected Marketing Authorization: Q1 2022

Product Licensed to Alkem for India Territory

Diabetic Foot Ulcer
Phase 3 Trial in progress

Product Licensed to Cipla for India Territory

Perianal Fistula
Phase 1/2 trial is in progress

Available for Licensing

Covid-19 ARDS
Phase 3 trial is approved

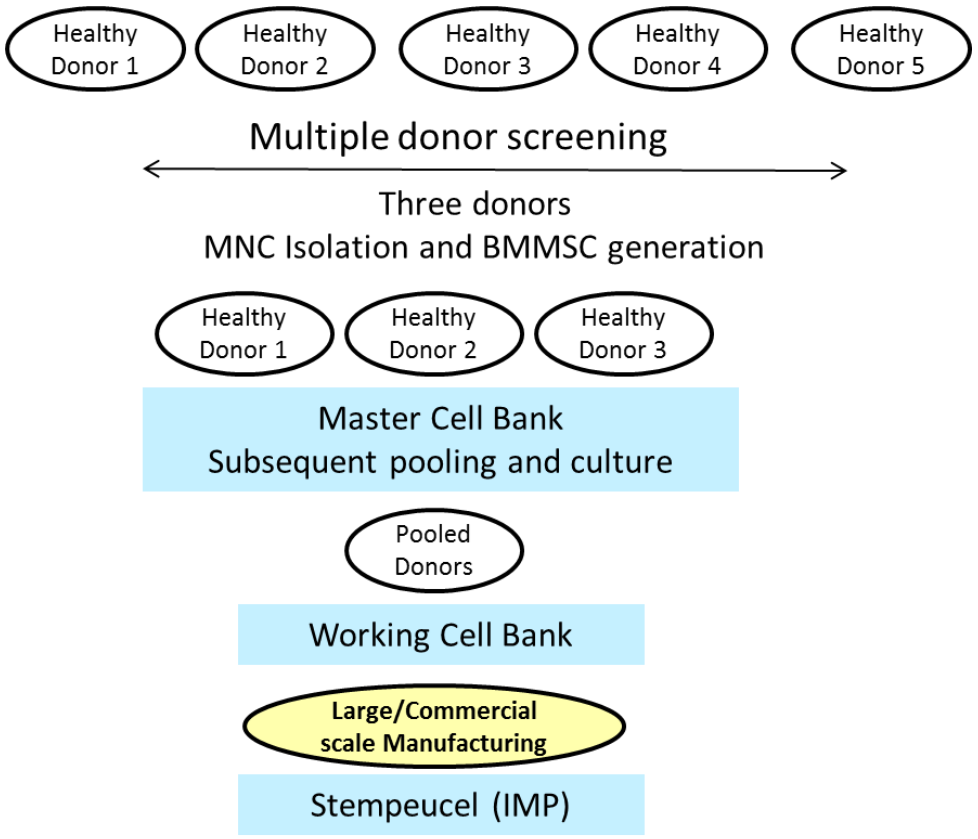
Available for Licensing

Stempeucel® Drug

About Stempeucel® Product

Key features of Stempeucel® include:

- Allogeneic, cryopreserved, off-the-shelf
- Derived from qualified and tested healthy adult donors
- Patented Pooling Technology - patents issued in 18 countries (including US, Japan and EU)
- Preclinical studies show reduction in inflammation, growth of collateral vessels and repair of damaged muscle
- Awarded Advance Therapy Medicinal Product (ATMP) classification and Orphan Drug Designation by the EMA
- Pre-IND meeting completed with US FDA
- Preliminary consultation meeting with PMDA completed



Stempeucel® Manufacturing process

Stempeucel® has been demonstrated to be safe in over 350 patients

Best-in-Class

Stempeutics' Proprietary Pooling Technology makes it Best-in-Class

Reduces Donor-donor Variability	Pooling of donors reduces donor-donor variability as experienced in other products. Regulatory agencies have expressed serious concerns in reproducibility when a single donor product is used.
Robust Large-scale Production	Pooling donors allows for larger scale of production thus enabling robust large-scale production and reducing lot to lot variability.
Broader Cytokines/ Growth Factor Array	Pooling of donors provides a larger cytokine/growth factor expression profile thus increasing the therapeutic potential. Dependency of an individual donor to provide the optimal profile is eliminated.
Low Cost of Production	Large scale production reduces cost of production with significant savings in facilities, personnel and quality control lot release tests (safety and characterization) related costs.
Proprietary Patented Process	The unique and non-obvious benefits of pooling have led to a granted patent protecting Stempeutics' approach in 18 countries including US, EU and Japan.

Stempeucel®
CLI product

About Critical Limb Ischemia

Peripheral Artery Disease → PAD is a cardiovascular disease characterized by narrowing of arteries in the legs limiting blood flow to the muscles due to the accumulation **of atherosclerotic plaques**

Buerger's Disease → BD is a rare form of **vasculitis characterized by acute inflammation** and **diffuse clotting of distal arteries and veins due to inflammatory thrombi**

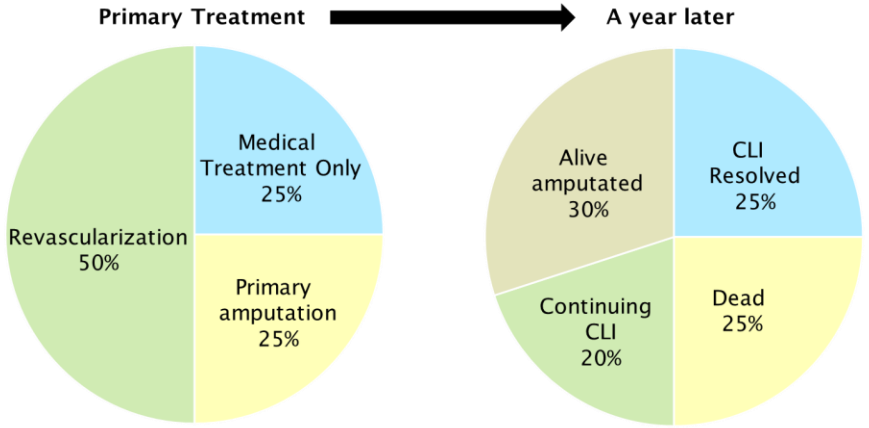
Gap in Treatment Options

Buerger's disease

- **Symptoms manifest in advanced stage**; stopping smoking will not stop progress of disease
- Diffuse **& distal nature of CLI** reduces the effectiveness of reconstructive vascular surgery
- Progress to limb amputation
- **No drugs approved for BD;** current standard of care focuses only on pain alleviation & vasodialators

Atherosclerotic PAD

- Current Standard Of Care – medications, endovascular surgery, angioplasty & atherectomy
- High risk of leg amputation and death

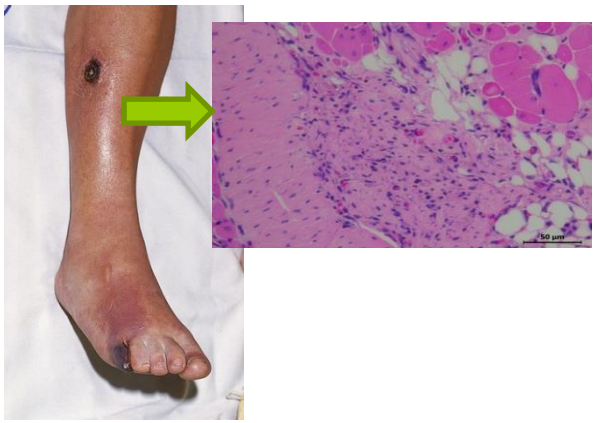


Stempeucel® drug addresses the Gaps in the current treatment

Mechanism of action

Ischemia

Inflammation | Loss of muscle tissue



VEGF
SDF1,IL-8
Angiopoietin1
HGF, IL-6
→ Angiogenesis

IDO
(Indoleamine – 2,3 dioygenase)
PG-E2
SDF-1
→ Immunomodulation : Reduction of inflammation

PG-E2,
TGF-β,
IL-6
→ Muscle regeneration

Outcomes: Relief of rest pain, Healing of ulcers, Increase in ABPI & Increased collaterals

stempeutics

CLI Clinical Trial Summary (n=184)

Parameter	Phase 1 2M/Kg (20 Patients)	Phase 2 (90 Patients)		Phase IV PMS Study (50 Patients)	CLI PAD Phase 3 study (24 patients)
		1M/Kg	2M/Kg	2M/kg	2M/Kg
Safety of the Product	✓	✓	✓	✓	✓
Efficacy of the Product					
Rest Pain	+ve trend		+ (Sig)	+ (Sig)	+ (Sig)
Ulcer healing	+ve trend		+ (Sig)	+ (Sig)	+ (Sig)
ABPI	+ (Sig)		+ (Sig)	+ (Sig)	+ (Sig)
ASP	+ (Sig)		+ (Sig)	+ (Sig)	+ (Sig)
TWD		+ (Sig)	+ (Approaching Sig)		+ (Sig)
QOL		+ (Sig)	+ (Sig)		+ (Sig)
MRA			+ (NS)		

Marketing approval granted in India …. 2M/kg dose is most efficacious

Stempeucel®
OA product

Osteoarthritis

About OA	• Chronic condition in which the material that cushions the joints, called cartilage, breaks down • Causes the bones to rub against each other, causing stiffness, pain and loss of joint movement • Linked to obesity, gender (more common in women), age (late 40s onwards), genetic factors and incidence of previous injury/ accident

Gap in Treatment Options	• Current standard of care includes:
	  ▪ Analgesics
	  ▪ Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)
	  ▪ Opioid Analgesics
	  ▪ Hyaluronan – Intra-articular HA therapy
	  ▪ Surgical procedures
	• Only symptomatic treatment exists & main objectives of physicians are to control pain adequately, improve function & reduce disability

Stempeucel® has the potential to reduce the pain for a longer period of time than HA and improve/sustain cartilage quality thus delaying the need for knee replacement surgery

Stempeucel® OA – Product Development

R & D

In vitro properties of Stempeucel®

- Hypoimmunogenic
- Anti-proliferative for allogeneic PBMC (immunosuppression)
- GF/CK secretion
- Necessary TSP2 secretion
- Stempeucel also produces PGE2, IDO etc.
- Unprimed cells shows more sGAG formation

Preclinical

In vivo properties of Stempeucel®

- Stempeucel administration ameliorates pain in MIA model of OA
- No. of animals with OA (gross examination) is considerably lower in Stempeucel® treated groups
- Proteoglycan staining demonstrated cartilage restoration upon Stempeucel® treatment
- The HNA labelled cells were found throughout the osteoarthritic cartilage at 4 week post transplantation

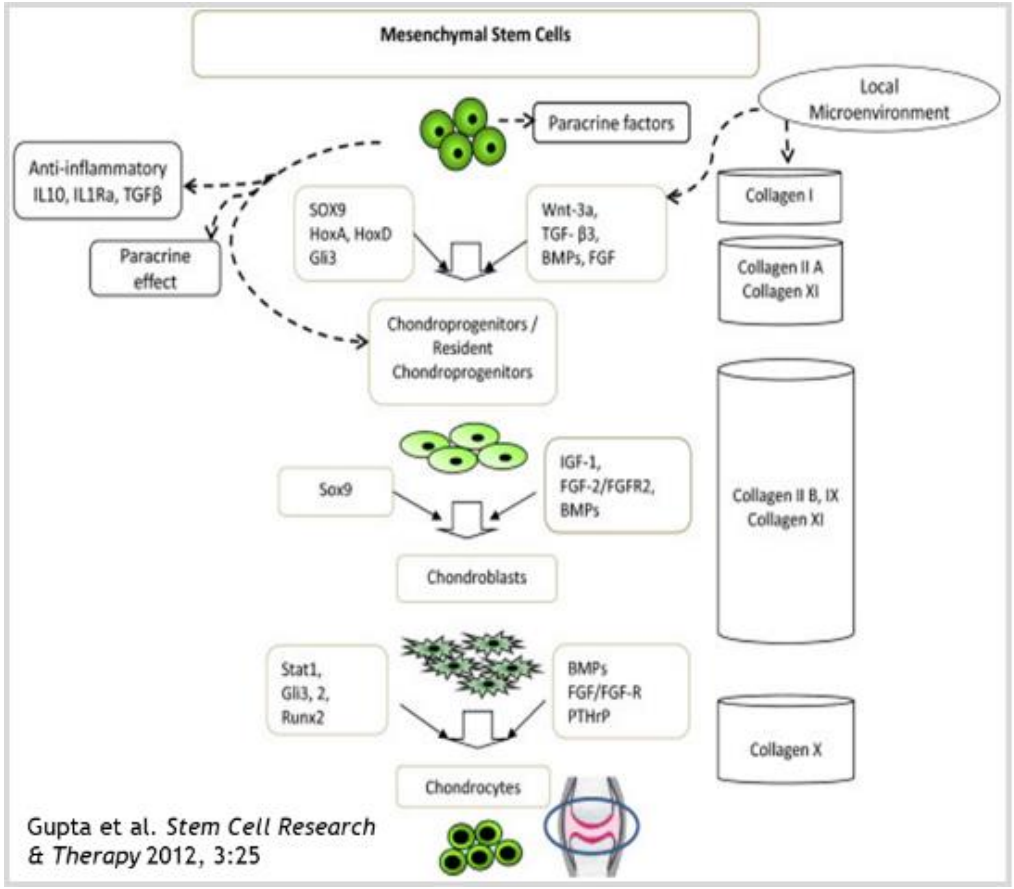
Clinical

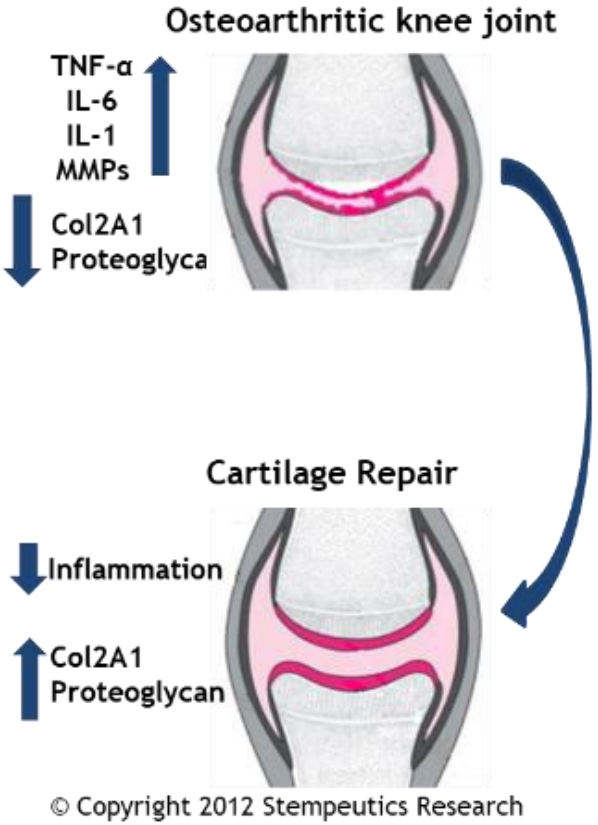
Clinical efficacy of Stempeucel®

- Stempeucel administration improves WOMAC composite score significantly
- Reduces Pain, stiffness and improves physical function of the affected knee
- MRI – T2 mapping shows Quality of cartilage maintained in the cell arm compared to placebo arm
- Increase in cartilage volume in the cell arm compared to placebo
- Inflammatory biomarker hsCRP shows decrease in the cell arm

Stempeucel® shown anti-inflammatory, immunomodulatory and chondrogeneic properties at key stages of development

Mechanism of action





Stempeucel® can reduce joint pain via anti-inflammatory effects, and possess chondrogenic differentiation potential

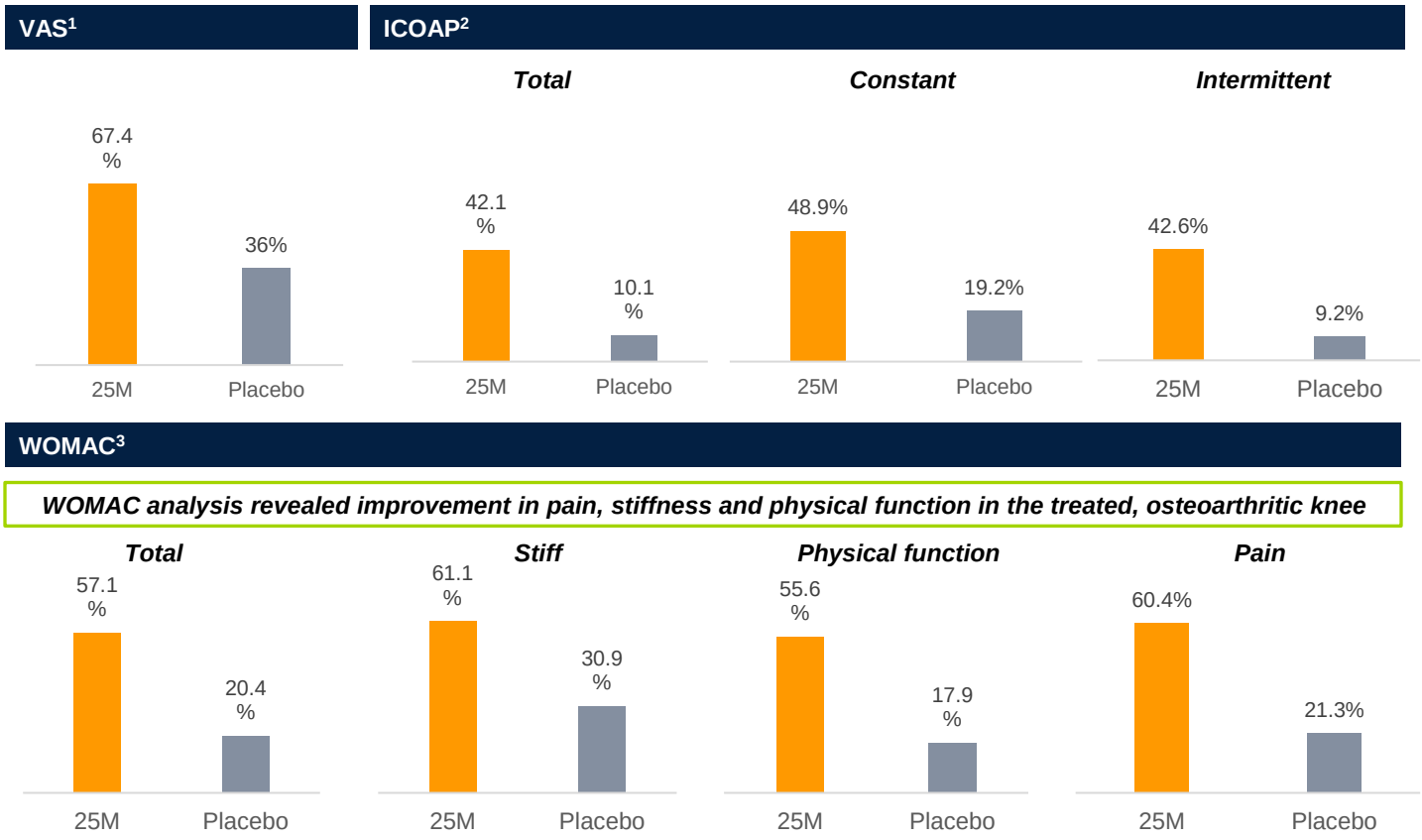
In addition, Stempeucel® could provide signal to resident chondro-progenitors of the host to differentiate into chondroblasts and further into chondrocytes, to repair cartilage damage

Stempeucel® : OA Phase 2 Study

OA (Phase 2 data) – positive efficacy trend at 12 months with 25M dose

60 patient, randomized, double blind, Phase 2, multi-centric, placebo controlled, dose finding study (25/50/75/150M cells)

Efficacy of Stempeucel over placebo in pain management Visit 1(base line) versus Visit 7 (at 12 months)



Notes

1. Visual Analogue Scale
2. Measure of Intermittent and Constant OA Pain
3. Western Ontario and McMaster Universities OA Index

Stempeucel demonstrated positive trend in efficacy for OA in a 60 patient, randomized, double blind, placebo controlled, dose finding study

OA Phase 3 Clinical Trial – 146 Patients

Study Design:

Randomized, double blind, Phase 3, multi-centric, Placebo controlled study assessing the efficacy & safety of IA administration of stempeucel®

Primary Efficacy end point:

- To assess the change from baseline **to one year in WOMAC (Western Ontario and McMaster Universities Osteoarthritis) Osteoarthritis Composite Index score** as compared to the placebo arm

Secondary Efficacy end points:

To assess the change from baseline to one year and two years follow-up as compared to the placebo arm in

- **WOMAC OA Pain Index/ Stiffness Index / Physical function Index**
- Patient's Assessment of Osteoarthritis Pain by **VAS**
- **MRI imaging (done at baseline, 6, 12 & 24 months) to evaluate:**
  - Assess the **cartilage quality by T2 mapping**
  - Assess the **cartilage morphology**
  - Assess the **cartilage volume**

Safety end points

- Assessment of AE(s) + ECG parameters/vital signs

Exploratory end points:

- Assessment of **biomarkers**: CTX – II (urine)
- Assessment of **antibodies:** Anti HLA antibody

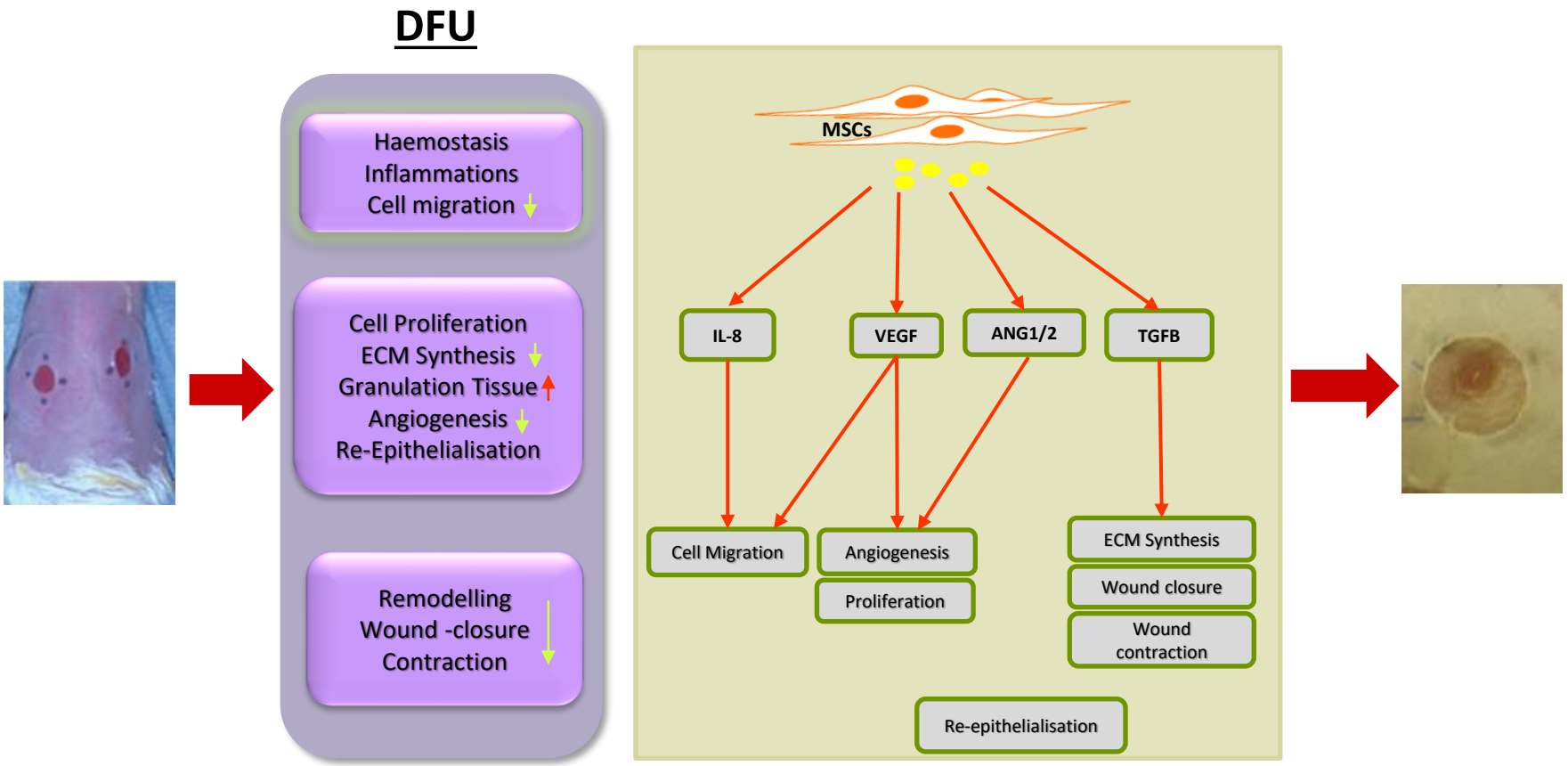
Cell arm: Stempeucel® + Hyaluronic acid (73 patients)

Placebo: Placebo + Hyaluronic acid (73 patients)

Volume: 2 ml of each, Single Intra-articular injection; USG guided

Stempeucel®
DFU product

Mechanism of action

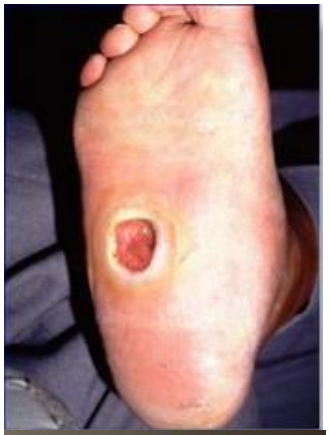


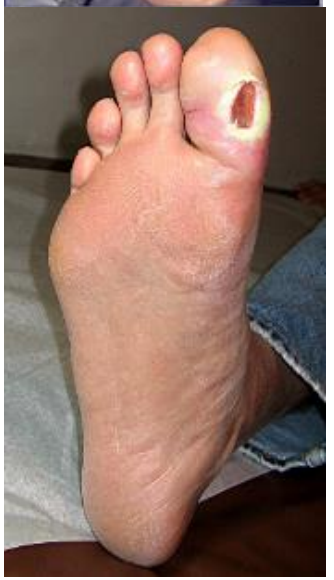
Anti-inflammatory, angiogenic and wound healing properties of MSCs are key to successfully treat patients with DFU

DFU Phase 3 Trial is in progress

Study Design

- A Label extension, Randomized, Double Blind, Placebo Controlled, Multicentre, Single Dose, Phase III Study Assessing the Efficacy and Safety of Peri-ulcer Administration of Stempeucel® (Adult Human Bone Marrow Derived, Cultured, Pooled, Allogeneic Mesenchymal Stromal Cells) in Patients with Non-Healing Diabetic Foot Ulcer





Primary Objective

- To evaluate the efficacy of periulcer administration of Stempeucel® in healing of DFU

- Primary efficacy endpoints:

- Proportion of patients with complete healing / closure of the target ulcer at any time during the 12 week treatment period with sustained complete closure for 12 additional weeks of follow-up (Time frame: 12+12= 24 weeks)
- Rate of reduction in size of the target ulcer

Secondary efficacy endpoints:

- Proportion of patients with at least 50% closure of target ulcer during the 24 wks. period
- Proportion of patients with complete healing / closure of the target ulcer at any

Total 84 patients: 42 patients in each arm. 50% patient recruitment completed

Stempeucel®
PAF product
due to Crohn's Disease

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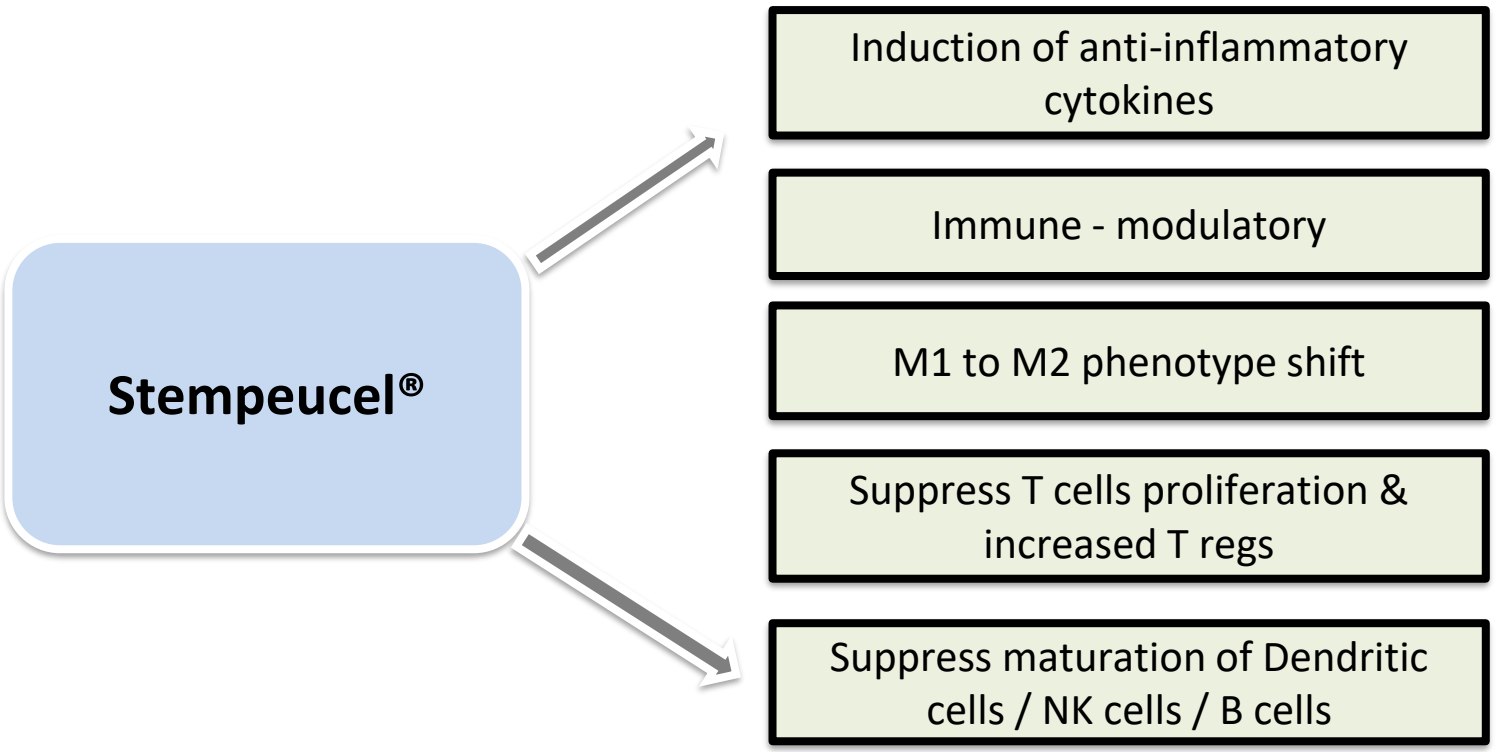
Background Information

- Crohn's disease (CD) is a chronic inflammatory disorder of gastrointestinal system with divergent clinical manifestations.
- Clinical manifestations depend of behaviour of disease such as inflammation of bowel, strictures and fistulas, among which fistulas are most difficult to treat.
- Fistulas can be enteroenteric, enterocutaneous, enterovesical, enterovaginal in females and perianal fistulae. Most common fistula associated with CD is perianal fistula.
- Treatment of perianal Crohn's disease has been a major problem till now. There are number of treatment modalities available including medical and surgical procedures. Medical treatment includes antibiotics, immunomodulators and biological. Surgical methods include fistulectomy, fistolotomy, Seton placement and drainage of abscesses. Success rates with any modality reach approximately 50% and 70% relapse on discontinuation of treatment
- Surgical therapies associated with high recurrence rate and side effects like sphincter dysfunction
- Hence there is need for effective modality with fewer side effects. One kind of such therapy is local injection of Mesenchymal Stem Cells (MSCs) into perianal fistula. In our study we would like to see for feasibility, efficacy and safety of local injection of MSCs into perianal fistula.

Phase 1/2 clinical trial has been initiated at AIIMS Delhi

Mechanism of action



Immunoregulatory activity reduces inflammation, which allows the tissues around the fistula tract to heal

Clinical Trial Design - Perianal fistulizing Crohn's disease

Study title	An open label, single arm, investigator initiated Phase I/II study to assess the safety and efficacy of local administration of Stempeucel® in Patients with perianal fistulizing Crohn's disease
Total patients	10 in single site (AIIMS, New Delhi) Investigator : Dr Vineet Ahuja, AIIMS
Primary objective	To evaluate the safety of perianal administration of Stempeucel® • The type of adverse events AE(s), number of AE(s) and proportion of patients with AE(s) • Assessment of clinical laboratory parameters • Physical examination findings and assessment of vital signs • Assessment of electrocardiogram (ECG) parameters
Secondary objective	To assess the efficacy of perianal administration of Stempeucel® • Remission of draining fistula at week 24, defined as the clinical closure of all treated external openings that were draining at baseline, and the absence of collections larger than 2 cm in MRI • Remission of draining fistula at week 104, defined as the clinical closure of all treated external openings that were draining at baseline, and the absence of collections larger than 2 cm in MRI • Changes in the Perianal Disease Activity Index (PDAI). • Change in IBD control quality of life questionnaire scores • Change in Crohn's Disease Activity Index (CDAI) • Change in MRI scores (Van Assche index) • Time to remission / Time to response / Time to relapse

9 patients completed Stempeucel® administration

Stempeucel® ARDS product due to COVID-19 Pneumonia

Phase 3 Covid-19 ARDS Study

A Label Extension, Single Arm, Multicentric, Two Dosage, Phase 3 Study Assessing the Efficacy and Safety of IV administration of Stempeucel® in Patients with Moderate to Severe ARDS due to COVID 19

BM-MSCs

Total sample size: 56 Patients

Stempeucel®(56 patients) - SPOC + 400 million cells in 2 doses (200 M each)

Stratification - 28 patients will be stratified into moderate ARDS and another 28 patients into severe ARDS

2 doses of 200M cells each : 3 to 5 days apart (Total dose = 400 million)

Primary efficacy end points:

- Percent mortality 28 days after administration of BMMSCs

Secondary efficacy end points:

- ICU free days 28 days after administration of BMMSCs
- Number of days alive and off ventilatory support at 28 days after administration of BMMSCs
- Oxygen index (OI) changes (from day 0 to day 14) (Oxygen index = FiO2 x MAP x 100 / PaO2)
- Acute Physiology And Chronic Health Evaluation (APACHE) II score (from Day 0 to Day 14
- Sequential organ failure assessment score (SOFA score) (at day 0, 1, 3,7,14,and 28)
- Mortality at Day 56 and Day 84

Secondary safety end points:

- The type of adverse events AE(s), number of AE(s) and proportion of patients with AE(s).
- Assessment of clinical laboratory parameters.
- Physical examination findings and assessment of vital signs.
- Assessment of electrocardiogram (ECG) parameters.

Exploratory end points

- Plasma cytokines – IL -6, IL-8 and IL-10 (at day 0, day 4, 7, 14 and 28)
- Other markers in plasma – TNFα, D-dimer, LDH, hs-troponin, Pro-calcitonin, CRP (at day 0, 4, 7, 14 and 28)

Phase 3 clinical study approved by DCGI ….

Stempeucel® Global

Commercializing Stempeucel® in Japan

PMDA Japan has revised Pharmaceutical Affairs Law for Regenerative Medicinal Products: Providing conditional marketing approval after Phase 2 clinical trial (fast track approval system implemented)

1. **Focussing on Buerger's Disease and Osteoarthritis indication in Japan**
2. Completed preliminary consultation meeting with PMDA in 2019 and Pre-meeting on Quality & Safety (CMC & Preclinical Safety) in 2020
3. Based on the feedback received from PMDA, working on creation of PMDA compliant cell banks, additional pooling data and comparability data between new cell banks and old cell banks
4. Signed a collaborative agreement with Novumcell, Japan – a regenerative medicine company for accelerating regulatory activities with PMDA, Japan

Next meeting with PMDA is planned in Q2, 2022

Commercializing Stempeucel® in USA & EU

US FDA

Initial discussions focused on determining a clinical development plan and obtaining pooling exemption.

- Completed Pre-IND meeting with FDA seeking guidance on CMC, non-clinical, and clinical development plans for Stempeucel® for CLI due to Buerger's disease
- Based on the feedback received from FDA, work in progress on product development

European Medicinal Agency

In Europe, Stempeucel® has been registered as an ATMP and has been awarded Orphan Drug Designation.

- Completed Scientific Advisory meeting with EMA seeking guidance on CMC, non-clinical, and clinical development plans for Stempeucel® for CLI due to Buerger's disease
- EMA in principle agreed for single pivotal Phase 3 study and Stempeucel® technology

Stempeucare®
Bio Cosmetics

The Bio-cosmetic Portfolio

Stempeucare® Cosmetics: First DCGI approved cosmetic products containing vital Bioactive factors secreted from the MSCs using a novel patented pooling technology

Skin care | **Eye Care** | **Hair Care** | **Multisera Facial bundle in pipeline**

Face Wash | Face Scrub | Day Cream | Night Serum

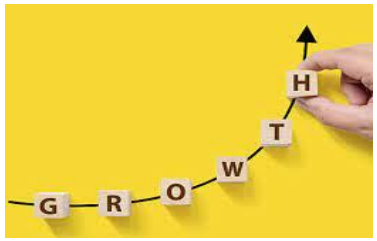
CUTTING EDGE TECHNOLOGY | 200+ GROWTH FACTORS | NATURAL REGENERATION | ZERO SIDE-EFFECTS

FASTEST GROWING BEAUTY & PERSONAL CARE SEGMENT IN INDIA

NOC for cosmetics granted by DCGI (for Cutisera, Trichosera and Peri-Optisera products)

The Bio-Cosmetic Opportunity

Market



Skincare and Cosmetics are the Fastest growing BPC segments

Indian Anti-aging skin and hair care market is growing at 12%, fastest in APAC

The USP

First and Only DCGI approved Stem Cell derived Cosmetics

Strong clinical data with 100% user acceptance and outcomes

Competition

Category creation opportunity in the anti-aging segment

Current Products-
Serum based
Vit-C
Retinol
Hyaluronic Acid

Plant based stem cell based cosmetic

Consumer

Evolving buying behaviour of consumers

- Higher disposable income
- Social media influence
- Increased adoption of premium anti-aging products
- Always looking for newer therapies and products to reverse aging effects

BPC – Beauty and Personal Care

Cutisera® Product

Intensive Skin Care Translucent liquid. Pack Size: 30 g
Topical application – 2-3 pump (0.5 gm), twice daily- morning and evening

Potential benefits of Cutisera skin care translucent liquid are:

- Reduction of fine lines and wrinkles
- Evens skin tone/enhances luminosity
- Lightens the dark spots
- Improves skin firmness
- Improves skin hydration

Sold approx. 27,000 units, safety established with good efficacy in three months

Growth factor supplementation for preventing the aging of skin is an emerging concept… Use of conditioned medium in a suitable formulation could be used to prevent skin aging

Trichosera® Product

Intensive Hair Care Translucent liquid. Pack Size: 30 g
Topical application, 2 g - once daily

❖ Potential benefits

- ✓ Controls hair fall
- ✓ Nourishes hair follicles
- ✓ Promotes healthy scalp
- ✓ Conditions and strengthens hair
- ✓ Improves hair regrowth

Hair loss is a distressing condition for an increasing number of men and women …… Conditioned media derived from adult stem cells have been shown to improve hair health

Perioptisera® Product

Under eye dark circle Bioactive concentrate. Pack Size: 15 g
Topical application, 0.2g – twice daily in the morning and evening

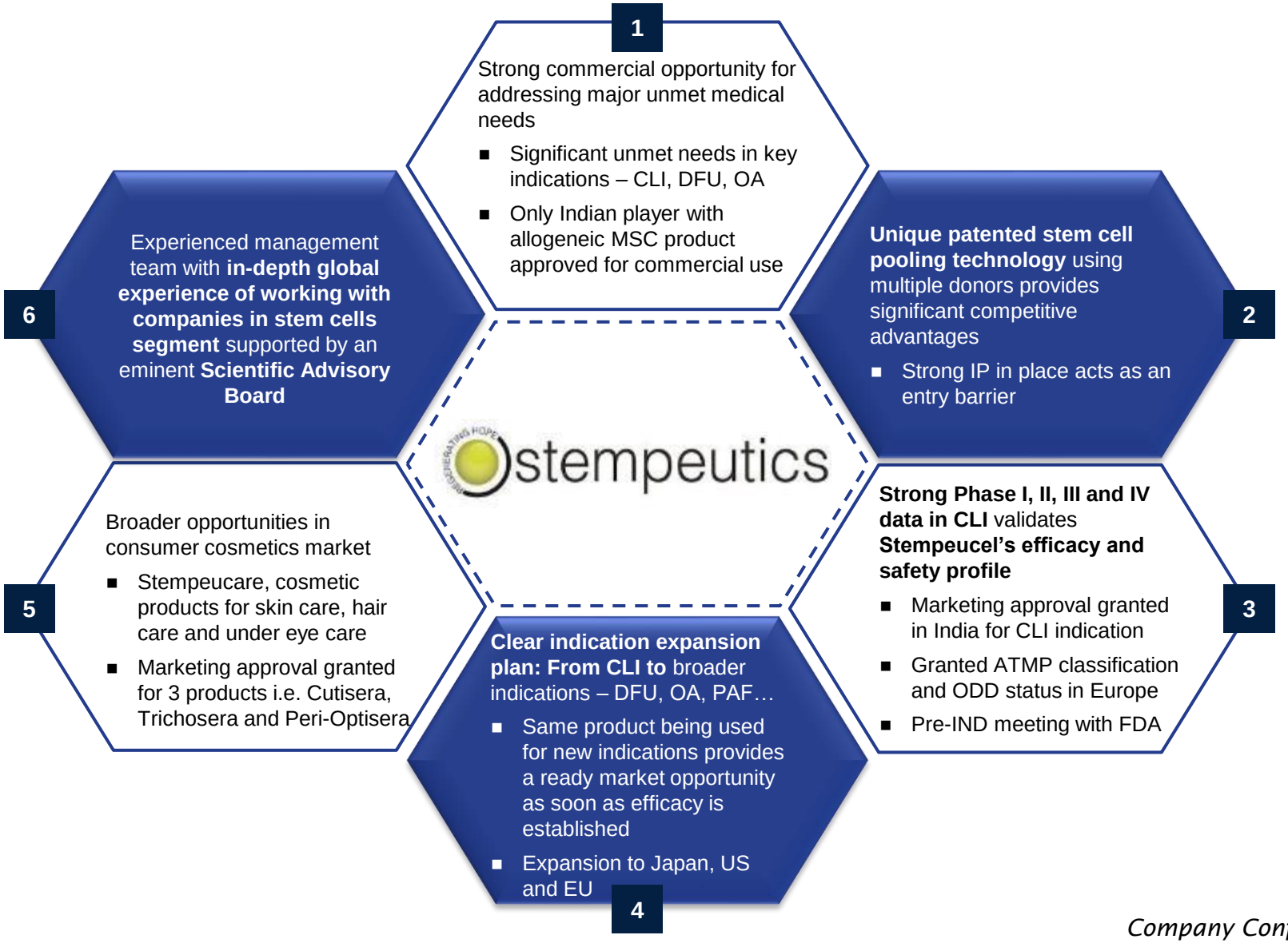
❖ Potential benefits

- ✓ Reduces under eye dark circles & eye bags
- ✓ Reduces under eye fine lines & Crow's feet
- ✓ Rehydrates and soothes the under eye skin
- ✓ Lightens dark spots on the under eye skin
- ✓ Leads to younger looking eye contour

Dark circles under the eyes are one of the top "beauty" concerns worldwide. Conditioned Medium derived from adult stem cells plays a significant role in skin rejuvenation probably by reducing melanin synthesis

Executive Summary

Executive Summary



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