Endonovo Therapeutics, Inc.
Overview of tPEMF Assets
December 26, 2017
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HIGHLIGHTS

Targeted-Pulsed Electromagnetic Field (tPEMF) Therapy

- Proven, science-based “platform technology” – targeted Electroceuticals™ for treatment of diseases
- Non-invasive, non-pharmacological treatment with no known side-effects
- FDA Cleared for treating post-operative pain and edema in soft tissue
  - 5 randomized controlled clinical trials in peripheral tissue
    - Reduced pain, pain medication, two trials with biomarkers
- CE Mark (Class 2a) for the treatment of pain, wounds and edema
- Medicare (CMS) issued National Coverage determination in 2004 for chronic wounds
- 27 issued patents with foreign patent protection
- Currently being developed for the treatment of central nervous system disorders – targeting neuroinflammation
  - Clinical trials planned for post-concussion syndrome, mild traumatic brain injury (mTBI), multiple sclerosis and stroke
PORTABLE, DISPOSABLE tPEMF

- Low Power, battery operated
- Disposable – possibility to leverage existing Pharma-model
  - Physician: writes a prescription for use at home
  - Patient: acquires product from pharmacy, broad distribution-ease of refill
    - Leverage large pharmacies, such as Costco, Wal-Mart, Target, Walgreens, etc.
  - Payer: pharmacy benefit reimbursement offers a level of utilization control
- Possibility to leverage recent over-the-counter decision for ActiPatch RecoveryRx
- FDA-Cleared for post-operative pain and edema
- CE Marked (Class 2a)
- Provides 150 treatments (15 minute treatments)
- CMS National Coverage for chronic wounds
TECHNOLOGY VALIDATION AND CLINICAL EVIDENCE

• **Technology Validation:**
  
  – CMS (Medicare) issued National Coverage Determination for PEMF for healing chronic wounds
  
  – AHCPR Federal Guidelines for Pressure Ulcers: “electrotherapies” only effective adjunctive treatment
  
  – ASAPS endorses 40% acceleration in healing in human burn model

• **Clinical Evidence:**

  – 72% reduction of sacral ulcers in paraplegics *(Kloth, et al 1999)*
  
  
  – 69% acceleration in tendon healing *(Strauch, Pilla et al; The Journal of Hand Surgery, September 2006)*
  
  
  – 59% increase in surgical wound healing *(Strauch, Pilla et al; Plastic and Reconstructive Surgery, August 2007)*
  
  – 40% acceleration in post-surgery recovery *(ASAPS, 2001)*
  
  – 80% acceleration in post-surgery pain relief *(Heden, 2007)*
  
  – 60% more significant soft-tissue repair than for bone growth *(Akai M, Hayashi K meta-analysis, Bioelectromagnetics, 2002)*
HOW ELECTROCEUTICALS WORK

Disease: Disruption of cellular electrochemistry

Healing: Restoration of key electrochemical processes that initiate the anti-inflammatory and growth factor cascades

- First class of Electroceuticals
  - Enhance healing
  - Easy-to-use, FDA-Cleared technology
  - Non-invasive
  - No known side effects
  - No effects on healthy tissue
  - Increases efficiency of natural anti-inflammatory response

“I think this is the industry that will replace the drug industry” – Kevin J. Tracy, President of the Feinstein Institute for Medical Research

“The only question is, how many different diseases will be treated with bioelectronic medicine” – Moncef Slaoui, Chairman of R&D, GlaxoSmithKline
OVERALL TARGETED tPEMF MECHANISM

→ tPEMF

Accelerates the production of the endogenous constitutive nitric oxide synthesis systems (cNOS): the anti-inflammatory system

Anti-inflammatory: increased blood flow and lymph flow
Pain and edema decrease (seconds)

NO → Cyclic Guanosine Monophosphate (cGMP) → Growth Factors (hours/days)

tPEMF has an effect on the following growth factors:

VEGF (Vascular Endothelial Growth Factor) Angiogenesis (hours/days)
FGF (Fibroblast Growth Factor) Collagen/Granulation (days)
TGF-β (Transforming Growth Factor) Remodeling (days/weeks)

Ca²⁺ = Calcium
CaM = Calmodulin
eNOS = endothelial nitric oxide synthase
EVOLUTION OF ELECTROCEUTICALS

• Pulsed Diathermy
  – High power PEMF to treat pain and edema (1930s)

• Bone Growth Stimulators
  – PEMF to heal recalcitrant fractures (1974)
  – Induce electrical currents into bone tissue
  – Standard care in orthopedics

• Targeted PEMFs
  – Target specific electrochemical processes (Calcium/Calmodulin Binding)
  – Exploits science of electrochemistry for therapy (like MRI and CAT scan does for diagnosis)
  – Portable, low power devices that can be integrated into sports or protective helmets to treat brain injuries (TBI)

Vacuum tube PEMF 1951
Helmet-integrated PEMF units (Sandia National Labs)
Tendon Repair Model (Strauch, et al, JHS 2006)

- tPEMF (SofPulse) shown to be more effective than older high power PEMF (MRT) and bone growth signals (BGS)
CLINICAL RESULTS VS. SIGNAL CONFIGURATION

- Bars show relative signal dose in nitric oxide (NO) signaling pathway
- tPEMF (SofPulse) delivers 100% to NO pathway compared to 15% for ActiPatch RecoveryRx
- Bone Growth Stimulator (BGS) included for comparison

**Multiple parameters of the signal were configured – not as simple as frequency only!**

Heden et al., Aesthetic Plast Surg. 2008
Rawe et al., Aesthetic Plast Surg. 2012
Case Studies

Wound Healing
POST-BREAST SURGERY HEALING

Post-breast CA, 2 failed flaps, radiation treatment inhibits healing

Failed TRAM post breast reconstruction

Begin tPEMF Therapy

Nine Weeks tPEMF

This slide contains before and after photographs showing the results of a single therapeutic use in humans. These photographs are presented for illustration purposes only and do not guarantee similar results in all cases.
INDIAN HEALTH SERVICE - VENOUS STASIS ULCER

Venous stasis ulcer unresponsive for 10 months

Venous stasis ulcer healed (3 wounds total) at 12 weeks

This slide contains before and after photographs showing the results of a single therapeutic use in humans. These photographs are presented for illustration purposes only and do not guarantee similar results in all cases.
Pre-Clinical and Clinical Data

Pain and Edema in Soft Tissues
tPEMF TARGETS PAIN AND EDEMA

Standard animal model for assessing anti-inflammatories\(^1\)

Pain tolerance remains the same in active group; decreased by 59% (P < 0.001) at 8 hours in sham group

Significantly greater edema in sham group 61% (P = 0.003) versus active group at 8 hours

Results equivalent to NSAIDS with nitric oxide donor\(^2\)

\(^1\) Carrageenan injection model Johnson et al., BEMS, San Diego, 2008
Effect of TPEMF on post-operative pain from breast augmentation. Pain decreased in the treated cohort 1.8x faster than that in the sham cohort (P < 0.001) – Heden 2008
Sham patients required 2-fold more narcotic medication in first 48 hours post-op (P < 0.01)

tPEMF IS A POTENT ANTI-INFLAMMATORY

TPEMF technology has been demonstrated in two randomized controlled clinical trials to significantly reduce post-operative pain, swelling, pain medication use and a key inflammatory biomarker IL-1β.

Equally important, three additional key inflammatory indicators: (i) pain; (ii) use of pain medication (opiate equivalents); and (iii) exudate volume (edema) were also reduced by between 33% and 50% in the active arms of both RCTs (n=24, n=32, respectively).

Potent anti-inflammatory that is clinically proven and FDA-cleared
tPEMF EFFECT ON POST-OP PAIN

Pain reduction nearly 3-fold faster in Active cohort by 5 hours post-op
Pain at 48/72 hours post-op nearly 4-fold higher in Sham cohort

Pilla et al., Biochim Biophys Acta. 2011; 1810:1236-1245
DOSING STUDY:
EFFECT OF tPEMF REGIMEN ON POST-OP PAIN

5 min Tx every 20 min regimen no more effective than sham, while 15 min Q2 or Q4 are effective

Taylor et al., J Surg Res. 2014 Epub
Left: Effect of tPEMF therapy on edema volume from grades I and II lateral ankle sprains. Mean edema decrease from Day 1 to Day 3 post study entry in the tPEMF treated group was >7x that in the sham treated group. Right: Effect of tPEMF therapy on the rate of edema decrease in grades I and II lateral ankle sprains. The mean rate of edema decrease was nearly 5x greater in the tPEMF treated group versus that in the sham treated group, suggesting less time in inflammatory phase leading to increased rate of healing.
Pre-Clinical and Clinical Data

Angiogenesis and Cardiovascular Disease
ANGIOGENESIS

- Angiogenesis – creation of new blood vessels
- Foundation of all regeneration – supply fresh blood and nutrients to growing tissues

Arterial loops in rats at 8 weeks show 500% increase

Placebo-treated arterial loop

Actively treated arterial loop

CARDIOVASCULAR ANGIOGENESIS

*tPEMF Effects on injured heart in animal model*

Without Treatment (sham)  
Heart tissue near injury  
New vessel growth

With Treatment  
Heart tissue near injury  
New vessel growth

100% increase in new blood vessels in treated animals
Initial Human Clinical Trial (EFFECT Trial)
- Randomized, double blinded, placebo controlled (RCT)
- End-stage ischemic heart disease (“No Option Patients”)
- 30 patients (15 active, 15 sham), self treated at home, 2x daily, 30 minutes
- Active phase: 3 months, 2 month wash-out
- Patients evaluated at 0, 1, 3 and 5 months: Seattle Angina Questionnaire (SAQ), SPECT imaging, echo cardiogram
- Outcome measures
  - Improvement in angina and exercise tolerance
  - Improvement in regional myocardial perfusion and function

EFFECT Summary Results:
- Significant between group differences
  - Improved SAQ subscales for: Anginal Frequency and Physical Activity in active cohort
- Significant within group improvements
  - Improved SAQ subscales for: Anginal Frequency, Severity and Physical Activity in active cohort
  - Comparable to results seen in successful angioplasty patients
- Trend in improved perfusion in active cohort
  - Requires more patients or longer therapy period for definitive results
- Echo: No significant differences between groups
- SPECT: No significant differences between groups
  - However, 3 patients in active cohort had 12-25% increase in perfusion compared to sham group

Cleveland Clinic Florida EFFECT Trial results used as rationale for creating new generation technology specifically designed to treat internal organs – currently under development
Revascularization (CABG or PCI) has been the standard care for patients with refractory angina from ischemic heart disease (IHD). However, many patients are not candidates for PCI or CABG due to diffuse coronary disease or total occlusion of the coronary arteries, high surgical risk or lack of conduits.

Following the applications of electrical stimulation to enhance healing of recalcitrant bone fractures and chronic wounds, newly developed signals and revised protocols with pulsed electromagnetic fields (PEMF) have been shown in clinical studies to enhance microvascular blood flow, promote endothelial cell growth, angiogenesis and hemodynamics post-infarct.

First clinical trial conducted, thus far, to assess PEMF safety & efficacy in pts with ischemic cardiomyopathy.

Aims:
- The study is a randomized, parallel, placebo-controlled and prospective pilot trial to assess PEMF therapy in pts with ischemia refractory angina for:
  - Safety
  - Efficacy on perfusion, function & clinical symptoms
  - Sustainability after completion of the therapy
- Regional myocardial perfusion and function (primary outcome). Patient angina and exercise tolerance (secondary outcome).

Methods
Patient Selection:
- Pts undergoing evaluation and TX for chronic IHD. All pts signed a consent form approved by the IRB.
- 33 patients randomized into 2 groups:
  - TX Group: 15 patients with PEMF TX for 3 mon.
  - Sham group: 17 patients with Sham PEMF TX for 3 mon.

Inclusion criteria:
- Pts between 30 – 70 yrs old
- Coronary stenosis >70%, on catheterization
- The coronary disease cannot be revascularized
- Ischemia on echocardiography or SPECT imaging.

Exclusion criteria:
- Coronary stenosis <70% by catheterization.
- Good candidates for revascularization.
- Unable to sign consent.
- With pacemaker/ICD.
- Stent placement < 1 month

Assessment of Safety
- The initial treatment was conducted at CCF. Hemodynamics (HR, blood pressure) was monitored at baseline, every 5 min during the 30 min treatment and 30 min after treatment. ECG was acquired at baseline, 15 min during, immediately post and 30 min post treatment.
- Any clinical symptom, hemodynamic response, arrhythmias, or ECG changes was documented. Chemistry labs (C18) and cardiac enzymes (CPK, MB and Tn) were checked at baseline and 24 hours after the 1st treatment. High sensitive CRP was measured at baseline, after 1, 3, mon treatment and 2 mon after completion of the therapy.
- 24 hrs home-telemetry monitoring was performed on all patients for 1 week pre and 1 week post-treatment.
- Hemodynamic monitoring was performed at patients home by homecare RNs at all visits in these 2 weeks.

PEMF Application
- The PEMF device cleared for pain and edema (SofPulse, hivri Technologies, Inc., Northvale, NJ) produces a low power, pulsed radio frequency (PRF) signal consisting of a 4 msec burst of 27.12 MHz sinusoidal waves repeating at 5/sec. The incident amplitude of the signal is 0.05 Gauss peak to peak (for reference, the earth’s magnetic field is 0.5 Gauss). The signal is delivered to the tissue target via a single turn circular electrical coil 8 inches in diameter, fitted in a garment worn around the chest, situated over the patient’s heart. No heat or muscle stimulation is produced.
- The procedure is repeated for 30 min twice a day for 3 months. The 1st Tx was conducted at CCF. Subsequently, all patients were treated and trained by experienced homecare RN at patient’s home for 1 week. The 1st week, the patients used the device at home by themselves.
- The PEMF signal was configured to modulate calmodulin-dependent NO and growth factor (e.g., FGF-2) production.

Cardiac Imaging
- SPECT imaging (Tc99m-mibi) & Echocardiography were performed at baseline, 1-mon, 3-mon during PEMF TX and 2 mon after completion of the TX using standard protocols.
- The perfusion defect was quantified as percentage of LV compared with normal database using a standard software package (QGS/QPS).

Clinical Evaluation
- All patients underwent clinical evaluation for medical history, symptoms of angina, functional capacity using Seattle Angina Questionnaire (SAQ). All pts received clinical guideline recommended standard care for IHD (beta-blockers, ACE inhibitors or ARBs, calcium channel blockers, etc). Clinical evaluation was conducted at baseline, 1-month, 3-months during TX and 2-months after completion of PEMF therapy.

Results
Two pts in Sham group (VT) and 1 pt in TX group (MI) dropped out due to complications unrelated to PEMF Tx. No adverse effects from PEMF Tx were noted.

Clinical Characteristics: No significant differences between groups.

Labs and Hemodynamics: No significant differences between groups.

Symptoms: Significant improvements in SAQ scores for angina severity and physical limitations were noted during PEMF Tx and 2 months after Tx in the active group vs no effects in the Sham group.

SAQ scores evaluated 25 months (average) after completion of trial showed all improved scores in the active group returned to baseline (see graphs), suggesting continued PEMF therapy is indicated. All contactable patients, except 5 in the sham group, desired to restart PEMF Tx.

Echo: No significant differences between groups.

SPECT: No significant differences between groups. However, 3 pts in the Tx group had 12-25% increase in perfusion (see images) compared to sham group.

Conclusions
- This is the first study using PEMF in pts with IHD. The trial shows that PEMF therapy is safe to use and effective improving angina severity and physical capacity in pts with IHD and failed medical therapy & revascularization options.
- Treated patients showed steady improvement in clinical symptoms which persisted at 2 months after cessation of PEMF therapy. This clinical improvement disappeared approximately 25 months post PEMF, suggesting a longer Tx regimen may be warranted.
- This unique device is non-invasive, non-pharmacological and self-operable at home.
- Future studies are needed to confirm angiogenesis, investigate mechanistic effects, quantify perfusion changes and clinical outcomes in larger trials.

References

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Central Nervous System Indications

Pre-clinical Data in CNS Disorders
NEUROLOGICAL INDICATIONS FOR tPEMF

- Traumatic Brain Injury (TBI)
- Post Concussion Syndrome
  - [https://clinicaltrials.gov/ct2/show/NCT02643836](https://clinicaltrials.gov/ct2/show/NCT02643836)
- Long Term Neurodegeneration and Possible Chronic Traumatic Encephalopathy (CTE)
- Multiple Sclerosis
- Stroke
OPEN-LABEL CLINICAL STUDY

- Open-label study to assess effects of short-term PEMF treatment with 30 patients in a neurosurgical ICU
- Open to patients with intracranial pressure monitoring (GCS > 5)
- 24 hr $T_x$ protocol 15 minutes every 2 hours
- No adverse events nor side effects seen
CLINICAL USE IN NEUROSCIENCES

Neurosciences ICU

Helmet-integrated tPEMF Units (Sandia National Labs)

Somatosensory Testing
TheraCap™ - CLINICAL TRIAL DEVICE

“TheraCap™” study device for sports concussion clinical trials (therapy embedded in cap)
FIRST TARGET: TRAUMATIC BRAIN INJURY (TBI)

• 1.8+ million cases present in US hospitals annually
  – Up to an additional 3 million go undiagnosed
  – Majority are mild TBI: concussions
    • At least 400,000 annually in youth sports
    • Over 250,000 in the past decade in the military

• Over 5 million Americans are living with permanent disability due to brain injury

• No treatments currently available
MODERATE TRAUMATIC BRAIN INJURY (mTBI) – PRIMARY AND SECONDARY INJURY

- **Primary Injury** – initial insult (e.g. hit to the head) causes a concussion (symptoms include dizziness, loss of consciousness, fogginess, etc.)
- **Secondary Injury** – neuroinflammation and its resulting chronic damage, reduced blood flow, edema and neuronal death
  - Inflammatory response produces further symptoms that can lead to long-term neurodegenerative pathologies
SIGNIFICANT BARRIERS TO TREATING TBI

Drugs:
• Fundamental challenge of pharmaceutical delivery across the blood-brain-barrier (BBB)
• Unattractive side effects profiles and toxicity problems
• Numerous failed clinical trials for stroke, TBI, etc.

Devices:
• Various non-invasive brain stimulation therapeutics, hyperbaric oxygen, cooling technologies, near infrared light therapy are all inhibited by:
  – Lack of effectiveness data
  – Lack of mechanism of action (MOA) understanding

_tPEMF has clinical relevant bioeffects in reducing inflammation and edema and is unimpeded by these barriers_
DEMONSTRATED CLINICALLY RELEVANT tPEMF EFFECTS IN NEUROLOGICAL MODELS

- Reduced microglial proliferation and activation
- Reduced inflammatory (e.g., IL-1β) and apoptotic (TNF family) cytokines and gene expression
- Increased anti-inflammatory (e.g., IL-10 and IL-11) cytokine gene expression
- Increased cyclic GMP and AMP production
- Improved blood vessel dilation and integrity
- Reduced capillary shunting
- Increased tissue perfusion and tissue oxygenation
DEMONSTRATED CLINICALLY RELEVANT tPEMF EFFECTS IN NEUROLOGICAL MODELS (CONT.)

- Improved blood brain barrier function and repair
- Increased synaptic transmission and long-term potentiation (i.e., synaptic plasticity)
- Improved neuronal mitochondrial efficiency
- Enhanced neuritogenesis and growth
- Promoted axonal growth and neuronal survival in the presence of inflammatory insults
- Provided neuroprotection in ischemic/metabolic injury
  - Potential for prophylactic application (heat shock protein mechanism)
tPEMF RATIONALE IN mTBI

Focused on treating mTBI Secondary Injury to alleviate neuroinflammation and enhance blood flow, thereby reducing neuropathology

Reduced microglial activation with tPEMF in brain injury

Reduced IL-1β (inflammatory biomarker in concussed animals treated with PEMF)
PLANNED CLINICAL RESEARCH PROGRAM

- Endonovo plans to initiate and fund clinical trials:
  - Treatment of Acute Concussion Syndrome: UT Southwestern, double-blind randomized controlled trial (RCT)
  - Post Concussion Syndrome: Harvard-Spaulding Rehabilitation Hospital, double-blind RCT
  - Moderate TBI/Brain Injury: University of New Mexico, double-blind RCT

- Expand indications:
  - Multiple Sclerosis (MS)
  - Stroke
  - Chronic Traumatic Encephalopathy (CTE)
tPEMF AND TRAUMATIC BRAIN INJURY

- Rodents with concussion were treated with SHAM or tPEMF for 6 hours
- Neuroinflammation occurs after brain injury and higher levels of inflammatory cytokine IL-1β are associated with worsened pathology and poor functional outcomes (i.e., greater disabilities)
- tPEMF treated animals had 5-fold less IL-1β in the cerebral spinal fluid (CSF) 6 hours after concussion compared to SHAM-treated animals
tPEMF AND TRAUMATIC BRAIN INJURY

- Rodents with a penetrating TBI treated with SHAM or tPEMF
- tPEMF treated animals had 5-fold less IL-1β in the cerebral spinal fluid 18 hours after injury compared to SHAM control animals
tPEMF EFFECTS IN HIGH INTRACRANIAL PRESSURE (ICP) MODEL

Rat model of high intracranial pressure

- ICP raised to 30 mmHG
- Treated with PEMF for 30 minutes
- Arteriole diameter was measured using intravital 2-photon microscopy
- Tissue oxygenation quantitated measuring NADH auto fluorescence
- NADH is fluorescent and whereas oxidized NAD+ is not

**Increased Arteriole Diameter**

**Increased Tissue Oxygenation**

mmHG = millimeters of mercury, measurement of pressure
NAD = nicotinamide adenine dinucleotide, NADH = product of NAD metabolism, oxidative cofactor, disruption of NAD/NADH redox state leads to tissue damage in the brain
tPEMF EFFECTS IN SUB-ACUTE STROKE MODEL

Sub-acute stroke study demonstrated substantial effects of Tpemf on gene expression in animals in later stage stroke recovery (7 days)

- Increased anti-inflammatory gene expression
- Decreased inflammatory & apoptotic gene expressions

PEMF 2T per day for 15 minutes starting 3 days post-stroke for 7 days
NEUROPROTECTIVE EFFECTS OF tPEMF

Neuronal Insult Model

- Primary cortical neurons exposed to oxygen and glucose deprivation (OGD) for 1, 2, or 3 hours
- PEMF treatment for 30 minutes at the onset of OGD
- Cells stained for TUNEL, a marker of DNA fragmentation and apoptosis
- 50% fewer apoptotic cells found in PEMF-treated compared with untreated cultures
EFFECTS OF tPEMF ON EXPERIMENTAL AUTOIMMUNE ENCEPHALOMYELITIS (EAE)

- Principal investigator: Sergio Baranzini (UCSF)
- EAE: Inflammatory autoimmune model of multiple sclerosis
- Scoring: 0 (healthy) – 5 (moribund)
- PEMF or Sham treatment of mice with EAE (n = 10 per group) for 15 minutes twice per day

Repeated Measures ANOVA, p = 0.077 Treatment * Time
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OTCQB: ENDV

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