STORZ MEDICAL

CLINICAL INVESTIGATION PLAN (STU 14/032)

TRANSCRANIAL EXTRACORPOREAL SHOCK WAVE THERAPY FOR NEUROLOGICAL DISEASES (HIRNSTIMULATION BEI NEUROLOGISCHEN PATIENTEN/INNEN)

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ABBREVIATIONS

AD	Alzheimer's Disease
ADAS	Alzheimer's Disease Assessment Scale
ADE	Adverse Device Effect
ADL	Activities of Daily Living
ASADE	Anticipated Serious Adverse Device Effect
AE	Adverse Event
ANOVA	Analysis of Variances
B-ADL	Bayer - Activities of Daily Living
BDI	Beck's Depression Inventory
BASG	Bundesamt für Sicherheit im Gesundheitswesen (Austrian Federal Office for Safety in Health Care)
BfArM	Bundesinstitut für Arzneimittel und Medizinprodukte (Federal Institute for Drugs and Medical Devices)
BP	Blood Pressure
CDT	Clock drawing test
CERAD	Consortium to Establish a Registry for Alzheimer's Disease
CIP	Clinical Investigation Plan
CRF	Case Report Form
CRS	Coma Remission Scale
CSWT	Cardiac ESWT
DMS	Deep Brain Stimulation
EC	Ethics Committee
EEG	Electroencephalography
ESWT	Extracorporeal Shock Wave Therapy
FAI	Forgetfulness Assessment Inventory
FGF-2	Fibroblast Growth Factor-2
fMRI	functional MRI

FZV	Leisure Behavior (German: Freizeitverhalten)
GDS	Geriatric Depression Scale
HUVEC	Human Umbilical Vein Endothelial Cells
IADL	Instrumental Activities of Daily Living
IRB	Institutional Review Board
LC	Locus Ceruleus
MEG	Magnetoencephalography
MMSE	Mini Mental State Examination
MOCA	Montreal Cognitive Assessment
MRI	Magnetic Resonance Imaging
NO	Nitric Oxide
NTBV	Neuropsychological Test Battery Vienna
QoL	Quality of Life
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
S.D.	Standard Deviation
SEKS	Scale for Expressive Communication and Self Actualization
S.E.M.	Standard Error of Mean
tDCS	Transcranial Direct Current Stimulation
TMS	Transcranial Magnetic Stimulation
USADE	Unanticipated Serious Adverse Device Effect
VAS	Visual Analogue Scale
VEGF	Vascular Endothelial Growth Factor

1. OVERALL SYNOPSIS OF THE CLINICAL INVESTIGATION

Study Design	Prospective double-blind randomized placebo-controlled crossover clinical trial
Duration of the Study	2 years
Population	Patients with cognitive (Alzheimer's Disease) and motor disease (e.g. Parkinson's Disease, Chronic Stroke, MS, ALS). Healthy controls for procedural optimizations.
Number of Patients	**120 in total:** (1) 60 cognitive disease patients in Austria (60 Verum and Placebo due to crossover) (2) 30 motor disease patients with arm motor deficits (3) 30 healthy controls in Austria
Devices	1 Duolith SD1 (BT.0546) – future name: Neurolith
Objective of the study	The objective is to show the efficacy and safety of TESWT on patients with cognitive or motor disease.
Primary cognitive study endpoint	**-** Corrected CERAD Total Score
Primary motor study endpoint	**-** Coin Rotation Score

Study Procedure and Overview (Cognitive Patients)

	CYCLE I						CYCLE II				
	Screening	Baseline Cycle I	TESWT-Treatments	Follow-Up 1	Follow-Up 2	Follow-Up 3	Baseline Cycle II	TESWT Treatments (Cross-over)	Follow-Up 4	Follow-Up 5	Follow-Up 6
	S	T1	B1-B6	T2	T3	T4	T5	B7-B12	T6	T7	T8
Timetable [weeks] Deviations of ± 1 week are allowed	W1	W1-2	W3-W4	W5	W8	W16	W22	W23-W24	W25	W28	W36
In-/Exclusion Criteria	X										
Patient information	X										
Patient Written Informed Consent		X									

TESWT-Treatments • Questionnaires for patients • Videomonitoring			X					X			
MRI (anatomical and functional)		X		X			X		X		
Tests (AD-Patients) • CERAD-Plus • NTBV * • ADAS * • IADL • B-ADL • FAI / SEG • FZV • Prosopagnosia • CDT • BDI • GDS * different test versions per replication		X NTBV (A) ADAS (A)		X NTBV (B) ADAS (D)	X NTBV (C) ADAS (E)	X NTBV (A) ADAS (A)	X NTBV (B) ADAS (D)		X NTBV (C) ADAS (E)	X NTBV (A) ADAS (A)	X NTBV (B) ADAS (D)
Subjective treatment success and recommendation				X		X			X		X
Tests (Care Taker) • NPI • IADL • B-ADL • FAI/SEG • FZV		X		X	X	X	X		X	X	X
Adverse Events			X	X	X	X	X	X	X	X	X

Study Procedure and Overview (Motor Patients)

	CYCLE I				CYCLE II			
	Screening	Baseline Cycle I	TESWT-Treatments	Follow-Up 1	Baseline Cycle II	TESWT Treatments (Cross-over)	Follow-Up 4	Follow-Up 5

	S	T1	B1-B6	T2	T5	B7-B12	T6	T7
Timetable [weeks] Deviations of ± 1 week are allowed	W1	W1-2	W3 - W4	W5	W22	W23 - W24	W25	W28
In-/Exclusion Criteria	X							
Patient information	X							
Patient Written Informed Consent		X						
TESWT-Treatments • Questionnaires for patients • Videomonitoring			X			X		
MRI (anatomical and functional)		X		X	X		X	
Tests (motor-Patients) • Clinical tests (motor performance) • Coin rotation Test • B-ADL • FZV • MOCA • GDS • BDI Handedness		X		X	X		X	X
• Subjective treatment success and recommendation				X			X	
Tests (Care Taker) • B-ADL FZV		X		X	X		X	X
• Adverse Events			X	X	X	X	X	X

1.1 COGNITIVE DISEASES

1.1.1 MEDICAL BACKGROUND OF ALZHEIMER'S DISEASE

Alzheimer's Disease is a neurodegenerative disease with a high prevalence among the population. 13% of all people older than 65 years and 45% of all people older than 85 years have Alzheimer's Disease (Alzheimer's Association 2012).

The development of multiple cognitive deficits manifested by both:

1. Memory impairment (impaired ability to learn new information or to recall previously learned information)
2. One (or more) of the following cognitive disturbances:
    a. Aphasia (language disturbance)
    b. Apraxia (impaired ability to carry out motor activities despite intact motor function)
    c. Agnosia (failure to recognize or identify objects despite intact sensory function)
    d. Disturbance in executive functioning (i.e. planning, organizing, sequencing, abstracting)

These cognitive deficits cause significant impairment in social or occupational functioning and represent a significant decline from a previous level of functioning.

Despite extensive and intensive research of the last decades, no causal treatment of Alzheimer's disease could be established, i.e. there are no therapeutic options to stop or even reverse neurodegenerative processes of this disease. Thus, only symptomatic therapies are approved and available.

1.1.2 TREATMENT OPTIONS

PHARMACOLOGICAL TREATMENT

There are mainly two pharmacological classes of substances in use, which have a mildly positive influence on the cognitive and behavioral symptoms: acetylcholinesterase inhibitors and glutamate modulators (Memantine). Since these therapy options are not causal, the disease progresses further despite the medication.

NON-PHARMACOLOGICAL TREATMENT

Non-pharmacological steps such as cognitive traning or physical activity can have a positive influence on the symptoms but effects are only small.

Since pharmacological and non-pharmacological therapy options have only limited efficacy, the search for therapeutic alternatives is of great importance. Transcranial extracorporeal shock wave therapy presents a novel treatment option: according to the current state of research, this method has great potential to slow down or even stop neurodegeneration.

1.1.3 COGNITIVE TESTING

CERAD-PLUS

The Consortium to Establish a Registry for Alzheimer's Disease (CERAD) was funded by the National Institute on Aging in 1986 to develop standardized, validated measures for the assessment of Alzheimer's disease (Fillenbaum et al. 2008). CERAD is a cognitive test battery which is normalized for age, gender and education (Morris et al. 1988).

The CERAD neuropsychological test battery consists of the following tests:

- Verbal Fluency (animals)
- Boston Naming Test (15 Items)
- Mini Mental State Examination
- Word Lists: Learn, Recall, Recognition
- Figure drawing and retrieval

The CERAD-Plus consists of the CERAD test battery including two additional tests:

- Trail Making Test A and B
- Phonemic Fluency (S-words)

CERAD TOTAL SCORE

The CERAD total score (Chandler et al. 2005) is a good measure for Alzheimer's Disease (Ehrensperger et al. 2010, Rossetti et al. 2010, Seo et al. 2010, Hallikainen et al. 2013).

It is calculated as follows:

Subtests	**Max points**
Verbal Fluency	24
Modified BNT	15
Word list learning	30
Constructional praxis	11
Word list recall	10
Word list recognition discriminability	10
Total Score (RAW)	**100**

The demographically corrected CERAD Total Score is defined as:

Corrected Total Score = RAW - (-0.324*Age [yr] + 0.897*Education [yr] - 2.858*Gender)

With Gender 0: female or 1: male.

MINI MENTAL STATE EXAMINATION (MMSE)

The mini mental state examination (MMSE) consists of 22 items that cover orientation, short term memory, attentional capabilities, constructive praxis and language functions. Scoring is possible between 0 (severe dementia) and 30 (normal).

Score	Meaning
27-30	Normal
18-26	Mild Dementia
10-17	Moderate Dementia
0-9	Severe Dementia

ALZHEIMER'S DISEASE ASSESSMENT SCALE (ADAS)

The Alzheimer's Disease Assessment Scale (ADAS) was designed to evaluate the severity of cognitive and noncognitive behavioral dysfunctions characteristic of persons with Alzheimer's disease (Rosen 1984). It consists of 21 items. Its sensitivity seems limited in mild AD (Irizarry et al. 2008) but it is commonly used with AD intervention studies.

Its cognition subscale (ADAS-COG) is a standard tool in pivotal clinical trials to detect therapeutic efficacy in cognition (Robert 2010). The ADAS-COG includes 11 items assessing the following cognitive domains:

- Memory (max. 22 points)
- Orientation / Praxis (max. 28 points)
- Language (max. 15 points)
- Remembering test instructions (max. 5 points)

There are 70 possible points on the ADAS-COG.

The non-cognitive areas of ADAS include 10 items assessing the following domains:

- Motor (max. 15 points)
- Depression (max. 10 points)
- Psychotic symptoms (max. 10 points)
- Concentration / Cooperation (max. 10 points)
- Appetite (max. 5 points)

There are 50 possible points on the non-cognitive ADAS (ADAS-NonCog).

In total, there are up to 120 possible points for the cognitive and non-cognitive areas (ADASSUM). The ADAS was designed as a rating scale for the severity of dysfunction. The higher the score, the more severely impaired is the AD patient.

According to Schrag et al. (2012) the minimal clinically relevant change is 3 points decline in ADAS-COG for patients with early AD, which corresponds to 4% improvement.

NEUROPSYCHOLOGICAL TEST BATTERY VIENNA (NTBV)

The Neuropsychological Test Battery Vienna (NTBV) was created to detect Alzheimer's Disease. Lehrner et al. (2007) reported its standardization, norms, and validation. All of its neuropsychological variables significantly separated dementia patients and controls on a group basis.

The NTBV consists of 20 items assessing the following domains:

- Attention: AKT, HAWIE-R Digit-Symbol-Test, c.I. Symbol Test, Trail Making Test TMT-B
- Language: Semantic Fluency Tests (Animals, Supermarket, Tools), Boston Naming Test
- Memory: Verbal Selective Reminding Test VSRT (immediate recall, delayed recall, recognition)
- Executive functioning I – Phonematic Fluency Tests (Letters B, F, L)
- Executive functioning II – Interference: NAI – Color Test, NAI – Stroop Test, c.I. Interference

Executive functioning III – Planning and nonverbal fluency: 5-Point Test, NAI Labyrinth Test, Trail Making Test TMT-A

CLOCK DRAWING TEST (CDT)

The clock drawing test shows the visuoconstructive skills (Shulman 1986). The subject is asked to draw the face of a clock with all numbers and to set the hands for a specified time (hh:mm). Scores range from 0 (worst) to 7 (best).

Criteria	Points (yes)	Points (no)
Does the clock have 12 numbers?	1	0
Is the number 12 up?	2	0
Are there two different hands?	2	0
Does the clock show the specified time?	2	0

FORGETFULNESS ASSESSMENT INVENTORY (FAI)

Kogler et al (2013) developed the forgetfulness assessment inventory FAI (German: Skala zur Erfassung der Gedächtnisleistung - SEG) to evaluate subjective complaints regarding everyday memory problems. Lehrner et al. (2014) validated the test. The FAI consists of 16 items to measure subjective memory problems in daily life based on a Likert scale. It focuses on the subjective evaluation of memory problems, particularly in relation to episodic memory, which has been found to be very sensitive in the early detection of mild cognitive impairment and AD (Lehrner 2014).). This questionnaire is supposed to be completed by the patient as well as by a person familiar with the patient.

Subjects are asked to rate "How often did you have problems during the past 4 weeks remembering… e.g. a shopping list?" on a scale from 1 to 5 (1 = never; 2 = rarely, 3 = sometimes, 4 often, 5 very often).

The average score across all 16 items will be used for statistical analyses. Higher scores reflect poorer subjective functioning and greater complaints (possible range: 1–5).

MONTREAL COGNITIVE ASSESSMENT (MOCA)

Montreal Cognitive Assessment (Nasreddine et al. 2005) is a clinical standard test for cognitive functions which will only be applied for the motor patients using a german verison. It is a short clinical test evaluating the following cognitive functions: visuospatial/executive, naming, memory, attention, language, abstraction, recall and orientation. The maximum score is 30 points.

1.1.4 DEPRESSION TESTING

Dementia and depression often coexist.

BECK DEPRESSION INVENTORY (BDI-II)

The Beck Depression Inventory (BDI-II) is one of the most widely used instruments for measuring the severity of depression. It is a 21-item questionnaire for self-evaluation with 0-3 scores per item, ranging from 0 (normal state) to 63 (severe depression).

Score	Meaning
0-9	Normal
10-18	Mild Depression
19-29	Moderate Depression
30-63	Severe Depression

GERIATRIC DEPRESSION SCALE (GDS)

The Geriatric Depression Scale (GDS) is a short questionnaire to assess depression in the elderly population. This scale generates self-evaluation scores concerning various aspects with relevance for the depressive disease (e.g. mood, drive, anxiety).

The long form contains 30 items (Yesavage 1983), the short form 15 items (Sheikh 1986). The GDS-15 scores range from 0 (normal state) to 15 (severe depression).

Score	Meaning
0-4	Normal
5-8	Mild Depression

9-11	Moderate Depression
12-15	Severe Depression

1.1.5 ACTIVITIES OF DAILY LIVING (TESTING)

INSTRUMENTAL ACTIVITIES OF DAILY LIVING (IADL)

The Lawton Instrumental Activities of Daily Living Scale (IADL) is an instrument to assess independent living skills (Lawton & Brody, 1969). This questionnaire is supposed to be completed by the patient as well as by a person familiar with the patient. There are 8 domains of function measured with the Lawton IADL scale.

- Telephone
- Shopping
- Food preparation
- Housekeeping
- Laundry
- Mode of transportation
- Medication
- Finances

The summary score ranges from 0 (low function, dependent) to 8 (high function, independent) For male patients the highest possible score is 5 (due to expected zero scores for food preparation, housekeeping, and laundry).

BAYER ACTIVITIES OF DAILY LIVING SCALE (B-ADL)

The Bayer Activities of Daily Living Scale (B-ADL) has been developed on an international basis to assess deficits in the performance of everyday activities (Hindmarch 1998). The scale's main target group is community dwelling patients who suffer from mild cognitive impairment or mild-to-moderate dementia. It comprises 25 items and is supposed to be completed by the patient and additionally by a caregiver or other informant sufficiently familiar with the patient.

Each item is scored from 1 (no difficulties at all) to 10 (always difficulties). The global B-ADL score is the arithmetic mean of all items.

LEISURE BEHAVIOR (GERMAN: FREIZZEITVERHALTEN FZV)

The leisure behavior questionnaire has 25 items covering the following activities:

- information / entertainment
- active movement
- social interactions
- creative activities
- church / cultural / educational activities

It was adapted from Hollneck et al. (2009) by changing the frequency from years to weeks in order to uncover possible changes by the neurostimulation. This questionnaire is supposed to be completed by the patient as well as by a person familiar with the patient.

Each activity is rated on Likert-Scales from 0 to 6 according to its frequency

Score	Meaning
0	never
1	less than every 2 weeks
2	every two weeks
3	every week
4	2-3 times per week
5	4-5 times per week
6	daily

The average score across all 25 items will be used for statistical analyses. Higher scores reflect more leisure activity (possible range: 0-6).

1.1.6 PSYCHOPATHOLOGY TESTING

NEUROPSYCHIATRIC INVENTORY (NPI)

The Neuropsychiatric Inventory (NPI) was developed to provide a means of assessing neuropsychiatric symptoms and psychopathology of patients with Alzheimer's disease and other neurodegenerative disorders (Cummings 1997). Ten behavioral and two neurovegetative areas are included in the NPI.

- Delusions
- Hallucinations
- Agitation/Aggression
- Depression/Dysphoria
- Anxiety
- Elation/Euphoria
- Apathy/Indifference
- Disinhibition
- Irritability/Lability
- Aberrant motor behavior
- Sleep and Nighttime Behavior Disorders
- Appetite and Eating Disorders

The NPI is based on responses from an informed caregiver, preferably one living with the patient. A caregiver can be defined as a person spending at least 4 hours per day at least 4 days per week with the patient and who is knowledgeable about the patient's daytime and nighttime behaviors.

The NPI is typically used to assess changes in the patient's behavior that have appeared in a defined period of time. The reliability and validity studies of the NPI were conducted using the 4-week time frame.

There is a screening question, which is asked to determine if the behavioral change is present or absent. If the answer to the screening question is positive or if there are any uncertainties in the caregiver's response or any inconsistencies between the response and other information known by the clinician, the category is marked "Yes" and explored in more depth with the subquestions. If the subquestions confirm the screening question, the severity and frequency of the behavior are determined according to the criteria provided with each behavior.

In very impaired patients or in patients with special medical circumstances, a set of questions may not be applicable. Analytically, "NA" responses must be treated as missing values.

When determining frequency and severity, use the behaviors identified by the subquestions as most aberrant.

Frequency is rated as:

Score	Frequency
1	Rarely – less than once per week
2	Sometimes – about once per week
3	Often – several times per week but less than every day
4	Very often – once or more per day

Severity is rated as:

Score	Severity
1	Mild – produces little distress in the patient
2	Moderate – more disturbing to the patient but can be redirected by the caregiver
3	Severe – very disturbing to the patient and difficult to redirect

Distress of the caregiver is scored as:

Score	Distress
0	Not at all
1	Minimally (almost no change in work routine)
2	Mildly (some change in work routine but little time rebudgeting required)
3	Moderately (disrupts work routine, requires time rebudgeting)
4	Severely (disruptive, upsetting to staff and other residents, major time infringement)
5	Very Severely or Extremely (very disruptive, major source of distress for staff and other residents, requires time usually devoted to other residents or activities).

The total NPI score is calculated as

$$\sum_{domains} (frequency \times severity)$$

The total NPI score varies from 0 to 120 for the behavioral domains and from 0 to 144 for all 12 domains.

PROSOPAGNOSIA INDEX (SHORT FORM)

From the original 20-item prosopagnosia index PI-20 by Shah et al. (2015), the ten most relevant items for identification of healthy and impaired subjects were chosen and translated in this short version. It serves as a measure for prosopagnosia, also called face blindness.

Each item is scored from 1 (no difficulties at all) to 5 (large difficulties).

The average score across all 10 items will be used for statistical analyses. Higher scores reflect impairment to recognize faces (possible range: 1-5).

1.2 MOTOR DISEASES

1.2.1 MEDICAL BACKGROUND OF ISCHEMIC STROKE

Stroke is the second most common cause of death and the leading cause of disability worldwide (Liu 2007). According to a report from the American Heart Association Statistics Committee and Stroke Statistics

Subcommittee, about 795 000 people experience a new or recurrent stroke each year. About 610 000 of these are first attacks, and 185 000 are recurrent attacks. Preliminary data from 2006 indicate that stroke accounted for about 1 of every 18 deaths in the United States. On average, every 40 seconds someone in the United States has a stroke and every 3-4 minutes, someone dies of stroke (Lloyd-Jones 2009). The age-adjusted incidence of first ischemic stroke per 100 000 was 88 in whites, 191 in blacks, and 149 in Hispanics, according to data from the Northern Manhattan Study (NOMAS, NINDS). Of all strokes, 87% are ischemic, 10% are intracerebral hemorrhage, and 3% are subarachnoid hemorrhage strokes (GCNKSS, NINDS 1999).

A report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee showed that in the United States the estimated direct and indirect cost of stroke for 2009 was USD 68.9 billion, with a mean per capita lifetime cost of USD 140,048 (Lloyd-Jones 2009).

1.2.2 TREATMENT OPTIONS FOR STROKE

The different phases, acute, postacute phases of stroke, need to be addressed by different treatment regimes.

In the acute stroke phase the focus lies on basic measures such as keeping the patient away from sources of ignition, suitable storage, sufficient oxygen supply, peripheral-venous access, control of blood pressure, testing of blood sugar. In most cases, the patient needs to be taken to the hospital for stationary treatment (S3-Leitlinie Stroke 2012) and some patients receive new vascular interventions or local fibrinolytic therapies.

Rehabilition targets prevention of reoccuring strokes. This includes diagnosis and treatment of relevant risk factors such as metabolic disorders (diabetes mellitus, reduced glucose tolerance, hypercholesterinemia, hyperhomocysteinemia, estrogen metabolism, hyperfibrinogenemia), cardiovascular disorders (hypertension, early strokes or transitory ischemic attacks, coronary heart diseases, atrial fibrillation, stenosis of the carotid artery), lifestyle and personal data (smoking, overweight, reduced physical activity, high alcohol consumption, depression), and general risk factors of arteriosclerosis (age, gender, hereditary factors). Specific therapies for symptom improvement concern primarily physiotherapy, logopedia and ergotherapy.

1.2.3 MEDICAL BACKGROUND OF PARKINSON'S DISEASE

Parkinson's disease is a neurological disorder with evolving layers of complexity. It has long been characterized by the classical motor features associated with Lewy bodies and loss of dopaminergic neurons in the substantia nigra. However, the symptomatology of Parkinson's disease is now recognized as heterogeneous, with clinically significant non-motor features. Similarly, its pathology involves extensive regions of the nervous system, various neurotransmitters, and protein aggregates other than just Lewy bodies. The cause of Parkinson's disease remains unknown, but Parkinson's disease seems to result from a complicated interplay of genetic and environmental factors affecting numerous fundamental cellular processes. The complexity of Parkinson's disease is accompanied by clinical challenges, including difficulties in the management of symptoms at later stages. In earlier stages effective medications exist and some patients benefit considerably from invasive deep brain stimulation. However, there are no treatments that slow the neurodegenerative process (Kalia 2015).

1.2.4 MOTOR DISEASE – EXPECTATIONS FROM BRAIN STIMULATION

Arm paresis is a frequent feature with a variety of motor system disorders. The general treatment rationale within the present study (activation of responsive neuronal tissue) and very new observations (case reports) in intractable cases at the center in Germany indicate, that the improvement of neuronal functioning expected for

Alzheimer's is also expectable for motor system patients. In this population, treatment-related risk should even be lower than with the cognitive study population, since brain pathology typically is focal and concomitant pathological problems (e.g. ubiquitous microbleeds) are less frequent.

1.2.5 MOTOR TESTING

Motor testing will include a thorough clinical examination for grading of the paresis and gross motor deficits. Deficits of fine skilled movements will be tested by the clinically well-established coin rotation test (Foki et al., 2010). Here, a coin hast to be flipped with the first 3 fingers of one hand as fast as possible for 30 seconds. The number of successful half rotations of the coin is the outcome measure. Performance of the healthy and diseased hand will be documented.

1.3 SHOCK WAVES

Shock waves are acoustic waves that are characterized by high pressure amplitudes and a steep increase in pressure in comparison to the ambient pressure.

Unlike ultrasound that usually consists of periodic oscillations with limited bandwidth, shock waves are represented by a single, mainly positive pressure pulse that is followed by comparatively small tensile wave components. Such a pulse contains frequencies ranging from a few kHz to over 10 MHz. Shock waves can lead to mechanical excitement but do not lead to tissue heating.

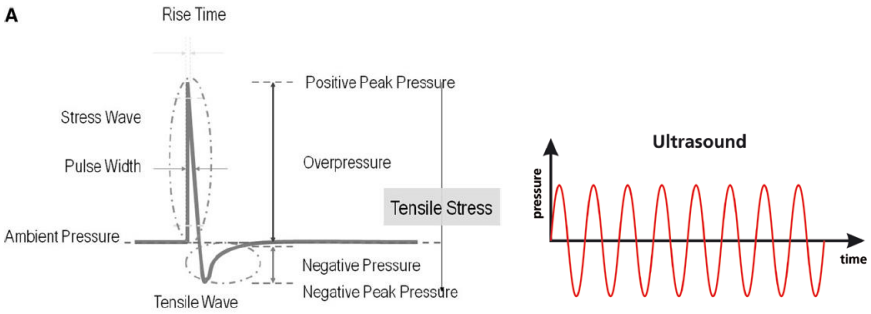

Figure 1: Shock waves compared to ultrasound

Medically used shock waves are generally generated in water and become effective in biological tissue. The pressure and energy is transmitted through the displacement of mass particles. Physically, the focal area is defined as the area of a shock wave field in which the measured pressure or energy are greater than or equal to half the peak measured in the center.

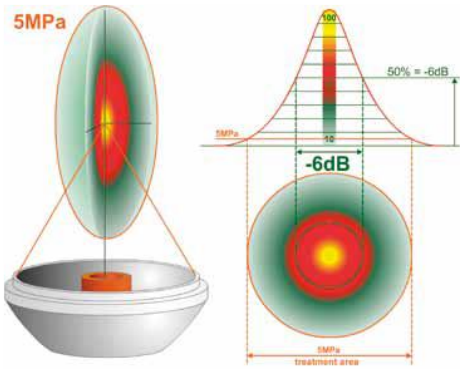

Figure 2: Shock wave focal area

1.4 EXTRACORPOREAL SHOCK WAVE THERAPY (ESWT)

The use of extracorporeal shock waves for the treatment of renal or ureteral calculi has fundamentally changed the way these disorders are treated. Since their development (beginning in 1974) and introduction into clinical use beginning in 1980 by Chaussy et al., urological management of urinary stones has changed fundamentally, with the result that this form of treatment has rapidly come to be used around the world.

Having become established in the urological field, ESWL, modified to use a weaker energy source and renamed Extracorporeal Shockwave Therapy (ESWT), soon came to be used in the orthopedic field for treating degenerative and painful joint disorders. Good results have been achieved, particularly for the treatment of pain. The therapeutic use of shock waves in other areas such as dermatology, orthopedics, cardiology, neurology, and urology has also been investigated.

Extracorporeal shock waves can induce vascular endothelial growth factor (VEGF) which is known to induce angiogenesis and collateral vessel formation (Oi 2008, Serizawa 2011, Shweiki 1992). Furthermore it was discovered in other in-vitro experiments, that nitric oxide (NO) can be produced by shock waves in a non-enzymatic way (Gotte 2002). NO is a potent vasodilator and has angiogenic properties. Besides, NO mediates anti-inflammatory action of extracorporeal shock waves (Ciampa 2005, Gotte 2002, Ito 2010, Mariotto 2005, Mariotto 2009, Oi 2008). In an in-vitro experiment the effect of shock waves on cultured single-donor Human Umbilical Vein Endothelial Cells (HUVEC) was investigated at the energy flux densities of 0, 0.02, 0.09, 0.18 and 0.35 mJ/mm^2 (Nishida 2004). A maximum effect on the mRNA expression of vascular endothelial growth factor (VEGF) and its receptor fms-like tyrosine kinase (Flt)-1 was found at the energy flux density of 0.09 mJ/mm^2, which is less than 10% of the energy flux density used for urinary lithotripsy. Kikuchi et al. found that CSWT (Cardiac Shock Wave Treatment) of the ischemic myocardium significantly improved chest pain symptoms and cardiac function without any complications or adverse effects in a human placebo-controlled double-blind study (Kikuchi 2010).

Good results have also been achieved with healing of fractures, pseudarthrosis, non-unions, and delayed unions (Rompe 2001, Schaden 1998, Schaden 2001, Wang 2001), injuries and poorly healing wounds (Hayashi 2012, Kuo 2009, Wang 2011).

1.4.1 JUSTIFICATION FOR THE DESIGN

In the first clinical pilot study by Dr. Lohse-Busch in Bad Krozingen, Germany, 15 patients with Alzheimer's disease were treated in 6 TESWT sessions within 2 weeks (3 sessions per week) with 6000 pulses in each session with an energy flux density of 0.2 mJ/mm². The device was a DUOLITH SD1 Tower Ultra (BT.0098) without additional camera system. The investigator constantly moved the hand piece and distributed the pulses evenly over the whole head. The ITT (LOCF) analysis of the data revealed an improvement in Corrected CERAD Total Score of 10.80 ± 10.93 std dev from baseline to 3 months after the last treatment. The longitudinal data was analyzed by looking at the improvement over time using repeated measures analysis of variance. Since the ITT (LOCF) data passed the Shapiro-Wilk normality test and the equal variance test, one-way repeated measures ANOVA was used, which showed highly significant improvement of the Corrected CERAD Total Score over time ($F = 12.044$, $P < 0.001$, 99.9% Power at $\alpha = 0.05$).

The efficacy and safety of ESWT in neurological conditions has also been shown in numerous clinical trials since 1997, partly in randomized placebo-controlled clinical trials. Spastic muscle paralyses due to stroke (Manganotti 2005, Moon 2013, Santamato 2013 and 2014, Troncati 2013) and cerebral palsy (Lohse-Busch 1997, 2006, 2010) have been treated. Improvements of muscle spasticity has been found in all studies which have been measured with passive range of motion, Ashworth Scale, and Modified Ashworth Scale. Depending on the severity and scope of paralysis, pronounced functional improvements were achieved either by shock wave therapy alone or as part of a complex treatment. Nearly all patients experienced improvement up to several months. Treatment with low energy flux densities is pain-free. Spastic muscle paralyses have been treated in 1-6 (focused) ESWT sessions applying 800-3200 pulses of shock waves with energy flux densities of 0.03-0.10 mJ/mm^2 to the affected muscle bellies. The treatment intervals varied from 1-7 days.

Cerebral palsy (cerebral paralysis) is understood to be a locomotor disorder arising from a functional disturbance of a number of brain cells. The related disability is characterized by an impairment of the neurological and muscle system resulting in involuntary movement. The most frequent manifestations are spastic mixed forms of cerebral palsy and increased muscle tension (muscular hypertonia). The rigidity of the muscles arising from disturbed neuronal control leads to local energy insufficiency. It has been demonstrated that shock waves can stimulate the production of nitrous oxide (NO) and hence decrease the rigidity of the affected muscles (Mariotto 2005). The improved biomechanical functioning of the muscles enhances mobility.

The proposed mechanisms for the neurological effects of shock waves are mechanical effects on ion channels, reversible increase of cell membrane permeability and changes in neuropeptide and nitric oxide concentrations. Specifically, changes in vascular endothelial growth factor (VEGF) and its receptor and fibroblast growth factor-2 (FGF-2) have been demonstrated which can promote neurogenesis (Laird 1995; Sun 2006). These effects could be observed up to 4 weeks after the end of the shock wave treatment.

Manganotti et al. (2005) proved the safety of ESWT in a clinical trial with healthy subjects. ESWT did not result in any significant changes of electrophysiological parameters. The peripheral nerve conduction and central motor conduction of the treated human muscles were not affected.

The efficacy of ESWT on the healing of peripheral nerve lesions after compression have been shown in animal studies. ESWT accelerated nerve healing, myelinization, and muscle functionality (Hausner 2012, Mense 2013).

Meanwhile there are first experiences in ESWT treatment of the central nervous system.

In an animal study 80 rats were exposed to transcranial ESWT to the striatum using different combinations of energy flux density (0.1-0.3 mJ/mm^2) and impulses (100-400) at 3 Hz frequency. In lithotripsy hematoma and bleedings are well known side effects of high-energy treatments. In this animal study none of the animals had

any signs of intracerebral bleedings, neither macroscopic nor microscopic. Two animals died because of narcotic overdose while shock waves were not cause of death (not yet published data by Andreas v. Ameln-Meyerhofer).

Human skull absorbs approximately 80% of the pressure of the extracorporeal shock wave in the focus. Rat skulls which are a lot thinner than human skulls thus do not absorb as much of the pressure of the ESW, only a few percent. Since TESWT on rats has shown to be safe, TESWT for patients is expected to be safe as well. Low-energy TESWT of about 0.2 mJ/mm^2 on patients with unresponsive wakefulness led to the improvement of vigilance and motor skills by 135.9% on the German Coma Remission Scale (CRS) and 81.7% on the German Scale for Expressive Communication and Self Actualization (SEKS, Ziegler) without showing any adverse effects (Lohse-Busch 2013). Werner et al. also showed improvement of vigilance in patients with unresponsive wakefulness, minimal conscious state and akinetic mutism, measured by the revised Coma Remission Scale (Werner 2013, 2014). No adverse effects were seen.

1.4.2 MECHANISM FOR TREATMENT EFFECTS

As with other brain stimulation techniques like TMS or TDCS, the primary hypothesis for the mechanism behind treatment effects is induction of neuroplasticity – particularly synaptic long term potentiation effects. This applies to observed memory as well as motor improvements. Likely, an important component for triggering neuroplasticity are mechanical effects on ion channels and reversible increase of cell membrane permeability. Certain ion channels are mechanically sensitive which may affect nerve-cell firing as may do the mechanical compression and expansion of the nerve cells. Changes in neuropeptide and nitric oxide concentrations as well as widening of vessels and increase of blood flow were also shown. Specifically, changes in vascular endothelial growth factor (VEGF) and its receptor and fibroblast growth factor-2 (FGF-2) have been demonstrated which can promote neurogenesis (Laird 1995; Sun 2006). These effects could be observed up to 4 weeks after the end of the shock wave treatment. A very recent investigation in Nature Scientific Reports with the system of the sponsor showed, that shock waves enhance proliferation and differentiation of neural stem cells (Zhang et al. 2017).

According to unpublished data by Lohse-Busch, Feuerstein and Marlinghaus, TESWT increases the neurotransmitter noradrenaline in rat brains. Alzheimer's disease is characterized by neocortical and hippocampal atrophy due to neuronal loss, the deposition of Aβ peptides, and the formation of neurofibrillar tangles. In addition, there is a progressive degeneration of cholinergic nuclei in the basal forebrain and of noradrenergic nuclei in the brainstem, most importantly the locus ceruleus (LC). This nucleus is the major source of noradrenaline supply in the mammalian brain. The LC provides the neurotransmitter via an extensive network of neuronal projections to all major brain regions. These regions include the neocortex and hippocampus, the seat of cognitive functions, learning, and memory. LC degeneration and loss of LC-derived axons are associated with decreased noradrenaline levels in target forebrain regions in Alzheimer's patients. An increase of noradrenaline is associated with a retardation of symptoms in Alzheimer's disease (Heneka 2010). Inoue et al. (2013) have shown that noradrenaline leads to emergence of new functional synapses.

2. IDENTIFICATION AND DESCRIPTION OF THE INVESTIGATIONAL DEVICE

2.1 IDENTIFICATION

The device has the following serial number: BT.0546.

2.2 DESCRIPTION OF THE INVESTIGATIONAL DEVICE

The Duolith® SD1 (see Figure 3: Duolith® SD1 Ultra, future Neurolith (Storz Medical AG)) is manufactured by Storz Medical AG (Lohstampfestr. 8, CH-8274 Tägerwilen, Switzerland). The Duolith SD1 is CE marked by the Notified Body TÜV Rheinland LGA Products GmbH (ID 0197) for the extracorporeal shock wave therapy ESWT (latest CE mark from Nov 19th 2013). The device corresponds to class IIb according to the Medical Device Directive 93/42/EEC.

The following modifications have been performed on the study device:

1) The only safety-relevant modification, which has been performed on the study devices concern the hardware modification of the maximum energy flux density output, which was reduced to 0.25 mJ/mm^2. The software is adjusted to display the energy flux density accordingly.
2) We use the Polaris Vicra System by Northern Digital Inc. (NDI), an optical measurement system that measures the 3D positions of active or passive markers affixed to application-specific tools. Using this information, the Polaris Vicra System is able to determine the position and orientation of tools within a specific measurement volume. The system is based on over 30 years experience, providing customization and integration into many medical OEM computer-assisted surgery and therapy systems. In our case, we use the system for tracking the handpiece in relationship to the patient. The camera's position sensor emits infrared light from its illuminators, similar to the flash on a conventional camera. The IR light floods the surrounding area and reflects back to the Position Sensor off passive sphere markers, which are fixed to the handpiece and a pair of glasses for the patient (see markers in instructions for use Sec. 3.2.2). The Position Sensor then measures the positions of the markers, and calculates the transformations (the positions and orientations) of the tools to which the markers are attached.
3) In order to standardize treatments for all patients by means of treatment visualization and recording, the software "Bodytrack" was added to interpret the data from the camera system. Thus, it is possible to define standardized target volumes of interest on each individual participants MRI. Individual tracking then allows standardized focal brain stimulation over the whole study population with adequate movements of the handpiece over the skull. It is also possible to track the handpiece movement. Each pulse leaves a colored mark in the software. The color scale is relative. If the target volumes are homogeneously colored, the stimulator can verify the homogeneous application of shock waves to the patient's brain. In a pilot serie, this procedure has been proven to be most effective for global brain activation. The software also allows to record and save the whole treatment session for post hoc evaluation of the hand piece movement and distribution of shock waves for each patient.
4) The device's future name will be NEUROLITH in order to market the device for treatment of neurological disorders, when CE-approval will have been granted. The NEUROLITH includes the reduction of energy flux density to 0.25 mJ/mm², the Polaris Vicra camera system by NDI, and the "BodyTrack" software.

The manufacturer plans to name the above-described device Neurolith so that the Duolith remains with its list of indications as before and in order to be able to market the Neurolith for neurological disorders in the future.

Figure 3: Duolith® SD1 Ultra, future Neurolith (Storz Medical AG)

The Duolith SD1 is intended exclusively for use by medical specialists and may only be used by such suitably qualified and trained medical personnel. They are expected to have practical knowledge of medical procedures, applications, and technology, and should be experienced in treating the stated indications.

The number and interval of treatment sessions, energy flux density (mJ/mm^2), pulses / session and frequency have been chosen according to the past use of the device, and in order to preserve the patient from any risks.

In order to evaluate the treatment, the shock wave application will be monitored by a camera system and mapped onto a standard head or onto individual MR data of the brain, if they are available. It is possible to evaluate and verify the even distribution of shock waves in each patient's head (see manual).

2.2.1 FOCUSED SHOCK WAVES: F-SW HAND PIECE

The shock waves are generated electromagnetically in a cylinder source with a parabolic reflector. Energy flux density of the F-SW hand piece can be adjusted within the range of 0.01 to 0.25 mJ/mm^2. It refers primarily to the focus area. The possible maximum frequency depends on the selected level of energy flux density (see Table 1).

Energy flux density [mJ/mm^2]	Max Frequency [Hz]
0.01	8
0.02	8
0.03	8
0.05	7
0.07	6
0.10	6

0.12	6
0.15	6
0.20	5
0.25	4

Table 1: Adjustable energy flux density and frequency

The maximum energy flux density 0.25 mJ/mm^2 corresponds to a maximal pressure of 25 MPa. The focus of the shock waves is very precise, only 2.8-5.4 mm in diameter, depending on the level of energy flux density: the higher the energy flux density, the smaller the focus diameter. Technical data can be found in Table 2.

Parameter	**Value**
Aperture Angle	53.1°
Focal Pressure	3 – 25 MPa
Energy flux density	0.01 – 0.25 mJ/mm^2
Frequency	1 – 8 Hz
Focal Volume	0.14 – 0.87 cm^3
Penetration Depth	50 mm without stand-off device

Table 2: Technical data

By using different stand-off devices on the hand piece one can change the penetration depth. Without stand-off device the penetration depth is 50 mm, using stand-off device I it is 30 mm and using stand-off device II it is 15 mm (see Figure 4).

Figure 4: Penetration Depth of the F-SW Hand Piece

The specified maximum energy flux density should not be exceeded. A layer of ultrasound gel serves as coupling medium between the device and the patient's skin.

The handpiece consists of a coupling diaphragm and a stand-off device which consists of a coupling cushion and a clamping ring (see Figure 5).

Figure 5 Handpiece components
(1: Coupling Diaphragm, 2: Coupling cushion, 3: Clamping ring)

Treatment reaching the full penetration depth is performed without any stand-off device.

2.2.2 TREATABLE INDICATIONS

The shock wave device Duolith SD1 is CE-certified for the following indications:

ORTHOPAEDICS / PAIN THERAPY

- Plantar fasciitis / heel spur / heel pain / calcaneal spur
- Trigger Point Therapy
  - Treatment of deep muscle trigger points
  - Treatment of superficial muscle trigger points
  - Myofascial pain syndrome / Myofascial trigger points / Acupuncture points
  - e.g. chronic back pain (cervical and lumbar parts of vertebral column), trapezius, pelvic floor muscle trigger points
- Tendinopathy / Tendinitis / Tendonitis / Tendinosis / Tendon Pain
  - Insertion tendonitis in general
  - Superficial insertion tendonitis (paratendinary area)
  - Shoulder pain with or without calcifications / tendinopathy of the shoulder, the supraspinatus, or / and the rotator cuff (with or without calcifications)
  - (Radial/ulnar humeral) epicondylitis / tennis elbow / golfer's elbow / elbow tendinopathy
  - Greater trochanteric pain syndrome (GTPS) / Trochanteric tendonitis / Trochanteric bursitis

- Hamstring tendinopathy
- Patellar tip syndrome/ proximal iliotibial band (friction) syndrome / Patellar tendonitis / Jumper's knee
- Tibial edge syndrome / tibial stress syndrome / tibial tendonitis
- Achillodynia / Achilles tendinitis

- Pseudarthrosis / non-unions / delayed unions

DERMATOLOGY

- Wound healing
  - Ulceration
    - Arterial ulcers
    - Venous ulcers
    - Diabetic foot ulcers
    - Pressure sore / Decubital ulcer
  - Burns
  - Acute and chronic lesions
  - Traumatic and post-traumatic skin lesions
  - Wounds with disturbed healing
  - Postsurgical wounds
- Cellulitis / lipo- / lymphedema

UROLOGY:

- Chronic pelvic pain syndrome (CPPS) / prostatitis
- Induratio Penis Plastica (IPP) / Peyronie's disease
- Vascular / vasculogenic / organic erectile dysfunction

NEUROLOGY

- Spastic muscle paralyses (caused by infantile cerebral palsy or stroke for example)

2.3 INTENDED PURPOSE OF THIS STUDY

The intended purpose of this study concerns low-energy transcranial extracorporeal shock wave therapy of patients with cognitive and motor disease. Unlike the energies in lithotripsy, applicable energies for TESWT are much smaller (0.2-0.25 mJ/mm^2), i.e. approximately 10% of the ESWL energy, in order to avoid any side effects.

There is a hardware modification to the device concerning the maximum energy flux density output. Because of safety reasons, it will be reduced to 0.25 mJ/mm^2 in order to avoid higher energies by malfunction or intention. Other than that, the device itself will not be altered for the treatment, only the treatment location will be changed from other parts of the body to the head.

The only part of the handpiece, which is in touch with the patient is the Platilon foil. Its safety has been sufficiently tested according to EN ISO 10993-1, Directive 93/42/EEC by Medical Device Services. It is not only used for the Duolith SD1 but also for the lithotripters of Storz Medical AG and has been in use for over 20 years.

The treatment will be described in detail in Section 5.6.5.

For generation of very first data about positive clinical effects we will include clinically stable Alzheimer patients and clinically stable patients with motor disease. This will provide the basic neurophysiological and clinical data necessary for future clinical applications in a technically standardized form.

The TESWT is not an alternative but an additional treatment to standard therapy.

3. RISKS AND BENEFITS OF THE INVESTIGATIONAL DEVICE AND CLINICAL INVESTIGATION

3.1 ANTICIPATED CLINICAL BENEFITS

The anticipated effects of TESWT are:

- Mechanical effects on ion channels of cell membranes, reversible increase of cell membrane permeability, changes in neuropeptide and nitric oxide concentration, widening of vessels, and increase of blood flow, promoting neurogenesis by stimulating vascular endothelial growth factor (VEGF) and fibroblast growth factor-2 (FGF-2)
- Stimulation of neurotransmitter noradrenaline (An increase of noradrenaline is associated with a retardation of symptoms in Alzheimer's disease and emergence of new functional synapses)

The anticipated clinical benefit of these effects for patients suffering from Alzheimer's Disease as well as for medical research of Alzheimer's Disease are:

- Retardation of neuro-degeneration.
- Improvement of cognitive abilities

Both can be measured by cognitive testings such as CERAD-Plus, ADAS, NTBV.

The anticipated clinical benefit of for patients with motor disease are:

- Improvement of motor capabilities (motor tests)

3.2 RISKS ASSOCIATED WITH THE DEVICE

According to the risk management analysis measures for the safety of patients, users and others have been enforced (see IB – Appendix 6).

3.2.1 RISKS FOR USERS AND OTHERS

There are no more risks associated with the device for users or others.

3.2.2 RISKS FOR THE PATIENT

The unique advantage of the shock wave technology is, that decades of research and clinical experience with this technology exist.

Possible risks for patients from shock waves are associated with a high amount of shock waves and high energy flux density. The severity of these risks to the brain is critical, as serious injuries such as cerebral hemorrhage are possible. Without enforcing measures the likelihood of such event was analyzed as frequent (1 in 10 treatments).

Unlike the energies in lithotripsy, applicable energies for TESWT are much smaller (0.2-0.25 mJ/mm^2), i.e. approximately 10% of the ESWL energy, in order to avoid any side effects. Furthermore, the manufacturer modified the device's hardware by installing a maximum energy flux density of 0.25 mJ/mm^2 within the hardware to ensure that higher energy flux density cannot be applied, neither by intention nor by device malfunction. The likelyhood of this risk has thus decreased from frequent (1 in 10 treatments) to improbable (1 in 100 000 treatments). The risk is thus acceptable.

Since the hand piece is hand-held and the investigators are trained to always move the hand piece during the treatment of the brain as well as an included hardware stop after a maximum of 1000 ESW, the likelyhood of the above mentioned risk of applying a high amount of shock waves has decreased from frequent (1 in 10 treatments) to improbable (1 in 100 000 treatments). The risk is thus acceptable.

Another possible risk for the patients is damage by acoustic sound of the shock waves. The severity of this risk is marginal as injuries are possible. Without enforcing measures the likelihood of such event was analyzed as frequent (1 in 10 treatments).

Safety measures include the avoidance of application at the region of the ear, as well as the above mentioned measures of low energy flux density and moving hand piece. The likelyhood of this risk has thus decreased from frequent (1 in 10 treatments) to improbable (1 in 100 000 treatments). The risk is thus acceptable.

Accordingly, there is already a promising body of laboratory and experimental data about the general efficacy and safety of the shock wave technique for neurological application. Besides the classic lithotripsy applications, shock wave research and application meanwhile exists for a large variety of neurological diseases including therapy of coma, cerebral palsy, stroke spasticity, nerve regeneration, dystonia, polyneuropathy, spinal cord injury, myelomeningocele (e.g. Lohse-Busch 2013, 2014, Mense 2013, Amelio 2010, Trompetto 2009, Manganotti 2005). Non-neurological applications include antiischemic therapy, improvement of microcirculation, angiogenesis, myocardial infarction, antiinflammatory therapy and stem cell activation.

Due to the comprehensive experience with human applications the possibilities and limitations of energy deposition to human tissue via shock waves can safely be judged by longstanding experts in the field. Accordingly, no complications have yet been observed or reported with previous neurological applications.

Thus the remaining risk could be the possible missing benefit for the patients, its severity is negligible because it is not associated with any further impairment of health. The likelihood of the missing benefit cannot be assessed yet but even if the risk was assumed to be frequent (1 in 10 treatments), it would be acceptable.

3.3 OTHER RISKS FROM PARTICIPATION IN THE CLINICAL INVESTIGATION

Cognitive testing will be accomplished by qualified and experienced personnel. It might be mentally exhausting for the patients but it will be possible to make breaks or even stop the testing at any given time. Patients will not be at risk for their health because of the testing.

3.4 POSSIBLE INTERACTIONS WITH CONCOMITANT MEDICAL TREATMENTS

Only patients who are stable in the amounts of intake of medication are allowed to be included in this clinical investigation. TESWT is not an alternative treatment but an additional treatment to standard therapy. No possible interaction with concomitant medical treatment is to be expected.

3.5 RISK-TO-BENEFIT RATIONALE.

All the possible risks have been reduced to an acceptable level. Thus the benefit clearly outweighs the amount of risk.

4. OBJECTIVES AND HYPOTHESES OF THE CLINICAL INVESTIGATION

4.1 OBJECTIVES

The study will provide basic neurophysiological and clinical data necessary for future clinical applications and a possible new neurological therapy. It is supposed to show the efficacy and safety of the medical device within the intended purpose of this study.

4.2 HYPOTHESES

TESWT will improve the cognitive abilities of Alzheimer's patients measured by the CERAD-plus. TESWT will improve the motor capabilities of motor disease patients measured by clinical motor tests as well as the Coin Rotation Test for fine motor skills.

4.3 OUTCOME PARAMETERS

Outcome parameters are:

I.) Cognitive Testing:

- CERAD-plus
    - Corrected CERAD Total Score
    - CERAD subtests
- Mini-Mental-State Examination
- Clock Drawing Test
- GDS
- BDI
- ADAS
    - ADAS-COG
    - ADAS-NonCog
    - ADASSUM
    - ADAS Domains
- NTBV
    - Psycho motor speed
        - C.I. symbol counting

        - Trail Making Test TMT-A
    - Attention
        - AKT
        - Digit-Symbol-Test
        - Trail Making Test TMT-B
    - Language
        - Semantic Fluency Test (Total)
        - SMT-Animals
        - SMT-Supermarket
        - SMT-Tools
        - Phonematic fluency Test PFT (Total)
        - PFT-Letter b
        - PFT-Letter f
        - PFT-Letter l
        - BNT
    - Memory
        - Verbal Selective Reminding Test VSRT (immediate recall)
        - VSRT (total recall)
        - VSRT (delayed recall)
    - Executive Functions
        - 5-Point Test
        - NAI Stroop Test – Color-Word -Test
        - NAI Maze Test
        - Interference: TMT-B – TMT-A
        - C.I. Interference
- Prosopagnosia Test
- Self- / third party evaluations of daily life activities / neuropsychological state:
    - IADL
    - B-ADL
    - FAI
    - FZV
- NPI
    - 12 domains with frequency, severity, distress
    - Total Score NPI-10
    - Total Score NPI-12

II.) Motor Testing:

- Standard clinical motor tests
- Coin Rotation Test for fine motor skill deficits (see Foki et al. 2010, 2015)
- Self- / third party evaluations of daily life activities / neuropsychological state
    - B-ADL
    - FZV
    - MOCA
    - GDS
    - BDI

- Handedness

III.) Imaging:

- Anatomical and functional MRI (3 Tesla Siemens Prisma MR Device)

IV.) EEG:

- In selected participants, standard EEG / EP (Electroencephalography / Evoked Potential) data will be recorded to help judge procedural optimizations. This will be done according to routine clinical procedures and is particlularly helpful for comparison and evaluation of most promising parameter settings of the stimulation system (energy level and pulse frequency).

5. STUDY DESIGN OF THE CLINICAL INVESTIGATION

5.1 GENERAL

This is a prospective double-blind randomized placebo-controlled crossover clinical trial.

5.2 INVESTIGATIONAL DEVICE(S) AND COMPARATOR(S)

There is one investigational device, the Duolith SD1, future name Neurolith (Storz Medical AG). The device is described in Section 2.

5.3 CONCOMITANT MEDICATION AND THERAPIES

Concomitant medication including antidementive standard medication or medication against motoric disorders as prescribed by the treating neurologist is allowed when compatible with the exclusion criteria. It should not be changed starting from 3 months before inclusion until the end of this study.

Concomitant medication and therapies as well as concomitant diseases will be documented in the CRFs.

5.4 STUDY DURATION

The total expected duration of the clinical investigation is two years.

The start of the clinical investigation is right after the approval of the ethics committee and the regulatory authorities, probably in 2017. The expected study duration for each patient is 4 + 4 months for cognitive and 2+2 months for motor studies (crossover). Enrolment is estimated to 6 months.

5.5 STUDY POPULATION

All patients and healthy controls enrolled in the clinical investigation (including those withdrawn from the clinical investigation or lost to follow-up) shall be accounted for and documented. Patients and healthy controls will be recruited via medical colleagues and public information using an information sheet approved by the ethics committee.

If a patient withdraws from the clinical investigation, the reason(s) shall be recorded. If such withdrawal is due to problems related to the investigational device safety or performance, the investigator shall ask for the patient's permission to follow his/her status/condition outside the clinical investigation.

5.5.1 INCLUSION CRITERIA

Alzheimer's Patients

- Clinically stable patients with probable Alzheimer's Disease (Diagnosis according to ICD-10 Criteria (F00))
- At least 3 months of stable antidementive therapy or no antidementive therapy necessary
  - Patients need to continue their standard therapy during the clinical investigation according to the current guidelines because TESWT is not an alternative but an additional treatment to standard therapy.

Motor Disease Patients

- Clinically stable motor disease patients with fine skilled and/or gross motor deficits (e.g. right arm with a clinical force level >2)

Healthy Participants

- Absence of exclusion criteria as detailed below.

All Participants

- Signed written informed consent
- Age ≥ 18 years
- Monthly pregnancy test for women in childbearing years

5.5.2 EXCLUSION CRITERIA

- Non-compliance with the protocol
- Pregnant or breastfeeding women
- Relevant intracerebral pathology unrelated to the Alzheimer's / Motor disease (e.g. Brain tumor)
- Hemophilia or other blood clotting disorders
- Cortison treatment within the last 6 weeks before first treatment
- Thrombosis

5.5.3 RANDOMIZATION

Patients will be randomized to a Verum and a Sham Startstimulation Group (15 each). The sponsor will generate a randomization list using block randomization with randomly permuted blocks of random length (http://randomization.com), which will be stored in sealed opaque envelopes, two for each patient. The first envelope is intended for the person responsible to change the verum and placebo standoff devices for each treatment, the second is for emergency cases. It will be included into the individual patient's file to be able to

unblind the patient in case of an emergency while the blinding for the rest of the clinical investigation remains intact.

5.5.4 BLINDING

This clinical study will be blinded. The patients and the evaluating investigators will all be blinded.

5.5.5 CRITERIA AND PROCEDURES FOR PATIENT WITHDRAWAL OR DISCONTINUATION.

If a patient withdraws from the trial, the circumstances will be recorded in the CRF. The drop out will however be asked to participate in the final assessment visit. Every effort will be made to contact drop outs. If a patient is absent at a visit, the investigator will try to contact him/her by phone, then by mail and by contacting the treating physician. If the patient could not be contacted by the end of the trial, the patient will be considered lost. The details of the whole procedure will be recorded in the CRF.

Premature discontinuation is possible at the request of:

- The patient: in accordance with the information mentioned in the written informed consent and in conformity with the declaration of Helsinki, patient can withdraw from the trial at any time and for any reason, without any consequences to their treatment, care or relationship with the investigator.
- The investigator: can request the discontinuation of a patient if he/she meets one of the following criteria susceptible to affect the assessment in the course of the trial:
    - Systemic disease (unrelated to the investigational products but occurring during the trial) requiring treatment
    - Non-compliance with the protocol
    - Pregnancy
    - Any other disease/problem relative to patient
- The sponsor / monitor: can request the discontinuation of a patient for major non-compliance with the protocol, or for administrative motives.

REPLACEMENT OF PATIENTS

The opportunity of the replacement of patients included then discontinued before the end of the study will be discussed by the sponsor's representative and the investigator on a case-by-case basis.

DISCONTINUATION BY THE SPONSOR

The sponsor can interrupt the trial at any time for one of the following reasons:

- no patient enrolled
- non-compliance with protocol
- inaccurate or incomplete data

5.6 PROCEDURES

5.6.1 SCHEME FOR AD PATIENTS

The following scheme visualizes the measurements and treatments for all AD patients.

	CYCLE I						CYCLE II				
	Screening	Baseline Cycle I	TESWT-Treatments	Follow-Up 1	Follow-Up 2	Follow-Up 3	Baseline Cycle II	TESWT Treatments (Cross-over)	Follow-Up 4	Follow-Up 5	Follow-Up 6
	S	T1	B1-B6	T2	T3	T4	T5	B7-B12	T6	T7	T8
Timetable [weeks] Deviations of ± 1 week are allowed	W1	W1-2	W3 - W4	W5	W8	W16	W22	W23 - W24	W25	W28	W36
In-/Exclusion Criteria	X										
Patient information	X										
Patient Written Informed Consent		X									
TESWT-Treatments • Questionnaires for patients • Videomonitoring			X					X			
MRI (anatomical and functional)		X		X			X		X		
Subjective treatment success and recommendation				X		X			X		X
Tests (AD-Patients) • CERAD-Plus • NTBV * • ADAS * • IADL • B-ADL		X NTBV (A) ADAS (A)		X NTBV (B) ADAS (D)	X NTBV (C) ADAS (E)	X NTBV (A) ADAS (A)	X NTBV (B) ADAS (D)		X NTBV (C) ADAS (E)	X NTBV (A) ADAS (A)	X NTBV (B) ADAS (D)

• FAI / SEG • FZV • Prosopagnosia • CDT • BDI • GDS * different test versions per replication											
Tests (Care Taker) • NPI • IADL • B-ADL • FAI/SEG • FZV		X		X	X	X	X		X	X	X
Adverse Events			X	X	X	X	X	X	X	X	X

5.6.2 SCHEME FOR MOTOR PATIENTS

The following scheme visualizes the measurements and treatments for all motor patients.

	CYCLE I				CYCLE II			
	Screening	Baseline Cycle I	TESWT-Treatments	Follow-Up 1	Baseline Cycle II	TESWT Treatments (Cross-over)	Follow-Up 4	Follow-Up 5
	S	T1	B1-B6	T2	T5	B7-B12	T6	T7
Timetable [weeks] Deviations of ± 1 week are allowed	W1	W1-2	W3 - W4	W5	W11	W12 - W13	W14	W17
In-/Exclusion Criteria	X							
Patient information	X							
Patient Written Informed Consent		X						
TESWT-Treatments • Questionnaires for patients			X			X		

• Videomonitoring								
MRI (anatomical and functional)		X		X	X		X	
Subjective treatment success and recommendation				X			X	
Tests (motor-Patients) • Clinical tests (motor performance) • Coin rotation Test • B-ADL • FZV • MOCA • GDS • BDI • Handedness		X		X	X		X	X
Tests (Care Taker) • B-ADL • FZV		X		X	X		X	X
Adverse Events			X	X	X	X	X	X

5.6.3 SCREENING

Participants will be selected according to the outcome of specific neuropsychological, clinical and motor tests. Patients indicating interest for participation in the treatment trial will first undergo prescreening for checking of inclusion and exclusion criteria. This typically involves telephone interviews (anamnesis) and judgement of external medical records including recent MRI findings. Patients judged eligible for study inclusion will enter the baseline tests T1. Only if all results of T1 are compatible with the inclusion and exclusion criteria, the participant will definitely be included in the trial after having given written informed consent. Patients will be asked for their concomitant medication, especially antidementiva, and concomitant diseases as well as study-relevant premedication and therapies. This will be noted in the CRF.

Since demographic data such as gender, age, and education are also important for the evaluation of the test results, they will be noted in the CRF.

The recorded study MR images will not serve for a clinical report, but for supporting the judgement of exclusion criteria and the effects of the intervention.

5.6.4 BASELINE TESTS (T1)

AD patients will perform the following tests at baseline:

- CERAD-plus
- NTBV (Test Version A)
- ADAS (Test Version A)
- CDT
- BDI
- GDS
- IADL
- B-ADL
- FAI / SEG
- FZV
- Prosopagnosia

The care taker of the patient will also be asked for:

- Indirect Anamnesis
- NPI
- IADL
- B-ADL
- FAI / SEG
- FZV

Motor disease patients will perform the following tests at baseline:

- Clinical Tests (motor performance)
- Coin Rotation Test Self- / third party evaluations of daily life activities / neuropsychological state
    - B-ADL
    - FZV
    - MOCA
    - GDS
    - BDI
    - Handedness

Each participant will receive an anatomical and functional MRI recording from his/her brain.

5.6.5 TESWT TREATMENT (B1-B6)

The participants will be stimulated using verum or sham TESWT in a sitting position.

We use the Polaris Vicra System by Northern Digital Inc. (NDI), an optical measurement system that measures the 3D positions of active or passive markers affixed to application-specific tools. Using this information, the Polaris Vicra System is able to determine the position and orientation of tools within a specific measurement volume. The system is based on over 30 years experience, providing customization and integration into many medical OEM computer-assisted surgery and therapy systems. In our case, we use the system for tracking the handpiece in relationship to the patient. The camera's position sensor emits infrared light from its illuminators,

similar to the flash on a conventional camera. The IR light floods the surrounding area and reflects back to the Position Sensor off passive sphere markers, which are fixed to the handpiece and a pair of glasses for the patient. The Position Sensor then measures the positions of the markers, and calculates the transformations (the positions and orientations) of the tools to which the markers are attached.

In order to standardize treatments for all participants by means of treatment visualization and recording, the software "Bodytrack" was added to interpret the data from the camera system. Thus, it is possible to define standardized target volumes of interest on each individual participant's MRI. Individual tracking then allows standardized focal brain stimulation over the whole study population with adequate movements of the handpiece over the skull. It is also possible to track the handpiece movement. Each pulse leaves a colored mark in the software. The color scale is relative. If the target volumes are homogeneously colored, the stimulator can verify the homogeneous application of shock waves to the patient's brain. In a pilot serie, this procedure has been proven to be most effective for global brain activation. The software also allows to record and save the whole treatment session for post hoc evaluation of the hand piece movement and distribution of shock waves for each patient. Immediately after stimulation, the data will be extracted on study-specific server disks. It is important to use sufficient amounts of ultrasound gel and to have direct contact to the skull. In a pilot series this procedure has been proven to be most effective for global brain activation.

For the motor arm of the study, additional pilots for optimized definition of standardized volumes of interest for maximization of sensorimotor effects will be required.

TESWT treatment will be performed in 6 sessions within 2 weeks (3 sessions per week). TESWT sessions will be separated by 1-2 days. Each session consists of 6000 shock waves with the energy flux density of 0.2-0.25 mJ/mm^2. One session lasts approximately 30 min.

Each TESWT stimulation will be videomonitored to optimize procedural and patient security. The video material will be deleted shortly after clinical evaluation.

After each stimulation session, participants will be asked about their experience (e.g. how they perceived the stimulation (verum/placebo) and if they felt pain, pressure, or any other AE/SAE).

After the 3^{rd} and 6^{th} session, the care giver will be asked if they noticed any changes in the patients, particularly any AE/SAE.

PLACEBO (SHAM) TREATMENT

Placebo treatment will be performed using the same medical device and handpiece as in the Verum treatment with the only difference: the standoff device (see Figure 5) at the end of the handpiece (Eur Urol. 2009 Aug;56(2):363-9. doi: 10.1016/j.eururo.2009.05.012). The placebo system is constructed to have the same look, touch, and sound as the verum system, however without transmitting any shock waves. The placebo standoff device is made by replacing the liquid inside of the verum standoff device with a shockwave nontransmitting material but keeping the outer shell, which is made of Platilon. The patients will only be in contact with the Platilon, which has been sufficiently tested for biological safety (see IB Appendix 5) and has been used in all Storz Medical AG Office and Hospital Devices with focused shock waves for decades.

Only the stimulation team will know the group reference and change the appropriate sham or verum standoff devices for each treatment.

Thus, the naive patients will be blinded as they will be unable to tell which of the two treatments (focused ESWT or placebo) is performed.

The evaluating investigators will also be blinded as they will not see the device and will not be told the treatment.

5.6.6 FOLLOW-UPS (T2-T4)

Follow-ups will be performed

- directly after the last session
- 1 month after the last session
- 3 months after the last session (only for AD)

The investigators will make a thorough anamnesis of each patient at each follow-up.

At each follow-up visit the following tests for patients with Alzheimer's will be done:

- CERAD-plus
- NTBV (Test Version B at T2, C at T3, A at T4)
- ADAS (Test Version D at T2, E at T3, A at T4)
- CDT
- BDI
- GDS
- IADL
- B-ADL
- FAI / SEG
- FZV
- Prosopagnosia

At each follow-up visit, the care taker of the AD patient will also be asked for:

- Indirect Anamnesis
- NPI
- IADL
- B-ADL
- FAI / SEG
- FZV

Motor disease patients will perform the following tests:

- Clinical Tests (motor performance)
- Coin Rotation Test
- Self- / third party evaluations of daily life activities / neuropsychological state
    - B-ADL
    - FZV
    - MOCA
    - GDS
    - BDI
    - Handedness

At follow-up T2, each participant will receive an anatomical and functional MRI recording from his/her brain.

5.6.7 BASELINE OF CYCLE II (CROSSOVER) (T5)

Before entering the crossover treatments, the baseline for cycle II will be determined.

AD patients will perform the following tests:

- CERAD-plus
- NTBV (Test Version B)
- ADAS (Test Version D)
- CDT
- BDI
- GDS
- IADL
- B-ADL
- FAI / SEG
- FZV
- Prosopagnosia

The care taker of the patient will also be asked for:

- Indirect Anamnesis
- NPI
- IADL
- B-ADL
- FAI / SEG
- FZV

Motor disease patients will perform the following tests:

- Clinical Tests (motor performance)
- Coin Rotation Test
- Self- / third party evaluations of daily life activities / neuropsychological state
    - B-ADL
    - FZV
    - MOCA
    - GDS
    - BDI
    - Handedness

Each participant will receive an anatomical and functional MRI recording from his/her brain.

5.6.8 CROSSOVER TREATMENTS (B7-B12)

The study design contains a crossover. Patients who were randomized to the verum start group will receive sham treatment in round II, while patients who were in the placebo start group will receive verum treatment in round II.

Round II consists of 6 sessions of verum or sham TESWT treatments within 2 weeks (3 sessions per week). TESWT sessions will be separated by 1-2 days. Each session consists of 6000 shock waves with the energy flux density of 0.2-0.25 mJ/mm^2. One session lasts approximately 30 min.

Each TESWT stimulation will be videomonitored to optimize procedural and patient security. The video material will be deleted shortly after clinical evaluation.

After each stimulation session, participants will be asked about their experience (e.g. how they perceived the stimulation (verum/placebo) and if they felt pain, pressure, or any other AE/SAE).

After the 3rd and 6th session, the care giver will be asked if they noticed any changes in the patients, particularly any AE/SAE.

5.6.9 FOLLOW-UPS (T6-T8)

The following Follow-ups (T6-T8) will be performed

- directly after the last session of round II
- 1 month after the last session of round II
- 3 months after the last session of round II (only for AD)

The investigators will make a thorough anamnesis of each patient at each follow-up.

At each follow-up visit the following tests for patients with Alzheimer's will be done:

- CERAD-plus
- NTBV (Test Version C at T6, A at T7, B at T8)
- ADAS (Test Version E at T6, A at T7, D at T8)
- CDT
- BDI
- GDS
- IADL
- B-ADL
- FAI / SEG
- FZV
- Prosopagnosia

At each follow-up visit, the care taker of the patient will also be asked for:

- Indirect Anamnesis
- NPI
- IADL
- B-ADL
- FAI / SEG
- FZV

Motor disease patients will perform the following tests :

- Clinical Tests (motor performance)

- Coin Rotation Test
- Self- / third party evaluations of daily life activities / neuropsychological state
    - B-ADL
    - FZV
    - MOCA
    - GDS
    - BDI
    - Handedness

At follow-up T6, each participant will receive an anatomical and functional MRI recording from his/her brain.

5.7 MONITORING PLAN

The study will be monitored by Storz Medical AG in accordance with the requirements of the Medical Products Act. The investigating physician will grant the monitor regular visits to provide support in conducting the study, to check that the conditions required for the study are being met, to monitor the correctness of the study procedure and to compare the data recorded on the case report forms and in the patient records (source data verification).

The purpose of clinical investigation monitoring is to verify that the conduct of the clinical investigation complies with the approved CIP, subsequent amendment(s), this International Standard, and the applicable regulatory requirement(s).

5.7.1 ASSESSMENT OF INVESTIGATION SITE

The monitor shall assess each investigation site to verify that the principal investigator has:

a) adequate qualifications;

b) adequate resources, including facilities, laboratories, equipment and a qualified investigation site team;

c) access to an adequate number of patients.

5.7.2 INITIATION OF THE INVESTIGATION SITE

The monitor shall initiate each investigation site to ensure that the principal investigator and investigation site team

a) have received and understood the requirements and contents of
    1) CIP,
    2) IB,
    3) the informed consent form,
    4) CRFs,
    5) the instructions for use,
    6) any written clinical investigation agreements, as appropriate,

b) have access to an adequate number of investigational devices,
c) have been trained in the use of the investigational device, and
d) are familiar with the responsibilities of the principal investigator

5.7.3 ROUTINE ON-SITE MONITORING VISITS

The monitor shall perform routine on-site monitoring visits to verify that

a) compliance with the CIP, any subsequent amendment(s), this International Standard and regulatory requirements is maintained; deviations shall be discussed with the investigators or authorized designee, documented and reported to the sponsor,
b) only authorized individuals are participating in the clinical investigation,
c) the investigational device is being used according to the CIP or instructions for use and that, where modifications are required to the device, its method of use or the CIP, these are reported to the sponsor,
d) investigation site resources, including laboratories, equipment and the investigation site team, remain adequate throughout the duration of the clinical investigation,
e) the principal investigator continues to have access to an adequate number of patients and investigational devices,
f) signed and dated informed consent forms have been obtained from each patient at the point of enrolment or before any clinical-investigation-related procedures are undertaken,
g) source documents and other clinical investigation records are accurate, complete, up to date, stored and maintained appropriately,
h) CRFs and queries are complete, recorded in a timely manner, and consistent with source documents,
i) appropriate corrections, additions or deletions are made to the CRFs, dated, explained if necessary and initialed by the principal investigator or by his/her authorized designee; the monitor shall not make corrections, additions or deletions to the CRFs,
j) all adverse events and device deficiencies are reported to the sponsor, and all serious adverse events and device deficiencies that could have led to a serious adverse device effect are reported to the sponsor without unjustified delay,
k) all serious adverse events and deviations are reported to the EC, if required,
l) the storage and investigational device accountability are correct and the traceability process is being followed,
m) all other required reports, notifications, applications, submissions and correspondence are maintained in the investigator's files and are accurate, complete, timely, legible, dated and identify the clinical investigation,
n) maintenance and calibration of the equipment relevant to the assessment of the clinical investigation is appropriately performed and documented, where applicable,
o) current laboratory normal values, laboratory certifications, accreditations, or other validations are present in the investigator's file, if required,
p) patient withdrawal has been documented; the monitor shall discuss this with the principal investigator or his/her authorized designee,
q) patient non-compliance with the requirements stated in the informed consent has been documented; the monitor shall discuss this with the principal investigator or his/her authorized designee,

r) the principal investigator and investigation site team are informed and knowledgeable of all relevant document updates concerning the clinical investigation, and

s) any corrective and preventive actions, as needed, have been implemented and are effective.

5.7.4 CLOSE-OUT ACTIVITIES

Routine close-out activities shall be conducted to ensure that the principal investigator's records are complete, all documents needed for the sponsor's files are retrieved, remaining clinical investigation materials are disposed of, previously identified issues have been resolved and all parties are notified.

a) Completing the records includes ensuring that
   1) all essential documents are complete and up to date,
   2) all CRFs are completed,
   3) all outstanding queries are resolved,
   4) the current status of all ongoing adverse events is documented,
   5) arrangements are made for archiving and record retention, and
   6) documenting disposition of any:
      i. investigational devices;
      ii. remaining samples (e.g. blood or tissue);
      iii. other clinical investigation materials.

b) Notification includes
   1) notification to EC, and
   2) notification to regulatory authorities, if required.

The sponsor shall

a) ensure all clinical investigation close-out activities are properly conducted

b) provide a statistical analysis of the data,

c) produce a clinical investigation report and submit it for review, and

d) ensure that the clinical investigation report, whether for a completed or prematurely terminated clinical investigation, is provided to the EC, participating investigators and regulatory authorities, as required by national regulations.

5.7.5 MONITORING REPORTS

All monitoring activities shall be documented in a written report to the sponsor and shall include

a) the date, investigation site identification, name of the monitor and name of the principal investigator or other individuals contacted, and

b) a summary of what the monitor reviewed and his/her observation(s) with regard to the completion of previous action items, significant findings, facts, deviations, conclusions, and recommended actions to be taken to secure compliance.

A copy of the monitoring report or a summary of key findings shall be shared with the principal investigator in writing.

6. STATISTICAL CONSIDERATIONS

6.1 SOFTWARE

Statistical analysis will be performed by Storz Medical AG using the Systat Software SigmaPlot 12.5. and by the group of the Principal Investigator.

6.2 PRIMARY ENDPOINT ANALYSIS

A statistical analysis will be performed for the study population (30 verum / placebo). The primary endpoint will be the Corrected CERAD total score.

We will perform a two-way repeated measures ANOVA because all patients will undergo both verum and placebo treatments as well as all measurement points. The two factors are treatment (placebo/verum) and time (baseline, after last TESWT, 1M Fol Up, 3M Fol Up). Significant interactions will be followed by appropriate pairwise comparisons (e.g. ttests with Bonferroni correction, Tukey test, Sidak-Holms test). It will be possible to analyze within and between group differences.

6.3 ANALYSIS OF SECONDARY ENDPOINTS

We will perform two-way repeated measures ANOVA for all other outcome parameters as well. Again, significant interactions will be followed by appropriate pairwise comparisons (e.g. t-tests with Bonferroni correction, Tukey test, Sidak-Holms test). It will be possible to analyze within and between group differences.

6.4 COHORTS

2 cohorts will be evaluated:

- Per protocol (PP): the number of patients who finished all required tests, treatments, and follow-ups, those who did not drop out the study.
- Intent to treat (ITT): all patients of the study, including drop-outs. Missing data will be substituted:
    - "Last observation carried forward" (LOCF) Analysis: Missing final values of the outcome variable are replaced by the last known value before the participant was lost to follow-up.

6.5 SAMPLE SIZE FOR AD COHORT

The sample size calculation was done with Systat Software SigmaPlot 12.5.

In the German AD trial, the ITT (LOCF) analysis showed an improvement of 10.80 ± 10.93 (std dev) in the corrected CERAD total score, which was achieved between baseline and 3 months follow-up.

If we assume the improvement was the desired difference between verum and placebo group and taking the more conservative literature standard deviation from Hallikainen et al. (2013) of 12.868, we calculate the following sample size for a desired power of 80% and significance level of 0.05: 24 patients per group. To account for possible dropouts, we should include a minimum of 30 patients per group.

Due to the considerable uncertainty about the true treatment effect size, a sample size re-estimation based on comparative (unblinded) interim data will be performed when 35 of the participants have received treatment. The aim is to evaluate conditional power at the interim look. The sample size may be increased if the interim result is in the "promising zone" (50 – 80 % conditional power). If the conditional power is lower (unfavorable

zone) or higher (favorable zone), we will not alter the sample size. An independent statistician who is not involved with the conduct of the study will perform the interim analysis.

7. DATA MANAGEMENT

This study will be carried out in accordance with the current regulations and ISO 14155:2011.

All documents and data shall be produced and maintained in a way that assures control and traceability. Where relevant, the accuracy of translations shall be guaranteed and documented. All documents, and subsequent versions, related to a clinical investigation shall be identifiable, traceable and appropriately stored to provide a complete history of the clinical investigation.

The investigator shall assure the accuracy, completeness, legibility and timeliness of the data reported to the sponsor on the CRFs and in all required reports. Where copies of the original source document as well as printouts of original electronic source documents are retained, these shall be signed and dated by a member of the investigation site team with a statement that it is a true reproduction of the original source document.

All clinical findings and collected data must be documented in the CRF of the respective patient. This also applies to drop out patients. Personal data of all patients who met all inclusion criteria but met one or more exclusion criteria and therefore did not enter the study must be recorded in the screening log.

The original document pages of the CRF will be regularly validated by the monitor, collected after study completion for each patient, then sent for medical review and finally captured by the data entry operator.

CRF must always be filled in with a black pen due to legibility reasons. In order to obtain complete information repetitive questions must also be answered. The investigator has to document missing data in any case.

Clinical data will be double recorded in Excel® files and checked by a third operator of the investigator's team.

Only authorized personnel are allowed to correct data in the CRF. The monitor is not empowered to do this on his/her own. False entries shall be crossed out with a single line but must remain legible. The correct entry shall be made next to the incorrect one, and needs to be signed and dated by the authorized person.

All documents relating to the study, including the protocol are the property of the investigator and must be regarded as confidential.

The investigator is responsible for ensuring storage of the source data, CRF and the study documentation contained in the investigator study file for at least 10 years.

All personnel of the sponsor will be obliged to strictly observe the patient's rights. For monitoring of the study and inspection of the obtained data, internationally agreed procedures are applied (Good Clinical Practice). This guarantees wide acceptance and consensus of the results and allows for both publication in highly rated journals and presentation in congresses.

On the basis of the patient's consent the data will be processed in a strictly anonymous manner. Monitors and auditors are obliged to maintain complete discretion.

7.1 PATIENT IDENTIFICATION LOG

Each investigation site shall maintain a log of all the patients enrolled in the clinical investigation, assigning an identification code linked to their names, alternative patient identification or contact information.

7.2 SOURCE DOCUMENTS

Source documents shall be created and maintained by the investigation site team throughout the clinical investigation. They contain source data that contains all information in original records, certified copies of original records of clinical findings, observations, or other activities in a clinical investigation, necessary for the reconstruction and evaluation of the clinical investigation

7.3 CASE REPORT FORMS

Case report forms are a set of printed, optical or electronic documents for each patient on which information to be reported to the sponsor is recorded, as required by the CIP.

CRFs shall be developed to capture the data for each enrolled patient. The CRFs shall include information on the condition of each patient upon entering, and during the course of, the clinical investigation, exposure to the investigational device and any other therapies.

The CRF documents the following data:

Data	**CRF-AD**	**CRF-Motor**
Informed Consent		
- Patient was informed	X	X
- Copies to patient	X	X
- Daily Practitioner	X	X
- Date and Investigator	X	X
Screening		
- Demographic data o Gender o Age [years] o Education [years]	X	X
- Medical diagnosis of AD o Date of diagnosis o Institution / Investigator	X	
- Medical diagnosis of motoric deficits of the arm(s) o Reason for motoric deficits: Parkinson's Disease, Stroke, MS, Other o Date of diagnosis o Institution / Investigator		X
- Current antidementiva medication	X	
- Current medication against motoric disorders		X
- Other current relevant medication and treatments	X	X
- Known concomittant diseases	X	X
- Known other particularities	X	X
- In-/Exclusion criteria (see Sec. 5.5.1, 5.5.2)	X	X
- Date and Investigator	X	X
- MRI	X	X
Study-specific testing before the 1. Treatment cycle (Baseline T1)		
- Admission to the study	X	X

o Date o Investigator		
Study-specific testing T1-T8		
- Age (AD T2-T8, Motor T2-T5) - Adverse Events (T2-T8)	X	X
- Test results as copies		
o CERAD-Plus incl. Corrected CERAD Total Score	X	
o NTBV	X	
o ADAS incl. ADASSUM, ADAS-Cog, ADAS-NonCog	X	
o NPI	X	
o Clinical tests (motor performance)		X
- Further test results		
o CDT	X	
o BDI	X	X
o GDS	X	X
o Prosopagnosia	X	
o FAI/SEG (patient / care giver)	X	
o IADL (patient / care giver)	X	
o B-ADL (patient / care giver)	X	X
o FZV (patient / care giver)	X	X
o Coin rotation score		X
- Anatomical and function MRI (AD T1, T2, T5, T6, Motor T1, T2, T3, T4)	X	X
- Subjective treatment success and recommendation (AD T2, T4, T6, T8, Motor T3, T5)	X	X
Treatments B1-B12		
- Treatment dates	X	X
- Execution of stimulation o Date and Investigator o Reason if not o Settings o Quality of sham: Which treatment does the patient believe to have received? o Homogeneous application of shock waves? o Interruption / stop of treatment o Product error o Complications during / after last treatment	X	X
- Adverse events (patient)	X	X
- Adverse events after last treatment (question for care giver AD) (B3, B6, B9, B12)	X	
Total AE and Product Errors	X	X
Special visits (outside of plan)	X	X
Drop out - Date - Reason	X	X
Deviation from CIP - Date - Description - Reason	X	X
End of clinical study for the individual patient - Date, Investigator	X	X
Unblinding	X	X

- Date, Investigator - Cycle I and II		

A procedure shall be in place to ensure, that when it is necessary to amend the CIP, the sponsor shall review the CRFs to determine if an amendment of these forms is also necessary.

8. AMENDMENTS TO THE CIP

The IB, CIP, CRFs, informed consent form and other patient information, or other clinical investigation documents shall be amended as needed throughout the clinical investigation, and a justification statement shall be included with each amended section of a document. Proposed amendments to the CIP shall be agreed upon between the sponsor and principal investigator, or the coordinating investigator. The amendments to the CIP and the patient's informed consent form shall be notified to, or approved by, the EC and regulatory authorities, if required. The version number and date of amendments shall be documented.

For non-substantial changes [e.g. minor logistical or administrative changes, change of monitor(s), telephone numbers, renewal of insurance] not affecting the rights, safety and well-being of human patients or not related to the clinical investigation objectives or endpoints, a simple notification to the EC and, where appropriate, regulatory authorities can be sufficient.

9. DEVIATIONS FROM CLINICAL INVESTIGATION PLAN

The investigator is not allowed to deviate from the CIP, except as specified before and in case of an emergency.

Under emergency circumstances, deviations from the CIP to protect the rights, safety and well-being of human patients may proceed without prior approval of the sponsor and the EC. If neccessary, the emergency envelope in the individual patient’s file will be opened to unblind the patient while the blinding for the rest of the clinical investigation remains intact. Such deviations shall be documented and reported to the sponsor and the EC as soon as possible. Access to investigational devices shall be controlled and the investigational devices shall be used only in the clinical investigation and according to the CIP.

The sponsor shall keep records to document the physical location of all investigational devices from shipment of investigational devices to the investigation sites until return or disposal.

The principal investigator or an authorized designee shall keep records documenting the receipt, use, return and disposal of the investigational devices, which shall include

a) the date of receipt,

b) identification of each investigational device (batch number/serial number or unique code),

c) the expiry date, if applicable,

d) the date or dates of use,

e) patient identification,

f) date on which the investigational device was returned/explanted from patient, if applicable, and

g) the date of return of unused, expired or malfunctioning investigational devices, if applicable

10. STATEMENTS OF COMPLIANCE

The investigator will conduct the study in accordance with the ethical principles that have their origins in the Declaration of Helsinki. These principles protect the rights, safety and well-being of human patients, which are the most important considerations and shall prevail over interests of science and society. These principles shall be understood, observed, and applied at every step in the clinical investigation.

The study will be conducted in accordance with law and local regulation governing clinical studies of medical devices for human patients and with the international standard ISO 14155:2011 addressing good clinical practice for the design, conduct, recording, and reporting of clinical investigations carried out in human patients to assess the safety or performance of medical devices for regulatory purposes.

The clinical investigation shall not begin until the favorable opinion from the EC or regulatory authority has been obtained.

Any additional requirements imposed by the EC or regulatory authority shall be followed, if appropriate.

11. PATIENT INSURANCE

Insurance will be covered in conformity with national legal terms. The sponsor will subscribe an insurance to cover civil liability for clinical trials. The insurance certificate is included in Appendix 8:

12. INFORMED CONSENT PROCESS

Informed consent shall be obtained in writing from the patient and the process shall be documented before any procedure specific to the clinical investigation is applied to the patient.

In accordance with the Declaration of Helsinki an informed consent form will be signed by the patients before their enrolment in the study: the patients will personally be informed by the investigator about potential risks and benefits of participation in the study as well as about rights and obligations.

The patient will be informed about

- The study
- MRI
- Electronic data transmission of patient data to treating doctors / study manager
- Videomonitoring during the treatment in the study.

During the first contact (by phone, mail or e-mail), and during the enrolment visit, the investigator will explain the objectives as well as the methodology, the risks and the benefits of the study, before the informed consent is obtained.

It will be clearly explained to the patients during this visit that they are entitled to refuse to participate in the study, or to remove their consent and to terminate the study whenever they want, for any reason, without consequences on their treatment, care or relationship with the investigator.

All four written informed consent forms of each patient (or of his/her parent / tutor) will be an obligatory criterion for study entry. An information note will also be given to the patient and/or his parents in order to better explain the study (see Appendix 3:).

13. ADVERSE EVENTS, ADVERSE DEVICE EFFECTS AND DEVICE DEFICIENCIES

13.1 DEFINITIONS

An *adverse event (AE)* is any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in patients, users or other persons. It does not need to be related to the investigational medical device. If it is related, it is called *adverse device effect (ADE)*.

A *serious adverse event (SAE)* is any adverse event that directly or indirectly led, could have led, or could lead to death, or to serious deterioration in the health of the patient, user, or any other person without regard to whether the event was related to the investigational medical device. The exact definition for SAE can be found in §2 MPSV. If it is related to the investigational medical device, it is called *serious adverse device effect (SADE).*

<table>
<tr><th>Adverse Event</th><th>Non-device-related</th><th colspan="2">Device- or procedure-related</th></tr>
<tr><td>Non-serious</td><td>Adverse Event (AE)[a]</td><td colspan="2">Adverse Device Effect (ADE)</td></tr>
<tr><td rowspan="3">Serious</td><td rowspan="3">Serious Adverse Event (SAE)[b]</td><td colspan="2">Serious Adverse Device Effect (SADE)</td></tr>
<tr><td>Anticipated</td><td>Unanticipated</td></tr>
<tr><td>Anticipated Serious Adverse Device Effect (ASADE)</td><td>Unanticipated Serious Adverse Device Effect (USADE)</td></tr>
<tr><td colspan="4">a Includes all categories.
b Includes all categories that are serious.</td></tr>
</table>

Table 3: Categories of adverse events

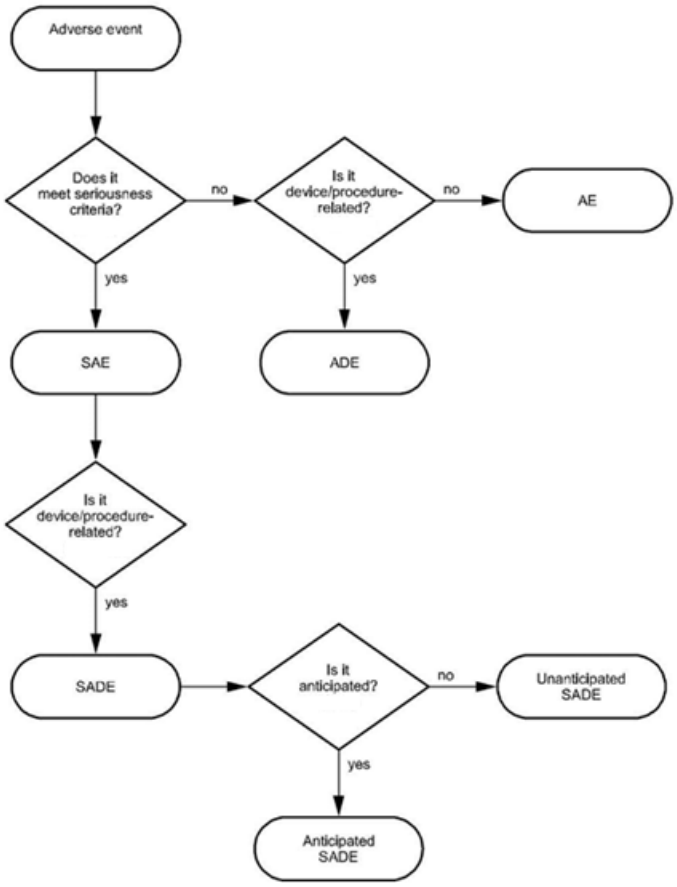

Figure 6: Adverse events categorization chart

Possible anticipated adverse device effects are listed in Section 3.

13.2 DOCUMENTATION

All the **adverse events** are actively sought, either from the patients' spontaneous comments, or during the clinical examinations and questionnaires at each visit.

All adverse events shall be documented in a timely manner throughout the clinical investigation and shall be reported. All adverse events shall be reported in an interim or final report of the clinical investigation.

If an adverse event arises during the study, the patient will contact:

- the principal investigator
- the investigators

Contact information is given to the patient in the informed consent.

All **device deficiencies** related to the identity, quality, durability, reliability, safety or performance of an investigational medical device shall be documented throughout the clinical investigation and appropriately managed by the sponsor.

The **principal investigator** shall

a) record every adverse event and observed device deficiency, together with an assessment,
b) report to the sponsor, without unjustified delay, all serious adverse events and device deficiencies that could have led to a serious adverse device effect; this information shall be promptly followed by detailed written reports, as specified in the CIP,
c) supply the sponsor, upon sponsor's request, with any additional information related to the safety reporting of a particular event.

The **sponsor** is responsible for the ongoing safety evaluation of the clinical investigation and shall

a) review the investigator's assessment of all adverse events and determine and document in writing their seriousness and relationship to the investigational device; in case of disagreement between the sponsor and the principal investigator(s), the sponsor shall communicate both opinions to concerned parties, as defined in c), d) and e) below,
b) review all device deficiencies and determine and document in writing whether they could have led to a serious adverse device effect; in case of disagreement between the sponsor and the principal investigator(s), the sponsor shall communicate both opinions to concerned parties, as defined in c), d) and e) below,
c) report or ensure the reporting, to the EC by the principal investigator(s), of all serious adverse events and device deficiencies that could have led to a serious adverse device effect, if required by national regulations or the CIP or by the EC,
d) report to regulatory authorities, within the required time period, all serious adverse events and device deficiencies that could have led to a serious adverse device effect, if required by national regulations or the CIP,
e) report all relevant safety information to the DMC, if established, according to written procedures,
f) in the case of a multicentre clinical investigation, inform all principal investigators in writing of all the serious adverse events at all investigation sites that have been reported to the sponsor, and ensure that they are reported to their EC, if required by national regulations or the CIP or by the EC, whichever is more stringent; this information shall be sent to all the principal investigators within a time frame established based on the perceived risk as defined in the risk analysis report,
g) ensure that the EC and the regulatory authorities are informed of significant new information about the clinical investigation, and
h) in case of serious adverse device effects and device deficiencies that could have led to serious adverse device effects, determine whether the risk analysis needs to be updated and assess whether corrective or preventive action is required.

13.3 INFORMATION TO BE COLLECTED FOR ALL ADVERSE EFFECTS

The adverse events must be recorded in the CRF with the indication of their nature, occurrence date/hour, duration, disappearance date/hour, severity, therapeutic consequences and evolution. The severity will also be detailed: Adverse Event or Serious Adverse Event.

13.3.1 INTENSITY

The intensity of the adverse effect should be graded according to the following scale:

Mild: Awareness of symptoms but easily tolerated

Moderate: Discomfort enough to cause interference with usual activity

Severe: Incapacitating with inability to work or do usual activity

13.3.2 NATURE OF EFFECT

The nature of the adverse effect should be graded according to the following scale:

- constant
- single episode
- multiple episodes
- not known

13.3.3 ACTION TAKEN

- none
- procedure interrupted
- procedure discontinued
- concomitant medication changed or discontinued
- new medication added
- hospitalization

13.3.4 OUTCOMES

- completely recovered
- recovered with sequelae
- ongoing and improved
- ongoing and unchanged
- ongoing and deteriorated
- death due to adverse event

13.4 DEVICE DEFICIENCY

Device deficiencies are inadequacies of a medical device with respect to its identity, quality, durability, reliability, safety or performance. All device deficiencies shall be documented throughout the clinical investigation and reported to the sponsor who then appropriately manages the list.

Device deficiencies that did not lead to an adverse event but could have led to a medical occurrence

a) if either suitable action had not been taken,
b) if intervention had not been made, or
c) if circumstances had been less fortunate,

shall be reported.

13.5 REPORTING

All adverse events or device deficiencies need to be immediately reported to the sponsor, by filling out the SAE report form (see Appendix 5:).

- In charge of vigilance: Dr. Markus Hübscher, Storz Medical AG, Lohstampfestr. 8, CH-8274 Tägerwilen
- Fax: +41 (71) 677 45 50
- E-Mail: vigilance@storzmedical.com

The sponsor is responsible for giving reports according to the applicable governmental regulations. A detailed standard operating procedure can be found at the sponsor's site (see QMV_SMAG_036_01_02).

Within the clinical study, the sponsor has to immediately report all SAEs concerning the patients to the Austrian Federal Office for Safety in Health Care "Bundesamt für Sicherheit im Gesundheitswesen (BASG)" including the SAEs from the other study center outside of Austria. In Austria, the BASG report form has to be used.

14. VULNERABLE POPULATION

A vulnerable patient is an individual whose willingness to volunteer in a clinical investigation could be unduly influenced by the expectation, whether justified or not, of benefits associated with participation or of retaliatory response from senior members of a hierarchy in case of refusal to participate.

Vulnerable population will not be included in this clinical investigation.

15. SUSPENSION OR PREMATURE TERMINATION OF THE CLINICAL INVESTIGATION

The sponsor may suspend or prematurely terminate either a clinical investigation in an individual investigation site or the entire clinical investigation for significant and documented reasons.

A principal investigator, EC, or regulatory authority may suspend or prematurely terminate participation in a clinical investigation at the investigation sites for which they are responsible.

If suspicion of an unacceptable risk to patients arises during the clinical investigation, or when so instructed by the EC or regulatory authorities, the sponsor shall suspend the clinical investigation while the risk is assessed. The sponsor shall terminate the clinical investigation if an unacceptable risk is confirmed.

The sponsor shall consider terminating or suspending the participation of a particular investigation site or investigator in the clinical investigation if monitoring or auditing identifies serious or repeated deviations on the part of an investigator.

If suspension or premature termination occurs, the terminating party shall justify its decision in writing and promptly inform the other parties with whom they are in direct communication. The principal investigator and sponsor shall keep each other informed of any communication received from either the EC or the regulatory authority.

If, for any reason, the sponsor suspends or prematurely terminates the investigation at an individual investigation site, the sponsor shall inform the responsible regulatory authority as appropriate and ensure that the EC is

notified, either by the principal investigator or by the sponsor. If the suspension or premature termination was in the interest of safety, the sponsor shall inform all other principal investigators.

If suspension or premature termination occurs,

a) the sponsor shall remain responsible for providing resources to fulfil the obligations from the CIP and existing agreements for following up the patients enrolled in the clinical investigation, and
b) the principal investigator or authorized designee shall promptly inform the enrolled patients at his/her investigation site, if appropriate.

The method and the timing of this communication will depend on the circumstances and the perceived risks.

15.1 PROCEDURE FOR RESUMING THE CLINICAL INVESTIGATION AFTER TEMPORARY SUSPENSION

When the sponsor concludes an analysis of the reason(s) for the suspension, implements the necessary corrective actions, and decides to lift the temporary suspension, the sponsor shall inform the principal investigators, the ECs, and, where appropriate, the regulatory authority of the rationale and provide them with the relevant data supporting this decision.

Concurrence shall be obtained from the ECs and, where appropriate, regulatory authorities before the clinical investigation resumes.

If patients have been informed of the suspension, the principal investigator or authorized designee shall inform them of the reasons for resumption.

16. PUBLICATION POLICY

The results of the clinical investigation will be submitted for publication.

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MPG Medizinproduktegesetz Deutschland (http://www.gesetze-im-internet.de/bundesrecht/mpg/gesamt.pdf)

MPKPV Verordnung über klinische Prüfungen von Medizinprodukten (http://www.gesetze-im-internet.de/bundesrecht/mpkpv/gesamt.pdf)

MPSV Medizinprodukte-Sicherheitsplanverordnung (http://www.gesetze-im-internet.de/bundesrecht/mpsv/gesamt.pdf)

QMV_SMAG_036_01_01 Standard Operating Procedure for the Medical Vigilance System (Storz Medical AG)

QMV_SMAG_096_01_01 Standard Operating Procedure for Clinical Studies and Monitoring (Storz Medical AG)

APPENDIX 1: SIGNATURE LIST

We hereby confirm that the study "Transcranical Extracorporeal Shock Wave Therapy for Neurological Diseases (Hirnstimulation bei neurologischen Patienten/innen" (STU 14/032) will be conducted in accordance with the Clinical Investigation Plan (STU 14/032) Version 17, the Declaration of Helsinki and ISO 14155:2011 + AC:2011.

Sponsor Legal Representative Date:

Dr. Rafael Storz, Storz Medical Deutschland GmbH (CEO starting from 01. Jan. 2018)

Sponsor Date:

Dr. Markus Hübscher, Storz Medical AG

Monitoring Date:

Dr. Markus Hübscher, Storz Medical AG

Principal Investigator Date:

Prof. Dr. Roland Beisteiner, Department of Neurology, University of Vienna

APPENDIX 2: DECLARATION OF CONFORMITY

APPENDIX 3: INFORMED CONSENT

APPENDIX 4: CASE REPORT FORM

APPENDIX 5: REPORT FORMS (AE AND PRODUCT ERROR)

APPENDIX 6: QUALIFICATION OF INVESTIGATORS

APPENDIX 7: SITE QUALIFICATION

APPENDIX 8: INSURANCE CERTIFICATE

APPENDIX 9: LEGAL REPRESENTATIVE

APPENDIX 10: DT. ZUSAMMENFASSUNG DES CIP

Sponsor	Storz Medical AG Lohstampfestr. 8 CH-8274 Tägerwilen Schweiz
Prüfstellen	Arbeitsgruppe Prof. Roland Beisteiner Universitätsklinik für Neurologie Währinger Gürtel 18-20 A-1090 Wien
Studiendesign	Prospektive doppelblinde randomisierte plazebokontrollierte crossover klinische Studie
Studiendauer	2 Jahre
Studienpopulation	60 Patienten mit Alzheimer-Erkrankung, 30 Pat. mit motorischen Störungen, 30 Gesunde Kontrollen
Einschlusskriterien	Alzheimer Patienten - klinisch stabile Patienten mit wahrscheinlicher Alzheimer-Erkrankung (Diagnose nach ICD-10 Kriterien (F00)) - mind. 3 Monate stabile antidementive Therapie oder keine antidementive Therapie notwendig ○ Patienten müssen ihre Standardtherapie während der klinischen Prüfung nach den bisherigen Leitlinien beibehalten, da TESWT eine Zusatzbehandlung zur Standardtherapie darstellt Motorik Patienten - klinisch stabile Patienten mit Fein- und Grobmotorikstörung (Störung der Armmotorik mit KG > 2) Alle Studienteilnehmer - Unterschrift der Einverständniserklärung des Patienten - Alter > 18 Jahre
Ausschlusskriterien	- Monatliche Schwangerschaftstests für Patientinnen im gebärfähigen Alter - Non-compliance mit dem Prüfplan (inkl. CERAD-plus bei AD) - Schwangerschaft (Wenn Patient weiblich und im gebärfähigen Alter bitte Schwangerschaftstest machen) - Stillende Frauen - Relevante intracerebrale Pathologie, die nicht mit der Grunderkrankung zusammenhängt (z.B. Gehirntumor) - Hämophilie oder andere Blutgerinnungserkrankung

- Kortisontherapie innerhalb von 6 Wochen vor der ersten Behandlung
- Thrombose

Medizinprodukte Duolith SD1 Tower bzw. zukünftig Neurolith (BT.0546)

Studienziel Das Ziel dieser Studie ist es die Wirksamkeit und Sicherheit der TESWT bei Patienten mit Alzheimer- oder Motorik-Erkrankung zu zeigen.

Primärer Endpunkt (AD) Corrected CERAD Total Score

Primärer Endpunkt (Motor) Coin Rotation Score

Studienablauf: AD Patienten

	Zyklus I						Zyklus II				
	Screening	Baseline Zyklus I	TESWT-Behandlungen	Follow-Up 1	Follow-Up 2	Follow-Up 3	Baseline Zyklus II	TESWT Behandlungen (Cross-over)	Follow-Up 4	Follow-Up 5	Follow-Up 6
	S	T1	B1-B6	T2	T3	T4	T5	B7-B12	T6	T7	T8
Zeitplan [Wochen] Abweichungen von ± 1 Woche sind erlaubt	W1	W1-2	W3-W4	W5	W8	W16	W22	W23-W24	W25	W28	W36
Ein-/Ausschlusskriterien	X										
Patienteninformation	X										
Patienteneinverständnis		X									
TESWT-Behandlungen • Fragen an Patienten • Videomonitoring			X					X			
MRT (anatomisch und funktional)		X		X			X		X		
Tests (AD-Patienten) • CERAD-Plus • NTBV *		X NTBV (A) ADAS (A)		X NTBV (B) ADAS (D)	X NTBV (C) ADAS (E)	X NTBV (A) ADAS (A)	X NTBV (B) ADAS (D)		X NTBV (C) ADAS (E)	X NTBV (A) ADAS (A)	X NTBV (B) ADAS (D)

• ADAS * • IADL • B-ADL • FAI / SEG • FZV • Prosopagnosia • CDT • BDI • GDS * verschiedene Testtversionen pro Replikation											
Subj. Behand-lungserfolg/Weiterempfehlung				X		X			X		X
Tests (Angehörige) • NPI • IADL • B-ADL • FAI/SEG • FZV		X		X	X	X	X		X	X	X
Unerwünschte Ereignisse			X	X	X	X	X	X	X	X	X

Studienablauf: Motorikpatienten

	Zyklus I	Zyklus II

	Screening	Baseline Zyklus I	TESWT-Behandlungen	Follow-Up 1	Baseline Zyklus II	TESWT Behandlungen (Cross-over)	Follow-Up 4	Follow-Up 5
	S	T1	B1-B6	T2	T5	B7-B12	T6	T7
Zeitplan [Wochen] Abweichungen von ± 1 Woche sind erlaubt	W1	W1-2	W3 - W4	W5	W11	W12 - W13	W14	W17
Ein-/Ausschluss-kriterien	X							
Patienten information	X							
Patienteneinverständnis		X						
TESWT-Behandlungen • Fragen an Patienten • Videomonitoring			X			X		
MRT (anatomisch und funktional)		X		X	X		X	
Tests (Motor-Patienten) • Klini. Tests (Motor performance) • Coin rotation Test • B-ADL • FZV • MOCA • GDS • BDI • Händigkeit		X		X	X		X	X
Subj. Behandlungserfolg/Weiterempfehlung				X			X	
Tests (Angehörige) • B-ADL • FZV		X		X	X		X	X
Unerwünschte Ereignisse			X	X	X	X	X	X

Weiterbehandlung nach der Studie

Bei der Stoßwellentherapie handelt es sich um eine zusätzliche Maßnahme, die die normale Standardtherapie ergänzt. Nach der Studie kann die normale Standardtherapie ohne Stoßwellentherapie fortgesetzt werden.