Clinical Study

Synopsis

Acne Scar Treatment Pen

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STUDY TITLE	Evaluation of the efficacy and safety of the Acne Scar Treatment Pen in the treatment of ice pick acne scars in the face.
SPONSOR	MEDICAL BRANDS B.V. Piet Heinkade 199 1019 HC AMSTERDAM THE NETHERLANDS
TRIAL SITE	Eurofins Dermscan
PRINCIPAL INVESTIGATOR	TBD
BACKGROUND	Scarring is a very common consequence of acne, estimated to occur in up to 95% of acne patients (Hession and Graber 2015). Scars are the consequence of an impaired wound healing process. Scars may be keloid, hypertrophic or atrophic. Keloid and hypertrophic scars are the result of increased tissue formation, while atrophic scars result from loss or damage of tissue (Rivera 2008). Atrophic acne scarring is by far the most common form, with 80 to 90% of people with acne scars exhibiting atrophic scars (Fabbrocini et al. 2010). There are three primary atrophic acne scars: the ice pick (60–70% of total scars), the boxcar type (20–30%) and the rolling (15–25%) (Jacob, Dover, and Kaminer 2001; Patel, McGrouther, and Chakrabarty 2014). Ice pick scars are usually the smallest in diameter (<2 mm) and relatively deep, with tracts often continuing to the dermis or subcutaneous tissue. Ice pick scars are commonly seen on the cheeks (Rivera 2008). Boxcars can be shallow (0.1-0.5 mm) or deep (>0.5 mm). They are round to oval depressions with sharply demarcated vertical edges, similar to varicella scars. Boxcars have a wide surface and do not taper to a point at the bottom. Rolling scars are usually wider than 4-5 mm. Abnormal fibrous anchoring of the dermis to the subcutis leads to superficial shadowing and a rolling or undulating appearance to the overlying skin (Jacob, Dover, and Kaminer 2001). Since acne scarring has a substantial negative impact on the overall social and functional well-being of affected individuals (Fried et al. 2015), a wide variety of therapeutic interventions has been developed to treat acne scars. The choice of treatment for acne scarring is generally determined based on scar type (Hession and Graber 2015). Examples of treatments include dermal fillers and resurfacing techniques, such as chemical peeling, dermabrasion, laser abrasion and electrosurgery. These techniques destroy the epidermis and allow re-epithelialization with collagen remodeling (Thiboutot et al. 2009).

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	A variation of trichloroacetic (TCA) chemical peeling, called Chemical Reconstruction of Skin Scars (CROSS) method, which involves local serial application of relatively high concentration TCA (50-100%) to ice pick skin scars using a sharpened wooden applicator, was found to decrease depth of the scars, improve overall appearance and reduce the risk of damaging adjacent normal skin (Lee et al. 2002). The Acne Scar Treatment Pen was developed by Medical Brands to treat mild ice pick scars in the face. By combining the CROSS method with a state-of-the-art precision applicator that delivers a controlled volume of TCA-Active™ instead of using a toothpick with uncontrolled and imprecise volumes, the Acne Scar Treatment Pen is expected to be as effective while safe for its use as an over-the-counter self-care medical device.
STUDY DESIGN	Single blind, within-subject (split face), placebo-controlled, randomised clinical trial comparing two concentrations of TCA-Active™.
STUDY DURATION	Maximum 18 weeks: ● 1 treatment per cycle of 3 weeks. ● Maximum of 6 cycles.
SAMPLE SIZE JUSTIFICATION	64 subjects ● 32 subjects per treatment arm (2 concentrations of TCA-Active). A sample-size of 32 subjects (simulations performed with East ® 6.5 and a Mac Nemar test for paired data) will ensure a power of 80% to show a significant difference versus placebo while taking into account the correlation between statistical units (hemifaces) if at least one of the active concentration is superior to placebo by at least 40% more subjects cleared after 6 cycles.
SELECTION CRITERIA	
Inclusion Criteria	1. Written informed consent must be obtained from the subject. 2. Must be ≥ 18 and < 45 years of age. 3. Subjects with at least 5 icepick acne scars per hemiface, and with comparable pathology on each hemiface as judged by the investigator. 4. Good general health. 5. Subject having stopped any topical anti acne treatment since at least 6 months before inclusion. 6. Willing to refrain from receiving cosmetic face treatments for the duration of the study. 7. Willing to use sunscreen for the duration of the study.

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	8. Female subjects of childbearing potential should use an accepted contraceptive regimen since at least 12 weeks before the beginning of the study, during all the study and at least 1 month after the study end. 9. Fitzpatrick skin types I, II, III, IV.
Exclusion Criteria	1. Subject considered by the Investigator likely to be non-compliant with the protocol. 2. Patient enrolled in another clinical trial during the test period. 3. Woman being pregnant, nursing or planning a pregnancy during the course of this study. 4. Subject having a known allergy to one of the constituents of the tested products. 5. Patient suffering from serious or progressive diseases (to investigator's discretion), including but not limited to diabetes, peripheral circulatory disease, HIV, immunosuppressive pathology. 6. Subject with cutaneous pathology on studied zone, including but not limited to acne, rosacea, angioma, dermatitis, herpes labialis. 7. People who were treated with tretinoin within 6 months prior to treatment in this study. 8. History of skin tightening or injectable filler of any type within the last year. 9. History of facial laser treatment, including ablative and non-ablative resurfacing laser treatments and rejuvenation laser treatments in the last 6 months. 10. History of cosmetic treatments with neurotoxins within the last 3 months. 11. History of chemical peel or dermabrasion of face and neck within the last 4 weeks. 12. History of keloid formation. 13. History of hyperpigmentation. 14. Fitzpatrick skin types V and VI. 15. Prior poor reaction to a chemical peel.
INVESTIGATIONAL PRODUCT	• 35% TCA-Active™ Acne Scar Treatment Pen • 50% TCA-Active™ Acne Scar Treatment Pen
COMPARATOR	Organoleptic matched Placebo
CONCOMITANT MEDICATION	
Allowed medication	Medication that is not expected to interact with the study treatment and is not expected to interfere with the objectives of this study may be allowed at the discretion of the investigator.
Prohibited medication	Any topical anti acne treatment and/or topical or oral tretinoin treatment since at least 6 months before inclusion, is not allowed

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LIFESTYLE RESTRICTIONS	Sunlight must be avoided and subjects are required to use provided UV protection when exposed to sunlight during study participation up to 4 weeks after the last treatment.
OBJECTIVES	
Primary Objectives	1. Determine optimal TCA-Active™ concentration by comparing the efficacy of 35%, and 50% TCA-Active™ in the treatment of ice pick acne scars, when administered by a clinician.
Secondary Objectives	1. Determine number of cycles required to achieve treatment efficacy. 2. Determine the impact of ice pick acne scars on the quality of life of subjects before and after treatment. 3. Evaluate visual changes in ice pick acne scars over treatment cycles: number and depth of scars, scar colour changes, duration of colour changes and number of lesions with scarring due to TCA-Active™ treatment. 4. Evaluate patient's pain tolerance during treatment and patient's satisfaction. 5. Evaluate the safety of 35% and 50% TCA-Active™ in the treatment of ice pick acne scars.
SUBJECTS/ GROUPS	● Acne Scar Treatment Pen vs Placebo (split face) ○ Cohort 1 (N=32), 35% TCA-Active™ ○ Cohort 2 (N=32), 50% TCA-Active™
ENDPOINTS	
Primary endpoint	● Clinician Global Impression (CGI) of improvement (Likert scale) change from baseline compared to placebo after 6 cycles of treatment
Secondary endpoints	● Required number of cycles of treatment to achieve efficacy level "almost clear" as determined by clinician ● Secondary assessment CGI ○ Photographs taken every visit, before and after treatment (2D or 3D photography) will be evaluated by a second clinician. ● Auto-evaluation of the impact of ice pick acne scars on the quality of life of subjects before and after treatment. ● Clinician evaluation of visual changes in ice pick acne scars after each treatment cycle: ○ Measurement of the number and type (superficial, shallow or deep) of ice pick acne scars ○ Scar colour changes (hypopigmentation, hyperpigmentation, no changes)

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	○ Duration of scar colour changes ■ Disappearance of colour changes before next treatment cycle (yes, no) ■ Disappearance of colour changes by end of follow up period (yes, no) ○ Number of lesions with scarring (N) ● Patient Global Impression (PGI) of improvement (Likert scale) change from baseline compared to placebo
Usability endpoints	● Patient's evaluation of pain/tolerance during treatment ○ Patient's subjective evaluation of pain during treatment application (Likert scale) ○ Patient's subjective evaluation of pain acceptability during treatment (Likert scale) ● Patient's satisfaction ○ Patient's satisfaction with the overall results of the treatment (Likert scale) ○ Patient's satisfaction with the number of treatments required (Likert scale) ○ Product meets expectations, would recommend (Likert scale)
Safety endpoints	● Adverse Events, concomitant medication
STATISTICAL ANALYSIS	CGI (5 points Likert scale) change from baseline after 6 cycles A generalized mixed model for repeated measures to take into account the correlation between the 2 hemifaces of a same subject and between visits will be used with as fixed effects Treatment (35% TCA-Active/50% TCA-active, placebo) and Visit (with 6 levels) and their interaction, the baseline CGI, and as random effect the ID subject effect. The contrast at Cycle 6 will be the main contrast of interest (comparison of actives vs placebo at cycle 6), for every subject (still treated or not). As a sensibility analysis, a Mac Nemar test will also be used to compare between groups the rates of subjects cleared at Cycle 6. In order to take into account the multiplicity due to the 2 concentrations the Hochberg method will be used: both p-values from the generalized mixed model (35% and 50% concentrations vs placebo) will be calculated then the higher p-value will be compared to 5%. If lower than 5%, both concentrations will be considered as superior to placebo. If higher than 5%, then the second p-value will be compared to 2.5%. If lower than 2.5%, this concentration will be considered superior to placebo. Evaluation of the required number of cycles of treatment to be "almost cleared".

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	Concerning this parameter, a time to event analysis (Kaplan-Meyer survival analysis) will be performed in order to estimate and compare this time (median cycle number) between treatment groups. Subjects with missing data will be censored at their last evaluation. This analysis will not take care of the correlation between intra-individual assessments (hemifaces). Other secondary endpoints will be described with descriptive statistics and with the 95% CI for the rates and means. Wilcoxon signed-rank test will be used to compare the change from baseline of the different scores of Active versus Placebo. ● Clinician evaluation skin healing process at 2 and 3 weeks: raw data in N and percentage ● Auto-evaluation of the impact of ice pick acne scars on the quality of life of subject: descriptive quantitative analysis.. ● Clinician evaluation of visual changes in ice pick acne scars after each treatment cycle: for each item category summary of raw data in N and percentage. ● PGI (Likert scale): ○ For each item category summary of raw data in N and percentage. ○ 0: Clear- 1: Almost clear- 2: Mild - 3: Moderate - 4: Severe ● Patient's evaluation of pain/tolerance and patient's satisfaction: for each item category summary of raw data in N and percentage ● Safety endpoints: Total number of adverse events and proportion of subjects experiencing adverse events will be displayed by concentrations groups. ● Local adverse events will be compared versus placebo for the 2 concentrations.

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VISIT AND ASSESSMENT SCHEDULE

Study Phase	**Screening**	**Study Visits**							**Follow-up Visit**
Visit/contact Number (t)		**1**		**2**	**3**	**4**	**5**	**6**	**7**
Study Days*	**Up to -21**	**0**	**14**	**21**	**42**	**63**	**84**	**105**	**135**
Informed Consent/Assent	X								
Review Inclusion/Exclusion Criteria	X								
Demographics/Medical History	X								
Allergies, hypersensitivities	X								
Prior/Concomitant Medications	X								
Clinical Evaluation	X	X		X	X	X	X	X	X
Photography		X		X	X	X	X	X	X
Application of treatment		X[a]		X[a]	X[a]	X[b]	X[a]	X[a]	X
CGI of improvement		X		X	X	X	X	X	X
Counting number and type of facial ice pick scars		X		X	X	X	X	X	X
PGI of improvement		X		X	X	X	X	X	X
Telephone check-up			X						
Patient pain evaluation		X		X	X	X	X	X	X
Patient satisfaction									X
DLQI		X							X
Assessment AE/ADE			X	X	X	X	X	X	X
Dispense Prevention Cream and explain instructions for use		<----------							---------->

[a]Treatment will be applied by the clinician.

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