1 SYNOPSIS

<table>
<tr><td>NAME OF COMPANY:
Grünenthal GmbH</td><td colspan="2">INDIVIDUAL STUDY SYNOPSIS</td></tr>
<tr><td rowspan="2">NAME OF INVESTIGATIONAL DEVICE:
MAR-CUTIS topical tissue adhesive</td><td>INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER
Volume:
Page:</td><td>(FOR NATIONAL AUTHORITY USE ONLY)</td></tr>
<tr><td colspan="2">Title of Study: A Randomized, Open-label, Multi-center, Controlled Clinical Study to Compare MAR-CUTIS with Dermabond Advanced in Closure of Surgical Incisions and Lacerations ≤15 cm</td></tr>
<tr><td colspan="3">Introduction: MAR-CUTIS is a new, polyurethane-based topical skin adhesive intended for topical application to close wounds of the skin, such as cuts and wounds from surgical incisions. It is completely different from existing skin adhesives based on cyanoacrylate. One single-center, prospective, nonrandomized, open-label study conducted in 10 subjects evaluated the safety and effectiveness of MAR-CUTIS in holding easily approximated skin edges of wounds from closed surgical incisions. The study confirmed the effectiveness of MAR-CUTIS as a topical skin adhesive. The current study was performed to compare MAR-CUTIS with an active comparator, Dermabond Advanced. The main efficacy endpoint was the dehiscence rate of the target incision/laceration and the main safety endpoint was to compare the incidence of adverse events (AEs) between the 2 devices. The study was subsequently terminated early as interim data review showed that the primary goal of the study to show noninferiority could not be achieved.</td></tr>
<tr><td colspan="3">Investigators: This section is not applicable for an abbreviated report.</td></tr>
<tr><td colspan="3">Study Sites: 16 sites in 4 countries in Europe – France, Germany, Spain, and United Kingdom</td></tr>
<tr><td colspan="3">Publication (Reference): None</td></tr>
<tr><td colspan="2">Studied Period: 30 Oct 2018 to 04 Sep 2019</td><td>Phase of Development: Pivotal</td></tr>
<tr><td colspan="3">Date of Clinical Investigation Initiation: 30 Oct 2018</td></tr>
<tr><td colspan="3">Termination Date of the Clinical Investigation: 04 Sep 2019</td></tr>
<tr><td colspan="3">Objectives: The primary efficacy objective of the study was to compare the dehiscence rate between MAR-CUTIS and Dermabond Advanced between Day 1 and Day 10.
The primary safety objective of the study was to compare the incidence of AEs between MAR-CUTIS and Dermabond Advanced.
Secondary objectives included the following:
• To compare the dehiscence rate between MAR-CUTIS and Dermabond Advanced at the Month 1 visit.
• To compare the incidence of AEs between MAR-CUTIS and Dermabond Advanced at additional study time points.
• To evaluate the subject satisfaction with the cosmetic outcome after treatment of the surgical incision/laceration with MAR-CUTIS versus Dermabond Advanced.
• To compare the wound infection incidence between both treatment groups.
• To evaluate the investigator satisfaction with the cosmetic outcome after the closure of the target surgical incision/laceration with MAR-CUTIS versus Dermabond Advanced.
• To evaluate the subject comfort with the device during and after treatment with MAR-CUTIS versus Dermabond Advanced.
• To evaluate the investigator overall satisfaction and ease of use with the device during and after the closure of the target surgical incision/laceration with MAR-CUTIS or Dermabond Advanced.</td></tr>
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Clinical Investigation Method: This was a randomized, open-label, multi-center, comparator-controlled clinical study to compare MAR-CUTIS with Dermabond Advanced in closure of surgical incisions ≥6 to ≤15 cm and lacerations ≤15 cm. Subjects were randomized 2:1 to MAR-CUTIS or Dermabond Advanced. Screening and baseline (randomization) could have occurred on the same day. Application of the investigational medical device (IMD) occurred on Day 0 with follow-up wound evaluation occurring on Day 1, Day 10, Month 1, and Month 3/Early Discontinuation. Training on the application of both devices was provided.

The study was put on hold in July 2019 to perform an interim data review, after which it was decided to terminate the study, as the primary goal of the study to show noninferiority could not be achieved. A substantial protocol amendment would be needed to correct the issue, which would lead to methodological issues resulting in a new, distinctly different study design.

Number of Subjects: The planned number of treated subjects was 189, in a ratio of 2:1 to MAR-CUTIS or Dermabond Advanced. The actual number of subjects enrolled was 107, with 29 allocated to Dermabond Advanced, 60 allocated to MAR-CUTIS, and 18 not allocated to any treatment. Of the 89 allocated subjects, 44 (15 Dermabond and 29 MAR-CUTIS) completed the study per protocol. The low number of completed subjects was due to the stop of collection of later data once it was decided to terminate the study prematurely.

Description of Clinical Investigation Population: Male and female subjects ≥2 years of age and body weight ≥10 kg, who were willing and capable of following the provided instructions for wound care and agreed to return for all treatment control visits were included in the study. For subjects with surgical incisions after a laparotomy, abdominal hysterectomy, inguinal hernia repair, or laparoscopic intervention, the allowed incision length was ≥6 to ≤15 cm. For subjects with lacerations, the laceration was to be on the face (avoiding the immediate area around the eye or lips/mouth and also excluding wounds which may be exposed regularly to body fluids or dense natural hair) or extremities and measuring ≤15 cm.

Investigational Device, Model, and Mode of Administration, and Batch Number(s): The investigational device was MAR-CUTIS, which is a polyurethane-based skin adhesive. At the time of use, the 2 components in the syringe were mixed in the mixing cannula. Complete hardening occurred within 5 minutes after application to the skin. The adhesive result could be corrected in the first 30 seconds.

Lot numbers of dispensed MAR-CUTIS: 810002-267821, 812002-3438751

Duration of Treatment/Intervention: The devices (MAR-CUTIS or Dermabond Advanced) were applied on Day 0.

Reference Device, Model, and Mode of Administration, and Batch Number(s): The reference device was Dermabond Advanced. It is a topical skin adhesive used in holding close approximated skin edges of wounds from surgical incisions, including incisions from minimally invasive surgery, and simple, thoroughly cleansed, trauma-induced lacerations.

Lot numbers of dispensed Dermabond Advanced: 810001-267821, 812001-3438751

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Criteria for Evaluation:

Clinical Performance:

- Total dehiscence rate assessed at the Day 1, Day 10, Month 1, and Early Discontinuation (if earlier than Month 1) study visits.
- Classification of dehiscence:
  - Partial dehiscence which did not require re-treatment;
  - Dehiscence to original depth/length which did not require re-treatment (eg, closure by secondary intention);
  - Any dehiscence which required re-treatment (including draining, debridement, closure, management of infection, etc.).
- Classification of dehiscence according to their grade (World Union of Wound Healing Societies Scale):
  - Dermal layer only
  - Subcutaneous layer exposed, fascia not visible
  - Subcutaneous layer and fascia exposed
  - Any area of fascial dehiscence with organ space, viscera, or bone exposed

Subject Satisfaction: Subject and investigator satisfaction with the devices were assessed using the following questionnaires: Patient and Observer Scar Assessment Scale (completed by both subject and investigator), Modified Hollander Cosmesis Scale (completed by investigator), a single product-related questionnaire for investigators, subject-related questionnaire completed by investigators, subject-completed questionnaire

Safety: Safety was assessed via monitoring of AEs, including adverse device effect (ADE), device deficiency, serious adverse event (SAE), serious ADE, and unanticipated serious ADE; and wound infection (incidence and presence of erythema, edema, pain at rest, and elevated temperature at target wound area).

Study Endpoints: This section is not applicable for an abbreviated report. See the protocol for details.

Statistical Methods: This section is not applicable for an abbreviated report. See the statistical analysis plan for details.

RESULTS OF CLINICAL INVESTIGATION

Clinical Performance/Effectiveness Results: The overall dehiscence rate for MAR-CUTIS was 22.0% and the rate in Dermabond was 3.6% . The estimated dehiscence rate difference was 0.1805 and the 90% CI was -0.6545 to 1.0000 (P = 0.3039). With regard to the subject and investigator satisfaction with the IMD, satisfaction was high in both groups, with no notable differences observed between the 2 groups. Device deficiencies/malfunction and glue detachment occurred at a higher frequency in the MAR-CUTIS group (device deficiencies/malfunction: 3 MAR-CUTIS subjects at Day 0, 4 MAR-CUTIS subjects at Day 1, 5 MAR-CUTIS subjects at Day 10; glue detachment: 1 MAR-CUTIS subject at Day 0, 3 MAR-CUTIS subjects at Day 1, 1 Dermabond subject and 24 MAR-CUTIS subjects at Day 10, 2 Dermabond subjects at Month 1).

Safety Results: Both IMDs, MAR-CUTIS and Dermabond Advanced, were safe and well tolerated in subjects undergoing surgery (laparotomy, abdominal hysterectomy, laparoscopic intervention, or inguinal hernia repair) and primary closure of lacerations. The proportion of subjects with treatment-emergent adverse events (TEAEs; both serious and nonserious TEAEs) and treatment-emergent ADEs was higher in the MAR-CUTIS group (TEAEs: 60.0% versus 44.8% in the Dermabond group; treatment-emergent ADEs: 10.0% versus 6.9% in the Dermabond group). Two MAR-CUTIS subjects experienced TEAEs leading to withdrawal, with 1 event (wound dehiscence) also considered a treatment-emergent ADE. Both TEAEs leading to withdrawal were not considered

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<tr><td colspan="2">to be related to IMD. The MAR-CUTIS group also had a higher proportion of TEAEs resulting in removal of IMD (2.4% versus 0% in the Dermabond group). The incidence rate of wound dehiscence was also higher in the MAR-CUTIS group.

Conclusions:
• The study was not able to prove noninferiority of MAR-CUTIS to Dermabond. This was at least in part considered to be due to the methodology which did not work out. It appeared that MAR-CUTIS, as a general wound closure device, was inferior to Dermabond based on the study results, which included a higher overall dehiscence rate for MAR-CUTIS and more premature glue detachments.
• Both MAR-CUTIS and Dermabond were generally safe and well tolerated. More subjects treated with MAR-CUTIS experienced TEAEs (both serious and nonserious; proportion of subjects with TEAEs was 60.0% and 44.8% in the MAR-CUTIS group and Dermabond group, respectively), including TEAE of wound dehiscence (proportion of subjects with TEAE of wound dehiscence was 10.0% and 3.4% in the MAR-CUTIS group and Dermabond group, respectively). There were also more subjects in the MAR-CUTIS group with TEAEs leading to withdrawal (2 subjects versus 0 in the Dermabond group) and removal of IMD (3 events versus 0 in the Dermabond group).

Date of Report: 13-JAN-2020</td></tr>
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