A clinical study To Compare The Performance Of AQUACEL® Ag+ Extra™ And Cutimed® Sorbact® Dressing In The Management Of Patients With Venous Leg Ulcers Over A 12-Week Period.

WC-22-435

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DOCUMENT HISTORY

Version	Date	Comment
1.0	1st July 2022	First Submission
2.0	6th October 2022	The following changes have been implemented following feedback from Colombian EC: • Added a clarification regarding unscheduled visits: "Interim visits are at the discretion of the investigator. At each scheduled visit, the number of dressing changes is collected. Any interim visit for a product-related AE or SAE would be captured on an additional visit form including the AE form". • Added a clarification regarding diabetic patients: "Subjects without diabetes do not require measurement of HbA1c if they have a recent glucose or HbA1c level over the past year". • Removed IC-11: subjects who don't have access to e-mail will be provided with an iPad to complete wound quality of life questionnaire during their site visits. • Added a clarification regarding secondary dressing: "Secondary dressing to be applied at the discretion of the investigator in accordance with the product's IFU". The following changes have been implemented in order to ensure that the inclusion and exclusion criteria and the schedule of events are in line with standard of care: • 'Chronic VLU' changed to 'VLU' • 'Aquacel Extra' changed to 'non-antimicrobial silver-free standard of care as per sites' normal practice' • Updated EC-7 to include patients with uncontrolled diabetes, HbA1c ≥10 • Removed EC-8 and EC-9 to include subjects who are breastfeeding or pregnant • Clarification added to the schedule of events: "After day 28, the PI or delegate will continue treatment of the wound according to the clinical needs based on their evaluation of the wound. If an antimicrobial wound dressing is required, the dressing that was randomly assigned during the initial phase of the study can be used." The flow chart on page 23 has been updated accordingly.

		Due to limited availability, Professor Dissemond can no longer act as country coordinator and investigator. Therefore, his details have been removed from the study protocol.
3.0	26th October 2022	Typo correction in Exclusion Criterion 7 (EC-7): Patients with uncontrolled diabetes with HbA1c ≥ 10 within last 3 months. Subjects without diabetes do not require measurement of HbA1c if they have a glucose or HbA1c level measured over the past year. Updated table of contents
4.0	3 May 2023	• Minor syntax and formatting changes throughout document to better reflect the intent of the protocol. • All references to version number updated to "4.0" with date 3 May, 2023. • Section 23, Abbreviations: The list of abbreviations updated for accuracy. • Synopsis: updates made to reflect the updates of the body of the protocol for accuracy. • Reference to CRO and Country Principal Investigator removed for accuracy. • Table of Contents updated for accuracy. • Inclusion criteria updated to allow inclusion of multiple wounds for the subject. • Secondary endpoints better defined in the protocol to reflect the current study design. • Exploratory endpoints defined to reflect the current study design. • Safety endpoints defined to reflect the current study design. • Completed subject definition added (Section 8.3) for accuracy. • Study wound identification added to reflect the current study design. • Study procedure diagram updated to reflect the current study design. • Section 9.4 "Enrolment of subjects with multiple wounds" added to reflect the current study design. • Schedule of Events has been updated to add End-of-Study Visit • Visit 2: Improved clarification of Investigator choice of treatment options. • Section 12 Safety and Event Report updated definitions of adverse events and reporting for regulatory compliance. • Section Role of Sponsor Representative removed as it is not applicable.

		• Section Statistical Consideration has been updated to reflect the current study design. • Section Protocol Deviations: removed language related to analyses populations and subject withdrawal to avoid redundancy. • Section 21 (Good Clinical Practice and statements of Compliance to Section 27 (Public Registration and Publication) collapse into single section for simplicity.
4.1	16 June 2023	• Sample size changed to 206 subjects corresponding to minimum of 206 wounds.

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SYNOPSIS

Study Title	A clinical study to compare the performance of AQUACEL® Ag+ Extra™ and Cutimed® Sorbact® dressing in the management of patients with Venous Leg Ulcers over a 12-week period
Study Type	Post-market
Principal Investigator (PI)	Catarina Saavedra, M.D.
Device(s) Under Investigation	AQUACEL® Ag+ Extra™ (Experimental Arm) and Cutimed® Sorbact® (Control Arm)
Sponsor	Convatec Limited, GDC, First Avenue, Deeside Industrial Park, Deeside, Flintshire, CH5 2NU, United Kingdom
Purpose	The primary purpose of this study is to evaluate performance of AQUACEL® Ag+ Extra™ in comparison to Cutimed® Sorbact® in the progression of wounds towards healing.
Design	Randomised, active-controlled, open label, multi-centre, global study
Selection of Subjects	**Inclusion Criteria** Subjects must meet the following criteria: IC-1 Venous insufficiency as defined by CEAP Classification of C6. IC-2 At least one chronic venous ulcer (wound) amendable to treatment with AQUACEL® Ag+ Extra™ and Cutimed® Sorbact®. IC-3 Wound(s) that have been present for at least 60 days (2 months) and ≤18 months IC-4 Reliable and available for follow-up, in the opinion of the investigator IC-5 18 years or older at the time of consent IC-6 Able and willing to provide informed consent IC-7 Able to tolerate compression therapy for VLU (40 mmHg) IC-8 Wound must be ≥1 cm^2 and ≤100 cm^2 IC-9 Must be able to be compliant with compression therapy IC-10 ABPI should be in the range between 0.8 and 1.3 **Exclusion Criteria** Subjects must be excluded from participating in this study if they meet any of the following criteria: EC-1 Known sensitivities or allergies to components of the AQUACEL® Ag+ Extra™ or Cutimed® Sorbact® EC-2 Continued use of petroleum gel/ creams/ oil-based products on the target wound

	EC-3 Active treatment for cancer or completed within the last 3 months
	EC-4 Documented severe malnutrition at any time
	EC-5 Malignant wounds
	EC-6 Systemic infection actively treated with antibiotics
	EC-7 Patients with uncontrolled diabetes with HbA1c ≥ 10 within last 3 months. Subjects without diabetes do not require measurement of HbA1c if they have a glucose or HbA1c level measured over the past year.
	EC-8 Chronic conditions such as autoimmune disorders in an acute flare phase, which in the opinion of the investigator, would directly impact wound healing. Use of immunosuppressant medications are allowed, as long as they have been on a stable dose and regimen over the past 3 months
MDR Device Regulatory Classification	AQUACEL® Ag+ Extra™ is a Class III device Cutimed® Sorbact® is a Class IIb device
Primary Objective(s)	The primary objective of the study is to compare the effectiveness of AQUACEL® Ag+ Extra™ to Cutimed® Sorbact® on wound management when used in accordance with the instructions for use.
Endpoint(s)	The primary end point is complete wound closure as defined by 100% epithelialisation of the wound surface. Secondary endpoints are percent change in target wound area at 4 weeks (primary treatment period); Satisfactory clinical progress defined as 40% reduction in study wound area at 4 weeks (primary treatment period) and percent change in target wound area at 12 weeks. Exploratory endpoints are time to complete wound closure, wound clinical characteristics (e.g. wound healing status, condition of surrounding skin and signs of infection), Wound Quality of Life (Wound-QoL) 14, pain, wound management after the study mandated treatment. Safety will be characterized by a summary of the incidence of adverse events (AEs), device-related AEs, and serious device-related AEs.
Randomisation	Subjects will be randomised on a 1:1 basis to either the AQAUCEL® Ag+ Extra™ or Cutimed® Sorbact® dressing. Subjects will be randomised to product at Visit 1 once it has been determined the subject is suitable to participate in the study.
Study Duration	The subject participation is up to 12 weeks. It is anticipated enrolment will take 12 months and the overall study duration is anticipated to be approximately 18 months.
Sponsor Study Contact	Kristina Aare Clinical Project Manager Convatec Limited Medical Affairs and Clinical Affairs GDC (Global Development Centre) First Avenue

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1 BACKGROUND & JUSTIFICATION

The burden of chronic wounds

Caring for patients with acute and chronic wounds represent a significant challenge on healthcare systems and societies around the world. Real-world data from the UK (2017/2018) has shown that the total costs to the UK health system of caring for patients with wounds was around GBP£8.3BN per year.[1] This is equivalent to the UK spend on systemic diseases such as osteoarthritis and rheumatoid arthritis which was GBP£10.2 billion in 2017/2018. Whilst 89% of acute wounds heal within a year, just 49% of chronic wounds close within the same period. Whilst the understanding of how to treat chronic wounds has improved over time, the increased age of the population and their attendant co-morbidities means that healing rates don't appear to have improved.[1,2]

The significance of venous leg ulcers

One of the most prevalent chronic wounds are venous leg ulcers (VLU). In Germany, about 0.6–1% of the population are diagnosed with a VLU, with the prevalence in people above the age of 60 being much higher (3.9%). VLU are wounds on the lower extremity resulting from venous hypertension and hypervolemia. The pooling of venous blood gives rise to oedema which leads to poor perfusion and tissue breakdown. The mainstay of conservative treatment is compression therapy to counteract the oedema and assist venous return. Many VLU are in fact mixed ulcers as patients often have a degree of arterial disease.[3] Only about half of VLUs heal within 4 months, leaving a significant proportion of non-healing ulcers to place a burden on heath resources and patient quality of life. Improvements in healing of VLU would have a significant impact.

The importance of bacteria and infection in chronic wounds

Much of the present day understanding of the clinical interventions required to improve healing in chronic wounds is enshrined in the widely used concept of Wound Bed Preparation (WBP). [5-8] Several derivations and additions to the TIME principles have since been developed.[9] The key concept at the heart of the WBP scheme is to break the clinical problem down into a series of interconnected barriers to intrinsic healing. The barriers are grouped into 4 areas: Tissue; Infection/Inflammation; Moisture/Exudate; Edge/Epithelialisation: the so called "TIME" paradigm.

Real world data show that chronic wounds which have required antimicrobial treatments for infection, have worse healing rates that wounds that have not become infected.[1] The importance of infection on chronic wounds has been a central tenet of healing since the studies of Robson showed that tissues that contained more than 10^5 colony forming units per gram of tissue were unlikely to heal without antimicrobial intervention.[10] It is now understood that an excessive inflammatory environment is counterproductive for healing as proteolytic activity from the inflammatory cell infiltrate secrete high levels of the matrix metalloproteases (MMP2 and MMP9) impedes the ability of cells to lay down extra cellular matrix that is critical for angiogenesis and epithelial migration. [5]

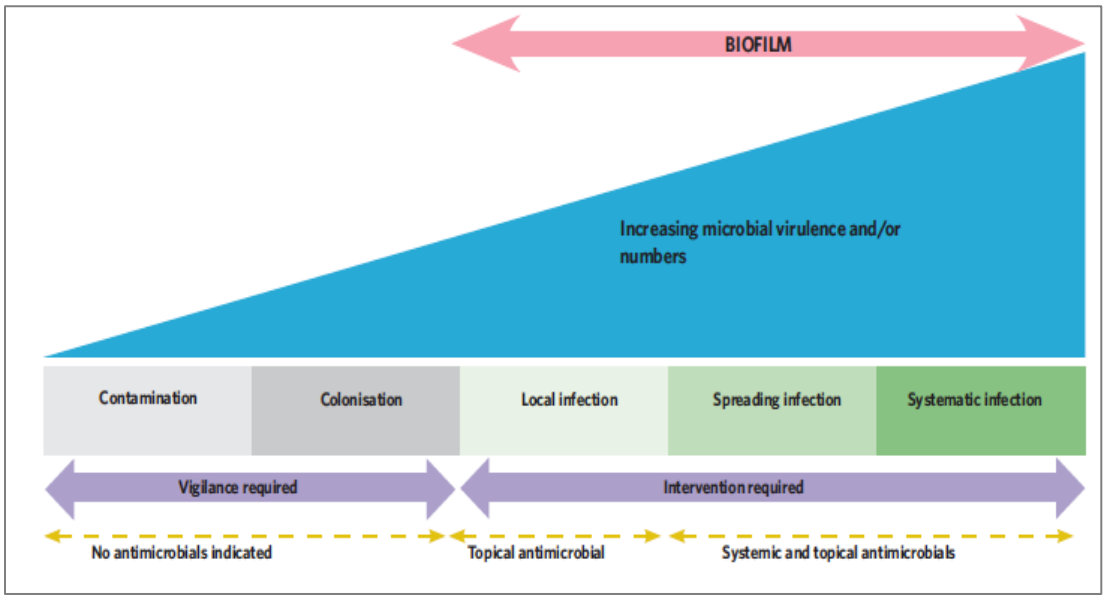
The Infection continuum

It is widely agreed that indiscriminate use of antibiotics in medicine and agriculture since their emergence in the middle of the previous century, has driven the selection and spread of antibiotic resistance. Research has established that it is unnecessary to set a target of zero bacteria in a healing wound, but rather that a balance between bacteria and host is a more desirable goal.[11] Evidence shows that systemic antibiotics do not lead to rapid improvement in chronic wound healing and long-term use of antibiotics would not be desirable because of concerns of selecting resistance. A useful way to

summarise the need for the deployment of antimicrobials in wound healing is the model known as the Infection Continuum.[12,13]

The Infection continuum characterises wounds into 5 categories according to increasing levels of bacteria:

1. Contamination
2. Colonisation
3. Local infection (has in the past been called Critical Colonisation)
4. Spreading infection
5. Systemic infection



As shown in the Figure reading left to right, Categories 1 and 2 represent wounds containing bacteria, but not at levels where antimicrobial intervention is recommended for prevention of infection or accelerating healing. Category 3 is a wound with clinical signs indicating local infection like pain, exudate, and erythema but not one where antibiotics show good efficacy. It is now widely recognised that systemic antibiotics have a poor efficacy on chronic, delayed healing wounds, because of their intrinsic poor perfusion and peri wound oedema. The evidence-based medicine Cochrane collaboration regularly reviews the use of antibiotics and topical antiseptics for the prevention or treatment of infection, or the acceleration of healing in VLU. There were no positive effects of antibiotics, systemic or topical, demonstrated versus standard care amongst 45 RCTs reporting 53 comparisons and recruiting a total of 4486 participants and only limited evidence for topical cadexomer iodine, a slow-release formulation eluting molecular iodine (I2) and very limited evidence for widely used silver-based antimicrobials.[14,15] Others have disputed the view that there is no platform of evidence for the use of antimicrobial dressings containing silver ions.[16] Infection continuum wound categories 4 and 5 indicate infection spreading into adjacent tissue (4) or systemic infection (5) (bacteraemia) and here evidence supports the use systemic antibiotics simultaneously with the use of topical antimicrobials and antiseptics to improve the wound.[12-14]

In routine clinical practice, the identification of the different categories of bacterial presence are based on the observation of clinical signs such as pain, erythema, exudate, oedema, rather than any attempt at

quantitative microbiology. Recently a panel of experts revisited the use of clinical signs of infection in order to identify wounds that should receive topical antimicrobials.[17] The Therapeutic Index for Local Infections (TILI score) has subsequently been validated as an easy to operate assessment tool for identification of locally infected wounds (category 3). In a study of a total of 307 patients with leg ulcers recruited from 5 European countries, 22% of proved to have a local infection.[18]

The importance of biofilms

It has been known for many years that bacteria can switch between two phenotypes: free-living single-cell planktonic forms and sessile forms growing as multicellular biofilms encased in extracellular polymeric substance (EPS).[19] However, evidence that a large fraction, and probably all non-healing wounds contain biofilms, was only published as recently as 2008.[20] Since that time, the science of biofilms and wound healing has developed quickly.[19] Evidence is also now accumulating that surgical wounds may also become colonised with multispecies biofilms, and these may play a role in the development of surgical site infections.[21] Wound dressings whose function is to sequester exudate and reduce the risk of a direct fluid path into the wound, may represent good conditions for the establishment of biofilms from which it is possible to repeatedly re-seed the healing wound below.[21] When present in a biofilm, the carbohydrate-based extracellular polymeric substance (EPS) ensures bacteria are many times more resistant to the presence of antibiotics than free-living bacteria and equally important, inflammatory cells are less able to attack and engulf bacterial cells living in a biofilm.[22] Investigations reveal that, biofilms are frequently composed of multiple species, and contrary to popular belief, biofilms are typically present as microcolonies embedded in granulation tissue, rather than a thin film on the surface of the wound. Anaerobic and aerobic species frequently co-exist, with certain sectors of the biofilm becoming significantly anoxic.[23]

For several years it was unclear whether biofilms were simply benign occupants of non-healing tissues, or whether biofilms themselves were implicated in the failure of the wound to heal. Evidence for a causal relationship between delayed wound healing and the presence of biofilm has been obtained with experiments in pigs. Researchers began by isolating a Methicillin-resistant Staphylococcus aureus (MRSA) strain from a contaminated pig wound, which when inoculated again into full thickness porcine wounds, gave a more extreme biofilm phenotype: it was more multicellular with more EPS than the parental strain. Moreover, it was observed that the new strain delayed healing to a greater extent than the parental strain.[24] Thus the link was made between the biofilm phenotype and the degree of inhibition of the normal healing trajectory.

Anti-biofilm strategies

The realisation that non-healing wounds are colonised by bacterial biofilms which have reduced sensitivity to topical and systemic antimicrobial therapies and cause inhibition of wound healing, has made clinicians think more carefully how they deliver antimicrobial therapy to chronic wounds. Seen in the context of the scheme of wound bed preparation, “biofilm-based wound care” builds on the concept that debridement is an excellent means of removing biofilm colonised tissue, but that at this point there is a window of opportunity to apply appropriate topical antimicrobials which will have increased efficacy on any planktonic bacteria liberated from the bulk biofilm population as the result of the debridement.[25,26] Application of the antimicrobial after debridement, rather than before, reduces the opportunity for biofilms to grow back. A cycle of debridement, followed by antimicrobial, followed by debridement, is now regarded as the most efficacious strategy.[27]

AQUACEL® Ag + Extra™

The understanding that biofilms are pivotal to the imposition of delayed healing on chronic wounds, has driven innovation in the antimicrobial sector. In one approach, the commercially successful silver gelling-

hydrofibre dressing Aquacel Ag™ (Convatec Inc) was modified, following a systematic search for synergistic activities, by the addition of the metal ion chelator EDTA and the surfactant antimicrobial benzethonium chloride. Branded Aquacel Ag+ (Convatec Inc) with the aim of allowing deeper penetration of silver ions into biofilms through destabilisation of the EPS.[28] Aquacel gelling fibre has subsequently been modified to have improved handling strength (Aquacel® Extra) and the Aquacel Ag+ dressing with Ag, EDTA and benzethonium is now available in the improved strength format: Aquacel Ag+ Extra. In vitro, in vivo, and clinical studies of AQUACEL® Ag+ Extra™ have been summarised.[29,30]

Cutimed® Sorbact®

A completely different approach to reducing the levels of bioburden in wounds is the development of hydrophobic dialkylcarbamoyl chloride (DACC) coated dressings. Hydrophobic bacteria become irreversibly bound to the DACC coated surfaces. Branded Cutimed® Sorbact® (BSN Medical GmbH), the bound bacteria can be removed at dressing changes, but DACC-bound bacteria don't proliferate and aren't lysed with subsequent release of potentially inflammatory substances. In vitro, in vivo, and clinical studies of Cutimed® Sorbact® dressings have recently been summarised.[31-33]

In an analysis of use in clinical practice in Germany, both AQUACEL® Ag+ Extra™ and Cutimed® Sorbact® are utilised significantly.[4] There have been no published reports of substantive randomized comparative trials with either dressing technology versus controls, and no direct head-to-head comparative studies of the two approaches to address the effects of microbial bioburden on the healing of VLU wounds. It is not clear how the DACC coated dressings might counter embedded biofilms. One recently published protocol describes a randomised comparison of Cutimed® Sorbact® DACC dressings versus AQUACEL® Ag+ Extra™ (the version without EDTA and benzethonium): NCT03667937 www.clinicaltrials.gov.[34] The study will look for effects on levels of bioburden in VLUs assessed with a primary endpoint of rDNA qRT-PCR determined levels of culturable and non-culturable bacteria. The wounds will be assessed following treatment with the two kinds of dressings at weeks 4, 8 and 12. It is not known how advanced this study is in recruitment.

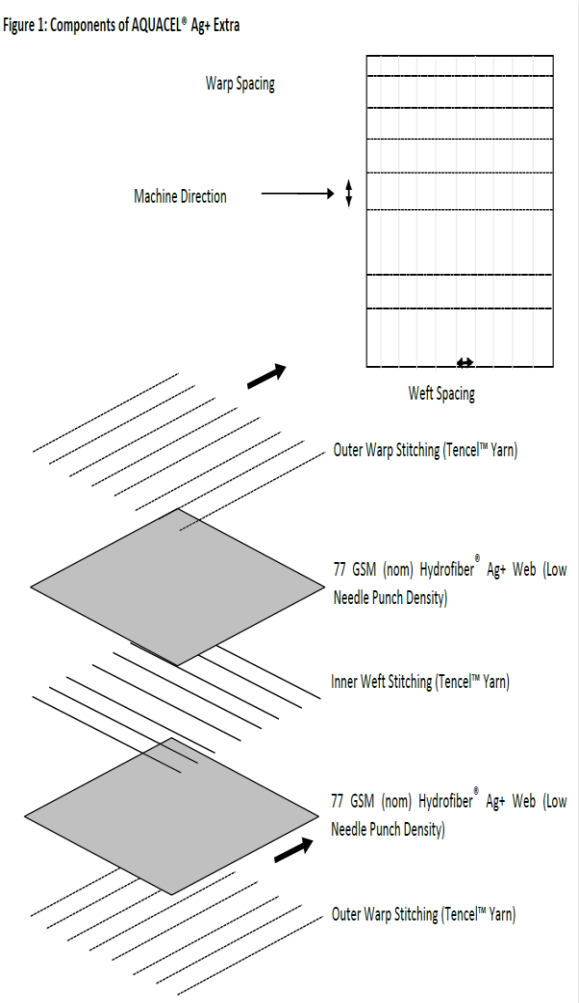
Purpose of the present study

The purpose of the present protocol is to compare effectiveness of two antimicrobial dressing technologies in patients with VLU. The study is justified as both dressings are in widespread clinical use, each has significant pre-clinical and clinical data that demonstrates safety, but no comparative trials including either product have previously been undertaken.

1.1 Identification and Description of the Study Devices

Table 1.1.1 provides an identification and description of the study devices.

TABLE: 1.1.1: Identification and Description of Study Devices

Study Device	Legal Manufacturer	Description	Identification
AQUACEL® Ag+ Extra™	Convatec Limited Deeside Industrial Park Deeside Flintshire CH5 2NU Convatec's Limited EU Representative is Unomedical A/S Aahomvej 1-3 Osted 4320 Lejre, Denmark	AQUACEL® Ag+ Extra™ dressings (Figure 1) comprise a needle-bonded nonwoven fabric layered and stitch-bonded to provide a dressing approximately 2-3 mm thick, and which is then cut to the dimensions specified on the packaging. They are constructed of two layers of optimally textiled 70 gsm Hydrofiber™ (sodium carboxymethylcellulose) into which ionic silver (antimicrobial agent) and the excipients ethylenediaminetetra-acetic acid di-sodium salt (EDTA) (a chelating agent) and benzethonium chloride (a surface-active agent) have been added to disrupt biofilm and expose microorganisms to the antimicrobial effects of ionic silver. The dressings are stitch-bonded together using Lyocell (Tencel™ regenerated cellulose) yarns.	Figure 1: Components of AQUACEL® Ag+ Extra 

Study Device	Legal Manufacturer	Description	Identification
Cutimed® Sorbact®	BSN medical GmbH, Quickbornstraße 24, 20253 Hamburg, Germany	Cutimed® Sorbact® dressing is approved as a bacterial and fungi binding wound dressing. It consists of a green Sorbact® wound contact layer combined with an absorbent core and a white backing. Sorbact® dressing absorbs and retains exudate, thereby reducing the risk of maceration and enabling a moist wound environment. The dressing can be used in combination with compression therapy.	 

1.2 Study Device Details

The table below demonstrates many aspects of the devices under study.

	AQUACEL® Ag+ Extra™	Cutimed® Sorbact®
Mode of Action	The mode of action of these wound dressings is by absorption and fluid retention. When in contact with wound exudate, the dressing forms a cohesive gel; this gelled material enables intimate contact of the dressing with the wound bed.	Cutimed® Sorbact® binds microorganisms, such as Staphylococcus aureus (including MRSA), Streptococcus species, Escherichia coli, Pseudomonas aeruginosa and Candida albicans, as shown in-vitro. These microorganisms are removed from the wound each time the dressing is changed.

	AQUACEL® Ag+ Extra™	Cutimed® Sorbact®
	The dressings demonstrate antimicrobial activity through the presence of silver, an antimicrobial agent. The addition of EDTA and benzethonium chloride enables the dressing to disrupt wound biofilm and sessile attached bacteria in contact with the dressing	
Duration of Use	AQUACEL® Ag+ Extra™ can be worn for up to 7 days, dressings should be changed earlier if clinically indicated. On partial thickness (second degree) burns, dressings may remain in place for up to 14 days. The need for AQUACEL® Ag+ Extra™ should be re-assessed after 14 days and alternative wound management considered where appropriate	Cutimed® Sorbact® can be left in place for up to 7 days, should the clinical condition allow
Intended Use	AQUACEL® Ag+ Extra™ Dressings have been designed to be used as a primary dressing. They are intended to be used under the direction of a healthcare professional for wounds, which are at risk of infection or show signs infection, or where biofilm is suspected to be present, and in accordance with the indications for use.	Cutimed® Sorbact® is indicated for use in management of clean, contaminated, colonised, or infected wounds with moderate to high levels of exudate, such as surgical wounds, traumatic wounds, pressure ulcers, diabetic ulcers, and leg ulcers.
Storage Conditions	According to manufacturer's packaging	According to manufacturer's packaging

1.3 Device Regulatory Classification

The study devices used in this study are approved in Europe and are classified according to MDR in the table below.

	AQUACEL® Ag+ Extra™	Cutimed® Sorbact®
MDR Classification	Class III	Class IIb

2 Risks and Benefits of the Devices used in this Study

The section below details the risks and benefits of the devices used in this study.

2.1 Risks of the Devices

The risks associated with using the study device(s) in the study are no different than in standard of care, as they will be used according to their intended use statements. Please refer to IFU Sections PRECAUTIONS and OBSERVATIONS for any information regarding adverse events and any steps that should be taken to avoid them, as well as information about other warnings and precautions in relation to the device.

Anticipated Adverse Device Effects

The anticipated adverse device effects are known reactions to the study devices. The list of known anticipated adverse device effects include, but are not limited to: allergic reaction, bleeding, pain/discomfort in area of wound, skin irritation around wound, and infection.

2.2 Residual Risks

The study devices used on this study are applied according to indications for use. By participating in this study, it is anticipated that the residual risks are the same as not participating in the study. The device manufacturers have performed qualification testing on the device and device components and appropriate quality control measures have been implemented into production.

2.3 Risk of Interactions with Concomitant Medical Treatments

No interactions with concomitant medications are noted in the IFU for either study device.

2.4 Mitigation of Risk

Additional action to mitigate risks are not anticipated, as the devices are used in a way that is standard of care.

2.5 Benefits of the Device

There are no additional benefits of using this device in the study than in standard of care.

2.6 Risk to Benefit Rationale

Considering the information listed in this section, it can be concluded that there are no additional risks to individuals exposed to devices in the study compared to in standard of care. There are no risks of physical harm associated with participation in this study, as this is a study evaluating a commercially approved wound dressing when used as intended, with follow up procedures performed per standard of care. No treatment is added or removed due to a patient's participation in the study. The device IFUs contain additional information related to the anticipated risks associated with the use of the dressings and wound care.

2.7 Other Medical Devices to be Used in the Study

Any additional dressings or complimentary therapies such as compression, off-loading devices, and similar used in this study will be applied as in intended use and availability in the market while following their respective IFUs.

3 DESIGN OF CLINICAL INVESTIGATION

3.1 Study Design

The study is a post market, multi-centre, randomised, open label, global prospective study to compare the performance of AQUACEL® Ag+ Extra™ and Cutimed® Sorbact® dressing in the management of patients with venous leg ulcers (VLUs).

The VLUs will be treated with AQUACEL® Ag+ Extra™ (Experimental Arm) or Cutimed® Sorbact® (Control Arm) for up to 4 weeks. The WLUs will then be managed the with Standard of Care for up to 10 weeks, or until the wound has healed or the dressing is no longer clinically indicated. Crossover of dressings is not permitted.

3.2 Justification and Scientific Rationale for Design

This study compares the performance of AQAUCEL® Ag+ Extra™ verses Cutimed® Sorbact® in patients with VLUs. Literature supports the use of silver dressings in these types of wounds, as this may promote healing. This study is designed to collect this type of data on Convatec's AQUACEL® Ag+ Extra™.

3.3 Minimisation of Bias

Bias in studies can impact results in any study. To minimise bias, the following steps, which include, but are not limited to, have been taken:

- Multiple sites and geographies have been selected, which reduces the instrumentation and performance biases.
- Randomization minimizes confounding bias.

4 OBJECTIVES OF THE CLINICAL STUDY

4.1 Primary Objective(s)

The primary objective of the study is to compare the effectiveness of AQUACEL® Ag+ Extra™ verses Cutimed® Sorbact® in the management of patients with venous leg ulcers (VLUs).

4.2 Endpoints

4.2.1 Primary Endpoint

- Complete wound closure as defined by 100% epithelialisation of the wound surface (Gould 2019).

4.2.2 Secondary Endpoints

- Percent change in study wound area at 4 weeks (primary treatment period).
- Satisfactory clinical progress defined as 40% reduction in study wound area at 4 weeks (primary treatment period)
- Percent change in target wound area at 12 weeks.

4.2.3 Exploratory Endpoints

- Time to complete wound closure.
- Wound characteristics:
    - Eschar tissue presence and percentage
    - Slogh/Fibring tissue presence and percentage
    - Healthy granulation tissue presence and percentage
    - Unhealthy granulation tissue presence and percentage
    - Epithelial tissue presence and percentage
    - Exudate volume category (low, medium, high)
    - Exudate type
    - Odour
    - Condition of the wound edge
    - Condition of the peri-wound skin
    - Presence of erythema
    - Signs of infection
- Wound-QOL-14.
- Pain on a Numeric Rating Scale from 0 to 10 where 0 is no pain at all and 10 is the worst imaginable pain.
- Wound treatment type after the study mandated treatment.

4.2.4 Safety endpoints

Safety will be characterized by a summary of the incidence of adverse events (AEs), device-related AEs, and serious device-related AEs.

5 POPULATION AND DURATION OF THE STUDY

It is proposed that the study is conducted in Poland, Germany, and Colombia. Additional sites in additional countries may be recruited. The study sample will be recruited from the Investigators available clinical population.

Individual subject duration of participation in the study is up to 12 weeks. It is anticipated enrolment will take 12 months and the overall study duration is anticipated to be approximately 18 months.

6 ENROLLMENT CRITERIA

6.1 Inclusion Criteria

Subjects must meet the following criteria:

TABLE: 6.1-1: Inclusion Criteria

Number	Inclusion Criteria
IC-1	Venous insufficiency as defined by CEAP Classification of C6
IC-2	At least one chronic venous ulcer (wound) amendable to treatment with AQUACEL® Ag+ Extra™ and Cutimed® Sorbact®
IC-3	Wound(s) that have been present for at least 60 days (2 months) and less than ≤18 months
IC-4	Reliable and available for follow-up, in the opinion of the investigator
IC-5	18 years or older at the time of consent
IC-6	Able and willing to provide informed consent
IC-7	Able to tolerate compression therapy for VLU (40 mmHg)
IC-8	Wound must be ≥1 cm^2 and ≤100 cm^2
IC-9	Must be able to be compliant with compression therapy
IC-10	ABPI should be in the range between 0.8 and 1.3

6.2 Exclusion Criteria

Subjects must be excluded from participating in this study if they meet any of the following criteria:

TABLE: 6.2-1: Exclusion Criteria

Number	Exclusion Criteria
EC-1	Known sensitivities or allergies to components of the AQUACEL® Ag+ Extra™ or Cutimed® Sorbact®
EC-2	Continued use of petroleum gel/ creams/ oil-based products on the target wound
EC-3	Active treatment for cancer or completed within the last 3 months
EC-4	Documented severe malnutrition at any time
EC-5	Malignant wounds or other than VLU wounds
EC-6	Systemic infection actively treated with antibiotics
EC-7	Patients with uncontrolled diabetes within last 3 months with HbA1c ≥ 10. Subjects without diabetes do not require measurement of HbA1c if they have a glucose or HbA1c level measured over the past year.

Number	Exclusion Criteria
EC-8	Chronic conditions such as autoimmune disorders in an acute flare phase, which in the opinion of the investigator would directly impact wound healing. Use of immunosuppressant medications are allowed as long as they have been on a stable dose and regimen over the past three months

6.3 Relationship of Investigation Population to the Target Population

Silver and non-silver wound dressings are used to assist in the management of chronic wounds. The inclusion and exclusion criteria are representative of the population with chronic wounds who would be prescribed AQUACEL® Ag+ Extra™ and Cutimed® Sorbact® dressing.

7 INFORMED CONSENT PROCESS

Informed Consent must be obtained for all subjects prior to any study activities being performed or data collected. The Investigator or designee will review all relevant aspects of the study with the potential study subject that are relevant to the subject's decision to participate throughout the study. The investigator or designee will provide ample time for the subject to read and understand the IRB/EC approved Informed Consent Form and to consider participation in the study.

Informed consent will not be collected until all the patient questions have been answered to their satisfaction. If agreeable, the subject (or legally authorised representative) must sign and date the Informed Consent Form, along with the Investigator or designee. As required by country-specific regulatory agencies, a witness will sign the Informed Consent Form. The Subject must receive a copy of the signed Informed Consent, with the original remaining with the Investigator.

8 POINT OF ENROLLMENT AND EXIT

The study will be conducted in accordance with ISO 14155:2020 and in compliance with national and local laws in the geographies the study will be conducted.

8.1 Point of Enrolment

Subjects are considered enrolled in this study at the time the Informed Consent process has been completed. In the event of subject withdrawal or discontinuation prior to study completion, study subjects will not be replaced.

8.2 Point of Exit

Study subjects may exit the study for a variety of reasons. The Investigator shall record the reason for study exit in the applicable Study Completion CRF. These reasons include, but are not limited to:

- Study completion.
- Withdrawal by the Subject.
- Withdrawal by the Investigator.
- Lost to follow-up.
- Death.
- Study Termination.

Data collected until the last known contact of study subject may be used in the analysis of study data. For study subjects lost to follow-up, the Investigator shall make three (3) documented attempts before confirming the subject is lost to follow-up. If the study subject withdraws from the study for any reason and there is an ongoing safety event, additional safety event information may need to be collected by the Investigator and shared with the Sponsor.

8.3 Completed Subject

Subject has completed the study if the subject has completed the final study visit (84 days follow-up visit) or earlier if all study wounds have healed prior to 84-day follow-up visit. If subject has multiple wounds, the subject exits the study when the last study wound heals or when subject attends the final study visit, whichever occurs first. Study completion can occur between the scheduled study visits.

8.4 Subject Identification

Subjects will be allocated a unique study identifier on all study documentation. The only documents which will contain any personal details is the consent form and the Subject Identification Log, which are maintained by the Investigator or designated study staff. Their identification is a number attributed regarding the country, number of the site and number dedicated to inclusion. For example: 57-0001-0005: country number 57, centre number 1, inclusion number 5.

8.5 Wound Identification

Each study wound will be allocated a sequential number within the subject starting with number 1. For example, subject 57-0001-0005, Wound 01, Wound 02; subject 57-0001-0006, Wound 01, Wound 02.

9 STUDY PROCEDURES

The following section describes the study procedures and data which will be collected at each procedure for the duration of the study.

9.1 Procedure Diagram

9.2 Study Visits

After Informed Consent has been obtained, the following study procedures will be performed. All data is to be entered into the applicable Case Report Form (CRF).

9.3 Schedule of Events

A schedule of events is in the table below.

9.4 Enrolment of Subject with Multiple Wounds

Subjects with multiple wounds are allowed into study. Each wound that meets all wound-specific inclusion and none of the wound-specific exclusion criteria should be enrolled into study. The randomization occurs at the subject level. All study wounds for a specific subject will be treated with the same study device (e.g., all study wounds in a subject randomized to AQUACEL® Ag+ Extra™ will be treated with AQUACEL® Ag+ Extra™. No wound-level cross-over is allowed.

TABLE 9.3-1: Schedule of Events

	Visit 1 Day 1	Visit 2 Day 14 (+/- 2 days)	Visit 3 Day 28 (+/- 2 days)	Visit 4 Day 42 (+/- 2 days)	Visit 5 Day 56 (+/- 2 days)	Visit 6 Day 70 (+/- 2 days)	Visit 7 Day 84 (+/- 2 days)	Additional Visit	End of Study Visit^
Informed Consent	X								
Inclusion / Exclusion	X								
Demographics	X								
Medical History	X								
Concomitant Medication	X	X	X	X	X	X	X		X
Wound History	X								
Wound-QoL-14	X	X*	X*				X		X@
Wound debridement per usual practice	X	X	X	X	X	X			
Wound Assessment	X	X	X	X	X	X	X	X	X
Randomisation	X								
Decision to continue with randomised dressing or Standard of Care		X							
Randomised Dressing Application	X	X	X$	X&	X&	X&			
Secondary Dressing Application#	X	X	X	X	X	X			
Apply compression therapy	X	X	X	X	X	X			
Adverse Events	X	X	X	X	X	X	X	X	X
Device Deficiency%	X	X	X	X	X	X	X	X	X

* Wound-QOL-14 will be completed following the completion of treatment with randomized dressing on Day 14 (+/- 2 days) or on Day 28 (+/- 2 days) if additional 14 days of treatment with the randomised dressing occurred.

@ Collect QOL-14 if the Additional Visit is Study Completion visit.

$ Application of the randomised dressing after Visit 2 (14-day visit) at the discretion of the investigator.

& After day 28, the PI or delegate will continue treatment of the wound according to the clinical needs based on their evaluation of the wound. If an antimicrobial wound dressing is required, the dressing that was randomly assigned during the initial phase of the study can continue to be used

Secondary dressing to be applied at the discretion of the investigator.

% If applicable

^ If end of study visit is not Visit 7

10 Visits

After Informed Consent has been obtained, the following study procedures will be performed.

10.1 Visit 1: Screening and Baseline: Day 1

The following procedures and data are collected at Visit 1. All information on this visit is required. Missing data and assessments will be considered a protocol deviation.

- Obtain Informed Consent
- Inclusion and Exclusion Criteria Review and Documentation
- Demographics (Sex, Age, Height, Weight, BMI calculation, Ethnicity)
- Medical History (Cardiovascular, Respiratory, Gastro-Intestinal, Endocrine, Haematological, Musculo-skeletal, Neoplasia, Neurological, Immunological, Dermatological, Allergies, Psychological, and Other)
- Obtain Concomitant Medications (Medication Used, Route, Dose, Unit, Frequency, Indication, Start Date, Stop Date or Ongoing)
- Study Wound(s) Assessment
    - Duration of wound
    - Location of the wound (I.e., left/right leg, posterior/ anterior, medial/ lateral, etc.)
    - Wound size (measured in cm at the longest point and across the widest point)
    - Wound bed appearance
    - Exudate level, colour, and consistency
    - Condition of peri-wound skin
    - Maximum pain level on a scale of 0 to 10 within the last 24 hours
    - Level of odour on a scale of 0 to 10 for the study participants and mild/medium/strong for the clinician.
    - Therapeutic Index for Local Infections (TILI) score
- Wound-QoL-14
- Randomisation to either AQUACEL® Ag+ Extra™ or Cutimed® Sorbact®
- Randomised dressing application (Size and Lot Number)
- Apply compression per standard of care (documentation of type used)
- Documentation of the use of secondary dressings, if applicable

Each study wound in subject with multiple study wounds is assessed independently.

10.2 Visit 2: Day 14 (+/- 2 days)

The following procedures and data are collected at this visit. All information on this visit is required. Crossover to the non-randomized study dressing is not permitted.

- Review of concomitant medications, documenting any changes (medication used, route, dose, unit, frequency, indication, start date, stop date or ongoing)
- Wound assessment
    - Wound size (measured in cm at the longest point and across the widest point, as well as depth)
    - Wound bed appearance
    - Exudate level, colour and consistency
    - Condition of peri-wound skin
    - Maximum pain level on a scale of 0 to 10 within the last 24 hours

    - Level of odour on a scale of 0 to 10 for the study participants and mild/medium/strong for the clinician.
    - Therapeutic Index for Local Infections (TILI) score
- Number of days, since last visit, where compression was not applied (including documentation of reason for no compression)

A clinician decision is required at this visit regarding continuation of the randomised dressing (AQUACEL® AG+ Extra™ or Cutimed® Sorbact®) or transition to long-term management per standard of care. In subject with multiple study wounds the decision is made for each study wound separately. For example, one wound can be selected for Option 1 and another wound for option 3.

Option 1: An additional 14 days of treatment with randomised dressing (AQUACEL™ Ag+ Extra™ or Cutimed® Sorbact®) is required.

Option 2: Further treatment with randomised dressing is not indicated. The wound should be further managed per standard of care.

Option 3: Clinician determines that a non-standard of care treatment is needed. Treatment with the randomised dressing is discontinued.

Regardless of the option chosen, the subject remains in the study and is followed-up until the study exit (see section 8.2)

Once the decision has been made on the treatment option, the following information will be collected.

- Dressing application according to clinician decision (randomised dressing or other dressing) (name, size and lot number is recorded)
- Documentation of any additional products used
- Document any additional therapies
- Document and address any Adverse Events
- Document and address any Serious Adverse Events
- Number of intermediate visits where dressings were changed between scheduled visits (this is the number of times a subject received a new dressing since the last visit)
- Wound-QOL-14 (only if Option 2 or 3 has been selected).

10.3 Visit 3: Day 28 (+/- 2 days)

The following procedures and data are collected at this visit. All information on this visit is required. Following this visit, if the wound has not healed, the type of the further treatment is per investigator discretion and it can include continuous application of randomised dressing (if per standard of care) and other standard of care and non-standard of care options. Regardless of the type of the treatment continuation chosen, the subject remains in the study and is followed-up until the study exit (see section 8.2)

- Review of concomitant medications, documenting any changes (medication used, route, dose, unit, frequency, indication, start date, stop date or ongoing)
- Wound assessment
    - Wound size (measured in cm at the longest point and across the widest point, as well as depth)
    - Wound bed appearance
    - Exudate level, colour and consistency
    - Condition of peri-wound skin
    - Maximum pain level on a scale of 0 to 10 within the last 24 hours

    - Level of odour on a scale of 0 to 10 for the study participants and mild/medium/strong for the clinician.
    - Therapeutic Index for Local Infections (TILI) score
- Number of days, since last visit, where compression was not applied (including documentation of reason for no compression)
- Dressing application according to clinician decision (randomised dressing or Standard of Care) (name, size and lot number is recorded)
- Documentation of any additional products used
- Document any additional therapies
- Document and address Adverse ~~Device~~ Events
- Document and address Serious Adverse Events
- Number of intermediate visits where dressings were changed between scheduled visits (this is the number of times a subject received a new dressing since the last visit)
- Wound-QOL-14 (only if not collected at Visit 2).

10.4 Visits 4 - 7: Day 42 thru 84 (every 14 days +/- 2 days)

The following procedures are performed and data collected at the intermediate visits (every 14 days +/- 2 days until day 84). All information is required.

- Review of concomitant medications, documenting any changes (medication used, route, dose, unit, frequency, indication, start date, stop date or ongoing)
- Wound Assessment
    - Wound size (measured in cm at the longest point and across the widest point, as well as depth)
    - Wound bed appearance
    - Exudate level, colour and consistency
    - Condition of peri-wound skin
    - Maximum pain level on a scale of 0 to 10 within the last 24 hours
    - Level of odour on a scale of 0 to 10 for the study participants and mild/medium/strong for the clinician.
    - Therapeutic Index for Local Infections (TILI) score
- Dressing application Care (required), documentation of any additional products used
- Document any additional therapies
- Document and address Adverse Events
- Document and address Serious Adverse Events
- Number of intermediate visits where dressings were changed between scheduled visits (this is the number of times a subject received a new dressing since the last visit)
- Wound-QOL-14 at the study exit or last visit (Visit 7).

10.5 Unscheduled Visit

Unscheduled visit is any visit that is not a scheduled study visit and is not a pre-planned standard of care clinical visit.

10.6 End of Study Visit (Study Exit)

The study exit visit will occur when:

- the subject exits the study for any reason, including that all study wounds have healed; or
- The subject attends Visit 7.

Completion of end of study or appropriate forms is required.

11 SAFETY AND EVENT REPORTING

The Medical and Clinical Affairs group at Convatec Ltd will be responsible for the safety of the study. The Medical and Clinical Affairs group are located at Convatec, Global Development Centre Deeside, First Avenue Deeside Industrial Park Deeside Flintshire CH5 2NU, Telephone +44 (0) 1244 284882.

11.1 Definitions

11.1.1 Adverse Event (AE).

An untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device and whether anticipated or unanticipated.

11.1.2 Serious Adverse Event (SAE).

An adverse event that results in one of the following outcomes:

- Death
- Serious deterioration in the health of the subject, users, or other persons as defined by one or more of the following:
    - a life-threatening illness or injury, or
    - a permanent impairment of a body structure or a body function including chronic diseases, or
    - in-patient or prolonged hospitalization, or
    - medical or surgical intervention to prevent life-threatening illness or injury, or permanent impairment to a body structure or a body function,
- Fetal distress, fetal death, a congenital abnormality, or birth defect including physical or mental impairment.

11.1.3 Adverse Device Effect (ADE)

An adverse device effect (ADE) is an AE related to the use of an Investigational Product. It includes AEs resulting from:

- Insufficient or inadequate Instructions for Use (IFU), deployment, implantation, installation, or operation,
- Any malfunction of the investigational medical device.
- Any event resulting from use error or from intentional misuse of the investigational medical device.

In this study, an investigational medical device is either of the randomised study dressings (AQUACEL® Ag+ Extra™ or Cutimed® Sorbact®).

11.1.4 Serious Adverse device Effect (SADE)

A serious adverse device effect (SADE) is an ADE that has resulted in any of the consequences characteristic of an SAE.

11.1.5 Unanticipated Serious Adverse Device Effect (USADE)

Serious adverse device effect, which by its nature, incidence, severity, or outcome has not been identified in the current version of the risk analysis report.

11.2 Adverse Events Categories and Relationship Determination

All AEs (regardless of relationship to the study procedures or severity) occurring from enrolment up to and including the subject's final study visit will be recorded by the Investigator. AEs may be either spontaneously reported to Investigator or elicited during questioning and examination of a subject. All identified AEs must be recorded in the patient record and on the Adverse Event case report form. If known, the diagnosis of the underlying illness or disorder should be recorded, rather than its individual symptoms.

11.3 Categories of Severity

The following definitions will be used for the categories of "Severity":

- Mild: awareness of sign or symptom, but easily tolerated
- Moderate: discomfort enough to cause interference with usual activity
- Severe: incapacitating, with inability to work or do usual activity

11.4 Relationship to Investigational Device

Causality assessment is required for AEs and SAEs that occur during clinical investigations. There is currently no standard international nomenclature to describe the degree of causality or relatedness of an AE with the Investigational Product. The following terms will be used during this study:

Related - The AE is directly and clearly related to the Investigational Product.

Possibly Related - There is a reasonable likelihood that the AE is due to the Investigational Product, as evidenced by the following:

- There may be temporal association with the Investigational Product (e.g., within 24 hours of device placement).
- The AE, or level of severity of the AE, is unlikely to be explained by other etiologies (known to be related to the study disease, Subject's baseline medical condition, or concomitant medication).

Not Related - The AE is definitely not related to the Investigational Product, or the AE is unlikely to be related to the Investigational Product because of a lack of temporal association or is known to be related to one or more of the following:

- Morbidity associated with underlying medical condition.
- Treatment procedure.
- Concomitant medication.
- A relationship to the Investigational Product is not biologically plausible.

11.5 Procedure for Monitoring and Recording of Serious Adverse Events

All SAEs occurring after from enrolment up to and including the subject's final study visit will be reported. All SAEs must be followed until the event no longer meets serious reporting criteria, resolves, stabilizes, or the subject is considered lost to follow-up.

All SAEs that occur during the collection period must be reported by the Investigator and/or their appointed Designee within 24 hours of first becoming aware of the occurrence of the SAE. Reports should be submitted to the responsible monitor and Convatec Safety & Compliance on an Initial SAE Report (SAER) form provided by Convatec Ltd. Available supporting documentation, if applicable, (e.g., discharge summary, laboratory reports) should be included. Personal identifiable information will be

deleted, and the subject number will be written on the report. All attempts should be made by the Investigator to follow the progress of the SAE.

Serious adverse events will be listed as a single diagnosis (e.g., septic shock, flu-like syndrome) or a single event (e.g., headache, bone pain) whenever possible. Each single event, even if concurrent, should be reported on separate SAE Form.

Convatec Ltd. has the responsibility to expeditiously review and report all SAEs to comply with regulatory requirements. Where applicable, Convatec Ltd. must:

- Report the SAE or SADE to the Lead Investigators at each site.
- Report the SAE or SADE to the appropriate regulatory authorities in accordance with local requirements.
- Ensure that Competent Authorities and all responsible IRB/Ethic Committees are notified of the events in the appropriate timeframe in accordance with local requirements.

If deemed appropriate (e.g. SADE) Convatec will update the Risk Assessment accordingly.

11.6 Safety Reporting Timelines

Type of Event	Report to Sponsor	Method
Adverse Event	Per Protocol Visit	Complete eCRF
Adverse Device Effect	Per protocol visits	Complete eCRF
SAE	Within 24 hours of study staff becoming aware of event	Initial: phone/email to sponsor Followed by: Complete CRF
SADE	Within 24 hours of study staff becoming aware of event	Initial: phone/email to sponsor Followed by: Complete CRF
USADE	Within 24 hours of study staff becoming aware of event	Initial: phone/email to sponsor Followed by: Complete CRF

11.7 Follow-Up Information for Serious Adverse Events

Subsequent or new information will be submitted by the site staff to the Sponsor or its designee, in the form of an updated Adverse Event Report Form. Personal identifiable information will be deleted/blacked out and the subject number will be written on the report. Every attempt should be made to obtain follow-up SAE information. All unresolved SAEs for subjects considered lost to follow up should be documented appropriately in source documentation and reported to Convatec Ltd. on a follow-up form.

11.8 Device Deficiency

A device deficiency is an inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety, or performance. This may include malfunctions, use errors, and inadequacy in the information supplied by the manufacturer including labelling. This definition includes device deficiencies related to the investigational medical devices or to a comparator, i.e., a medical device, therapy (e.g., active treatment, normal clinical practice), placebo or no treatment, used in the control group in a clinical investigation (ISO 14155:2020). Device deficiencies may occur before use, during use, or after use. All Investigational Product deficiencies will be collected throughout the study and captured on the Device Deficiency eCRF. Any treatment delay that was caused by the device deficiency will be collected as well if the device will be returned to the Sponsor.

The Investigator is responsible for assessing the reportability of each event, and submitting the Device Deficiency Report when the deficiency meets the following criteria:

- Any device deficiency that led to an SAE (the PI must submit both an SAE Report and the associated Device Deficiency Report to the Sponsor/designee).
- Any device deficiency that might have led to an SAE if any of the following is true.
    - Suitable action had not been taken.
    - Intervention had not been made.
    - Circumstances had been less fortunate.

The PI must submit the Device Deficiency Report to the Sponsor as soon as possible, but not later than 5 business days, following the date of awareness of the event. The PI is responsible for reporting the device deficiency to the ethics committee, if required per ethics committee regulations.

The Sponsor will promptly evaluate the report to determine further actions. When applicable, appropriate Corrective and Preventive Actions (CAPAs) will be taken to protect the safety of Subjects, users, and other persons. The Sponsor will arrange for the safe return of the Investigational Product that is subject to a Device Deficiency.

12 PROTOCOL DEVIATIONS

Except for a change that is intended to eliminate an immediate hazard to the subjects, the approved protocol shall be conducted as described. Any significant protocol deviation must be documented. Every deviation recorded on Deviation Form will be evaluated for its impact.

12.1 Deviation Reporting Timelines

Type of Deviation	Report to Sponsor	Method
Subject safety, rights, OR welfare; OR data integrity; OR compromise the statistical analysis of the study; OR Lack of Informed Consent; OR Inclusion/Exclusion Criteria	Within 24 hours of study staff becoming aware of event	Initial: phone/email to sponsor Followed by: Complete CRF
All other protocol deviations	Per protocol visits	Complete CRF

13 PREMATURE TERMINATION, SUSPENSION OR ROUTINE CLOSE-OUT OF THE STUDY

13.1 Premature Termination or Suspension

Convatec may suspend or prematurely terminate a clinical investigation for significant and documented reasons or for no reasons or if requested by regulatory authorities.

Convatec may terminate or suspend the participation of a site or investigator if the monitor and/or auditor identify serious or repeated deviations on the part of an investigator. If the suspension or premature termination occurs, Convatec shall justify its decision in writing and promptly inform the Investigator and IRB/Ethics Committee.

If suspension or premature termination occurs,

- Convatec will remain responsible for providing resources to fulfil the obligations of the study and existing agreements
- The investigators or authorised designee will inform the enrolled subjects, if appropriate

13.2 Procedure for resuming the clinical investigation after temporary suspension

When the analysis of the reason for the suspension is complete, the corrective actions are implemented and the decision to lift the suspension reached, Convatec will inform the investigator and ethics committee of the rationale.

13.3 Routine Close-Out

Routine close out activities shall be conducted to ensure that the investigator records are complete, all documents needed for Convatec's files are retrieved and previously identified issues have been resolved and all parties are notified.

Within 90 days after the closure of the study Convatec will notify the Ethics Committee of the end of the study. Within 1 year after the end of the study, the final report will be submitted to the Ethics Committee.

14 MONITORING

Study Monitoring is conducted to ensure that the rights, safety, and well-being of study participants are protected, that the reported study data are accurate, complete, and verifiable, and that the conduct of the study is in compliance with the currently approved protocol, GCP, and with applicable regulatory requirements.

Convatec is responsible for ensuring the proper conduct of the clinical investigation with regard to protocol adherence and validity of the data recorded on the CRFs. Convatec has assigned study monitor(s) to this clinical investigation. The progress of the clinical investigation will be monitored by:

- Periodic and/or remote review
- Telephone communications
- Review of CRFs and source documentation (e.g., subject records)

The study monitor(s), other authorized representatives of the Sponsor, representatives of the IRB/EC, or regulatory authorities may inspect all documents and records required to be maintained by the Investigator, including, but not limited to subject records for the participants in this study. The clinical study site will permit access to such records. The Investigator will give Convatec study monitor(s) direct access to source documents that support data on the CRFs. This includes electronic records.

Investigator non-compliance of required study responsibilities will require Sponsor sanctions to alleviate the non-compliance, including corrective and preventative actions up to and including disqualification of the Investigator/Site.

Details of the clinical site monitoring are documented in a Monitoring Plan (MP), which will be written prior to the first monitoring visit. The MP describes in detail who will conduct the monitoring, at what frequency monitoring will be done, at what level of detail monitoring will be performed, and the distribution of monitoring reports.

Independent audits may be conducted by Convatec or designee to ensure monitoring practices are performed consistently across all participating sites and that monitors are following the MP.

Any Monitoring Visits will comply with the Government restrictions on travel due to the Covid-19 pandemic, if applicable.

15 DEVICE ACCOUNTABILITY

Investigative sites will use formulary/on-the shelf inventory for treatment of the subjects with AQUACEL® Ag+ Extra™ and Cutimed® Sorbact®. The sponsor will not provide any products. Therefore, device accountability is not required.

16 CONFIDENTIALITY

Participant confidentiality and privacy is strictly held in trust by the participating Investigators, their staff, the Sponsor, and their authorised representatives. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants. Therefore, the Clinical Investigational Plan, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study, or data will be released to any unauthorized third party without prior written approval of the Sponsor. All research activities will be conducted in as private a setting as possible.

Study data, which is for the purposes of statistical analysis and reporting, will be transmitted to and stored at Convatec or an approved supplier. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The electronic data capture system used by clinical sites and by Convatec research staff will be secured and password protected.

17 DATA HANDLING AND RECORD KEEPING

Data collected for this study will be analysed and stored at Convatec or an approved supplier for use by researchers, including those outside of the study. Permission to transmit, store and use data outside of the study will be included in the informed consent.

17.1 Data Collection and Management Responsibilities

Data collection is the responsibility of the clinical study staff at the site under supervision of the site Investigator. The Investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents should be completed in a neat, legible, permanent, and un-editable manner to ensure accurate interpretation of data. Data recorded in the electronic case report form derived from source documents must be consistent with the data recorded on the source documents.

Data will be entered into a compliant data capture system provided by Convatec. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate.

17.2 Study Records Retention

The study participant's information will be securely stored at each clinical site for internal use during the study. At the end of the study, all study records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB/EC, Institutional policies, regulatory authorities, or Sponsor requirements.

No records will be destroyed without the written consent of the Sponsor. It is the responsibility of the Sponsor to inform the Investigator when these documents no longer need to be retained.

17.3 Sponsor Oversight

Routine review of submitted study information by the Sponsor will be conducted to ensure Protocol compliance. Items reviewed include, but are not limited to: adverse events, deviations, number of withdrawn / terminated subjects; which all may impact completion of the study. Appropriate measures may be taken to ensure Investigator compliance with the Protocol.

18 STATISTICAL CONSIDERATIONS

This study is a multi-center, prospective, parallel, concurrent RCT. Details of the statistical analysis will be described in the SAP. This section provides key elements of the statistical approach.

18.1 Alpha Value

Alpha value will be 0.05 for both one-way and two-way testing.

18.2 Statistical Approach for the Primary Endpoint

The study hypothesis is that the Experimental Treatment with AQUACEL® Ag+ Extra™ will have similar effectiveness to the Control Treatment with Cutimed® Sorbact® in proportion of wounds that have completely healed by 84 days. The statistical hypothesis is that Experimental Treatment with AQUACEL® Ag+ Extra™ will be non-inferior to Control Treatment with Cutimed® Sorbact® in proportion of wounds that have completely healed by 84 days.

The statistical null and alternative hypotheses are as follows:

$$H_0: \pi_{Exp} - \pi_{Con} \leq \delta$$
$$H_A: \pi_{Exp} - \pi_{Con} > \delta$$

where π_{Exp} and π_{con} represent the true proportion of target wounds that have healed by 84 days in patients treated with AQUACEL® Ag+ Extra™ and Cutimed® Sorbact®, respectively, and δ is the non-inferiority margin. The non-inferiority margin (δ) is set to -15%.

The statistical definition of success is the rejection of H_0. The null hypothesis (H0) will be tested by constructing a two-sided 90% confidence interval for the difference in the proportions of ulcers that have completely healed between the Experimental Arm and the Control Arm. If the lower boundary of the interval does not include δ, then the null hypothesis will be rejected. If non-inferiority of AQUACEL® Ag+ Extra™ to the Cutimed® Sorbact is demonstrated, its superiority will be tested.

18.3 Statistical Approach to Secondary and Exploratory Endpoints

A pre-planned analysis of the secondary endpoints will be performed testing the non-inferiority, followed by superiority, of the Experimental Arm compared to the Control Arm conditioned by success in testing of the primary efficacy endpoint. The multiplicity and Type 1 Error within the secondary endpoints' family will be controlled using the fixed sequence approach and alpha value of 0.05. SAP provides details on the analysis of the secondary endpoints including non-inferiority margins, where applicable.

Statistical approaches for exploratory endpoints are described in SAP.

18.4 Sample Size Determination

Under the assumption that the proportion of completely healed ulcers by day 84 is 0.8 (80%), the sample size of 206 subjects and minimum of 206 wounds randomized 1:1 to Experimental and Control arms will have 85% power to reject the null hypothesis.

Sample size assumptions concerning the proportion variance and average number of wounds per subject will be verified during the study in a blinded fashion. Such verification does not inflate alpha-value.

18.5 Multiplicity

Testing of secondary endpoints will be performed in a gateway fashion and fixed sequence. No adjustment for the multiplicity is required. Details of the fixed sequence will be presented in SAP.

18.6 Randomisation

Subjects will be randomised on a 1:1 basis to either the AQAUCEL® Ag+ Extra™ or Cutimed® Sorbact® dressing at the subject level. All wounds for the same subject will be treated using the randomised dressing. The randomization sequence will be stratified by study centre. Other details concerning the randomization are described in the Randomisation Plan.

18.7 Statistical Populations

All subjects that are randomized are considered participants.

Safety Population includes all subjects that are randomized to and receive one of the study treatments.

Full Analysis Data Set. This will be constructed following the Intent-to-Treat (ITT) principle and will include all subjects that are randomized, receive one of the study treatments, and have at least one follow-up visit after the baseline (Visit 1).

Per Protocol Population (PP) This will all subjects that are randomized, receive one of the study treatments, do not discontinue the trial prior to 4-week follow-up visit except for the reason that all study ulcers have closed and have no major protocol deviations that would impact integrity of the statistical analysis of primary endpoint.

Completed Cases (CC) Population is a subset of Full Analysis Data Set Population and includes all subjects who have the final study visit (Day 84) or have exited the study earlier due to all study wounds have healed.

19 CONFLICT OF INTEREST

The independence of this study from any actual or perceived influence, such as by the medical device industry, is critical. Therefore, any actual conflict of interest of a person who has a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial. The Sponsor has established procedures for all Investigators to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

20 GOOD CLINICAL PRACTICE AND STATEMENTS OF COMPLIANCE

20.1 Ethical Approval

The protocol will be reviewed by a properly constituted ethics committee. A copy of the written ethical approval will be sent to the Sponsor/designee.

Subject recruitment will not commence until appropriate ethical approvals/opinions have been received, and as appropriate, the applicable agreement(s) between the Sponsor and the Investigator have been documented. Any additional requirements imposed by the ethics committee will be incorporated into the protocol as required.

20.2 Protocol Modifications

Modifications to this protocol may be necessary. In collaboration with the Investigator(s), modification will be documented and submitted for ethical and regulatory approval (as required) prior to implementation. All changes will be evaluated for impact per Sponsor standard operating procedures (SOPs). Modifications will be considered implemented after all ethical and regulatory approvals (as required) are received and all key Sponsor and site staff have been trained.

20.3 Periodic Reviews

Ongoing review by IRB/EC is required for the duration of the clinical study. The Investigator will comply with local IRB/EC requirements for ongoing reviews.

20.4 Insurance

The Sponsor shall provide clinical study related insurance covering the reasonable, and necessary costs of diagnostic, therapeutic and medical treatment including hospitalization costs (treatment costs) for such participant injuries following the administration or use of the study device(s) in accordance with this clinical investigational plan and in accordance with the national regulations. The Sponsor may reimburse the institution and/or study participants for treatment costs, depending on who incurred such treatment costs if (i) the injury is attributable to the negligence or misconduct of any agent or employee of the institution or Investigator, or the failure of such persons to comply with a study protocol, (ii) the treatment costs are covered by the study participant's medical or hospital insurance coverage, or (iii) the treatment costs arose as a result of the treatment of normal progression of the study participant's disease or injuries resulting from interventions that the study participants would have incurred had they not participated in the study.

20.5 Patients' Compensation

Subjects may be compensated for their time and inconvenience. Details of any remuneration will be documented in the Patient/Participant Information Sheet.

20.6 Principal Investigator, Coordinating Investigator(S), Investigational Sites and External Organisations

The Name(s) and Address(es) of the sites at which this study is to be conducted is maintained as part of the Sponsor's files. The files will include the different roles, responsibilities, and qualifications of these investigators.

The Name(s) and Address(es) of the external organisation(s), such as core laboratories, CRO consultants, etc. which may assist in this study are maintained as part of the Sponsor's files.

20.7 Public Registration and Publication

The Sponsor shall ensure that this study will comply with required national registration requirements. This study will be conducted in accordance with the applicable publication and data sharing policies and regulations. When applicable, attempts will be made to publish results. Publication rules will follow international recommendations.

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AQAUCEL® Ag+ Extra™ IFU Ref No. 170881G6

22 GLOSSARY, ABBREVIATIONS & ACRONYMS

Abbreviation	Term
AE	Adverse Event
BMI	Body Mass Index
CRF	Case Report Form
CRO	Contract Research Organisation
EC	Ethics Committee
EU	European Union
FDA	Food and Drug Administration
GCP	Good Clinical Practice
IC	Informed Consent
ICH	International Conference for Harmonisation
IEC	Independent Ethics Committee
IFU	Instructions for Use
ITT	Intent to Treat
IRB	Institutional Review Board
MDR	Medical Device Regulations
PP	Per Protocol Population
QoL	Quality of Life
RCT	Randomised Control Trial
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOP	Standard Operating Procedure
TILI	Therapeutic Index for Local Infections score
UADE	Unanticipated Adverse Device Effect
VLU	Venus Leg Ulcer